FUNCTIONAL DIFFICULTIES IN CRANIOFACIAL MICROSOMIA

BREATHING AND FEEDING

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CHAPTER

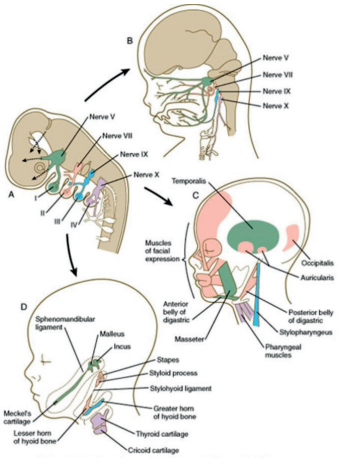
1

General introduction

Background: embryology and etiopathogenesis

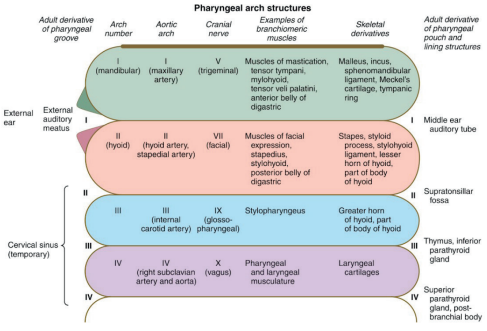
During the first six weeks of embryonic life the first and second pharyngeal arches play an essential role in the development of structures of the head and neck region. The first pharyngeal arch gives rise to the mandible, maxilla, zygoma, trigeminal nerve, muscles of mastication, malleus and incus of the middle ear and a part of the external ear. The second pharyngeal arch gives rise to the muscles of facial expression, the facial nerves, the stapes, styloid process, upper half of the body of the hyoid bone and the majority of the external ear (Figures 1 and 2).

Figure 1. Derivatives of the pharyngeal arches.[1]



In green the structures derived from the first pharyngeal arch.
In pink the structures derived from the second pharyngeal arch.

Figure 2. Schematic overview of the derivatives of the pharyngeal arches.[1]



In green the structures derived from the first pharyngeal arch.
In pink the structures derived from the second pharyngeal arch.

Any structure derived from the first and second pharyngeal arches can be affected in patients with craniofacial microsomia (CFM), leading to a heterogeneous phenotype that is predominantly characterized by asymmetrical underdevelopment of aforementioned facial structures. The dysmorphologies seen in patients with CFM range from mild to severe and could lead to both aesthetic and functional problems.

In 1952 Maurice Goldenhar published a case series of patients with unilateral, congenital mandibular hypoplasia, accessory tragus, and epibulbar dermoids, which he labelled i.e., Goldenhar syndrome.[2] Later, the disorder was called 'otomandibular dysostosis' and 'first and second branchial arch syndrome'.[3, 4] The term branchial is derived from the Greek word 'braches' and refers to the gill slits, however these do not appear in mammalian development and therefore the term 'pharyngeal arches' is preferred in describing the etiology of CFM. Gorlin and colleagues named the condition 'oculo- auriculo-vertebral syndrome' (OAVS), a term often found in genetics literature.[5] Gorlin and Pindborg reviewed the various terms by which this condition has been referred to, and added their term 'hemifacial microsomia', which implies that the deformity is exclusively unilateral.[6] However, previous literature states that in ten percent of the cases the facial structures are involved bilaterally. Ongkosuwito et al. demonstrated underdevelopment of the contralateral/unaffected side as well, although not truly hypoplastic.[7-9] Therefore, the term craniofacial microsomia is often used in recent literature.

Despite a considerable understanding of the embryology of the head and neck region, the exact etiopathogenesis of CFM is still subject to debate. Several theories have been suggested in previous literature of which the two most well-known theories concern: *1)* a vascular defect or local hemorrhage of the stapedial and/or external carotid artery and *2)* disturbed migration of cranial neural crest cells.[10-15]

Most cases of CFM are sporadic with no relevant family history and is thought to be caused by both extrinsic and genetic factors. Based on growing evidence from previous studies that investigated genomic alterations in patients with CFM, a genetic predisposition has been suggested. Several chromosomal anomalies were detected in patients with CFM, however the most frequent alteration was a deletion or duplication in the 22q11 region.16-18 Within the scope of this thesis no research has been performed on determining extrinsic and genetic risk factors for developing CFM. Future research is needed to identify and describe these.

The phenotype of CFM is highly variable and the dysmorphologies range from mild to severe. Therefore, a comprehensive classification is needed to describe the severity of the different anomalies to ensure clear communication between physicians of various specialties and researchers. The Pruzansky classification, later subcategorized by Kaban

et al., is one of the most frequently used classification systems and solely describes the severity of mandibular hypoplasia and is scored on radiographic images.19, 20 (Figures 3 and 4).

Figure 3. The Pruzansky classification.[20]

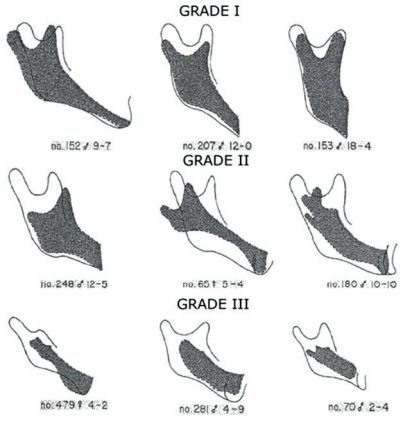
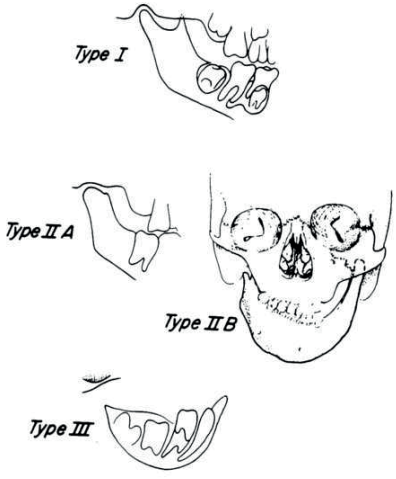


Figure 4. Modification of the Pruzansky classification by Kaban et al.[19]



The Pruzansky-Kaban classification was later expanded into the O.M.E.N.S. classification by Vento et al. to describe the anomalies of the Orbit, Mandible, Ear, Nerve, Soft tissue, hence the acronym (Figure 5).[21] To encompass the extracraniofacial anomalies, the acronym was expanded to the O.M.E.N.S-plus.[22] The most recent derivative of the O.M.E.N.S-plus is The

pictorial Phenotypic Assessment Tool-Craniofacial Microsomia (PAT-CFM) by Birgfeld et al.[23] The PAT-CFM includes scoring of the mandible on both radiography and on medical photography, presence of cleft-lip and/or macrostomia, and includes an additional detailed assessment of minor deformities, such as epibulbar dermoids, and skin- and ear tags (Figure 6).

