CRANIOFACIAL MICROSOMIA
BEYOND THE FIRST AND SECOND PHARYNGEAL ARCH

Ruben Willem Renkema

ISBN: 978-94-6506-158-0
ISBN EBOOK: 978-94-6506-144-3

Provided by thesis specialist Ridderprint, ridderprint.nl
Printing: Ridderprint
Layout and design: Bart Roelofs, persoonlijkproefschrift.nl

Financial support for the printing and distribution of this thesis was kindly supported by:

KNMT	Materialise	NoordNegentig
NVMKA	KLS Martin	Chipsoft
Megagen	Ed Stouten Tandtechniek	Examvision
Straumann	BAP Medical	DAM Medical
Nobel Biocare	Laposa	

Craniofacial Microsomia
Beyond the first and second pharyngeal arch

Craniofaciale microsomie
Voorbij de eerste en tweede kieuwboog

Thesis

to obtain the degree of Doctor from the
Erasmus University Rotterdam
by command of the
rector magnificus

Prof. dr. A.L. Bredenoord

and in accordance with the decision of the Doctorate Board.

The public defence shall be held on
Wednesday 4 September 2024 at 13:00 hrs

by
Ruben Willem Renkema
Born in Wageningen.

Erasmus University Rotterdam

Doctoral Committee

Promotor:	Prof. dr. E.B. Wolvius
Other members:	Prof. dr. D. Eygendaal Prof. dr. A.B. Mink Van Der Molen Prof. dr. A.G. Becking
Co-promotor:	Dr. C.J.J.M. Caron

Contents

Part I

1

General introduction

Embryology and etiology

In the first six weeks of embryologic development many structures of the body are being formed, including different facial parts, such as the mandible, maxilla, orbit, ears, facial nerve and soft tissue. A disturbance in embryogenesis could lead to a unilateral or bilateral underdevelopment of these facial structures and can be characterized as craniofacial microsomia (CFM). CFM is a relatively rare congenital disorder with an incidence of 1:3000 to 1:5000 live births (1-4). Both, the type and severity of the hypoplastic structures varies largely among patients. The exact origin of CFM is unknown.

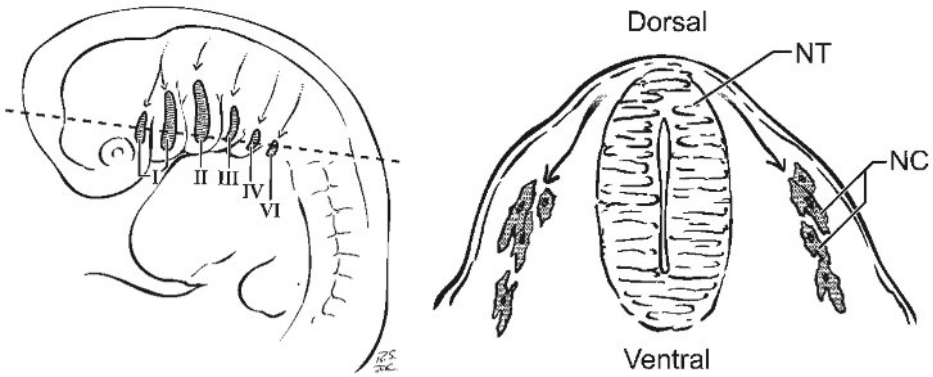
The affected structures in patients with CFM are related to the first and second pharyngeal arches. These pharyngeal arches are subdivided in a pouch, arch, a groove, and a membrane. Each arch is comprised by three layers, the endoderm, mesenchyme and the ectoderm. The mesenchyme originates from the ectomesenchyme and mesoderm which is formed by neural crest cells that migrate from the neural tube during neurulation to the arches (see figure 1.1). The first pharyngeal arch forms the zygoma, maxilla, mandible, masticatory muscles, trigeminal nerve, anterior auricle and the malleolus and incus. The second pharyngeal arch forms the facial musculature and nerve, the auricle, stapes and the hyoid bone (see figure 1.2 & 1.3).

Various theories on the etiology of CFM have been proposed including a hemorrhage of the stapedial artery, environmental factors such as vasoactive medication use of the mother, or an error in neural crest cells differentiation/migration (2, 5, 6). Poswillo showed in 1973, by using animal models, that a hemorrhage of the stapedial artery can lead to underdevelopment of the structures derived from the first and second pharyngeal arches. A more severe clinical presentation with underdevelopment of multiple structures, including muscles, multiple facial bones and nerves might be explained from the severity of the hemorrhage. Nonetheless, the bilateral presentation and expanded phenotypes cannot be explained by this theory. Another pathogenic model for the development of CFM is an error in migration or differentiation of the neural crest cells into the first and second pharyngeal arches (7, 8). Neural crest cells are essential in the development of various craniofacial and extracraniofacial structures. Genetic defects, teratogens and environmental factors, such as elevated embryonic glucose levels, might cause

apoptosis of neural crest cells or errors in development (9, 10). This could lead to a hypoplasia of the structures that are related to CFM. The phenotypical characteristics of patients with CFM are heterogeneous and might show overlap with other developmental disorders such as VACTERL (vertebral defects, anal atresia, cardiac defects, tracheo-esophageal fistula, renal anomalies, and limb abnormalities) or CHARGE syndrome (coloboma, heart defects, atresia choanae, growth retardation, genital abnormalities, and ear abnormalities) (5).

In recent years, genetic studies on CFM have focused on identifying genes/loci for CFM. Beleza-Meireles et al. performed comparative genomic hybridization microarray studies of 22 patients with CFM and identified a variety of copy-number variations (CNVs) in the 22q11 region which may contribute to CFM (11). Silva et al. performed cytological analysis on 23 patients with CFM and found karyological abnormalities in three patients, including one patient with mosaicism (mos47,XX-,+mar/46,XX) (12). FISH analyses on 22q11 and 5p microdeletions did not show any abnormalities. The variety in chromosomal abnormalities highlight the heterogeneity of CFM, according to the authors (12). To further study the genetic pathogenesis, the first genome-wide association study on CFM with additional whole genome sequencing was performed by Zhang et al. in 2016 (13). A total of 939 patients with CFM and 2012 controls were studied. Thirteen loci and eleven genes (SHROOM3, DCAKD, NID2, PARD3B, ROBO1, ARID3B, KLF12, FGF3, EPAS1, EDNRB, FRMD4A) were considered associated with CFM; all playing a role in neural crest cell development and vasculogenesis. Additional whole genome sequencing in 21 patients with CFM showed loss-of-function mutations in the associated loci. This is the first study linking candidate genes for CFM to the presumed biological pathophysiological mechanism of CFM, namely neural crest cell migration and differentiation (13). As previously delineated, an error in neural crest cell migration or differentiation might lead to the facial characteristics of CFM but could also cause congenital malformations of extracraniofacial structures.

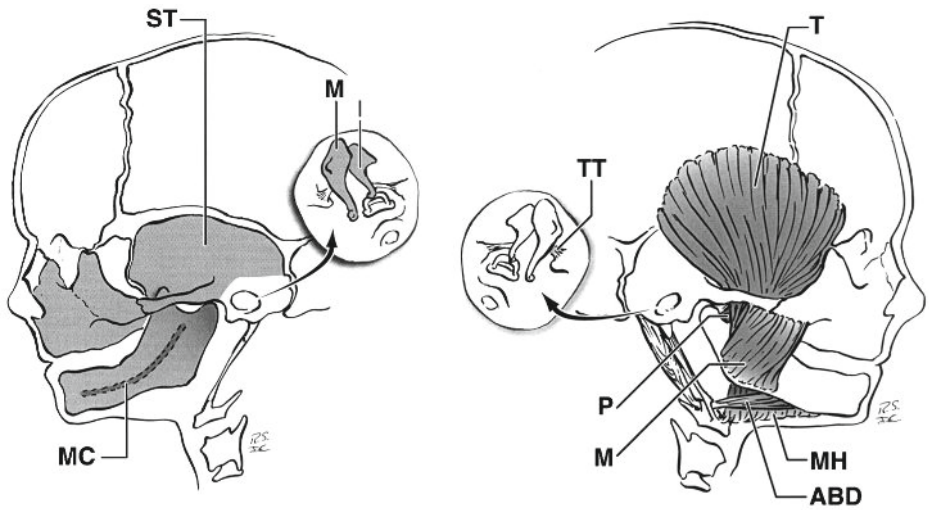
Figure 1.1: *Pharyngeal arches and neural crest cells (adapted from Sze et al. 2002 (14))*



A. Embryonic pharyngeal arches (I-VI) – lateral view

B. Formation of neural crest cells from the neural plate folds as its forms the neural tube - coronal view

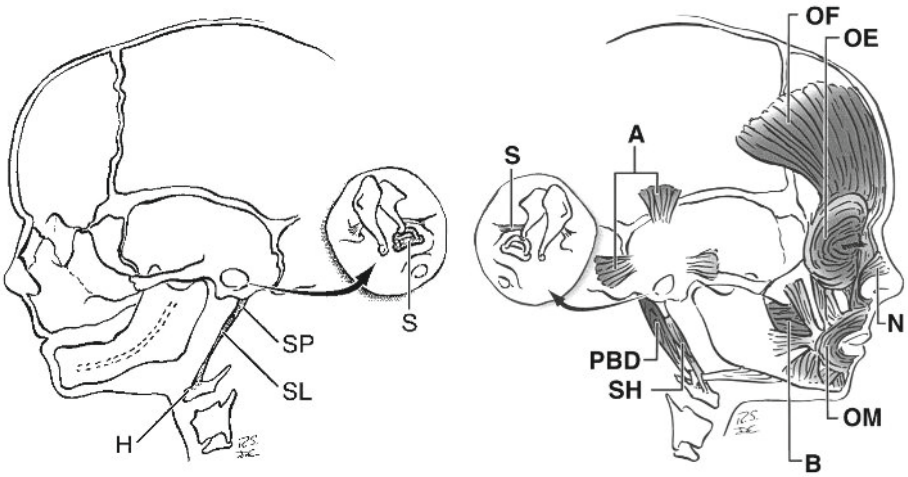
Figure 1.2: *Derivatives from the first pharyngeal arches (adapted from Sze et al. 2002 (14))*



Left: the mesenchyme forms the squamous temporal bone (ST), zygoma, maxilla, mandible by the Meckel's cartilage (MC) and the malleus (M), incus (I), and greater wing of the sphenoid bone.

Right: muscles for mastication originate from the first pharyngeal arch, including temporal (T), masseter (M), pterygoids (P), anterior belly of the digastric muscle (ABD), mylohyoid muscle (MH), tensor tympani muscle (TT) and the tensor veli palatini muscle.

Figure 1.3: *Derivatives from the second pharyngeal arches (adapted from Sze et al. 2002 (14))*



Left: cartilage derivatives, including the stapes (S), styloid process (SP), stylohyoid ligament (SL) and the hyoid bone (H)

Right: facial musculature, including orbicular muscle of the eye (OE) and mouth (OM), occipitofrontal muscle (OF), nasal muscle (N), buccinator (B), auricular muscle (A), stapedius muscle (S), posterior belly of the digastric muscle (PBD) and the stylohyoid muscle (SH), and the levator muscle of the upper lip and the zygomatic muscles.

Phenotypical characteristics and classification

A variety of names has been used to describe patients with craniofacial microsomia. This includes hemifacial microsomia, oculo-auriculo-vertebral spectrum of dysplasia, first and second pharyngeal arch syndrome, and Goldenhar syndrome. Goldenhar syndrome was originally described by Maurice Goldenhar in 1952 and consisted of an association of malformations of the ear, eye and mandible (15). In literature, Goldenhar syndrome is often defined as mandibular dysostosis with epibulbar dermoids and vertebral anomalies. Gorlin et al. used a different triad in 1963, and concluded that the Goldenhar syndrome consists of epibulbar- or lipodermoids, auricular appendices or pretragal fistulas, and vertebral anomalies (16). In a case series, he firstly described oculo-auriculo-vertebral dysplasia as a distinct entity and a variant of hemifacial microsomia, consisting of the Goldenhar triad with characteristics of hemifacial microsomia (16). Gorlin, together with Pindborg, also introduced the term hemifacial microsomia which is characterized

by hypoplasia of the ears, mandible and oral structures (17). Nowadays, research showed that these separate entities are not present when studying large groups of patients with CFM (18). The term Goldenhar syndrome is often used as a subjective term to describe patients with a more severe form of facial hypoplasia (19). CFM could rather be seen as a spectrum or continuum of anomalies, varying in type and severity. In this thesis, the term craniofacial microsomia is used as the authors believe this encompasses the syndrome best as bilateral involvement is present in up to thirty percent of the patients (20).

Various classification systems have been developed for CFM. A comprehensive phenotypical classification system makes it possible to assess patients in a standard manner and could be used to create reliable and reproducible data for documentation. Pruzansky segregated three grades of mandibular hypoplasia, based on the morphology of the ramus and condyle in 1969 (21). A type I mandible has a normal morphology of the ramus but the condyle and ramus are smaller. In a type II mandible, the ramus, condyle and sigmoid notch are distorted in shape and size. The most severe form, type III, has a severely hypoplastic ramus and absent temporomandibular joint. Kaban et al. modified the classification and subdivided the type II mandible in IIA and IIB. In type IIA, the positioning of the deformed joint is adequate for symmetrical opening of the mandible, whereas in type IIB the temporomandibular joint is malpositioned (figure 1.4) (22, 23). Many other classification systems have been developed, but failed to be versatile, easy and accurate to use in clinical practice (24). The O.M.E.N.S. classification, developed by Vento et al in 1991 and which includes the Pruzanksy-Kaban classification, is currently the standard classification that is used to grade patients with CFM (25). Each item of the O.M.E.N.S., an acronym for Orbital asymmetry, Mandibular hypoplasia, Ear deformity, Nerve dysfunction, Soft tissue deficiency, is scored on a scale from 0 to 3 or 4. The 'plus' category, by using a '+' sign, was added by Horgan et al. in 1995 to note the presence of associated extracraniofacial anomalies (6). Scoring is based on radiographic assessment as well as physical examination. Gougoutas et al. (24), and later modified by Birgfeld et al. (20), created a pictorial representation of the O.M.E.N.S.-Plus classification to enable usage in a clinical setting and rapidly characterize the severity of CFM by circling the appropriate images (see figure 1.5 & 1.6). Besides the global assessment, a detailed assessment was added to include preauricular tags, facial tags, preauricular pits, epibulbar dermoids, colobomas of the iris, and tongue malformations (20).

Figure 1.4: *Pruzansky-Kaban classification of the mandible in craniofacial microsomia (adapted from Kaban et al. 1988 (22))*

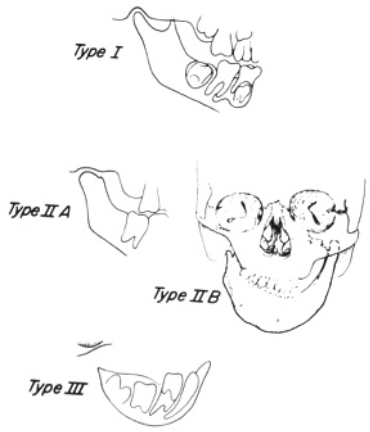


Figure 1.5: *Global Assessment of the modified pictorial OMENS-Plus classification system (adapted from Birgfeld et al. 2011 (20))*

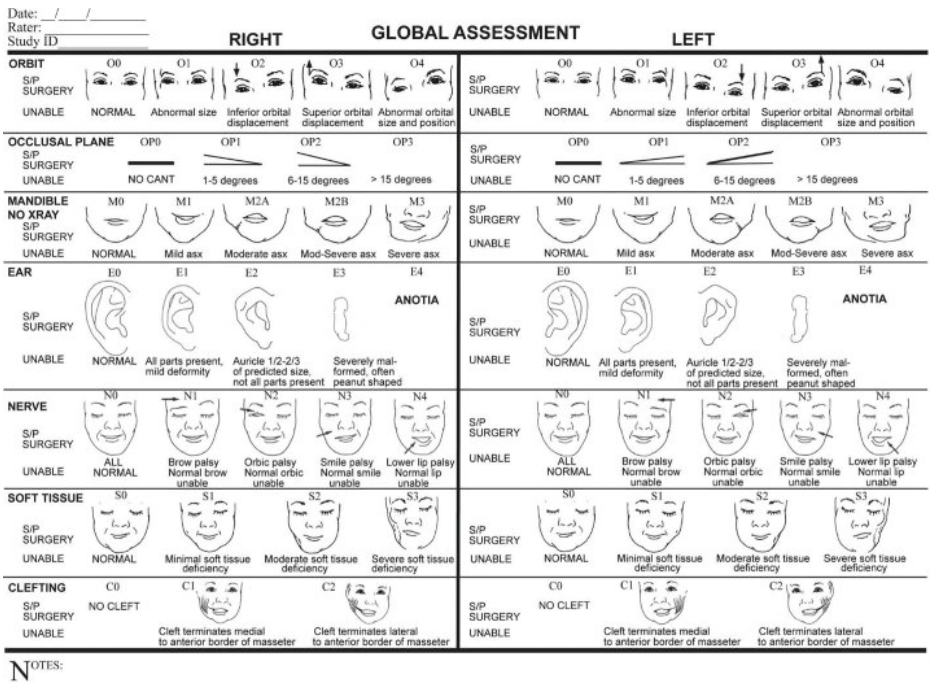
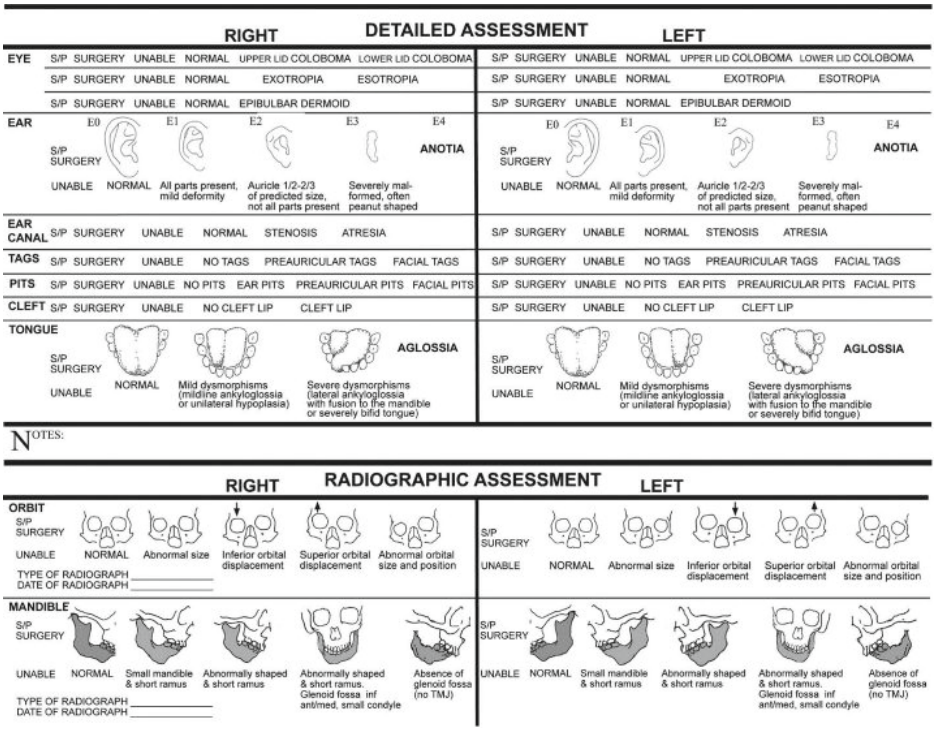


***Figure 1.6:** Detailed Assessment of the modified pictorial OMENS-Plus classification system (adapted from Birgfeld et al. 2011 (20))*



The term craniofacial microsomia suggests that the anomalies occurring in patients are restricted to the head and neck. Nonetheless, anomalies of other organs, so called extracraniofacial anomalies, are common in CFM (17, 26, 27). Up to 55% of the patients have extracraniofacial anomalies, sometimes referred to as the 'expanded spectrum' of CFM as described earlier in this introduction (6). These anomalies include anomalies in various tracts such as cardiovascular, renal, central nervous system, skeletal, gastro-intestinal or pulmonary. Awareness for these anomalies is required to timely diagnose the anomaly if present and, if needed, treat it in an early state.

Historically, the link between vertebral anomalies and CFM is relatively well known due to the Goldenhar syndrome and the oculo-auriculo-vertebral spectrum. In these entities, vertebral anomalies are part of the triad of symptoms. Nonetheless, literature on the variation in type, severity and prevalence on extracraniofacial

anomalies in CFM is scarce. The available literature is mostly based on case series including a relatively small group of patients.

Some risk factors for the presence of extracraniofacial anomalies in CFM are known. Patients with a more severe form of CFM, represented by a higher O.M.E.N.S. score, are more frequently diagnosed with extracraniofacial anomalies (6) and patients with an extracraniofacial anomaly are prone to have additional anomalies in other tracts too (18, 26). A more detailed assessment on the risk factors for the presence of extracraniofacial anomalies could help determine a potential screening protocol for these anomalies.

Identifying characteristics and risk factors for associated disorders in patients with CFM help to increase the quality of care for these patients. The heterogeneity of the syndrome and the absence of diagnostic criteria make it challenging to compare patients with CFM. Use of diagnostic criteria could help to create comparable outcomes between different craniofacial centers and thereby improving research and care. Development of such criteria is challenging due to the heterogeneity of the disorder and the large overlap with other syndromes. Recently, two sets of criteria have been developed for clinical research, including the ICHOM and FACIAL criteria (28, 29). Both criteria were developed based on consensus among experts. Comparison of both criteria and studying the sensitivity could enhance implementation of these criteria and improve comparison of research on CFM.

Mandibular hypoplasia is one of the most familiar characteristics of CFM. Unilateral mandibular hypoplasia leads to a rotation of the mandible to the affected side, causing the chin to deviate (30, 31). The degree of chin point deviation is related to the severity of facial asymmetry (32, 33). This asymmetry, in CFM often caused by mandibular hypoplasia, could lead to functional difficulties with breathing, feeding or aesthetics that warrant treatment. The timing of treatment of facial asymmetry is debated in literature (34-38). Early treatment could lead to better function and less aesthetic concerns, but secondary surgery later in life might be needed if the asymmetry is progressive due to surgical trauma and scar tissue (39-41). Research on the potential progressiveness of CFM could determine optimal timing of treatment.

Besides mandibular hypoplasia, facial nerve palsy and facial soft tissue deficiency are well known characteristics of CFM and items of the O.M.E.N.S. classification. Nonetheless, other cranial nerves or facial muscles might be affected too. Velopharyngeal dysfunction, defined as the inability to adequately close the velopharyngeal sphincter, is seen in patients with CFM and a cleft lip/palate, but also in up to 15% of the CFM patients without a cleft lip/palate (42). The pathophysiologic mechanism is unknown, but underdevelopment of muscles or nerves related to the first and second pharyngeal arches might play a role. To further investigate the relationship between CFM and velopharyngeal dysfunction studies with larger sample size could help to determine risk factors and the potential need for screening.

Management of patients

Clinical characteristics of CFM vary largely in both type and severity of the affected structures. As the treatment options and needs are different for each patient, an individual, patient specific, approach is needed. Various specialists are involved in the care for patients with CFM, including ENT-surgeons, genetics, maxillofacial surgeons, paediatric, plastic surgeons, psychologists, ophthalmologists, orthodontists, and speech and language therapists. As treatments could influence outcome of other treatments later in life, coordination of the care process between specialists is essential. Therefore, care for patients in CFM should be performed in a multidisciplinary setting.

Improvement of the care process for patients with CFM could be achieved by development of an evidence-based clinical guideline. It is a framework for clinical decision-making and supports best practices. It contains recommendations intended to optimize patient care, based on a systematic review of the available evidence. Other facets, including potential benefits and harms or alternative options are taken into account. Development of such a document helps to increase the quality of care for patients internationally. A translation of such guideline in 'non-medical' language helps patients to acquire information about CFM, the potential treatment options, and improves the process of shared-decision making.

Aims of this thesis

Studying the phenotype of CFM and its variations could identify factors that warrant screening or treatment. By recognizing these factors, the quality of care for patients with CFM might increase. As most studies on CFM include a limited number of patients it is difficult to study the extensiveness of the clinical variability in detail and research potential risk factors. A multicenter collaboration, including the craniofacial centers of Rotterdam, London, Boston, Toronto and Seattle was setup to increase the number of patients that can be studied. Besides researching the phenotype, this thesis aims to improve the quality of care by providing recommendations for clinical care. Establishing an optimal treatment algorithm in CFM is difficult due to the wide variety in clinical presentation, variable treatment options, and limited evidence-based treatment options. Nonetheless, an evidence-based clinical guideline helps to optimally organize care for CFM.

The overall aim of this thesis is to research the phenotypical characteristics of patients with CFM and provide recommendations for future management of these patients. Therefore, the following research questions were formulated:

1. What type of extracraniofacial anomalies occur in CFM and what is their prevalence?
2. Which patients with CFM are at risk for extracraniofacial anomalies?
3. What is the sensitivity of the available diagnostic criteria in a real-life dataset and what are characteristics of patients with CFM that do not meet these criteria?
4. What is the relation between mandibular and facial soft tissue hypoplasia on chin point deviation in CFM and does chin point deviation change during growth?
5. What is the prevalence of velopharyngeal dysfunction in CFM with and without cleft lip/palate and are there differences in clinical presentation compared to patients with isolated cleft lip/palate?
6. What knowledge on CFM has been discovered is the last decade and does this provide evidence for recommendations for clinical care?
7. What is the best treatment for the different facets of care in CFM based on the available literature?

Outline of this thesis

This thesis consists of several parts. In part II the phenotypical characteristics of CFM are studied. Chapters 2 to 6 addresses the expanded spectrum of CFM. All types, prevalence rates and risk factors for extracraniofacial anomalies are studied in these chapters. In chapter 2 a systematic search of literature on vertebral anomalies in CFM is performed, followed by a retrospective cohort study on vertebral anomalies in CFM in chapter 3. The type and prevalence of central nervous system anomalies is studied in a systematic review of literature in chapter 4. Chapter 5 researches the types and risk factors for extracraniofacial anomalies in CFM. A more detailed assessment of limb anomalies in CFM is performed in chapter 6. Chapter 7 aims to investigate the potential relationship between velopharyngeal dysfunction and CFM. This may shed light on the extensiveness of the syndrome as craniofacial nerves and muscles that are not primarily part of 'CFM spectrum' play a role in adequate velopharyngeal closure. In chapter 8 the available diagnostic criteria in CFM are studied, as such criteria might be helpful for future research on CFM. In the last chapter of part II, chapter 9, the potential progressiveness of facial asymmetry in CFM is studied by researching deviation of the chin point over time in patients with unilateral CFM.

Part III of this thesis addresses management of patients with CFM. In chapter 10 all literature on CFM published in the last decade is reviewed, followed by clinical recommendations based on the literature. The final chapter, chapter 11, is a summary of the European Clinical Guideline for CFM, in which evidence-based recommendations are made. This encompasses recommendations for screening, diagnostics and treatment for all different medical specialties that are involved in the care for patients with CFM.

Part IV and V are respectively the general discussion and (Dutch) summary. The possible answers to the questions of this thesis are discussed in the general discussion. Strengths, limitations as well as clinical implications are deliberated. Lastly, suggestions for future research are made.

Part II

Phenotypical characteristics of craniofacial microsomia

2

Vertebral anomalies in craniofacial microsomia

a systematic review

Based on:
Ruben W. Renkema, Cornelia J.J.M. Caron, Irene M.J. Mathijssen, Eppo B. Wolvius, David J. Dunaway, Christopher R. Forrest, Bonnie L. Padwa, Maarten J. Koudstaal. Vertebral anomalies in craniofacial microsomia: a systematic review, International Journal of Oral and Maxillofacial Surgery. 2017 Oct;46(10):1319-1329. doi: 10.1016/j.ijom.2017.04.025. Epub 2017 Jun 29. PMID: 28669484.

Abstract

Craniofacial microsomia is characterized by a heterogeneous underdevelopment of the facial structures arising from the first and second branchial arches, but extracraniofacial malformations such as vertebral anomalies also occur. This systematic review provides an overview of the literature on the type and prevalence of vertebral anomalies found in patients with craniofacial microsomia. A systematic search was conducted and data of number of patients, patient characteristics, type and prevalence of vertebral anomalies and other associations between craniofacial microsomia and vertebral anomalies were extracted. Thirty-one articles were included. Seventeen articles described both the prevalence and type of vertebral anomalies in craniofacial microsomia, five articles described solely the type of vertebral anomalies in craniofacial microsomia and nine articles reported solely the prevalence of vertebral anomalies in craniofacial microsomia. Most often reported vertebral anomalies in craniofacial microsomia include: hemivertebrae, blockvertebrae, scoliosis/kyphoscoliosis and spina bifida. These anomalies are mostly present in the cervical and thoracic spine and ribs. The prevalence of vertebral anomalies in craniofacial microsomia varies from 12% to 79%. To diagnose vertebral anomalies early in patients with craniofacial microsomia, further research should focus on determining which patients with craniofacial microsomia are at risk of vertebral anomalies.

Introduction

Craniofacial microsomia (CFM) is a heterogeneous disorder, causing a wide variety of facial malformations ranging in severity (1, 43-46). After cleft lip and palate, CFM is the most common congenital craniofacial disorder, with an incidence of 1:3000 to 1:5000 live births (1, 3, 4, 47). The craniofacial anomalies found in CFM are believed to be related to the first and second branchial arches (1, 43, 44). In CFM the mandible, zygoma, external and middle ear, facial musculature, facial nerve, and soft tissues can be affected. Although ear deformities are part of CFM, isolated microtia is generally not regarded as CFM (16, 44). However, it is still discussed whether isolated microtia might be a minor form of CFM (4, 44).

CFM is primarily known for its craniofacial malformations, but extracranial manifestations, such as vertebral, renal, heart, central nervous system, lung and gastrointestinal defects may occur as well (6, 16, 17, 25, 46, 48-50). Goldenhar reported what he believed to be a specific variant of CFM; these patients have the clinical features of CFM in combination with epibulbar dermoids and vertebral anomalies (16, 51). However, Vento and colleagues documented no association between these anomalies and refuted the existence of this variant (25). More recently Tuin et al. attempted to differentiate Goldenhar syndrome from craniofacial microsomia and concluded that the term Goldenhar syndrome was inconsequential (19). The most frequently seen vertebral anomalies in patients with CFM are hemivertebrae, fusion of vertebrae, scoliosis, accessory vertebrae, occipitalization of the atlas and spina bifida (1, 52).

Several terms are used for CFM, such as oculo-auriculo-vertebral spectrum, hemifacial microsomia, lateral facial dysplasia, first and second branchial arch syndrome. Presumably, these conditions are part of the CFM spectrum (19, 26, 53, 54). In this manuscript we will refer to the deformity by CFM, as this is currently most often used in literature.

The exact origin of CFM is unknown. The most widely accepted theory is that CFM is the result of a disturbance in the embryologic development of the first and second branchial arches, during the first six weeks of gestation (16, 45, 49). During these first six weeks of embryologic development, both the skull and spine are formed (49). Therefore, a common pathogenic mechanism is likely to be the basis of both

craniofacial and vertebral malformations in patients with CFM. Although the precise link between the facial and vertebral malformations has not been clarified, the deficiency presumably occurs during vertebral somite formation, resulting in incorrect formation of the vertebrae and the skull (55). This may lead to congenital scoliosis or instability of the cervical spine (55-57). Instability of the cervical spine may also be the result of abnormal development of ligamentous structures and could cause compression of the spinal cord during movement (55). The clinical presentation of vertebral instability is largely variable and may or may not be associated with signs or symptoms (55). Symptoms of cervical spine instability include neck pain, torticollis or limited neck movement, and neurological symptoms may occur if there is compression of the spinal column or vertebral artery (55, 58). The cerebellum and cranial nerves can be involved, which may lead to a wide range of neurologic symptoms, including ataxia, coordination disturbances and diplopia (55). Basilar impression, which is associated with cervicovertebral anomalies, can cause similar symptoms (59, 60). Excessive cervical spine manipulation, which may be induced by sports activities, may result in spinal cord impingement in patients with unrecognized cervical instability (61). Besides the possible neurological effects, fusion or underdevelopment of the vertebrae could also result in fractures of the ankylosed segments or in progressive scoliosis (62-67). It is important to keep these, often asymptomatic, vertebral anomalies in mind when performing surgery, as cervical spine instability can put these patients at risk for spinal cord injury during intubation or surgical manipulation (68-71).

Since vertebral anomalies occur in CFM patients and may cause serious complications, it is important that clinicians are aware of the possible anomalies and their consequences. The aim of this systematic review is to study the available literature on vertebral anomalies and the respective prevalence's found in patients with CFM.

Methods

Search strategy

This study was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (72). A systematic search of the literature was performed to identify papers focusing on CFM and its synonyms combined with synonyms for spinal and central nervous system anomalies. The search was conducted in embase.com, medline in Ovid, Cochrane central, web of science, PubMed

(articles not yet indexed in Medline) and Google Scholar (most relevant articles) from inception until 21 June 2016. Results were limited to human studies written in English. No date limits were applied, but conference abstracts, letters, notes and editorials were excluded. See the online appendix for the full search strategies of all databases.

The studies were independently selected by two researchers (R.W.R. and C.J.J.M.C.). Titles and abstracts were screened for relevance based on the inclusion and exclusion criteria. Studies concerning CFM in relation to vertebral anomalies were further reviewed. Studies were included when prevalence and/or type of vertebral anomalies in CFM were mentioned. The studies had to be original studies. Case reports were excluded. Although there is still debate on whether isolated microtia is a form of CFM, we consider it to be a different entity for the purpose of this study. Therefore, studies describing solely patients with isolated microtia were not included. However, from papers describing both patients with microtia and CFM, data was extracted concerning the CFM patients.

Data extraction

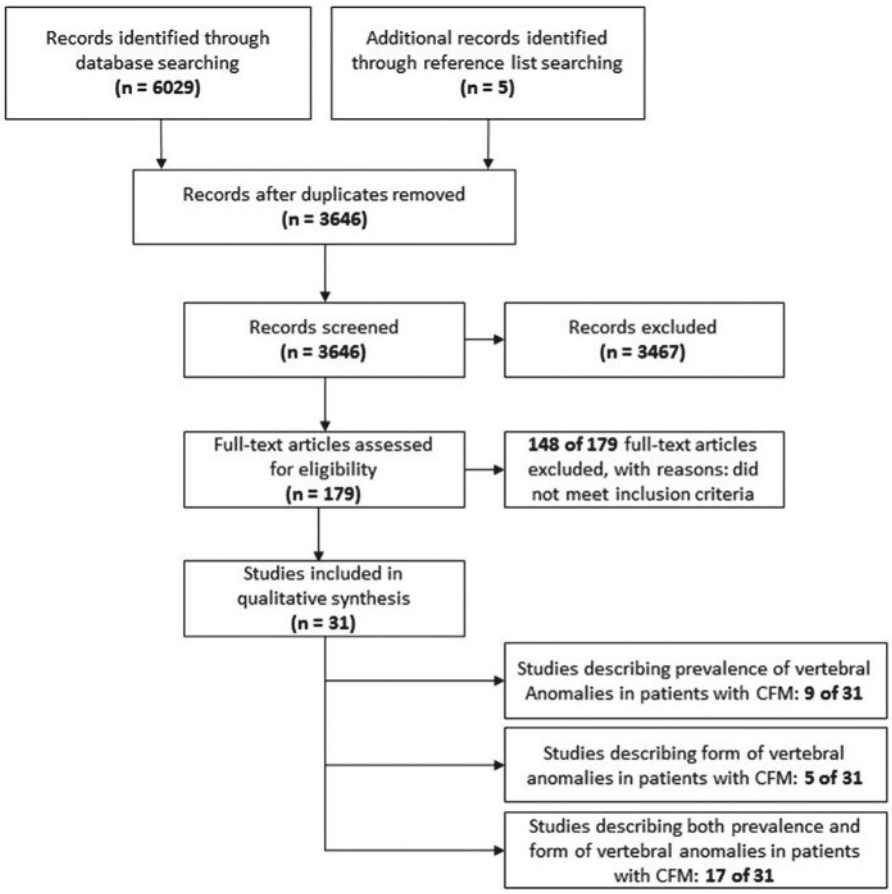
A table with predetermined characteristics was made prior to full text review of the articles. All papers were graded on quality of evidence using the Oxford Centre for Evidence-Based medicine (CEBM) criteria. Data on the number of patients, inclusion criteria of the studies, Prevalence of vertebral anomalies in CFM, type of vertebral anomalies and other correlations between CFM and vertebral anomalies, were extracted when available.

Results

Study selection

In total 6034 articles were identified after the initial search and after including articles identified through reference list searching. After removing duplicate articles, 3646 articles were examined based on title and abstract. In total 3467 articles were excluded as a result of not meeting the inclusion criteria. The remaining 179 articles were reviewed full-text, leaving thirty-one articles to be included for review. Twenty-six articles described the prevalence of vertebral anomalies in their study and twenty-two articles described the type of vertebral anomalies in their investigated population (figure 2.1).

Figure 2.1: *PRISMA diagram of the systematic review methodology used for the review*



Study characteristics

The characteristics of the included studies are described in table 2.1. Several studies included patients diagnosed with isolated microtia (26, 53, 73-75). These patients were extracted from the studies and not included in this literature review for further analysis (table 2.2, table 2.3). Patients with incomplete data were excluded from our analysis. Radiographs or CT-scans were used to evaluate the vertebral anomalies. Most studies were retrospective (6, 11, 19, 25, 49, 52, 61, 73, 74, 76-84), although some prospective studies and case series were found (26, 46, 48, 50, 53, 62, 75, 85-89). The number of patients studied ranged from 6 to 259 per study (6, 11, 19, 25, 26, 46, 48-50, 52, 53, 61, 62, 73-90).

Table 2.1: *Study characteristics*

Year	Author	CEBM level of evidence	Methodology	Total number of patients	Included patients in this study	Aim of the study	Inclusion criteria of the study
2015	Al Kaissi et al. (62)	4	Case series	6	6	To elicit the underlying spine pathology in Goldenhar patients	Goldenhar syndrome: microtia with facial asymmetry, ear anomalies, skin tags, epilbulbar dermoids and extracranial malformations
2005	Anderson et al. (76)	3	Retrospective study	15	7	To clarify the nature and extent of spinal anomalies in Goldenhar patients	Goldenhar syndrome, spinal radiographs and chest radiographs
1998	D'Antonio et al. (77)	3	Retrospective study	41	41	To describe the occurrence and magnitude of pharyngeal and laryngeal anomalies in OAVS patients	OAVS
1988	Avon et al. (52)	3	Retrospective study	23	21	To report orthopaedic findings in Goldenhar syndrome patients	Goldenhar syndrome or hemifacial microsomia
2014	Barisic et al.(78)	3	Retrospective study	259	259	To provide population-based information on OAVS patients	Microtia and at least one major anomaly of the OAV spectrum (HFM, epibulbar dermoid, vertebral malformations)
2015	Beleza-Meireles et al. (11)	3	Retrospective study	51	51	To provide an assessment of the OAVS phenotype and revaluation of the minimal diagnostic criteria	The presence of HFM of facial asymmetry together with microtia or milder ear malformations

Table 2.1: *Continued.*

Year	Author	CEBM level of evidence	Methodology	Total number of patients	Included patients in this study	Aim of the study	Inclusion criteria of the study
1995	Cohen et al. (90)	3	Cross-sectional study	24	18	To examine the neurodevelopmental profile of children with OAVS	Diagnosis of OAVS: malformation of the aural, oral and mandibular structures
2007	Engiz et al. (85)	3	Prospective study	31	31	To describe the phenotypic features and laboratory findings of patients with OAVS or Goldenhar	Diagnosis of OAVS: variety of craniofacial, auricular and vertebral anomalies
2000	Ewart-Toland et al. (79)	3	Retrospective study	14	14	To describe individuals born to diabetic mothers having OAVS features	Children of diabetic mothers with hemifacial microsomia
1978	Feingold et al. (46)	4	Case series	16	16	To present 16 patients with Goldenhar's syndrome	Minimal 2 out of 3 Goldenhar syndrome criteria: eye abnormality associated with ear, mandibular, or vertebral anomalies
1985	Figueroa et al. (73)	3	Retrospective study	204	156	To investigate the cervicovertebral malformations in CFM	Hemifacial microsomia, Goldenhar syndrome and OAVS
1996	Gibson et al. (86)	3	Prospective study	35	35	To report the vertebral anomalies in Goldenhar patients	At least one of the basic criteria for Goldenhar syndrome

Table 2.1: *Continued.*

Year	Author	CEBM level of evidence	Methodology	Total number of patients	Included patients in this study	Aim of the study	Inclusion criteria of the study
1994	Gosain et al. (80)	3	Retrospective study	18	18	To establish the type and prevalence of cervicovertebral anomalies in Goldenhar syndrome	Goldenhar syndrome: microtia, mandibular hypoplasia and epibulbar
2007	Johansson et al. (87)	3	Prospective study	20	20	To analyze the relations between OAVS and Autism spectrum disorder, and identify CNS and chromosomal abnormalities	Malformation in two of the four areas: orocraniofacial, ocular, auricular and vertebral
1989	Kaye et al. (74)	3	Retrospective study	297	129	To identify and look for patterns in the associated anomalies in microtia patients.	Patients with malformations of the cervical base/spine in patients with microtia and mandibular hypoplasia
2015	Manara et al. (88)	3	Prospective study	29	29	To investigate the cranial nerve abnormalities in OAVS	Hemifacial microsomia and microtia
1992	Morrison et al. (89)	3	Prospective study	25	24	To document the precise cardiovascular status of each patient to determine the prevalence of cardiac disease in OAVS	Microtia plus one of mandibular hypoplasia, skeletal anomalies, ocular abnormalities and palate abnormalities

Table 2.1: *Continued.*

Year	Author	CEBM level of evidence	Methodology	Total number of patients	Included patients in this study	Aim of the study	Inclusion criteria of the study
2016	Pegler et al. (84)	3	Retrospective study	41	41	To describe the most prominent clinical features of a cohort of patients with oculo-auriculo-vertebral (OAV) dysplasia in Brazil	OAVS: involvement of minimal 2 of the 4 domains (face, eyes, ears, vertebrae)
1987	Rollnick et al. (26)	4	Case series	294	202	To describe the phenotypic characteristics of individuals affected with OAVS and variants	Hemifacial microsomia, Goldenhar syndrome, OAVS
2009	Rooryck et al. (81)	3	Retrospective study	95	93	To identify new genomic loci that are potentially involved in OAVS	Isolated microtia or hemifacial microsomia together with microtia
2010	Rosa et al. (82)	3	Retrospective study	34	17	To describe the CNS abnormalities in a sample of OAVS patients	Malformation in minimal two of the four areas: oro-cranial-facial, ocular, auricular, vertebral
1982	Sherk et al. (83)	3	Retrospective study	26	26	To report patients with specific facial abnormalities and document accompanying spinal anomalies	Hemifacial microsomia and Goldenhar syndrome
1977	Shokeir et al. (48)	3	Prospective study	24	24	To delineate the natural history of Goldenhar syndrome, with regard to the possible therapeutic implications	Goldenhar syndrome: ocular manifestations, auricular involvement, facial abnormalities, skeletal dysplasia

Table 2.1: *Continued.*

Year	Author	CEBM level of evidence	Methodology	Total number of patients	Included patients in this study	Aim of the study	Inclusion criteria of the study
2007	Strömland et al. (50)	3	Prospective study	18	13	To survey the systemic and functional defects in a group of OAVS patients	Malformation in minimal two of the four areas: oro-cranio-facial, ocular, auricular or vertebral malformations
2005	Tasse et al. (53)	3	Prospective study	53	44	To investigate patients with OAVS and develop a new classification and scoring system	Microtia with or without HFM
2006	Touliatou et al. (75)	4	Retrospective study	17	14	To describe the phenotypic data and evaluation of a group of 17 Goldenhar patients	Craniofacial anomalies and microtia as minimum
2006	Tsirikos et al. (49)	3	Retrospective study	14	14	To determine the prevalence, type and treatment of congenital spine deformities in Goldenhar syndrome	Hemifacial microsomia
2015	Tuin et al. (19)	3	Retrospective study	255	138	To evaluate the use of the term Goldenhar syndrome	Clinical diagnosis of CFM or Goldenhar syndrome
1991	Vento et al. (25)	3	Retrospective study	154	154	To create a new classification system to organize the dysmorphic manifestations in a logical, concise and comprehensive manner	HFM and/or microtia

*OAVS: oculo-auriculo-vertebral spectrum; HFM: hemifacial microsomia; CFM: craniofacial microsomia; CNS: central nervous system

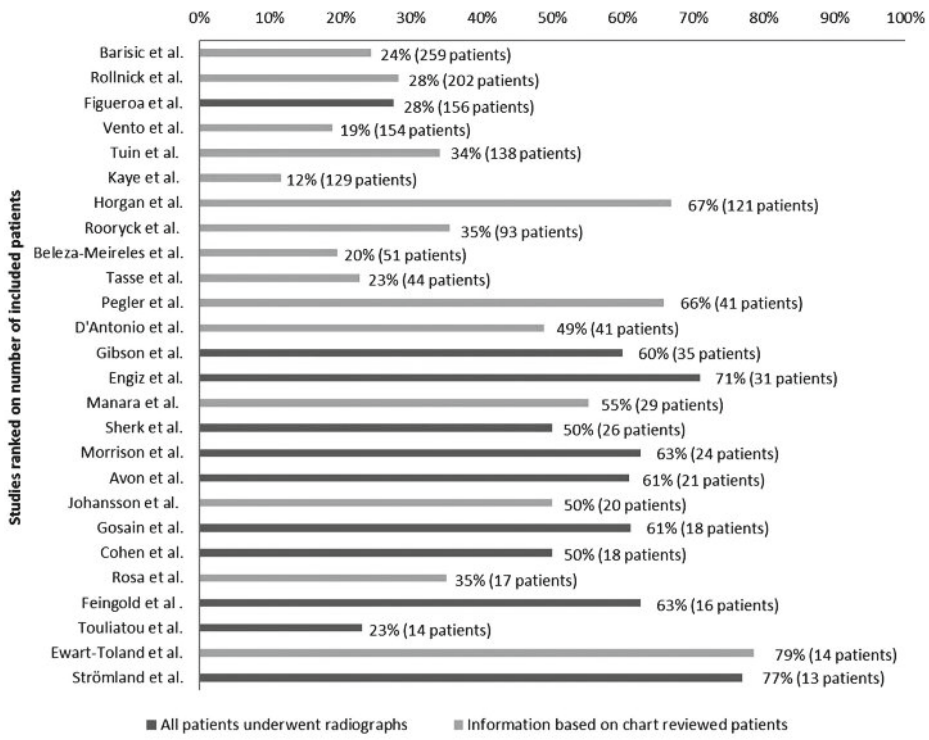
Table 2.2: *Number of patients and level of spinal examination in articles on the prevalence of vertebral anomalies in CFM*

Author	Total number of patients	Number of isolated microtia patients in study	Included patients	Number affected patients	Spinal Examination		
					Full spine	Only cervical spine	Not specified
D'Antonio et al.	41	n/a	41	20	x		
Avon et al.	23	n/a	21	14	x		
Barisic et al.	259	n/a	259	63	x		
Beleza-Meireles et al.	51	n/a	51	10	x		
Cohen et al.	24	n/a	18	9		x	
Engiz et al.	31	n/a	31	22	x		
Ewart-Toland et al.	14	n/a	14	11	x		
Feingold et al .	16	n/a	16	10			x
Figueroa et al.	204	48	156	43	x		
Gibson et al.	35	n/a	35	21	x		
Gosain et al.	18	n/a	18	11		x	
Horgan et al.	181	n/a	121	57			x
Johansson et al.	20	n/a	20	10			x
Kaye et al.	297	60	129	10		x	
Manara et al.	29	n/a	29	16			x
Morrison et al.	25	n/a	24	15			x
Pegler et al.	41	n/a	41	27			x
Rollnick et al.	294	92	202	59			x
Rooryck et al.	95	n/a	93	33			x
Rosa et al.	34	n/a	17	6			x
Sherk et al.	26	n/a	26	13	x		
Strömland et al.	18	n/a	13	10			x
Tasse et al.	53	9	44	10			x
Touliatou et al.	17	3	14	3	x		
Tuin et al.	255	n/a	138	47	x		
Vento et al.	154	n/a	154	29			x

Prevalence of vertebral anomalies in CFM

The reported prevalence of vertebral anomalies in CFM varied from 12 to 79 percent (74, 79). A distinction was made between the studies because in some studies all patients underwent radiographs (46, 50, 52, 73, 75, 80, 83, 85, 86, 89, 90), while in other studies data on vertebral anomalies was based on reviewing patient's charts, therefore the exact number of patients who underwent radiographs was unknown (figure 2.2) (6, 11, 19, 25, 26, 53, 74, 77-79, 81, 82, 84, 87, 88). In most studies the complete spine was studied, reported prevalence of vertebral anomalies in these studies varied from 19 to 79 percent (25, 79). However, Cohen et al, Gosain et al, and Kaye et al. only studied the cervical spine reporting prevalence's of 12 to 61 percent (74, 80, 90). Figueroa et al. included patients with cervical spine radiographs and studied radiographs of the thoracic and lumbar spine when available (73). However, interestingly no spine anomalies beside the cervical spine anomalies were found.

***Figure 2.2:** Reported prevalence of vertebral anomalies in craniofacial microsomia per study*



Types of vertebral anomalies

The different types of vertebral anomalies diagnosed in patients with CFM are documented in table 2.3. Although the exact location of vertebral anomalies was not always specified, the type of vertebral anomalies was described. Most often reported anomalies without specification of the location are hemivertebrae, scoliosis and spina bifida occulta (6, 11, 26, 48-50, 52, 61, 75, 78, 79, 82-86). In the cervical region, hemivertebrae, blockvertebrae, occipitalization of the atlas and cervical ribs are most often described (48, 61, 62, 73, 76, 80, 84). The only study mentioning actual cervical spine instability, by using flexion-extension radiographs, was done by Healey et al. (61). In the thoracic region hemivertebrae and blockvertebrae are the most common vertebral anomalies (11, 49, 52, 61, 62, 75, 76, 84, 85). Scoliosis, spina bifida occulta and butterfly vertebrae are observed (49, 52, 61, 62, 76, 86). In the lumbar region vertebral anomalies are seen less frequently. When present, hemivertebrae, blockvertebrae, and/or scoliosis are most often described (48, 49, 76, 78, 85, 86). Anomalies of the ribs are detected in ten studies, describing fusion of ribs, aplasia of ribs, hypoplasia of ribs and extra ribs (6, 49, 52, 75, 76, 78, 79, 82, 85, 86).

Table 2.3: *Vertebral anomalies described in CFM*

					Spinal examination			Location not specified								Cervical									
	Total number of patients	Isolated microtia patients	Included patients	Number affected patients	Full spine	Only cervical spine	Not specified	Butterfly vertebrae	Hemivertebrae	Blockvertebrae	Transitional vertebrae	Incomplete fusion vertebral arches	Scoliosis/ Kyphoscoliosis	Spina bifida occulta	Not specified	Butterfly vertebrae	Hemivertebrae	Blockvertebrae	Scoliosis/ Kyphoscoliosis	Spina bifida occulta	Occipitalization of the atlas	Hypoplastic atlas	Platybasia	Instability C1-C2	Split vertebrae	Basilar invagination
Al Kaissi et al.	6	n/a	6	6	X												1	5	4		2					
Anderson et al.	15	n/a	7	7	X											1		4	4		3	1				
D'Antonio et al.	41	n/a	41	20	X																					
Avon et al.	23	n/a	21	14	X								1				3	4	1	1						
Barisic et al.	259	n/a	259	63	X				14				8		18		4	2							1	
Beleza-Meireles et al.	51	n/a	51	10	X								5				2	5								
Cohen et al.	24	n/a	18	9		X										1	4	4								
Engiz et al.	31	n/a	31	22	X								5	1		1	1	8		5						
Ewart-Toland et al.	14	n/a	14	11	X				1	1								5								
Figueroa et al.	204	48	156	43		X											3	#	5	4	7		4			2
Gibson et al.	35	n/a	35	21	X				#	13			10	11	4							1				
Gosain et al.	18	n/a	18	11		X												11			3					
Healey et al.	8	n/a	8	8	X				1								1	3			1			3		
Horgan et al.	181	n/a	121	57			X		21				#													
Pegler et al.	41	n/a	41	27			x		3	2	4	4	13	4				7								
Rollnick et al.	294	92	202	59			X		#				#	#	19			#								#
Rosa et al.	34	n/a	17	6			X	1	5					2												
Sherk et al.	26	n/a	26	13	X								9							1						
Shokeir et al.	24	n/a	24	21	X			2	12	5				2							2					
Strömland et al.	18	n/a	13	10			X						3													
Touliatou et al.	17	3	14	3	X				#				#													
Tsirikos et al.	14	n/a	14	14	X								1					6								

Table 2.3: *Continued.*

	Cervical						Thoracic						Lumbar										Ribs				
	Accessory vertebrae	Rotary subluxation	Displaced vertebrae	Hypoplastic odontoid	Ribs cervical	Not specified	Butterfly vertebrae	Hemivertebrae	Blockvertebrae	Scoliosis/ Kyphoscoliosis	Spina bifida occulta	Not specified	Butterfly vertebrae	Hemivertebrae	Blockvertebrae	Scoliosis/ Kyphoscoliosis	Sacralization	Accessory vertebrae	Agenesis vertebrae	Agenesis sacral	Not specified	Fusion	Aplasia	Hypoplasia	Extra ribs	Not specified
Al Kaissi et al.								2	3	1																	
Anderson et al.					2			4	3	3				1	1	2	1					2	2	1		
D'Antonio et al.						9						13									1					
Avon et al.		1			2			5	1	4	2											2	1	1		
Barisic et al.						10						8						1	1	1	2					18
Beleza-Meireles et al.								1																		
Cohen et al.																										
Engiz et al.					2			4	2						2	1				1		1				
Ewart-Toland et al.																						1				
Figueroa et al.	1		3																							
Gibson et al.					5		2						1									14				
Gosain et al.																										
Healey et al.				3	2			2	2	3																
Horgan et al.																										14
Pegler et al.								7																		
Rollnick et al.						#																				
Rosa et al.																										3
Sherk et al.					2	1																				
Shokeir et al.					1												2									
Strömland et al.						9																				
Touliatou et al.									#																#	
Tsirikos et al.							3	12	5	10				2		1						1				

Other associations in CFM patients with vertebral anomalies

Beleza-Meireles et al. found a higher frequency of additional heart, brain, limb or other anomalies in CFM patients with vertebral anomalies (11). Although only ten patients in their study had vertebral anomalies, five of these patients also had heart, brain and other organ abnormalities. Rollnick et al. reported that cervical spine anomalies often occur with anomalies in other organ systems (26). Cohen et al. also found patients with CFM and cervical spine anomalies had lower cognitive, fine motor and expressive language scores and sixty-four percent had torticollis (90). Anomalies of the thoracic spine coexist with anomalies in the cervical region in the study of Anderson et al (76).

An association between the severity or site of the spinal anomaly and the degree of facial malformation could not be found in the seven patients analyzed by Anderson et al (76). However, Horgan et al. found an increased incidence of extracraniofacial anomalies in CFM patients with higher OMENS scores (calculated as the sum of each OMENS category) (6). No association was found between the presence of epibulbar dermoids and vertebral anomalies in the 138 patients in the study of Tuin et al (19).