Figure 5. The O.M.E.N.S classification.[21]

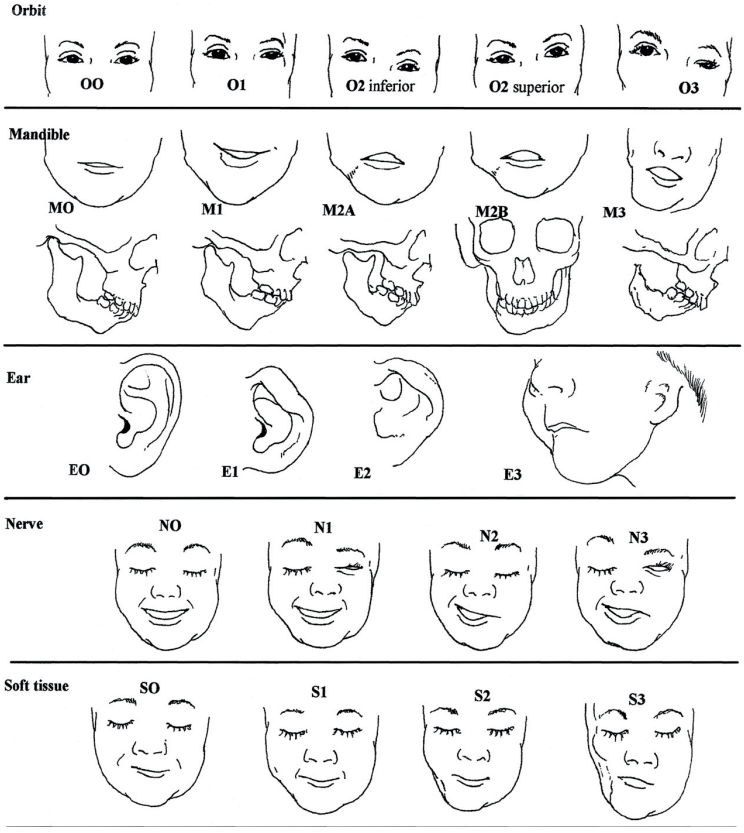
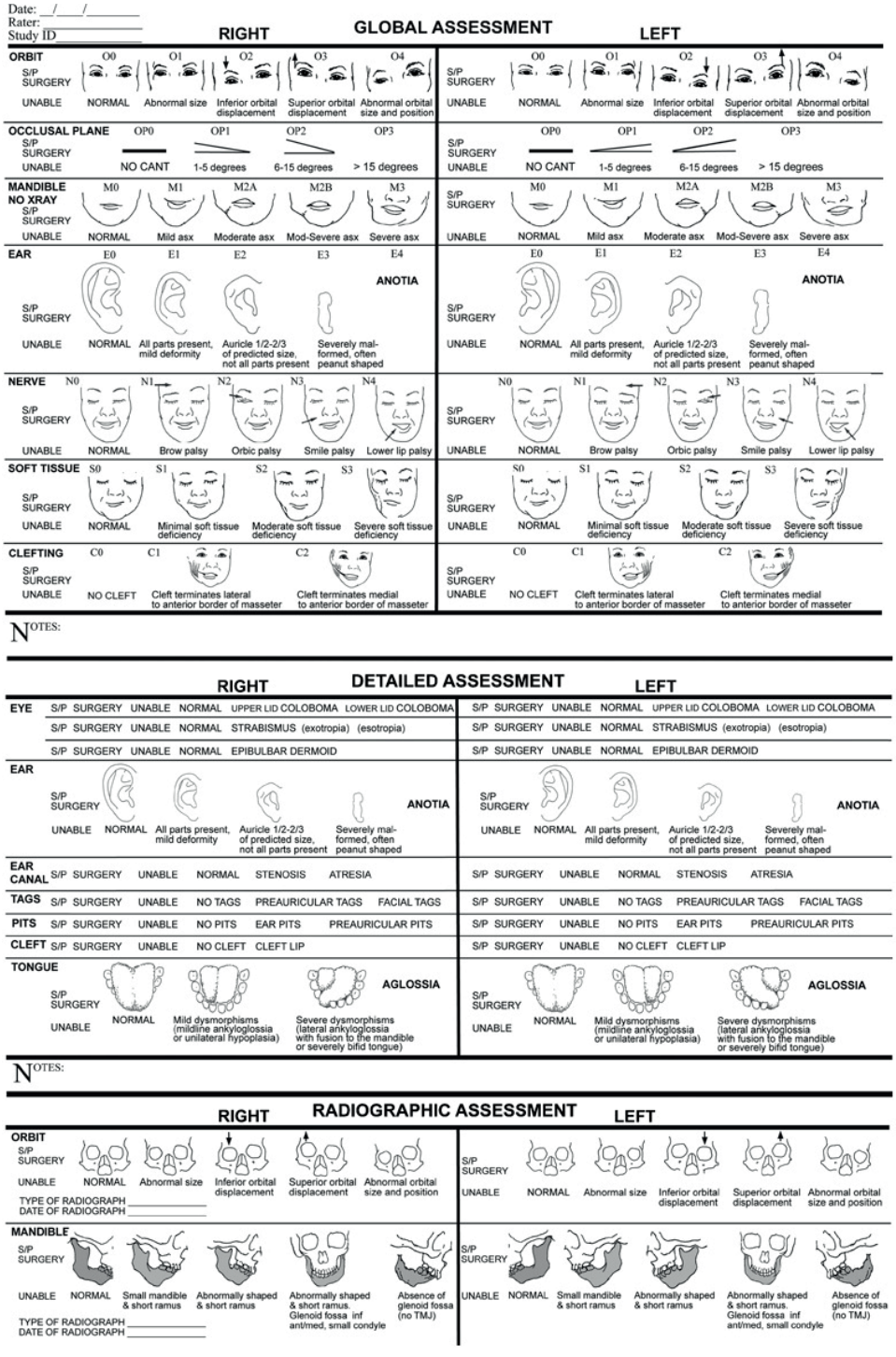


Figure 6. The Phenotypic Assessment Tool – Craniofacial Microsomia (PAT-CFM).[23]



Several studies provided insight into the prognosis and treatment of CFM by assessing correlations between the degree of mandibular hypoplasia and the other variables of the O.M.E.N.S.-plus classification.[21, 22, 24-27] A correlation between the degree of mandibular hypoplasia and the other anatomic dysmorphologies was observed in all studies. In addition, Tuin et al. concluded that underdevelopment of structures derived from the first pharyngeal arch are associated in degree of severity, as are the structures derived from the second pharyngeal arch.[27]

Functional problems: obstructive sleep apnea and feeding difficulties

The dysmorphologies in CFM could lead to functional problems such as obstructive sleep apnea (OSA), feeding difficulties (FD), and swallowing difficulties. These symptoms have scarcely been studied and described in the existing literature on CFM.

The definition of obstructive sleep disordered breathing (SDB) by the European Respiratory Society reads 'a syndrome of upper airway dysfunction during sleep characterized by snoring and/or increased respiratory effort that results from increased upper airway resistance and pharyngeal collapsibility'.[28] Obstructive SDB includes a spectrum of clinical entities with variable severity ranging from primary snoring to OSA.[28, 29] Polysomnography is currently still the golden standard in diagnosing OSA.[30, 31]

Undiagnosed or untreated OSA has been associated with learning impairment and behavioral problems such as daytime hyperactivity, aggression or attention deficit hyperactivity disorder (ADHD). More serious complications include neurologic and developmental delay, failure to thrive, cardiovascular disease, including pulmonary hypertension and right ventricular hypertrophy, and sudden death.[32-41] As a result of OSA, it is noticed patients do not wake-up fit in the morning, can be quickly irritated and may feel chronically tired.[40-42] In all, this may disturb daily life of patients and their parents/caregivers considerably. Therefore, several authors, including the European Respiratory Society, emphasized early and accurate diagnosis of OSA by routinely screening patients who are at higher risk for OSA, e.g., patients with craniofacial anomalies.[28, 35, 41]

Patients with craniofacial malformations have been reported to have a higher incidence of OSA than the healthy population.28, 43, 44 Airway obstruction in these patients is related to facial skeletal dysmorphologies such as midface hypoplasia and/or mandibular hypoplasia. Mandibular hypoplasia is associated with a small posterior airspace and previous studies to Robin sequence and Treacher Collins syndrome showed a higher incidence of OSA in these patients, i.e., 46% to 100%, respectively. 45-52 In the healthy population OSA is diagnosed in 2,2 – 3,8%.53-57 As a result of unilateral or bilateral

mandibular hypoplasia in CFM it is thought that these patients are also more frequently diagnosed with OSA.

In addition, OSA is associated with feeding difficulties and failure to thrive.[58, 59] Several theories explain the correlation between OSA and failure to thrive, and include *(1)* the need for more energy as breathing during the night is harder, *(2)* a decrease in caloric intake as a result of dysphagia, and *(3)* an interrupted nocturnal growth hormone secretion. All three theories have been extensively studied, and it is thought that the interruption of nocturnal growth hormone secretion plays the key role in developing failure to thrive as a result of OSA.[59-63]

However, feeding is a complex process and difficulties with feeding can be the result of several factors. The normal feeding process consists of three phases: *(1)* the pre-oral phase, the sensation of feeling hungry, which leads to nutritional intake; *(2)* the oro-pharyngeal phase, food is prepared orally, then transported from the oral cavity to the pharynx, and then swallowed; leading to *(3)* the gastro-intestinal phase, necessary for satiation and digestion. Difficulties in any of these phases, due to medical, anatomical, developmental, social and/or environmental issues, can interrupt or delay typical feeding development, resulting in poor nutrition.[64, 65]

Especially the oropharyngeal phase might be affected in patients with CFM. Depending on the severity of the anatomical deformities, underdevelopment of the mandible and the oropharyngeal musculature, and co-existence of cleft lip/palate could play an essential role in the development of FD in patients with CFM.

When patients (with FD) are unable to receive their feeding orally, tube feeding might be necessary to meet their nutritional requirements. Sometimes this is necessary for a prolonged period of time and in these patients transferring onto, or back to, oral feeding is not an easy task. Aversion of oral intake, food refusal, and vomiting and gagging are a few examples of difficulties patients might face when transferring to oral intake. This is stressful and can have psychosocial impact on both patients and their parents/caregivers.[66, 67]

Several types of FD in CFM have been described in literature, including problems with suckling, chewing, choking, restricted mouth opening, and difficulties swallowing.[68, 69] Difficulties swallowing could result from a wide variety of functional or structural deficits of the oral cavity, pharynx, larynx or esophagus. Swallowing difficulties in CFM may be the result of mandibular hypoplasia, presence of cleft lip/palate, possible underdevelopment of the oropharyngeal apparatus, and/or decreased innervation of the masticatory and pharyngeal muscles.[65, 70-72] Thus far, no large cohorts have been studied for the prevalence of and the risk factors for developing FD and SD in CFM.

Aims of this thesis

Although several studies have described the aesthetic and functional problems in patients with CFM, there are still aspects that remain unclear and inconclusive. The studies in this thesis focus on the prevalence of and risk factors for developing OSA and FD in CFM. Furthermore, we focused on possible correlations between anatomic anomalies, according to the O.M.E.N.S classification, and the presence of OSA and FD. The conclusions of previous publications are mainly based on studies with low levels of evidence and on studies with limited patient numbers. To be able to study certain correlations between all variables of the O.M.E.N.S.-plus and functional problems, research of a large patient cohort is needed. Therefore, a multicentre study between Erasmus University Hospital, Rotterdam, The Netherlands; Great Ormond Street Hospital London, United Kingdom; and Boston Children's Hospital, Boston, Massachusetts, the United States of America was initiated to collect data of nearly 1000 patients with craniofacial microsomia.

In short, the overall aim of this thesis was to analyse a large population of patients with CFM and their phenotype and functional difficulties, i.e., obstructive sleep apnea and feeding difficulties. This lead to the following research questions:

- What are the correlations between all scored variables of the O.M.E.N.S. – plus?
- Do certain combinations of anomalies occur more frequently than others?
- What is described in previous literature regarding the prevalence and treatment of OSA?
- How often is OSA diagnosed in our study population, which patients are at risk and how is it treated?
- Can a specific level of obstruction be determined in patients with CFM and OSA?
- What is described in previous literature regarding the prevalence and treatment of FD?
- How often are FD diagnosed in our study population, which patients are at risk and how is it treated?
- What is the prevalence of swallowing disorders and do swallow studies differentiate in the causes of swallowing difficulties?

Outline of this thesis

Chapter 2 focuses on determining the correlations between all scored variables of the O.M.E.N.S-plus and if certain combinations of anomalies occurred more frequently than others. This could provide more insight into the embryologic processes that cause CFM.

Chapter 3 gives an overview of all publications on OSA in CFM describing the prevalence and treatment of OSA in CFM, and the risk factors for developing OSA in CFM.

Chapter 4 describes our cohort of patients diagnosed with CFM and OSA. Furthermore, the treatment modalities used to treat OSA in our cohort, including the follow-up, are described.

Chapter 5 was set up to identify the level of obstruction in patients with CFM and OSA by measuring the upper airway volume on CT scans of the head and neck. These measurements were compared with measurements of the upper airway in a control population.

Chapter 6 describes the outcome of our systematic review to the prevalence and treatment options of FD in patients with CFM.

Chapter 7 gives an overview of FD and the treatment of FD in our cohort of 755 patients with CFM. As a result of this study, it became evident that swallowing difficulties were mentioned in a large number of patients with CFM and FD, which lead to a retrospective study to these swallowing difficulties in CFM.

Chapter 8 describes the outcomes of the videofluoroscopic swallow studies performed in patients with CFM and swallowing difficulties.

Chapter 9 was set up to separately describe the patients diagnosed with both CFM and cleft lip/palate as it was hypothesized that these patients were more severely affected with functional difficulties than patients diagnosed with CFM without co-existing cleft lip/palate.

Chapter 10, the general discussion, provides a basis for future research and aims to assist physicians in their clinical decision-making.