Discussion

The aim of this review was to document the type and prevalence of vertebral anomalies in patients with CFM reported in the literature. Following a systematic search of literature according to the PRISMA protocol, thirty-one articles were included for analysis. Twenty-six of these articles described the prevalence of vertebral anomalies in CFM and in twenty-two studies the type of vertebral anomalies in CFM were documented. The documented prevalence of vertebral anomalies is 12 to 79% (6, 11, 19, 25, 26, 46, 50, 52, 53, 73-75, 77-90). The vertebral anomalies in CFM are most common in the cervical spine, followed by the thoracic spine and ribs. Although vertebral anomalies can be present in the lumbar spine as well, this is less frequent, given that only seven out of fourteen papers studying the complete spine reported lumbar spine anomalies (48, 49, 76-78, 85, 86). Most frequently seen vertebral anomalies include hemivertebrae, blockvertebrae, scoliosis/kyphoscoliosis and spina bifida. In the cervical spine other anomalies such as occipitalization of the atlas and cervical ribs are also reported frequently.

The reported prevalence of 12 to 79% of vertebral anomalies in CFM is highly variable due to differences in sample size, study characteristics, patient selection and the level of spine investigation (6, 25, 26, 52, 53, 78, 85). However, the study that included the most patients (n=259) found a prevalence of 24%. Since not all vertebral anomalies result in clinically symptomatic features, there is a chance the prevalence of these malformations is underestimated (49, 62, 91). Although the actual prevalence remains uncertain, this systematic review shows vertebral anomalies are common in CFM patients.

The exact origin of vertebral anomalies in CFM patients is still unknown. A defect in the mesodermal or neural crest cell migration may be responsible for the craniofacial and vertebral anomalies in CFM (92, 93). Retinoic acid plays a role in the neural crest cell migration (94). When given during the embryologic development in mice, this results in malformations similar to CFM (95, 96). This error in neural crest cell migration is found to form craniofacial malformations and vertebral anomalies (96, 97). The common origin of the facial malformations and vertebral anomalies in CFM has to be further examined.

Further research is needed to identify if there are specific CFM patients that are of higher risk for vertebral anomalies. Studies, both pro- and retrospective in nature, with large sample sizes might determine these groups to allow for better screening of and care for CFM patients. Only a prospective trial with physical examination, questionnaires and on indication, radiographs can determine the true prevalence of vertebral anomalies in CFM. An international research consortium has been founded between Erasmus MC Rotterdam, Great Ormond Street Hospital London, SickKids Toronto, and Boston Children's Hospital to obtain more knowledge about CFM by studying a large number of CFM patients.

In dealing with patients with CFM, clinicians should not only focus on the craniofacial malformations, as the prevalence of vertebral anomalies is high and can have detrimental effects when undetected. These anomalies can cause instability of the cervical spine, progressive scoliosis, compression of the spinal column or vertebral artery and the cerebellum or cranial nerves can be damaged as well (55-57). An imbalance in growth of the spine may be the result of these anomalies, causing an increasing deformity in the growing child (63-66). Treatment of these vertebral

anomalies is performed best at an early stage, so the growth of the spine can be as optimal as possible (63-66).

From this literature study it may be concluded that vertebral anomalies are present in a substantial part of the CFM patients. Mostly, these anomalies are present in the cervical spine, but thoracic and rib anomalies often occur. Hemivertebrae, blockvertebrae, scoliosis/kyphoscoliosis and spina bifida are frequently seen. Since these vertebral anomalies can present without symptoms but can have harmful effects, careful and extensive physical and neurologic examination of CFM patients is important to diagnose these anomalies at an early stage.

3

Vertebral anomalies in craniofacial microsomia

a retrospective analysis of 991 patients

Based on:
Ruben W. Renkema, Cornelia J.J.M. Caron, Eppo B. Wolvius, Wietse Rooijers, Jan-Aart M. Schipper, David J. Dunaway, Christopher R. Forrest, Maarten J. Koudstaal, Bonnie L. Padwa. Vertebral anomalies in craniofacial microsomia: a retrospective analysis of 991 patients, International Journal of Oral and Maxillofacial Surgery. 2018 Nov;47(11):1365-1372. doi: 10.1016/j.ijom.2018.05.016. Epub 2018 Jun 22. PMID: 30722936.

Abstract

Craniofacial microsomia (CFM) is characterized by an underdevelopment of the facial structures arising from the first and second branchial arches, but extracraniofacial anomalies such as vertebral anomalies may be present. This is a retrospective study of the prevalence and types of vertebral anomalies and the association with other extracraniofacial anomalies in patients with CFM. The charts of all patients diagnosed with CFM seen in four craniofacial centers were reviewed for the presence of vertebral anomalies, symptoms, extracraniofacial anomalies, and O.M.E.N.S. classification including the Pruzansky-Kaban type of mandibular deformity. A total of 991 patients were included and 28% of the patients had vertebral anomalies. The most common vertebral anomalies included scoliosis, blockvertebrae, and hemivertebrae. Only 44% of the patients with vertebral anomalies had clinical symptoms; torticollis, back or neck pain, or limited neck movement were seen. The prevalence of vertebral anomalies was greater in patients with bilateral CFM, and in patients with a more severe mandibular deformity, and/or orbit, facial nerve, and/or soft tissue involvement. Patients with vertebral anomalies had significantly more extracraniofacial anomalies than patients without vertebral anomalies. Therefore, patients with vertebral anomalies should have cardiac, renal and neurologic evaluation.

Introduction

Craniofacial microsomia (CFM) is a heterogeneous congenital disorder characterized by various uni- or bilateral facial malformations. The incidence of CFM is 1:3000 to 1:5000, which makes CFM the most common congenital facial anomaly after cleft lip and palate (1, 3, 4, 47). The craniofacial anomalies found in CFM are believed to be related to the first and second branchial arches, therefore the mandible, zygoma, ear, facial nerve, musculature and soft tissue may be underdeveloped or absent (1, 43, 44). Although microtia is part of CFM, isolated microtia is generally not considered to be CFM (98). Several terms, such as oculo-auriculo-vertebral spectrum, hemifacial microsomia, Goldenhar syndrome, and first and second branchial arch syndrome have been used to describe patients with CFM (1, 25, 50).

The facial anomalies seen in CFM are highly variable and differ in severity (1, 43-46). Various classification models have been proposed to define the malformations seen in CFM (6, 25, 53, 99-102). Pruzansky et al. proposed a classification to grade the mandibular hypoplasia in CFM patients (99). This system was later subcategorized by Kaban et al (23, 34, 99). In this classification hypoplasia of the mandible and temporomandibular joint is graded in I, IIA, IIB, and III (23, 34, 99). The O.M.E.N.S.-plus classification is used to classify patients with CFM concerning the level of underdevelopment of the Orbit (O), Mandible (M), Ear (E), Facial Nerve (N), Soft tissue (S), and the presence of extracraniofacial anomalies (6, 25).

Extracraniofacial anomalies may be present in 55 percent of the patients with CFM (6, 18). These anomalies are commonly present in the circulatory tract, central nervous system, urogenital tract, gastro-intestinal tract and/or the vertebral column and ribs (6, 16-18, 25, 46, 48-50).

Vertebral anomalies are most common in the cervical spine, thoracic spine and ribs, but may also be present in the lumbar spine (52, 61, 76, 78, 85). Most often seen vertebral anomalies in CFM are hemivertebrae, blockvertebrae, scoliosis, and specific anomalies of the cervical spine such as occipitalization of the atlas and cervical ribs (52, 61, 62, 73, 76). These anomalies may be present without any clinical symptoms, however they may have serious health consequences for the patient (55, 67). Incorrect formation or fusion of the vertebrae may result in a progressive scoliosis or cause fractures of the ankylosed segments (62-67). Furthermore,

instability of the cervical spine may develop due to an abnormal development of the vertebrae or ligamentous structures (55-57). Manipulation of an instable cervical spine can result in compression of the spinal cord or vertebral artery, and can therefore have many neurological effects, varying from muscle weakness or ataxia to seizures (55, 61, 69-71). Awareness of these vertebral anomalies in CFM is essential to prevent these consequences and provide optimal care.

The diagnosis of vertebral anomalies is based on radiographic evaluation (55, 67, 103). Vertebral anomalies have been shown to be associated with other extracraniofacial anomalies (11, 26), such as cardiac anomalies (104, 105), urogenital anomalies (104, 106, 107), or brain or spinal cord anomalies such as tethered cord, syrinx, diastematomyelia and Chiari malformation (104, 108-110).

The reported prevalence of vertebral anomalies in CFM varies from 12 to 79 percent (6, 11, 19, 25, 26, 46, 50, 52, 53, 73-75, 77-83, 85-90). The variability of this prevalence is high due to differences in study characteristics, sample size, patient selection, and the level of spinal investigation (6, 11, 19, 25, 26, 46, 50, 52, 53, 73-75, 77-83, 85-90, 111).

As data to guide clinicians to which CFM patients are at risk of vertebral anomalies is missing, the aim of this study is to report the prevalence, types, and symptoms of vertebral anomalies in a large group of patients. Furthermore, which CFM patients are at risk of having vertebral anomalies and whether these anomalies are associated with other extracraniofacial anomalies in CFM was the secondary objective of this endeavor. For this, a research consortium between four major craniofacial centers was founded to obtain a large dataset of patients with CFM.

Methods

Subjects and Data collection

A multicenter retrospective study was initiated to obtain more knowledge on vertebral anomalies in patients with CFM. A uniform database was created at the craniofacial centers of Erasmus University Medical Center (EMC), Rotterdam, The Netherlands; Great Ormond Street Hospital (GOSH), London, United Kingdom; Boston Children's Hospital (BCH), Boston, United States of America, and The Hospital for Sick Children, Toronto, Canada. This study was approved by the Institutional

Review Boards (Rotterdam: MEC-2012-248; London: 14DS25; Boston: X05-08-058; Toronto: 1000053298).

All patients diagnosed with CFM seen in the four craniofacial centers were included for further analysis. Since CFM is a clinical diagnosis, patients with clinical and/or radiographic images, i.e. panoramic x-rays and/or CT head, were included in this study. Although microtia is part of CFM, isolated microtia was not seen as CFM, therefore these patients were excluded. Patients in which the diagnoses of CFM was uncertain were excluded as well.

Medical charts were reviewed to obtain data on age, sex, affected side, Pruzansky-Kaban classification, O.M.E.N.S. score and the presence of extracraniofacial anomalies. Since vertebral anomalies have shown to be associated with other extracraniofacial anomalies (11, 26), data on these other anomalies was extracted to report the extracraniofacial anomalies in patients with vertebral anomalies and to study this potential association in patients with CFM.

The extracraniofacial anomalies were divided in anomalies of the vertebral column and ribs, brain and spinal cord, respiratory system, cardiac system, gastro-intestinal tract, and urogenital tract. Although the brain is located in the cranium, we categorize anomalies of the brain as extracranial since these anomalies are not regarded to be primarily part of CFM. Additionally, rib anomalies were seen as anomalies of the thoracic spine, since ribs are attached to the thoracic spine.

The diagnosis of extracraniofacial anomalies was based on clinical and/or imaging notes reported in the medical charts of the patients with CFM. If extracraniofacial anomalies were present, patients were further reviewed for data on the type and location of the anomaly, symptoms, date of diagnostics, type and date of treatment.

The Pruzansky classification modified by Kaban et al. was used to determine the severity of mandibular hypoplasia in CFM patients (23, 34, 99), using panoramic x-rays or 3D-CT scans. The O.M.E.N.S. classification system was used to grade the severity of the craniofacial malformations in patients with CFM (25). Although both facial and mandibular sides were scored in patients with uni- and bilateral CFM, only the most severe score was used for analyses.

Statistical analysis

Statistical analyses were performed using SPSS version 20.0 for Windows (2011, SPSS Inc., Chicago, IL, USA). Descriptive statistics were used. Equality of groups was tested with the Pearson's Chi-square Test for Independence. Fisher's Exact Test was used when the assumptions for Pearson-Chi square test were violated (i.e. expected count less than 10). An univariate binary logistic regression model was used to evaluate the association between the O.M.E.N.S. score, and the presence of vertebral anomalies. A P-value of <.05 was considered to be statistically significant.

Results

Characteristics of population

A total of 1132 patients with CFM were seen in the four craniofacial centers, of which 228 were seen in the Erasmus University Medical Center, 366 patients in the Great Ormond Street Hospital, 327 patients in Boston Children's Hospital, and 211 patients in The Hospital for Sick Children. After exclusion of 141 patients based on diagnostic uncertainty or isolated microtia, 991 patients were included for further analyses. More males (n=527) than females (n=464) were included. Most patients had unilateral CFM (n=827), 177 were bilateral, in 47 the affected side was unknown.

Characteristics of patients with vertebral anomalies

Of the 991 patients included in this study, 28% of the patients (n=275) presented with vertebral anomalies. The median number of vertebral anomalies in patients with vertebral anomalies was 2.00 per patient (Figure 3.1). Vertebral anomalies were diagnosed at the median age of 2.0 years (range 0-27 years) (Figure 3.2).

Figure 3.1: *Number of vertebral anomalies per patient in patients with vertebral anomalies*

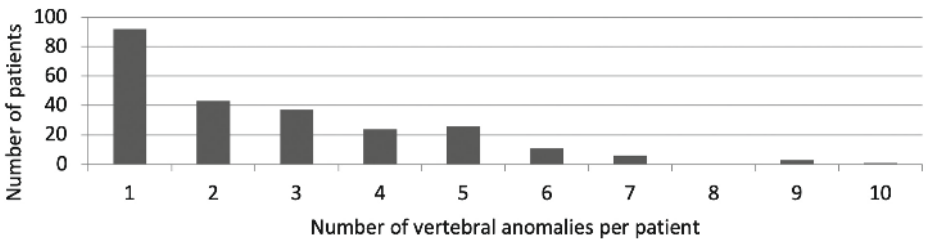
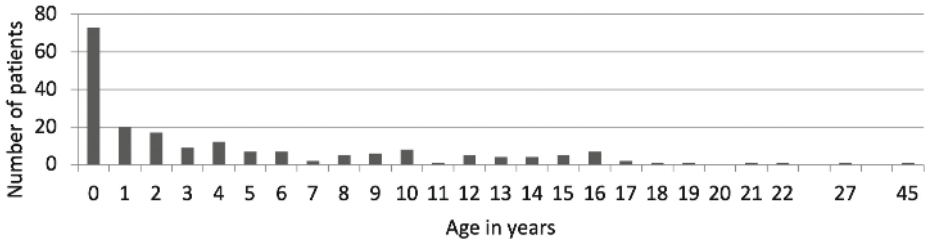


Figure 3.2: *Age at diagnosis of vertebral anomaly*



In table 3.1. the description of patients with and without vertebral anomalies is presented. The ratio of males to females in patients with vertebral anomalies was 1 : 1.1. Of the patients with vertebral anomalies, 214 had unilateral CFM, 51 bilateral CFM, and of 10 patients the affected side was unknown. The prevalence of vertebral anomalies in bilateral CFM patients was found to be higher than in unilateral patients (Pearson's χ^2 (df 1)= 15.93, Odd's ratio= 2.21, P-value=<0.001).

Table 3.1: *Demographics for patients with and without vertebral anomalies*

		Vertebral anomalies			
		Yes	No	Total	P-value
Total		275 (28%)	716 (72 %)	991 (100 %)	
Sex	Male	143 (27 %)	384 (73 %)	527 (53 %)	p=0.65
	Female	132 (28 %)	332 (72 %)	464 (47 %)	
Laterality	Unilateral	214 (26 %)	613 (74 %)	827 (83 %)	p=<0.001
	Bilateral	51 (44 %)	66 (56 %)	117 (12 %)	
Affected side (UCFM)*	Right	120 (26 %)	344 (74 %)	463 (56 %)	p=0.98
	Left	94 (26 %)	269 (74 %)	364 (44 %)	

UCFM=unilateral craniofacial microsomia ; *In unilateral cases of craniofacial microsomia

The various components of the O.M.E.N.S. score in patients with and without vertebral anomalies is shown in table 3.2. Assessment of the O.M.E.N.S. score was not possible in all patients. In 217 patients the Orbit score was unknown, of 327 patients the Mandible score, of 242 patients the Ear score, of 598 patients the Nerve score, and of 233 patients the Soft Tissue score.

The risk for vertebral anomalies increased with an increase of the Orbit, Mandible, Nerve and Soft Tissue score on the O.M.E.N.S. scale. The Ear score was not significantly positively correlated with vertebral anomalies.

Table 3.2: *Statistical analysis of the O.M.E.N.S. score in patients with/without vertebral anomalies*

	Vertebral anomalies *(in percentage of patients)*													
	Yes	*No*		*Yes*	*No*		*Yes*	*No*		*Yes*	*No*		*Yes*	*No*
O*			***M****			***E****			***N****			***S****		
0	47	56	***0***		1	***0***	12	17	***0***	48	62			
1	20	15	***1***	17	27	***1***	14	15	***1***	10	13	***0***	17	16
2	15	13	***2A***	21	28	***2***	16	11	***2***	22	14	***1***	34	46
3	11	12	***2B***	31	24	***3***	53	55	***3***	15	6	***2***	37	30
4	7	4	***3***	31	20	***4***	5	2	***4***	5	5	***3***	12	8
Total %	100	100		100	100		100	100		100	100		100	100
B-coefficient	0.120			0.329			0.101			0.238			0.203	
Odd's ratio	1.13			1.39			1.11			1.268			1.225	
95% CI***	1.00-1.27			1.19-1.62			0.97-1.27			1.07-1.50			1.02-1.47	
P-value	0.049			<0.001			0.146			0.005			0.031	

*Orbit, Ear, Nerve, Soft Tissue score on the O.M.E.N.S. scale ; **Mandible score based on Pruzansky-Kaban classification ; ***Confidence Interval

Types of vertebral anomalies

Blockvertebrae, hemivertebrae, rib anomalies, and scoliosis were the most frequently seen vertebral anomalies. Other vertebral anomalies that were present are shown in table 3.3. Vertebral anomalies of the cervical spine were seen in 158 patients; anomalies of the thoracic spine in 187 patients, and anomalies of the lumbar spine in 77 patients. In 57 patients with vertebral anomalies the location of the anomaly was not specified. Multiple vertebral anomalies in different segments of the spine were present in 131 patients.

Eighty-three patients presented with scoliosis in more than one region of the spine. There were 26 patients with a cervicothoracic scoliosis, 49 patients with a thoracolumbar scoliosis, and 4 patients had a scoliosis in all segments of the spine (table 3.3).

Specific vertebral anomalies of the cervical spine, such as cervical ribs, instability of the cervical spine, occipitalization of the atlas, and os odontoideum, were seen in multiple patients. Various rib anomalies, such as fusion, aplasia, hypoplasia or extra ribs were seen.

Table 3.3: *Types of vertebral anomalies*

Vertebral anomalies (n=275)							
Cervical (n=158)		Thoracic (n=187)		Lumbar (n=77)		Location not specified (n=57)	
Type vertebral anomaly	*Number of patients*	*Type vertebral anomaly*	*Number of patients*	*Type vertebral anomaly*	*Number of patients*	*Type vertebral anomaly*	*Number of patients*
Blockvertebrae	100	Scoliosis	156	Scoliosis	84	Scoliosis	31
Scoliosis	54	Hemivertebrae	67	Hemivertebrae	19	Not specified	13
Hemivertebrae	32	Blockvertebrae	49	Blockvertebrae	12	Hemivertebrae	10
Not specified	15	Ribs fusion	27	Hypoplasia vertebrae	7	Blockvertebrae	7
Cervical ribs	12	Ribs aplasia	25	Not specified	5	Butterfly vertebrae	1
Dysplastic vertebrae	10	Ribs extra	22	Butterfly vertebrae	3		
Lack of fusion vertebrae	9	Butterfly vertebrae	20	Sacralization	3		
Butterfly vertebrae	8	Ribs hypoplasia	15	Ribs extra	1		
Cervical spine Instability	7	Pectus deformity	12	Extra vertebrae	1		
Hypoplasia vertebrae	7	Not specified	11	Agenesis vertebrae	1		
Occipitalization of the atlas	6	Rib anomaly not specified	7				
Rotated subluxation C1-C2	4	Hypoplasia vertebrae	5				
Os odontoideum	2	Lack of fusion vertebrae	3				
Agenesis vertebrae	2	Extra vertebrae	1				
Omo vertebral body	1	Bifid vertebrae	1				

Clinical symptoms in patients with vertebral anomalies

Of the 275 patients with vertebral anomalies, 44% of the patients (n=122) had clinical symptoms. Most frequently reported symptoms were torticollis (n=40), back or neck pain (n=28), or limited movement of the neck (n=22). Although most symptoms were mainly seen in patients with vertebral anomalies, some symptoms were also noted in patients without these anomalies (table 3.4).

***Table 3.4:** Symptoms in patients with and without vertebral anomalies*

	Vertebral anomalies		Total
	No	*Yes*	
Torticollis	15	40	55
Back- or neck pain	2	28	30
Limited neck movement	2	22	24
Head tilt	5	8	13
Short neck	0	8	8
Webbed neck	0	3	3
Headache	1	1	2
Short length	0	2	2
Numbness or tingling	0	2	2
Dizziness	0	1	1
Hemiplegia	0	1	1
Myelopathy	0	1	1
Tired feeling neck	0	1	1
Paraplegia	0	1	1
Poor balance	0	1	1
Incontinence problems	0	1	1
Radiculopathy	0	1	1
Total	25	122	147

Types of extracraniofacial anomalies

Besides vertebral anomalies other extracraniofacial anomalies were present. Forty-seven percent of all included patients had other extracraniofacial anomalies (n=462), which could be present in multiple tracts simultaneously. Anomalies of the central nervous system were present in 105 patients, anomalies of the circulatory tract in 205 patients, respiratory anomalies in 29 patients, gastro-intestinal anomalies in 89 patients and urogenital anomalies in 108 patients. Of the 275

patients with vertebral anomalies, 169 patients had additional extracraniofacial anomalies in other tracts.

The extracraniofacial anomalies seen in CFM patients with vertebral anomalies varied. Anomalies of the central nervous system were seen in 70 of the 275 patients with vertebral anomalies. Fifty of these patients had anomalies of the brain and 27 had anomalies of the spinal cord. Most seen anomalies of the brain were hydrocephalus, ventriculomegaly, Chiari malformation, and microcephaly. Most reported anomalies of the spinal cord were spina bifida, tethered cord, and syringomyelia. Anomalies of the circulatory tract were seen in 97 patients with vertebral anomalies. A septum defect of the atria or ventricle, patent ductus arteriosus, and valve malformation were the most frequently reported cardiac anomalies. Anomalies of the respiratory tract occurred less frequently and were only seen in 13 patients. Gastro-intestinal anomalies were present in 49 patients with vertebral anomalies. An inguinal hernia, imperforate anus, umbilical hernia, and esophageal atresia were mostly seen. Anomalies of the urogenital tract were reported in 57 patients with vertebral anomalies. Renal aplasia and hydronephrosis were reported frequently. Most seen anomalies of the genitalia were phimosis, undescended testis and hypospadias.

Anomalies associated with vertebral anomalies

Patients with vertebral anomalies had significantly more often additional extracraniofacial anomalies in other tracts than CFM patients without vertebral anomalies *(Pearson's χ^2 (df 1)=108.8, odd's ratio=4.54, p=<0.001)* (table 3.5). CFM patients with vertebral anomalies were significantly more often diagnosed with anomalies of the brain *(Pearson's χ^2 (df 1)=46.2, odd's ratio=4.46, p=<0.001)* and spinal cord *(odd's ratio=77.8, p=<0.001)* than in CFM patients without vertebral anomalies. Anomalies of the circulatory tract *(Pearson's χ^2 (df 1)=49.4, odd's ratio=3.01, p=<0.001)*, gastro-intestinal tract *(Pearson's χ^2 (df 1)=36.4, odd's ratio=3.67, p=<0.001)*, and urogenital tract *(Pearson's χ^2 (df 1)=37.9, odd's ratio=3.41, p=<0.001)* were also more frequently seen in patients with vertebral anomalies than without vertebral anomalies. The prevalence of anomalies of the respiratory tract was not significantly higher in patients with vertebral anomalies, although some evidence of a correlation may be present *(odd's ratio=2.17, p=0.055)*.

Table 3.5: *Associated extracraniofacial anomalies*

	Vertebral anomalies			Statistical analysis			
	Yes	No	Total	Pearson χ^2	Phi coefficient	Odd's ratio	P-value
Extracraniofacial anomalies not vertebral	169 (17%)	186 (19%)	355 (36%)	108.8	0.33	4.54	<0.001
Central Nervous System	70 (7%)	35 (4%)	105 (11%)	88.7	0.30	6.64	<0.001
Brain anomalies	50 (5%)	34 (3%)	84 (8%)	46.2	0.22	4.46	<0.001
Spinal cord anomalies	27 (3%)	1 (0.1%)	28 (3%)	*	*	77.84	<0.001
Circulatory tract	97 (10%)	108 (11%)	205 (21%)	49.4	0.22	3.01	<0.001
Respiratory tract	13 (1%)	16 (2%)	29 (3%)	*	*	2.17	0.055
Gastro-intestinal tract	49 (5%)	40 (4%)	89 (9%)	36.4	0.19	3.67	<0.001
Urogenital tract	57 (6%)	51 (5%)	108 (11%)	37.9	0.20	3.41	<0.001

Extracraniofacial anomalies in number of patients and percentage of total population. *Assumptions for Pearson-Chi square test were violated, therefore the Fisher's Exact Test was used.

Discussion

The aim of this study was to shed light on the prevalence, types, and symptoms of vertebral anomalies in a large group of patients with CFM, to determine which patients are at risk for having vertebral anomalies and whether these anomalies are associated with other extracraniofacial anomalies.

Of the 991 patients included, almost one third (28%, n=275) had vertebral anomalies. This prevalence of vertebral anomalies in CFM is considerably higher than the prevalence of vertebral anomalies in the normal population (which is 0.1-2%) (112, 113). Previous reports have documented vertebral anomalies in 12% to 79% of the patients with CFM (6, 11, 19, 25, 26, 46, 50, 52, 53, 73-75, 77-83, 85-90, 111). The variability is due to variations in sample size, study characteristics, patient selection, spinal segments studied, and the small sample size. Studies with a relatively large patient sample tend to show a lower prevalence (approximately 30%) than studies with a smaller patient sample. Since this study is retrospective and not all vertebral anomalies result in clinical symptoms, not all patients with vertebral anomalies may have been detected and the actual prevalence of vertebral anomalies in CFM may be even higher (49, 62, 91).

Patients with bilateral CFM, a higher Pruzanksy-Kaban score, and/or a higher Orbit, Nerve, and/or Soft Tissue score on the O.M.E.N.S. scale had a significantly higher risk for having vertebral anomalies. The odd's ratios were respectively 2.21, 1.39, 1.13, 1.27, and 1.23. Horgan et al. found CFM patients with a higher O.M.E.N.S. score, by using the sum of individual O.M.E.N.S. categories, had a higher risk for extracraniofacial anomalies (6). Anderson et al. could not find an association between vertebral anomalies and the severity of the craniofacial malformation, but there were only seven patients in this study (76).

Most common vertebral anomalies were scoliosis, blockvertebrae, and hemivertebrae, which is in line with the vertebral anomalies reported in literature (6, 11, 26, 48-50, 52, 61, 62, 73, 75-80, 82, 83, 85, 86, 90, 111). The anomalies were present in all sections of the spine.

Patients with vertebral anomalies had a higher risk for other extracraniofacial anomalies, including anomalies of the central nervous system, circulatory, gas-

tro-intestinal, and urogenital tracts. This association was also described by Beleza-Meireles et al. and Rollnick et al. (11, 26). The odd's ratios for these associated extracraniofacial anomalies in this study were: 6.64 for CNS anomalies (4.46 for brain anomalies and 77.84 for spinal cord anomalies), 3.01 for anomalies of the circulatory tract, 3.67 for anomalies of the gastro-intestinal tract, and 3.41 for anomalies of the urogenital tract. Since this study is retrospective, it is uncertain whether patients with extracraniofacial anomalies were screened more frequently for additional extracraniofacial anomalies. The results of this study indicate that the presence of an extracraniofacial anomaly requires further screening for anomalies in other tracts, including vertebral anomalies. In addition, the data suggest that further screening for other extracraniofacial anomalies is indicated in patients with CFM and vertebral anomalies (67). In particular renal, cardiac and neurologic evaluation should be performed, since anomalies of those organs are associated with vertebral anomalies and treatment of these anomalies may be necessary to prevent further harm (67, 103, 104, 107). If neurological examination is abnormal, an MRI of the brain and entire spine should be obtained to rule out any spinal cord anomalies (67, 104).

Diagnosing vertebral anomalies may be difficult since patients may not show any symptoms (49, 55, 91). Of the 275 patients with vertebral anomalies, 44% showed clinical symptoms. Frequently noted symptoms were torticollis, back or neck pain, or limited movement of the neck, but neurological symptoms such as myelopathy, hemi or paraplegia, or tingling were also reported. Thorough evaluation of the patient and physical and neurological examination is essential to identify potential vertebral anomalies (55, 67, 103). Standard upright posterior-anterior and lateral radiographs should be taken if vertebral anomalies are suspected (67, 103). If cervical spine anomalies are present, flexion-extension radiographs should be obtained to rule out cervical spine instability (59, 67).

The origin of CFM, and thereby the origin of vertebral anomalies and other extracraniofacial anomalies in CFM, is still unknown. A disruption in the first six weeks of development of the first and second branchial arches is thought to be potentially the cause of CFM (44, 45). Exposure to retinoic acid during embryonic development has found to form craniofacial, vertebral, cardiovascular, and central nervous system anomalies (6, 96, 97). Therefore, a defect in mesodermal or neural crest cell migration may be the cause of CFM and the extracraniofacial anomalies, since

retinoic acid influences neural crest cell migration (92-94). Further research is needed to identify the origin of CFM and its associated extracraniofacial anomalies.

Conclusion

This study shows that vertebral anomalies are present in 28% of the patients with CFM. Screening for vertebral anomalies with extensive physical and neurological examination, and upright radiographs, should be performed in patients with bilateral CFM, and patients with CFM and a high Pruzansky-Kaban score, or a high Orbit, Nerve and/or Soft Tissue score on the O.M.E.N.S. scale, since these characteristics are correlated with vertebral anomalies. Patients with CFM and vertebral anomalies have an increased risk of having other extracraniofacial anomalies and therefore, additional cardiac, renal and neurologic evaluation is indicated for patients with CFM and vertebral anomalies.

4

Central nervous system anomalies in craniofacial microsomia

a systematic review

Based on:

Ruben W. Renkema, Cornelia J.J.M. Caron, Eppo B. Wolvius, David J. Dunaway, Christopher R. Forrest, Bonnie L. Padwa, Maarten J. Koudstaal. Central nervous system anomalies in craniofacial microsomia: a systematic review, International Journal of Oral and Maxillofacial Surgery. 2018 Jan;47(1):27-34. doi: 10.1016/j.ijom.2017.06.009. Epub 2017 Jul 20. PMID: 28736116.

Abstract

Extracraniofacial anomalies, including central nervous system anomalies, may occur in craniofacial microsomia. To recognize and possibly treat these anomalies, this systematic review provides an overview of the literature on the prevalence and types of central nervous system anomalies and developmental disorders in craniofacial microsomia. A systematic search was conducted and data on the number of patients, patient characteristics, type and prevalence of central nervous system anomalies or developmental delay and correlations between craniofacial microsomia and central nervous system anomalies were extracted. Sixteen papers were included; ten papers described developmental disorders. The most common reported anomalies were: neural tube defects, corpus callosum agenesis or hypoplasia, intracranial lipoma, Arnold-Chiari malformations, hydrocephaly, ventriculomegaly or cerebral hypoplasia. The prevalence of central nervous system anomalies in craniofacial microsomia varied from 2% to 69%. The prevalence of developmental disorders, such as intellectual disability, language or speech developmental delay and neuropsychomotor delay, varied from 8% to 73%. This study suggests central nervous system anomalies and developmental disorders can be seen in a substantial part of the patients with craniofacial microsomia. Further research should focus on determining which patients with craniofacial microsomia are at risk of central nervous system anomalies to allow for adequate screening and timely care.

Introduction

Craniofacial microsomia (CFM) is a heterogeneous congenital disorder occurring in every 1:3000 to 1:5000 live births (1, 3, 4, 47). CFM results in a unilateral or bilateral underdevelopment of the structures formed by the first and second branchial arches. The mandible, maxilla, zygoma, ear, facial soft tissues and musculature, and the facial nerve may be underdeveloped or absent (1, 43, 44). Although some familial cases of CFM are described in literature and several genes have been proposed to cause this disorder, the exact origin of CFM is still unknown (3, 11, 114-116). The most conventional theory is that CFM is the result of a disturbance in the development of the first and second branchial arches during the first six weeks, since this may cause the facial malformations typical for CFM (16, 45, 49). CFM is a clinical diagnosis and the dysmorphology of CFM ranges from mild to severe. Isolated microtia might be a minor form of CFM, but it is generally not regarded as CFM (4, 16, 44).

The O.M.E.N.S classification is most often used to grade craniofacial malformations in CFM patients (25). This classification system is based on the degree of underdevelopment of the Orbit, Mandible, Ear, Facial Nerve and the Soft tissues. The main focus in this classification system lies on the craniofacial malformations. Extracraniofacial anomalies can be present in CFM as well. These anomalies can occur in different organ systems including the central nervous system (CNS), skeletal, renal, heart, lung and gastrointestinal organs (6, 16, 17, 25, 46, 48-50). Therefore, the O.M.E.N.S+ classification was created to document the presence of associated extracraniofacial anomalies (6). Over the years several terms have been used for CFM including hemifacial microsomia (HFM), Goldenhar syndrome, oculo-auriculo-vertebral dysplasia or spectrum, lateral facial dysplasia, first and second branchial arch syndrome (19, 43, 53, 54, 74).

The presence of CNS anomalies in CFM is well documented. There are a variety of anomalies and these may or may not cause symptoms. Epilepsy, motor disabilities, or developmental disorders may occur (82, 87, 117, 118); these may be the result of a CNS anomaly, but are often non-specific (118). The aim of this review is to document the prevalence of CNS anomalies and developmental disorders in patients with CFM, in order for them to be recognized and possibly treated early.

Methods

Search strategy

This study was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (72). A systematic search of the literature was performed to identify papers focusing on CFM and its synonyms combined with synonyms for central nervous system and spinal anomalies. The search was conducted in embase.com, Medline in Ovid, Cochrane central, web of science, PubMed (articles not yet indexed in Medline) and Google Scholar (most relevant articles) from inception until 21 June 2016. Results were limited to human subjects and studies written in English. No date limits were applied, but conference abstracts, letters, notes and editorials were excluded. See the online appendix for the full search strategies of all databases.

Two researchers (R.W.R. and C.J.J.M.C.) selected the studies independently. Titles and abstracts were screened for relevance based on the inclusion and exclusion criteria. Studies concerning CFM in relation to central nerve system anomalies were further examined. Studies were included when type and/or prevalence of CNS anomalies or developmental disorders in CFM were mentioned. Only original studies were included. Case reports were excluded. Patients with isolated microtia were not considered as CFM patients; therefore studies describing solely patients with isolated microtia were not included. However, from papers describing both patients with microtia and CFM, data was extracted concerning the CFM patients.

Data extraction

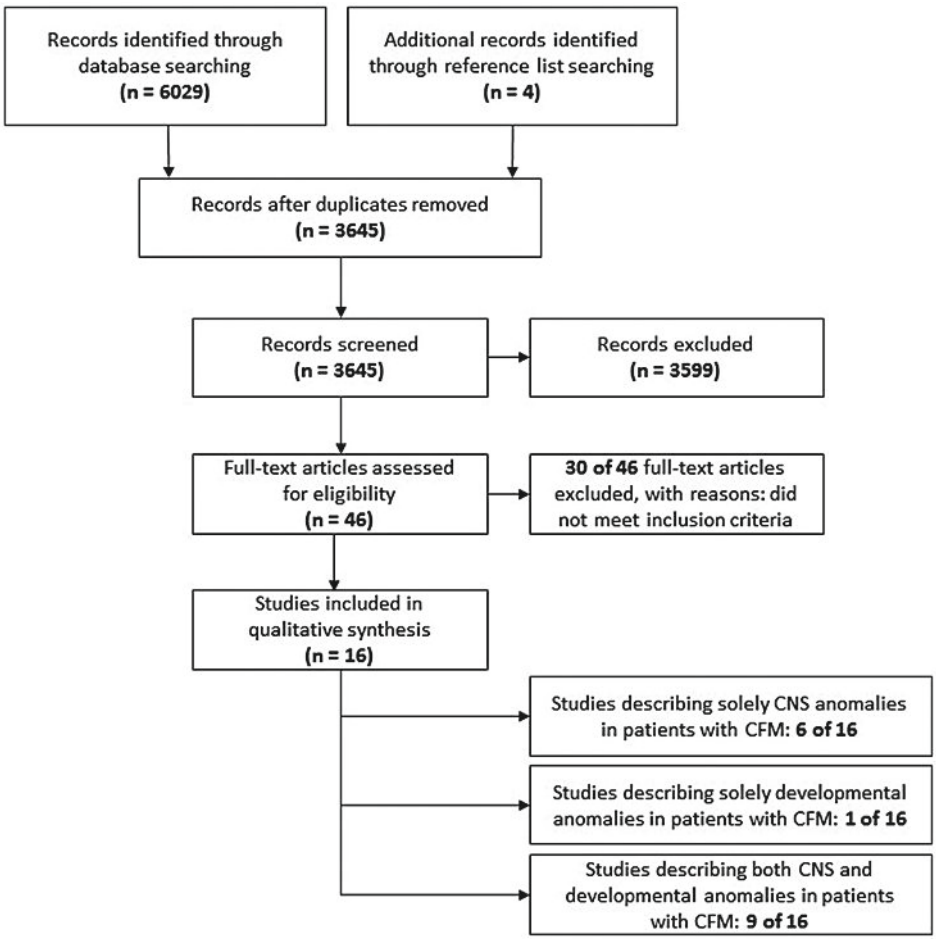
A table with predetermined characteristics was made prior to full text review of the papers. All studies were graded on quality of evidence using the Oxford Centre for Evidence-Based medicine (CEBM) criteria. Data on the number of patients, inclusion criteria of the studies, type of CNS anomalies, prevalence of CNS anomalies in CFM, and other correlations between CFM and CNS anomalies, were extracted when available.

Results

Study selection

The flowchart of the literature search is presented in figure 4.1. After the search, a total of 6029 papers were identified. After removing duplicate articles, 3646 papers were suitable for screening of title and abstract. After exclusion of 3600 records for being irrelevant, full-text versions of forty-six papers were read. Subsequently sixteen studies were included for qualitative data analysis. Nine studies described both CNS anomalies and developmental disorders in their study, one study solely described developmental disorders and six studies described only CNS anomalies in CFM.

Figure 4.1: *PRISMA diagram of the systematic review methodology used for the review*



Study characteristics

The study characteristics of all included articles are shown in table 4.1. Eight retrospective studies (6, 11, 26, 75, 78, 81, 82, 84), six prospective studies (48, 50, 53, 87, 89, 90), and two case series were included (85, 119). The prospective studies had a retrospective component in which the patients charts were reviewed and the presence of extracraniofacial anomalies described (48, 50, 53, 87, 90). Patients with isolated microtia were included in three studies (26, 53, 81). These patients were extracted from these studies and not included in this literature review for further analysis. Patients with incomplete data were excluded from the analysis. The studied patient population varied from 6 to 259 patients in the included studies (78, 90) (table 4.2, table 4.3).

Table 4.1: Study characteristics

Year	Author	CEBM level of evidence	Number of patients included	Methodology	Aim of the study	Inclusion criteria of the study
1984	Aleksic et al. (119)	4	13	Case series	To present 13 cases with Goldenhar syndrome	Goldenhar syndrome
2014	Barisic et al. (78)	3	259	Retrospective study	To provide population-based information on OAVS patients	Presence of microtia/ear anomalies and at least one major anomaly of the OAV spectrum (HFM, epibulbar dermoid, vertebral malformations)
2015	Beleza-Meireles et al. (11)	3	51	Retrospective study	To provide an assessment of the OAVS phenotype and revaluation of the minimal diagnostic criteria	The presence of HFM of facial asymmetry together with microtia or milder ear malformations
1995	Cohen et al. (90)	3	24	Prospective study	To examine the neurodevelopmental profile of children with OAVS	Diagnosis of OAVS: malformation of the aural, oral and mandibular structures
2007	Engiz et al. (85)	4	31	Case series	To describe the phenotypic features and laboratory findings of patients with OAVS or Goldenhar	Diagnosis of OAVS: variety of craniofacial, auricular and vertebral anomalies
1995	Horgan et al. (6)	3	121	Retrospective study	To document the frequency of extracranial anomalies in HFM; determine associated anomalies; to analyze possible correlations between extracranial and craniofacial abnormalities	Hemifacial microsomia

Table 4.1: *Continued.*

Year	Author	CEBM level of evidence	Number of patients included	Methodology	Aim of the study	Inclusion criteria of the study
2007	Johansson et al. (87)	3	20	Prospective study	To analyze the relations between OAVS and autism spectrum disorder, and identify CNS and chromosomal abnormalities	Malformation in two of the four areas: orocraniofacial, ocular, auricular and vertebral
1992	Morrison et al. (89)	3	20	Prospective study	To document the precise cardiovascular status of each patient to determine the prevalence of cardiac disease in OAVS	Microtia plus one of mandibular hypoplasia, skeletal anomalies, ocular abnormalities and palate abnormalities
2016	Pegler et al. (84)	3	41	Retrospective study	To describe the most prominent clinical features of a cohort of patients with oculo-auriculo-vertebral (OAV) dysplasia in Brazil	OAVS: involvement of minimal 2 of the 4 domains (face, eyes, ears, vertebrae)
1987	Rollnick et al. (26)	4	202	Retrospective study	To describe the phenotypic characteristics of individuals affected with OAVS and variants	Hemifacial microsomia, Goldenhar syndrome, OAVS
2010	Rooryck et al. (81)	3	90	Retrospective study	To identify new genomic loci that are potentially involved in OAVS	All index patients had isolated microtia or HFM together with mild ear malformations
2010	Rosa et al. (82)	3	17	Retrospective study	To describe the CNS abnormalities in a sample of OAVS patients	Minimal 2 of the 4 main areas that belong to OAVS(oro-cranial-facial, ocular, auricular, vertebral)

Table 4.1: *Continued.*

Year	Author	CEBM level of evidence	Number of patients included	Methodology	Aim of the study	Inclusion criteria of the study
1977	Shokeir et al. (48)	3	24	Prospective study	To delineate the natural history of Goldenhar syndrome, with regard to the possible therapeutic implications	Goldenhar syndrome: ocular manifestations, auricular involvement, facial abnormalities, skeletal dysplasia
2007	Strömland et al. (50)	3	18	Prospective study	To survey the systemic and functional defects in a group of OAVS patients	OAVS: oro-cranio-facial, ocular, auricular or vertebral malformations (minimal 2 out of 4)
2005	Tasse et al. (53)	3	41	Prospective study	To investigate patients with OAVS and develop a new classification and scoring system	HFM together with mild ear malformations
2006	Touliatou et al. (75)	4	17	Retrospective study	To describe the phenotypic data and evaluation of a group of 17 Goldenhar patients	Craniofacial anomalies and microtia as minimum

Documented anatomical central nervous system anomalies

A wide variety of CNS anomalies were documented (table 4.2). Neural tube defects, corpus callosum agenesis or hypoplasia, intracranial lipoma's, Arnold-Chiari malformations, hydrocephaly, ventriculomegaly, cerebral hypoplasia, or microcephaly were most often reported (11, 26, 48, 50, 53, 78, 82, 84, 85, 87, 90, 119). Other CNS anomalies such as microcephaly, cerebral cysts, asymmetric lateral ventricles, cortical dysplasia, septum pellucidum agenesis or epilepsy are also described in multiple studies, however less frequently (6, 11, 26, 50, 53, 78, 82, 84, 85, 87, 119). Microcephaly/partial anencephaly and Dandy Walker/encephalocele were described in six patients (6) (table 4.2).

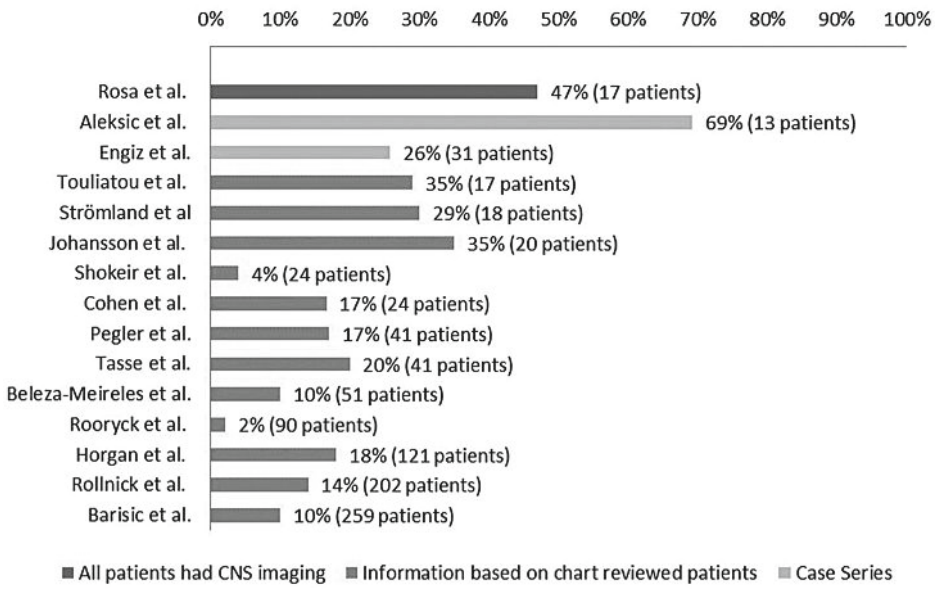
***Table 4.2:** Documented central nervous system anomalies in CFM*

Author	Total number of patients	Number of patients with isolated microtia	Included patients	Number affected patients	Neural tube defects (including encephalocele)	Microcephaly	Corpus callosum agenesis/hypoplasia	Cerebellum agenesis/dysgenesis/hypoplasia	Cerebellar vermis agenesis	Intracranial lipoma/cyst	Arnold-Chiari malformation	Hydrocephaly	Ventriculomegaly	Asymmetric lateral ventricles	Asymmetric cerebral hemispheres	Small white matter volume	Small lobe or cerebral hypoplasia	Cortical dysplasia/atrophy	Polymicrogyria	Frontal hypodensities	Diffuse cerebral hypodensities	Intracranial calcifications	Septum pellucidum agenesis	Small pituitary gland	Circle of Willis anomaly	Haemorrhage subependymal	Hamartoma	Cerebral palsy	Hemiparese	Gait abnormality	Hypotonia/hypertonia	Epilepsy	Abnormal EEG	Dandy Walker variant
Aleksic et al.	13	n/a	13	9	1				1	3	1	5	1				2	1					1											
Barisic et al.	259	n/a	259	27	6		5	4		2		5	6																					
Beleza-Meireles et al.	51	n/a	51	5		2																			1		1				1			
Cohen et al.	24	n/a	24	4									#		#											#					18/24			
Engiz et al.	31	n/a	31	8			5	1		4	3		1																					1
Horgan et al.	181	n/a	121	22	2*	4*	2				2	7					4*											4				1		2*
Johansson et al.	20	n/a	20	7	1		1				1		3			1	2	1													3/20	6/7		
Pegler et al.	41	n/a	41	7	1		2						3										1											
Rollnick et al.	294	92	202	29																								#		#	#	#	#	
Rooryck et al.	95	1	90	2																														
Rosa et al.	34	n/a	17	8		1	2			1		1	2	1			2			2	1			1			1				5			
Shokeir et al.	24	n/a	24	1	1																		1											
Strömland et al	18	n/a	18	6	1						1		4	1			2	1	1					1										
Tasse et al.	53	7	41	8		3/38				4	1	1		1								1												
Touliatou et al.	17	n/a	17	5			#			#												#												

HFM: hemifacial microsomia; OAVS: oculo-auriculo-vertebral spectrum; CNS: central nervous system
n/a: not applicable; #: number unknown; *: patients with "microcephaly/partial anencephaly" and patients with "Dandy Walker/encephalocele"; ../..: studied number of patients is different from the number of included patients

The prevalence of CNS anomalies in CFM varies from 2% to 69% (81, 119) (figure 4.2). When analysing this prevalence, different types of studies can be identified. Most studies used reviewing patient charts to obtain information about CNS anomalies (6, 11, 26, 48, 50, 53, 75, 78, 81, 84, 87, 90). Some of these studies noted how many patients underwent CNS imaging. In the study of Rosa et al., all patients underwent a CT or MRI scan (82). Aleksic et al. and Engiz et al. described all patients separately since these are case control studies (85, 119). Six of the 24 patients in the study of Cohen et al. underwent CNS imaging as there was suspicion of brain dysgenesis, resulting in the diagnosis of CNS anomalies in four patients (90). In the study of Strömland et al. 10 of the 18 patients underwent CNS imaging, of which 6 patients had CNS anomalies (50). Johansson et al. reviewed 20 patients. Brain imaging was available for 11 patients, which showed CNS anomalies in 6 patients (87). Of the 31 patients studied by Engiz et al., 19 patients underwent CNS imaging, of which 8 patients had CNS anomalies (85).

Figure 4.2: *Reported prevalence of CNS anomalies in CFM per study*



Developmental disorders

Besides anatomical CNS anomalies, developmental disorders are described in CFM (table 4.3). These developmental disorders, such as intellectual disability and neu-

ropsychomotor delay, may be present in patients without evidence for CNS anomalies (50, 82). Intellectual disability is defined as an IQ lower than 70 points, and is documented in a substantial number of patients in six studies (48, 75, 85, 87, 89, 90). The prevalence of intellectual disability in CFM varies between 18% and 58%. Developmental disorders such as a language or speech delay and neuropsychomotor delay are reported in three studies, and present in respectively 8% - 68% and 17% - 73% in their tested population (53, 82, 90).

Tasse et al. studied 41 patients with CFM and found that both, CNS anomalies and delay in motor development was found more frequently in CFM patients with a more severe form of CFM (53). Classification of CFM in this study was graded from mild to severe based on the presence of main clinical findings, consisting of microtia, microtia/preauricular tags plus CFM and microtia/preauriculair tags plus CFM and vertebral anomalies. Besides these findings, an association of brain anomalies with ocular anomalies (Pearson correlation coefficient=0.475, p=0.000), epibulbar dermoids (Pearson correlation coefficient=0.670, p=0.000), orofacial clefts (Pearson correlation coefficient=0.326, p=0.017), and motor developmental delay (Pearson correlation coefficient=0.374, p=0.005) was found (53). The association of brain and ocular anomalies may be explained by the fact that these structures belong to the same developmental field (22). The association of CNS anomalies and ocular anomalies was also found in the 17 patients studied by Rosa et al., as 63% of the patients had ophthalmologic abnormalities and CNS anomalies and 11% of the patients had ophthalmologic abnormalities without CNS anomalies (p=0.0498). No association between cerebral anomalies and the side of facial malformation, the presence of orofacial clefts, vertebral anomalies and neurological alterations, such as neuropsychomotor delay and behavioural disorders was found (82). Thereby, patients with a higher O.M.E.N.S. score had a higher risk for extracraniofacial anomalies in general, reported by Horgan et al. by using the sum of the individual O.M.E.N.S. categories (6).

Table 4.3: *Documented developmental disorders in CFM*

Author	Total number of patients	Number of patients with isolated microtia	Included patients	Number affected patients	Mental retardation (IQ: <70)	Mild mental retardation (IQ: 50-70)	severe mental retardation (IQ: 20-35)	profound mental retardation (IQ: <20)	learning disabilities (not specified)	behavioral disorder	language or speech development delay	neuropsychomotor delay	developmental delay (not specified)
Beleza-Meireles et al.	51	n/a	51	9									9
Cohen et al.	24	n/a	24	14		5					13/19	9	
Engiz et al.	31	n/a	12	7	7								
Johansson et al.	20	n/a	20	9		4	3	2					
Morrison et al.	25	n/a	20	10	10								
Roorryck et al.	95	1	80	10									10
Rosa et al.	34	n/a	17	#					1/7	2/7	6/14	11/15	
Shokeir et al.	24	n/a	17	3	3								
Strömland et al	18	n/a	18	7									7
Tasse et al.	53	7	41	#							2/24	5/29	
Touliatou et al.	17	n/a	17	4	4								

n/a: not applicable; #: number unknown; *: patients with "microcephaly/partial anencephaly" and patients with "Dandy Walker/encephalocele"; ../.. : studied number of patients is different from the number of included patients

Discussion

The aim of this review was to to study the prevalence and types of CNS anomalies and developmental disorders in CFM. A systematic search of literature was performed according to the PRISMA protocol. In total, sixteen articles were included. The documented CNS anomalies in CFM are diverse. Most often reported CNS anomalies in CFM are neural tube defects, e.g. encephaloceles, corpus callosum agenesis or hypoplasia, cerebral hypoplasia, microcephaly, intracranial lipomas, Arnold-Chiari malformation, ventriculomegaly and hydrocephaly (6, 11, 48, 50,

53, 75, 78, 82, 84, 85, 87, 90, 119). The wide variation of CNS anomalies in CFM suggests a complex origin of this disorder, which is yet to be discovered. The origin of these defects may lie in the first six weeks of embryologic development since the skull, vertebrae and organs are formed in this period (45, 49, 55). This makes a common pathogenic mechanism for both the craniofacial and extracraniofacial malformations likely. Several embryonic pathways play an important role in the development of the central nervous system and the facial structures. The etiology of CNS anomalies in CFM may be a defect in the mesodermal or neural crest cell migration (92, 93). Mesenchymal cells form the notochord and induce formation of the neuroectoderm that forms both the central nervous and peripheral nervous system (120). An error in the migration of neural crest cells have found to form craniofacial, skeletal and cardiovasculair malformations and can also lead to CNS anomalies (96, 97, 120-122).

The reported prevalence of CNS anomalies in CFM varies from 2% to 69% (81, 119). This wide variety may be the result of several factors, such as differences in sample size, patient selection and study characteristics. When studies only included patients who had CT or MRI scans, the reported prevalence was 42% – 69% (50, 82, 85, 87, 90, 119). While the prevalence of CNS anomalies in CFM in studies only reviewing patient charts was 2% – 29% (6, 11, 26, 48, 53, 75, 78, 81, 84). Selection bias is created when only patients with CT or MRI scans are included, since patients that are not suspected of having CNS anomalies are usually not examined. Some CNS anomalies, such as corpus callosum abnormalities or intracranial lipomas, may not present with clinical symptoms (82). These factors presumably lead to an underestimation of the prevalence of CNS anomalies in CFM patients. The prevalence of CNS anomalies in patients without CFM is 0.05% - 0.16% (123, 124). Since the prevalence of CNS anomalies in CFM is substantially higher than in the 'normal' population and the clinical presentation of these anomalies may be variable, clinicians should be aware of the risk of CNS anomalies in patients with CFM. To diagnose these anomalies timely, neurological examination should be part of the standard examination of CFM patients.

Beside the anatomical CNS anomalies, developmental disorders are seen in CFM patients. Intellectual disability is described in six studies, with a prevalence of 18% - 58% (48, 75, 85, 87, 89, 90). Language or speech developmental delay or neuropsychomotor delay is described in three studies, with a respective prevalence of

8% - 68% and 17 – 73% (53, 82, 90). The etiology these disorders in CFM patients is unknown, however these numbers suggest a complex and common origin between facial anomalies found in CFM and developmental disorders. The prevalence of intellectual disabilities in the general population is 0.33% - 1.43% (125-127). Although the prevalence of developmental disorders in CFM is highly variable and based on small patient numbers, this data suggest a correlation between CFM and developmental disorders. Developmental screening and awareness of clinicians is important to diagnose these developmental disorders timely and provide patients with good, multidisciplinary care.