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CHAPTER

2

Craniofacial and extracraniofacial anomalies in craniofacial microsomia: A multicenter study of 755 patients

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Abstract

Purpose: Craniofacial microsomia (CFM) is a congenital malformation of structures derived from the first and second pharyngeal arches leading to underdevelopment of the face. However, besides the craniofacial underdevelopment, extracraniofacial anomalies including cardiac, renal and skeletal malformation have been described. The aim of this study is to analyse a large population of patients with regard to demographics, typical phenotypes including craniofacial and extracraniofacial anomalies, and the correlations between the different variables of this condition.

Material and methods: A retrospective study was conducted in patients diagnosed with CFM with available clinical and/or radiographic images. All charts were reviewed for information on demographic, radiographic and diagnostic criteria. The presence of cleft lip/palate and extracraniofacial anomalies were noted. Pearson correlation tests and principal component analysis was performed on the phenotypic variables.

Results: A total of 755 patients were included. The male-to-female ratio and right-to-left ratio were both 1.2:1. A correlation was found among Pruzansky-Kaban, orbit and soft tissue. Similar correlations were found between ear and nerve. There was no strong correlation between phenotype and extracraniofacial anomalies. Nevertheless, extracraniofacial anomalies were more frequently seen than in the 'normal' population. Patients with bilateral involvement had a more severe phenotype and a higher incidence of extracraniofacial and cleft lip/palate.

Conclusion: Outcomes were similar to those of other smaller cohorts. Structures derived from the first pharyngeal arch and the second pharyngeal arch were correlated with degree of severity. Extracraniofacial anomalies were positively correlated with CFM. The findings show that bilaterally affected patients are more severely affected and should be approached more comprehensively.

Introduction

Craniofacial microsomia (CFM) is generally considered to be the second most common congenital craniofacial malformation following cleft lip and palate.[1,2] Goldenhar characterized the disorder as a triad of accessory tragus, mandibular hypoplasia and epibulbar dermoid.[3] Later, the disorder was called 'otomandibular dysostosis' and 'first and second branchial arch syndrome'.[4,5] Gorlin et al. called this condition 'oculo-auriculo-vertebral syndrome' (OAVS), a term often found in genetics literature.[6] However, in the surgical field, CFM is nowadays most often used.

Any structure derived from the first and second pharyngeal arches can be affected, leading to a phenotype predominantly characterized by asymmetrical hypoplasia of the facial skeleton. Although several theories have been proposed, the exact aetiology has not yet been clarified. The well-known hypotheses are local haemorrhage of the stapedial artery[7] and disturbed migration of cranial neural crest cells[8,9], leading to asymmetrical development of structures derived from the first and second pharyngeal arches.[5,10]

The first pharyngeal arch gives rise to the mandible, maxilla, zygoma, trigeminal nerve, muscles of mastication, and a part of the external ear, whereas the second pharyngeal arch gives rise to the facial nerve, stapes, styloid process, portions of the hyoid bone, facial musculature, and the majority of the external ear.[11] CFM is most often regarded as a unilateral malformation; however the facial structures have been reported to be involved bilaterally in 10% of cases.[12,13] Previous studies suggested that, in most cases, the contralateral side is abnormal as well, although not truly hypoplastic.[14]

Patients with CFM are phenotypically heterogeneous; their dysmorphologies range from minor to severe. Therefore, a comprehensive classification is needed to describe the severity of the different anomalies to ensure clear communication among physicians in various specialties and researchers. The Pruzansky classification was the first such system, which was later subcategorized by Kaban et al.[15,16] This schema focuses only on mandibular hypoplasia. The Orbit, Mandible, Ear, Nerve, Soft tissue (O.M.E.N.S.), proposed by Vento et al., includes the five major malformations in craniofacial regions.[17]

Other anomalies seen in patients with CFM include malformations of the vertebrae, cervical spine, cardiorespiratory system, urogenital system, limbs, central nervous system and gastrointestinal system. Most often reported are skeletal, cardiac and renal anomalies.[18]

To encompass the extracraniofacial anomalies, the acronym was expanded to the O.M.E.N.S-plus.[19] The most recent derivative of the O.M.E.N.S-plus is the pictorial Phenotypic Assessment Tool-Craniofacial Microsomia (PAT-CFM) by.[20] The PAT-CFM also

includes scoring of both the mandible on radiography as on medical photography, cleft lip, macrostomia and an additional detailed assessment of minor deformities such as epibulbar dermoids and skin and ear tags.

Several studies provided insight into the aetiology, prognosis and treatment of CFM by assessment of correlations between the degree of mandibular hypoplasia and the other anatomic variables in the O.M.E.N.S.-plus.[9,17,19,21-24] A correlation between the degree of mandibular hypoplasia and the other anatomic dysmorphologies is observed in all studies, especially the correlation between the degree of mandibular hypoplasia and orbital deformity.[9,17,21-23] Tuin et al. concluded that structures derived from the first pharyngeal arch are associated in degree of severity, as are the structures derived mainly from the second pharyngeal arch.[15] Furthermore, there are studies of possible association between the O.M.E.N.S score and the likelihood of coexistent extracraniofacial anomalies.[9,17,19,21-24]

None of the previous studies on this topic used principal component analysis (PCA) to correlate multiple variables at the same time. PCA is a way to reduce the data description into a smaller amount of relevant variables, without reduction of the data themselves.[25-27]

Previous studies on this condition, included a relatively small number of patients, varying from 65 to 100. One exception is an analysis of 259 patients; however, this study documented the prevalence of OAVS at birth. These numbers might explain the differences in distribution of the O.M.E.N.S. score and the reported correlations and associations.[9,17,19,21-24] To study a large group of patients with CFM, we initiated a multicenter collaboration including the craniofacial units of Rotterdam, London and Boston.

The aim of this study is to analyse the largest population of patients with CFM with regard to severity, laterality and gender ratio as well as possible correlations among the different components of the PAT-CFM, including cleft lip and palate, and extracraniofacial anomalies. Furthermore, we investigated whether certain combinations of anomalies occur more frequently than others by using PCA, which might provide more insight into the embryologic processes that cause CFM.

Materials and methods

This retrospective study was conducted in a population diagnosed with CFM at the Craniofacial Units of Erasmus MC, Rotterdam, The Netherlands; Great Ormond Street Hospital in London, UK; and Boston Children's Hospital in Boston Massachusetts, USA. This study was approved by the Institutional Review Boards (Rotterdam: MEC-2013-575; London: 14 DS25; Boston: X05-08-058).

We identified patients diagnosed with CFM who presented at one of the units from January 1980 until January 2016. Patients were included only if medical photography and/or radiography of the face and medical history were available. Patients with isolated microtia, i.e., without mandibular hypoplasia on radiologic images, and patients diagnosed with other craniofacial syndromes that include craniofacial hypoplasia (e.g., Treacher Collins syndrome) were excluded. All charts were reviewed for information on demographic, radiographic and diagnostic criteria.

The severity of the deformity was scored in patients with the help of O.M.E.N.S.-plus or PAT-CFM. The orbit (O) is based on the size and position: scores ranging from O0 to O4. The mandible was scored on both, photography (M0-M3) and radiography (Pruzansky-Kaban Type I-Type III). Type I mandibles are smaller in size with normal dimensions and position of the condyle and ramus. Type IIA mandibles are smaller in size with decreased overall dimensions, but normal position, of the condyle and ramus. Type IIB mandibles are smaller in size with decreased overall dimensions of the condyle and ramus, furthermore the temporomandibular joint (TMJ) is malformed and displaced. In the Type III mandible, the ramus, condyle and TMJ are absent. External auricular anomalies are graded from E0 to E4, i.e., normal ear to anotia. Facial nerve weakness is categorized from N0 to N4. Soft tissue deficiency varied from normal soft tissues, S0, to severe soft tissue deficiency, S3.

There were few records with photography that depicted facial nerve paresis (N0-N4); therefore, facial nerve function was taken from the chart or was not included. According to PAT-CFM, both a global and detailed assessment, i.e., cleft lip/palate, ophthalmic anomalies and presence of ear and/or skin tags, were performed.[20] All medical charts were reviewed for extracraniofacial anomalies, i.e., cardiac, renal and vertebral/spine anomalies. Cardiac, renal and vertebral/spine anomalies were separately scored. When no information on a history of cardiac, renal and/or vertebral/spine anomalies was found, patients were categorized as having 'no extracraniofacial anomaly'.

Statistical analysis was performed using IBM SPSS Statistics for Windows, version 21.0 (IBM Corp., Armonk, NY) and R Core Team (2016). R: a language and environment for statistical computing (R Foundation for Statistical Computing, Vienna, Austria; http://www. R-project.org/).

Descriptive statistics were used to describe sex, laterality and diagnostic data. Pearson correlation coefficients were used to correlate the different components of the PAT-CFM and extracraniofacial anomalies.

PCA was used to measure the correlation between multiple variables and to detect clustering of the data, using the Ward method. The principal components are calculated from the eigenvectors of the covariance matrix of the data set. These eigenvectors align with the main axes of variation within the data set and thereby reduce the redundancy of the data. Biplots based on the extraction of the data represent as closely as possible the correlation between multiple variables. Furthermore, hierarchal data clustering is used to distinguish phenotypic groups within the biplot. Within the biplots, clusters/combinations of anomalies were further analysed. In the calculations concerning correlations, i.e., Pearson correlation coefficients and PCA, bilateral cases were not included. All variables are ordinal and not numeric; we used PCA instead of correspondence analysis because of the small numbers.

Results

Study Population

Craniofacial microsomia was diagnosed in 955 patients. Clinical pictures and/or radiographic images were available in 755 patients; these were included for further analysis. Facial structures were affected bilaterally in 86 patients (11,4%) and unilaterally in 669 patients (88,6%). In the unilateral cases, 371 patients were affected on the right side and 298 on the left side, with an overall left-to-right ratio of 1,2:1 as well. In total, 408 males (54%) and 347 females (46%) were included, with an overall male-to-female ratio of 1,2:1.

Pruzansky-Kaban classification

The Pruzansky-Kaban classification was scored in 526 patients. Overall, Types I (26,2%) and IIA (26,6%) were most often diagnosed (Table 1).

The Pruzansky-Kaban classification of the more severely affected side in patients with bilateral CFM was significantly more frequently scored as Type IIB or III compared to the mandibles of the unilaterally affected patients (Pearson's $X^2(3) = 18,527$, $p < 0.001$). However, the least affected side in patients with bilateral CFM did not significantly differ from the Pruzansky-Kaban classification compared to those in the unilaterally affected patients (Pearson's $X^2(3) = 1,357$, $p = 0.716$). The most frequently seen combination of Pruzansky-Kaban classifications in patients with bilateral CFM was a Type III on both sides.

Table 1. Pruzansky-Kaban classification in patients with Craniofacial Microsomia.

Pruzansky-Kaban classification	Right	Left	Bilateral severe	Bilateral less severe	Total
n	253	210	63	63	526 (100%)
Type I	78	51	9	17	138 (26,2%)
Type IIa	72	59	9	22	140 (26,6%)
Type IIb	57	51	20	12	128 (24,5%)
Type III	46	49	25	12	120 (22,6%)

Bilateral severe = most severely affected side; Bilateral less severe = less severely affected side

Global assessment of PAT-CFM in patients with unilateral CFM

PAT-CFM was scored in 649 patients with unilateral CFM. Orbital involvement was present in 44,9%, of which most patients (16,1%) were scored as O1. In total 90,6% presented with a mandibular deformity visible on clinical photography. There was a positive correlation ($r = 0{,}608$; $p < 0.001$; $n = 253$) between Pruzanksy-Kaban classification and the M on photography. In most patients (40,9%), deviation of the chin was classified as M1. Auricular anomalies were present in 82,7% of the patients; E3 was scored in 64,1%. Like the mandible, deficiency in soft tissue was more often on the right side and was most often characterized as minimal (S1). Orbital displacement and size, and the involvement of the facial nerve were the variables in which 'normality', i.e., O0 and N0, was the most common score. Macrostomia was diagnosed in 21,5% of the unilaterally affected patients (Table 2).

Facial nerve paresis was mentioned in the medical charts of 238 patients, but could not be assessed on photographs and was therefore classified as 'unable' in 431 patients. As preoperative photographs were unavailable in 20 patients, the PAT-CFM was determined on postoperative photographs (Table 3).

Table 2. Phenotypic Assessment Tool – Craniofacial Microsomia of patients with unilateral Craniofacial Microsomia.

PAT-CFM	Right side	Left Side	Total
Orbit	**360**	**281**	**641**
- O0	214	139	353 (55,1%)
- O1	57	46	103 (16,1%)
- O2	46	43	89 (13,9%)
- O3	33	42	75 (11,7%)
- O4	10	11	21 (3,3%)
Mandible	**233**	**178**	**411**
- M0	19	19	38 (9,2%)
- M1	104	64	168 (40,9%)
- M2A	61	47	108 (26,3%)
- M2B	31	27	58 (14,1%)
- M3	18	21	39 (9,5%)
Ear	**345**	**274**	**619**
- E0	59	48	107 (17,3%)
- E1	42	42	84 (13,6%)
- E2	47	38	85 (13,3%)
- E3	189	139	328 (53,0%)
- E4	8	7	15 (2,4%)
Nerve	**129**	**109**	**238**
- N0	70	64	134 (56,3%)
- N1	13	20	33 (13,9%)
- N2	29	18	47 (19,7%)
- N3	17	7	24 (10,1%)
Soft tissue	**356**	**278**	**634**
- S0	72	44	116 (18,3%)
- S1	164	111	275 (43,4%)
- S2	88	99	187 (29,5%)
- S3	32	24	56 (8,8%)
Macrostomia	**371**	**298**	**669**
- Yes	82	62	144 (21,5%)
- No	289	236	525 (69,5%)

PAT-CFM=Phenotypic Assessment Tool-Craniofacial Microsomia

Table 3. Missing data of Phenotypic Assessment Tool – Craniofacial Microsomia in patients with unilateral Craniofacial Microsomia.