Further research is needed to identify specific CFM patients who are at high risk for CNS anomalies and/or developmental disorders in order to give them timely and optimal care. Retrospective studies with a larger sample size could be helpful in determining which CFM patients are at risk of CNS anomalies or developmental disorders. This identification of specific patients groups at risk for CNS anomalies or developmental disorders will allow for better screening and treatment. Since not all anomalies give clinical symptoms, only a prospective study could determine the exact prevalence of CNS anomalies in CFM. An international research consortium has been founded between Erasmus MC Rotterdam, Great Ormond Street Hospital London, SickKids Toronto, and Boston Children's Hospital to obtain more knowledge about CFM by studying a large number of CFM patients.

Since the variety of CNS anomalies and developmental disorders in CFM patients is wide, careful and thorough examination of patients with CFM is important. Although the exact relationship between CNS anomalies and CFM remains unknown, it may be concluded CNS anomalies can be expected in a substantial part of the CFM patients. Neurological examination, developmental screening, and subsequently additional investigation such as MRI, should be part in the workup of CFM patients to diagnose CNS anomalies or developmental disorders timely and to provide patients optimal care.

5

Extracraniofacial anomalies in craniofacial microsomia

a retrospective analysis of 991 patients

Based on:
Ruben W. Renkema, Cornelia J.J.M. Caron, Erwin Pauws, Eppo B. Wolvius, Jan-Aart M. Schipper, Wietse Rooijers, David J. Dunaway, Christopher R. Forrest, Bonnie L. Padwa, Maarten J. Koudstaal. Extracraniofacial anomalies in craniofacial microsomia: retrospective analysis of 991 patients, International Journal of Oral and Maxillofacial Surgery. 2019 Sep;48(9):1169-1176. doi: 10.1016/j.ijom.2019.01.031. Epub 2019 Mar 13. PMID: 30878275.

Abstract

Craniofacial microsomia (CFM) is characterized by a unilateral or bilateral underdevelopment of the facial structures arising from the first and second pharyngeal arches, but extracraniofacial anomalies may be present. This retrospective study provides an overview of the prevalence, types and characteristics of extracraniofacial anomalies in patients with CFM. All patients diagnosed with CFM seen in four craniofacial centers were included. Patients charts were reviewed and data on patient characteristics and extracraniofacial anomalies were extracted. Of the 991 patients included, 47% had extracraniofacial anomalies. The prevalence of extracraniofacial anomalies in all various tracts was: vertebral 28%, central nervous system 11%, circulatory system 21%, respiratory tract 3%, gastro-intestinal tract 9%, and urogenital tract 11%. Patients with an extracraniofacial anomaly had a higher risk for having additional extracraniofacial anomalies in other tracts compared to patients without extracraniofacial anomalies. The prevalence of extracraniofacial anomalies was greater in patients with bilateral CFM, a more severe mandibular deformity or facial nerve or soft tissue deformity. Patients with CFM should be screened for extracraniofacial anomalies by physical examination with specific attention aimed at the circulatory, renal, and neurological tracts. Diagnostically, electrocardiography, echocardiogram, spine radiography and renal ultrasound should be obtained in patients at risk for extracraniofacial anomalies.

Introduction

The first and second pharyngeal arches give rise to various facial structures such as the mandible, maxilla, zygoma, ears, facial nerves and/or facial soft tissues (1). In patients with craniofacial microsomia (CFM) the structures arising from these arches may be underdeveloped or absent. The exact origin of this congenital disorder is yet unknown, although various theories have been proposed. A disruption in the development of the first and second pharyngeal arches during the first six weeks of development is potentially the cause of CFM (44, 45, 128). An error in migration of neural crest cells has found to form craniofacial anomalies as found in patients with CFM (6, 97). The clinical spectrum varies from a mild to severe phenotype and can be unilateral or bilateral (17, 44, 47). Although the ears may be underdeveloped or absent, isolated microtia is generally not regarded to be CFM (45).

Various classification systems have been proposed to categorize patients with CFM (6, 25, 53, 99-102). The Pruzansky-Kaban classification is based on radiographic evaluation of the underdevelopment of the mandible and temporomandibular joint, and is graded from mild to severe in type I, -IIA, -IIB, or –III (23, 34, 99). An alternative model, the O.M.E.N.S-plus classification, focuses on the level of underdevelopment of the Orbit (O), Mandible (M), Ears (E), Facial Nerve (N), Soft Tissue (S), and the presence of extracraniofacial anomalies (6, 25).

These extracraniofacial anomalies may be present in up to 55% of the patients with CFM and may occur in the vertebral column and ribs, the central nervous system (CNS), the circulatory-, respiratory-, gastro-intestinal-, and/or urogenital tract (6, 18, 26, 78). According to previous literature, the prevalence of extracraniofacial anomalies in CFM varies from 2% to 79% (6, 26, 78). Patients with a higher O.M.E.N.S. score are thought to have increased incidence of extracraniofacial anomalies (6). Additionally, patients with an extracraniofacial anomaly have a higher incidence of additional extracraniofacial anomalies in other tracts (11, 18). To recognize and potentially treat these anomalies in an early state, clinicians should be aware of the potential extracraniofacial anomalies in CFM. However, no literature is available on which patients with CFM are at an increased risk of having extracraniofacial anomalies and should be screened for these anomalies.

The aim of this study is to provide an overview of the extracraniofacial anomalies found in CFM and to determine which patients with CFM have an increased likelihood of having extracraniofacial anomalies.

Methods

Subjects and data collection

A global multicenter retrospective study was initiated at the craniofacial centers of Erasmus University Medical Center (EMC), Rotterdam, The Netherlands; Great Ormond Street Hospital (GOSH), London, United Kingdom; Boston Children's Hospital (BCH), Boston, United States of America, and The Hospital for Sick Children, Toronto, Canada. This study was approved by the Institutional Review Boards (Rotterdam: MEC-2012-248; London: 14DS25; Boston: X05-08-058; Toronto: 1000053298).

All patients diagnosed with CFM seen in these craniofacial centers were included for further analyses. Since CFM is a clinical diagnosis, patients with clinical and/or radiographic images, i.e. panoramic x-rays and/or CT head, were included in this study. Patients in which the diagnosis of CFM could not be confirmed with the use of clinical and/or radiographic imaging and patients with isolated microtia were excluded. Patient charts of all included patients were reviewed and data on age, sex, affected side, Pruzansky-Kaban classification, O.M.E.N.S. classification and the presence of extracraniofacial anomalies was extracted. Patients with extracraniofacial anomalies were further analyzed. For each extracraniofacial anomaly present, data on type, location and date of diagnosis of the anomaly were noted.

The O.M.E.N.S. classification system was used to grade the facial malformations in CFM patients (20, 25). The severity of the mandibular hypoplasia was determined by using the Pruzansky classification modified by Kaban et al. (23, 34, 99). In patients with bilateral CFM both facial- and mandibular sides were scored, but only the scores of the most affected side of the face were used for analysis. In this study, the M-score of the O.M.E.N.S. score was based on the Pruzansky-Kaban classification scored on radiography as proposed by Vento et al.(25) and not on clinical photography as suggested in the PAT-CFM developed by Birgfeld et al (20).

Statistical analysis

Statistical analyses were performed using SPSS version 20.0 for Windows (2011, SPSS Inc., Chicago, IL, USA). Descriptive statistics were used. Equality of groups was tested with the Pearson's Chi-square Test for Independence. Fisher's Exact Test was used when the assumptions for Pearson-Chi square test were violated (i.e. expected count less than 10). A univariate binary logistic regression model was used to evaluate the association between the extracraniofacial anomalies, and between the O.M.E.N.S. and Pruzansky score. A P-value of <.05 was considered to be statistically significant.

Results

Characteristics of patient population

A total of 1132 patients with CFM were diagnosed between all four craniofacial centers. Following exclusion of 141 patients due to diagnostic inconclusiveness or isolated microtia, 991 patients were included for further analyses. Fifty-three percent (n=527) was male and 47% (n=464) was female. Most patients had unilateral CFM (n=827), 177 had bilateral CFM and in 47 the affected side was unknown. Patient characteristics are shown in table 5.1.

***Table 5.1:** Demographics for patients with and without extracraniofacial anomalies*

		Extracraniofacial anomalies					
		Yes		No		Total	
Total		462	(47%)	529	(53%)	991	(100%)
Sex	Male	252	(48%)	275	(52%)	527	(53%)
	Female	210	(45%)	254	(55%)	464	(47%)
Laterality	Unilateral	367	(44%)	460	(56%)	827	(83%)
	Bilateral	79	(68%)	38	(32%)	117	(12%)
	Unknown	16	(34 %)	31	(66%)	47	(5%)
Affected side (UCFM)#	Right	199	(43%)	264	(57%)	463	(56%)
	Left	168	(46%)	196	(54%)	364	(44%)
Orbit*	0	183	(45%)	227	(55%)	410	(53%)
	1	69	(53%)	60	(47%)	129	(17%)
	2	53	(51%)	50	(49%)	103	(13%)
	3	41	(44%)	53	(56%)	94	(12%)
	4	24	(63%)	14	(37%)	38	(5%)

***Table 5.1:** Continued.*

		Extracraniofacial anomalies					
		Yes		No		Total	
Mandible**†	0	0	(0%)	1	(100%)	1	(1%)
	1	63	(39%)	98	(61%)	161	(24%)
	2A	72	(42%)	100	(58%)	172	(26%)
	2B	89	(51%)	86	(49%)	175	(26%)
	3	97	(63%)	57	(37%)	154	(23%)
Ear*	0	45	(39%)	69	(61%)	114	(15%)
	1	51	(46%)	60	(54%)	111	(15%)
	2	56	(59%)	39	(41%)	95	(13%)
	3	193	(47%)	214	(53%)	407	(54%)
	4	14	(64%)	8	(36%)	22	(3%)
Nerve*	0	100	(44%)	126	(56%)	226	(57%)
	1	21	(46%)	25	(54%)	46	(12%)
	2	39	(59%)	27	(41%)	66	(17%)
	3	24	(69%)	11	(31%)	35	(9%)
	4	11	(55%)	9	(45%)	20	(5%)
Soft Tissue*	0	55	(46%)	65	(54%)	120	(16%)
	1	132	(41%)	193	(59%)	325	(43%)
	2	127	(52%)	116	(48%)	243	(32%)
	3	47	(67%)	23	(33%)	70	(9%)

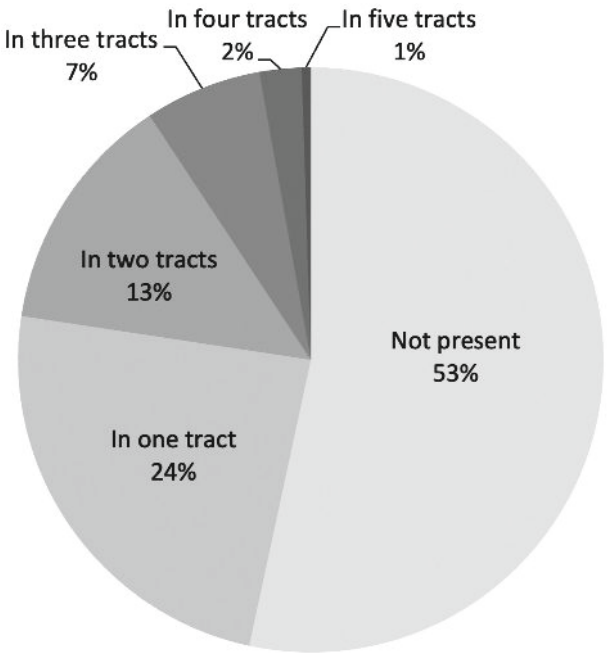
UCFM=unilateral craniofacial microsomia ; #In unilateral cases of craniofacial microsomia ; *Orbit, Ear, Nerve, Soft Tissue score on the O.M.E.N.S. scale ; **†Mandible score based on Pruzansky-Kaban classification ; ^See Table 4. for statistical analysis

Characteristics of patients with extracraniofacial anomalies

Of the 991 patients included in this study, 47% (n=462) of patients were diagnosed with at least one extracraniofacial anomaly. The number of extracraniofacial anomalies per patient varied and could by present in the same or other tracts simultaneously, as shown in figure 5.1. Fifty-five percent of the patients with an extracraniofacial anomaly was male (n=252) and forty-five percent was female (n=210). Seventy-nine percent (n=367) of the patients with an extracraniofacial anomaly had unilateral CFM, 17% (n=79) had bilateral CFM and of 4% (n=16) of the patients with an extracraniofacial anomaly the affected side was unknown. The prevalence of extracraniofacial anomalies was found to be significantly higher in patients with

bilateral CFM than in patients with unilateral CFM *(Pearson's χ^2 (df 1)=22.03, odds ratio=2.61, 95% CI 1,7-3,9, p-value=<0.0001).*

***Figure 5.1:** Percentage of patients with extracraniofacial anomalies in multiple tracts*



Types of extracraniofacial anomalies

The various types of extracraniofacial anomalies diagnosed in our study population are shown in table 5.2. Vertebral anomalies were most frequently seen, in 28% of the patients with CFM (n=275). Most seen anomalies were scoliosis, block vertebrae, hemivertebrae, and anomalies of the ribs. Anomalies of the central nervous system were reported in 11% of the patients with CFM (n=105). Hydrocephaly, ventriculomegaly, intracranial cysts, and Arnold Chiari malformation were mostly seen. Of the 28 patients with anomalies of the spinal cord, such as spina bifida or tethered cord, 27 patients had vertebral anomalies too *(odds ratio=77.84, p-value=<0.001).* Anomalies of the circulatory system were present in 21% of the patients with CFM (n=205). Mostly seen were ventricular or atrial septal defects, patent ductus arteriosus, and anomalies of the valves. Three percent of all patients with CFM (n=29)

had an anomaly of the respiratory tract (n=14), such as laryngo- or tracheomalacia, or lung hypoplasia. Of these 29 patients with a respiratory anomaly, 14 patients had a cardiac anomaly too. Anomalies of the gastro-intestinal tract were present in 9% of the patients (n=89). Although the variety of anomalies is large, inguinal hernia, imperforate anus, esophageal atresia, and umbilical hernia were mostly seen. Urogenital anomalies occurred in 11% of the patients (n=108). Mainly, renal aplasia, undescended testis, and hydronephrosis were observed.

Table 5.2: *Description of extracraniofacial anomalies*

Vertebral anomalies (n=275)	Number patients	Central nervous system anomalies (n=105)	Number patients	Circulatory system anomalies (n=205)	Number patients	Respiratory tract anomalies (n=29)	Number patients	Gastro-intestinal tract anomalies (n=89)	Number patients	Urogenital tract anomalies (n=108)	Number patients
Scoliosis	162	Hydrocephaly	18	VSD	95	Laryngomalacia	15	Inguinal hernia	30	Renal aplasia	28
Block vertebrae	118	Ventriculomegaly	17	ASD	71	Lung hypoplasia	8	Imperforate anus	16	Undescended testis	15
Hemivertebrae	98	Intracranial cyst	17	Patent ductus arteriosus	42	Tracheomalacia	7	Esophageal atresia	11	Hydronephrosis	14
Not specified	49	Arnold Chiari	12	Valve anomaly	22	Tracheal stenosis	2	Umbilical hernia	11	Renal ectopia	10
Ribs fusion	27	Microcephaly	11	Tetralogy of Fallot	16	Absence of tracheal rings	1	Tracheoesophageal fistula	8	Hypospadias	10
Butterfly vertebrae	25	Intracranial lipoma	11	Artery malformation	15	Not specified	1	Intestines anomaly	6	Phimosis	9
Ribs aplasia	25	Spina bifida occulta	10	Pulmonic valve stenosis	13			Diaphragmatic hernia	5	Internal genital anomalies	7
Ribs extra	23	Hypoplastic corpus callosum	9	Arrhythmia	11			Meckel's diverticulum	4	Vesicoureteral reflux	6
Vertebral hypoplasia	18	Cerebral dysgenesis	9	Venous malformation	10			Intestinal malrotation	4	Bladder anomaly	6
Ribs hypoplasia	15	Not specified	8	Transposition of the great arteries	10			Polysplenia	3	External genital anomalies	6
Cervical ribs	12	Tethered cord	7	Ventricle anomaly	10			Diaphragm anomaly	3	Ureter anomaly	5

***Table 5.2:** Continued.*

Vertebral anomalies (n=275)	Number patients	Central nervous system anomalies (n=105)	Number patients	Circulatory system anomalies (n=205)	Number patients	Respiratory tract anomalies (n=29)	Number patients	Gastro-intestinal tract anomalies (n=89)	Number patients	Urogenital tract anomalies (n=108)	Number patients
Lack of fusion vertebrae	12	Cerebral hemorrhage/ infarction	8	Aortic anomaly	9			Liver anomaly	3	Hydrocele testis	5
Pectus deformity	12	Fatty filum terminale	5	TAPVR	6			Anal fistula	2	Renal hypoplasia	4
Cervical spine instability	7	Meningocele	5	Dextrocardia	4			Omphalocele	2	Duplex kidney anomalies	4
Rib anomaly n.s.	7	Cerebral hypoplasia	4	Situs inversus	1			Pyloric stenosis	2	Renal fusion	3
Occipitalization atlas	6	Encephalocele	4	Cardiomegaly	1			Situs ambiguous	1	Renal dysplasia	3
Atlanto-axial subluxation	4	Syringomyelia	4	Mesocardia	1					Renal anomaly n.s.	3
Vertebral agenesis	3	Macrocephaly	4	Not specified	1						
Sacralization	3	Intracranial mass n.s.	3								
Os odontoideum	2	Absent septum pellucidum	2								
Extra vertebrae	2										
Omo vertebral body	1										

n.s.: not specified, *TAPVR: Total anomalous pulmonary venous return

Correlations extracraniofacial anomalies

Table 5.3 shows the statistical analysis of which patients with an extracraniofacial anomaly had a higher incidence of additional extracraniofacial anomalies in other tracts. Patients with an extracraniofacial anomaly in any tract were found to have a significant higher risk for additional extracraniofacial anomalies in other tracts, except for anomalies of the respiratory tract. The correlation strength for the presence of extracraniofacial anomalies in different tracts varied from a Pearson's χ^2 (df 1) of 88.72 and an odds ratio of 6.64 (p=<0.001) for vertebral anomalies and anomalies of the central nervous system, to a Pearson's χ^2 (df 1) of 15.53 and an odds ratio of 2.33 (p=<0.001) for circulatory anomalies and anomalies of the urogenital tract. Anomalies of the respiratory tract were observed in fewer patients than anomalies of other tracts and were positively correlated with the presence of anomalies of the circulatory system *(odds ratio=3.77, P-value=0.001)* and gastro-intestinal tract *(odds ratio=4.96, P-value=0.001)*.

Table 5.3: *Statistical analysis of the extracraniofacial anomalies in the various tracts*

		Extracraniofacial anomalies (number of patients)					
		CNS (n=105)	Circulatory (n=205)	Respiratory (n=29)	GI# (n=89)	Urogenital (n=108)	
Extracraniofacial anomalies (number of patients)	Vertebral (n=275)	88.72	49.36	*	36.37	37.87	***Pearson's*** χ^2
		6.64	3.01	2.17	3.67	3.41	Odds ratio
		0.30	0.22	-	0.19	0.20	Phi coefficient
		4.30-10.26	2.23-4.23	0.99-1.06	2.35-5.71	2.27-5.13	95% CI†
		<0.0001	**<0.0001**	0.055	**<0.0001**	**<0.0001**	P-value
	CNS (n=105)		24.13	*	*	17.30	***Pearson's*** χ^2
			2.82	0.62	3.49	2.83	Odds ratio
		-	0.16	-	-	0.13	Phi coefficient
			1.84-4.32	0.15-2.64	2.06-5.90	1.70-4.70	95% CI†
			<0.0001	0.76	**<0.0001**	**<0.0001**	P-value
	Circulatory (n=205)			*	41.87	15.53	***Pearson's*** χ^2
				3.77	4.05	2.33	Odds ratio
		-	-	-	0.21	0.13	Phi coefficient
				1.79-7.94	2.59-6.35	1.52-3.58	95% CI†
				0.001	**<0.0001**	**<0.0001**	P-value
	Respiratory (n=29)				*	*	***Pearson's*** χ^2
					4.96	2.71	Odds ratio
		-	-	-	-	-	Phi coefficient
					2.19-11.26	1.13-6.51	95% CI†
					0.001	**0.031**	P-value
	GI# (n=89)					*	***Pearson's*** χ^2
						4.13	Odds ratio
		-	-	-	-	-	Phi coefficient
						2.48-6.87	95% CI†
						<0.0001	P-value

#Gastro-Intestinal; *criteria for Pearson-Chi square test were not met, therefore the Fisher's Exact Test was used; †Confidence Interval

The O.M.E.N.S. score was used to examine a possible correlation between the facial malformations in CFM and the presence of extracraniofacial anomalies. Of various patients, data of components of the O.M.E.N.S. score was missing: in 217 patients the Orbit score was unknown, in 328 patients the Mandible score was unknown, the Ear score was unknown in 242 patients, in 598 patients the Nerve score were not available, and the Soft Tissue score was unknown in 233 patients.

The statistical analysis of the correlation of the O.M.E.N.S. score with extracraniofacial anomalies is displayed in table 5.4. A higher incidence of extracraniofacial anomalies was observed in patients with a higher Mandible score, Nerve score***s***, or Soft Tissue score of the O.M.E.N.S. score. This significant correlation was not observed in patients with a higher Orbit or Ear score. A positive correlation between the Orbit score and extracraniofacial anomalies was solely present for vertebral anomalies and not for extracraniofacial anomalies in other tracts. The Ear score was positively correlated with circulatory anomalies and not with extracraniofacial anomalies in other tracts. The mandible score had the highest correlation strength for the presence of extracraniofacial anomalies compared to other components of the O.M.E.N.S. score (Pearson's r=0.331, Odds ratio=1.39, P-value=<0.001).

Table 5.4: *Statistical analysis of the O.M.E.N.S. score in patients with extracraniofacial anomalies*

	Extracraniofacial anomalies (n=462)	Vertebral anomalies (n=275)	CNS anomalies (n=105)	Circulatory anomalies (n=205)	Respiratory anomalies (n=29)	Gastro-intestinal anomalies (n=89)	Urogenital anomalies (n=108)	
Orbit*	0.086	0.120	0.022	0.088	0.130	0.051	0.005	***Pearson's r***
	1.09	1.13	1.02	1.09	1.14	1.05	1.01	Odds ratio
	0.97-1.22	1.00-1.28	0.85-1.23	0.95-1.25	0.84-1.54	0.87-1.27	0.84-1.12	95% CI†
	0.133	**0.049**	0.814	0.201	0.398	0.592	0.959	P-value
Mandible**	0.331	0.329	0.186	0.201	0.356	0.342	0.240	***Pearson's r***
	1.39	1.39	1.20	1.22	1.43	1.41	1.27	Odds ratio
	1.21-1.61	1.19-1.62	0.97-1.50	1.03-1.45	0.91-2.23	1.11-1.79	1.02-1.59	95% CI†
	<0.0001	**<0.0001**	0.094	**0.022**	0.118	**0.006**	0.033	P-value
Ear*	0.101	0.101	-0.014	0.161	0.121	0.143	-0.008	***Pearson's r***
	1.11	1.11	0.99	1.18	1.13	1.15	0.99	Odds ratio
	0.98-1.25	0.97-1.27	0.81-1.20	1.01-1.38	0.78-1.64	0.93-1.43	0.82-1.20	95% CI†
	0.10	0.146	0.889	**0.046**	0.524	0.189	0.934	P-value
Nerve*	0.233	0.238	0.107	0.188	0.048	0.292	0.236	***Pearson's r***
	1.26	1.27	1.11	1.21	1.05	1.34	1.27	Odds ratio
	1.07-1.49	1.07-1.50	0.89-1.39	1.01-1.45	0.49-2.26	1.05-1.70	1.02-1.57	95% CI†
	0.005	**0.005**	0.340	**0.045**	0.902	**0.017**	**0.033**	P-value
Soft Tissue*	0.300	0.203	-0.114	0.319	0.567	0.497	0.182	***Pearson's r***
	1.35	1.23	0.89	1.38	1.76	1.64	1.20	Odds ratio
	1.14-1.60	1.02-1.47	0.68-1.18	1.12-1.70	1.09-2.85	1.23-2.20	0.92-1.56	95% CI†
	0.001	**0.031**	0.421	**0.003**	**0.020**	**0.001**	0.173	P-value

*Orbit, Ear, Nerve, Soft Tissue score on the O.M.E.N.S. scale ; **Mandible score based on Pruzansky-Kaban classification; †Confidence IntervalDiscussion

The aim of this study was to present an overview of the extracraniofacial anomalies in CFM and to determine which patients with CFM have an increased likelihood for having these anomalies. A total of 991 patients were included, with a male to female ratio of 1.14:1, which is in line with previous literature (129). Eighteen percent of the patients were diagnosed with bilateral CFM, which is higher than the 13,6% reported by meta-analysis by Xu et al (129).

Forty-seven percent of all patients studied (n=462) were diagnosed with extracraniofacial anomalies. The extracraniofacial anomalies were observed in all various tracts, such as the vertebral column (in 28%), central nervous system (in 11%), circulatory (in 21%), gastro-intestinal (in 9%), and urogenital (in 11%) tract, but were considerably scarce in the respiratory tract (in 3%). This may be due to a difference in the embryological development of these organs. The etiology of CFM is unknown, yet various theories have been proposed (44, 45, 128). Hereditary cases of CFM are known and when examining family members of patients with CFM with more detail for dysmorphologies, 45% of the family members tend to have some manifestation that could be part of CFM (3). Various genes have been proposed to cause CFM, but no single origin has been identified (11, 45). However, a recent genome-wide association study has identified a number of genetic loci associated with CFM that express neural crest genes (13). An alteration in the development of the first and second pharyngeal arches during the first six weeks of development appears to be the cause of CFM (44, 45). During these weeks the facial structures are formed by the first and second pharyngeal arches after neural crest cells migrated into these arches forming ectomesenchyme (7, 8, 130). A defect in the generation or migration of neural crest cells has been suggested to be the origin of the developmental deformities found in CFM (7, 8, 130). Abnormal migration of neural crest cells has been found to form the basis of craniofacial, vertebral, central nervous system, cardiovascular, and urogenital anomalies (6, 96, 97). The lungs are formed out of the primitive foregut and are further developed by epithelia, which is of endodermal descent, and mesenchymal cells (131). During development of the lung, neural crest cells play a role in the development of the intrinsic neurons which innervate the airway smooth muscles (132). Disturbing this process may originate in inadequate formation of the lungs. Although neural crest cells play a role in the development of the respiratory tract, less evidence is available on a link between neural crest cells and anomalies in this tract. This may be the reason why less

anomalies of the respiratory tract were found in our studied cohort compared to anomalies in other tracts.

The prevalence of extracraniofacial anomalies in CFM in our studied cohort is 47%, which is considerably higher than the incidence of 0,001%-2% in live births in the healthy population (112, 133, 134). The prevalence found in our studied population is similar to the 44% found by Rollnick et al. (26), but lower than the 55% reported by Horgan et al. (6) and the 69% by Barisic et al (78). This may be due to differences in patient selection, study characteristics and sample size. In the study by Rollnick et al. (n=294) 31% of the included patients had isolated microtia, which may have led to a lower prevalence of extracraniofacial anomalies in their studied population since these patients do not fit the criteria of CFM used in this study (26). The study by Horgan et al. (n=121) included patients with "hemifacial microsomia" without further specification of the clinical criteria used (6). Barisic et al. (n=269) included patients with microtia/ear anomalies and at least one major anomaly of the oculo-auriculo-vertebral spectrum (78). The prevalence of extracraniofacial anomalies found in our study may be higher since our study is retrospective and data are based on chart review. Thereby, not all extracraniofacial anomalies lead to clinical symptoms and may therefore remain undiagnosed. Although the actual prevalence remains uncertain, this large retrospective study shows extracraniofacial anomalies are common in CFM. Only a well-designed prospective study could comprehensively characterize extracraniofacial anomalies in CFM.

Horgan et al. found, by using the sum of the O.M.E.N.S. score, that patients with a higher O.M.E.N.S. score had a higher risk for extracraniofacial anomalies (6). In our studied cohort, patients with bilateral CFM, a higher Pruzanksy-Kaban score, and/or a higher Nerve, and/or Soft Tissue score on the O.M.E.N.S. scale had a significant higher incidence of extracraniofacial anomalies. Caron et al. and Tuin et al. found that deformities of the Orbit, Mandible, and Soft Tissue, which originate from the first pharyngeal arch, are significantly correlated with each other (18, 135). A correlation between the structures derived from the second pharyngeal arch as scored in the Nerve and Ear score, and the Nerve and Soft Tissue score was also found (135). This study did not find a correlation between the presence of extracraniofacial anomalies and the O.M.E.N.S. score clusters as described by Caron et al. and Tuin et al. This could be due to a different, systemic pathophysiological mechanism compared to patients with isolated facial anomalies.

Patients with an extracraniofacial anomaly had a significant higher risk for additional extracraniofacial anomalies in other tracts compared to patients without extracraniofacial anomalies. This correlation was present in all various tracts these anomalies can occur in, except for the respiratory tract and vertebrae, and the respiratory tract and central nervous system. Tasse et al. found a significant correlation between genito-urinary anomalies and vertebral anomalies, but anomalies of the brain were not correlated with the presence other extracraniofacial anomalies in their studied cohort (53). The significant correlation between anomalies of the circulatory system and respiratory tract was also observed by Kumar et al. (136) but not by Barisic et al (78). Both studies did not observe a significant correlation between anomalies of the circulatory system and urogenital tract, as found in our study (78, 136).

Since our study is retrospective, it is uncertain whether patients with an extracraniofacial anomaly were assessed in more detail for the presence of additional anomalies. Therefore, a detection bias may be present. Nevertheless, based on the large size of this multicenter cohort we have been able to clearly demonstrate that extracraniofacial anomalies are common in patients with CFM. Patients with CFM should be screened for potential harmful anomalies. Therefore, thorough physical examination should be performed in all patients with CFM. Anomalies of the circulatory system should be ruled out by cardiac evaluation using electrocardiography and/or echocardiogram in patients with a higher risk for extracraniofacial anomalies (134, 137). A renal ultrasound to diagnose urogenital anomalies in an early stage should be obtained in these patients as well (107). Neurological evaluation should be performed and if abnormal, an MRI of the brain and spine should be performed to rule out any anomalies (67, 104). If vertebral anomalies are suspected, standard upright posterior-anterior and lateral radiographs should be obtained (67, 103).

Conclusion

The prevalence of extracraniofacial anomalies in CFM in our studied cohort of 991 patients was 47%. Patients with bilateral CFM, and/or a high Pruzansky-Kaban score, or a high Nerve and/or Soft Tissue on the O.M.E.N.S. scale have a higher risk for extracraniofacial anomalies. Having extracraniofacial anomalies increases the risk for having additional extracraniofacial anomalies. All patients with CFM should be screened for extracraniofacial anomalies by a thorough physical examination with specific attention aimed at the circulatory, renal, and neurological tracts. Additionally, electrocardiography, echocardiogram, spine radiography and a renal ultrasound should be obtained in patients at risk for extracraniofacial anomalies.

Regarding the pathogenesis of CFM, the abundance of extracraniofacial anomalies in CFM patients and the strong correlation between them and with craniofacial (pharyngeal arch) defects suggests that the basis for this disorder lies with the neural crest cells. The fact that the pharyngeal arches are involved could be due to the fact the correct formation of these structures relies heavily on correct migration of neural crest cells during early embryonic development.

6

Upper and lower limb anomalies in craniofacial microsomia and its relation to the O.M.E.N.S.+ classification

a multicentre study of 688 patients

Based on:

Ruben W. Renkema, Thymen Houwen, Christianne A. van Nieuwenhoven, Bonnie L. Padwa, Christopher R. Forrest, David J. Dunaway, Maarten J. Koudstaal, Cornelia J.J.M. Caron. Upper and Lower Limb Anomalies in Craniofacial Microsomia and Its Relation to the OMENS+ Classification: A Multicenter Study of 688 Patients Plastic and Reconstructive Surgery. 2023 May 1;151(5):1053-1061. doi: 10.1097/PRS.0000000000010090. Epub 2022 Dec 21. PMID: 36729069; PMCID: PMC10125112.

Abstract

Craniofacial microsomia (CFM) is characterized by several malformations related to the first and second pharyngeal arch. Patients typically present with facial asymmetry, but extracraniofacial organ systems might be involved, including limb anomalies. The purpose of this study is to analyze the occurrence of upper and lower limb anomalies in CFM patients. Furthermore, the relation between limb-anomalies and the O.M.E.N.S.+ classification was examined. A retrospective study was conducted including patients with craniofacial microsomia from craniofacial units in three different countries. Patients were included when clinical and/or radiographic images were available. Demographic, radiographic and clinical information was obtained. A cohort of 688 patients was available and selected for analysis. In total, 18.2% of the patients were diagnosed with at least one upper and/or lower limb anomaly. Upper and lower limb anomalies were seen in respectively 13.4% and 7.8% patients. Patients with other extracraniofacial anomalies had a significantly higher risk for limb anomalies (odd ratio 27.98, p=0.005). Laterality of CFM and a higher O.M.E.N.S. score were not associated with limb anomalies. As more than 1 in 6 patients with CFM have limb anomalies, clinical awareness for these anomalies is warranted. Examination and, if present, follow up on limb abnormalities in patients with CFM should be implemented in the standard assessment of CFM patients.

Introduction

Craniofacial microsomia (CFM) is, following cleft lip and palate, the second most frequent congenital disorder of the head and neck. It is estimated to occur in 1:3000 to 1:5000 new-borns (1, 47, 138). CFM is the general term for hypoplasia of facial structures related to the first and second pharyngeal arch (43, 44, 138). Main characteristics of CFM, resulting in facial asymmetry, include maxillary and/or mandibular hypoplasia, soft tissue deficiencies, orbital anomalies, pre-auricular and/or facial tags, and ear anomalies (1, 43, 44, 138, 139). Wide phenotypic variability resulted in several terms proposed for CFM including hemifacial microsomia, Goldenhar syndrome, oculo-auriculo-vertebral spectrum, first and second branchial arch syndrome, otomandibular dysostosis, facio-auriculo-vertebral syndrome and lateral facial dysplasia (6, 138, 139)

Several classification systems have been developed for CFM. The most well-known and used classifications are the Pruzansky-Kaban classification and the O.M.E.N.S.-plus classification (21, 25, 34). The Pruzansky-Kaban classification is used to score the severity of mandibular hypoplasia. The O.M.E.N.S.-plus classification documents anomalies of the orbit, mandible, ear, nerve function and soft tissue deficiencies. The ''plus'' is used for the expanded spectrum with respect to extracraniofacial anomalies (6).

Extracraniofacial anomalies might be present in the vertebrae, central nervous system (CNS), circulatory tract, gastrointestinal tract and/or urogenital tract (6, 18, 139, 140). Analyses of the presence of these anomalies in patients with CFM indicated that they are correlated with more severely affected facial phenotypes (6, 140).

Early studies have documented limb anomalies in patients with CFM (6, 11, 52, 141-146). In the general population, upper limb anomalies are estimated to be present in 11.4-19.7 (0.001-0.002%) per 10.000 new-borns (147-149). Some anomalies such as hip dysplasia/dislocation occur more frequently in females, whereas others such as club foot and polydactyly occur more frequently in males (150). Limb anomalies might be more prevalent in patients with CFM. Horgan et al. described in a population of 121 patients with CFM that 41% were diagnosed with skeletal anomalies. This included both limb and non-limb skeletal anomalies (6). Other studies by Werler et al. and Beleza-Meireles et al. included respectively 239 and 51 patients with CFM and described anomalies of the limbs in 7 to 12% of the patients (11, 146).

A variety of limb anomalies were described including radial dysplasia, thumb hypoplasia, scaphoid aplasia (52, 142, 143, 145), clubfoot, congenital hip dislocation, Sprengel deformity (6, 52), pre-axial polydactyly (6, 143) and finger-anomalies (6). Even though the previous literature described the presence of limb anomalies in patients with CFM, research with detailed data on limb anomalies in a larger cohort has not been done.

The purpose of this study is to analyze the occurrence of upper and lower limb anomalies in patients with CFM, by studying the type and prevalence of these anomalies. Secondly, we aim to determine whether there is an association between the phenotypic severity of CFM and the presence of limb anomalies. We hypothesise that, in accordance with other extracraniofacial anomalies, limb anomalies are more frequently present in patients with CFM compared to the general population and more frequently seen in patients with severe facial hypoplasia and/or the 'expanded spectrum' of CFM (140).

Materials and methods

Subjects

This retrospective study was conducted in the population of patients diagnosed with CFM at the craniofacial centres of the Erasmus University Hospital, Rotterdam, The Netherlands, the Great Ormond Street Hospital, London, United Kingdom and the Hospital for Sick Kids in Toronto, Canada.

Following IRB approval (Rotterdam: MEC-2012-248; London: 14 DS25; Toronto: 1000053298), the medical files of all patients diagnosed with CFM were reviewed. Although microtia might be seen as a mild phenotype of CFM, patients with microtia as an isolated anomaly were excluded from further analyses in this study.

CFM is a clinical diagnosis based on physical examination and examination of radiographic images. Therefore, only patients with panoramic X-rays, computed tomography scans of the head and/or available clinical photographs supporting the diagnosis CFM were included. All medical charts of patients meeting our inclusion criteria were searched for date of birth, sex, affected side, presence of extremity anomalies, treatment of extremity anomalies, and available clinical photographs.

The severity of CFM was scored in patients using the Pruzansky-Kaban classification and the O.M.E.N.S.-plus classification (6, 151). For bilateral cases, the most severely affected side was used for descriptive and statistical analyses. Patients unable to be classified with the Pruzansky-Kaban classification were graded as unknown. This group was excluded from further statistical analysis and only used for descriptive statistics. Extracraniofacial anomalies included vertebral, cardiac, central nervous system, renal, gastro-intestinal and respiratory anomalies. Limb anomalies were categorized as a separate entity.

Limb anomalies were considered as congenital aberrations of arms and/or legs from the proximal shoulder –or hip joint to the distal end of the limbs, i.e. from shoulder to fingertip and from hip to toes. The Blauth classification (Blauth I, II, IIIA, IIIB, IV, V) was used for scoring severity of thumb hypoplasia. Blauth 1 is present when only minor hypoplasia is seen, Blauth 2 shows MCP instability and thenar hypoplasia, Blauth III is characterised by musculotendinous and osseous deficiencies, Blauth IV is the floating thumb and Blauth V is total absence of the thumb (152).

Since patients could be affected with multiple different observational extremity anomalies, each individual classifiable limb anomaly was recorded and counted as one separate anomaly. As an example, bilateral cases and multiple unilateral cases of anomalies were counted as individual problems. The total number of separate identifiable limb anomalies was therefore higher than the total number of patients with any limb anomaly.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 24.0 (IBM Corp., Armonk, NY, USA). Descriptive analyses were initially performed. A chi-square test was used to assess the correlation between sex, laterality of CFM and extracraniofacial anomalies and the presence of limb anomalies. Fisher's Exact Test was used if the assumptions for Pearson-Chi square test were violated (i.e. expected count less than 5). The correlation between the affected facial and limb side was studied, in which patients with unilateral CFM and bilateral limb anomalies were considered to have limb anomalies on the contralateral side. Analyses were repeated after exclusion of patients with isolated clinodactyly, isolated camptodactyly, or isolated trigger thumb, as these anomalies are also regularly seen in non-syndromic persons. The association between the O.M.E.N.S. categories and

limb anomalies were assessed by univariable and multivariable binary logistic regression analysis. This was expressed by odd ratio's, 95% confidence intervals and p values. All statistical tests used a two-sided significance level of 0.05. Goodness of model fit was based on the model $\chi 2$ (p value). Multicollinearity (correlations within all components of the model) was examined. The discriminative ability of the multivariable logistic regression model was validated by a receiver operating characteristic (ROC) curve.

Results

Study characteristics

A total cohort of 688 patients were available for analyses. The patient characteristics are shown in table 6.1. Unilateral CFM was seen in 615 patients (89%) and bilateral CFM in 73 patients (11%). Slightly more males (n=367) than females (n=321) were included.

***Table 6.1:** Description of the population*

Limb anomalies		Yes		No		P value
Total		125	*18%*	563	*82%*	
Sex	Male	65	*18%*	302	*82%*	0.74
	Female	60	*19%*	261	*81%*	
Laterality	Unilateral Right	58	*17%*	280	*83%*	0.23
	Unilateral Left	50	*18%*	227	*82%*	
	Bilateral	17	*24%*	55	*76%*	
Orbit	0	28	*14%*	168	*86%*	0.27
	1	21	*22%*	74	*78%*	
	2	17	*18%*	76	*82%*	
	3	15	*17%*	74	*83%*	
	4	9	*24%*	29	*76%*	
	U/A	34	*20%*	137	*80%*	
Mandible	1	22	*15%*	122	*85%*	0.49
	2A	41	*26%*	119	*74%*	
	2B	14	*13%*	91	*87%*	
	3	16	*15%*	88	*85%*	
	U/A	32	*18%*	143	*82%*	

***Table 6.1:** Continued.*

Limb anomalies		Yes		No		P value
Ear	0	11	*19%*	48	*81%*	0.50
	1	14	*17%*	70	*83%*	
	2	20	*32%*	43	*68%*	
	3	37	*15%*	206	*85%*	
	4	4	*18%*	18	*82%*	
	U/A	38	*18%*	173	*82%*	
Nerve	0	11	*14%*	67	*86%*	0.78
	1	1	*11%*	8	*89%*	
	2	2	*20%*	8	*80%*	
	3	1	*20%*	4	*80%*	
	4	3	*15%*	17	*85%*	
	U/A	106	*19%*	454	*81%*	
Soft Tissue	0	8	*19%*	35	*81%*	0.19
	1	31	*14%*	189	*86%*	
	2	38	*20%*	149	*80%*	
	3	12	*21%*	44	*79%*	
	U/A	35	*20%*	141	*80%*	
Extracraniofacial	Yes	77	28%	197	72%	
	No	23	7%	283	93%	**<0.001**

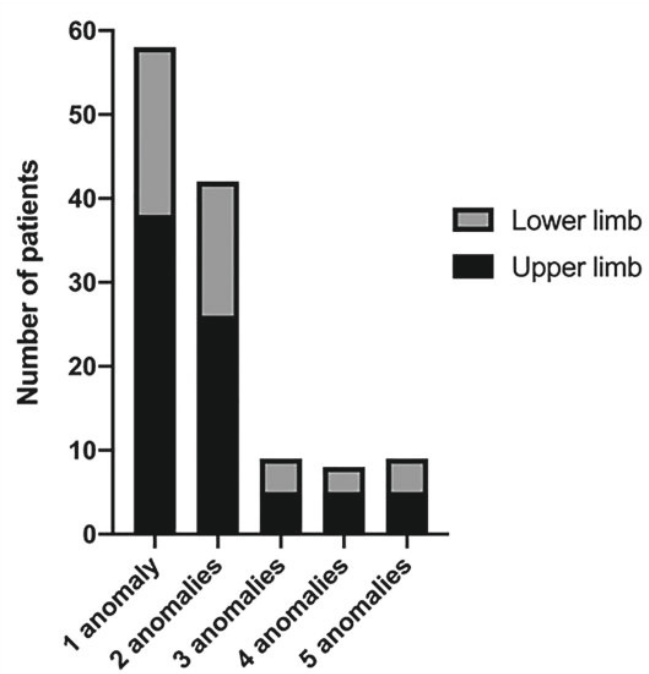
U/A: unavailable data; *acronyms of the O.M.E.N.S.; Statistically significant p-values are bold

Presence of limb anomalies

In total, 18.2% (n=125) of the patients were diagnosed with at least one anomaly of the upper and/or lower limbs (table 6.1). Limb anomalies were observed in 17.6% of the patients with unilateral CFM and in 23.3% of the patients with bilateral CFM. There was no statistical difference in the prevalence of limb anomalies in unilateral versus bilateral CFM (Pearson's $\chi 2$ (1, N=688)=1.4; p=0.23).

Fifty-seven patients (46%) had one limb anomaly and 68 patients (54%) had multiple anomalies of the upper- and/or lower limb (figure 6.1). Most patients (57%) had anomalies of the upper limbs, 26% had anomalies of the lower limbs, and 17% of the patients had both upper and lower limb anomalies.

Figure 6.1: *Number of extremity anomalies per patient*



Upper limb anomalies

There were 92 patients (13.4%) with upper limb anomalies. This included both unilateral and bilateral limb involvement with a wide spectrum of anomalies.

Radial ray deficiencies and abnormalities were observed in 78 cases including thumb hypoplasia, thumb in palm, triphalangeal thumb, thumb duplication and radial dysplasia. Table 6.2 shows the individual numbers of all upper limb anomalies. Finger-abnormalities were the second biggest group observed in our cohort and included brachydactyly, camptodactyly, clinodactyly, syndactyly and central polydactyly (table 6.2).

Less frequent anomalies included cleft hand, Sprengel deformity, abnormal broad thumbs, hemi-hypoplasias of the upper limb, trigger thumbs, congenital scaphoid malformation, finger aplasia, ulna hypoplasia, and a rudimentary clavicle. The number of patients affected with these anomalies varied from one to four (table 6.2).

Table 6.2: *Type of upper limb anomalies*

Type of upper limb anomaly	Frequency of occurrence (n)		Number of patients affected (n)	
Total	159		92	
Thumb hypoplasia				
Blauth I	7	(4.4%)	6	(6.5%)
Blauth II	11	(6.9%)	11	(12.0%)
Blauth IIIA	3	(1.9%)	3	(3.3%)
Blauth IIIB	5	(3.1%)	3	(3.3%)
Blauth IV	5	(3.1%)	5	(5.4%)
Blauth V	10	(6.3%)	9	(9.8%)
Unspecified	16	(10.1%)	10	(10.9%)
Thumb in palm	2	(1.3%)	2	(2.2%)
Triphalangeal thumb	3	(1.9%)	3	(3.3%)
Thumb duplication	9	(5.7%)	8	(8.7%)
Radial dysplasia	22	(13.8%)	18	(19.6%)
Brachydactyly	9	(5.7%)	6	(6.5%)
Camptodactyly	4	(2.5%)	3	(3.3%)
Clinodactyly	21	(13.2%)	13	(14.1%)
Syndactyly	11	(6.9%)	10	(10.9%)
Central polydactyly	1	(0.6%)	1	(1.1%)
Broad thumb	6	(3.8%)	3	(3.3%)
Cleft hand	1	(0.6%)	1	(1.1%)
Congenital scaphoid malformation	1	(0.6%)	1	(1.1%)
Ulna hypoplasia	1	(0.6%)	1	(1.1%)
Hemihypoplasia of upper limb not specified	4	(2.5%)	4	(4.3%)
Rudimentary clavicle	1	(0.6%)	1	(1.1%)
Sprengel deformity	4	(2.5%)	3	(3.3%)
Trigger thumb	1	(0.6%)	1	(1.1%)
Finger aplasia	1	(0.6%)	1	(1.1%)

Sidedness of upper limb anomalies compared to the hypoplastic facial side is shown in table 6.3. Although not significant, anomalies of the upper extremities occurred more frequently on the same side as CFM affected side (Pearson's $\chi 2$ (1, N=75)=0.04; p=0.85). This was the case in 46 (61.3%) patients of the 75 patients with unilateral CFM and upper extremity anomalies. Exclusion of the thirteen patients with isolated clinodactyly, isolated camptodactyly, or isolated trigger thumb

had a small effect on the overall prevalence of limb anomalies in patients with CFM (18.2% to 16.6%) and had no effect on any statistical analysis.

***Table 6.3:** Laterality CFM and limb anomaly*

	Left sided CFM	Right sided CFM	Bilateral CFM
Left limb anomaly	22 (44%)	1 (2%)	3 (18%)
Left upper anomaly	12 (24%)	0 (0%)	3 (18%)
Left lower anomaly	5 (10%)	1 (2%)	0 (0%)
Left upper & lower	5 (10%)	0 (0%)	0 (0%)
Right limb anomaly	10 (20%)	28 (48%)	5 (29%)
Right upper anomaly	4 (8%)	23 (40%)	2 (12%)
Right lower anomaly	6 (12%)	3 (5%)	3 (18%)
Right upper & lower	0 (0%)	2 (3%)	0 (0%)
Bilateral limb anomaly	16 (32%)	27 (47%)	8 (47%)
Bilateral upper	6 (12%)	13 (22%)	4 (24%)
Bilateral lower	7 (14%)	6 (10%)	1 (6%)
Bilateral upper & lower	3 (6%)	8 (14%)	3 (18%)
Unknown side anomaly	2 (4%)	2 (3%)	1 (6%)
Unknown upper	2 (4%)	1 (2%)	1 (6%)
Unknown lower	0 (0%)	1 (2%)	0 (0%)
Total	50 (100%)	58 (100%)	17 (100%)
Pearson $\chi 2$; p value	0,26 ; p =0,61		

*CFM: craniofacial microsomia, in number of affected cases.

Lower limb anomalies

There were 54 patients (7.8%) with one or multiple lower limb anomalies. Patients presented with a wide spectrum of problems ranging from hip dislocation or hip dysplasia to feet anomalies. Clubfeet were documented as equines valgus, talipes equinovarus, calcaneovalgus, talus deformity or unspecified clubfeet. The remaining group of anomalies consisted of a range of deformities including flat feet, hemihypotrophia of the leg, toe deformities, flexion contractures, and metatarsus adductus (table 6.4).

Table 6.4: *Type of lower limb anomalies*

Type of lower limb anomaly	Frequency of occurrence (n)		Number of patients affected (n)	
Total	83		54	
Clubfoot				
Quines valgus	7	(8.4%)	4	(6.1%)
Talipes quinovarus	5	(6.0%)	4	(6.1%)
Calcaneovalgus	2	(2.4%)	1	(1.5%)
Talus deformity	2	(2.4%)	1	(1.5%)
Unspecified	4	(4.8%)	2	(3.0%)
Flat feet (pes planus /plano valgus)	13	(15.7%)	9	(13.6%)
Congenital hip dislocation/ dysplasia	9	(10.8%)	7	(10.6%)
Clinodactyly	5	(6.0%)	4	(6.1%)
Syndactyly	7	(8.4%)	7	(10.6%)
Flexion contracture	3	(3.6%)	3	(4.5%)
Hemihypotrophia	7	(8.4%)	7	(10.6%)
Metatarsus adductus	2	(2.4%)	2	(3.0%)
Other	14	(16.9%)	13	(19.7%)
Unspecified	3	(3.6%)	2	(3.0%)

Sidedness of lower limb anomalies compared to the hypoplastic facial side is shown in table 6.3. Anomalies of the lower limbs occurred in 35.7% (n=15) on the same side as CFM affected side. Patients were not significantly more affected on the same side with lower limb anomalies as their CFM affected side (Pearson's $\chi 2$ (1, N=42)=0.078; p=0.78). The laterality of CFM was not correlated with the laterality of the limb anomaly (Pearson's $\chi 2$ (1, N=101)=0.26; p=0.61).

Associated factors

The odds for having limb anomalies were analysed by univariable and multivariable postadjusted logistic regressions, as shown in table 6.5. The individual O.M.E.N.S.+ categories, sex, and uni- or bilaterality of CFM were analysed separately in logistic regressions. This showed a statistically significant association between the presence of extracraniofacial anomalies and limb anomalies (odd ratio 4.81, 95% CI: 2.92 – 7.91, p=<0.001). Multicollinearity (correlation between sex, laterality, and the individual O.M.E.N.S.+ categories) was checked for the multivariable model, leading to exclusion of the Soft tissue score as this was correlated to the Mandible score

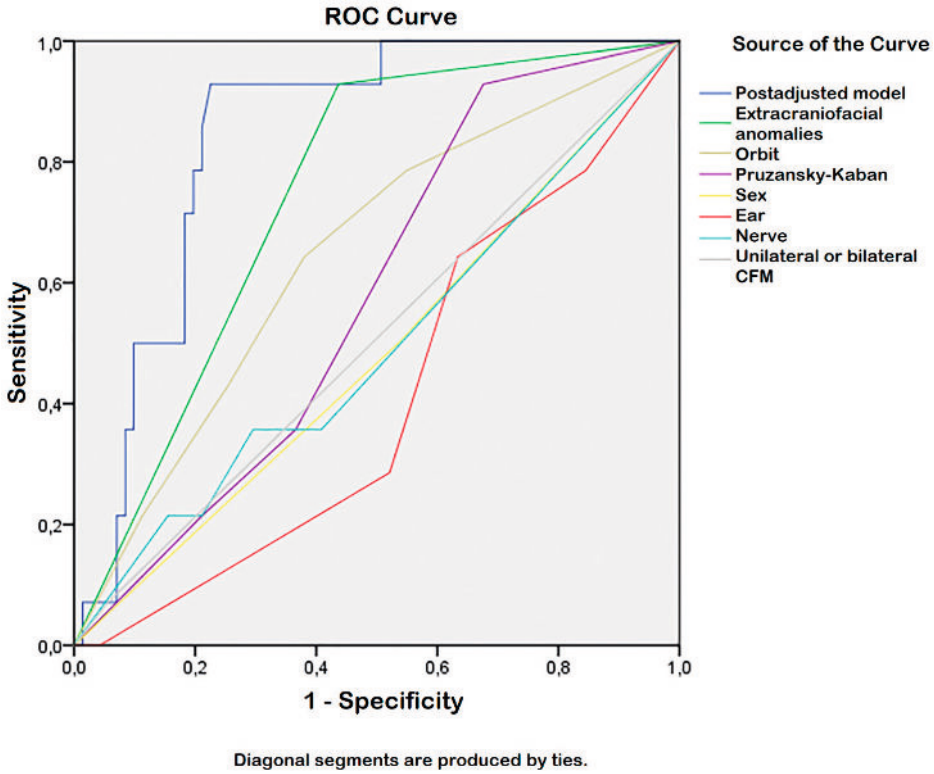
(Pearson *R:* 0,24, p=<0.001). The final multivariable model showed that the presence of extracraniofacial anomalies was significantly associated with an increased risk for limb anomalies, when adjusted for sex, laterality of CFM, and the Orbit-, Mandible-, Ear- and Nerve score (odd ratio 27.98, 95% CI: 2.68 – 291.96, p=0.005). The area under the ROC curve (AUC) was 0.84 (95% CI: 0.75 – 0.93) (figure 6.2).

Table 6.5: *Univariable and multivariable logistic regression analyses: association between patient characteristics and limb anomalies*

	Univariate logistic regression		Multivariate logistic regression model	
Covariate	OR (95% CI)	P value	OR (95% CI)	P value
Constant	-	-	0.035	0.014
Female gender	1.07 (0.73 – 1.57)	0.74	1.26 (0.31 – 5.17)	0.75
Bilateral CFM	1.43 (0.80 – 2.55)	0.23	0.28 (0.02 – 3.90)	0.34
Orbit score*	1.10 (0.93 – 1.30)	0.27	1.41 (0.86 – 2.30)	0.18
Mandible score*	0.93 (0.75 – 1.14)	0.49	0.81 (0.40 – 1.61)	0.55
Ear score*	9.94 (0.77 – 1.14)	0.50	0.64 (0.36 – 1.16)	0.14
Nerve score*	1.05 (0.76 – 1.44)	0.78	1.02 (0.67 – 1.55)	0.94
Soft Tissue score*	1.21 (0.91 – 1.61)	0.19	-	-
Extracraniofacial anomalies*#	4.81 (2.92 – 7.91)	<0.001	27.98 (2.68 – 291.96)	0.005

*Acronyms of the O.M.E.N.S.+ classification; #includes non-limb extracraniofacial anomalies only; Statistically significant p-values are bold. Goodness of model fit= 18.47, p=0.01

Figure 6.2: *ROC Curve*



Discussion

The purpose of this study was to analyze the occurrence of both upper- and lower limb anomalies in patients with CFM. We hypothesized that limb anomalies would occur more than expected in the general population. All limb anomalies were described, including prevalence and type of upper and lower limb anomalies. Furthermore, we aimed to study factors in patients with CFM that might be associated with a higher risk for limb anomalies.

A total of 18.2% (n=125) of CFM patients in this cohort were diagnosed with anomaly of the upper and/or lower limb. Ninety-two (13.4%) patients had upper limb anomalies which were mainly characterized by malformations of the radio-ulnar axis as dominant affected axis, ninety-six anomalies were observed. Associated problems with the radial ulnar axis can be severely impairing since it is crucial

for strength and grip in our daily use. Finger-anomalies were documented in thirty-three patients.

Fifty-four patients (7.8%) were had lower limb anomalies. Clubfeet were seen in 12 (1.7%) patients. The general incidence of a clubfoot is approximately 10 per 10.000 in live births for the isolated condition. However, clubfeet are frequently seen as part of a skeletal dysplasia or syndrome (152). The prevalence of clubfeet in this study is 17 times higher than in the general population.

Analysis on risk factors showed that patients with CFM and extracraniofacial anomalies have a significantly higher risk for limb anomalies (odd ratio: 27.98), adjusted for sex, laterality (uni- or bilateral CFM) and O.M.E.N.S. severity. The severity of facial hypoplasia, as displayed in the O.M.E.N.S. score, or the presence of bilateral CFM were not associated with limb anomalies. This is interesting, as previous studies on non-limb extracraniofacial anomalies in CFM showed a higher prevalence of these anomalies among more severely affected patients (6, 18, 140). The correlation between limb anomalies and other extracraniofacial anomalies could suggest a shared pathophysiological mechanism for patients with the 'expanded spectrum' of CFM. Limbs develop in the 4th week of development by formation of limb buds, initiated by undifferentiated mesenchyme and ectodermal covering (153). The origin of CFM is yet unknown. It is hypothesized that an error in neural crest cell migration might be responsible for the anomalies observed in patients with CFM (5, 6). The embryonic origin of limb anomalies in patients with CFM remains unknown.

The prevalence of 18% indicates that extremity anomalies are common in CFM patients next to other extracranial anomalies (6, 18, 140). Upper limb anomalies in the general population occur in 11.4-19.7 per 10.000 (1 in 877 to 1 in 508) new-borns according to the literature (147-149). Comparing the results of our findings with the previous studies, shows a prevalence higher than Werler et al (7% limb anomalies in a studied cohort of 239 patients) and Beleza-Meireles et al (12% limb anomalies in a studied cohort of 51 patients), but lower than Horgan et al. (20.7% in a studied cohort of 121 patients) (6, 11, 146). All three studies especially described radial ray abnormalities, including thumb hypoplasia (6, 11) and pre-axial polydactyly (11, 146). Furthermore, syndactyly and limb reduction defects were described in Werler et al. (146). Beleza-Meireles et al showed hip dysplasia to be present in two cases (11). The description of especially Werler et al. is limited as only the presence of limb

anomalies is described and divided in limb reduction defects and poly -or syndactyly without further specification. Several case reports and retrospective studies described especially radial ray problems and other observed extremity anomalies (6, 11, 141, 143-145). This retrospective cohort study presents all limb anomalies observed in different categories, by studying a large cohort of patients with CFM. All previously described limb anomalies in CFM were observed in this study too.

Incorporation in standard CFM-care

Birgfeld et al. suggested a standard protocol for CFM in 2012. A surgical and medical treatment timeline is presented for individuals with CFM (45). Treatment and evaluations are divided into different age groups with most endangering and critical triaged (i.e. breathing -and feeding first). Internal organ assessment for renal problems and cardiac anomalies are a next important step, but simultaneously all other possible anomalies should be examined. The subcategory of limb anomalies should be implemented. As limb anomalies might be minor and difficult to diagnose, evaluation and discussion of potential treatment should take place by experienced (plastic or orthopaedic) surgeons shortly after birth. Treatment and rehabilitation can contribute to improved body functions, aimed to increase the manual activity capacity to better perform daily activities. Regular check-ups for manual capacity and foot function is indicated for all patients with limb anomalies.

Limitations

This study has several limitations. First of all, no age limit was used to include patients with CFM. This is necessary to avoid selection bias, but also bears the risk of information bias. The retrospective nature of this study increases the risk for incomplete data, which is even higher in older patients. Numbers of extremity anomalies are possibly higher than we have found in our study. A prospective study would be able to determine the precise prevalence of limb anomalies in CFM.

As already discussed in the timeline created by Birgfield et al. (45), patients with CFM can present with numerous difficulties that might require attention first. Subtle and possible insignificant abnormalities can therefore be missed and not be documented in the patient files. This might also have led to an underestimation of the observed limb anomalies. However, knowing that limb anomalies occur in a substantial number of patients with CFM, it is clinically important to document all anomalies to monitor motoric skills and progress.

Conclusion

More than one in six patients with CFM showed limb anomalies. Patients with other extracraniofacial anomalies are at increased risk for limb anomalies. No correlations between facial phenotype and limb anomalies were found. As a significant number of patients with CFM experience limb anomalies, clinical awareness for these anomalies is warranted.

7

Velopharyngeal dysfunction and speech related characteristics in craniofacial microsomia

a retrospective analysis of 223 patients

Based on:

Ruben W. Renkema, Karan R.R. Ramdat Misier, Wietse Rooijers, Antonia Osolos, Henriëtte H.W. de Gier, Henriëtte G. Poldermans, Bonnie L. Padwa, David J. Dunaway, Cornelia J.J.M. Caron, Maarten J. Koudstaal. Velopharyngeal dysfunction and speech-related characteristics in craniofacial microsomia: a retrospective analysis of 223 patients, International Journal of Oral and Maxillofacial Surgery. 2024 Apr 16:S0901-5027(24)00095-X. doi: 10.1016/j.ijom.2024.04.001. Epub ahead of print. PMID: 38631989.

Abstract

The aims of this study were to document the prevalence, severity, and risk factors of velopharyngeal dysfunction (VPD) in craniofacial microsomia (CFM) and to analyse differences in VPD-related speech characteristics between CFM patients without cleft lip and/or palate (CL/P), CFM patients with CL/P, and CL/P patients without CFM (control). A total of 223 patients with CFM were included, of whom 59 had a CL/P. Thirty-four CFM patients had VPD, including 20 with a CL/P. The control group of 34 non-CFM CL/P patients was included to study differences in speech characteristics. VPD was significantly more prevalent in CFM with CL/P than in CFM without CL/P (odds ratio (OR) 4.1, 95% confidence interval (CI) 1.9–8.7; P < 0.001). Multivariate logistic regression showed a significant association between CL/P and VPD in CFM patients (OR 7.4, 95% CI 2.1–26.3; p=0.002). The presence of VPD was not associated with sex, or the laterality or severity of CFM. Speech problems related to VPD appeared to be similar among the different groups. As 15.2% of all CFM patients and 8.5% of CFM patients without a CL/P had VPD, it is proposed that all patients with CFM, with or without CL/P, should be assessed by a speech and language therapist for the potential risk of VPD.

Introduction

Craniofacial microsomia (CFM) is a congenital anomaly characterized by a unilateral or bilateral heterogeneous underdevelopment of the facial structures derived from the first and second pharyngeal arches. Structures including the mandible, maxilla, ears, facial soft tissues, and facial nerves may be affected (138). Incidence rates vary between 1:3500 and 1:26000 live births, making it the second most common craniofacial deformity following cleft lip and palate (1, 154, 155). The anatomical variations may cause functional problems such as breathing, feeding, or speech difficulties, including velopharyngeal dysfunction (VPD)(156-162). VPD is defined as the inability to accomplish adequate closure of the velopharyngeal sphincter. During speech, adequate velopharyngeal sphincter closure is essential for separating the oral and nasal cavities in order to achieve the proper airstream during nasal consonants, and for coupling the oral and nasal cavities to allow for build-up of oral pressure for oral plosives and fricatives (163, 164). Not achieving full velopharyngeal closure may therefore result in audible hypernasal speech, decreased speech intelligibility, nasal air emission, compensatory misarticulations, and facial grimacing. Secondary effects include nasal regurgitation of liquids and solids and swallowing difficulties (164).

Multiple modalities can be used to diagnose and classify the severity of VPD. Direct observation of the velopharyngeal valve by means of multi-view videofluoroscopy or nasopharyngoscopy are considered the standard methods for the assessment of VPD (165). Additionally, standardized speech assessment tools, such as the Pittsburgh Weighted Speech Scale (PWSS) and the Great Ormond Street Speech Assessment (GOS.SP.ASS.), are available to assess and classify speech characteristics related to VPD (166, 167).

The relationship between VPD and CFM has been researched in two studies with rather small sample sizes. Luce et al.(161) reported a VPD prevalence of 33.3% in 18 CFM patients, having excluded cleft palate patients, while Funayama et al.(42) reported a prevalence of 14.6% in 48 non-cleft palate patients and 100% in four cleft palate patients. The aetiology of VPD in CFM is yet unknown. In patients with a cleft palate, a shortage of tissue could lead to the development of VPD. In CFM patients without cleft palate, it is hypothesized that differences in tissue or innervation of the soft palate might cause VPD. Further research is needed to assess the

risk factors of VPD in CFM. As the pathophysiological mechanism of VPD in CFM patients without a cleft palate may differ from that in patients with a cleft palate, studies on potential differences in characteristics between VPD in cleft palate patients and CFM patients are needed.

The aims of this study were to document the prevalence and severity of VPD in a large cohort of patients with CFM, analyse differences in VPD-related speech characteristics in both CFM and non-CFM patients with and without cleft lip and/or palate (CL/P), and identify those patients with CFM who are at greater risk of developing an impaired velopharyngeal mechanism.

Methods

This retrospective study describes the clinical characteristics of patients diagnosed with CFM at the craniofacial centres of Boston Children's Hospital (BCH; Boston, MA, USA) and Great Ormond Street Hospital (GOSH; London, UK). A control group of non-syndromic CL/P patients seen at Sophia Children's Hospital, Erasmus Medical Center (EMC; Rotterdam, The Netherlands) was also included. The study was approved by the institutional review boards at BCH (X05-08-058), GOSH (14 DS25), and EMC (MEC-2013-575). Patients with CFM who had a confirmed diagnosis by either clinical photographs and/or radiographic imaging and who were examined by a speech and language pathologist were included. Patients with missing charts or a discrepancy regarding their diagnosis were excluded. The control group included non-syndromic CL/P patients who were examined by a speech and language therapist; this group was included to compare speech characteristics in patients with VPD. The number of included patients in this control group matched the number of CFM patients with VPD.

Data extracted from the patients' medical records included sex, age, laterality of CFM, Pruzansky–Kaban classification, O.M.E.N.S. classification, length of follow-up, presence of a palatal cleft, speech examinations by a speech and language pathologist, deployment of diagnostic VPD tests, and indications for VPD surgery.

The O.M.E.N.S. classification was used to grade the facial manifestations of CFM18. With this classification, CFM manifestations are divided into five groups: O, orbital distortion; M, mandibular hypoplasia; E, ear anomalies; N, facial nerve involvement;

S, soft tissue deficiency. Each category is graded on a numerical scale from 0 to 4, with 0 indicating no malformations and 4 indicating the most severe malformations. This study applied groups O, E, N, and S of the O.M.E.N.S. classification.

Mandibular manifestations of CFM were described using the Pruzansky classification, modified by Kaban et al. (21, 22). This classification divides CFM into four grades, based on the radiographic severity of the mandibular hypoplasia in CFM patients. Type I consists of a small ramus and temporomandibular joint (TMJ) with normal identifiable anatomy. Type IIa consists of an abnormally shaped and sized ramus, where the deformed TMJ is still in an acceptable anatomical position, while type IIb is characterized by the former but with an aberrant TMJ position. Type III is characterized by a completely absent mandibular ramus, TMJ, and condyle.

Patients underwent speech evaluation by a qualified speech and language pathologist, applying the PWSS or GOS.SP.ASS. for the assessment of VPD and associated speech characteristics whenever VPD was suspected. Both scales assess multiple factors that may be present during compromised speech, including nasal air emission, facial grimacing, hypo- or hypernasality, and problems with phonation and articulation. Focus was placed on VPD-related nasal resonance and compensatory articulation patterns in the data extraction. VPD was diagnosed either by multi-view videofluoroscopy or nasoendoscopy. The prevalence of VPD in the patient population and the speech characteristics of patients diagnosed with VPD were analysed. Speech intelligibility was based on the Meijer scale (168). This scale grades speech intelligibility from 1 to 5, where 1 is normal, easily understandable speech; 2 is speech that differs from peers, is understandable, and does not lead to comments from others; 3 is speech that differs from peers, is understandable but does lead to comments from others; 4 is speech that is difficult to understand; 5 is speech that is not understandable. Furthermore, risk factors for VPD were identified based on the O.M.E.N.S. and Pruzansky–Kaban characteristics of patients with and without VPD.

Statistical analysis

The statistical analyses were performed using IBM SPSS Statistics for Windows version 24.0 (IBM Corp., Armonk, NY, USA). Descriptive analyses were initially performed. A $\chi 2$ test was used to assess the correlation between laterality of the CFM and the cleft, and the presence of VPD. The associations between sex, laterality, O.M.E.N.S. categories, and VPD were assessed by multivariable binary logistic re-

gression analysis. Multicollinearity was examined and components of the regression analysis were excluded if correlated.

Results

A total of 559 patient with CFM were identified, of whom 336 were excluded as they did not fulfil the inclusion criteria (i.e., no reported examination by a speech and language pathologist), leaving 223 patients for further analysis. Two groups of patients were identified: CFM patients without a CL/P (n=164; 73.5%) and CFM patients with a CL/P (n=59; 26.5%) (table 7.1).

***Table 7.1:** Patient demographics*

	CFM without CL/P		CFM with CL/P		Control (CL/P)	
	N	%	N	%	N	%
Total	164		59		34	
Sex						
Male	95	57.9%	42	71.2%	21	61.8%
Female	69	42.1%	17	28.8%	13	38.2%
Laterality CFM						
Unilateral	132	80.5%	46	78.0%	NA	
Bilateral	32	19.5%	13	22.0%	NA	
Type cleft						
CLP	NA		29	49.2%	28	82.4%
CP	NA		30	50.8%	6	17.6%
Unilateral cleft	NA		37	62.7%	25	73.5%
Bilateral cleft	NA		22	37.3%	9	26.5%
Naso- or videoscopy	21	12.8%	25	42.3%	34	100%
VPD	14	8.5%	20	33.9%	34	100%

CFM: craniofacial microsomia; CL/P: cleft lip and/or palate; CLP: cleft lip and palate; CP: cleft palate; VPD: velopharyngeal insufficiency; NA: not applicable

Of the 223 patients, 137 (61.4%) were male and 86 (38.6%) were female. Most patients had unilateral CFM (n=178; 79.8%), while approximately a fifth (n=45; 20.2%) were bilaterally affected. Fifty-nine of the 223 patients (26.5%) had CL/P, of whom 29 had a cleft lip and palate (CLP) and 30 had a cleft palate (CP).

Of the 223 patients with CFM, 46 (20.6%) underwent further examination to assess the presence of VPD. Twenty-five of these patients had CL/P. Most of these patients (n=28) were further assessed by multi-view videofluoroscopy, while six were examined by nasoendoscopy and nine by both nasoendoscopy and videofluoroscopy; the diagnostic modality was unknown for three of the patients who were suspected to have VPD. In total, 34 of the 46 examined patients (73.9%) were diagnosed with VPD.

Of the 34 CFM patients with VPD, 15 had a CP and five had a CLP. In three patients, orthognathic surgery was performed before the VPD was diagnosed; all three underwent mandibular distraction surgery. VPD was significantly more prevalent in CFM patients with CL/P than in CFM patients without CL/P (odds ratio (OR) 4.1, 95% confidence interval (CI) 1.9–8.7; Pearson $\chi 2$ (df=1, n=223)=14.461, P < 0.001). Multivariate logistic regression showed a significant association between CL/P and VPD, independent of sex, laterality of CFM, and the severity of CFM as determined using the O.M.E.N.S. and Pruzansky–Kaban classification (B=1.997; OR 7.4, 95% CI 2.1–26.3; p=0.002). The presence of VPD was not associated with sex, laterality of CFM, or the severity of CFM (table 7.1 & 7.2). There was no statistical difference in the prevalence of VPD in unilateral versus bilateral CFM (Pearson's $\chi 2$ (df=1, n=223)=0.756, p=0.388).

Table 7.2: *Multivariate binary logistic regression analysis for the relationship between the O.M.E.N.S.-classification and the presence of VPD*

	VPD					VPD					VPD					VPD					VPD				
	Yes		No			Yes		No			Yes		No			Yes		No			Yes		No		
	N	%	N	%		N	%	N	%		N	%	N	%		N	%	N	%		N	%	N	%	
O0	17	50.0%	107	56.6%	M0*	0		0		E0	3	8.8%	24	12.7%	N0	11	32.4%	55	29.1%	S0	4	11.8%	28	14.8%	
O1	10	29.4%	32	16.9%	M1*	4	11.8%	33	17.5%	E1	3	8.8%	27	14.3%	N1	4	11.8%	17	14.8%	S1	7	20.6%	59	31.2%	
O2	0		15	7.9%	M2a*	10	29.4%	39	20.6%	E2	2	5.9%	22	11.6%	N2	2	5.9%	26	13.8%	S2	14	41.2%	55	29.1%	
O3	1	2.9%	11	5.8%	M2b*	12	35.3%	51	27.0%	E3	22	64.7%	97	51.3%	N3	1	2.9%	14	7.4%	S3	4	11.8%	21	11.1%	
O4	2	5.9%	5	2.6%	M3*	3	8.8%	38	20.1%	E4	2	5.9%	4	2.1%	N4	3	8.8%	3	1.6%						
Unknown	4	11.8%	19	10.1%	Unknown	5	14.7%	28	14.8%	Unknown	2	5.9%	15	17.9%	Unknown	13	38.2%	74	39.2%	Unknown	5	14.7%	26	13.8%	
B-coefficient	-0.396					-0.538					0.035					-0.024					0.370				
OR	0.673					0.584					1.036					0.977					1.448				
95% CI	0.296 - 1.532					0.294 - 1.159					0.632 - 1.697					0.632 - 1.596					0.647 - 3.243				
P-value	0.345					0.124					0.888					0.925					0.368				

* O.M.E.N.S.; M score is replaced with Pruzanksy-Kaban classification

VPD: velopharyngeal insufficiency; OR: odds ratio; 95% CI: 95% confidence interval

For the purpose of subgroup analyses, a control group of 34 patients with CL/P and VPD without CFM was included. This group had a similar sex distribution to the CFM group, with 21 (61.8%) male patients and 13 (38.2%) female patients (Pearson $\chi 2$ (df=1, n=68)=0.442, p=0.609) (table 7.1). Twenty-eight (82.4%) of these patients had a CLP, while six (17.6%) had a CP. All of these patients were diagnosed with VPD based on nasoendoscopy. Speech assessments (i.e., PWSS, GOS.SP.ASS.) were performed in both groups, at a mean age of 8.77 years (standard deviation (SD) 4.87, range 2.02–21.37 years) in the CFM group and 6.87 years (SD 5.38, range 0.48–21.75 years) in the non-syndromic CL/P group. Outcomes of the speech assessment for the different groups are shown in table 7.3.

Table 7.3. Speech characteristics in patients with VPD

		CFM without CL/P		CFM with CL/P		Control (CL/P)	
		N (14)	%	N (20)	%	N (34)	%
Articulation disorder	Present	3	21%	7	35%	33	97%
	Absent	11	79%	13	65%	1	3%
Facial grimacing	Present	2	14%	4	20%	19	56%
	Absent	12	86%	16	80%	15	44%
Nasality	Hyper	6	43%	13	65%	28	82%
	Normal	5	36%	4	20%	0	0%
	Hypo	1	7%	0	0%	0	0%
	Mixed	2	14%	3	15%	6	18%
Hypernasality[1]	No	6	43%	5	25%	0	0%
	Mild	5	36%	6	30%	2	6%
	Moderate	2	14%	4	20%	14	41%
	Severe	1	7%	5	25%	18	53%
Speech intelligibility[2]	Unknown	6	42%	10	50%	0	0%
	1	1	7%	3	15%	0	0%
	2	1	7%	0	0%	3	9%
	3	3	22%	2	10%	10	29%
	4	3	22%	4	20%	19	56%
	5	0	0%	1	5%	2	6%

CL/P: cleft lip and/or palate. Percentages in respect to total number of patients with VPD per group.
[1] degree of hypernasality in group with hypernasality and mixed nasality. A single patient with CFM and CL/P with hypernasality with unknown degree. [2] speech intelligibility according the Meijer scale

Articulation disorders were caused by compensation strategies in two patients with CFM without CL/P, seven patients with CFM and CL/P, and 33 patients with non-syndromic CL/P. Compensation strategies consisted mostly of nasal fricatives and substitutions in both the CFM patients with CL/P (five of the seven patients) and the non-syndromic CL/P patients (all 33 patients), whereas none of the patients with CFM without CL/P used nasal fricatives and substitutions. One patient with CFM without CL/P had an articulation disorder caused by both compensation strategies and developmental problems. In contrast, articulation disorders were not caused by developmental problems in the other groups.

Discussion

The aims of this study were to determine the prevalence of VPD and associated speech disorders in CFM, analyse differences in VPD-related speech characteristics in both CFM and non-CFM patients with and without CL/P, and to identify patients at risk of VPD. It was hypothesized that CFM patients are at risk of VPD, even in the absence of a CL/P, due to underdevelopment of the soft tissues of the velopharyngeal sphincter and partial paralysis of the velopharyngeal musculature, and that the prevalence of VPD would be greater in patients who are more severely affected by CFM.

Thirty-four of 223 patients (15.2%) were diagnosed with VPD, which is on the lower end of the 14–33% prevalence rates reported in previous research (42, 162, 169, 170). However, these studies described relatively small patient populations, and the inclusion criteria were not always clearly stated, making them prone to the risk of selection bias. The current study included patients from a relatively large patient cohort, but excluded patients who were not examined by a speech and language pathologist. The prevalence reported in this study could therefore be an overestimation.

The associated speech anomalies found consisted of grimacing and articulation errors, which were the result of compensation strategies, ultimately resulting in reduced speech intelligibility in 13 patients. Furthermore, 20 of 34 patients with VPD also had CL/P. Patients with CFM and CL/P used more VPD-related compensatory articulations, such as nasal fricatives, substitutions, and glottal articulation in comparison to patients without CL/P. Moreover, patients with CFM and CL/P were

four times more likely to have VPD compared to patients without CL/P. Interestingly, a substantial proportion of patients with CFM without CL/P experienced some form of open nasality. The speech-related symptoms of VPD in both the CFM CL/P group and the CFM non-CL/P group appear to be similar.

Interestingly, 8.5% of the patients with CFM but without a CL/P in this study cohort were diagnosed with VPD. While a shortage of tissue plays a role in the development of VPD in cleft patients, the origin of VPD in non-cleft patients is less clear. The relationship between VPD and CFM has been described by several authors in various patient populations (1, 42, 161, 162, 169). In order to understand this relationship, a thorough understanding of the aetiology of CFM and VPD is essential. As mentioned before, CFM is the result of a congenital underdevelopment of structures derived from the first and second pharyngeal arches, which may include muscles and cranial nerves involved in velopharyngeal closure (1, 42, 162). Velopharyngeal closure is achieved by closure of the velopharyngeal sphincter, which consists of the tensor veli palatini, levator veli palatini, musculus uvulae, superior pharyngeal constrictor, palatopharyngeus, palatoglossus, and salpingopharyngeus muscles (171). The tensor and levator veli palatini muscles are derived from the first and second pharyngeal arches, respectively. Based on its embryological origins, at least part of the velopharyngeal sphincter may thus be hypoplastic in CFM (42).

Furthermore, it has been proposed that VPD in CFM constitutes a neurological disorder, resulting in (hemi-)palatal palsy or paralysis of the levator veli palatini muscles (161, 172, 173). Faulty sensory innervation of the muscles that contribute to the velopharyngeal sphincter may cause speech anomalies and VPD (171, 174). The soft palate is primarily innervated by the trigeminal nerve, derived from the first pharyngeal arch, and the pharyngeal plexus nerves. The tensor veli palatini muscle is innervated by the mandibular nerve, a branch of the trigeminal nerve. Partial paralysis of the velopharyngeal sphincter has indeed been observed in CFM, both in patients with and without CL/P (42, 161). However, not all patients with palatal paresis exhibit evidence of VPD (1). As the pathophysiological mechanism of VPD in (non-cleft) CFM patients is likely to be different from that in non-CFM patients with CL/P, the prognoses and treatment outcomes might be different. Future studies on the pathophysiology and treatment outcomes of VPD in (non-cleft) CFM patients could help to improve the quality of care for these patients. This might

be performed with (non-invasive) electromyography or by comparing treatment outcomes of non-CL/P patients with CL/P patients.

Funayama et al. (42) and Luce et al. (161) reported a significant association between VPD and more severe forms of mandibular and soft tissue hypoplasia. However, this study did not confirm these associations in the included patient cohort. This may be attributed to differences in methodology between the present study and that of Funayama et al. (42); however, the lack of association may also be explained by the uneven involvement of anatomical structures deriving from the first and second pharyngeal arches in CFM. Consequently, the underlying pathology that causes a severely hypoplastic mandible does not necessarily lead to a severely hypoplastic velopharyngeal sphincter. Rather, different clusters of anomalies within the CFM spectrum exist, as has been shown by Caron et al. (18).

The results of this study are limited by several factors, which are mostly inherent to the retrospective study design. First of all, only 20.6% of the patients with CFM who were assessed by a speech and language pathologist were examined using videofluoroscopy and/or nasoendoscopy. Velopharyngeal closure anomalies may therefore be underreported. However, all patients were examined at tertiary care centres by multidisciplinary teams with ample experience in speech, language, and velopharyngeal closure anomalies. Patients were further assessed when velopharyngeal closure anomalies were suspected. The degree of underreporting of clinically significant anomalies is therefore expected to be limited. Nevertheless, the assessment of, for example, the degree of hypernasality is subjective and has a poor reputation for consistency and inter-rater reliability (175). The results should be interpreted with this in mind.

Second, the aim was not to report closed nasality, as this is not related to VPD. Due to the retrospective nature of this study, the type of nasality could not always be determined. As all patients were examined by experienced speech and language therapists, this potential risk of bias is believed to be minimal. Furthermore, closed nasality was incidentally specifically mentioned in the medical files and thus excluded by the authors.

Third, the results are limited by the level of detail displayed in the medical files. Major anomalies were presumably recorded due to their clinical significance. How-

ever, subtle or minor anomalies may not have been recorded due to perceived insignificance.

In conclusion, this study described the prevalence of velopharyngeal dysfunction and associated speech anomalies in a large cohort of patients with craniofacial microsomia. Both patients with and without cleft lip and/or palate exhibited velopharyngeal dysfunction, although patients with cleft lip and/or palate were found to be significantly more at risk of velopharyngeal dysfunction. No association was found between the presence of velopharyngeal dysfunction and the severity of craniofacial microsomia as derived from the O.M.E.N.S. and Pruzansky–Kaban classifications. As velopharyngeal dysfunction is common in craniofacial microsomia, it is proposed that all patients with craniofacial microsomia, with or without cleft lip and/or palate, should be assessed at least once by a speech and language therapist for the potential risk of velopharyngeal dysfunction.

8

Evaluation of research diagnostic criteria in craniofacial microsomia

Based on:
Ruben W. Renkema, Vera de Vreugt, Carrie L. Heike, Bonnie L. Padwa, Christopher R. Forrest, David J. Dunaway, Eppo B. Wolvius, Cornelia J.J.M. Caron, Maarten J. Koudstaal. Evaluation of Research Diagnostic Criteria in Craniofacial Microsomia, Journal of Craniofacial Surgery. 2023 Sep 1;34(6):1780-1783. doi: 10.1097/SCS.0000000000009446. Epub 2023 Jun 2. PMID: 37264504; PMCID: PMC10445631.

Abstract

Characteristics of patients with craniofacial microsomia (CFM) vary in type and severity. The diagnosis is based on phenotypical assessment and no consensus on standardized clinical diagnostic criteria is available. The use of diagnostic criteria could improve research and communication among patients and healthcare professionals. Two sets of phenotypic criteria for research were independently developed and based on multidisciplinary consensus: the FACIAL and ICHOM criteria. This study aimed to assess the sensitivity of both criteria with an existing global multicenter database of patients with CFM and study the characteristics of patients that do not meet the criteria. A total of 730 patients with CFM from were included. Characteristics of the patients were extracted, and severity was graded using the O.M.E.N.S. and Pruzansky-Kaban classification. The sensitivity of the FACIAL and ICHOM was respectively 99.6% and 94.4%. The Cohen's kappa of 0.38 indicated a fair agreement between both criteria. Patients that did not fulfill the FACIAL criteria had facial asymmetry without additional features. It can be concluded that the FACIAL and ICHOM criteria are accurate criteria to describe patients with CFM. Both criteria could be useful for future studies on CFM to create comparable and reproducible outcomes.

Introduction

Craniofacial microsomia (CFM) is a clinical diagnosis based on the presence of facial features that are commonly associated with this congenital condition. This includes uni- or bilateral hypoplasia of facial structures related to the first and second pharyngeal arch, such as the mandible, orbit, ears, facial nerve and soft tissue (1, 17, 44). The type and severity of affected structures varies largely among patients. Different diagnostic terms have been used to describe patients with these features, including Goldenhar syndrome, hemifacial microsomia and oculo-auriculo-vertebral spectrum. Research has shown however that the phenotypes of patients who were diagnosed with these conditions do not meaningfully differ from those diagnosed with CFM (15, 18, 19). It remains debated in literature whether isolated microtia is a distinct entity or minor variant of CFM (4, 176, 177). The wide phenotypic and etiologic heterogeneity of CFM makes it difficult to establish standardized diagnostic criteria and evaluate treatment outcomes for large populations (18, 178).

Establishing diagnostic criteria can be used to improve clinical care to guide individual patients, improve communication among healthcare providers and set standards for research (179). Diagnostic criteria are a set of sings and/or symptoms that reflect the different features of any disease to accurately identify patients with the disorder (179). Such criteria are broad, to be able to cover the heterogeneity of clinical phenotypes. Nonetheless, development of such criteria in CFM is challenging due to the variation of clinical phenotypes, low prevalence and potential overlap with other craniofacial syndromes, such as Treacher Collins, Nager and CHARGE syndromes.

In recent years, two sets of phenotypic criteria for CFM have been developed for clinical research. Each set was developed independently and based on consensus among distinct multidisciplinary health care providers with expertise treating patients with CFM and researchers. The multicenter consortium 'Facial Asymmetry Collaborative for Interdisciplinary Assessment and Learning (FACIAL)', which started in 2009, is a network established to develop standardized definitions and study protocols to facilitate clinical research on CFM. This collaborative created eligibility diagnostic criteria for research based on the different CFM features (29). A similar initiative was done in 2017 by the 'International Consortium for Health Outcomes

Measurement (ICHOM)', which aims to implement a global standard set to obtain comparable data for benchmarking and research (28).

Comparison of these criteria might help implementation of the standards on a larger scale and improve comparison of research. This study aims to evaluate the FACIAL and ICHOM CFM criteria with an existing database of patients with CFM to research the sensitivity of the criteria and study the characteristics of CFM patients that do not reach the criteria.

Method

A global multicenter database including patients with CFM diagnosed at the craniofacial centers of Erasmus University Hospital, Rotterdam, The Netherlands, Great Ormond Street Hospital, London, United Kingdom, Boston Children's Hospital, Boston, U.S.A., and the Hospital for Sick Kids in Toronto, Canada was used for this study (Institutional Review Boards approval: Rotterdam: MEC-2012-248; London: 14 DS25; Boston: X05-08-058; Toronto: 1000053298). Patients who presented at one of the craniofacial units from January 1980 until January 2016 and received the clinical diagnosis CFM were included in the database, which was setup in 2016. Patients were identified using a search strategy on facial asymmetry, mandibular hypoplasia or microtia in the electronic patient management systems of all hospitals. Additionally, all patients seen at the craniofacial outpatient clinics were checked to identify patients with CFM. Patients were included after they received the clinical diagnosis CFM after clinical assessment by an experienced craniofacial team followed by verification by peers (C.J.J.M.C and B.P.) using clinical photographs, panoramic X-rays and/or computed tomography scans of the head. Patients with isolated anomalies, such as isolated microtia or isolated mandibular hypoplasia that did clinically not receive the diagnosis CFM were not included. Review of medical charts was performed and data on date of birth, sex, laterality and characteristics of facial features and extracraniofacial anomalies was extracted.

The type and severity of the affected tissues was scored according to the PAT-CFM as described by Birgfeld et al. which is based on the O.M.E.N.S.+ and Pruzansky-Kaban classification (6, 20, 25). This classification scores the degree of underdevelopment of the Orbit (O), Mandible (M), Ear (E), Facial Nerve (N) and Soft tissue (S) based clinical examination or facial photographs. The '+' stands for the presence

of extracraniofacial anomalies, including vertebral, cardiac or renal anomalies. The Pruzansky-Kaban classification is based on radiographic assessment and grades the severity of mandibular and temporomandibular joint hypoplasia in type I, IIA, IIB and III (21, 23, 34). Patients were considered eligible for this study if at least four items of the O.M.E.N.S. classification could be scored, in which the M score could be both the soft tissue PAT-CFM 'M' or the Pruzansky-Kaban classification.

The consensus-based diagnostic criteria for CFM that are examined were compiled by the FACIAL network and the ICHOM CFM group (28, 29). The FACIAL criteria for CFM include one or more of the following diagnoses (table 8.1): 1) microtia or anotia; 2) facial asymmetry and preauricular tag; 3) facial asymmetry and facial tag; 4) facial asymmetry and epibulbar dermoid; 5) facial asymmetry and lateral oral cleft 6) preauricular tag and epibulbar dermoid; 7) preauricular tag and lateral oral cleft; 8) facial tag and epibulbar dermoid; 9) lateral oral cleft and epibulbar dermoid. Facial asymmetry was in this study defined as skeletal hypoplasia, facial nerve deficit and/or soft tissue hypoplasia. Patients with other syndromic diagnosis or chromosomal abnormalities are excluded. The ICHOM CFM diagnostic criteria are based on a combination of 2 major criteria, or 1 major + 1 minor criteria, or 3+ minor criteria (table 8.2) (28). Major criteria are 1) mandibular hypoplasia; 2) microtia; 3) orbital/facial bone hypoplasia; 4) asymmetric facial movement. Minor criteria include 1) facial soft tissue deficiency; 2) preauricular tags; 3) lateral oral cleft; 4) clefting; 5) epibulbar dermoids; 6) hemivertebrae. Patients with other craniofacial syndromes or isolated typical Tessier clefting are also excluded in these criteria.

The main outcome of this study is to assess the sensitivity of both sets of CFM criteria (FACIAL and ICHOM) and the characteristics of patients who do not fulfil to either the FACIAL or ICHOM CFM criteria. The CFM criteria will be applied on the clinical characteristics according to the PAT-CFM of all patients with CFM included in our database. Patients with other craniofacial syndromes are excluded in both criteria and these were not included in the study.

Table 8.1: *FACIAL diagnostic criteria*

FACIAL Inclusion criteria: (³ 1 of the diagnoses below)
1. Microtia
2. Anotia
3. Facial asymmetry + Preauricular tag
4. Facial asymmetry + Facial tag
5. Facial asymmetry + Epibulbar dermoid
6. Facial asymmetry + Lateral oral cleft
7. Preauricular tag + Epibulbar dermoid
8. Preauricular tag + Lateral oral cleft
9. Facial tag + Epibulbar dermoid
10. Lateral oral cleft + Epibulbar dermoid
Exclusion criteria:
1. Other syndromic diagnosis (e.g. Treacher Collins syndrome) with microtia and/or underdevelopment of the jaw
2. Abnormal genetic studies

Table 8.2: ICHOM CFM diagnostic criteria

Conditions:	2 major criteria		1 major + 1 minor criteria or	3+ minor criteria		
Major Criteria:	Mandibular hypoplasia	Microtia	Orbital/facial bone hypoplasia	Asymmetric facial movement		
Minor criteria:	Facial soft tissue deficiency	Pre-auricular tags	Lateral oral cleft	Clefting	Epibulbar dermoids	Hemivertebrae
Exclusion criteria:	Mandibulofacial dysostosis with microcephaly, Townes-Brocks Syndrome, Treacher Collins Syndrome, Auriculocondylar Syndrome, Bixler Syndrome, Branchiootorenal (BOR) Syndrome, CHARGE Syndrome, Miller Syndrome, Nager Syndrome, Oculoauriculofrontonasal Syndrome, Parry Rhomborg, Branchiooculofacial Syndromes (BOFS), isolated typical Tessier clefting (with no associated facial hypoplasia)					

Statistical analysis

Statistical analyses were performed using SPSS (2011, SPSS Inc., Chicago, IL, USA). Descriptive statistics were initially performed. A Cohen's Kappa statistic was used to compare the ICHOM CFM diagnostic criteria to the FACIAL diagnostic criteria (180). This was interpreted following the guidelines of Landis and Koch (180). The effect of missing data on the outcomes was checked using multiple imputation analysis. If no effect was present, multiple imputation was not used.

Results

Study population

The clinical database included 730 patients with CFM (table 8.3). Patients were diagnosed at the Boston Children's Hospital (35%, n=253), Great Ormond Street Hospital London (34%, n=246), Erasmus Medical Center Rotterdam (22%, n=166), and The Hospital for Sick Kids Toronto (9%, n=65). It included more males (55%) than females (45%). Unilateral CFM (88%) was more common than bilateral CFM (12%). Patients with unilateral CFM had more right side (57%) than left side (43%) facial involvement. Among the patients with a skin tag (n=267), 216 (81%) patients had a facial tag, and 51 (19%) patients had a preauricular tag. Cleft palate was present in 98 (13%) patients, hemivertebrae in 65 (9%) patients, epibulbar dermoids in 84 (12%) patients and lateral oral cleft in 143 patients (20%).

***Table 8.3:** Characteristics of the complete study sample.*

Variable N	Total study sample (730)		FACIAL Criteria (689)		ICHOM Criteria (727)	
Male	398	(54.5%)	374	(54.3%)	396	(54.5%)
Female	332	(45.5%)	315	(45.7%)	331	(45.5%)
Bilateral CFM (yes)	98	(12.3%)	93	(12.9%)	98	(12.6)
Unilateral CFM	640	(87.7%)	603	(87.5%)	637	(87.6%)
Right side	364	(56.9%)	345	(57.2%)	361	(56.7%)
Left side	276	(43.1%)	258	(42.8%)	276	(43.3%)
Hemivertebrae (Yes)	65	(8.9%)	63	(9.1%)	63	(8.9%)
Cleft Palate (Yes)	98	(13.4%)	90	(13.1%)	98	(13.5%)
Skin tag	216	(29.6%)	216	(31.3%)	214	(29.4%)
Pre auricular tag	51	(7.0%)	51	(7.4%)	51	(7.0%)
Epibulbair dermoid (yes)	84	(11.5%)	84	(12.2%)	84	(11.6%)

***Table 8.3:** Continued.*

Variable N	Total study sample (730)	FACIAL Criteria (689)	ICHOM Criteria (727)
Lateral oral cleft	143 (19.6%)	143 (20.8%)	142 (19.5%)
Unilateral	105 (14.4%)	105 (15.2%)	104 (14.3%)
Bilateral	9 (1.2%)	9 (1.3%)	9 (1.2%)
Side unknown	29 (4.0%)	29 (4.2%)	29 (4.0%)
Mandibular hypoplasia (yes)	705 (98.3%)	664 (98.2%)	703 (98.3%)
Microtia or anotia (yes)	613 (85.6%)	613 (89.5%)	613 (86.0%)
Orbital bone hypoplasia (yes)	342 (46.9%)	323 (46.9%)	342 (47.1%)
Asymmetric facial movement (yes)	160 (43.1%)	150 (43.7%)	160 (43.4%)
Soft tissue deficiency (yes)	612 (84.8%)	578 (84.9%)	611 (84.9%)

FACIAL diagnostic criteria

The FACIAL criteria were met by 689 patients, corresponding with a sensitivity of 94.4% A total of 41 patients did not meet these criteria and the false negative rate was 5.6% (table 8.4). All patients that did not meet the FACIAL diagnostic criteria (n=41) had facial asymmetry without other additional features that are included in the FACIAL criteria. As displayed in table 8.5, most patients fulfilled the FACIAL criteria based on the presence of microtia or anotia (89%). Ten percent of the patients (n=72) that met the FACIAL criteria did not have microtia or anotia. The presence of facial asymmetry with facial tags (31.3%) or with lateral oral cleft (20.8%) were other common characteristics to meet the FACIAL criteria, whereas 1.6% to 5.4% of the patients met the criteria without the presence of facial asymmetry (table 8.5).

***Table 8.4:** Sensitivity and false negative rate FACIAL diagnostic criteria.*

	CFM		No CFM	
Patients that meet FACIAL criteria	689	(94.4%)	0	689
Patients that do not meet FACIAL criteria	41	(5.6%)	0	41
	730	(100%)	0	730

***Table 8.5:** Patients who did meet the FACIAL diagnostic criteria.*

Features	Patients (n=689)
Microtia or anotia	613 (89.0%)
Facial asymmetry + Preauricular tag	52 (7.5%)
Facial asymmetry + Facial tag	216 (31.3%)
Facial asymmetry + Epibulbar dermoid	84 (12.2%)
Facial asymmetry + Lateral oral cleft	143 (20.8%)
Preauricular tag + Epibulbar dermoid	11 (1.6%)
Preauricular tag + Lateral oral	20 (2.9%)
Facial tag + Epibulbar dermoid	37 (5.4%)
Lateral cleft + Epibulbar dermoid	30 (4.4%)

ICHOM CFM diagnostic criteria

A total of 727 patients met the ICHOM CFM criteria and 3 patients with CFM did not. The ICHOM CFM diagnostic criteria had a sensitivity of 99.6% and a false negative rate of 0.4% (table 8.6). Of the patients that met the ICHOM CFM diagnostic criteria, 667 patients (91.4%) had 2 major criteria, 669 patients (91.6%) 1 major and at least 1 minor, and 79 patients (10.8%) met the ICHOM criteria based on 3 or more minor criteria. Of the 79 patients with 3+ minor criteria, 68 patients (86.1%) had 2 major criteria as well and 77 patients (97.5%) had 1 major and 1 minor criterium.

The characteristic of the 3 patients that did not meet the ICHOM criteria are displayed in table 8.7.

***Table 8.6:** Sensitivity and false negative rate ICHOM CFM diagnostic criteria.*

	CFM		No CFM	
Patients that meet ICHOM criteria	727	(99.6%)	0	727
Patients that do not meet ICHOM criteria	3	(0.4%)	0	3
	730	(100%)	0	730

Table 8.7: *Patients who did not meet the ICHOM CFM diagnostic criteria.*

Patient	1	2	3
Unilateral or bilateral CFM	Unilateral	Unilateral	Unilateral
Orbital hypoplasia	No	No	No
Mandibular hypoplasia	Yes	*	Yes
Microtia or anotia	No	No	No
Asymmetric facial movement	No	No	No
Soft tissue deficiency	*	Yes	No
Epibulbar dermoids	No	No	No
Lateral oral cleft	No	Yes	No
Cleft	No	No	No
Skin tags	Yes	Yes	No
Pre-auricular tags	No	No	No
Hemivertebrae	No	No	No

*Unknown

Comparison diagnostic criteria

The Cohen's kappa statistic to compare the ICHOM CFM criteria and the FACIAL CFM criteria was 0.38, indicating a fair agreement between both criteria. Multiple imputation of data showed no differences in outcome.

Discussion

This study aimed to research the sensitivity of the FACIAL and ICHOM criteria for CFM and study the characteristics of patients that did not meet the criteria. Both criteria show a high sensitivity (FACIAL 94.4% and ICHOM 99.6%) with a fair agreement between both criteria. In this studied cohort, the ICHOM criteria tend to be most accurate. All patients who did not meet the FACIAL criteria did have facial asymmetry without additional factors or microtia. Congenital facial hypoplasia with underdevelopment of one or more O.M.E.N.S. items without other additional anomalies could be identified as CFM. Those patients are not included as CFM by the FACIAL criteria.

Patients with isolated microtia were excluded in this study. In the FACIAL criteria, patients with isolated microtia are regarded to be part of the 'CFM-spectrum'. Ap-

plying the FACIAL criteria would lead to a different cohort of CFM patients, possibly with a less severe phenotype as only the ears are affected. Those patients are missing in the CFM cohort studied in this study. The effect of including patients with microtia, who should be included according to the FACIAL criteria on the sensitivity of the ICHOM criteria could thus not be studied.

Both criteria were developed to study patients with CFM and compare outcomes. The usefulness of diagnostic criteria in CFM for clinical purposes is debatable. As CFM is heterogeneous, the treatment plan is based on individual needs and varies largely among patients. Also, there is overlap between other craniofacial conditions, e.g. Treacher Collins or Robin sequence, in which some aspects of the treatment plan during life might be similar. Therefore, it might be better to use eligibility criteria to study outcomes of treatment then diagnostic criteria. If the studied outcome is not dependent of a certain syndrome but of a specific characteristic, the studied cohort can be based on eligibility criteria rather than diagnostic criteria. By doing this, the outcomes are applicable to all patients with the defined criteria. Especially since most craniofacial syndromes show much overlap in their clinical presentation. Also, use of eligibility criteria could increase the sample size that can be studied, enhancing research on relatively rare craniofacial syndromes.

It is also questionable whether craniofacial microsomia is a true distinct entity. It is a syndrome with a specific phenotype as delineated in the Pruzansky-Kaban and O.M.E.N.S. classification (20, 21, 25). CFM is heterogeneous, without showing clusters of specific patient groups (18). Some articles showed that CFM occurs more frequently in certain families, which is related to specific pre-natal factors, or associated with genetic mutations (3, 5, 13, 81, 181). Nonetheless, the pathophysiology of CFM is yet unknown. Besides the facial anomalies, extracraniofacial anomalies might occur too (140). The heterogenic presentation, overlapping or possibly co-occurring with other syndromes might indicate that CFM is not a distinct entity but could be seen as a developmental disorder that constitute to a spectrum. This spectrum, varying in type and severity of affected structures, might include syndromes like the VACTERL association, limb-body wall complex or Mullerian duct aplasia, renal anomalies, cervicothoracic somite dysplasia (MURCS), and could be described as a "recurrent constellation of embryonic malformations" (RCEM) (182). By abandoning the idea that CFM is a distinct entity but part of a spectrum with other developmental disorders, a RCEM, many more patients with overlapping

features can be studied (182, 183). This also advocates the use of eligibility criteria instead of diagnostic criteria.

There are some limitations in this study. An analysis on the specificity could not be performed as no control group with the characteristics of other craniofacial syndromes was included. The large cohort of CFM patients enabled us to study these criteria. Comparing the outcomes with other syndromes, which also creates the ability to identify diagnostic criteria using logistic regression, was not considered possible due to the high number of patients with other, rare, craniofacial syndromes that needed to be included.

Another consideration of this study is the included CFM cohort. All patients were identified using after a thorough search using search terms in all electronic patient management systems. After receiving the diagnosis CFM by an experienced craniofacial surgeon/team, the diagnosis was verified using radiographic or clinical images by peers. Nonetheless, no strict inclusion criteria were set-up to include the patients. As there is no 'golden standard' for CFM, the included cohort is based on an extensive approach to create a reproducible group of patients based on double checked clinical evaluation. By using this cohort, we can study whether the theoretically developed criteria match clinical patients with CFM, enabling future prospective research to include a well-defined cohort of patient with CFM.

Diagnostic criteria are set-up to score during consultation with the patient. Applying the criteria on retrospective data might be challenging as not all clinical characteristics are known. In our studied cohort patients were included from 1980 until 2016. Inclusion of older data could be challenging as more data might be missing. To encompass this difficulty in this retrospective analysis, only patients with at least four known items of the O.M.E.N.S. score were included. Additionally, a multiple imputation analysis was used to score missing data. As this did not lead to any differences in outcome, the effect of missing data was considered neglectable.

It can be concluded that both the FACIAL and ICHOM criteria are useful criteria to describe patients with CFM with a high sensitivity and fair agreement between both criteria. The ICHOM criteria showed the highest sensitivity in this studied cohort. Both criteria are considered useful for future studies on CFM to create comparable and reproducible outcomes.

9

The effect of natural growth on chin point deviation in patients with unilateral craniofacial microsomia

Based on:
Ruben W. Renkema, Irene van Beelen, Maarten J. Koudstaal, Cornelia J.J.M. Caron. The effect of natural growth on chin point deviation in patients with unilateral craniofacial microsomia: A retrospective study, Journal of Craniomaxillofacial Surgery. 2022 Aug;50(8):615-620. doi: 10.1016/j.jcms.2022.07.006. Epub 2022 Jul 19. PMID: 35872040.

Abstract

This study aimed to investigate the potential progressiveness of mandibular asymmetry and study factors that influence chin point deviation in patients with unilateral craniofacial microsomia (CFM). Paediatric patients with unilateral CFM with available radiologic imaging and medical photographs were included. Chin point deviation was measured on clinical photographs. A Jonckheere-Terpstra test and linear mixed model for repeated measurements assessed the relation of chin point deviation on natural growth, Pruzansky-Kaban score, and soft tissue score. A total of 110 patients were included. The linear mixed model showed no statistically significant changes of chin point deviation during growth (effect estimate -0.004°, 95% CI -0.04° – 0.03°, p=0.76). A statistical significant relation between both the Pruzansky-Kaban and soft tissue score on chin point deviation was found (effect estimate -5.10°, 95% CI -6.45° – -3.75°, p=<0.001 and effect estimate -3.42°, CI -5.86° – -0.98°, p=<0.001, respectively). It can be concluded that the Pruzansky-Kaban and soft tissue score have a strong effect on chin point deviation in patients with unilateral CFM, although the variation between patients is considerable. Chin point deviation does not change during growth, suggesting CFM is a non-progressive disorder.

Introduction

Craniofacial microsomia (CFM) is characterized by unilateral or bilateral hypoplasia of facial tissues. Although the exact cause of CFM remains unknown, it is hypothesized that during the first six weeks of gestation a disturbance occurs in the development of the first and second pharyngeal arches. Although CFM is often regarded as a unilateral condition, 11-14% of the patients are bilaterally affected (129, 184). And recent studies are suggestive that perhaps all CFM patients are bilaterally affected although most often one side being affected more severely (30, 31). The phenotype of CFM is heterogeneous as the affected structures differ in type and severity. Affected structures include hypoplasia of the mandible, maxilla, orbit, zygoma, ears, soft tissue, and facial nerve (1). Besides the facial anomalies in patients with CFM, extracraniofacial anomalies such as vertebral, cardiac and/or renal anomalies are found in 47-55% of the patients (6, 140).

Various models have been developed to classify the degree of facial hypoplasia in patients with CFM (6, 21, 22, 185). Mandibular hypoplasia, which is seen in 89% to 100% of the patients, is commonly described by the Pruzansky-Kaban classification (23, 34, 185). This classification, which is based on radiographic evaluation, ranks the severity of mandibular hypoplasia from type I, to IIa, IIb and III. The degree of hypoplasia of all involved facial structures in patients with CFM is often assessed by the O.M.E.N.S. classification, which scores hypoplasia of the Orbit, Mandible, Ears, Facial Nerve, and Soft Tissues (20, 25).

Functional problems associated with mandibular hypoplasia such as feeding, breathing, or aesthetic difficulties may necessitate treatment (45, 186, 187). Timing of treatment depends on various aspects, including natural growth of the mandible. Potential progressiveness of mandibular growth in CFM is debated in literature (34, 35, 37, 38, 44, 188-190). Some authors advocate early treatment to prevent increasing facial asymmetry and increase function, whereas others advice to postpone treatment until adulthood to prevent tissue damage and unnecessary surgery as it has been shown that early intervention increases the chances of needing additional surgery oater in life, most likely due to the iatrogenic damage done. (40, 190).

Deviation of the chin point on clinical photographs is a simple technique that can be used to estimate the severity of facial asymmetry (32, 33, 191, 192). Previous

studies on 3D-analysis of the mandible in CFM showed that mandibular hypoplasia in CFM leads to a rotation to the affected side, which is greater in patients with more severe mandibular hypoplasia (30, 31). Although these studies based on radiographic data are essential to study the extent of CFM, the effect of hypoplasia and growth on facial asymmetry in patients with CFM has not been studied. The aim of this study is to investigate the influence of mandibular and facial soft tissue hypoplasia on chin point deviation in patients with unilateral CFM. Additionally, this study aims to shed light on the potential progressiveness of CFM by studying the potential changes in chin point deviation over time as this may have impact on the potential timing of surgery.

Methods

This was a retrospective study, performed at the Craniofacial Unit of the Erasmus University Medical Center, Rotterdam, the Netherlands. The use of clinical data was approved by the Institutional Review Board (MEC-2013-575). Patients with unilateral CFM were included if facial clinical photographs, radiologic images and medical history were available. Patients with bilateral CFM or other craniofacial syndromes were excluded. All patients with craniofacial anomalies are regularly and structurally seen at the outpatient clinic, after first presentation, at the age of 4, 6, 9, 12 15, 18 and 21 years old. At these visits clinical photographs are taken. All available photos were assessed for analysis. The chin point deviation was measured if the photograph was taken right in front of the patient. Photos of patients smiling, crying, or with a fully open mouth were excluded as the chin point could not be measured reliably. If a patient had craniofacial surgery that affected the mandible and/or chin, only the pre-operative photographs were used. Photographs were also excluded if there was any uncertainty on the type of surgery that was performed.

The severity of mandibular hypoplasia was classified by the Pruzansky-Kaban classification, based on CT-scans or panoramic radiographs (21, 23, 34). Type I mandibles are small but have normal morphology. Type II is divided by type IIa and IIb. In type IIa the mandibular ramus is abnormal in size and morphology, in type IIb the mandibular ramus is abnormal in size and morphology and the TMJ is abnormally placed. Type III contains mandibles with an absent ramus, condyle and temporomandibular joint. Potential involvement of soft tissue deficiency on chin point deviation was assessed by using the O.M.E.N.S. classification. In this classifi-

cation the soft tissue is scored from 0 to 3, ranging from no soft tissue deficiency to a severe soft tissue deficiency (25, 193).

Chin point deviation (CPD) was measured on frontal facial medical photographs, using Adobe Illustrator CS6. Frontal view photographs were taken with the nose pointing towards the lens showing equal amounts of both sides of the face. To establish reproducible and reliable measurements, chin point deviation was measured according standardized reference points suitable for 2D analysis in patients with facial asymmetry, as described by Berlin et al (194). A sagittal line crossing the nasion and subnasal point was defined as the midline. A second line from the nasion through the gnathion was made. The angle between this line and the midline was defined as the chin point deviation (32). Figure 9.1 shows the obtained measurements in a patient over a decade.