PAT-CFM	Unable	Surgery	Total
Orbit	26	2	28
Mandible	253	5	258
Ear	32	18	50
Nerve	431	-	431
Soft tissue	31	4	35

PAT-CFM = Phenotypic Assessment Tool-Craniofacial Microsomia
Two patients had undergone surgery for all four of these variables.

Global assessment of PAT-CFM in patients with bilateral CFM

PAT-CFM was scored in 63 patients with bilateral involvement. The phenotype of these patients was diverse, and several combinations of the categories between the left and right side were found. When auricular deformities were present, most patients presented with an E3 anomaly on at least one side (Table 4).

Table 4. Phenotypic Assessment Tool – Craniofacial Microsomia in patients with bilateral Craniofacial Microsomia.

PAT-CFM	Right side	Left Side
Orbit	**81**	**52**
- O0	55	36
- O1	7	5
- O2	8	5
- O3	8	4
- O4	3	2
Mandible	**58**	**54**
- M0	7	16
- M1	17	13
- M2A	16	15
- M2B	11	6
- M3	7	4
Ear	**58**	**55**
- E0	8	15
- E1	12	10
- E2	5	9
- E3	29	20
- E4	4	1

Table 4. Phenotypic Assessment Tool – Craniofacial Microsomia in patients with bilateral Craniofacial Microsomia.

PAT-CFM	Right side	Left Side
Nerve	**24**	**24**
- N0	20	20
- N1	0	0
- N2	3	2
- N3	1	1
- N4	0	1
Soft tissue	**54**	**51**
- S0	12	18
- S1	23	18
- S2	14	12
- S3	5	3
Macrostomia		
- Yes	25 (39,7%)	
- No	38 (60,3%)	

PAT-CFM = Phenotypic Assessment Tool-Craniofacial Microsomia

None of the bilaterally affected patients had undergone previous operations on one or more anatomic variable of the PAT-CFM. In 38 patients, at least one anatomic variable of the PAT-CFM was scored as 'unable' and therefore could not be categorized (Table 5).

Table 5. Missing data of Phenotypic Assessment Tool-Craniofacial Microsomia in patients with bilateral craniofacial microsomia.

PAT-CFM	Unable Right Side	Unable Left Side	Total
Orbit	5	34	39
Mandible	28	32	60
Ear	28	31	59
Nerve	62	62	104
Soft tissue	32	35	67

PAT-CFM = Phenotypic Assessment Tool-Craniofacial Microsomia

Detailed assessment of the PAT-CFM

Ophtalmic anomalies, i.e., epibulbar dermoid and colobomata, were present in 13,4% of the patients. Epibulbar dermoids were present more often than colobomata. Ocular anomalies were significantly more commonly diagnosed in patients with bilateral CFM than in patients with unilateral CFM (Pearson $x^2(1) = 27,191$, $p < 0,001$).

Ear and/or skin tags were diagnosed in a total of 311 patients (41,2%). Ear and/or skin tags were significantly more often diagnosed in patients with bilateral CFM than in patients with unilateral CFM (Pearson $x^2(1) = 16,825$, $p < 0,001$) (Table 6).

Table 6. Numbers of patients with and without epibulbar dermoid, coloboma and/or tags.

Detailed assessment	Unilateral CFM	Bilateral CFM	Total
Eye	**669**	**86**	**755**
- Epibulbar dermoid	60	21	81
- Colobomata	6	3	9
- Epibulbair dermoid and colobomata	8	3	11
- No anomalies	595	59	654
Tags	**669**	**86**	**755**
- Ear - and skin	258	53	311
- No anomalies	411	33	444

CFM= Craniofacial Microsomia

Extracraniofacial anomalies and cleft lip/palate in patients with CFM

Extracraniofacial anomalies included vertebral and/or spinal anomalies, cardiac anomalies and renal anomalies.

Extracraniofacial anomalies were documented in 35,0% of patients, including both unilateral and bilateral involvement. Vertebral/spine anomalies were diagnosed in 26,1% of the 755 patients with CFM. Vertebral/spine anomalies were not only significantly more frequent in patients with a more severe mandibular hypoplasia (Pearson $x^2(3) = 10,604$, $p = 0,014$), they were also significantly more often present in patients with bilateral CFM than in patients with unilateral anomalies (Pearson $x^2(1) = 10,735$, $p = 0,001$).

In total, 140 patients (18,5%) with CFM were diagnosed with a cardiac anomaly. Cardiac anomalies are not significantly more frequent in bilaterally affected patients than in unilaterally affected patients (Pearson $x^2(1) = 3,183$, $p = 0,074$).

Renal anomalies were found in 10,5% of all patients, and were seen significantly more often in patients with bilateral CFM than in patients with unilateral CFM (Pearson $x^2(1) = 5,045$, $p = 0,025$).

Of the 755 patients diagnosed with CFM, 120 patients (15,9%) were also diagnosed with cleft lip/palate. There was no significant correlation between the Pruzansky-Kaban classification and presence of cleft lip/palate ($r = 0,084$; $p = 0,054$; $n = 525$). Cleft lip/ palate was diagnosed significantly more often in patients with bilateral CFM than in patients with unilateral CFM (Pearson $x^2(1) = 10,431$, $p = 0.001$) (Table 7).

Table 7. Extracraniofacial anomalies and cleft/lip palate in patients with CFM.

		Unilateral CFM	Bilateral CFM	Total
Extracraniofacial anomaly	Cardiac anomaly			
	- Yes	118	22	140 (18,5%)
	- No	551	64	615 (81,5%)
	Renal anomaly			
	- Yes	64	15	79 (10,5%)
	- No	605	71	676 (89,5%)
	Vertebral anomaly			
	- Yes	162	35	197 (26,1%)
	- No	507	51	558 (73,9%)
Cleft lip/palate				
	- Yes	96	24	120 (15,9%)
	- No	573	62	635 (84,1%)

CFM= Craniofacial Microsomia

Once an extracraniofacial anomaly is found, there is a higher chance that it coexists with anomalies in other organ systems. For example, of the patients diagnosed with a cardiac anomaly 20,7% also had a renal anomaly and 50,7% had vertebral anomalies. No strong correlations were found among these variables (Table 8).

Table 8. Pearson correlation coefficient; detailed assessment of Phenotypic Assessment Tool-Craniofacial Microsomia.

	Variables	Correlation coefficient	P-value
Detailed assessment and Pruzansky-Kaban	Ear/skin tags vs. eye anomaly	0.210 N = 669	<0.001*
	Ear/skin tags vs. Pruzansky-Kaban	0.030 N = 463	0.518
	Eye anomaly vs. Pruzansky-Kaban	0.110 N = 463	0.018*
Extra cranial anomalies and Pruzansky-Kaban	Cardiac anomaly vs. renal anomaly	0.129 N = 669	0.001*
	Cardiac anomaly vs. vertebral/spine anomaly	0.242 N = 669	<0.001*
	Cardiac anomaly vs. Pruzanksy-Kaban	0.092 N = 463	0.048*
	Renal anomaly vs. vertebral spine/anomaly	0.243 N = 669	<0.001*
	Renal anomaly vs. Pruzansky-Kaban	0.070 N = 463	0.134
	Vertebral/spine anomaly vs. Pruzanksy-Kaban	0.097 N = 463	0.036*

Pruzansky-Kaban = Pruzansky-Kaban classification.