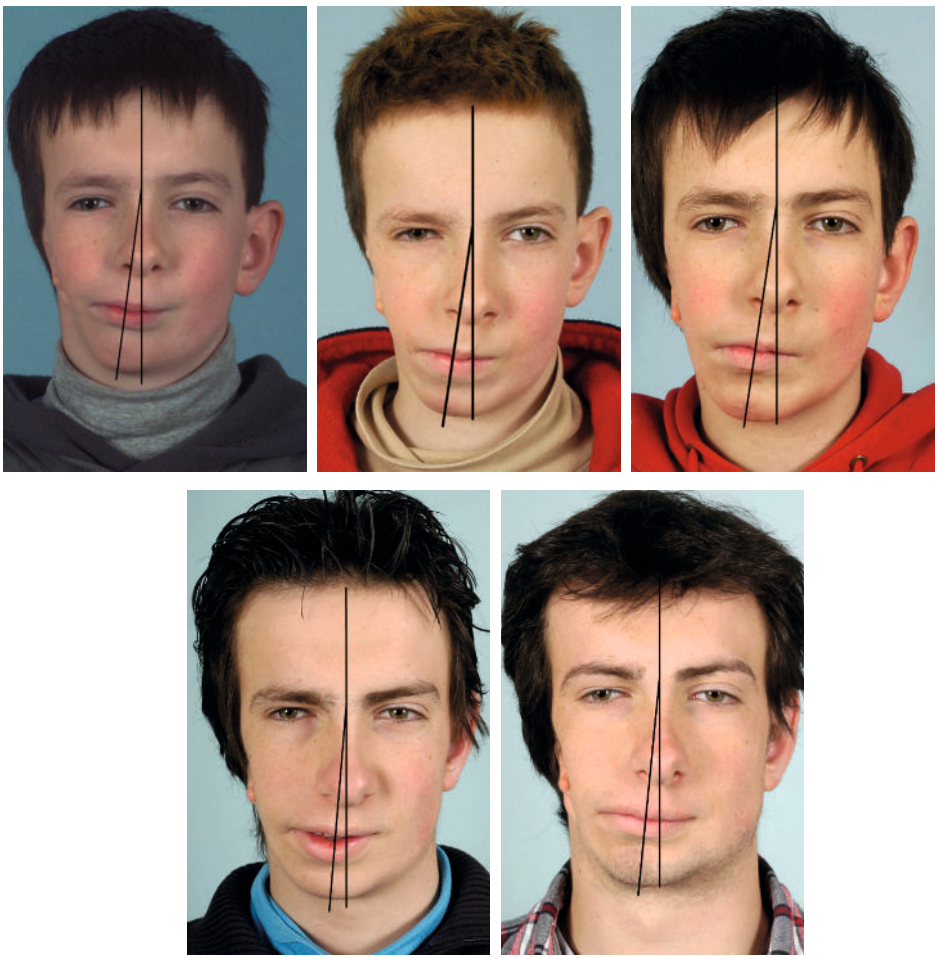
Two observers R.W.R. and I.V.B. measured the chin point deviation in all photographs, to measure the inter-rater reliability. One observer, R.W.R., measured the deviation twice in a three-month time-interval, to calculate the intra-rater reliability.

Statistics

Descriptive statistics were used. The intra- and inter-rater reliability was calculated using the intraclass correlation (ICC) coefficient based on a two-way random model with an absolute agreement definition, reporting single measures. The values of the ICC range from 0 to 1, values of 0.8 and higher are interpreted as excellent agreement. A Jonckheere-Terpstra test was used to assess the association between the Pruzansky-Kaban classification and the soft tissue score and the first measured CPD. This test was used because it determines if there is a statistically significant trend between an ordinal independent variable and a continuous variable in an a priori ordering. We used a linear mixed model to see how the CPD changes with respect to age. The independent variables in this model were age, sex, the Pruzansky-Kaban classification, and the soft tissue score of the O.M.E.N.S. classification. The association of the Pruzansky-Kaban classification and soft tissue score on the CPD were assessed in separate models as the variables are not dependent of each other, taking into consideration that patients with a severe phenotype of CFM show hypoplasia of multiple facial tissues. A random intercept and a random slope of age were used to account for the within-subject correlations. Statistical analysis

was performed using IBM SPSS, version 24. All statistical tests used a two-sided significance level of 0.05.

***Figure 9.1:** Measurement example*



Results

In total, 218 patients with unilateral CFM were evaluated during the study period. Of the 218 patients, 110 were included in the study, aged between 3 to 56 years old. A total of 108 patients were excluded due to the presence of other facial anomalies, surgeries of the mandible or chin, or due to insufficient imaging data. Slightly more males (n=56) than females (n=54) were included; the affected side was equally

distributed in the studied cohort (55 left and 55 right). Table 9.1 shows the patient characteristics, Pruzansky-Kaban classification and the soft tissue score of the O.M.E.N.S. score in the studied cohort.

***Table 9.1:** Patient characteristics*

Sample characteristics	
Sample, n	110
Age (year), range	3 - 56
Gender, n	
Male	56
Female	54
Affected side, n	
Left	55
Right	55
Pruzansky-Kaban classification, n (%)	
Type I	41 (37)
Type IIa	29 (26)
Type IIb	18 (17)
Type III	22 (20)
Soft Tissue score of O.M.E.N.S., n (%)	
0	19 (17%)
I	45 (41%)
II	38 (35%)
III	8 (7%)

The total number of measurements per patient varied, as did the age at which patients were measured (table 9.2). All 110 included patients had one measurement, 69 patients had two measurements, 49 patients had three measurements and 23 patients had four or more measurements. The mean chin point deviation of all patients at first measurement was 3.8° (SD 3.2°). Subdivided in Pruzansky-Kaban type I, IIa, IIb and III, the mean chin point deviations were 2.3°, 2.9°, 4.2°, and 7.4°, respectively (table 9.3). The ICC coefficient was 0.96 (95% CI 0.94 - 0.97) for the inter-rater reliability and 0.88 (95% CI 0.82 - 0.92) for the intra-rater reliability. They are both interpreted as excellent agreement.

Table 9.2: *Numbers and age of measurements*

Total number of measurements per patient	Number of patients with measurement	Median age at time of measurement *(in years)*	Age range at time of measurement *(in years)*
1	111	7	3 – 56
2	69	10	5 – 29
3	49	12	9 – 22
4	23	15	12 – 19
5	11	17	14 – 18
6	5	19	18 – 21
7	1	20	20

Table 9.3: *Pruzanksy-Kaban score and chin point deviation*

	N	Mean *(in degrees) (including 95% CI)*		Minimum and maximum measurement *(in degrees)*
P-K type I	41	2.30	(1.81 – 2.79)	0.0 – 6.9
P-K type IIa	29	2.91	(1.86 – 3.97)	0.0 – 9.9
P-K type IIb	18	4.18	(2.74 – 5.62)	0.0 – 10.8
P-K-type III	22	7.37	(5.78 – 8.96)	2.6 – 14.0
Total	110	3.21	(3.18 – 4.39)	0.0 – 14.0

*P-K: Pruzansky-Kaban ; CI: Confidence Interval

A linear mixed model for repeated measurements showed no significant association between age and chin point deviation (p=0.76), as for sex and chin point deviation (p=0.41). The Pruzansky-Kaban score was significantly associated with chin point deviation (p=<0.001). Patients with a Pruzansky-Kaban type III mandible had a 5.1° larger chin point deviation to the affected side compared to patients with a Pruzansky-Kaban type I mandible (effect estimate -5.10°, 95% CI -6.45° – -3.75°). The soft tissue score was also significantly associated with chin point deviation (p=<0.001). The chin point deviation to the affected side was 3.4° larger in patients with a soft tissue score III compared to patients with a soft tissue score I (effect estimate -3.42°, CI -5.86° – -0.98°). All measurements were taken into account in this analysis, except for one patient who was considered an outlier due to her age of 56 years at first measurement and was therefore excluded from this analysis (median age at first measurement: 7 years; 90th percentile of all first measure-

ments: 18 years). Measurements of patients above 18 years of age were excluded in the analysis on the relation between chin point deviation and growth. The results of the models is shown in table 9.4.

***Table 9.4:** Estimates of Fixed Effects on chin point deviation*

Parameter	Effect estimates *(in degrees)*	Confidence interval *(in degrees)*
Age	-0.004	-0.04 – 0.03
Male	-0.41	-1.39 – 0.58
Female	0 (redundant)	.
Pruzansky-Kaban I	-5.1	-6.45 – -3.75
Pruzansky-Kaban IIa	-4.5	-5.97 – -3.07
Pruzansky-Kaban IIb	-3.2	-4.83 – -1.57
Pruzansky-Kaban III	0 (redundant)	.
Soft tissue 0	-3.42	-5.86 – -0.98
Soft tissue I	-2.15	-4.38 – 0.08
Soft tissue II	0.02	-2.24 – 2.27
Soft tissue III	0 (redundant)	.

The Jockheere-Terpstra test, which only used the first CPD measurement of all 110 patients, also showed that patients with a higher Pruzansky-Kaban score had a significant more deviant chin point (p=<0.001), as was for patients with a higher soft tissue score (p=<0.001).

Discussion

This study aimed to research the potential progressiveness of mandibular asymmetry in unilateral CFM and studied factors that influence mandibular asymmetry. A total of 110 patients were included. More patients with a Pruzansky-Kaban type I or IIa were included than patients with type IIb or III, which is in line with literature. Both sex and the affected side were equally divided in our population. Other studies did find differences in sex and affected side predominance in CFM, although the meta-analysis by Xu et al. showed no differences in male-female and left-right ratio (129, 184).

No significant changes occur in chin point deviation during growth. It can therefore be assumed that growth of both the affected and unaffected side of the mandible is similar in patients with unilateral CFM. This was also shown by Ongkosuwito et al., who studied panoramic x rays, found that patients with CFM experience similar growth compared to a normal population, but start and end with a smaller mandible (189). Polley et al. studied longitudinal records of 26 patients with unilateral CFM and assessed posterioranterior cephalometric radiographs. They concluded that the mandibular asymmetry is not progressive and both the affected and unaffected side show parallel growth (190). Newer methods such as 3D CT-scans can be used to describe the mandibular deformity in more detail. Kaya et al. showed, by using principal component analysis, that the mandible rotates to the affected side due to lateral rotation and shortening of the condyle-gonial height with outward bending of the mandibular angle (30). The "unaffected" mandibular side in patients with unilateral CFM is often bending inwards due to compensatory remodeling. No differences were observed during growth as both young and old patients showed inward bending of the unaffected side (30). Kim et al. studied 3D reconstructed mandibles from CT-scans of patients with CFM to investigate growth of the anatomical regions of the mandible separately (31). They found that the angulation in milder patients (Pruzansky-Kaban type II), but not severe hypoplastic mandibles (Pruzansky-Kaban type III), may decrease with age although the type II mandibles still show more than 6° angulation compared to healthy controls (31). This study was based on cross-sectional analysis of 28 patients with CFM divided in various age-groups, which could explain the different outcome compared to our study, which assessed 110 patients with CFM in a longitudinal analysis.

Deviation of the chin point is influenced by the Pruzansky-Kaban score and the soft tissue score on the O.M.E.N.S. scale. This study shows a strong average effect of the Pruzansky score and soft tissue score on the chin point deviation. However, the variation between patients, especially in the effect of the soft tissue score on the chin point deviation, is considerable as is displayed by the wide confidence interval.

Identifying reliable landmarks and thus measure chin point deviation in patients with CFM is difficult as facial anatomy varies between patients. A horizontal lines through the lateral canthi with a perpendicular sagittal line can be used to determine the midline of the face. However, this is questionable in patients with CFM as orbital dystopia, a common feature in these patients, may influence placement of

the landmarks (32). In this study, frontal view photographs were taken in a straight direction showing equal amounts of both sides of the face. The midline of the face was determined by placing a sagittal line through the nasion and subnasal point. Additionally, the chin point, defined as gnathion, can be difficult to determine on medical photographs as it is not always as visible compared to radiologic images. Although these difficulties with landmark placement in studying patients with CFM are inevitable, excellent intra- and interobserver agreement was reached because of the strict methodology.

In the last decades conflicting results on the progressiveness of CFM have been published. Early treatment could stimulate midfacial growth and lead to better facial symmetry (22, 34, 35, 195, 196). Especially in patients with mild mandibular hypoplasia, additional surgery was not always needed (22, 34). However, recent systematic reviews by Nagy et al. and Pluijmers et al. showed no evidence for long-term stability of early treatment in patients with CFM (40, 197). The earlier correction of mandibular asymmetry is performed, the more surgical procedures are needed to correct the asymmetry later in life (39). The findings in this study support informing parents and children that the condition will not get worse over time and should also support avoiding early surgery for the sake of 'prevention of increasing facial asymmetry'.

Conclusion

It can be concluded that there is a strong effect of the Pruzansky-Kaban and soft tissue score on the chin point deviation in patients with unilateral CFM, although the variation between patients is considerable. No change in chin point deviation is seen during growth which might suggest that CFM is not a progressive condition.

Part III

Management of patients with craniofacial microsomia

10

A decade of clinical research on clinical characteristics, medical and surgical treatments for individuals with craniofacial microsomia

what have we learned?

Based on:

Ruben W. Renkema, Cornelia J.J.M. Caron, Carrie L. Heike, Maarten J. Koudstaal, A decade of clinical research on clinical characteristics, medical treatments, and surgical treatments for individuals with craniofacial microsomia: What have we learned? Journal of Plastic, Reconstructive & Aesthetic Surgery. 2022 Jun;75(6):1781-1792. doi: 10.1016/j.bjps.2022.02.058. Epub 2022 Mar 7. PMID: 35365411.

Abstract

This article provides a review of a decade of clinical research studies on clinical features, medical and surgical interventions for individuals with craniofacial microsomia (CFM). We also provide recommendations for future clinical research. A systematic search of literature was conducted in Embase and Pubmed/Medline Ovid. All publications from 2010 until 2020 that included at least 10 individuals with CFM were considered relevant for this study. A total of 91 articles were included. In the past decade, many new studies on CFM have been published providing more insight on the diagnosis and management of patients with CFM. This review encompasses findings on the clinical difficulties patients with CFM encounter, including the craniofacial and extracraniofacial characteristics of patients with CFM and its related clinical consequences on breathing, feeding, speech, and hearing. A considerable number of large multicentre studies have been published in recent years, providing new insights in the clinical consequences of CFM. The phenotypic variety between patients with CFM makes patient specific treatment tailored to individual needs essential. Research and development of clinical care standards might be challenging due to the heterogeneity of CFM. Future research on clinical and patient reported outcomes can help identify optimal treatment strategies. Cooperation between craniofacial centers, using uniform registration and outcome measurement tools, could enhance research and future care for these patients.

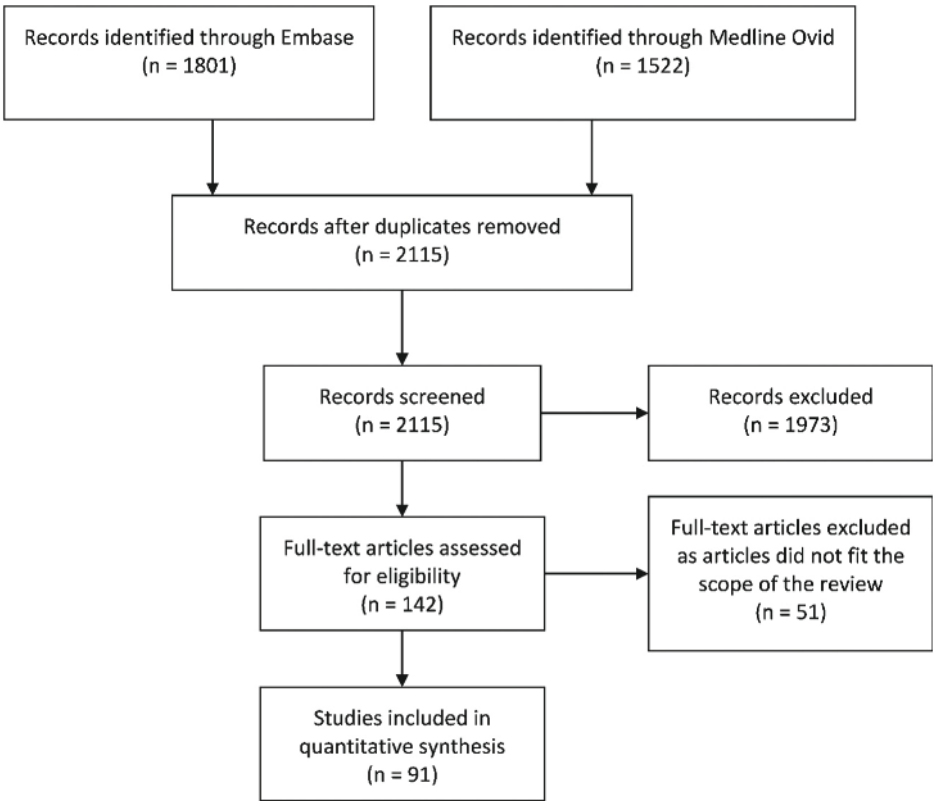
Introduction

One in approximately 5000 newborns is diagnosed with craniofacial microsomia (CFM), making it the second most common craniofacial condition following cleft lip and/or palate. Patients with CFM are born with uni- or bilateral underdevelopment of the structures arising from the first and second pharyngeal arches, including the mandible and ears (1, 47). The number and severity of the affected structures vary among individuals. As no diagnostic criteria nor common associated genetic mutations exist, the diagnosis is based on clinical assessment. Extracraniofacial anomalies including cardiac, renal or vertebral anomalies are also common in patients with CFM (6). The clinical consequences of these anomalies vary. Patients may experience difficulties with breathing, feeding, speech or hearing, and many children undergo multiple surgical interventions throughout child and early adulthood. In the last decade, many studies on CFM have been published and provide new insights on phenotypic spectrum, medical and surgical screening evaluations and treatments. The aim of this manuscript is to present an overview of the recent clinical research on CFM for clinicians and researchers.

Methods

We conducted a systematic search of literature to identify articles on CFM published in the last decade. The search was conducted in Embase and PubMed/Medline Ovid. The full search strategy is available as online appendix. All clinical studies on CFM, written in English, published between 2010 until 2020 that included 10 or more patients were included in this review. A total of 2115 articles were screened on title and abstract, leading to excluding 1973 articles. After full text review of 142 articles, a total of 91 articles were included in this article (figure 10.1).

Figure 10.1: *Flowdiagram literature search*



Clinical characteristics and terminology

Craniofacial microsomia is a heterogeneous clinical diagnosis characterized by hypoplasia of facial structures that are derived from the first and second pharyngeal arches. The most common features associated with CFM include: mandibular hypoplasia, microtia, orbital hypoplasia, facial palsy, facial soft tissue deficiency, preauricular skin tags, lateral oral clefts, epibulbar dermoids and vertebral anomalies (20, 28). A variety of terms have been proposed to describe patients with CFM, including otomandibular dysostosis, first and second branchial arch syndrome, fascio-auriculo-vertebral sequence or syndrome, oculo-auriculo-vertebral dysplasia, spectrum or syndrome, hemifacial microsomia and Goldenhar syndrome.

In 1952, Maurice Goldenhar described three patients with mandibular dysostosis, epibulbar dermoids, pre-auricular skin tags and cervical vertebral anomalies; sub-

sequently called Goldenhar syndrome (15). A decade later, in 1963, Gorlin et al. proposed the term oculo-auriculo-vertebral spectrum for patients with auricular appendages and fistulas, epibulbar- or lipodermoids and vertebral anomalies (16, 17). Gorlin and Pindborg also introduced the term hemifacial microsomia to describe patients with an underdevelopment of the ears, oral and mandibular structures (5). The clinical features of all these patients had much overlap and no clear distinction between the syndromes could be made, suggesting a continuous spectrum (17). Studies have shown that the clinical features were indistinguishable among patients who had received a diagnosis of Goldenhar syndrome compared with those diagnosed with CFM (18, 19). The term craniofacial microsomia accounts for the high prevalence of bilateral facial features, including bilateral hypoplasia of the facial structures in 11-33% of patients (18, 129, 139, 198), presence of contralateral hearing loss in 8% of individuals with apparent unilateral CFM (199), and recent studies suggest that CFM is probably never truly unilateral (30, 200, 201). ,

Quantitative analysis of the craniofacial skeleton to detect differences in the "unaffected" side in patients diagnosed with unilateral CFM have produced mixed results. While one study used principal component analysis (PCA) and identified inward deviation of the unaffected mandibular angle (30) contradictory results were found by Kim et al. who performed a mandibular skeletal unit analysis and concluded that the unaffected mandibular side was not significantly different from healthy controls (31). Chen et al. studied 48 patients with unilateral CFM and found shorter mandibular body and ramal lengths of the contralateral side in patients with severe (Pruzansky-Kaban type IIB-III) compared to mild (type I-IIA) mandibular hypoplasia (202). The cranial base angle and axis deviation was studied by Paliga et al. who found no differences compared to healthy controls (203). Later studies of the cranial base using techniques such as PCA and found cranial base malformations on both the affected and unaffected side, which may be either compensatory or directly attributable (200, 201). Schaal et al. state that their results differed from the results by Paliga et al. because of a more detailed selection and higher number of landmarks (200).

Three independent studies in large populations (n=105, 100, and 755) investigated the relationships among the CFM facial anomalies and detected correlations between orbital, mandibular and soft tissue hypoplasia, between soft tissue hypoplasia and microtia, and between microtia and facial nerve dysfunction in patients with

CFM (18, 135, 204). Evaluation using principle component analysis of 755 patients with CFM showed no specific clusters within CFM (18).

Classification systems

The O.M.E.N.S. classification system is one of the most commonly used scoring systems for the features typically associated with CFM and includes scores for the degree of hypoplasia of the orbit (O), mandible (M), ears (E), facial nerve (N), and soft tissue (S) and is based on clinical assessment (25). Later, the presence of extracraniofacial anomalies was added by Horgan et al., creating the O.M.E.N.S.-plus. In 2011, Birgfeld et al. created the phenotypic assessment tool (PAT-CFM) which includes a photographic protocol the O.M.E.N.S. score, additional detailed assessment of other deformities including colobomata, strabismus, dermoids, skin tags, pits, clefts, tongue anomalies, and radiographic assessment of the orbit and mandible (20, 24). Radiographic evaluation of mandibular hypoplasia is done with the help of the Pruzansky-Kaban classification, which categorizes the degree of mandibular hypoplasia from type I to IIA, IIB, and III (21-23). Birgfeld et al. (2016) found high reliability of the PAT-CFM based on photographs and compared with direct physical examination (205). In 2016, Heike et al used the PAT-CFM to study a sample of 142 individuals with CFM patients and 290 controls to develop a systematic approach to describe their facial characteristics by using the O.M.E.N.S. score (206). Categorization of phenotype using the PAT-CFM has been used in several subsequent studies and allows for comparison of study findings across cohorts (198, 207, 208).

The topics in this review are sorted by the structural features of the O.M.E.N.S. classification. Functional difficulties, as hearing, breathing, feeding and speech are discussed according their related anatomic structure of the classification.

Orbit

Asymmetries in size and/or position of the orbit (orbital dystopia) are observed in 4% to 43% of the patients with CFM (139, 209), but rarely require surgical treatment. (45). In 2018, Gribova et al. (210) identified an average difference of 10% ($p=0.001$) in the orbital volume of the affected and unaffected side in patients with unilateral CFM. No healthy controls were included in this study, but in the variation in orbital size within an individual from the general population is considered to be less (211, 212). In addition to hypoplasia of the orbit, ocular anomalies are

frequently observed in patients with CFM and might require treatment to optimize visual acuity.

Eye

Twenty-five articles were included in a 2020 systematic review on ocular and adnexal anomalies in CFM (209). Epibulbar dermoids and eyelid colobomata are common in patients with CFM, with a prevalence of 7%-69% and 4%-40%, respectively (209, 213). Other CFM-associated anomalies include lacrimal duct or gland anomalies, microphthalmia, anophthalmia, iris colobomata, lipodermoids, optic nerve anomalies, blepharoptosis, strabismus, astigmatism, amblyopia. Patients with bilateral facial features were more likely to have ocular anomalies than patients with unilateral CFM (18). Epibulbar dermoids, astigmatism, and/or exposure keratitis may impair vision, and timely evaluation and treatment is needed. Therefore, all patients with CFM should be evaluated by an ophthalmologist during visual development, i.e. before the age of 5 years (209).

Mandible

Mandibular hypoplasia is a characteristic feature in CFM and is present in approximately 73% to 91% of the patients (18, 206). Severity varies from mild hypoplasia to complete absence of the ramus, condyle and temporomandibular joint (21, 22). Variations in the course of the mandibular canal are more common in patients with a Pruzanksy-Kaban type IIb or type III mandible (214). In a study of 84 pediatric patients with CFM and 329 controls, patients with unilateral mandibular hypoplasia had a significantly smaller mandibular ramal height but demonstrated similar growth during development compared to healthy controls (215). Maxillary hypoplasia could also be observed in up to 90% of the patients, which may lead to canting of the occlusal plane (216). However, Wink et al. found no significant difference in maxillary bony volumes in a cohort of 30 patients with CFM despite the presence of significant differences in mandibular volume. No relation between the severity of mandibular hypoplasia and occlusal cant was found (217). Ongkosuwito et al. showed, using cephalometric analysis, that patients with CFM have more retruded mandibles and maxillae and a more vertical morphology compared to healthy controls. This difference was also seen comparing the affected to the unaffected side, and comparing patients that were severely and mildly affected (36). Another cephalometric study by Tokura et al. showed that mandibular body hypoplasia on the affected side was unrelated to the severity of hypoplasia of the mandibular

ramus and TMJ, and was stronger correlated to the degree of chin point deviation than the ramus hypoplasia in patients with CFM (218). Functional difficulties due to hypoplasia of the mandible and maxilla are common in patients with CFM and can have adverse impacts on breathing, feeding, speech and/or occlusion. Facial asymmetry due to mandibular hypoplasia can also have adverse aesthetic impacts (219, 220).

Upper airway obstruction

Patients with mandibular hypoplasia are at increased risk for obstructive sleep apnea (OSA) due to obstruction at tongue base level (221, 222). In 2015, a systematic review on OSA in CFM identified a prevalence of OSA in CFM between 7% to 24% and patients with a more severe form of CFM and/or bilateral CFM features were at the highest risk for OSA (222). A retrospective study of 62 patients with CFM, showed those with a unilateral severe mandibular hypoplasia (Pruzansky-Kaban type IIb and III) are also at increased risk for OSA, whereas no patient with a Pruzansky-Kaban type I or IIa mandible was diagnosed with OSA (223). In 2017, a large retrospective study of 755 patients with CFM showed a prevalence of 18% of OSA in CFM (186). Again, patients with severe mandibular hypoplasia or bilateral CFM were at increased risk for OSA. Severe OSA was observed in patients with severe mandibular hypoplasia (186). In 2019, a cross-sectional study by Klazen et al. showed by studying CT scans of 79 patients with CFM and 88 controls that patients with CFM have a smaller oropharynx volume and retropalatal area compared to controls (160). Patients with CFM and OSA showed, compared to other CFM patients, a smaller retroglossal area and different uniformity and sphericity. Multivariate regression analysis showed sphericity is the main predicting variable for OSA in patients with CFM (157, 160, 186). Retrospective data showed that placement of a tracheostomy is often considered a first choice of treatment for patients with CFM and severe OSA (186). Unilateral mandibular distraction in patients with unilateral CFM expanded the oropharynx and nasopharynx, and led to less airflow resistance in a retrospective study of 20 patients by Wang et al (224). The high prevalence of OSA in CFM and potential adverse events of not recognizing the disease timely, warrants screening for all patients with CFM and consideration of further testing with polysomnography for those at increased risk (186). Considering no literature is available on any superiority of a type of surgical treatment for OSA in CFM, treatment options should be discussed within a multidisciplinary team.

Feeding difficulties

Mandibular hypoplasia, muscle weakness, tongue anomalies, cleft palate and pharyngeal/laryngeal anomalies can contribute to feeding problems. A 2015 systematic review of feeding difficulties and CFM identified only eight articles that met inclusion criteria (156). These studies reported a prevalence of feeding difficulties in 42% to 83% of children with CFM (156). Feeding difficulties were identified in 26% of the 755 patients included in a CFM retrospective study published in 2018 (187). Most (60%) feeding difficulties were diagnosed before the age of six months. Type of feeding difficulties included suckling, swallowing or chewing errors, reflux complaints, or a restricted mouth opening. Feeding difficulties were observed in half of the patients with cleft lip/palate, bilateral CFM, obstructive sleep apnea, or extracraniofacial anomalies (187). Conservative treatments such as using a cleft bottle/nipple or antireflux therapies may be sufficient for some patients while others require alternative methods (such as nasogastric or gastric tubes) (187). In 2018, van de Lande et al. further investigated the swallowing difficulties identified in 102 of 755 (14%) patients with CFM (225). Videofluoroscopic swallow studies showed that young patients (<6 months) showed problems with nasopharyngeal reflux, bolus formations and aspirations, whereas older patients (>6 months) showed difficulties with bolus formation, swallow trigger and stasis of food after swallowing. Patients with severe mandibular hypoplasia showed significant more difficulties in appropriate bolus formation. No difference was seen between patients with unilateral and bilateral CFM (225). The authors advise that all patients should be screened for feeding difficulties. A cross-sectional study of 20 patients with CFM and 10 controls found no differences in bite force on the affected side, although the electromyography value of the masseter muscle was diminished on the affected side compared to the contralateral side and healthy controls (226). Due to the high prevalence, the authors advice that all patients with CFM should be screened for feeding difficulties and growth should be monitored (187). Treatment should always be discussed within the multidisciplinary team.

Saliva is required for appropriate swallowing and Brotto et al. evaluated MRI scans of 25 patients with CFM and 11 controls for parotid and submandibular gland anomalies (227). While all controls had normal salivary glands, 84% of the patients with CFM demonstrated hypoplasia/aplasia of the parotic gland in with additional submandibular gland hypoplasia in 26% of these patients. All gland hypoplasia was ipsilateral to the affected side in patients with unilateral craniofacial features,

and parotid gland hypoplasia was correlated with ipsilateral nerve V and VII abnormalities (227).

Speech

Patients with CFM are at risk for speech and language difficulties due to underdevelopment of facial tissues, including mandibular hypoplasia, microtia, facial hypotonia, malocclusion, lateral oral clefts, cleft lip/palate and/or velopharyngeal insufficiency (139, 162, 185). Collet et al. studied speech and language skills in 107 adolescents (age 11-17 years) with CFM and 306 controls (228). Lower scores of speech intelligibility, articulation, expressive language skills and communication were observed in patients with CFM compared to controls. Individuals with mandibular hypoplasia plus microtia and/or patients with hearing difficulties scored lower on all measures compared to controls (228). In line with this study and the CFM overview paper by Heike et al. it is advised that all patients with CFM should be evaluated for speech difficulties before the age of 2 years and be monitored during childhood by a speech and language therapist (139).

Dental

Hypodontia or dental hypoplasia is present in 8% to 25% of the patients with CFM (139). A 2020 systematic review on dental anomalies in patients with CFM included thirteen articles (229). Tooth agenesis was observed in 7% to 33% of the patients and was more frequently diagnosed on the affected side compared to the unaffected side, more often observed in bilateral patients compared to unilateral patients, and more frequently seen in patients with severe mandibular hypoplasia compared to mild hypoplasia. A delay in dental development was seen in 20% to 54% of the patients, which was higher compared to a control population. One of the authors reported a "catch-up phenomenon" in which less delayed dental development was found in older patients compared to younger patients (230). Patients with CFM also show anomalies in tooth size or tooth morphology, which was more frequently seen on the affected side than on the unaffected side (229). All these anomalies could affect occlusion, which might necessitate treatment. The orthodontist should screen patients for dental deformities and discuss treatment within the multidisciplinary team. Often patients require coordinated orthodontic treatment followed by orthognathic surgery to improve skeletal symmetry (139).

Treatment options for mandibular hypoplasia

Surgical correction of the mandibular deformity in CFM may improve breathing, feeding, occlusal and/or aesthetic concerns and treatment selection depends on the degree of mandibular hypoplasia. Anesthesiologists should be aware of the potential a challenging intubation in children with CFM. Xu et al. studied 136 patients with CFM who underwent surgery and found a 100% success rate of intubation for primary fibroscopy and video laryngoscopy, but 79.5% success for direct laryngoscopy. Difficult laryngeal visualization was correlated with failed intubation by direct laryngoscopy, which might be improved by mandibular distraction (231). A systematic review on the mandibular reconstruction in patients with unilateral CFM, showed patients with mild mandibular hypoplasia (Pruzansky-Kaban type I and IIa) often underwent distraction osteogenesis (30%) or osteotomies (2%) (197), while those with severely affected mandibles (Pruzansky-Kaban type IIb and III) were more frequently treated with mandibular reconstruction using a bone graft (44%) or distraction osteogenesis (14%). Treatment outcomes varied and no superior treatment modality was identified. The authors concluded that treatment outcomes are primarily based on the severity of mandibular hypoplasia (197). In a retrospective, multicenter study of surgical interventions in 565 patients with CFM, a third of all patients with CFM underwent mandibular surgery, which was more frequently performed in patients with severe mandibular hypoplasia (39). Patients with severe hypoplasia were frequently treated with mandibular reconstruction using a bone graft, while patients with mild mandibular hypoplasia were more likely to undergo osteotomies, genioplasties and distraction osteogenesis. Patients with severe mandibular hypoplasia often needed secondary orthognathic surgery. Severe mandibular hypoplasia and/or bilateral CFM were indicators that multiple surgeries are usually needed and patients required more surgeries if the first surgery was performed at a younger age, independent from the severity of mandibular hypoplasia (39).

The ideal timing of mandibular correction is still debated. In recent studies, Zhang et al. (232), Weichmann et al. (195), Suh et al. (233) and Ko et al. (33) studied outcomes of early mandibular distraction osteogenesis (MDO) in CFM. Zhang et al. studied 38 patients with comparable degrees of mandibular hypoplasia CFM, including 17 who received early MDO at a mean age of 9 years and 21 who did not. No significant difference in the need for orthognathic surgery at skeletal maturity between both groups was observed (232). Weichmann et al. studied the long-term

results of early MDO performed at a mean age of 3 years in 19 patients with mild CFM (Pruzansky-Kaban type I and IIa). Twelve patients had satisfactory outcomes and seven unsatisfactory, which was based on clinical assessment. Comparison of the groups showed that unsatisfactory results could be due to earlier distraction and a greater overcorrection from the midline (195). In a retrospective study of 26 patients with unilateral CFM who were treated with MDO at a mean age of 6 years, occlusal and mandibular tilting was significantly decreased after 1 year, but this result was no longer present at 4 to 11 years after treatment (233). Similar results were found by Ascenço et al., who observed recurrence of asymmetry after 44 months in 90% of the 33 patients with unilateral CFM treated with MDO at a mean age of 7 years (234). Ko et al. also analyzed long-term facial growth after early MDO in twenty patients with mild CFM (Pruzansky-Kaban type II), including nine who underwent MDO between 5 to 9 years and eleven patients without MDO. During follow-up the ramus length ratio (affected/nonaffected) decreased from 91% to 69%. Treated patients showed a similar mandibular growth pattern compared to untreated patients. Both groups of patients showed clinical asymmetry at follow-up, although early MDO led to a smaller chin deviation in the long term (8 versus 13 mm) (33). After final orthognathic surgery, patients with CFM who received early MDO did not significantly differ in skeletal and dental outcomes compared to previously untreated patients (n=20) (235). Advancement of the chin point was greater in the MDO group, but not statistically significant due to individual variability and surgical inaccuracy (235). Early MDO may improve facial symmetry and psychosocial acceptance in a cost-effective manner, according to a panel of 463 non-CFM participants studied by Almadani et al., although the potential risks of treatment were not taken into account in this study (236).

Bertin et al. performed a retrospective study of 39 patients with CFM in 2017 to evaluate outcomes of vertical ramus osteotomies and mandibular reconstruction with a rib graft (237). Patients were treated at a mean age of 13 years (3.5 SD) and all demonstrated improvement in the degree of the occlusal canting, although a slight recurrence of mandibular asymmetry was observed during follow-up. Additional orthognathic revision was indicated in 23% of the patients due to the relapse in chin deviation and maxillary occlusal canting (237). Ascenço et al. reported that 30 of the 33 patients had orthognathic surgery after previous MDO (234).

For patients with severe mandibular hypoplasia, reconstruction with costochondral grafting is an option. Tahiri et al. retrospectively reviewed outcomes of this type of treatment in 22 patients with CFM and Pruzansky-Kaban type IIb and III (238). Treatment was performed at an average age of 7 years. Some mandibles (18%) required secondary distraction osteogenesis. No graft resorption, malunion or nonunion was observed. One patient developed ankylosis of the graft (238). Long-term results of mandibular reconstruction with costochondral rib graft at age 6-8 years, was studied in a retrospective case-control study of 10 patients with CFM and a Pruzansky-Kaban type III mandible by Meazinni et al (239). No overgrowth was observed. The mandibular ratio of the affected versus the non-affected side showed 8% relapse at a mean follow-up of 8 years. Interestingly, facial and dental symmetry did no longer differ after 8 years in patients with a costochondral graft compared to non-treated patients (239). Another possible solution for severely hypoplastic mandibles is reconstruction with alloplastic materials. Polley et al. studied outcomes of ten patients with CFM who were treated with titanium mandibular implants after failed previous reconstructions (240). All patients achieved a good occlusal relationship and no adverse events were reported. This type of treatment may be suitable for skeletally mature patients with no other treatment options available (240).

In 2018, a systematic review on surgical correction of the midface in unilateral CFM was published. Both LeFort I osteotomies with mandibular distraction and bimaxillary osteotomies were reported in literature with good results. Bimaxillary osteotomies in patients with severe mandibular hypoplasia were often performed after treatment with distraction osteogenesis or placement of a bone graft. Midface correction was commonly performed during adulthood (241). The use of patient specific cutting guides in Le Fort I surgeries increased accuracy compared to the use of a surgical wafer in a cohort of 18 patients with CFM (242). No ideal surgical treatment protocol was identified due to the lack of sufficient outcome data. A retrospective study on this subject, also published in 2018, included 81 patients with unilateral CFM to review types of maxillary correction in CFM and to study the relation between the maxillary cant and mandibular hypoplasia (243). Maxillary surgery was performed in 29% of the patients and included: bimaxillary osteotomies, Le Fort I with mandibular distraction, Le Fort I, and Le Fort I with mandibular reconstruction with bone graft. A significant positive correlation between the degree of maxillary canting and the severity of mandibular hypoplasia was found (243). Xu

et al. also found an independent association between the mandibular ramus height and corpus length with maxillary volume in 70 patients with unilateral CFM (244). Maxillary volumes were lower on the affected side compared to the contralateral side (245). Also, no differences in maxillary sinus volume were observed (245).

Ear

Microtia is common in CFM and reconstruction of the external ear may be performed to restore a more typical appearance (18, 19, 139). Various treatments are available, and the choice of intervention depends on the patient's wishes (which includes no treatment), burden of treatment, the patient's anatomy and age. An external prosthesis attached on osseointegrated implants is generally only considered in adult patients (246). Placement of an external silicone prosthesis attached with adhesives may be a temporary treatment modality for young children if needed (246). Alloplastic implants, such as Medpore, can be placed at a young age and has a lower burden compared to autologous reconstruction with a rib graft. A drawback of this type of treatment is that if complications occur, such as extrusions or fractures of the implants, other types of reconstruction are not possible (246). Reconstruction with autologous rib provides good long-term results and is considered the most durable treatment option, but outcomes are dependent on surgical skill and have a higher treatment burden compared to other modalities (246). Microtia reconstruction in patients with CFM may be challenging as soft tissue deficiencies could make covering of the auricular reconstruction difficult. In 2018, Park et al. studied 52 patients with CFM to evaluate three types of coverage techniques in microtia reconstruction with rib (247). Results showed that in patients with severe CFM features, including mastoid hypoplasia, low hairline, anotia or small vestige, the fascia flap is considered most optimal, whereas in other patients the embedding technique should be used according to the authors (247). An expanded scalp flap without skin graft can be an effective procedure for patients with a low hairline (248). Qian et al. and Xing et al. describe the use of a retroauricular tissue expander in an expanded two-flap reconstruction method with costal cartilage (249, 250). Outcomes of autologous reconstruction with rib was studied in 60 patients with auricular anomalies (251). Patients with severe microtia needed significantly more surgeries and had decreased aesthetic outcomes, which was based on observer assessment.

Hearing

Awareness for hearing problems in patients with CFM is essential to prevent developmental delay, learning difficulties, speech development delay and/or impaired social functioning. Patients with CFM are at risk for hearing loss due to anomalies of the outer, middle and/or inner ear structures which can result in conductive, sensorineural or mixed hearing loss. In 2017, a retrospective study of 79 patients (40 unilateral and 39 bilateral) with CFM identified that most patients (82%) had hearing loss, which was unilateral in 53 patients and bilateral in 12 patients (199). Hearing loss was mostly conductive (73%), mixed (10%) or unable to be determined (16%). Only 1% of the patients had solely sensorineural hearing loss. The severity of microtia, which was present in 94% of the patients, was positively correlated with the severity of hearing loss. Interestingly, 8% of the patients had unilateral hearing loss contralateral to the hypoplastic ear or mandible (199). Sleifer et al. analyzed audiological findings in 10 patients with CFM and found hearing loss in 9 patients which was mild or moderate in 8 patients (252). The same group published a cross-sectional study in 2016 on hearing loss in another 10 patients with CFM. All patients had microtia and half of the patients were diagnosed with hearing loss (three conductive, two sensorineural) (253). In a larger cross-sectional study from 2017 by Cohen et al., all 89 patients were evaluated for hearing impairment (27). Microtia was present in 83% of the patients and hearing loss in 79% of the patients. Five patients (6%) were bilaterally deaf as a result of acoustic nerve or cochlear anomalies (27). Inner ear anomalies were seen on CT or MRI imaging in one-third of 33 patients included in two separate studies by Hennersdorf et al. and Rosa et al. (254, 255). Davide and Renzo et al. also studied CT and MRI imaging of the head of respectively 35 and 32 patients with CFM (256). Malformations of the inner ear were found in 31% of the patients and were correlated with ipsilateral 7th and 8th cranial nerve anomalies (256). These studies confirm the high prevalence of hearing loss in patients with CFM. Treatment of hearing loss led to improvement of psychosocial functioning (251).Screening and timely treatment is essential to support child development. Complete audiologic evaluation should be performed in early infancy (139).

Facial nerve

Facial nerve palsy is present in 10% to 55% of the patients with CFM (18, 139). This may cause difficulties with eyelid closure, speech or oral continence, and aesthetic concerns(257). In 2015, Manara et al. identified facial nerve abnormalities on CT

and/or MRI images in 61% of the 18 patients with CFM, (88). Abnormalities were also observed in cranial nerves, including the fifth, sixth and eighth nerve (58%, 50% and 44% of patients, respectively). Li et al. studied facial palsy in 786 patients with isolated microtia and 339 patients with CFM (258). A quarter (24%) of the patients with CFM had facial palsy, which was positively correlated with the presence of mandibular hypoplasia, microtia and soft tissue deficiency. None of the patients with isolated microtia had facial palsy. The severity of facial palsy based on the House-Brackmann system was not related to any O.M.E.N.S. category (258). Treatment selection is based on the indication and is patient specific.

Soft tissue

Soft tissue deficiency can be seen in up to 82% of the patients with CFM (18). In 2019, a systematic review on the techniques used to treat soft tissue deficiency in CFM (259) included 38 papers that covered five types of treatment: fat grafting, microvascular free tissue transfer, the pedicled flap, alloplastic implants, and functional reconstruction with cross-facial nerve grafting. The outcomes of treatment were not quantified, nor were complications or need for revisional surgery specified in the included articles (259). Reconstruction with free flaps was reported in 24 articles and 129 patients with CFM, typically those with severe soft tissue deformities. The parascapular fasciocutaneous flap (n=67) and inframammary extended circumflex scapular flap (n=18) were most frequently used and outcomes were considered positive or satisfactory in most studies. Twenty percent of the flaps needed debulking procedures. Structural fat grafting as initial and sole treatment to correct facial asymmetry in CFM was reported in eight articles. A mean number of 2.7 fat grafting sessions were needed (range 1-6). Quantitative outcomes in three studies showed a statistically significant increase in symmetry (259, 260). Complications were reported in 5% of the patients and included infections and contour irregularities. Fat grafting can be an effective procedure to improve facial symmetry in patients with mild to moderate mandibular hypoplasia who are unable to undergo other, more complex procedures (261). Abduch at el. performed a retrospective analysis on 17 patients with unilateral CFM who received a dermal-fat graft three years prior, at a mean age of 24 years (range 14-34 years) and had previous orthognathic surgeries. Facial symmetry, measured by horizontal lines at the nasal base and upper lip limit increased significantly (respectively 93.0% to 97.8% and 87.8% to 98.2%, p=<0.05) and no relation between the Pruzansky-Kaban type and outcome of fat graft treatment was observed (262). A prospective cohort study in 142

patients which included 46 patients with CFM on fat graft retention after structural fat grafting by Denadai et al. was published in 2017 (263). A significant progressive reduction of soft-tissue thickness was found after the first three months, which stabilized in the months thereafter. This may have been due to confounding factors such as swelling and inflammation. The fat graft retention rate was 67.7%. Negative predictors for fat retention were older age, previous bone surgery at treatment place, and grafted volumes. Retention rates were higher in paediatric patients compared to adults (263). Fat grafting of the lower face to reconstruct volumetric asymmetries in growing patients led to a significant increase in symmetry up to one-year after surgery in the studied cohort of 73 patients with CFM by Denadai et al. (264). Tanna et al. studied the use of a microvascular free flap compared to serial fat grafting in a cohort of 31 patients with CFM. Both groups had a similar degree of facial asymmetry. Serial fat grafting showed lower complication rates (12% versus 5%) and a significantly higher degree of facial symmetry, whereas no significant difference in patient or physician satisfaction was noted (265). The positive outcomes of fat grafting and the low complications rates and a low treatment burden makes fat grafting a reasonable option for most CFM patients in whom soft tissue correction is indicated. Soft tissue reconstruction may influence other types of treatment, such as mandible or ear reconstruction and should therefore be coordinated within a multidisciplinary treatment plan.

Extracraniofacial anomalies

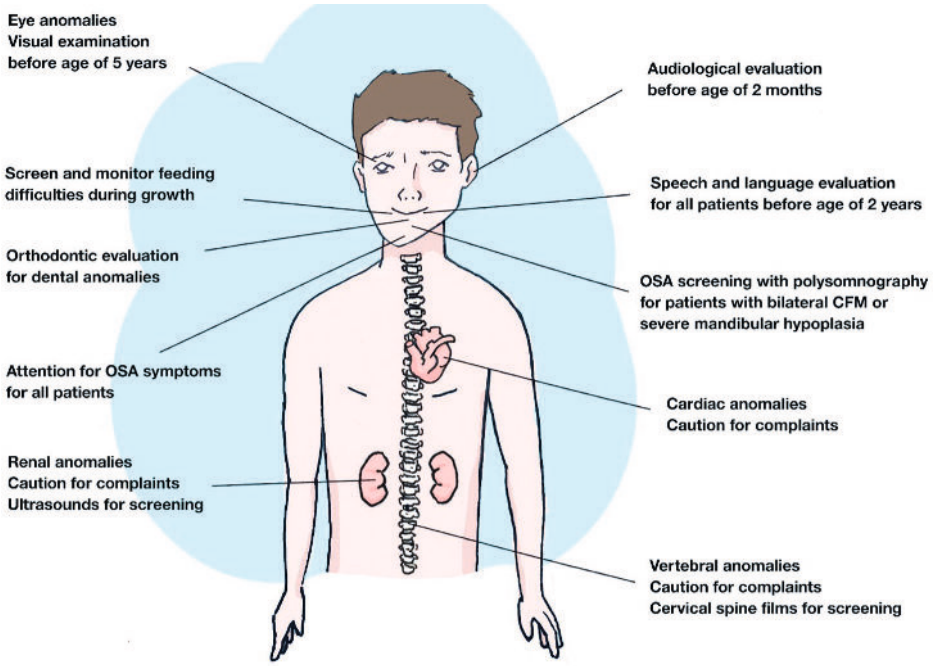
An international multicenter retrospective study of 991 patients with CFM identified extracraniofacial anomalies in 47% of participants (140). Vertebral (28%), cardiac (21%), renal (11%) and central nervous system (11%) anomalies were most common, while gastrointestinal (9%) and respiratory (2%) anomalies were less frequently observed (140). Recent systematic reviews by Renkema et al. on vertebral anomalies and anomalies of the central nervous system in patients with CFM showed a prevalence of these anomalies of respectively 8% to 79% and 2% to 69% (266, 267) The true prevalence of extracraniofacial anomalies may be higher due to a lack of systematic screening. Cohen et al. reported 85% of their 86 studied patients had extracraniofacial anomalies (27). Whereas Barisic et al. found extracraniofacial anomalies in 69% of their 259 studied patients with CFM (78). Obtaining cervical spine films and renal ultrasounds for screening is advised (139).

Discussion

This article aimed to give an overview of new insights on CFM that were published in the last decade. Large retrospective studies showed that no distinct phenotypic subgroups within cohorts of patients diagnosed with CFM have been identified, suggesting CFM is a continuous spectrum varying in type and severity of affected structures. Goldenhar syndrome does not appear to represent a distinct clinical entity. Orbital dystopia and ocular anomalies are common in patients with CFM. All patients should be examined by an ophthalmologist before the age of 5 years. Mandibular hypoplasia can be associated with obstructive sleep apnea. Attention for symptoms of OSA is essential for all patients with CFM and patients with severe mandibular hypoplasia or bilateral CFM features at are highest risk (268). Feeding and swallow difficulties are also common in patients with CFM and most are diagnosed before the age of six months. Screening for feeding difficulties monitoring of growth is recommended. As patients with CFM, especially those with hearing problems and/or mandibular hypoplasia plus microtia, are at increased risk for developing speech and language difficulties, evaluation by a speech and language therapist is indicated for all patients before the age of 2. Patients should also be examined by an orthodontist as dental and occlusal anomalies occur frequently. Most patients with CFM have microtia, and multiple treatment options are available. Reconstruction with autologous rib is considered the most durable treatment option with good long-term results for patients with CFM, but outcomes are dependent on surgical skill. Hearing loss is associated with microtia but can be observed on the unaffected side. The high prevalence of hearing loss warrants complete audiologic evaluation in early infancy for all patients with CFM. Facial nerve palsy in CFM is common and varies in severity. Common treatments for soft tissue deficiency include fat grafting, local flaps, free flaps, or alloplastic implants. Due to the positive outcomes and low complication rate with a low burden of treatment, fat grafting is considered beneficial for most patients who wish soft tissue correction. The choice for treatment should always be discussed within the multidisciplinary team as it might influence other types of treatment and improves parent satisfaction and knowledge (269). The high prevalence of vertebral, cardiac, and renal anomalies necessitates alertness for clinical signs associated with these anomalies to prevent potential harm.

This review focused on the medical and surgical studies that have recently been published on CFM; however, it did not encompass all facets of the condition. Our review did not include recent publications focused on the etiology of CFM nor studies focused on the psychosocial outcomes in CFM.

Figure 10.2: *Recommendations for care*



Future research

Several large multicenter studies have been conducted in the past 10 years and advanced our understanding of CFM. Future research that incorporates patient reported outcomes And leverages multicenter networks to conduct prospective studies will enhance our ability to study treatment outcomes. Use a of uniform registration and outcome measurement tool can help identify optimal treatment strategies (39). Furthermore, it would be helpful to establish consensus on diagnostic criteria and gain more knowledge on the etiology of CFM to be able to help patient better in the future and provide better information (220). Cooperation between craniofacial centers is needed to improve care for future patients.

11

European guideline craniofacial microsomia

a summary

A summary of the European Guideline Craniofacial Microsomia, based on: Ruben W. Renkema and the ERN CRANIO Working Group on Craniofacial Microsomia, European Guideline Craniofacial Microsomia, Journal of Craniofacial Surgery. 2020 Nov/Dec;31 Suppl 8:2385-2484. doi: 10.1097/SCS.0000000000006691. PMID: 32804824.

Introduction

Craniofacial microsomia (CFM) is estimated to occur in 1:3000 to 1:5000 live births and is the second most common congenital disorder of the face after cleft lip and palate (45). CFM is a heterogeneous congenital disorder which is characterised by a unilateral or bilateral underdevelopment of the structures arising from the first and second pharyngeal arch. The mandible, zygoma, ears, facial soft tissue, orbits, and facial nerve may be underdeveloped in patients with CFM and extracraniofacial anomalies such as vertebral, renal or cardiac anomalies may be present. The cause of this condition is unknown, though CFM has been associated with prenatal exposures and genetic abnormalities (45). The diagnosis is based on clinical assessment, and no clear diagnosis criteria exist. Although microtia is common in patients with CFM, it is still debated in literature whether isolated microtia is a separate entity or part of the CFM 'spectrum' (4, 78).

Various classification models have been proposed to categorise patients with CFM based on its severity (21, 25, 53, 100-102). The most commonly used system is the O.M.E.N.S. classification, which describes the degree of hypoplasia of the Orbit (O), Mandible (M), Ears (E), Facial Nerve (N), and Soft Tissue (S) (6, 25). Extracraniofacial anomalies, facial clefting, canting of the occlusal plane, and detailed assessment of eye and ear anomalies is included in this classification as well (6, 20). A more detailed classification of the mandibular deformity, based on radiography, was proposed by Pruzansky and later subcategorised by Kaban (21, 23, 34). In this classification model the level of underdevelopment of the mandible is graded as I, IIA, IIB, and III.

Diagnosis, treatment and outcome assessment is challenging due to a wide phenotypic spectrum (45). As a result, treatment options vary within and among different European countries and are often based on expert opinion. However, craniofacial microsomia (CFM) remains one of the most common congenital conditions treated in craniofacial centers worldwide.

The facial characteristics of patients with CFM show an overlap with other craniofacial anomalies, such as facial clefts or Treacher Collins (mandibulofacial dysostosis). These patients experience similar difficulties due to the underdevelopment of craniofacial structures, such as the mandible, midface, eyes and/or ears (270).

This may include difficulties with breathing, feeding, speech, hearing, and/or developmental delay. Potential screening and treatment and the multidisciplinary approach needed for these patients has overlap with the policy for patients with CFM. This guideline might be helpful to organise and optimise care for patients with similar craniofacial characteristics.

Objective

This guideline provides recommendations for medical practice on all patients with craniofacial microsomia. This includes patients with Goldenhar syndrome, hemifacial microsomia, oculo-auriculo-vertebral spectrum/dysplasia and facio-auriculo-vertebral sequence. It is based on the results of scientific research and subsequent forming of recommendations by a multidisciplinary working group, composed of representatives of the medical specialties involved in the treatment of craniofacial microsomia, related professional disciplines, and other parties involved.

The guideline can support healthcare professionals in discussing the use of certain techniques or instruments with other healthcare professionals or their national council. In addition, this guideline will provide CFM patients (and their parents) and healthcare professionals with an overview of the optimal care concerning the various and multidisciplinary aspects of craniofacial microsomia.

This guideline is primarily written for all healthcare professionals involved in the care for patients with CFM, including: paediatricians, oral and maxillofacial surgeons, plastic surgeons, orthodontists, otorhinolaryngologists, neurosurgeons, orthopaedic surgeons, ophthalmologists, anaesthesiologists, geneticists, psychologists, and speech therapists. Secondly, this guideline is made to provide patients and parents of patients or other persons who are involved in the medical care of adults or children with CFM with more information about the care process.

ERN-CRANIO

This guideline is an initiative from the ERN-CRANIO. European Reference Networks (ERNs) are virtual networks of healthcare providers from across Europe. The networks aim to pool expertise on complex and rare diseases and concentrate knowledge and resources. ERN-CRANIO focuses on rare and/or complex craniofacial anomalies and ear, nose and throat (ENT) disorders. ERN-CRANIO seeks to facilitate cooperation between multidisciplinary experts across Europe to support

the provision of high-quality care. It is a multidisciplinary network of highly specialised healthcare professionals. More information and updates can be found on the website of the ERN-CRANIO: https://ern-cranio.eu/

Methods

The multidisciplinary steering group, appointed to develop the guideline, consisted of eight professionals specialised in maxillofacial surgery and plastic surgery. Professionals represented the following countries: the Netherlands, the United Kingdom, France, Spain, and Finland. The steering group members were mandated by their professional organisation. Experts on non-surgical topics of the guideline were consulted to review the chapters and write recommendations.

The content of this guideline is based on evidence from published scientific research. One systematic search of literature was performed to identify all available literature on craniofacial microsomia and synonyms. The search was conducted in Embase, Pubmed/Medline Ovid. Searches were limited to the Dutch and English languages. In addition, articles were extracted from reference lists of relevant literature. A total of 1,747 articles were screened on title and abstract. Most articles (1,488) were excluded and 259 articles were reviewed on full text. A total of 101 articles were included in the guideline. The selected studies were categorised according to the framework of the guideline. The full search strategy is reported in the full version of the guideline.

Each chapter is based on a similar outline consisting of an: introduction, literature search, literature review, conclusions, considerations, recommendations, and future research. Under the headings Summary of the literature/Conclusions only published studies/guidelines are discussed. Case Reports, expert opinions, editorial and letters were excluded. Narrative reviews were likewise excluded except for chapter 4.5, 5.2, and 5.3. Since there was hardly any evidence, the available narrative review was of importance. Individual studies were systematically assessed, based on pre-established methodological quality criteria, using the EBRO method. The methodological quality of individual studies was categorised in five levels (table 11.1) and the level of evidence was categorised in four levels (table 11.2). The level of conclusion was not assessed for studies referring to prevalence.

***Table 11.1:** Classification of methodological quality*

	Intervention	Diagnostic accuracy research	Side effects*, aetiology, prognosis
A1	Systematic review of at least two independent studies of the level A2		
A2	Randomised, double blind, comparative clinical research of good quality and with adequate size.	Research compared with a reference test (golden standard) with predefined cut-off values and independent rating of results and the golden standard, with an adequate number of patients who have all had the index and the reference test.	Prospective cohort research of adequate size and follow-up with adequate control for confounding and selective follow-up is sufficiently excluded.
B	Comparative research but not with all the characteristics included in A2 (including patient-control research and cohort research).	Research compared with a reference test but not with all characteristics included in A2.	Prospective cohort research but not with all characteristics included in A2 or a retrospective cohort research or patient-control research.
C	Not comparative research		
D	Opinion of experts		

* This classification only applies in situations were controlled trials are not possible for ethical reasons. If they are possible, then the classification applies to interventions.

***Table 11.2:** Level of conclusions*

	Conclusion based on
1	Research of level A1 or at least two independent studies of level A2
2	One study of level A2 or at least two independent studies of level B
3	One study of level B or C
4	Opinion of experts

The articles are assessed under the heading ''Summary of the literature.'' Next, the scientific evidence is briefly summarized in ''Conclusions.'' The main literature on which a conclusion is based is mentioned as well, including the level of evidence (table 11.2). Other aspects than scientific evidence may be relevant to making a recommendation as well, such as patient preferences (derived from the results of the focus group sessions or relevant literature on the patient perspective), costs, availability, or organizational aspects. These kinds of aspects, provided they have not been subject of research, are mentioned under the heading ''Considerations.''

The experience and the opinion of the working group members have been key to the other considerations. The "recommendations" provide an answer to the basic question and are based on the best available scientific evidence and the most important considerations. The strength of the scientific evidence and the weight that the working group assigns to the considerations together determine the strength of the recommendation.

Patient perspective

When developing this guideline, the working group particularly strived for incorporating the patient perspective. All doctors included in the ERN-CRANIO, subgroup 'craniofacial microsomia', were asked to approach their CFM patients. This led to the identification of a group of 32 interviewees: 14 from Italy, 13 from Germany, 4 from the Netherlands, and 1 from Sweden, including 9 patients and 23 parents of patients. An online survey was set up with open and closed questions. All patients and parents of patients were asked what difficulties they (had) experienced in the healthcare process and in their lives. The questionnaire was built up according to the proposed guideline chapters and the healthcare process, namely diagnosis and referral, organization of care, communication and information, breathing difficulties, feeding difficulties or speech difficulties, surgical treatments, care for microtia, orthodontic treatment, vertebral anomalies, psychosocial aspects of care, and follow-up. Additionally, all patients were asked to name the top three difficulties they experienced in the care process. Results were analyzed by the research fellow (R.W. Renkema) and nurse specialist (E.L. Weissbach).

Content

This summary of the European Guideline Craniofacial Microsomia will discuss the main conclusions of literature and the recommendations of each chapter of the guideline. The following chapters were included in the guideline:

Chapter 3 – Diagnostic criteria for craniofacial microsomia
Chapter 4 – Screening, monitoring and indication for treatment
- 4.1 Breathing difficulties in craniofacial microsomia
- 4.2 Feeding difficulties in craniofacial microsomia
- 4.3 Speech difficulties in craniofacial microsomia
- 4.4 Hearing difficulties in craniofacial microsomia

Diagnostic criteria

In patients with craniofacial microsomia (CFM), the facial structures arising from the first and second pharyngeal arches may be underdeveloped. The variety in type and severity of underdevelopment of these structures make CFM a heterogeneous disorder. The diagnosis of CFM is based on clinical assessment, though no clear diagnostic criteria exist. A wide range of terminology is used to refer to patients with CFM. The use of different terminology and lack of diagnostic criteria is confusing for patients and healthcare professionals.

The main questions focuses on which criteria a child or adult with craniofacial microsomia is diagnosed.

Literature shows that in patients with craniofacial microsomia the mandibular deformity, orbital deformity and soft tissue deficiency are correlated. However, no specific clusters of patient groups within craniofacial microsomia are present, indicating craniofacial microsomia is a continuum of anomalies. In addition, Goldenhar syndrome is not a separate diagnosis from craniofacial microsomia but is part of the phenotypic spectrum of craniofacial microsomia.

Recommendations
Exclusively use the term craniofacial microsomia. Discard the use of other terms such as Goldenhar syndrome, hemifacial microsomia or auriculo-oculo-vertebral spectrum.

It is advised to use the diagnostic criteria for craniofacial microsomia developed by the ICHOM Craniofacial Microsomia group (shown in table 11.3) (28).

***Table 11.3:** Diagnostic criteria for Craniofacial Microsomia*

CFM is defined by:	2 major criteria, or 1 major + 1 minor criteria, or 3+ minor criteria
Major criteria	Mandibular hypoplasia Microtia Orbital / facial bone hypoplasia Asymmetric facial movement
Minor criteria	Facial soft tissue deficiency Pre-auricular tags Macrostomia Clefting Epibulbar dermoids Hemivertebrae

Breathing difficulties

Obstructive sleep disordered breathing (SDB) can be considered as a syndrome of upper airway dysfunction during sleep (268). It is characterized by snoring and/or increased respiratory effort due to increased airway resistance and pharyngeal collapsibility (271, 272). Of the obstructive SDB entities, obstructive sleep apnea (OSA) in particular is known to be of clinical significance. It is defined by a disruption of the normal oxygenation, ventilation and sleep pattern due to recurrent upper airway obstructions (223). Patients with craniofacial microsomia (CFM) are at increased risk for obstructive SDB and OSA due to the underdevelopment of the mandible, which leads to obstruction of the upper airway. Describing the policy for breathing problems in patients with CFM is of importance since these patients are at increased risk for OSA. Untreated OSA may lead to metabolic, cognitive and/or cardiovascular pathology and can have a negative impact on the quality of life. Therefore, timely diagnosis and treatment of OSA in patients with CFM is considered of importance to patients.

Questions focused on three specific issues regarding breathing problems (OSA) in patients with craniofacial microsomia: 1) type, prevalence and severity, 2) policy for screening and monitoring, and 3) indications and policy for treatment.

Literature shows that the prevalence of obstructive sleep apnoea in CFM is 7 - 24%, presumably approximating 18%. In addition, the severity of obstructive sleep apnoea was mild in 19-29%, moderate in 17-29%, severe in 36-43%, and in 29% the severity of obstructive sleep apnoea was unknown.

Recommendations

The working group recommends that all patients with CFM should be screened with a questionnaire biannually (the Paediatric Sleep Questionnaire (PSQ)), at least up to the age of six, in the outpatient department for a clinical history of obstructive sleep apnoea. If there is a suspicion for obstructive sleep apnoea a polysomnography has to be performed. All patients who have Pruzansky-Kaban IIb or III mandibles and/or are bilaterally affected have to undergo a polysomnography (sleep study) to screen for obstructive sleep apnoea in the first year of life.

In addition they recommend that treatment of children with CFM and OSA has to be discussed in a multidisciplinary team. Furthermore, in young infants and children with CFM and OSA, non-surgical respiratory support has to be considered to treat OSA. In older children with mild to severe obstructive sleep apnoea, adenotonsillectomy (ATE) may be the treatment of first choice. In children with CFM and severe OSA a tracheostomy has to be considered at all ages. Mandibular distraction osteogenesis (MDO) should be considered to treat patients with severe obstructive sleep apnoea who have a tracheostomy or to reduce the necessity for a tracheostomy or respiratory support.

Feeding problems

Characteristic features of patients with CFM, such as mandibular hypoplasia, facial nerve and/or masticatory muscle weakness, or anomalies of the oropharynx and larynx may all play a contributing factor in the feeding difficulties. Feeding problems may relate to difficulties in suckling, mastication, dysphagia, and/or failure to thrive. In 15-22% of the cases a cleft lip/palate is diagnosed in patients with CFM, which may further enhance the risk for feeding problems (185, 273). Diagnosis and treatment of feeding problems in an early phase is essential to prevent further harm. Especially in children with CFM, who may be at increased risk for these problems, vigilance for feeding problems is essential.

Questions focused on three specific issues regarding feeding problems in patients with craniofacial microsomia: 1) type, prevalence and severity, 2) policy for screening and monitoring, and 3) indications and policy for treatment.

The prevalence of feeding difficulties in craniofacial microsomia varies from 26% to 63%, presumably approximating 26%. Type of feeding difficulties encountered in craniofacial microsomia are: difficulties in suckling, swallowing, chewing, complains of reflux, a restricted mouth opening, failure to thrive. Severity (based on the criteria defined by Caron et al. (187)) of feeding difficulties in patients with craniofacial microsomia:

- 46% of the patients had mild feeding difficulties
- 13% of the patients had moderate feeding difficulties
- 41% of the patients had severe feeding difficulties

Recommendations
The working group recommends children with craniofacial microsomia should be screened with a questionnaire biannually (The WHO or national Growth Charts), at least up to the age of six, and monitored regularly for feeding difficulties by a paediatrician or multidisciplinary team. A speech and language therapist should be involved in patients who require tube feeding. In addition, children with craniofacial microsomia with feeding problems should be treated by a multidisciplinary team consisting a paediatrician, speech and language therapist and a dietician.

Close monitoring of growth and development should be done by a multidisciplinary team during hospital admission and after discharge. This multidisciplinary should consist of a paediatrician or paediatric gastroenterologist, speech and language therapist and dietician. In addition, depending on the severity of feeding problems different feeding strategies should be considered in order to achieve optimal growth and development.

Speech and language

Speech, language and communication are crucial to the development of children and young people which impact on educational achievement; emotional, social and mental wellbeing, and opportunities in life. Individuals with speech, language and

communication needs (SLCN) present with a range of receptive and expressive difficulties. Early detection of delays in the development of speech and language is imperative to facilitate good communication, social interaction and improved quality of life (45, 274). As patients with CFM may be of increased risk for and language difficulties, early screening is indicated.

Questions focused on three specific issues regarding speech and language difficulties in patients with craniofacial microsomia: 1) type, prevalence and severity, 2) policy for screening and monitoring, and 3) indications and policy for treatment.

Prevalence rates of speech difficulties reported in CFM vary from 38% - 74%. Communication difficulties that may present in craniofacial microsomia include: velopharyngeal dysfunction; dysphonia; impaired speech articulation; receptive and expressive language difficulties and social communication difficulties.

Recommendations

Regarding policy for screening and monitoring, it is advised to screen preverbal communication and babbling skills at the age of nine months to decide if intervention is warranted. In addition, it is advised to evaluate receptive and expressive language skills at the age of two years and biannually until the age of eight years in all patients with craniofacial microsomia. Children with CFM with and without a cleft palate should be screened at the age of two years to examine for potential risk of velopharyngeal dysfunction. Patients with tracheostomy should be screened for speaking valve suitability or an augmentative and alternative communication system.

In addition, facilitate receptive and expressive language development using a range of behavioural techniques such as modelling, imitation, repetition and extension. Furthermore, intervention for social communication difficulties is recommended; e.g. development of non-verbal communication skills (e.g. eye contact, turn-taking); conversational skills, recognitions of emotions and emotional regulation. Patients with cleft speech characteristics should have articulation therapy when identified. Intervention for social communication difficulties is recommended.

Hearing difficulties

Hearing is a sensory experience that facilitates communication and social interaction. Hearing impairment may lead to difficulties in learning, language and cognitive development, academic achievements, and can have a negative social impact on children (275). Early detection and intervention of hearing loss is associated with improved outcomes in all children, hence the implementation of neonatal hearing screening programmes worldwide.

Questions focused on three specific issues regarding hearing difficulties in patients with craniofacial microsomia: 1) type, prevalence and severity, 2) policy for screening and monitoring, and 3) indications and policy for treatment.

The prevalence of hearing difficulties in patients with craniofacial microsomia is:

- Unspecified hearing loss: 50% - 82%
- Conductive hearing loss: 30% - 86%
- Sensorineural hearing loss: 1% - 20%
- Mixed hearing loss: 6% - 17%

In 6% - 10% of the patients with unilateral craniofacial microsomia, hearing difficulties can be present bilaterally or solely on the contralateral side. Patients with bilateral craniofacial microsomia were not found to have a higher risk for hearing difficulties compared to patients with unilateral craniofacial microsomia.

The most common anomalies of the ear in patients with craniofacial microsomia are:

- Outer ear: atresia or stenosis of the external auditory canal
- Middle ear: dysplastic or absent ossicles
- Inner ear: vestibule deformity or semicircular canal anomalies

Recommendations

Regarding policy for screening and monitoring, it is advised to perform neonatal hearing test in all new-borns with craniofacial microsomia. If indicated, complete audiological evaluation in an experienced audiology center should be performed

before the age of three months to ensure timely treatment. Re-evaluate hearing tests in patients with craniofacial microsomia by the age of 24-30 months. Audiologic intervention should be initiated before the age of six months in patients with congenital hearing loss. Regularly perform otoscopy and audiometry in patients with CFM including microtia and/or cleft palate by the ENT doctor/otolaryngologist.

Furthermore, treat moderate to severe hearing loss, either with non-surgical or surgical options. Coordinate surgical approach and timing in a multidisciplinary team regarding hearing augmentation and other surgical procedures including ear reconstruction and mandibular surgeries.

Eye anomalies

Originally, the triad of Goldenhar syndrome, now believed to be part of the craniofacial microsomia (CFM) 'spectrum', consisted of mandibular dysostosis, ear malformations and epibulbar dermoids (16). This illustrates the prominent role eye anomalies have in CFM. Patients with CFM regularly present with epibulbar dermoids or other eye anomalies. Commonly seen eye anomalies in patients with CFM, such as epibulbar dermoids and colobomata, can lead to various patient relevant consequences. Limbal dermoids can cause amblyopia, difficulties with eyelid closure, irritation, corneal erosion, and/or aesthetic difficulties. Other eye anomalies, as colobomata, can lead to exposure keratopathy, corneal ulceration, retinal detachment and/or cataract (276).

Questions focused on three specific issues regarding eye anomalies in patients with craniofacial microsomia: 1) type, prevalence and severity, 2) policy for screening and monitoring, and 3) indications and policy for treatment.

Most reported eye anomalies in CFM include: lipodermal dermoids (prevalence: 4%-61%), epibulbar dermoids (prevalence: 10%-56%), colobomata (eyelid) (prevalence: 3%-32%), blepharoptosis (prevalence: 9%-37%), microphthalmus (prevalence: 5%-71%), strabismus (prevalence: 12%-22%), and lacrimal duct or gland anomalies (prevalence: 5%-11%). Patients with bilateral craniofacial microsomia have a significant higher risk for eye anomalies (studied in 755 patients, p=<0.001). Visual loss could be seen in 8% of the patients with craniofacial microsomia, although this was reported in a single study with small sample size (n=49).

Recommendations

All patients with craniofacial microsomia should be screened at least once during the visual development (before the age of five) by an orthoptist and ophthalmologist. Depending on the results, follow-up visits need to be scheduled on a regular basis.

Children with ocular disturbances need to be evaluated by a specialised orthoptist and ophthalmologist during the visual development (before the age of five). In addition, optimal spectacle correction should be provided in case of a refractive error. Amblyopia should be treated before the age of six. When surgery is considered this has to be discussed in a multidisciplinary team, carefully evaluating the harms and the benefits, especially in the case of young children in whom vision is still developing. Ultrasound imaging of the ocular dermoid needs to be conducted if extension posteriorly and into the orbit is suspected.

Dental deformities

Patients with craniofacial microsomia (CFM) are presumably at increased risk for teeth agenesis or other dental deformities. A relation with mandibular hypoplasia or other characteristics of CFM may be present. Awareness of dental deformities in patients with CFM is essential to identify problems in an early phase and start treatment if needed. Occlusal problems may occur due to dental anomalies, which could lead to oral health damage and/or feeding difficulties. Orthodontic treatment may be indicated to treat these deformities.

Questions focused on three specific issues regarding dental deformities in patients with craniofacial microsomia: 1) type, prevalence and severity, 2) policy for screening and monitoring, and 3) indications and policy for treatment.

The prevalence of tooth agenesis in craniofacial microsomia varies from 8% to 33%, excluding third molar agenesis, and is thus more frequent than in the general population (range 1% - 11%). Patients with severe craniofacial microsomia (Pruzansky-Kaban type IIb/III) showed a delay in dental development compared to milder patients (Pruzansky-Kaban type I/IIa) and to healthy children ($p<0.05$).

Recommendations

Regarding policy of screening and monitoring, patients with craniofacial microsomia should have routine dental care. In addition, patients with craniofacial microsomia should be seen from age five by an orthodontist within a multidisciplinary team to diagnose dental deformities. Perform screening for dental deformities by intra-oral inspection and standard dental records. Take orthodontic records in a structured schedule, at 5-6, 9-10, 12, 15 and 17-18 years of age.

Regarding policy for treatment, dentofacial orthopaedic treatment can be considered appropriate in very mild craniofacial microsomia cases. In severe craniofacial microsomia patients, current evidence does not promote activator treatment. Orthodontic treatment should be discussed and coordinated in a multidisciplinary team depending on the decision to conduct orthognathic surgery or not.

Vertebral anomalies

Various types of vertebral anomalies have been reported in patients with CFM, such as hemivertebrae, blockvertebrae, or scoliosis (52, 76, 78). Vertebral anomalies may have several negative consequences and be present without symptoms (55, 67). Dysplastic cervical vertebrae can lead to cervical spine instability, which could have various neurological consequences if manipulated (67). Another risk of vertebral anomalies is the development of progressive scoliosis or fractures of ankylosed vertebrae. Early identification and treatment of vertebral anomalies is relevant to prevent these potential harms.

Questions focused on three specific issues regarding vertebral anomalies in patients with craniofacial microsomia: 1) type, prevalence and severity, 2) policy for screening and monitoring, and 3) indications and policy for treatment.

The prevalence of vertebral anomalies in craniofacial microsomia is 8 - 79%, presumably approximating 28%. Almost half of the patients (44% of 991 patients studied) with craniofacial microsomia show symptoms of vertebral anomalies: torticollis, back or neck pain, and/or limited neck movement. Patients with bilateral craniofacial microsomia have a higher risk for having vertebral anomalies compared to patients with unilateral craniofacial microsomia. Patients with craniofacial microsomia and vertebral anomalies have a higher risk for additional extracraniofacial anomalies in other tracts.

Recommendations

Screening questions and clinical examinations related to neck/back symptoms should be undertaken at initial consultation and as part of pre-operative workup. All patients with craniofacial microsomia who have neurologic symptoms (e.g., paraesthesia, numbness, or weakness) or neck pain suggestive of neuronal injury should be evaluated as soon as possible by a (paediatric) neurologist. Patients should be referred appropriately and attention to the cervical spine should be payed when patients are undergoing general anaesthesia.

Regarding treatment, surgical fusion and/or bracing in patients with vertebral anomalies may be necessary to obtain spinal stability and to prevent secondary injury of the spinal structures. A multidisciplinary approach in treatment and timing is warranted to optimise outcomes for these patients.

Psychosocial difficulties

Atypical facial appearance can lead to poor social acceptance by others and cause psychosocial difficulties (277, 278). Patients with an unusual facial appearance or craniofacial syndromes can have difficulties with psychological adjustment and experience teasing. Difficulties in facial expressiveness or eye contact may be caused by facial nerve deficits in some patients with CFM (279). Difficulties with hearing, speech or vision have been associated with psychiatric disorders, behavioural problems, and/or social difficulties (280-283). Additionally, the increased risk for teasing or potential neurodevelopmental delays may also cause a higher risk for psychosocial difficulties in patients with CFM. Although patients with craniofacial syndromes are at increased risk for psychosocial difficulties, parents/caregivers of these patients also experience difficulties.

Questions focused on three specific issues regarding psychosocial difficulties in patients with craniofacial microsomia: 1) type, prevalence and severity, 2) policy for screening and monitoring, and 3) indications and policy for treatment.

Younger children (age 8-10) with a craniofacial anomaly may experience more problems with anxiety, low mood, anger, and peer relationships compared to older children (age 11-17). Patients and/or parents of patients with craniofacial microsomia have a higher risk of experiencing social stigma, low self-esteem and active

or passive bullying, especially in childhood. Patients with craniofacial microsomia may have a slightly lower IQ score and more learning difficulties compared to healthy controls. Patients with craniofacial microsomia might have a higher risk for language- and motor skills delays compared to healthy controls.

Recommendations

The working group recommends that all craniofacial microsomia patients should have access to a clinical psychology service with appropriate professional expertise and knowledge of craniofacial microsomia. Time points for reviews and screening should observe key life transitions such as birth, starting school, transition to secondary school, etc. In addition, to measure psychosocial wellbeing and family stress, validated self-reported psychological outcome measures should be obtained from to all craniofacial microsomia patients as a matter of routine to screen for the presence of behavioural, emotional, social and/or learning difficulties. This includes the CleftQ, CFEQ, YP-CORE, HADS and Distress Thermometer for Parents and should be performed at age 2, 5, 8 and 22. Elevated scores should alert clinicians to the potential need for further assessment or support. Standardised measures should assess levels of emotional distress as well as evaluate difficulties related to visible differences.

Parents of newly diagnosed children with craniofacial microsomia should have access to a specialist clinical psychology service with expertise and knowledge of the condition. Information on support groups and organisations should be provided, both at initial contact and at regular review.

When appropriate, clinicians should liaise with local services and schools to discuss the child's support needs. Cognitive assessment may be offered if warranted. Patients with craniofacial microsomia should have access to specialist psychological support, particularly those who are presenting with low self-esteem, depression/low mood, anxiety, appearance- or treatment-related concerns, including adjustment difficulties or trauma as a result of surgical/medical interventions.

Furthermore, the psychologist is part of the coordinated care in the multidisciplinary team. Psychological input is required pre- and post- facial surgery to monitor expectation and acceptance.

Mandible and maxilla

Mandibular hypoplasia is seen in 73% to 91% of patients with CFM with varying severity (184, 206). Maxillary hypoplasia in patients with CFM could be secondary to the mandibular deformity. A deviation of the mandible to the affected side is seen in patients with CFM, causing facial asymmetry and canting of the occlusal plane (216). Besides occlusal problems, other functional problems may occur due to the mandibular/maxillary deformity in CFM. The risk for obstructive sleep apnoea (OSA) increases in patients with mandibular hypoplasia due to obstruction of the upper airway at tongue base level (157).

Questions focused on the indications and most optimal treatment modality to treat the for mandibular/maxillary deformity in craniofacial microsomia.

Bilateral mandibular distraction osteogenesis (MDO) appears to be an effective treatment in patients with micrognathia, respiratory distress and a tracheostomy (mean age range two months to five years). Most patients with a tracheostomy can be decannulated after bilateral MDO: 78% - 94% ('tracheostomy first' group). Some patients still require a tracheostomy after initial treatment with bilateral MDO: 5% - 11% ('MDO first' group). In patients with CFM, large differences in outcomes of MDO for treatment of breathing problems are observed. The success rate of mandibular distraction osteogenesis for obstructive sleep apnoea in patients with unilateral craniofacial microsomia appears to be low (36.4%).

Mandibular and facial asymmetry in patients with craniofacial microsomia is non-progressive. The total number of mandibular/maxillary surgeries increases if patients are treated at a younger age, independent of the severity of the mandibular hypoplasia. The long-term stability of early unilateral MDO (performed <16 years) in patients with CFM appears to be poor. Facial asymmetry often reoccurs, necessitating secondary (orthognathic) surgery.

Mandibular reconstruction with a free vascularised fibula flap may be an option for patients with craniofacial microsomia and severe mandibular hypoplasia who have no other therapeutic options. Placement of custom-made TMJ implants at skeletal maturity may be a good solution for patients with failed autogenous mandibular reconstructions.

Recommendations

The working group recommends to consider surgical management (tracheostomy, adenotonsillectomy, mandibular and/or maxillary surgery) in patients with craniofacial microsomia for the treatment of breathing problems if non-surgical therapy fails or to end non-surgical therapy. Inform patients and parents about of the uncertainty of respiratory outcomes following mandibular and/or maxillary surgery for OSA in patients with CFM.

If surgical treatment of the mandibular/maxillary deformity in patients with craniofacial microsomia is indicated to prevent or treat psychosocial problems, it is important to inform the patient about the potential benefits and harms and to ensure that the patients/parents have a realistic view of what can be expected.

It is advised to integrate the (surgical) treatment of the mandibular/maxillary deformity in patients with craniofacial microsomia in the planning of other surgeries, especially for those that affect facial symmetry, palsy, soft tissue augmentation and treatment of atresia or microtia. Use 3D planning to optimise surgical outcome of mandibular and maxillary surgery in patients with CFM.

Regarding the most optimal treatment for the mandibular/maxillary deformity in patients with CFM and OSA it is recommended to start with non-surgical treatment for the management (e.g. oxygen, CPAP) of mild-moderate OSA. Perform a tracheostomy or mandibular distraction osteogenesis in infants with mandibular hypoplasia and severe OSA who do not respond to non-surgical treatment. If the aim of surgical treatment is to end non-surgical treatment (e.g. CPAP), perform elective mandibular distraction osteogenesis. Mandibular reconstruction with costochondral bone grafts should be performed after the age of six.

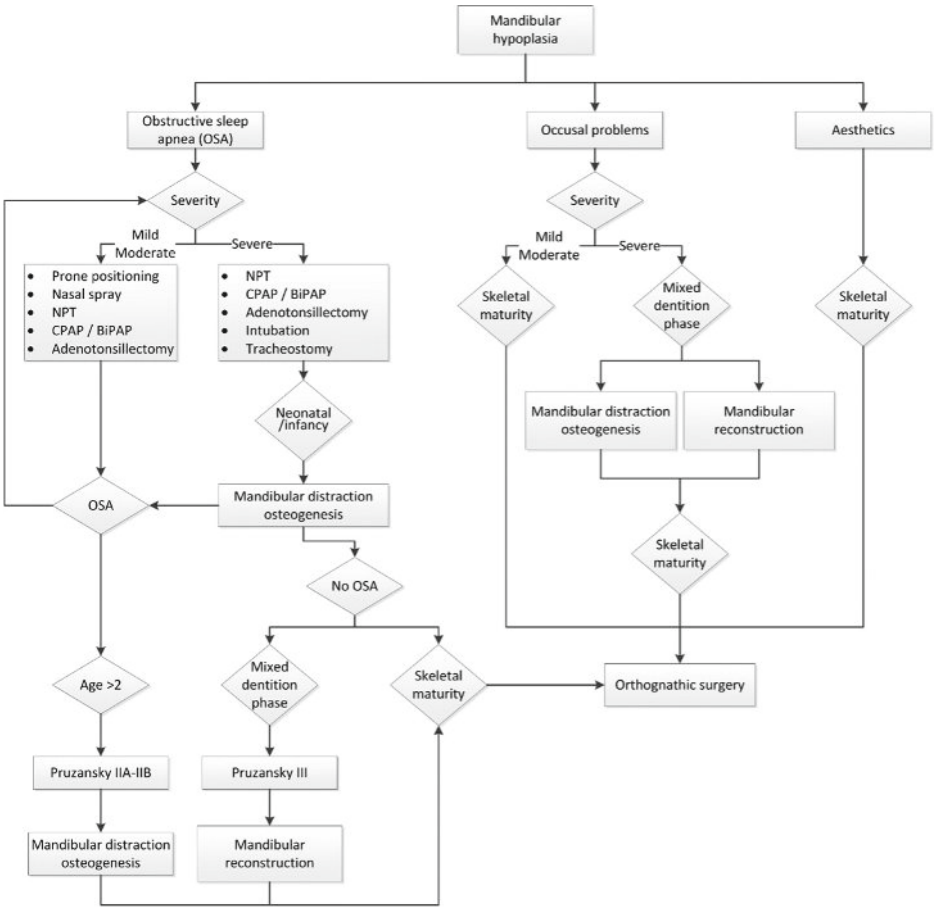
For patients with craniofacial microsomia and severe occlusal problems, perform mandibular distraction osteogenesis in mixed dentition phase. A combined orthodontic and orthognathic surgery plan is mandatory to achieve and optimise stable long-term outcomes. Perform secondary orthognathic surgery to correct occlusion at skeletal maturity.

Postpone surgical correction of the mandibular/maxillary deformity for aesthetic reasons in patients with craniofacial microsomia until skeletal maturity. The im-

plications of early surgery (i.e. repeat surgery) for psychosocial reasons should be discussed within the multidisciplinary team and with patient and caregivers. Psychological input is required pre- and post-operatively to monitor expectation and acceptance.

See figure 11.1 for an overview of the recommendations for treatment of the mandibular/maxillary deformity in patients with CFM.

***Figure 11.1:** Recommendations for treatment of facial palsy in patients with craniofacial microsomia*



Facial nerve

Palsy of the facial nerve can be seen in patients with craniofacial microsomia (CFM). The prevalence of facial palsy in patients with CFM is 22% - 53% and may be unilateral or bilateral (88, 184, 284, 285). Facial palsy, which is due to congenital underdevelopment in patients with CFM, may cause problems with eye closure, articulation of speech, oral continence, or asymmetric facial mimics and smile (257).

Questions focused on the indications and most optimal treatment modality.

In patients with peripheral facial palsy, quality of life significantly increases after treatment ($p<0.001$). No studies on patients with CFM is available on this topic. The use of tarsorrhaphy is discouraged due to poor cosmetic outcome and risk of peripheral vision loss.

To restore facial animation and a spontaneous smile, cross-facial nerve grafting is considered to be the preferred treatment for unilateral craniofacial microsomia. Other motor nerves, such as the masseter, hypoglossal, accessory or cervical nerves can be used if cross-facial nerve grafting is not possible. Most patients (91%) needed additional surgical revisions after free flap transfers, such as debulking or reanchoring of the muscle graft. Regional flaps, such as temporalis muscle transfers, can be considered for dynamic facial reanimation if cross-facial nerve grafting or free-muscle transfers are not possible.

Recommendations

The working group recommends to provide all patients with craniofacial microsomia with psychosocial support and to refer all craniofacial microsomia patients with lagophthalmos to an ophthalmologist. Surgical treatment of the upper or lower eyelids should be considered in patients with craniofacial microsomia and loss of function of the upper facial nerve branches. Coordinate the timing of facial reanimation surgery in patients with craniofacial microsomia in the planning of other major surgeries. Facial movement should by assessed with the CleftQ Appearance at age 8, 12, and 22.

Regarding the most optimal treatment the working group recommends to correct lagophthalmos due to facial palsy in patients with craniofacial microsomia with

placement of a gold weight or platinum chain, muscle transfers and/or tendon slings, or cross-facial nerve grafting. Tarsorrhaphy as a treatment for lagophthalmos in patient with craniofacial microsomia is discouraged.

Start with the injection of botulinum toxin in the non-affected depressor labii inferioris muscle if therapy is indicated in patients with craniofacial microsomia and asymmetrical lip depression due to facial palsy. Consider myomectomy of the non-affected depressor labii inferioris muscle if the outcome of treatment with botulinum toxin injections are satisfactory or dynamic techniques such as digastric muscle transfers if the outcomes are not satisfactory. Perform imaging of the digastric muscle prior to surgical muscle transfer due to the high prevalence of agenesis of the anterior belly of the digastric muscle.

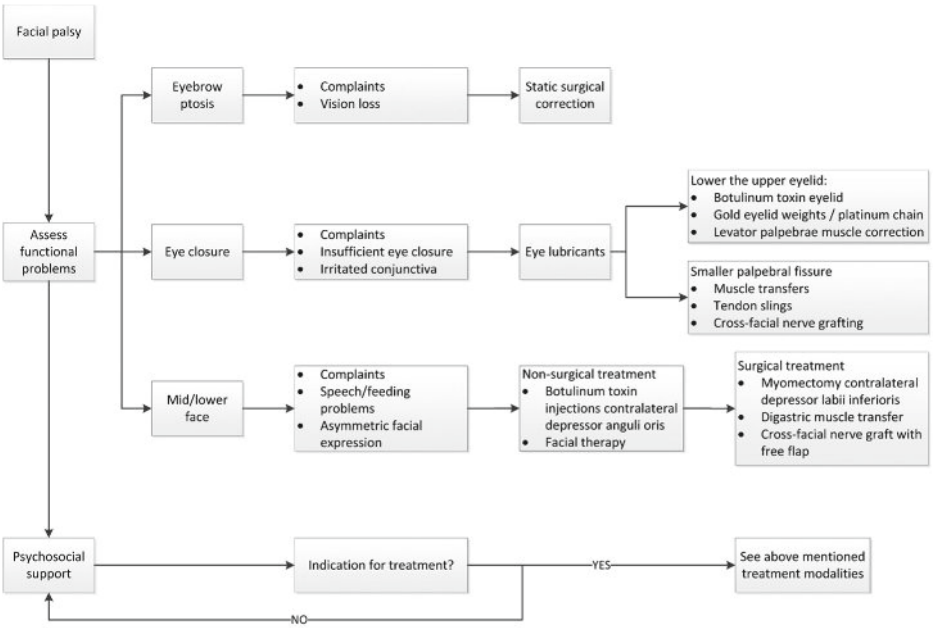
Psychological input is required pre- and post-operatively to monitor expectation and acceptance. Strive for spontaneous facial animations by using a cross-facial nerve graft with a free flap. Consider functional muscle transfer from the age of four onwards.

Reserve the use of the masseteric nerve to innervate the free muscle transfer for patients in whom cross-facial nerve grafting is not favourable, in bilateral cases, or as a babysit procedure. Consider the use of regional muscle transfers to achieve facial animation in patients with craniofacial microsomia and facial palsy if cross-facial nerve grafting with free muscle transfers is not preferred.

A facial physical therapist is part of the multidisciplinary team. Collect clinician- and patient-reported outcome measures pre- and posttreatment.

See figure 11.2 for an overview of the recommendations for treatment of the facial nerve deformity in patients with CFM.

Figure 11.2: *Recommendations for treatment of facial palsy in patients with craniofacial microsomia*



Soft tissues

One of the relevant factors leading to asymmetry in patients with craniofacial microsomia (CFM) is soft tissue deficiency. This is mainly characterised by a lack of subcutaneous fat or a deficiency of the musculature. Various types of treatment are currently used to treat soft tissue deficiency, including fat grafting, pedicles flaps, free tissue transfers, or alloplastic implants. The main factors in the selection of a type of treatment are the severity of the soft tissue deficiency, the presence of other (bony) facial deformities, and the patient's age. Recommendations on the indications and optimal treatment strategy for soft tissue deficiency in patients with CFM are important to optimise outcomes. It is essential to inform the patient on the potential harms and benefits of treatment and to ensure that the patient has a realistic view on what can be expected, especially if the indication for treatment is patient specific and based on aesthetic concerns.

Questions focused on the indications and most optimal treatment modality for the soft tissue deficiency in patients with CFM.

The results of free tissue transfers to treat soft tissue deficiency in patients with craniofacial microsomia are considered to be satisfactory or positive in most studies. Fat grafting leads to a higher level of post-treatment symmetry in patients with craniofacial microsomia compared to free tissue transfers. The severity and rate of complications of free tissue transfers is significantly higher compared to fat grafting in patients with craniofacial microsomia (27% vs 4%, p=<0.001).

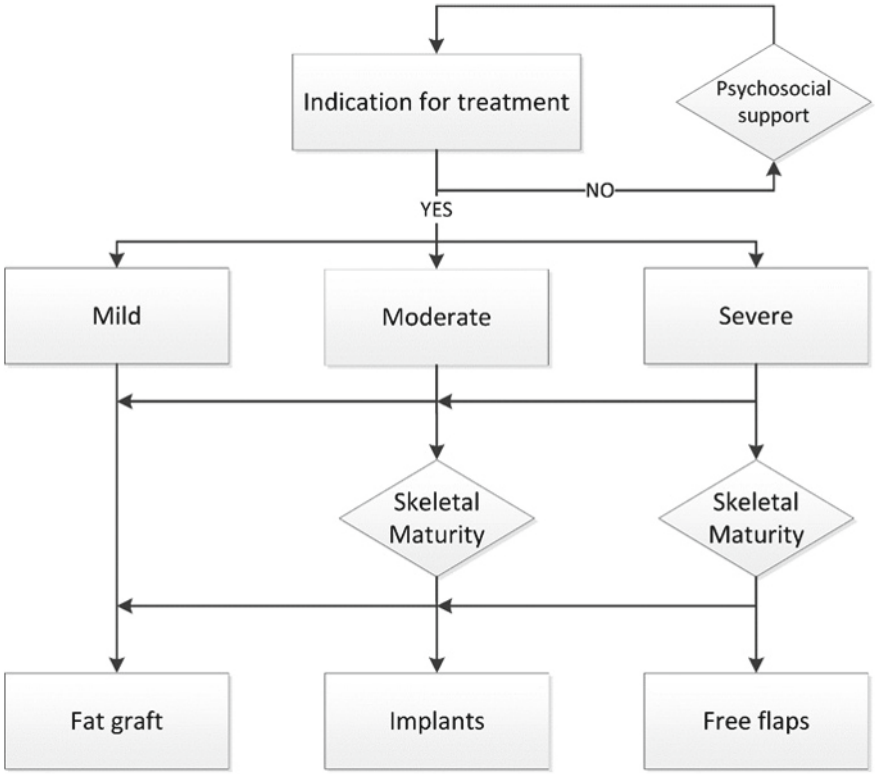
Recommendations

The indication for surgical treatment of soft tissue deficiency in patients with craniofacial microsomia is mainly aesthetic. Inform the patient about the potential benefits and harms to ensure that the patient has a realistic view of what can be expected. Patients' difficulties with facial form/asymmetry should be assessed with the CleftQ Appearance at age 8, 12, and 22.

Regarding the most optimal treatment the working group recommends psychological input is required pre- and post-operatively to monitor expectations and acceptance. Reconstruct soft tissue deficiencies in patients with craniofacial microsomia with fat grafting from childhood. Free tissue transfer is only considered in patients with a very severe soft tissue deficiency. Alloplastic implants to correct soft tissue deficiency in patients with craniofacial microsomia are ideally performed at skeletal maturity. The use of pedicled flaps for correction of soft tissue deficiency in patients with craniofacial microsomia is strongly discouraged. Coordinate the timing of surgical treatment of soft tissue deficiency in patients with craniofacial microsomia with the planning of other surgeries, especially for surgeries that affect facial symmetry such as mandibular surgeries or placement of facial implants..

See figure 11.3 for an overview of the recommendations for treatment of the soft tissue deficiency in patients with CFM.

Figure 11.3: *Recommendations for treatment of the soft tissue deficiency in patients with craniofacial microsomia*



Microtia

Microtia is one of the most common characteristics of patients with CFM as it is seen in 83% to 88% of the patients (19, 184). Besides external ear malformations, patients may have other malformations such as middle ear malformations or atresia, or the presence of branchial remnants (45). In the management of microtia and atresia improving hearing is the most important functional goal, followed by external ear reconstruction if the patient and family feel that is required. It is essential to inform the patient on the potential harms and benefits of treatment and to ensure that the patient has a realistic view on what can be expected, especially if the indication for treatment is patient specific and based on aesthetic concerns.

Questions focused on the indications and most optimal treatment modality of the ear deformity in patients with CFM.

Non-craniofacial microsomia patients who wear an osseointegrated implant- supported external silicone prosthesis are often satisfied with the result (placed at a mean age of 37-44 years). Most patients (73%) report an increase in quality of life and are satisfied with the aesthetic result (73-75%) after ear reconstruction with porous polyethylene implants. Ear reconstruction with rib is considered a durable treatment option with minimal long-term complications. The reconstructed ears show a similar growth pattern to the normal ear.

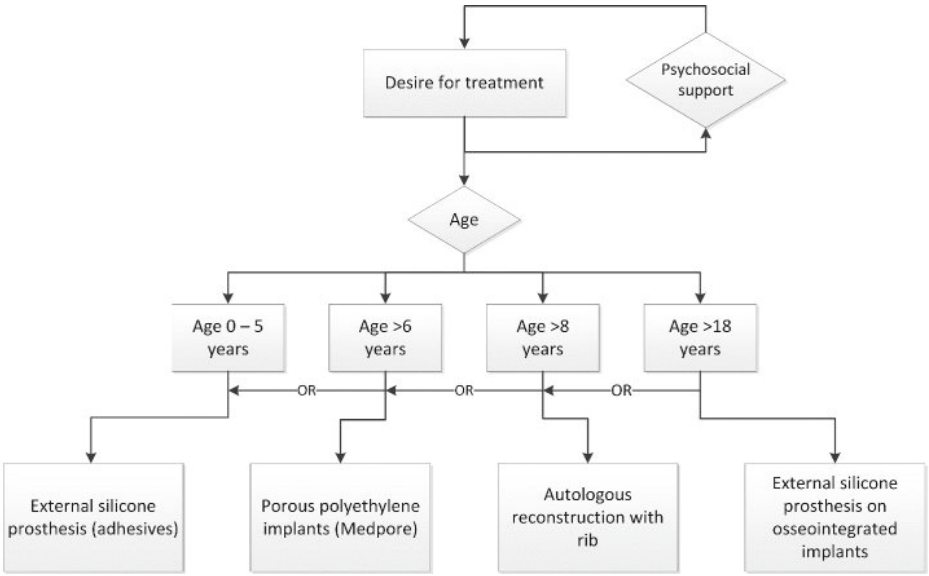
Recommendations

The indication for auricular reconstruction in patients with craniofacial microsomia is aesthetic and psychosocial. Inform the patient about the potential benefits and harms to ensure that the patient has a realistic view of what can be expected. Provide all patients with craniofacial microsomia with psychosocial support. Use the PROM Ear-Q pre- and postoperatively to assess benefit of treatment.

Regarding the most optimal treatment, patients should be treated within a multidisciplinary team setting. In addition, discus the advantages and disadvantages of the various treatment modalities with the patient and base the choice for treatment on patients' preferences. Psychological input is required pre- and postoperatively to monitor expectation and acceptance. Ear reconstruction with rib grafts is the first choice of treatment and should be performed from the age of eight onwards. Treatment before the age of eight is not recommended, but if chosen, use external silicone prosthesis attached with adhesives. If chosen, place polyethylene implants (Medpore) from the age of six onwards. Osseointegrated implants are an option for salvage procedures. Outcome measures should be obtained pre- and postoperatively with all techniques and interventions.

See figure 11.4 for an overview of the recommendations for treatment of microtia in patients with CFM.

Figure 11.4: *Recommendations for treatment of microtia in patients with craniofacial microsomia*



Organisation of care

Craniofacial microsomia (CFM) is a condition involving various congenital disorders which requires the involvement of multiple healthcare professionals. A multidisciplinary team is needed to provide and align the complex, long-lasting care for patients with CFM. Multidisciplinary care requires good coordination and communication among healthcare professionals, but also with patients and parents of patients. The responsibility and division of tasks of all professionals should be clear for all team members. Centralisation of care and formation of multidisciplinary craniofacial teams makes it possible to perform comparative studies between centers, which would have a positive effect on the quality of care.

Questions focused on the minimal care standard to treat patients with CFM and how to monitor outcomes of care.

The most frequently reported difficulties in care for patients and parents of patients with craniofacial microsomia include healthcare professionals' lack of knowl-

edge regarding the diagnosis craniofacial microsomia, lack of guidance during treatment and unclear coordination of care.

Recommendations

It is recommended that patients care for patients with craniofacial microsomia should be delivered by the multidisciplinary team and patients should be referred to this team in a timely manner. The clinical pathway based on this guideline should be followed. The multidisciplinary team should provide information regarding the condition and treatment options based on the present craniofacial microsomia guideline in their own language.

Communication between and within teams (also in different hospitals) should be initiated to facilitate the best possible treatment. A contact person in each center - a care coordinator - clarify and facilitate communication between different institutions and within her/his own institution. Continuity of care should be ensured for patients with craniofacial microsomia who reach adulthood. Patient measure should be performed as stated in each chapter.

Patients with craniofacial microsomia are only treated for craniofacial microsomia-related difficulties in a centers that meets the criteria (including volume of care) defined by the ERN-CRANIO. Adhere to the ERN-CRANIO registry.

A craniofacial center has the following care providers: Maxillofacial surgeon, Plastic surgeon, ENT/audiology, Psychology, Orthodontics, Ophthalmologist, Paediatric anaesthesiologists, Team coordinator, Paediatrician, Clinical geneticist, Paediatric intensivist, Neurosurgeon and/or orthopaedic surgeon for spinal anomalies, Paediatric radiologist, Social worker, Speech therapists, Pedagogical worker, (Facial) physical therapist, Prosthetist, Respiratory team.

A craniofacial center has access to the following care facilities: (3D)photography, roentgen, CT, MRI, 3D-planning facility, Paediatric ICU, Sleep study facility, Audiological evaluation, Dental lab.

Acknowledgements

The guideline steering group would like to thank all experts that contributed to the guideline, especially those who reviewed and wrote the recommendations for the non-surgical chapters. This includes: K. Joosten, N. Prendeville, N. Behari, M.P. Van der Schroeff, S.E. Loudon, E. Ongkosuwito, B.S. Harhangi, C. Moffat, and N. Rooney. Additionally, we would like to thank E.L Weissbach for her help with the patient perspective of the guideline.

Part IV

12

General discussion and future perspectives

Craniofacial microsomia (CFM) is characterized by an underdevelopment of facial structures related to the first and second pharyngeal arches, but extracraniofacial anomalies can be present (1, 6, 16, 17, 25). The reported incidence of CFM varies from 1:3000-5000. The presentation of CFM varies largely in patients, both in the type of affected structures as the severity.

This thesis aimed to study the phenotype of CFM and its associated anomalies and give evidence-based recommendations for future management of these patients. A collaboration between various craniofacial centers was initiated to establish a large dataset of patients with CFM, to enable studying associated anomalies in detail and investigate potential risk factors. The following craniofacial centers cooperated in this international collaboration: Erasmus Medical Center, Rotterdam, The Netherlands, Great Ormond Street Hospital (GOSH), London, United Kingdom, Boston Children's Hospital, Boston, United States of America, SickKids, Toronto, Canada, and Seattle Children's Hospital, Seattle, United States of America.

Traits of CFM

In the chapters 2, 3, 4, 5 and 6 the expanded spectrum of CFM was studied. The types, prevalence rates and severity of extracraniofacial anomalies were analyzed. Horgan et al. showed that extracraniofacial anomalies might be present in up to 55% of the patients with CFM, which led to the modification of the O.M.E.N.S. classification by adding a '+' category (6). Historically, anomalies of the cervical spine are a part of the Goldenhar triad (15, 16). To research the prevalence and types of vertebral anomalies in CFM, a systematic review of literature was undertaken (chapter 2). A total of 31 articles specified vertebral anomalies in CFM and reported a prevalence of 12% to 79%. Hemivertebrae, blockvertebrae and scoliosis were most often reported and commonly seen in the cervical and thoracic spine. The wide variety of the reported prevalence was due to a difference in the studied sample size and individual study characteristics. To assess the prevalence, types, symptoms and potential risk factors for vertebral anomalies in more detail, a retrospective multicenter study was setup as described in chapter 3. A total of 881 patients with CFM were included, whereof 29% had vertebral anomalies. Almost half of these patients, 43%, presented with clinical symptoms related to their vertebral anomalies including torticollis, back or neck pain, or limited movement of the neck. Patients with bilateral CFM or a more severe form of hypoplasia, as graded on the O.M.E.N.S. scale, were more frequently diagnosed with vertebral anomalies. Additionally, pa-

tients with vertebral anomalies had more frequently anomalies in other tracts too. The high prevalence of vertebral anomalies emphasizes the need for awareness for such anomalies. Clinical examination of the spine and, if indicated, additional radiographic imaging should be performed in patients with CFM. Especially since only half of the patients presented with clinical symptoms. The true prevalence of these anomalies in CFM might be higher due to the retrospective nature of the study and as anomalies of the spine could be present without clinical symptoms. Identification of vertebral anomalies is important as progressive scoliosis or fractures of ankylosed fragment of the spine might occur in patients with inadequate formation of the vertebrae (64, 67). Also, vertebral anomalies can induce instability of the cervical spine and was seen in 7 of the 991 studied patients (55). Gomes et al. studied 27 patients with CFM who all underwent radiographic evaluation of the cervical spine and showed that 30% of the patients had craniocervical instability (286). All these patients had other anomalies of the spine as well. In a study by Xu et al., which included 88 patients with unilateral CFM, the morphology of the craniovertebral junction was assessed with computed tomography (CT) showing that that 33% of the patients had cervical spine instability. The risk for cervical spine instability was not related to the severity of the facial hypoplasia (287). Manipulation of an instable cervical spine should cautiously be performed as it can result in compression of the spinal cord or vertebral artery. Especially, since patients with CFM might require multiple surgeries in life and the cervical spine could be manipulated during intubation (69, 71). The relatively high prevalence of vertebral anomalies emphasizes the need for physical and radiographical spinal assessment in all patients with CFM (286, 288). Although seldom reported, vertebral anomalies could lead to neurological symptoms. The retrospective study in chapter 3 studied 991 patients with CFM and showed that neurological symptoms in 9 of the 275 patients with vertebral anomalies. However, neurologic symptoms, such as motor disabilities, epilepsy or developmental disorders, could also be the result of anomalies of the central nervous system (CNS), which makes a clear distinction challenging.

The types and prevalence rates of CNS anomalies were studied in a systematic review of literature in chapter 4. A total of 16 articles were included. Anomalies of the central nervous system were reported in 2% to 69% of the patients. Most seen were neural tube defects, agenesis or hypoplasia or the corpus callosum, or intracranial lipomas. Developmental disorders, including intellectual disability, delay in

speech or language development or neuropsychomotor delay were observed in 8% to 73% of the studies. Again, the wide variety of reported prevalence rates is due to variations in the studied sample size and study characteristics. The neurodevelopmental profile and intelligence were extensively studied by Speltz et al. and Collett et al. They reported, in relatively large cross-sectional studies, that patients with CMF score significantly lower on IQ and academic achievements, although the effect size was small (289). In young children, age 12-24 months, no evidence for neurodevelopmental delay was found in patients with CFM compared to healthy controls (290). Later in life, patients in CFM showed lower language skills compared to healthy controls, which might be due to associated CFM related factors such as hearing loss, vision impairment or CNS anomalies (228). These studies emphasize the importance for routine neurodevelopmental screening for all patients with CFM.

The types, prevalence rates and risk factors for extracraniofacial anomalies and limb anomalies were studied in respectively chapters 5 and 6. In the retrospective cohort study described in chapter 5, 881 patients with CFM were investigated. A total of 48% of the patients had extracraniofacial anomalies. Anomalies were most frequently seen in the vertebral tract (29%), circulatory tract (21%), urogenital tract (11%) and central nervous system (11%). Less frequently reported were anomalies in the gastro-intestinal tract (9%) and respiratory tract (3%). Patients with bilateral CFM and a more severe form of mandibular hypoplasia, facial nerve deficit or soft tissue hypoplasia were more frequently diagnosed with extracraniofacial anomalies. The prevalence of extracraniofacial anomalies reported in literature varies in studies with larger sample sizes among 31% to 69% (6, 26, 78). Variations in patient selection and sample size might explain the variation in reported prevalence rates. The large sample size of 991 patients in this studied cohort strengthens the reliability of the prevalence rates found. However, due to the retrospective nature of the study, the true prevalence of extracraniofacial anomalies in CFM might be higher. Also, it could be that patients with an extracraniofacial anomaly were assessed in more detail for other anomalies, leading to a detection bias.

Some craniofacial syndromes are strongly associated with anomalies of the hand, including Apert's, Saethre-Chotzen, Nager and Pfeiffer's syndromes (291, 292). The association with such anomalies and CFM is unknown. In chapter 6, the type, prevalence and risk factors for limb anomalies were studied in a total of 688 patients with CFM. Limb anomalies were diagnosed in 18% of the patients. More frequently

in the upper limb (13%) than in the lower limb (8%). This is in line with literature, reporting a prevalence of 7% to 21% (6, 11, 146). Especially anomalies of the radial ulnar axis were observed, which can cause impairment during daily activities. Limb anomalies might be minor and challenging to diagnose. Timely diagnoses can contribute to improved function in daily activities.

Although these studies on extracraniofacial anomalies did not strictly investigate the necessity or effects of screening for such anomalies, the high prevalence rates of extracraniofacial anomalies and its potential harmful effects emphasize awareness among clinicians. Especially anomalies of the circulatory system, renal system and vertebral tract are common among patients with CFM. Such anomalies, including cardiac septum defects, valve anomalies, arrhythmia's, renal aplasia, undescended testis, blockvertebrae or scoliosis should be screened for by physical examination, renal ultrasound and if indicated electrocardiography and/or echocardiogram. Assessment by experienced plastic or orthopedic surgeons is advised to rule out the presence of limb anomalies as these might be difficult to diagnose. Neurological examination should be performed in all patients with CFM, and if abnormal, additional imaging could rule out anomalies of the central nervous system.