Correlations between affected anatomic variables in CFM

A Pearson correlation test was performed for the unilateral cases to identify correlations between the severity of each individual variable of the PAT-CFM. The highest correlation was found between the Pruzansky-Kaban classification, scored on radiography, and the mandible (M), scored on clinical photography ($r = 0,624$; $p < 0.001$; $n = 254$); followed by the correlation between the mandible (M) and soft tissue deficiency ($r = 0,534$; $p < 0,001$; $n = 405$); and the correlation between soft tissue deficiency and the Pruzansky-Kaban classification ($r = 0.450$; $p < 0,001$; $n = 436$) (Table 9).

The triad mandibular hypoplasia, presence of vertebral/spine anomalies and epibulbar dermoid (Goldenhar syndrome) was present in 3,8% of the patients, with no strong correlation between vertebral/spine anomalies and presence of epibulbar dermoid (r = 0,092; p = 0,011; n = 755). Furthermore, a Pearson correlation test was performed for variables of the detailed assessment of the PAT-CFM, extracraniofacial anomalies and Pruzansky-Kaban classification. No strong correlations were found (Table 8).

Table 9. Pearson correlation coefficient Phenotypic Assessment Tool – Craniofacial Microsomia.

Pearson correlation	Correlation coefficient	P-value
Orbit vs. Mandible	0.108 (N = 406)	0.029*
Orbit vs. Ear	0.109 (N = 610)	0.007*
Orbit vs. Nerve	0.087 (N = 230)	0.188
Orbit vs. Soft tissue	0.315 (N = 631)	<0.001*
Orbit vs. Macrostomia	-0.030 (N = 640)	0,442
Orbit vs. Pruzansky-Kaban	0.191 (N = 411)	<0,001*
Mandible vs. Ear	0.209 (N = 379)	<0.001*
Mandible vs. Nerve	-0,250 (N = 5)	0,685
Mandible vs. Soft tissue	0.534 (N = 405)	<0.001*
Mandible vs. Macrostomia	0,081 (N = 410)	0,100
Mandible vs. Pruzansky-Kaban	0.624 (N = 254)	<0.001*
Ear vs. Nerve	0.069 (N = 234)	0.292
Ear vs. Soft tissue	0.206 (N = 604)	<0.001*
Ear vs. Macrostomia	0.057 (N = 618)	0.158
Ear vs. Pruzanksy-Kaban	0.165 (N = 437)	<0.001*
Nerve vs. Soft tissue	0.073 (N = 227)	0.276
Nerve vs. Macrostomia	-0.076 (N = 238)	0.244
Nerve vs. Pruzanksy-Kaban	-.018 (N = 196)	0.807
Soft tissue vs. Macrostomia	-0.070 (N = 633)	0.080
Soft tissue vs Pruzansky-Kaban	0.450 (N = 436)	<0.001*
Macrostomia vs. Pruzansky-Kaban	0.052 (N = 526)	0.232

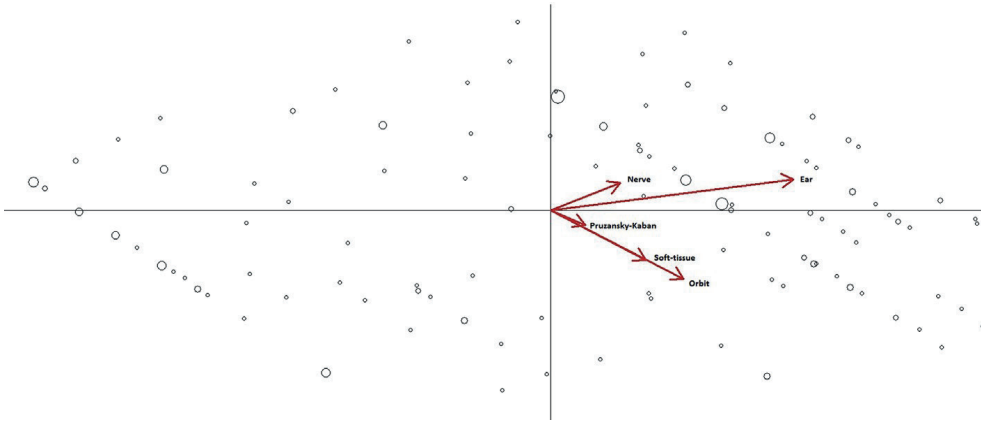
Pruzansky-Kaban = Pruzansky-Kaban classification. *Significant.

Principal component analysis in CFM

PCA was performed on data from unilaterally affected patients with complete datasets, including Pruzansky-Kaban classification, orbit, ear, soft tissue and nerve. PCA showed a pattern in severity: the higher the score in one variable, the higher the probability that the other variables had a high score as well. Furthermore, there was a trend within the direction of the vector: the vectors of orbit, Pruzansky-Kaban classification, and soft tissue had another direction than the vectors of the ear and nerve (Figure 1).

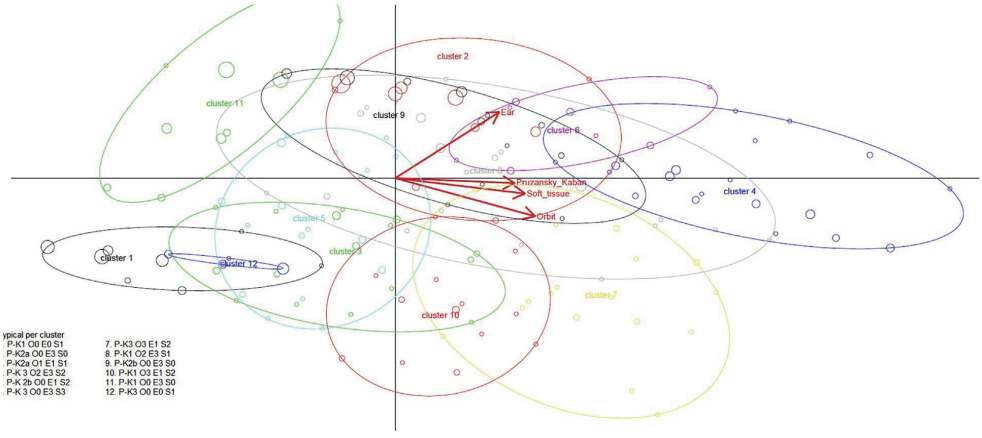
Because there was a significant number of patients in which the nerve could not be assessed ('Unable'), a total of 239 patients were not included in the first PCA. Therefore, this variable was excluded in a second PCA, in which a total of 435 unilateral cases were available. This second PCA showed a correlation between the severity of the Pruzansky-Kaban classification, the score on the orbital deformity and the soft-tissue hypoplasia. The ear had the lowest correlation with the orbit, followed by the soft tissue and the Pruzansky-Kaban classification. Hierarchal clusters of the data were made using the Ward method; however, no distinct clusters with specific combinations of typical phenotypes were found. Nonetheless, patients in cluster 3 were different from patients in cluster 8 (Figure 2).