In chapter 7, the extent of CFM was explored by studying potential deficits of cranial nerves and muscles that are not primarily regarded to be part of the CFM spectrum, as described in the O.M.E.N.S. classification. A variety of nerves and muscles play a role in adequate closure of the velopharyngeal sphincter (171, 293). Inadequate velopharyngeal closure, resulting in velopharyngeal dysfunction (VPD), can cause speech and swallow difficulties (164). Patients with cleft lip/palate are known to be at risk for VPD, as those patients experience an aberration in anatomy of the velum, leading to inadequate velopharyngeal closure (294). Patients with CFM and a cleft lip/palate are at risk for VPD too (42, 169, 170, 295). In a study of 41 patients with microtia and signs of the oculo-auriculo-vertebral spectrum velar palsy was present in 80% of the patients (295). Funayama et al. showed in a sample of 48 patients with unilateral CFM that 50% of the patients had a unilateral hypodynamic palate and 15% had VPD (42). To further examine this relationship, a study was setup which included a total of 223 patients with CFM that were examined by a speech and language therapist. A total of 34 patients were diagnosed with VPD, whereof 20 had a cleft lip/palate. The presence of VPD was associated with cleft lip/palate in CFM. The severity of CFM was not related to the presence of VPD. No

major differences in speech characteristics between patients with VPD and (1) CFM, (2) CFM with cleft lip/palate, or (3) isolated cleft lip/palate could be observed. This study showed that both patients with CFM with or without a cleft lip/palate exhibit VPD. Fourteen of the 164 (8.5%) patients with CFM without a cleft lip/palate was diagnosed with VPD. The pathophysiological mechanism of VPD in these patients remains unknown. A disturbance in appropriate innervation of the soft palate could play a role in developing VPD. The tensor veli palatini muscle, playing an important role in velopharyngeal closure, is primarily innervated by the mandibular branch of the trigeminal nerve, which finds its origin from the first pharyngeal arch (171). This could be a reason why patients with CFM without a cleft lip/palate might develop VPD. The retrospective nature of this study might have led to underreporting the true prevalence and exact symptoms of VPD. Nonetheless, as all patients included in this study were examined by a speech and language therapist in a craniofacial center, it is expected that the most significant clinical symptoms were noted. The reported prevalence of 15.2% VPD in patients with CFM in this study emphasize the importance for clinicians to be aware of its potential presence and screen for VPD by assessment of a speech and language therapist.

The presence of extracraniofacial anomalies in CFM might provide insight in the potential pathophysiological mechanism of CFM. The traditional hypothesis on the pathogenesis of CFM is based on a hemorrhage of the stapedial artery (5, 128). Animal studies showed this could result in facial hypoplasia of structures characteristic to CFM. But the presence of extracraniofacial anomalies cannot be explained by this hypothesis (6). Another hypothesis involves a defect in migration of the neural crest cells. These cells migrate from the neural tube to the pharyngeal arches forming the ectomesenchyme and playing a role in formation of various facial structures (130). Errors in formation or migration of neural crest cells could result in facial anomalies as observed in CFM (7, 8). But anomalous migration of neural crest cells has also found to form anomalies of the spine, cardiovascular tract, urogenital tract and central nervous system (96, 97). Interestingly, the link between neural crest cells and the development of the respiratory tract is less clear, although the intrinsic neurons of the lung are formed by neural crest cells (131, 132). Lung anomalies were seen in only 3% of the patients with CFM. Limb anomalies were more frequently diagnosed in patients with other extracraniofacial anomalies. Formation of the limbs is originated by limb buds, forming from the mesenchyme and ectoderm (296). Neural crest colonize the limb buds and play a role in neural

development of the muscles of the limbs (297). Potentially the observed anomalies could be the result of wrong formation or migration of neural crest cells and share a etiologic link with the facial anomalies observed in CFM.

The heterogenic phenotype of CFM makes it challenging to perform and compare research. Throughout the years different criteria have been established to describe or classify patients with CFM. In chapter 8, two recently developed phenotypic criteria were evaluated by comparing these with a clinical, real-life database. The ICHOM and FACIAL criteria, both developed for research purposes, were applied on 730 patients with CFM. The sensitivity was 99.6% for the ICHOM criteria and 94.4% for the FACIAL criteria. A false negative rate of 5.6% in the FACIAL criteria was due to the fact that these patients had facial asymmetry without additional features such as tags, dermoids or clefts. It can be concluded that both criteria show a high sensitivity and can therefore be used for research on CFM, enabling to create reproducible cohorts of patients and increase the ability to compare outcomes. A drawback of this study is the retrospective nature of the study. To apply diagnostic criteria, all separate items of such criteria should be able to be scored. By using data that was gathered by chart review, the full scope of the individual phenotype is not known, and one is dependent of the imaging and medical files that are present. This issue was addressed by applying strict inclusion criteria in this study. Also, patients with isolated microtia were not included, although these patients should be seen as patients with CFM according to the FACIAL criteria. The need for diagnostic criteria in a clinical setting is debatable as no standard treatment is available. Clinically, patients should be treated based on their individual needs and diagnostic criteria do not provide advantages in daily care. Such criteria could help to improve research as outcomes of studies can be compared and the added value for the single patient can be interpreted. Nonetheless, it might be argued that applying eligibility criteria are more useful than diagnostic criteria to study specific characteristics or treatment outcomes in CFM. Eligibility criteria are inclusion criteria based on shared characteristics of patients that play a role in the issues that are aimed to be studied. The phenotype of CFM shows overlap with other craniofacial syndromes including CHARGE syndrome, Treacher Collins, Nager or Robin sequence. These patients need treatment of a specific difficulty which is related to the syndrome, rather than the syndrome itself. These difficulties can be similar across syndromes, making outcomes of studies relevant for other syndromes too. By applying eligibility criteria rather than diagnostic criteria, such

specific difficulties can be studied without studying one specific syndrome. By doing this, the number of patients that can be studied increases, which is relevant when studying rare diseases.

The heterogenic nature of CFM without specific clusters of patients and overlap with other craniofacial syndromes raises the question whether CFM is a distinct entity or part of a spectrum which overlaps with other syndromes (18, 182, 183). Adam et al. proposed the term "recurrent constellations of embryonic malformations" (RCEM) (182). This involves a recognizable pattern of anomalies, in which the frequency of reported twins is greater than expected and no teratogenic or genetic cause is known. Craniofacial microsomia, in their study referred to as oculo-auriculo-vertebral-spectrum (OAVS), met the criteria for RCEM. Other RCEM includes VACTRL (vertebral-anal-cardiac-tracheoesophageal fistula-renal-limb), MURCS (Mullerian duct aplasia, renal anomalies, cervicothoracic somite dysplasia), VATER (vertebral-anal-tracheoesophageal fistula-renal), LBWC (limb–body wall complex) (182). In this view, CFM could be regarded to be part of a spectrum of developmental disorders which are presumably causally related. A disturbance in early embryonic development, such a hypoxia, genetic susceptibility or a methylation defect might cause anomalies related to the RCEM spectrum (182). Hartsfield et al. described these developmental abnormality associations and the overlap with CFM (5). Thomas et al. also show in their studied cohort that some cases (10%) with CFM have an additional diagnosis of VACTERL or MURCS (298). It necessitates the examination of patients with such associations for anomalies in tracts not directly related to the original anomaly, as there could be overlap with other syndromes or RCEM (5). Also, by studying RCEM as a group instead of distinct conditions, large epidemiological and prospective studies can be undertaken (182). The variation of patients included in such studies might compromise adequate comparison among patients, although strict diagnostic or eligibility criteria could help to encompass this issue.

Chapter 9 aimed to shed light on the discussion whether CFM is a progressive disorder. Some clinicians advocate early treatment of mandibular hypoplasia to increase function and prevent potential increasing asymmetry (22, 35). A study by Liu et al. from 2022 showed improvements on facial symmetry after mandibular distraction on the age of 8 years performed to enhance 'oral system development and the social psychology condition' in 36 patients with a Pruzansky-Kaban type

IIb-III mandible, but long-term results or need for secondary surgery were not assessed (299). Others promote postponing treatment, if possible, until adulthood to prevent tissue damage and potential secondary surgery later in life (37, 190). Pluijmers et al. showed that outcome of treatment is more patient-dependent rather than treatment-dependent (197). Patients treated at a younger age will undergo more surgeries to correct the asymmetry later in life, independent of the severity of mandibular hypoplasia (39). To study the potential progressiveness of facial asymmetry in CFM, a total of 110 patients with unilateral CFM were included that did not undergo any surgery to correct facial asymmetry during growth. The deviation of the chin point was measured longitudinal. The severity of mandibular and soft tissue hypoplasia was strongly related to the degree of chin point deviation. Deviation of the chin point did not change during growth, suggesting that CFM is a non-progressive disorder. Early correction of facial asymmetry to prevent increase of asymmetry later in life might, based on this study, not be a valid argument. Although this study included a respectively high number of patients and investigated growth until adolescence, it has some limitations. Determining adequate and reproducible landmarks for measurements is difficult in patients with facial asymmetry. Nonetheless, a high intra- and interobserver variability was obtained. This study used 2D-photographs, enabling to study a larger number of patients over a longer period of time. But by studying 3D CT-scans of photographs, the facial changes in CFM might be assessed in more detail (30, 31). Shetye et al. also studied the longitudinal growth in patients with unilateral CFM and based its findings on lateral cephalograms in thirty patients (300). They showed that patients with a Pruzansky type I mandible have symmetrical growth of the mandible, whereas patients with a Pruzansky type II mandible have lesser growth on the affected side (0.84mm vs 1.79mm per year, $p<.05$). If mandibular distraction is indicated on a young age, the surgeon should possibly overcorrect the mandibular ramus length on the affected side to anticipate for a lower growth rate on that side (300). There is a risk for early stage condylar resorption if mandibular distraction is performed with a larger distraction rate, especially in patients with a Pruzansky type IIa mandible (301). If orthognathic surgery is indicated during adulthood, it produces stable results both in patients who have not had mandibular distraction on a younger age as in patients who underwent mandibular distraction (302). The ideal timing of surgery remains a topic of debate and should be based on the available evidence, individual difficulties and needs of the patient.

Management of patients with CFM

In the last decade, the phenotype of CFM and therapeutical interventions have extensively been studied and numerous, especially retrospective or cross-sectional studies on CFM have been published. In chapter 10, a review of literature was performed that included all literature on clinical features and therapeutic interventions in CFM, published between 2010 until 2020. A total of 91 articles were reviewed and summarized, and recommendations for clinical care were given. The broad scope of this review led to the inclusion of many articles and discussed all facets of care in CFM as described by the PAT-CFM (20, 25). A downside of this method is that a more in-depth, systematic approach of literature is difficult to achieve, although this was beyond the aim of the review. In the last decade, research showed that CFM is a spectrum, in which the affected structures vary in type and severity. Functional problems are common in CFM and include difficulties involving vision, breathing, feeding, swallowing, hearing, speech and language, facial expression and aesthetics. The variety in expressed traits of CFM advocate the need for treatment tailored to the individual patient.

The last chapter of this thesis, chapter 11, summarizes the European Guideline for CFM which was developed to optimize care for patients with CFM. The chapters of the guideline were based on the various difficulties patients with CFM experience. A bottleneck analyses was undertaken in which patients with CFM from various nations were asked to report topics they wished to be addressed in the guideline. Patients reported problems in timely referral to specialized centers, receiving too little information about the disorder and its potential consequences, and suboptimal coordination of care. Such experiences of patients with CFM and caregivers are also studied by an international research network, the CARE program, and study results will follow (303). The European guideline on CFM included chapters on: breathing, feeding, speech, hearing, eye, dentofacial deformities, vertebral anomalies, psychosocial, mandible and maxilla, facial nerve, soft tissue, microtia, and organization of care. All available literature on CFM that matched the inclusion criteria was systematically reviewed. Based on the conclusions of literature and the possible consequences, recommendations for clinical practice were made. In case of insufficient or absence of evidence the recommendations were based on agreement among the experts. Also, a summarized version of the guideline, written in plain language, was developed for patients. Development of a guideline on rare diseases is challenging as the quality of the available evidence is limited. Studies

are mostly retrospective or cross-sectional, and comparative studies are scarce. Recommendation for clinical care were therefore mostly based on low or very-low quality of evidence or on expert opinion. To handle this difficulty, recommendations were made following a strict methodology to achieve the highest degree possible of evidence-based recommendations, nonetheless most recommendations were based on low quality of evidence or expert opinion. Future well-designed studies with large sample size and/or comparison of treatment outcomes help to increase the quality of recommendations for clinical care. Ronde et al. studied the guideline recommendations on standardized screening and monitoring in a survey study (304). 61% to 97% of the 57 respondents agreed on these recommendations in the guideline. Although 65% of the respondents in this study stated isolated microtia should be regarded as a minor form of CFM, 51% stated that the recommendations in the guideline should not be applied for patients with isolated microtia. Future studies could help determining the necessity for screening of the above-mentioned issues for patients with isolated microtia.

In conclusion

Based on this thesis, it can be concluded that extracraniofacial anomalies are present in almost half of the patients with CFM. Especially patients with bilateral CFM and patients with a more severe form of mandibular hypoplasia, facial nerve deficit, or soft tissue deformity have an increased risk for extracraniofacial anomalies. Also, the presence of extracraniofacial anomalies increases the likelihood of having additional anomalies in other tracts too. Anomalies occur most frequently in the vertebral tract, circulatory system, limbs, urogenital tract and central nervous system. Velopharyngeal dysfunction occurs in approximately one in seven patients with CFM and might also be present in patients without a cleft lip/palate. Criteria for the diagnosis CFM such as the ICHOM and FACIAL criteria could be useful for research to improve comparison of results, as both criteria show a high sensibility. Facial asymmetry in unilateral CFM appears to be non-progressive. The degree of mandibular of soft tissue hypoplasia is strongly related to deviation of the chin point. The developed overview article and European clinical guideline on CFM should further improve the care for patients with CFM.

Future perspectives and recommendations

CFM is primarily characterized by hypoplasia of structures related to the first and second pharyngeal arches and thus frequently seen by clinicians specialized in

the craniofacial field. Nonetheless, extracraniofacial anomalies are common in CFM and awareness is needed. The etiology of CFM is unknown. A disruption in the first six week of embryonic development, when the facial structures and organs are being developed, presumably leads to CFM. Future studies on the etiology, such as whole-genome sequencing, should be undertaken to help determine the origin of CFM.

As CFM is relatively rare and the clinical phenotype varies strongly, patient specific treatment is needed. So far, this has led to a limited amount of evidence for various treatments. Treatment should be based on functional difficulties and individual wishes of the patient, and, in case of children, the wishes of parents too. The use of eligibility criteria instead of strict diagnostic criteria could help to increase the numbers of patients that can be studied. Which is, especially in rare diseases, needed to study certain therapeutical or surgical interventions. Assessment of treatment outcomes can be performed by networks of international craniofacial centers, such as the European Reference Network CRANIO or other international collaborations. This increases the number of patients that can be studied. Uniform registries and development of prospective studies on treatment outcomes will help to optimize treatment for patients with CFM. Especially in CFM, due to its heterogenetic nature, treatments should be based on the individual patients' needs. Only with the use of patient reported outcomes measures (PROM), clinicians can identify patients' needs and optimize the timing of treatment. The outcome of treatment reported by patients should be assessed both pre- and post-surgically. A variety of PROMS that can be used are freely available, including the FACE-Q and CLEFT-Q. With this we strive for the right type of care for the right patient on the right moment.

Clinical recommendations

The aim of this thesis was to study the phenotype of CFM and its associated anomalies and give evidence-based recommendations for future care.

Based on the studies included in this thesis, the following recommendations for clinical practice were made:

- All patients with CFM should be physically examined for extracraniofacial anomalies by a pediatrician on initial presentation.
- Patients with a higher risk for extracraniofacial anomalies, including bilateral CFM, severe mandibular hypoplasia, facial nerve deficit or soft tissue deformity, should additionally be screened by electrocardiography, echocardiogram, spine radiography and renal ultrasound.
- All patients with CFM should be assessed by a speech and language therapist from the age of two years to examine potential speech disorders and velopharyngeal dysfunction.
- Use well-defined criteria such as the ICHOM or FACIAL criteria for inclusion of patients with CFM in clinical research.
- Postpone surgical treatment of facial asymmetry until adulthood if no functional or psychosocial difficulties are present.
- Adherence to the European Guideline Craniofacial Microsomia recommendations is advised.

Part V

Summary

Chapter 1 provides a general introduction on craniofacial microsomia (CFM) and the outline and aims of this thesis. With an incidence of approximately 1 in 3000 to 5000 newborns, CFM is the most common congenital craniofacial anomaly following cleft lip and palate. The clinical characteristics vary largely in type and severity of the involved structures, which includes the orbit, mandible, ears, facial nerves and soft tissues. Besides these craniofacial anomalies, patients may present anomalies in various tracts, so called extracraniofacial anomalies. Identification of phenotypical characteristics that warrant timely screening or treatment could increase the quality of care for patients with CFM. This thesis aimed to study these characteristics and provide recommendations for clinical care. A multicenter collaboration was initiated to study a large number of patients, including the following craniofacial centers: Erasmus University Hospital, Rotterdam, The Netherlands; Great Ormond Street Hospital, London, The United Kingdom; Boston Children's Hospital, Boston, The United States of America; SickKids Hospital, Toronto, Canada; Seattle Children's Hospital, Seattle, The United States of America.

Chapter 2 gives a review of literature on the prevalence and types of vertebral anomalies in CFM. Thirty-one articles were assessed. Vertebral anomalies were reported in 12% to 79% of the patients with CFM. The variation in the reported prevalence was considered to be related to differences in sample size, study characteristics, patient selection and the level of spine investigation. Most frequently reported vertebral anomalies were hemivertebrae, blockvertebrae, scoliosis and spina bifida. Anomalies were most common in the cervical spine, thoracic spine and ribs.

The prevalence, types and risk factors for vertebral anomalies was further studied in **chapter 3**. A total of 991 patients with CFM were included, of which 28% presented with vertebral anomalies. Most commonly observed were hemivertebrae, blockvertebrae and scoliosis. Clinical symptoms of these vertebral anomalies were present in 44% of the patients and included torticollis, back or neck pain, and limited neck movement. Vertebral anomalies were more frequently diagnosed in patients with bilateral CFM or a more severe form of mandibular, orbital, facial nerve and/or soft tissue involvement. Also, patients with vertebral anomalies were more frequently diagnosed with additional extracraniofacial anomalies in other tract too.

In **chapter 4** the prevalence and types of central nervous system anomalies and developmental disorders in CFM was studied in a literature review. Sixteen articles were included, reporting a prevalence of respectively 2% to 69% central nervous system anomalies and 8% to 73% developmental disorders in patients with CFM. Most common cranial anomalies were neural tube defects, corpus callosum agenesis or hypoplasia, intracranial lipoma, Arnold-Chiari malformations, hydrocephaly, ventriculomegaly or cerebral hypoplasia. Developmental disorders included intellectual disability, language or speech developmental delay and neuropsychomotor delay.

The prevalences, types and risk factors for extraniofacial anomalies was further studied in **chapter 5**. Almost half, 47%, of the 991 included patients with CFM had extracraniofacial anomalies. Anomalies were most frequently seen in the vertebral tract (28%), circulatory system (21%) and central nervous system (11%). But also in the urogenital tract (11%), gastrointestinal tract (9%) and respiratory tract (3%). Patients with an extracraniofacial anomalies had a higher risk for additional anomalies in other tracts compared to patients without extracraniofacial anomalies. Patients with bilateral CFM or a more severe form of mandibular hypoplasia, facial nerve palsy or soft tissue hypoplasia were more often diagnosed with extracraniofacial anomalies.

Chapter 6 studied the potential association of limb anomalies in CFM and the prevalence, type and risk factors. Of the 688 included patients with CFM, 18% was diagnosed with an upper and/or lower limb anomaly. Anomalies in the upper limb were more frequently observed to lower limb anomalies, in respectively 13% and 8% of the patients. Patients with an extracraniofacial anomaly had a higher risk for limb anomalies. The laterality of CFM and the severity of facial hypoplasia as described in the O.M.E.N.S. classification was not associated with limb anomalies.

Chapter 7 describes the prevalence of velopharyngeal dysfunction (VPD) in 223 with CFM, with and without a cleft lip-palate and studied speech characteristics and risk factors for VPD. A total of 34 patients were diagnosed with VPD; 15% of all patients. Twenty of the 59 patients with CFM and a cleft lip/palate had VPD. Fourteen patients with VPD had no cleft lip/palate. The presence of cleft lip/palate was associated with a higher risk for VPD, whereas the severity of facial hypoplasia or laterality of CFM was not.

Two sets of diagnostic research criteria for CFM were evaluated in **chapter 8**. The FACIAL and ICHOM criteria were compared with an existing global multicenter database of 730 patients with CFM and the sensitivity was assessed. Most patients that received the clinical diagnosis CFM fitted both criteria. The sensitivity of the FACIAL and ICHOM criteria was respectively 94.4% and 99.6%. Agreement between both criteria was fair (Cohen's kappa 0.38). All 41 patients with CFM that did not meet the FACIAL criteria had facial asymmetry without additional facial features as specified in the criteria.

In **chapter 9** the potential progressiveness of CFM was studied in 110 patients with unilateral CFM that did not receive any surgical correction. Deviation of the chin point was measured on all available clinical photographs and the relation with mandibular and soft tissue hypoplasia was studied. No statistically significant changes of deviation of the chin point was observed during growth. A higher degree of mandibular or soft tissue hypoplasia was associated with an increase in deviation of the chin point.

Chapter 10 provides an overview of all developments published in the last decade on the clinical characteristics, medical and surgical treatments in craniofacial microsomia. A total of 91 articles are included and its findings are discussed following the different clinical facets of CFM including craniofacial and extracraniofacial characteristics, and clinical difficulties such as breathing, feeding, speech and hearing. The phenotypical variety in CFM warrant a tailored patient specific treatment plan based on its individual needs and wishes.

Chapter 11 is a summary of the European Guideline for craniofacial microsomia, which was developed within the European Reference Network for Craniofacial anomalies and Ear, Nose and Throat disorders. This guideline was developed to optimize care for patients with CFM and is based on various clinical and psychological difficulties patients and caregivers for patients with CFM experience. In each chapter, a systematic search of literature was performed and based on conclusions from literature and the respected quality of evidence, recommendations for care were given.

The final chapter, **chapter 12**, discusses the findings of this thesis and gives an update of the available literature on CFM. The recommendations for clinical care for patients with CFM, based on the findings in this thesis, is summarized at the end of chapter 12.

Samenvatting

Hoofdstuk 1 biedt een algemene introductie over craniofaciale microsomie (CFM) en de opzet en doelstellingen van dit proefschrift. Met een incidentie van ongeveer 1 op de 3000 tot 5000 pasgeborenen is CFM de meest voorkomende aangeboren craniofaciale aandoening na schisis. De klinische kenmerken variëren sterk, waarbij de aangedane structuren zoals de orbita, mandibula, oren, nervus facialis en weke delen in zowel ernst als uitgebreidheid van hypoplasie wisselen tussen patiënten. Naast deze craniofaciale aandoeningen kunnen patiënten ook aandoeningen hebben in verschillende orgaansystemen, de zogenoemde extracraniofaciale aandoeningen. Het identificeren van fenotypische kenmerken die vroegtijdige screening of behandeling mogelijk maken kan de kwaliteit van zorg voor patiënten met CFM verbeteren. Dit proefschrift heeft als doel deze kenmerken te bestuderen en aanbevelingen te doen voor de klinische zorg van patiënten met CFM. Er werd een samenwerking opgezet tussen meerdere centra om een grote groep patiënten te kunnen onderzoeken, bestaande uit de volgende craniofaciale centra: Erasmus Medisch Centrum, Rotterdam, Nederland; Great Ormond Street Hospital, Londen, Verenigd Koninkrijk; Boston Children's Hospital, Boston, Verenigde Staten, SickKids Hospital, Toronto, Canada; Seattle Children's Hospital, Seattle, Verenigde Staten.

Hoofdstuk 2 geeft een overzicht van de literatuur over de prevalentie en de soorten wervelafwijkingen bij CFM. Er werden 31 artikelen beoordeeld. Wervelafwijkingen werden gezien bij 12% tot 79% van de patiënten met CFM. De variatie in de beschreven prevalentie werd gerelateerd aan verschillen in steekproefgrootte, variatie in studieopzet, patiëntselectie en het uitgebreidheid van wervelkolomonderzoek. De meest voorkomende wervelafwijkingen waren wigwervels, blokwervels, scoliose en spina bifida. Deze aandoeningen kwamen met name voor in de cervicale wervelkolom, thoracale wervelkolom en de ribben.

De prevalentie en typen wervelafwijkingen en de risicofactoren hiervoor werden verder onderzocht in **hoofdstuk 3**. In totaal werden 991 patiënten met CFM geïncludeerd, waarvan 28% van de patiënten wervelafwijkingen hadden. De meest waargenomen wervelafwijkingen betrokken wigwervels, blokwervels en scoliose. Klinische symptomen van deze wervelafwijkingen waren aanwezig bij 44% van de patiënten en betrof torticollis, rug- of nekpijn en/of een beperkte bewegelijkheid van de nek. Wervelafwijkingen werden vaker vastgesteld bij patiënten met dubbelzijdige CFM of een ernstigere vorm van hypoplasie van de mandibula, orbita, nervus

facialis en/of weke delen. Daarnaast werd bij patiënten met wervelafwijkingen vaker additionele extracraniofaciale afwijkingen in andere tracti gezien.

In **hoofdstuk 4** werd de prevalentie en typen centraal zenuwstelselafwijkingen en ontwikkelingsproblemen bij CFM onderzocht in een literatuurstudie. Zestien artikelen werden geïncludeerd en meldden respectievelijk een prevalentie van 2% tot 69% voor centraal zenuwstelselafwijkingen en 8% tot 73% ontwikkelingsproblemen bij patiënten met CFM. De meest voorkomende zenuwstelselafwijkingen waren neurale buis defecten, agenesie of hypoplasie van het corpus callosum, intracraniele lipomen, Arnold-Chiari, hydrocefalie, ventriculomegalie of cerebrale hypoplasie. Ontwikkelingsproblemen omvatten intellectuele beperkingen, vertragingen in taal- of spraakontwikkeling en neuropsychomotorische ontwikkelingsachterstand.

De prevalentie, typen en risicofactoren voor extracraniofaciale aandoeningen werd verder onderzocht in **hoofdstuk 5**. Bijna de helft, 47%, van de 991 geïncludeerde patiënten met CFM had één of meerdere extracraniofaciale aandoening(en). Dit werd meest frequent gezien in de wervelkolom (28%), de tractus circulatorius (21%), het centrale zenuwstelsel (11%). Maar ook in de urogenitale tractus (11%), het maagdarmkanaal (9%) en de longen (3%). Patiënten met extracraniofaciale aandoeningen hadden een hoger risico op additionele aandoeningen in andere tracti in vergelijking met patiënten zonder extracraniofaciale aandoeningen. Patiënten met dubbelzijdige CFM of een ernstigere vorm van mandibulaire hypoplasie, nervus facialis uitval of hypoplasie van de weke delen werden vaker gediagnosticeerd met een extracraniofaciale aandoening.

In **hoofdstuk 6** werd de mogelijke associatie van extremiteitsaandoeningen bij patiënten met CFM onderzocht, waarbij de prevalentie, type en risicofactoren werden bestudeerd. Van de 688 geïncludeerde patiënten met CFM werd bij 18% een bovenste en/of onderste extremiteitsaandoening vastgesteld. Aandoeningen in de bovenste extremiteiten werden vaker waargenomen dan aandoeningen in de onderste extremiteiten, bij respectievelijk 13% en 8% van de patiënten. Patiënten met een extracraniofaciale aandoening hadden een hoger risico op extremiteitsaandoeningen. De mate van gezichtshypoplasie zoals beschreven in de O.M.E.N.S. classificatie was niet geassocieerd met extremiteitsaandoeningen.

Hoofdstuk 7 beschrijft de prevalentie van velopharyngeale disfunctie (VPD) bij 223 patiënten met CFM, met en zonder schisis, waarbij tevens spraakkenmerken en risicofactoren voor VPD werden bestudeerd. Er werden 34 patiënten gediagnosticeerd met VPD, wat overeenkomt met 15% van het totaal aantal patiënten. Twintig van de 59 patiënten met CFM en schisis hadden VPD, terwijl 14 CFM patiënten met VPD geen schisis hadden. De aanwezigheid van een schisis was geassocieerd met een hoger risico op VPD, waarbij de ernst van de aangezichtshypoplasie of lateraliteit van CFM dat niet was.

In **hoofdstuk 8** worden twee verschillende diagnostische criteria voor de diagnose CFM geëvalueerd. De FACIAL- en ICHOM-criteria werden vergeleken met een bestaande wereldwijde multicenter database van 730 patiënten met CFM, waarbij de sensitiviteit van de criteria werd beoordeeld. Het merendeel van de patiënten die de klinische diagnose CFM kregen voldeed aan beide diagnostische criteria. De sensibiliteit van de FACIAL- en ICHOM-criteria was respectievelijk 94.4% en 99.6%. De overeenstemming tussen beide criteria was redelijk. Alle 41 patiënten die niet voldeed aan de FACIAL-criteria hadden asymmetrie van het aangezicht zonder aanvullende gelaatskenmerken zoals gespecificeerd in de criteria.

Hoofdstuk 9 onderzocht de mogelijke progressiviteit van aangezichtsasymmetrie bij CFM en bestudeerde 110 patiënten met eenzijdige CFM die geen correctieve chirurgie hadden ondergaan. Deviatie van de kinpunt werd gemeten op alle beschikbare klinische foto's, waarna de relatie met hypoplasie van de mandibula en weke delen werd bestudeerd. Er werden geen statistisch significante veranderingen in kinpunt deviatie waargenomen tijdens de groei. Een grotere mate van hypoplasie van de mandibula of weke delen werd geassocieerd met een toename van deviatie van de kinpunt.

Hoofdstuk 10 geeft een overzicht van alle ontwikkelingen die in het afgelopen decennium zijn gepubliceerd met betrekking tot de klinische kenmerken, medische en chirurgische behandelingen bij craniofaciale microsomie. Er werden 91 artikelen geïncludeerd waarbij de bevindingen werden besproken aan de hand van de verschillende klinische aspecten van CFM, waarbij craniofaciale en extracraniofaciale aandoeningen, evenals problemen gerelateerd aan ademhaling, voeding, spraak en gehoor. De fenotypische variatie van CFM zorgt ervoor dat iedere patiënt een

op maat gemaakt behandelingsplan dient te hebben op basis van de individuele behoeften en wensen.

In **hoofdstuk 11** wordt een samenvatting gegeven van de Europese richtlijn voor craniofaciale microsomia, ontwikkeld door het 'European Reference Network' voor craniofaciale afwijkingen en keel- neus en ooraandoeningen. Deze richtlijn is ontwikkeld om de zorg voor patiënten met CFM te optimaliseren en is gebaseerd op de verschillende klinische en psychologische moeilijkheden waarbij patiënten en zorgverleners van patiënten met CFM te maken krijgen. Voor elk hoofdstuk werd een systematische zoekopdracht van de literatuur uitgevoerd, waarna op basis van conclusies uit de literatuur en de kwaliteit van bewijs, aanbevelingen werden gedaan voor de zorg voor patiënten met CFM.

Het laatste hoofdstuk, **hoofdstuk 12**, bespreekt de bevindingen van dit proefschrift en geeft een update van de beschikbare literatuur over CFM. De aanbevelingen voor klinische zorg voor patiënten met CFM, gebaseerd op de bevindingen uit dit proefschrift, worden samengevat aan het einde van hoofdstuk 12.

Part VI

Appendices

References

1. Grabb WC. The first and second branchial arch syndrome. Plast Reconstr Surg. 1965;36(5):485-508.
2. Poswillo D. The pathogenesis of the first and second branchial arch syndrome. Oral Surg Oral Med Oral Pathol. 1973;35(3):302-28.
3. Rollnick BR, Kaye CI. Hemifacial microsomia and variants: pedigree data. Am J Med Genet. 1983;15(2):233-53.
4. Bennun RD, Mulliken JB, Kaban LB, Murray JE. Microtia: a microform of hemifacial microsomia. Plast Reconstr Surg. 1985;76(6):859-65.
5. Hartsfield JK. Review of the etiologic heterogeneity of the oculo-auriculo-vertebral spectrum (Hemifacial Microsomia). Orthod Craniofac Res. 2007;10(3):121-8.
6. Horgan JE, Padwa BL, LaBrie RA, Mulliken JB. OMENS-Plus: analysis of craniofacial and extracraniofacial anomalies in hemifacial microsomia. Cleft Palate Craniofac J. 1995;32(5):405-12.
7. Johnson JM, Moonis G, Green GE, Carmody R, Burbank HN. Syndromes of the first and second branchial arches, part 1: embryology and characteristic defects. AJNR Am J Neuroradiol. 2011;32(1):14-9.
8. Twigg SR, Wilkie AO. New insights into craniofacial malformations. Hum Mol Genet. 2015;24(R1):R50-9.
9. Wentzel P, Eriksson UJ. Altered gene expression in rat cranial neural crest cells exposed to a teratogenic glucose concentration in vitro: paradoxical downregulation of antioxidative defense genes. Birth Defects Res B Dev Reprod Toxicol. 2011;92(5):487-97.
10. Su Z, Zhang Y, Liao B, Zhong X, Chen X, Wang H, et al. Antagonism between the transcription factors NANOG and OTX2 specifies rostral or caudal cell fate during neural patterning transition. J Biol Chem. 2018;293(12):4445-55.
11. Beleza-Meireles A, Hart R, Clayton-Smith J, Oliveira R, Reis CF, Venancio M, et al. Oculo-auriculo-vertebral spectrum: clinical and molecular analysis of 51 patients. Eur J Med Genet. 2015;58(9):455-65.
12. Silva AP, Rosa RF, Trevisan P, Dorneles JC, Mesquita CS, Mattos VF, et al. Clinical and cytogenetic features of a Brazilian sample of patients with phenotype of oculo-auriculo-vertebral spectrum: a cross-sectional study. Sao Paulo Med J. 2015;133(3):191-8.
13. Zhang YB, Hu J, Zhang J, Zhou X, Li X, Gu C, et al. Genome-wide association study identifies multiple susceptibility loci for craniofacial microsomia. Nat Commun. 2016;7:10605.
14. Sze RW, Paladin AM, Lee S, Cunningham ML. Hemifacial microsomia in pediatric patients: asymmetric abnormal development of the first and second branchial arches. AJR Am J Roentgenol. 2002;178(6):1523-30.
15. Goldenhar M. Associations malformatives de l'oeil et de l'oreille, en particulier le syndrome dermoïde épibulbaire - appendices auriculaires - fistula auris congenita et ses relations avec la dysostose mandibulofaciale. J Genet Hum. 1952;1:243-82.
16. Gorlin RJ, Jue KL, Jacobsen U, Goldschmidt E. Oculoauriculovertebral Dysplasia. J Pediatr. 1963;63:991-9.
17. Gorlin RJ PJ. Syndromes of the head and neck. New York: McGraw-Hill. 1964:546-52.

18. Caron C, Pluijmers BI, Wolvius EB, Looman CWN, Bulstrode N, Evans RD, et al. Craniofacial and extracraniofacial anomalies in craniofacial macrosomia: A multicenter study of 755 patients. J Craniomaxillofac Surg. 2017;45(8):1302-10.
19. Tuin J, Tahiri Y, Paliga JT, Taylor JA, Bartlett SP. Distinguishing Goldenhar Syndrome from Craniofacial Microsomia. J Craniofac Surg. 2015;26(6):1887-92.
20. Birgfeld CB, Luquetti DV, Gougoutas AJ, Bartlett SP, Low DW, Sie KC, et al. A phenotypic assessment tool for craniofacial microsomia. Plast Reconstr Surg. 2011;127(1):313-20.
21. Pruzansky S. Not all dwarfed mandibles are alike. Birth defects: Original Article Series. 1969;5:120-9.
22. Kaban LB, Moses MH, Mulliken JB. Surgical correction of hemifacial microsomia in the growing child. Plast Reconstr Surg. 1988;82(1):9-19.
23. Kaban LB, Mulliken JB, Murray JE. Three-dimensional approach to analysis and treatment of hemifacial microsomia. Cleft Palate J. 1981;18(2):90-9.
24. Gougoutas AJ, Singh DJ, Low DW, Bartlett SP. Hemifacial microsomia: clinical features and pictographic representations of the OMENS classification system. Plast Reconstr Surg. 2007;120(7):112e-20e.
25. Vento AR, LaBrie RA, Mulliken JB. The O.M.E.N.S. classification of hemifacial microsomia. Cleft Palate Craniofac J. 1991;28(1):68-76; discussion 7.
26. Rollnick BR, Kaye CI, Nagatoshi K, Hauck W, Martin AO. Oculoauriculovertebral dysplasia and variants: phenotypic characteristics of 294 patients. Am J Med Genet. 1987;26(2):361-75.
27. Cohen N, Cohen E, Gaiero A, Zecca S, Fichera G, Baldi F, et al. Maxillofacial features and systemic malformations in expanded spectrum Hemifacial Microsomia. Am J Med Genet A. 2017;173(5):1208-18.
28. Measurement ICfHO. ICHOM Craniofacial Microsomia Data Collection Reference Guide. 2017.
29. Luquetti DV, Saltzman BS, Vivaldi D, Pimenta LA, Hing AV, Cassell CH, et al. Evaluation of ICD-9-CM codes for craniofacial microsomia. Birth Defects Res A Clin Mol Teratol. 2012;94(12):990-5.
30. Kaya O, Pluijmers BI, Staal F, Ruff C, Padwa BL, Koudstaal MJ, et al. Describing the mandible in patients with craniofacial microsomia based on principal component analysis and thin plate spline video analysis. Int J Oral Maxillofac Surg. 2019;48(3):302-8.
31. Kim BC, Bertin H, Kim HJ, Kang SH, Mercier J, Perrin JP, et al. Structural comparison of hemifacial microsomia mandible in different age groups by three-dimensional skeletal unit analysis. J Craniomaxillofac Surg. 2018;46(11):1875-82.
32. Fattah AY, Caro C, Khechoyan DY, Tompson B, Forrest CR, Phillips JH. Cephalometric outcomes of orthognathic surgery in hemifacial microsomia. J Craniofac Surg. 2014;25(5):1734-9.
33. Ko EW, Chen PK, Lo LJ. Comparison of the adult three-dimensional craniofacial features of patients with unilateral craniofacial microsomia with and without early mandible distraction. Int J Oral Maxillofac Surg. 2017;46(7):811-8.
34. Kaban LB, Moses MH, Mulliken JB. Correction of hemifacial microsomia in the growing child: a follow-up study. Cleft Palate J. 1986;23 Suppl 1:50-2.

35. Kearns GJ, Padwa BL, Mulliken JB, Kaban LB. Progression of facial asymmetry in hemifacial microsomia. Plast Reconstr Surg. 2000;105(2):492-8.

36. Ongkosuwito EM, van Neck JW, Wattel E, van Adrichem LN, Kuijpers-Jagtman AM. Craniofacial morphology in unilateral hemifacial microsomia. Br J Oral Maxillofac Surg. 2013;51(8):902-7.

37. Kusnoto B, Figueroa AA, Polley JW. A longitudinal three-dimensional evaluation of the growth pattern in hemifacial microsomia treated by mandibular distraction osteogenesis: a preliminary report. J Craniofac Surg. 1999;10(6):480-6.

38. Meazzini MC, Mazzoleni F, Bozzetti A, Brusati R. Comparison of mandibular vertical growth in hemifacial microsomia patients treated with early distraction or not treated: follow up till the completion of growth. J Craniomaxillofac Surg. 2012;40(2):105-11.

39. Pluijmers BI, Caron C, van de Lande LS, Schaal S, Mathijssen IM, Wolvius EB, et al. Surgical Correction of Craniofacial Microsomia: Evaluation of Interventions in 565 Patients at Three Major Craniofacial Units. Plast Reconstr Surg. 2019;143(5):1467-76.

40. Nagy K, Kuijpers-Jagtman AM, Mommaerts MY. No evidence for long-term effectiveness of early osteodistraction in hemifacial microsomia. Plast Reconstr Surg. 2009;124(6):2061-71.

41. Rune B, Selvik G, Sarnas KV, Jacobsson S. Growth in hemifacial microsomia studied with the aid of roentgen stereophotogrammetry and metallic implants. Cleft Palate J. 1981;18(2):128-46.

42. Funayama E, Igawa HH, Nishizawa N, Oyama A, Yamamoto Y. Velopharyngeal insufficiency in hemifacial microsomia: analysis of correlated factors. Otolaryngol Head Neck Surg. 2007;136(1):33-7.

43. Stark RB, Saunders DE. The first branchial syndrome. The oral-mandibular-auricular syndrome. Plast Reconstr Surg Transplant Bull. 1962;29:229-39.

44. Converse JM, Coccaro PJ, Becker M, Wood-Smith D. On hemifacial microsomia. The first and second branchial arch syndrome. Plast Reconstr Surg. 1973;51(3):268-79.

45. Birgfeld CB, Heike C. Craniofacial microsomia. Semin Plast Surg. 2012;26(2):91-104.

46. Feingold M, Baum J. Goldenhar's syndrome. Am J Dis Child. 1978;132(2):136-8.

47. Poswillo D. The aetiology and pathogenesis of craniofacial deformity. Development. 1988;103 Suppl:207-12.

48. Shokeir MH. The Goldenhar syndrome: a natural history. Birth Defects Orig Artic Ser. 1977;13(3C):67-83.

49. Tsirikos AI, McMaster MJ. Goldenhar-associated conditions (hemifacial microsomia) and congenital deformities of the spine. Spine (Phila Pa 1976). 2006;31(13):E400-7.

50. Stromland K, Miller M, Sjogreen L, Johansson M, Joelsson BM, Billstedt E, et al. Oculo-auriculo-vertebral spectrum: associated anomalies, functional deficits and possible developmental risk factors. Am J Med Genet A. 2007;143A(12):1317-25.

51. Goldenhar M. Associations malformatives de l'oeil et de l'oreille, en particulier le syndrome dermoïde épibulbaire - appendices auriculaires - fistula auris congenita et ses relations avec la dysostose mandibulofaciale. J Genet Hum. 1952;1:243-82.

52. Avon SW, Shively JL. Orthopaedic manifestations of Goldenhar syndrome. J Pediatr Orthop. 1988;8(6):683-6.

53. Tasse C, Bohringer S, Fischer S, Ludecke HJ, Albrecht B, Horn D, et al. Oculo-auriculo-vertebral spectrum (OAVS): clinical evaluation and severity scoring of 53 patients and proposal for a new classification. Eur J Med Genet. 2005;48(4):397-411.
54. Cousley RR, Wilson DJ. Hemifacial microsomia: developmental consequence of perturbation of the auriculofacial cartilage model? Am J Med Genet. 1992;42(4):461-6.
55. Wills BP, Dormans JP. Nontraumatic upper cervical spine instability in children. J Am Acad Orthop Surg. 2006;14(4):233-45.
56. Tsou PM, Yau A, Hodgson AR. Embryogenesis and prenatal development of congenital vertebral anomalies and their classification. Clin Orthop Relat Res. 1980(152):211-31.
57. Morin B, Poitras B, Duhaime M, Rivard CH, Marton D. Congenital kyphosis by segmentation defect: etiologic and pathogenic studies. J Pediatr Orthop. 1985;5(3):309-14.
58. Cook C, Brismee JM, Fleming R, Sizer PS, Jr. Identifiers suggestive of clinical cervical spine instability: a Delphi study of physical therapists. Phys Ther. 2005;85(9):895-906.
59. Kim HJ. Cervical spine anomalies in children and adolescents. Curr Opin Pediatr. 2013;25(1):72-7.
60. Chopra JS, Sawhney IM, Kak VK, Khosla VK. Craniovertebral anomalies: a study of 82 cases. Br J Neurosurg. 1988;2(4):455-64.
61. Healey D, Letts M, Jarvis JG. Cervical spine instability in children with Goldenhar's syndrome. Can J Surg. 2002;45(5):341-4.
62. Al Kaissi A, Ben Chehida F, Ganger R, Klaushofer K, Grill F. Distinctive spine abnormalities in patients with Goldenhar syndrome: tomographic assessment. Eur Spine J. 2015;24(3):594-9.
63. McMaster MJ, Ohtsuka K. The natural history of congenital scoliosis. A study of two hundred and fifty-one patients. J Bone Joint Surg Am. 1982;64(8):1128-47.
64. McMaster MJ, Singh H. Natural history of congenital kyphosis and kyphoscoliosis. A study of one hundred and twelve patients. J Bone Joint Surg Am. 1999;81(10):1367-83.
65. Winter RB MJ, Eilers VE. Congenital scoliosis. A study of 234 patients treated and untreated. J Bone Joint Surg Am 1968(50):1-15.
66. Winter RB, Moe JH, Wang JF. Congenital kyphosis. Its natural history and treatment as observed in a study of one hundred and thirty patients. J Bone Joint Surg Am. 1973;55(2):223-56.
67. Chan G, Dormans JP. Update on congenital spinal deformities: preoperative evaluation. Spine (Phila Pa 1976). 2009;34(17):1766-74.
68. White AA, 3rd, Panjabi MM. The clinical biomechanics of the occipitoatlantoaxial complex. Orthop Clin North Am. 1978;9(4):867-78.
69. Durga P, Sahu BP. Neurological deterioration during intubation in cervical spine disorders. Indian J Anaesth. 2014;58(6):684-92.
70. Donaldson WF, 3rd, Heil BV, Donaldson VP, Silvaggio VJ. The effect of airway maneuvers on the unstable C1-C2 segment. A cadaver study. Spine (Phila Pa 1976). 1997;22(11):1215-8.
71. Lewanda AF, Matisoff A, Revenis M, Harahsheh A, Futterman C, Nino G, et al. Preoperative evaluation and comprehensive risk assessment for children with Down syndrome. Paediatr Anaesth. 2016;26(4):356-62.

72. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med. 2009;151(4):264-9, W64.

73. Figueroa AA, Friede H. Craniovertebral malformations in hemifacial microsomia. J Craniofac Genet Dev Biol Suppl. 1985;1:167-78.

74. Kaye CI, Rollnick BR, Hauck WW, Martin AO, Richtsmeier JT, Nagatoshi K. Microtia and associated anomalies: statistical analysis. Am J Med Genet. 1989;34(4):574-8.

75. Touliatou V, Fryssira H, Mavrou A, Kanavakis E, Kitsiou-Tzeli S. Clinical manifestations in 17 Greek patients with Goldenhar syndrome. Genet Couns. 2006;17(3):359-70.

76. Anderson PJ, David DJ. Spinal anomalies in Goldenhar syndrome. Cleft Palate Craniofac J. 2005;42(5):477-80.

77. D'Antonio LL, Rice RD, Jr., Fink SC. Evaluation of pharyngeal and laryngeal structure and function in patients with oculo-auriculo-vertebral spectrum. Cleft Palate Craniofac J. 1998;35(4):333-41.

78. Barisic I, Odak L, Loane M, Garne E, Wellesley D, Calzolari E, et al. Prevalence, prenatal diagnosis and clinical features of oculo-auriculo-vertebral spectrum: a registry-based study in Europe. Eur J Hum Genet. 2014;22(8):1026-33.

79. Ewart-Toland A, Yankowitz J, Winder A, Imagire R, Cox VA, Aylsworth AS, et al. Oculoauriculovertebral abnormalities in children of diabetic mothers. Am J Med Genet. 2000;90(4):303-9.

80. Gosain AK, McCarthy JG, Pinto RS. Cervicovertebral anomalies and basilar impression in Goldenhar syndrome. Plast Reconstr Surg. 1994;93(3):498-506.

81. Rooryck C, Souakri N, Cailley D, Bouron J, Goizet C, Delrue MA, et al. Array-CGH analysis of a cohort of 86 patients with oculoauriculovertebral spectrum. Am J Med Genet A. 2010;152A(8):1984-9.

82. Rosa RF, Graziadio C, Lenhardt R, Alves RP, Paskulin GA, Zen PR. Central nervous system abnormalities in patients with oculo-auriculo-vertebral spectrum (Goldenhar syndrome). Arq Neuropsiquiatr. 2010;68(1):98-102.

83. Sherk HH, Whitaker LA, Pasquariello PS. Facial malformations and spinal anomalies. A predictable relationship. Spine (Phila Pa 1976). 1982;7(6):526-31.

84. Pegler JR, Soares DC, Quaio CR, Fernandes N, Oliveira LA, Honjo RS, et al. Clinical description of 41 Brazilian patients with oculo-auriculo-vertebral dysplasia. Rev Assoc Med Bras. 2016;62(3):202-6.

85. Engiz O, Balci S, Unsal M, Ozer S, Oguz KK, Aktas D. 31 cases with oculoauriculovertebral dysplasia (Goldenhar syndrome): clinical, neuroradiologic, audiologic and cytogenetic findings. Genet Couns. 2007;18(3):277-88.

86. Gibson JN, Sillence DO, Taylor TK. Abnormalities of the spine in Goldenhar's syndrome. J Pediatr Orthop. 1996;16(3):344-9.

87. Johansson M, Billstedt E, Danielsson S, Stromland K, Miller M, Granstrom G, et al. Autism spectrum disorder and underlying brain mechanism in the oculoauriculovertebral spectrum. Dev Med Child Neurol. 2007;49(4):280-8.

88. Manara R, Brotto D, Ghiselli S, Mardari R, Toldo I, Schifano G, et al. Cranial Nerve Abnormalities in Oculo-Auriculo-Vertebral Spectrum. AJNR Am J Neuroradiol. 2015;36(7):1375-80.

89. Morrison PJ, Mulholland HC, Craig BG, Nevin NC. Cardiovascular abnormalities in the oculo-auriculo-vertebral spectrum (Goldenhar syndrome). Am J Med Genet. 1992;44(4):425-8.

90. Cohen MS, Samango-Sprouse CA, Stern HJ, Custer DA, Vaught DR, Saal HM, et al. Neurodevelopmental profile of infants and toddlers with oculo-auriculo-vertebral spectrum and the correlation of prognosis with physical findings. Am J Med Genet. 1995;60(6):535-40.

91. Letts M, Slutsky D. Occipitocervical arthrodesis in children. J Bone Joint Surg Am. 1990;72(8):1166-70.

92. Russell LJ, Weaver DD, Bull MJ. The axial mesodermal dysplasia spectrum. Pediatrics. 1981;67(2):176-82.

93. Stewart FJ, Nevin NC, Brown S. Axial mesodermal dysplasia spectrum. Am J Med Genet. 1993;45(4):426-9.

94. Johnston MC BP. Embryology of the head and neck. Plastic surgery. 1990;4:2410-95.

95. Johnston MC, Bronsky PT. Animal models for human craniofacial malformations. J Craniofac Genet Dev Biol. 1991;11(4):277-91.

96. Sulik KK, Johnston MC, Smiley SJ, Speight HS, Jarvis BE. Mandibulofacial dysostosis (Treacher Collins syndrome): a new proposal for its pathogenesis. Am J Med Genet. 1987;27(2):359-72.

97. Lammer EJ, Chen DT, Hoar RM, Agnish ND, Benke PJ, Braun JT, et al. Retinoic acid embryopathy. N Engl J Med. 1985;313(14):837-41.

98. Heike CL, Luquetti DV, Hing AV. Craniofacial Microsomia Overview. In: Pagon RA, Adam MP, Ardinger HH, Wallace SE, Amemiya A, Bean LJH, et al., editors. GeneReviews(R). Seattle (WA)1993.

99. S.P. Not all dwarfed mandibles are alike. Birth defects: Original Article Series. 1969;5:120-9.

100. Converse JM, Wood-Smith D, McCarthy JG, Coccaro PJ, Becker MH. Bilateral facial microsomia. Diagnosis, classification, treatment. Plast Reconstr Surg. 1974;54(4):413-23.

101. David DJ, Mahatumarat C, Cooter RD. Hemifacial microsomia: a multisystem classification. Plast Reconstr Surg. 1987;80(4):525-35.

102. Lauritzen C, Munro IR, Ross RB. Classification and treatment of hemifacial microsomia. Scand J Plast Reconstr Surg. 1985;19(1):33-9.

103. Brand MC. Examination of the newborn with congenital scoliosis: focus on the physical. Adv Neonatal Care. 2008;8(5):265-73; quiz 74-5.

104. Basu PS, Elsebaie H, Noordeen MH. Congenital spinal deformity: a comprehensive assessment at presentation. Spine (Phila Pa 1976). 2002;27(20):2255-9.

105. Reckles LN, Peterson HA, Weidman WH, Bianco AJ, Jr. The association of scoliosis and congenital heart defects. J Bone Joint Surg Am. 1975;57(4):449-55.

106. Cowell HR, MacEwen GD, Hubben C. Incidence of abnormalities of the kidney and ureter in congenital scoliosis. Birth Defects Orig Artic Ser. 1974;10(4):142-5.

107. MacEwen GD, Winter RB, Hardy JH. Evaluation of kidney anomalies in congenital scoliosis. J Bone Joint Surg Am. 1972;54(7):1451-4.

108. Bradford DS, Heithoff KB, Cohen M. Intraspinal abnormalities and congenital spine deformities: a radiographic and MRI study. J Pediatr Orthop. 1991;11(1):36-41.

109. Gillespie R, Faithfull DK, Roth A, Hall JE. Intraspinal anomalies in congenital scoliosis. Clin Orthop Relat Res. 1973(93):103-9.

110. Hensinger RN. Congenital scoliosis: etiology and associations. Spine (Phila Pa 1976). 2009;34(17):1745-50.

111. Pegler JR, Soares DC, Quaio CR, Fernandes N, Oliveira LA, Honjo RS, et al. Clinical description of 41 Brazilian patients with oculo-auriculo-vertebral dysplasia. Rev Assoc Med Bras (1992). 2016;62(3):202-6.

112. Shands AR, Jr., Eisberg HB. The incidence of scoliosis in the state of Delaware; a study of 50,000 minifilms of the chest made during a survey for tuberculosis. J Bone Joint Surg Am. 1955;37-A(6):1243-9.

113. Alexander PG, Tuan RS. Role of environmental factors in axial skeletal dysmorphogenesis. Birth Defects Res C Embryo Today. 2010;90(2):118-32.

114. Taysi K, Marsh JL, Wise DM. Familial hemifacial microsomia. Cleft Palate J. 1983;20(1):47-53.

115. Kaye CI, Martin AO, Rollnick BR, Nagatoshi K, Israel J, Hermanoff M, et al. Oculoauriculovertebral anomaly: segregation analysis. Am J Med Genet. 1992;43(6):913-7.

116. Kelberman D, Tyson J, Chandler DC, McInerney AM, Slee J, Albert D, et al. Hemifacial microsomia: progress in understanding the genetic basis of a complex malformation syndrome. Hum Genet. 2001;109(6):638-45.

117. Schrander-Stumpel CT, de Die-Smulders CE, Hennekam RC, Fryns JP, Bouckaert PX, Brouwer OF, et al. Oculoauriculovertebral spectrum and cerebral anomalies. J Med Genet. 1992;29(5):326-31.

118. Verity C, Firth H, ffrench-Constant C. Congenital abnormalities of the central nervous system. J Neurol Neurosurg Psychiatry. 2003;74 Suppl 1:i3-8.

119. Aleksic S, Budzilovich G, Greco MA, McCarthy J, Reuben R, Margolis S, et al. Intracranial lipomas, hydrocephalus and other CNS anomalies in oculoauriculo-vertebral dysplasia (Goldenhar-Gorlin syndrome). Childs Brain. 1984;11(5):285-97.

120. Fotos J, Olson R, Kanekar S. Embryology of the brain and molecular genetics of central nervous system malformation. Semin Ultrasound CT MR. 2011;32(3):159-66.

121. Catala M. Embryology Applied to Neural Tube Defects (NTDs). The Spina Bifida: Management and Outcome. Milano: Springer Milan; 2008. p. 19-42.

122. Flores-Sarnat L, Sarnat HB. Axes and gradients of the neural tube for a morphological/molecular genetic classification of nervous system malformations. Handb Clin Neurol. 2008;87:1-11.

123. Trimble BK, Baird PA. Congenital anomalies of the central nervous system incidence in British Columbia, 1952-72. Teratology. 1978;17(1):43-9.

124. Onkar D, Onkar P, Mitra K. Evaluation of Fetal Central Nervous System Anomalies by Ultrasound and Its Anatomical Co-relation. J Clin Diagn Res. 2014;8(6):AC05-7.

125. Beange H, Taplin JE. Prevalence of intellectual disability in northern Sydney adults. J Intellect Disabil Res. 1996;40 (Pt 3):191-7.

126. Leonard H, Petterson B, Bower C, Sanders R. Prevalence of intellectual disability in Western Australia. Paediatr Perinat Epidemiol. 2003;17(1):58-67.

127. McConkey R, Mulvany F, Barron S. Adult persons with intellectual disabilities on the island of Ireland. J Intellect Disabil Res. 2006;50(Pt 3):227-36.

128. Poswillo D. Hemorrhage in development of the face. Birth Defects Orig Artic Ser. 1975;11(7):61-81.

129. Xu S, Zhang Z, Tang X, Yin L, Liu W, Shi L. The influence of gender and laterality on the incidence of hemifacial microsomia. J Craniofac Surg. 2015;26(2):384-7.

130. Snider TN, Mishina Y. Cranial neural crest cell contribution to craniofacial formation, pathology, and future directions in tissue engineering. Birth Defects Res C Embryo Today. 2014;102(3):324-32.

131. Schittny JC. Development of the lung. Cell Tissue Res. 2017;367(3):427-44.

132. Freem LJ, Escot S, Tannahill D, Druckenbrod NR, Thapar N, Burns AJ. The intrinsic innervation of the lung is derived from neural crest cells as shown by optical projection tomography in Wnt1-Cre;YFP reporter mice. J Anat. 2010;217(6):651-64.

133. Wiesel A, Queisser-Luft A, Clementi M, Bianca S, Stoll C, Group ES. Prenatal detection of congenital renal malformations by fetal ultrasonographic examination: an analysis of 709,030 births in 12 European countries. Eur J Med Genet. 2005;48(2):131-44.

134. Hoffman JI, Kaplan S. The incidence of congenital heart disease. J Am Coll Cardiol. 2002;39(12):1890-900.

135. Tuin AJ, Tahiri Y, Paine KM, Paliga JT, Taylor JA, Bartlett SP. Clarifying the relationships among the different features of the OMENS+ classification in craniofacial microsomia. Plast Reconstr Surg. 2015;135(1):149e-56e.

136. Kumar A, Friedman JM, Taylor GP, Patterson MW. Pattern of cardiac malformation in oculoauriculovertebral spectrum. Am J Med Genet. 1993;46(4):423-6.

137. Allan LD, Sharland GK, Milburn A, Lockhart SM, Groves AM, Anderson RH, et al. Prospective diagnosis of 1,006 consecutive cases of congenital heart disease in the fetus. J Am Coll Cardiol. 1994;23(6):1452-8.

138. Gorlin RJ, Cohen, M. M., and Hennekam, R. C. M. . Syndromes of the Head and Neck. New York: Oxford University Press. 2001:790–8.

139. Carrie L Heike DVL, Anne V Hing. Craniofacial Microsomia Overview. GeneReviews - NCBI Bookshelf A service of the National Library of Medicine, National Institutes of Health. 2014.

140. Renkema RW, Caron C, Pauws E, Wolvius EB, Schipper JAM, Rooijers W, et al. Extracraniofacial anomalies in craniofacial microsomia: retrospective analysis of 991 patients. Int J Oral Maxillofac Surg. 2019;48(9):1169-76.

141. Bernard JA, O'Daly A, Laporte DM. Dorsal radiocarpal dislocation in a patient with Goldenhar syndrome: case report. Hand (N Y). 2013;8(3):320-3.

142. Biswas S, Adhikari A, Meyur R, Kundu P. A rare case of Goldenhar syndrome with radial aplasia. Folia Morphol (Warsz). 2013;72(4):362-5.

143. Mishra D, Sinha BP, Kumar R. Goldenhar syndrome with unusual association of pre-axial polydactyly. Eur J Ophthalmol. 2009;19(6):1063-4.

144. Vendramini S, Richieri-Costa A, Guion-Almeida ML. Oculoauriculovertebral spectrum with radial defects: a new syndrome or an extension of the oculoauriculovertebral spectrum? Report of fourteen Brazilian cases and review of the literature. Eur J Hum Genet. 2007;15(4):411-21.

145. Das A, Ray B, Das D, Das S. A case of Goldenhar-Gorlin syndrome with unusual association of hypoplastic thumb. Indian J Ophthalmol. 2008;56(2):150-2.

146. Werler MM, Sheehan JE, Hayes C, Padwa BL, Mitchell AA, Mulliken JB. Demographic and reproductive factors associated with hemifacial microsomia. Cleft Palate Craniofac J. 2004;41(5):494-50.

147. A.E. F. The care of congenital hand anomalies. 2nd ed St Louis: Quality Medical Publishing. 1994:366-410.

148. Lamb DW, Wynne-Davies R, Soto L. An estimate of the population frequency of congenital malformations of the upper limb. J Hand Surg Am. 1982;7(6):557-62.

149. Giele H, Giele C, Bower C, Allison M. The incidence and epidemiology of congenital upper limb anomalies: a total population study. J Hand Surg Am. 2001;26(4):628-34.

150. Sokal R, Tata LJ, Fleming KM. Sex prevalence of major congenital anomalies in the United Kingdom: a national population-based study and international comparison meta-analysis. Birth Defects Res A Clin Mol Teratol. 2014;100(2):79-91.

151. Wink JD, Goldstein JA, Paliga JT, Taylor JA, Bartlett SP. The mandibular deformity in hemifacial microsomia: a reassessment of the Pruzansky and Kaban classification. Plast Reconstr Surg. 2014;133(2):174e-81e.

152. Horn SMaD. Limb Malformations, an Atlas of Genetic Disorders of Limb Development. 2014:176.

153. Keith L. Moore TVNP, Mark G. Torchia The Developing Human: Clinically Oriented Embryology.

154. Melnick M. The etiology of external ear malformations and its relation to abnormalities of the middle ear, inner ear, and other organ systems. Birth Defects Orig Artic Ser. 1980;16(4):303-31.

155. Poswillo D. Otomandibular deformity: pathogenesis as a guide to reconstruction. J Maxillofac Surg. 1974;2(2-3):64-72.

156. Caron CJ, Pluijmers BI, Joosten KF, Mathijssen IM, van der Schroeff MP, Dunaway DJ, et al. Feeding difficulties in craniofacial microsomia: a systematic review. Int J Oral Maxillofac Surg. 2015;44(6):732-7.

157. Caron CJ, Pluijmers BI, Joosten KF, Mathijssen IM, van der Schroeff MP, Dunaway DJ, et al. Obstructive sleep apnoea in craniofacial microsomia: a systematic review. Int J Oral Maxillofac Surg. 2015;44(5):592-8.

158. Dufton LM, Speltz ML, Kelly JP, Leroux B, Collett BR, Werler MM. Psychosocial outcomes in children with hemifacial microsomia. J Pediatr Psychol. 2011;36(7):794-805.

159. Cohen SR, Levitt CA, Simms C, Burstein FD. Airway disorders in hemifacial microsomia. Plast Reconstr Surg. 1999;103(1):27-33.

160. Klazen YP, Caron C, Schaal SC, Borghi A, Van der Schroeff MP, Dunaway DJ, et al. What Are the Characteristics of the Upper Airway in Patients With Craniofacial Microsomia? J Oral Maxillofac Surg. 2019;77(9):1869-81.

161. Luce EA, McGibbon B, Hoopes JE. Velopharyngeal insufficiency in hemifacial microsomia. Plast Reconstr Surg. 1977;60(4):602-6.

162. Shprintzen RJ, Croft CB, Berkman MD, Rakoff SJ. Velopharyngeal insufficiency in the facio-auriculo-vertebral malformation complex. Cleft Palate J. 1980;17(2):132-7.

163. Ruda JM, Krakovitz P, Rose AS. A review of the evaluation and management of velopharyngeal insufficiency in children. Otolaryngol Clin North Am. 2012;45(3):653-69, viii.

164. Rudnick EF, Sie KC. Velopharyngeal insufficiency: current concepts in diagnosis and management. Curr Opin Otolaryngol Head Neck Surg. 2008;16(6):530-5.

165. Golding-Kushner KJ, Argamaso RV, Cotton RT, Grames LM, Henningsson G, Jones DL, et al. Standardization for the reporting of nasopharyngoscopy and multiview videofluoroscopy: a report from an International Working Group. Cleft Palate J. 1990;27(4):337-47; discussion 47-8.

166. McWilliams BJ PB. Velopharyngeal incompetence (audio seminars in speech pathology). Elsevier Health Sciences Division. 1979;-.

167. Sell D, Harding A, Grunwell P. GOS.SP.ASS.'98: an assessment for speech disorders associated with cleft palate and/or velopharyngeal dysfunction (revised). Int J Lang Commun Disord. 1999;34(1):17-33.

168. Meijer M. Het logopedisch onderzoek van kinderen, geboren met een schisis. ZonMw. 2003.

169. Chan CH, Hu AC, Jain NS, Dang BN, Liu MT, Bertrand AA, et al. Velopharyngeal Insufficiency in Craniofacial Microsomia: Prevalence, Diagnosis, and Treatment. J Craniofac Surg. 2021;32(8):2771-3.

170. D'Antonio LL, Rice Jr RD, Fink SC. Evaluation of pharyngeal and laryngeal structure and function in patients with oculo-auriculo-vertebral spectrum. Cleft Palate-Craniofac J. 1998;35(4):333-41.

171. Perry JL. Anatomy and physiology of the velopharyngeal mechanism. Semin Speech Lang. 2011;32(2):83-92.

172. Dellon AL, Claybaugh GJ, Hoopes JE. Hemipalatal palsy and microtia. Ann Plast Surg. 1983;10(6):475-9.

173. Randall P, Bakes FP, Kennedy C. Cleft-palate-type speech in the absence of cleft palate. Plast Reconstr Surg Transplant Bull. 1960;25:484-95.

174. Kuehn DP, Templeton PJ, Maynard JA. Muscle spindles in the velopharyngeal musculature of humans. J Speech Hear Res. 1990;33(3):488-93.

175. Yamashita RP, Borg E, Granqvist S, Lohmander A. Reliability of Hypernasality Rating: Comparison of 3 Different Methods for Perceptual Assessment. Cleft Palate Craniofac J. 2018;55(8):1060-71.

176. Llano-Rivas I, Gonzalez-del Angel A, del Castillo V, Reyes R, Carnevale A. Microtia: a clinical and genetic study at the National Institute of Pediatrics in Mexico City. Arch Med Res. 1999;30(2):120-4.

177. Keogh IJ, Troulis MJ, Monroy AA, Eavey RD, Kaban LB. Isolated microtia as a marker for unsuspected hemifacial microsomia. Arch Otolaryngol Head Neck Surg. 2007;133(10):997-1001.

178. Renkema RW, and the ERNCWGoCM. European Guideline Craniofacial Microsomia. J Craniofac Surg. 2020;31 Suppl 8:2385-484.

179. Aggarwal R, Ringold S, Khanna D, Neogi T, Johnson SR, Miller A, et al. Distinctions between diagnostic and classification criteria? Arthritis Care Res (Hoboken). 2015;67(7):891-7.

180. Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics. 1977;33(1):159-74.

181. Werler MM, Sheehan JE, Mitchell AA. Gulf War veterans and hemifacial microsomia. Birth Defects Res A Clin Mol Teratol. 2005;73(1):50-2.

182. Adam AP, Curry CJ, Hall JG, Keppler-Noreuil KM, Adam MP, Dobyns WB. Recurrent constellations of embryonic malformations re-conceptualized as an overlapping group of disorders with shared pathogenesis. Am J Med Genet A. 2020;182(11):2646-61.

183. Biesecker LG, Adam MP, Alkuraya FS, Amemiya AR, Bamshad MJ, Beck AE, et al. A dyadic approach to the delineation of diagnostic entities in clinical genomics. Am J Hum Genet. 2021;108(1):8-15.

184. Caron C, Pluijmers BI, Wolvius EB, Looman CWN, Bulstrode N, Evans RD, et al. Craniofacial and extracraniofacial anomalies in craniofacial microsomia: a multicenter study of 755 patients'. J Craniomaxillofac Surg. 2017;45(8):1302-10.

185. Cousley RR, Calvert ML. Current concepts in the understanding and management of hemifacial microsomia. Br J Plast Surg. 1997;50(7):536-51.

186. Caron C, Pluijmers BI, Maas B, Klazen YP, Katz ES, Abel F, et al. Obstructive sleep apnoea in craniofacial microsomia: analysis of 755 patients. Int J Oral Maxillofac Surg. 2017;46(10):1330-7.

187. Caron C, Pluijmers BI, Joosten KFM, Dunaway D, Padwa BL, Wolvius EB, et al. Feeding difficulties in craniofacial microsomia: A multicenter retrospective analysis of 755 patients. J Craniomaxillofac Surg. 2018;46(10):1777-82.

188. Murray JE, Kaban LB, Mulliken JB. Analysis and treatment of hemifacial microsomia. Plast Reconstr Surg. 1984;74(2):186-99.

189. Ongkosuwito EM, van Vooren J, van Neck JW, Wattel E, Wolvius EB, van Adrichem LN, et al. Changes of mandibular ramal height, during growth in unilateral hemifacial microsomia patients and unaffected controls. J Craniomaxillofac Surg. 2013;41(2):92-7.

190. Polley JW, Figueroa AA, Liou EJ, Cohen M. Longitudinal analysis of mandibular asymmetry in hemifacial microsomia. Plast Reconstr Surg. 1997;99(2):328-39.

191. Gursoy S, Hukki J, Hurmerinta K. Five year follow-up of mandibular distraction osteogenesis on the dentofacial structures of syndromic children. Orthod Craniofac Res. 2008;11(1):57-64.

192. Ohtani J, Hoffman WY, Vargervik K, Oberoi S. Team management and treatment outcomes for patients with hemifacial microsomia. Am J Orthod Dentofacial Orthop. 2012;141(4 Suppl):S74-81.

193. Birgfeld CB, Heike CL, Saltzman BS, Leroux BG, Evans KN, Luquetti DV. Reliable classification of facial phenotypic variation in craniofacial microsomia: a comparison of physical exam and photographs. Head & Face Medicine. 2016;12(1):14.

194. Berlin NF, Berssenbrugge P, Runte C, Wermker K, Jung S, Kleinheinz J, et al. Quantification of facial asymmetry by 2D analysis - A comparison of recent approaches. J Craniomaxillofac Surg. 2014;42(3):265-71.

195. Weichman KE, Jacobs J, Patel P, Szpalski C, Shetye P, Grayson B, et al. Early Distraction for Mild to Moderate Unilateral Craniofacial Microsomia: Long-Term Follow-Up, Outcomes, and Recommendations. Plast Reconstr Surg. 2017;139(4):941e-53e.

196. Shetye PR, Grayson BH, Mackool RJ, McCarthy JG. Long-term stability and growth following unilateral mandibular distraction in growing children with craniofacial microsomia. Plast Reconstr Surg. 2006;118(4):985-95.

197. Pluijmers BI, Caron CJ, Dunaway DJ, Wolvius EB, Koudstaal MJ. Mandibular reconstruction in the growing patient with unilateral craniofacial microsomia: a systematic review. Int J Oral Maxillofac Surg. 2014;43(3):286-95.

198. Heike CL, Wallace E, Speltz ML, Siebold B, Werler MM, Hing AV, et al. Characterizing facial features in individuals with craniofacial microsomia: A systematic approach for clinical research. Birth Defects Res Part A Clin Mol Teratol. 2016;106(11):915-26.

199. Mitchell RM, Saltzman BS, Norton SJ, Harrison RG, Heike CL, Luquetti DV, et al. Hearing Loss in Children With Craniofacial Microsomia. Cleft Palate Craniofac J. 2017;54(6):656-63.

200. Schaal SC, Ruff C, Pluijmers BI, Pauws E, Looman CWN, Koudstaal MJ, et al. Characterizing the skull base in craniofacial microsomia using principal component analysis. Int J Oral Maxillofac Surg. 2017;46(12):1656-63.

201. Chen X, Zin AM, Lin L, Xin Y, Chen W, Han W, et al. Three-dimensional analysis of cranial base morphology in patients with hemifacial microsomia. J Craniomaxillofac Surg. 2018;46(2):362-7.

202. Chen YF, Baan F, Bruggink R, Bronkhorst E, Liao YF, Ongkosuwito E. Three-dimensional characterization of mandibular asymmetry in craniofacial microsomia. Clin Oral Investig. 2020;24(12):4363-72.

203. Paliga JT, Tahiri Y, Wink J, Bartlett SP, Taylor JA. Cranial base deviation in hemifacial microsomia by craniometric analysis. J Craniofac Surg. 2015;26(1):e61-4.

204. Park JU, Do TH, Kwon GY, Choi TH, Kim S. Statistical analysis using the OMENS classification in Oriental patients with hemifacial microsomia: a comparative analysis with Western centers. Ann Plast Surg. 2014;72(1):50-5.

205. Birgfeld CB, Heike CL, Saltzman BS, Leroux BG, Evans KN, Luquetti DV. Reliable classification of facial phenotypic variation in craniofacial microsomia: a comparison of physical exam and photographs. Head Face Med. 2016;12:14.

206. Heike CL, Wallace E, Speltz ML, Siebold B, Werler MM, Hing AV, et al. Characterizing facial features in individuals with craniofacial microsomia: A systematic approach for clinical research. Birth Defects Res A Clin Mol Teratol. 2016;106(11):915-26.

207. Collett BR, Wallace ER, Kapp-Simon KA, Johns AL, Drake AF, Heike CL, et al. Cognitive, Motor, and Language Development of Preschool Children With Craniofacial Microsomia. Cleft Palate Craniofac J. 2020:1055665620980223.

208. Johns AL, Wallace ER, Collett BR, Kapp-Simon KA, Drake AF, Heike CL, et al. Behavioral Adjustment of Preschool Children With and Without Craniofacial Microsomia. Cleft Palate Craniofac J. 2021;58(1):42-53.

209. Rooijers W, Caron C, Loudon SE, Padwa BL, Dunaway DJ, Forrest CR, et al. Ocular and adnexal anomalies in craniofacial microsomia: a systematic review. Int J Oral Maxillofac Surg. 2020.

210. Gribova MN, Pluijmers BI, Resnick CM, Caron C, Borghi A, Koudstaal MJ, et al. Is There a Difference in Orbital Volume Between Affected and Unaffected Sides in Patients With Unilateral Craniofacial Microsomia? J Oral Maxillofac Surg. 2018;76(12):2625-9.

211. Shyu VB, Hsu CE, Chen CH, Chen CT. 3D-assisted quantitative assessment of orbital volume using an open-source software platform in a Taiwanese population. PLoS One. 2015;10(3):e0119589.

212. Andrades P, Cuevas P, Hernandez R, Danilla S, Villalobos R. Characterization of the orbital volume in normal population. J Craniomaxillofac Surg. 2018;46(4):594-9.

213. Singh M, Kaur M, Grewal AM, Yangzes S, Yadav D, Zadeng Z, et al. Ophthalmic features and management outcomes of 30 children having Goldenhar syndrome. Int Ophthalmol. 2020;40(3):667-75.

214. Liu Z, Cao J, Qian Y, Sun H, Sun Y, Shen SG, et al. Course of the mandibular canal in hemifacial microsomia: a retrospective computed tomography study. Oral Surg Oral Med Oral Pathol Oral Radiol. 2019;128(5):558-63.

215. Ongkosuwito EM, Van Vooren J, Van Neck JW, Wattel E, Wolvius EB, Van Adrichem LN, et al. Changes of mandibular ramal height, during growth in unilateral hemifacial microsomia patients and unaffected controls. J Cranio-Maxillofac Surg. 2013;41(2):92-7.

216. Grayson BH, Boral S, Eisig S, Kolber A, McCarthy JG. Unilateral craniofacial microsomia. Part I. Mandibular analysis. Am J Orthod. 1983;84(3):225-30.

217. Wink JD, Paliga JT, Tahiri Y, Goldstein JA, Taylor JA, Bartlett SP. Maxillary involvement in hemifacial microsomia: an objective three-dimensional analysis of the craniofacial skeleton. J Craniofac Surg. 2014;25(4):1236-40.

218. Tokura TA, Miyazaki A, Igarashi T, Dehari H, Kobayashi JI, Miki Y, et al. Quantitative Evaluation of Cephalometric Radiographs of Patients With Hemifacial Microsomia. Cleft Palate Craniofac J. 2019;56(6):711-9.

219. Johns AL, Luquetti DV, Brajcich MR, Heike CL, Stock NM. In Their Own Words: Caregiver and Patient Perspectives on Stressors, Resources, and Recommendations in Craniofacial Microsomia Care. J Craniofac Surg. 2018;29(8):2198-205.

220. Luquetti DV, Brajcich MR, Stock NM, Heike CL, Johns AL. Healthcare and psychosocial experiences of individuals with craniofacial microsomia: Patient and caregivers perspectives. Int J Pediatr Otorhinolaryngol. 2018;107:164-75.

221. Kaditis AG, Alonso Alvarez ML, Boudewyns A, Abel F, Alexopoulos EI, Ersu R, et al. ERS statement on obstructive sleep disordered breathing in 1- to 23-month-old children. Eur Respir J. 2017;50(6).

222. Caron CJJM, Pluijmers BI, Joosten KFM, Mathijssen IMJ, Van Der Schroeff MP, Dunaway DJ, et al. Obstructive sleep apnoea in craniofacial microsomia: A systematic review. Int J Oral Maxillofac Surg. 2015;44(5):592-8.

223. Szpalski C, Vandegrift M, Patel PA, Appelboom G, Fisher M, Marcus J, et al. Unilateral Craniofacial Microsomia: Unrecognized Cause of Pediatric Obstructive Sleep Apnea. J Craniofac Surg. 2015;26(4):1277-82.

224. Wang R, Chen S, Yang R, Liu H, Liu Y, Liu D. Morphologic and Aerodynamic Changes of Upper Airway in Pediatric Hemifacial Microsomia Patients Undergoing Distraction Osteogenesis. J Craniofac Surg. 2020;31(8):2132-5.

225. van de Lande LS, Caron C, Pluijmers BI, Joosten KFM, Streppel M, Dunaway DJ, et al. Evaluation of Swallow Function in Patients with Craniofacial Microsomia: A Retrospective Study. Dysphagia. 2018;33(2):234-42.

226. Telich-Tarriba JE, Contreras-Molinar C, Orihuela-Rodriguez A, Lesta-Compagnucci L, Carrillo-Cordova JR, Cardenas-Mejia A. Bite force and electromyographic activity of the masseter muscle in children with hemifacial microsomia. J Plast Surg Hand Surg. 2019;53(5):316-9.

227. Brotto D, Manara R, Vio S, Ghiselli S, Cantone E, Mardari R, et al. Salivary glands abnormalities in oculo-auriculo-vertebral spectrum. Clin Oral Investig. 2018;22(1):395-400.

228. Collett BR, Chapman K, Wallace ER, Kinter SL, Heike CL, Speltz ML, et al. Speech, Language, and Communication Skills of Adolescents With Craniofacial Microsomia. Am J Speech Lang Pathol. 2019;28(4):1571-81.

229. Elsten E, Caron C, Dunaway DJ, Padwa BL, Forrest C, Koudstaal MJ. Dental anomalies in craniofacial microsomia: A systematic review. Orthod Craniofac Res. 2020;23(1):16-26.

230. Ongkosuwito EM, de Gijt P, Wattel E, Carels CE, Kuijpers-Jagtman AM. Dental development in hemifacial microsomia. J Dent Res. 2010;89(12):1368-72.

231. Xu J, Deng X, Yan F. Airway management in children with hemifacial microsomia: a restropective study of 311 cases. BMC Anesthesiol. 2020;20(1):120.

232. Zhang RS, Lin LO, Hoppe IC, Swanson JW, Taylor JA, Bartlett SP. Early Mandibular Distraction in Craniofacial Microsomia and Need for Orthognathic Correction at Skeletal Maturity: A Comparative Long-Term Follow-Up Study. Plast Reconstr Surg. 2018;142(5):1285-93.

233. Suh J, Choi TH, Baek SH, Kim JC, Kim S. Mandibular distraction in unilateral craniofacial microsomia: longitudinal results until the completion of growth. Plast Reconstr Surg. 2013;132(5):1244-52.

234. Ascenco AS, Balbinot P, Junior IM, D'Oro U, Busato L, da Silva Freitas R. Mandibular distraction in hemifacial microsomia is not a permanent treatment: a long-term evaluation. J Craniofac Surg. 2014;25(2):352-4.

235. Suppapinyaroj C, Lin CH, Lo LJ, Ko EW. Outcome of surgical-orthodontic treatment in hemifacial microsomia with and without early mandibular distraction osteogenesis. Int J Oral Maxillofac Surg. 2020.

236. Almadani YH, Gilardino MS. Cost-Effectiveness Analysis, Psychosocial, and Utility Outcomes of Early Mandibular Distraction in Craniofacial Microsomia. J Craniofac Surg. 2020;31(7):1888-94.

237. Bertin H, Mercier J, Cohen A, Giordanetto J, Cohen N, Lee SH, et al. Surgical correction of mandibular hypoplasia in hemifacial microsomia: A retrospective study in 39 patients. J Craniomaxillofac Surg. 2017;45(6):1031-8.

238. Tahiri Y, Chang CS, Tuin J, Paliga JT, Lowe KM, Taylor JA, et al. Costochondral grafting in craniofacial microsomia. Plast Reconstr Surg. 2015;135(2):530-41.

239. Meazzini MC, Battista VMA, Brusati R, Mazzoleni F, Biglioli F, Autelitano L. Costochondral graft in growing patients with hemifacial microsomia case series: Long-term results compared with non-treated patients. Orthod Craniofac Res. 2020;23(4):479-85.

240. Polley JW, Girotto JA, Fahrenkopf MP, Dietze-Fiedler ML, Kelley JP, Taylor JC, et al. Salvage or Solution: Alloplastic Reconstruction in Hemifacial Microsomia. Cleft Palate Craniofac J. 2019;56(7):896-901.

241. van de Lande LS, Pluijmers BI, Caron C, Wolvius EB, Dunaway DJ, Koudstaal MJ, et al. Surgical correction of the midface in craniofacial microsomia. Part 1: A systematic review. J Craniomaxillofac Surg. 2018;46(9):1427-35.

242. Liu K, Sun H, Zhang L, Li B, Chakraborty S, Wang X. Do patient-specific cutting guides and plates improve the accuracy of maxillary repositioning in hemifacial microsomia? Br J Oral Maxillofac Surg. 2020;58(5):590-6.

243. Pluijmers BI, van de Lande LS, Caron C, Wolvius EB, Dunaway DJ, Padwa BL, et al. Part 2: Is the maxillary canting and its surgical correction in patients with CFM correlated to the mandibular deformity? J Craniomaxillofac Surg. 2018;46(9):1436-40.

244. Xu X, Tang XJ, Zhang ZY, Li BH, Yin L, Feng S, et al. Association of Mandibular Dysplasia With Maxillary Volumetric and Linear Measurements in Children With Hemifacial Microsomia. J Craniofac Surg. 2020;31(8):2204-7.

245. Xu X, Zhang ZY, Li BH, Tang XJ, Yin L, Liu W. Three-Dimensional Measurement of Maxillary Involvement in Hemifacial Microsomia in Children. J Craniofac Surg. 2020;31(2):444-7.

246. UK Care Standards for the Management of Patients with Microtia and Atresia.

247. Park JY, Park C. Microtia Reconstruction in Hemifacial Microsomia Patients: Three Framework Coverage Techniques. Plast Reconstr Surg. 2018;142(6):1558-70.

248. Chen Q, Wang B, Wang Y, Hu J, Zhang Q. Using an expanded scalp flap without fascial flap harvest or skin grafting for total auricular reconstruction in hemifacial microsomia with low hairline. Int J Pediatr Otorhinolaryngol. 2020;128:109726.

249. Qian J, Li Z, Liu T, Zhou X, Zhang Q. Auricular Reconstruction in Hemifacial Microsomia with an Expanded Two-Flap Method. Plast Reconstr Surg. 2017;139(5):1200-9.

250. Xing W, Qian J, Wang B, Wang Y, Hu J, Zhang Q. Auricular reconstruction with modified expanded two-flap method in Goldenhar Syndrome: 7-Year experiences. Int J Pediatr Otorhinolaryngol. 2020;139:110228.

251. Mandelbaum RS, Volpicelli EJ, Martins DB, Park SH, Dubina E, Ishiyama A, et al. Evaluation of 4 Outcomes Measures in Microtia Treatment: Exposures, Infections, Aesthetics, and Psychosocial Ramifications. Plast Reconstr Surg Glob Open. 2017;5(9):e1460.

252. Sleifer P, Gorsky Nde S, Goetze TB, Rosa RF, Zen PR. Audiological findings in patients with oculo-auriculo-vertebral spectrum. Int Arch Otorhinolaryngol. 2015;19(1):5-9.

253. Goetze TB, Sleifer P, Rosa RF, da Silva AP, Graziadio C, Zen PR. Hearing characterization in oculoauriculovertebral spectrum: A prospective study with 10 patients. Am J Med Genet A. 2017;173(2):309-14.

254. Hennersdorf F, Friese N, Lowenheim H, Tropitzsch A, Ernemann U, Bisdas S. Temporal bone changes in patients with Goldenhar syndrome with special emphasis on inner ear abnormalities. Otol Neurotol. 2014;35(5):826-30.

255. Rosa RFM, da Silva AP, Goetze TB, de Almeida Bier B, de Almeida ST, Paskulin GA, et al. Ear abnormalities in patients with oculo-auriculo-vertebral spectrum (Goldenhar syndrome). Braz J Otorhinolaryngol. 2011;77(4):455-60.

256. Davide B, Renzo M, Sara G, Elisa L, Rodica M, Irene T, et al. Oculo-auriculo-vertebral spectrum: going beyond the first and second pharyngeal arch involvement. Neuroradiology. 2017;59(3):305-16.

257. Reddy S, Redett R. Facial paralysis in children. Facial Plast Surg. 2015;31(2):117-22.

258. Li Q, Zhou X, Wang Y, Qian J, Zhang Q. Facial Paralysis in Patients With Hemifacial Microsomia: Frequency, Distribution, and Association With Other OMENS Abnormalities. J Craniofac Surg. 2018;29(6):1633-7.

259. Sinclair N, Gharb BB, Papay F, Rampazzo A. Soft Tissue Reconstruction in Patients With Hemifacial Microsomia: A Systematic Review of the Literature. J Craniofac Surg. 2019;30(3):879-87.

260. Denadai R, Raposo-Amaral CA, Buzzo CL, Raposo-Amaral CE. Isolated Autologous Free Fat Grafting for Management of Facial Contour Asymmetry in a Subset of Growing Patients With Craniofacial Microsomia. Ann Plast Surg. 2016;76(3):288-94.

261. Rajan S, Ajayakumar K, Sasidharanpillai S, George B. Autologous Fat Graft for Soft Tissue Camouflage in Craniofacial Microsomia. J Cutan Aesthet Surg. 2019;12(4):223-6.

262. Abduch LSF, Rocha PBD, Nasser IJG, Ono MCC, Freitas RDS. Dermal-Fat Graft for Facial Contouring in Patients With Craniofacial Microsomia. J Craniofac Surg. 2019;30(7):2134-7.

263. Denadai R, Raposo-Amaral CA, Pinho AS, Lameiro TM, Buzzo CL, Raposo-Amaral CE. Predictors of Autologous Free Fat Graft Retention in the Management of Craniofacial Contour Deformities. Plast Reconstr Surg. 2017;140(1):50e-61e.

264. Denadai R, Raposo-Amaral CA, Buzzo CL, Raposo-Amaral CE. Isolated Fat Grafting for Reconstruction of Lower Face Volumetric Asymmetry in Skeletally Immature Patients: A Clinical Outcome Study. Ann Plast Surg. 2019;83(5):529-37.

265. Tanna N, Wan DC, Kawamoto HK, Bradley JP. Craniofacial microsomia soft-tissue reconstruction comparison: inframammary extended circumflex scapular flap versus serial fat grafting. Plast Reconstr Surg. 2011;127(2):802-11.

266. Renkema RW, Caron C, Mathijssen IMJ, Wolvius EB, Dunaway DJ, Forrest CR, et al. Vertebral anomalies in craniofacial microsomia: a systematic review. Int J Oral Maxillofac Surg. 2017;46(10):1319-29.

267. Renkema RW, Caron C, Wolvius EB, Dunaway DJ, Forrest CR, Padwa BL, et al. Central nervous system anomalies in craniofacial microsomia: a systematic review. Int J Oral Maxillofac Surg. 2018;47(1):27-34.

268. Kaditis AG, Alonso Alvarez ML, Boudewyns A, Alexopoulos EI, Ersu R, Joosten K, et al. Obstructive sleep disordered breathing in 2- to 18-year-old children: diagnosis and management. Eur Respir J. 2016;47(1):69-94.

269. Hoffman C, Yuan M, Boyke A, Perera I, Rabbin-Birnbaum C, O'Connor A, et al. Impact of a Multidisciplinary Craniofacial Clinic for Patients With Craniofacial Syndromes on Patient Satisfaction and Outcome. Cleft Palate Craniofac J. 2020;57(12):1357-61.

270. Franceschetti A, Klein D. The mandibulofacial dysostosis; a new hereditary syndrome. Acta Ophthalmol (Copenh). 1949;27(2):143-224.

271. Kaditis A, Kheirandish-Gozal L, Gozal D. Algorithm for the diagnosis and treatment of pediatric OSA: a proposal of two pediatric sleep centers. Sleep Med. 2012;13(3):217-27.

272. Katz ES, D'Ambrosio CM. Pathophysiology of pediatric obstructive sleep apnea. Proc Am Thorac Soc. 2008;5(2):253-62.

273. Adam MP AH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2019.

274. Roberts RM, Shute R. Children's experience of living with a craniofacial condition: perspectives of children and parents. Clin Child Psychol Psychiatry. 2011;16(3):317-34.

275. Tonn CR, Grundfast KM. What an otolaryngologist should know about evaluation of a child referred for delay in speech development. JAMA Otolaryngol Head Neck Surg. 2014;140(3):259-65.

276. Schubert HD. Structural organization of choroidal colobomas of young and adult patients and mechanism of retinal detachment. Trans Am Ophthalmol Soc. 2005;103:457-72.

277. Dion K, Berscheid, E. Physical attractiveness and peer perception among children. Sociometry. 1974;37(1):1-12.

278. Gertner BL, Rice ML, Hadley PA. Influence of communicative competence on peer preferences in a preschool classroom. J Speech Hear Res. 1994;37(4):913-23.

279. Rives Bogart K, Matsumoto D. Facial mimicry is not necessary to recognize emotion: Facial expression recognition by people with Moebius syndrome. Soc Neurosci. 2010;5(2):241-51.

280. Brown R, Hobson RP, Lee A, Stevenson J. Are there "autistic-like" features in congenitally blind children? J Child Psychol Psychiatry. 1997;38(6):693-703.

281. Fellinger J, Holzinger D, Sattel H, Laucht M, Goldberg D. Correlates of mental health disorders among children with hearing impairments. Dev Med Child Neurol. 2009;51(8):635-41.

282. McAlpine LM, Moore, C. The development of social understanding in children with visual impairments. Journal of Visual Impairment and Blindness. 1993;89:349–58.

283. van Daal J, Verhoeven L, van Balkom H. Behaviour problems in children with language impairment. J Child Psychol Psychiatry. 2007;48(11):1139-47.

284. Bassila MK, Goldberg R. The association of facial palsy and/or sensorineural hearing loss in patients with hemifacial microsomia. Cleft Palate J. 1989;26(4):287-91.

285. Carvalho GJ, Song CS, Vargervik K, Lalwani AK. Auditory and facial nerve dysfunction in patients with hemifacial microsomia. Arch Otolaryngol Head Neck Surg. 1999;125(2):209-12.

286. Gomes LP, Ferraz BG, Brandão MM, Alonso N, Pittoli SV, Tonello C. Craniocervical Instability in Oculoauriculovertebral Spectrum. J Craniofac Surg. 2023;34(4):1283-6.

287. Xu X, Chen X, Zhao SBG, Jin JL, Tang XJ, Yin L, et al. Three-Dimensional Morphology and Configuration Analyses of the Craniovertebral Junction in Children with Hemifacial Microsomia. Spine. 2022;47(11):817-24.

288. Gonçalves Ferraz B, Vendramini-Pittoli S, Gomes LP, Madeira Brandão M, Alonso N, Tonello C. Craniofacial Microsomia: New Updates in Spinal Anomalies. J Craniofac Surg. 2023;34(4):e398-e401.

289. Speltz ML, Wallace ER, Collett BR, Heike CL, Luquetti DV, Werler MM. Intelligence and Academic Achievement of Adolescents with Craniofacial Microsomia. Plast Reconstr Surg. 2017;140(3):571-80.

290. Speltz ML, Kapp-Simon KA, Johns AL, Wallace ER, Collett BR, Magee L, et al. Neurodevelopment of Infants with and without Craniofacial Microsomia. J Pediatr. 2018;198:226-33 e3.

291. Panthaki ZJ, Armstrong MB. Hand abnormalities associated with craniofacial syndromes. J Craniofac Surg. 2003;14(5):709-12.

292. Chummun S, McLean NR, Anderson PJ, Nieuwenhoven C, Mathijssen I, David DJ. The Craniofacial and Upper Limb Management of Nager Syndrome. J Craniofac Surg. 2016;27(4):932-7.

293. Nishio J, Matsuya T, Machida J, Miyazaki T. The motor nerve supply of the velopharyngeal muscles. Cleft Palate J. 1976;13:20-30.

294. Fisher DM, Sommerlad BC. Cleft lip, cleft palate, and velopharyngeal insufficiency. Plast Reconstr Surg. 2011;128(4):342e-60e.

295. Kolodzynski MN, van Hoorn BT, Kon M, Breugem CC. Abnormal soft palate movements in patients with microtia. J Plast Reconstr Aesthet Surg. 2018;71(10):1476-80.

296. Keith L. Moore TVNP, Mark G. Torchia. The Developing Human: Clinically Oriented Embryology2019. 522 p.

297. Grim M, Christ B. Neural crest cell migration into the limb bud of avian embryos. Prog Clin Biol Res. 1993;383A:391-402.

298. Thomas MA, Bedard T, Crawford S, Grevers X, Lowry RB. Craniofacial Microsomia, Associated Congenital Anomalies, and Risk Factors in 63 Cases from the Alberta Congenital Anomalies Surveillance System. J Pediatr. 2023;261.

299. Liu W, Xu X, Zhao S, Peng QL, Shu KY, Liu BY, et al. Mandibular Distraction Osteogenesis First for Children With Severe Unilateral Hemifacial Microsomia: Treatment Strategy and Outcomes. J Craniofac Surg. 2022;33(2):485-90.

300. Shetye PR, Grayson BH, McCarthy JG. Longitudinal Skeletal Growth Analysis of Mandibular Asymmetry in Unoperated Patients With Unilateral Craniofacial Microsomia (UCFM). Cleft Palate-Craniofac J. 2023;60(1):69-74.

301. Li X, Zhang Z, Tang X, Li C, Liu W. Bone Density of the Condyle of Children with Craniofacial Microsomia and its Correlation with Condylar Resorption After Mandible Distraction Osteogenesis. Cleft Palate-Craniofac J. 2023.

302. DeMitchell-Rodriguez EM, Mittermiller PA, Avinoam SP, Staffenberg DA, Rodriguez ED, Shetye PR, et al. Clinical Outcomes in Orthognathic Surgery for Craniofacial Microsomia Following Mandibular Distraction Using CBCT Analysis: A Retrospective Study. Cleft Palate-Craniofac J. 2022.

303. Stock NM, Crerand CE, Johns AL, McKinney CM, Koudstaal MJ, Drake A, et al. Establishing an International Interdisciplinary Research Network in Craniofacial Microsomia: The CARE Program. Cleft Palate Craniofac J. 2023.

304. Ronde EM, Nolte JW, Kruisinga FH, Maas SM, Lapid O, Ebbens FA, et al. Evaluating International Diagnostic, Screening, and Monitoring Practices for Craniofacial Microsomia and Microtia: A Survey Study. Cleft Palate Craniofac J. 2022:10556656221093912.

Publications

Renkema RW, Caron CJJM, Mathijssen IMJ, Wolvius EB, Dunaway DJ, Forrest CR, Padwa BL, Koudstaal MJ. Vertebral anomalies in craniofacial microsomia: a systematic review. Int J Oral Maxillofac Surg. 2017 Oct;46(10):1319-1329. doi: 10.1016/j.ijom.2017.04.025. Epub 2017 Jun 29. PMID: 28669484.

Renkema RW, Caron CJJM, Wolvius EB, Dunaway DJ, Forrest CR, Padwa BL, Koudstaal MJ. Central nervous system anomalies in craniofacial microsomia: a systematic review. Int J Oral Maxillofac Surg. 2018 Jan;47(1):27-34. doi: 10.1016/j.ijom.2017.06.009. Epub 2017 Jul 20. PMID: 28736116.

Renkema RW, Caron CJJM, Wolvius EB, Rooijers W, Schipper JAM, Dunaway DJ, Forrest CR, Koudstaal MJ, Padwa BL. Vertebral anomalies in craniofacial microsomia: a retrospective analysis of 991 patients. Int J Oral Maxillofac Surg. 2018 Nov;47(11):1365-1372. doi: 10.1016/j.ijom.2018.05.016. Epub 2018 Jun 22. PMID: 30722936.

Renkema RW, Caron CJJM, Pauws E, Wolvius EB, Schipper JAM, Rooijers W, Dunaway DJ, Forrest CR, Padwa BL, Koudstaal MJ. Extracraniofacial anomalies in craniofacial microsomia: retrospective analysis of 991 patients. Int J Oral Maxillofac Surg. 2019 Sep;48(9):1169-1176. doi: 10.1016/j.ijom.2019.01.031. Epub 2019 Mar 13. PMID: 30878275.

Renkema RW; ERN CRANIO Working Group on Craniofacial Macrosomia; "Normality is a paved road. It's comfortable to walk on, but no flowers grow on it."—V. van Gogh. The Need for a Guideline to Impact Patients Outcome in Craniofacial Microsomia. J Craniofac Surg. 2020 Nov/Dec;31 Suppl 8:2384. doi: 10.1097/SCS.0000000000006676. PMID: 32649552.

Renkema RW; and the ERN CRANIO Working Group on Craniofacial Microsomia. European Guideline Craniofacial Microsomia. J Craniofac Surg. 2020 Nov/Dec;31 Suppl 8:2385-2484. doi: 10.1097/SCS.0000000000006691. PMID: 32804824.

Rooijers W, **Renkema RW**, Loudon SE, Khoshnaw T, Padwa BL, Dunaway DJ, Koudstaal MJ, Forrest CR, Caron CJJM. Ocular and adnexal anomalies in craniofacial microsomia: Type and prevalence in a multicentre cohort study. Int J Oral Maxillofac Surg. 2021 Oct;50(10):1303-1311. doi: 10.1016/j.ijom.2021.02.032. Epub 2021 Mar 20. PMID: 33752938.

Renkema RW, Spivack OKC; ERN CRANIO Working Group on Craniofacial Microsomia. European Guideline on Craniofacial Microsomia: A Version for Patients and Families. J Craniofac Surg. 2022 Jan-Feb 01;33(1):11-14. doi: 10.1097/SCS.0000000000007987. PMID: 34320587.

Renkema RW, Caron CJJM, Heike CL, Koudstaal MJ. A decade of clinical research on clinical characteristics, medical treatments, and surgical treatments for individuals with craniofacial microsomia: What have we learned? J Plast Reconstr Aesthet Surg. 2022 Jun;75(6):1781-1792. doi: 10.1016/j.bjps.2022.02.058. Epub 2022 Mar 7. PMID: 35365411.

Renkema RW, van Beelen I, Koudstaal MJ, Caron CJJM. The effect of natural growth on chin point deviation in patients with unilateral craniofacial microsomia: A retrospective study. J Craniomaxillofac Surg. 2022 Aug;50(8):615-620. doi: 10.1016/j.jcms.2022.07.006. Epub 2022 Jul 19. PMID: 35872040.

Renkema RW, Houwen T, van Nieuwenhoven CA, Padwa BL, Forrest CR, Dunaway DJ, Koudstaal MJ, Caron CJJM. Upper and Lower Limb Anomalies in Craniofacial Microsomia and Its Relation to the OMENS+ Classification: A Multicenter Study of 688 Patients. Plast Reconstr Surg. 2023 May 1;151(5):1053-1061. doi: 10.1097/PRS.0000000000010090. Epub 2022 Dec 21. PMID: 36729069; PMCID: PMC10125112.

Renkema RW, de Vreugt V, Heike CL, Padwa BL, Forrest CR, Dunaway DJ, Wolvius EB, Caron CJJM, Koudstaal MJ. Evaluation of Research Diagnostic Criteria in Craniofacial Microsomia. J Craniofac Surg. 2023 Sep 1;34(6):1780-1783. doi: 10.1097/SCS.0000000000009446. Epub 2023 Jun 2. PMID: 37264504; PMCID: PMC10445631.

Renkema RW, Ramdat Misier KRR, Rooijers W, Osolos A, de Gier HHW, Poldermans HG, Padwa BL, Dunaway DJ, Caron CJJM, Koudstaal MJ. Velopharyngeal dysfunction and speech-related characteristics in craniofacial microsomia: a retrospective analysis of 223 patients. Int J Oral Maxillofac Surg. 2024 Apr 16:S0901-5027(24)00095-X. doi: 10.1016/j.ijom.2024.04.001. Epub ahead of print. PMID: 38631989.

Portfolio

	Year	Workload (hours/ECTS)
General courses		
Introduction to the GRADE methodology	2018	0,3
Research integrity	2019	0,3
Consultation center for Patient Oriented Research Couse	2019	0,3
Introduction to data-analysis	2019	1
Basic course Rules and Organisation for Clinical researchers (BROK)	2022	1,5
Teach the Teacher II Course	2022	0,3
Specific courses (e.g. research school, medical training)		
Medical training	2012-2018	
Dentistry training	2019-2022	
Residency Oral and Maxillofacial Surgery	2021-2025	
Seminars and workshops		
Kaakchirurgie in opleiding cursus		
Mandibulaire bewegingsstoornissen en orofaciale pijn	2021	1
Dentoalveolarie chirurgie	2022	1
Pre-prothetische en pre-implantologische chirurgie en implantologie	2022	1
Mond-, Speekselklier- en Kaakbotpathologie	2022	1
Maxillofaciale traumatologie	2023	1
Orthognatische chirurgie	2023	1
Maxillofaciale Oncologie	2024	1
Ziekenhuismanagement	2022	0,6
AO management of facial trauma	2022	1,5
Masterclass slijmvliesafwijkingen	2023	0,3
Presentations		
International conference of oral and maxillofacial surgery	2017	1
International society of craniofacial surgeons	2017	1
National conference of the Dutch Society of Oral and Maxillofacial Surgery (NVMKA)	2018	1
European Union Health Conference	2019	1
ERN-CRANIO Rome conference	2019	1
European Association of Craniomaxillofacial Surgery Conference	2021	1

	Year	Workload (hours/ECTS)
European Association of Craniomaxillofacial Surgery Conference	2021	1
(Inter)national conferences		
National conference of the Dutch Society of Oral and Maxillofacial Surgery (NVMKA)	2017-2023	9
Lambert de Bont conferentie	2023	0,3
International Conference Craniofacial Surgery	2023	1
Other		
Organisatie en bijwonen 'education and research meetings Department of Oral and Maxillofacial Surgery'	2021-2023	3
2. Teaching		
Supervising medical and dental students in the outpatient clinic and operation theatre	2021-2023	5
Supervising research students	2018-2023	6

Dankwoord

Na vele jaren is het proefschrift af. Voornamelijk geschreven in al die uren tussen de studie en opleiding door. Maar dit heb ik niet alleen gedaan en ik wil hierbij graag iedereen in mijn omgeving bedanken voor de hulp, steun en noodzakelijke ontspanning tussendoor. Graag wil ik een aantal mensen in het bijzonder bedanken.

Allereerst de patiënten die meegewerkt hebben aan onderzoek. Dank daarvoor. Samen zijn we weer iets meer te weten gekomen en hopen we de zorg te verbeteren.

Prof. dr. E.B. Wolvius, beste prof, bedankt voor alle hulp en ondersteuning bij het onderzoek. Uw snelle reactie op artikelen, waardevolle feedback en vrijheid die u geeft binnen het onderzoek heeft er voor gezorgd dat dit proefschrift gemaakt kon worden. Zowel in het onderzoek als de kliniek bent u altijd bereikbaar en bedenkt u altijd wat de volgende stap kan gaan worden. Dank voor alles.

Dr. C.J.J.M. Caron, Linda, dank je wel voor alles. Onze eerste samenwerking startte in 2014 na de minor die ik volgde, waarna ik aanklopte met de vraag of ik onderzoek kon komen doen en Maarten me bij jou onderbracht. Uiteindelijk zijn we altijd blijven samenwerken en heb ik de kneepjes van het onderzoek van jou geleerd. Dank je wel voor alles, de nuttige discussies, vele ideeën en vrolijke bijpraat momenten.

Dr. M.J. Koudstaal, beste Maarten, dank je voor alle kansen die je me gegeven hebt. Tijdens de studie geneeskunde heb je mij kennis laten maken met de MKA-chirurgie en nadien alle mogelijkheden geboden om mezelf te ontwikkelen. Je was altijd laagdrempelig benaderbaar, creatief en gaf altijd constructieve feedback. Dank je wel voor alles.

Hartelijk dank voor de leden van de leescommissie, prof. dr. Eygendaal, prof. dr. Becking, en prof. dr. Mink van der Molen voor het beoordelen van mijn proefschrift. En dank voor de leden van de oppositie, prof. dr. Padwa, prof. dr. Mathijssen, prof. dr. Khonsari voor uw tijd en moeite om mij te bevragen over het proefschrift. Dank prof. Mathijssen voor de samenwerking op het gebied van onderzoek naar CFM en het ontwikkelen van de richtlijn. Thank you prof. Padwa, Bonnie, for the initial introduction in research and the opportunities you have given me in Boston Children's Hospital. A esteemed hospital for craniofacial care and wonderful city to live in. Thank you for hosting me in 2016 and all contributions and valuable feedback

later on. And thank you prof. Roman Khonsari for the good collaboration during the development of the guideline.

Dank aan alle co-auteurs en studenten, in het bijzonder Karan, Vera en Irene, die hebben geholpen met het onderzoek. Dank jullie wel. And thank you prof. dr. Carrie Heike for the cooperation and eagerness to improve care for patients with CFM. The online discussions on research topics were always interesting and fun. Hopefully more shared projects will follow.

Alle stafleden, Elske, Hetty, Brend, Antoinette, Atilla, Justin en Justin, Frithjof, Anouar, en Ali bedankt voor de fijne opleiding tot het mooiste vak dat er is. En dank aan alle anderen voor de fijne samenwerking: José, Cees, Hanneke, Joeri, Joyce, Annemiek. Alle dames op de poli, bedankt voor de fijne samenwerking. En natuurlijk Sandra, dank je voor alle hulp en flexibiliteit waardoor bijna alles altijd mogelijk is.

MKAIOS, dankzij jullie is (bijna) elke dag een feestje! De heerlijke sfeer, matige koffie en slechte grappen maken de opleiding een toptijd. Dank je Valerie, Mona, Vincent, Wietse, Max, Anisha, Khalid, Lara, Tim und Tom!

TOVA 10, Jorrit, Rick, Jacelyn, Stan, Robin, Fons, Maria, Florine, Chesron, dank voor de mooie tijd! Opnieuw de schoolse schoolbanken in werd door jullie een top tijd. Zonder jullie was dit proefschrift vast eerder af geweest. Gelukkig is het elke KIO en voor/najaars weer een feest om elkaar te zien.

Alle vrienden en vriendinnen, Steven, Geert, Pepijn, Derk, Michiel, Niels, Rodney, Sonny, Wouter, Yu Ri, Thijs, Marcus, Demi, Marre, Sofie, Esther, Henry, Anne-Laure, Merel, Fleur, Li, Clemens en Sophie, bedankt voor de fantastische studententijd en de mooie tijd die we nu hebben. Tussen het werken door maken jullie het leven een feest (regelmatig letterlijk). Opdat er nog vele mooie avonden, weekenden en wintersport vakanties mogen komen!

Mannen uit Groningen, Jan-Rik, Jonne, Daniël, Matthijs, Bas en Bas, dank voor de mooie dagen die we eens in de zoveel tijd nog hebben en dat jullie alles kapot kunnen relativeren.

Sjoerd, sinds de wandeling naar de decentrale selectie zijn onze wegen niet meer geweken. Heel mooi dat we nu ook nog samen (gaan) promoveren. Dank je voor alle goede gesprekken, goede muziek en goede whisky. Opdat er nog vele volgen!

Familie Renkema en Muntinga, bedankt voor alle steun en betrokkenheid in goede en minder goede tijden afgelopen jaren.

Peter, Willeke, Marloes, Niels en Adriaan, bedankt dat ik inmiddels al vele jaren deel uitmaak van jullie warme gezin. Bedankt Peter en Willeke voor de motiverende gesprekken en stimulans om onderzoek te gaan en blijven doen. Jullie en de familie Kwakkel zijn een voorbeeld als het gaat om academische ontwikkeling en maatschappelijke verantwoordelijkheid. Het is een voorrecht daar deel vanuit te mogen maken.

Miriam, dank je voor alle mooie momenten samen. Je bent een enorm sterk persoon en hebt samen met je topvent Stephan een fantastisch Thomashuis opgezet. De passie en liefde voor je omgeving zijn indrukwekkend. Ik ben er trots op dat jij mijn zusje bent. We hebben samen heel wat doorstaan, maar dat maakt een team extra hecht. Dank je voor alles.

Pap en mam, bedankt voor alles. Bedankt voor de opvoeding die jullie mij gegeven hebben. Een veilig thuis waar alles gedeeld kon worden. Bedankt voor de manier waarop jullie stimuleerden om te studeren en door te blijven gaan, waarbij tegelijkertijd duidelijk werd gemaakt dat iedereen er evenveel toe doet, ook diegenen die niet kunnen studeren. Jullie waren en zijn het vangnet waardoor ik door kon en kan gaan. Bedankt voor alles.

Cathelijne, bedankt dat jij er altijd bent. We zijn al lang samen en groeien nog elke dag. Naast dat je mijn leven verrijkt ben je ook nog mijn sparringpartner en huisstatisticus als het om onderzoek gaat. Gelukkig is je eigen proefschrift ook nagenoeg af. En nu kunnen we ook nog genieten van onze Remi. Dank je dat je er altijd bent en dat je mijn leven meer kleur geeft. Dank je voor alles.

About the author

Ruben W. Renkema was born on June 3, 1992, in Wageningen and grew up in the province of Groningen. After completing high school, he studied biomedical engineering at the University of Groningen for one year, after which he started studying in Rotterdam in 2012. He earned his medical degree from Erasmus University Rotterdam in 2018, followed by his dental degree from Radboud University Nijmegen in 2022.

During his medical training, he embarked on research into craniofacial microsomia. Throughout his medical studies, he conducted research for six months at the Boston Children's Hospital in the United States, which continued during his further medical and dental education, leading to this current dissertation.

In 2021, he began his training as an Oral and Maxillofacial Surgeon, which he hopes to complete in 2025.

In his free time, he enjoys spending time with friends and family and engaging in sports. Ruben is married to Cathelijne van Zelst-Renkema and has a son.