Figure 1. Biplot of the Pruzansky-Kaban, Orbit, Ear, Nerve, Soft tissue (N = 192).



The X-axis shows a gradient from least severe to most severe (left to right), and the Y-axis divides the biplot according to the structures. The dots are (groups of) patients with specific scores on the Phenotypic Assessment Tool-Craniofacial Microsomia. A larger dot represents a larger group.

Figure 2. Typical patients per cluster within the biplot of the Pruzansky-Kaban, Orbit, Ear, Nerve, Soft tissue (N = 435).

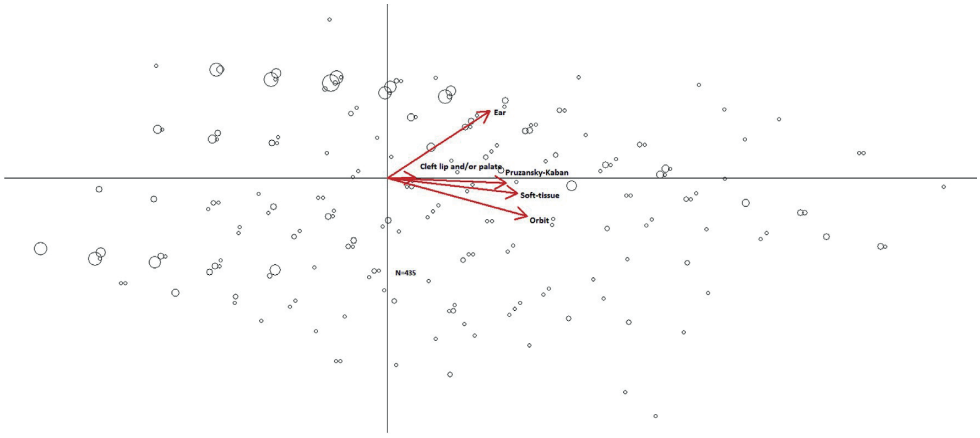


The X-axis shows a gradient from least severe to most severe (left to right), and the Y axis divides the biplot according to the structures. The dots are (groups of) patients with specifics scores on Phenotypic Assessment Tool-Craniofacial Microsomia. The circles represent specific clusters found via hierarchal clustering. A typical patient per cluster is annotated.

A third PCA was performed including Pruzansky-Kaban classification, orbit, ear, soft tissue, and presence of cleft lip/palate. There was a low correlation between cleft lip/palate and structures of the first pharyngeal arch (Figure 3).

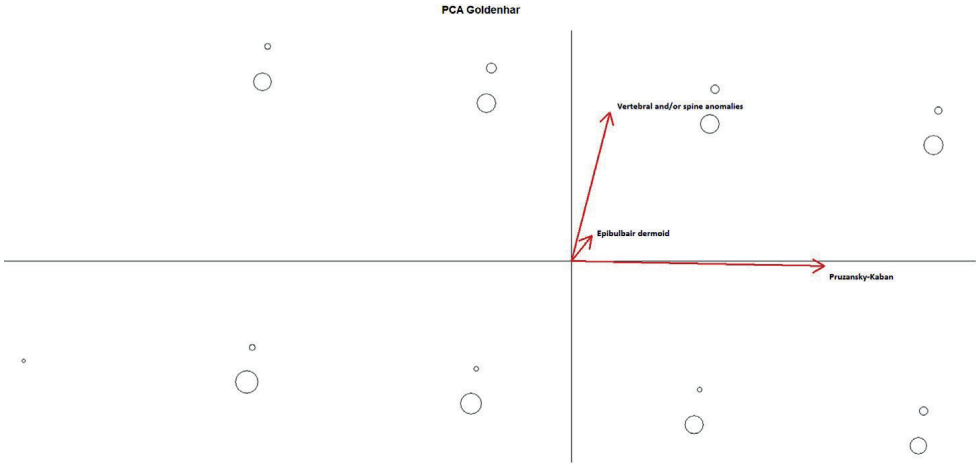
A fourth PCA was performed with data including Pruzansky-Kaban classification, orbit, ear, soft tissue and extracraniofacial anomalies. Results were similar to those of the Pearson correlation test. Finally, PCA on data that included Pruzansky-Kaban classification, presence of an epibulbar dermoid and vertebral and/or spine anomalies was performed, i.e., the classic Goldenhar syndrome. In total, 463 patients were included. The biplot suggests no correlation among the three variables (Figure 4).

Figure 3. Close-up of the biplot of the Pruzansky-Kaban, Orbit, Ear, Soft-tissue and presence of cleft lip/palate (N = 435).



The X-axis shows a gradient from least severe to most severe (left to right), and the Y-axis divides the biplot according to the structures. The dots are (groups of) patients with specifics scores on the Phenotypic Assessment Tool-Craniofacial Microsomia.

Figure 4. Close-up of the biplot of the Pruzansky-Kaban, presence of epibulbar dermoid and vertebral/spine anomalies, i.e., Goldenhar syndrome (N = 463).



The X-axis shows a gradient from least severe to most severe (left to right), and the Y-axis divides the biplot according to the structures. The dots are (groups of) patients with specific scores on the Pruzansky-Kaban classification and presence of epibulbar dermoid and vertebral/spine anomalies.

Discussion

Study population

By combining the datasets of three major craniofacial units, it was possible to study 755 patients with CFM. In this study, patients were diagnosed solely with bilateral CFM when radiographic images showed bilateral mandibular hypoplasia. Diagnosis of bilateral CFM was not influenced by external facial aspects, such as presence of ear and/or skin tags on both sides. In the literature, 2,5%-34% of patients with CFM are diagnosed with bilateral CFM. This wide range might be the result of selection bias or use of different selection criteria.[28] In this study, 12% of the patients were diagnosed with bilateral CFM, which is slightly lower than the 13,6% (n = 977) found in the meta-analysis of Xu et al.[29] A male-to-female ratio was found in our study (1,2:1) that was similar to the ratio in the meta-analysis (1,09:1 n = 908). Earlier studies showed similar results with right-to-left ratios varying from 1,2:1 to 1,8:1. [9,17,22,23]

PAT-CFM and extracraniofacial anomalies and their correlations

Unlike in other studies, the Pruzansky-Kaban classification was equally divided in our cohort, whereas other studies found higher numbers among patients with Type I and IIA. Possibly, this might be due to selection bias, as patients with the most severe cases are referred to specialized craniofacial centers (Table 10).

Table 10. Extended version of the table used in Park et al.[22]

Study	Vento et al.	Poon et al.	Park et al.	Tuin et al.	Caron, Pluijmers et al.
Total n of patients	**154**	**65**	**100**	**105**	**755**
Orbit (%)					
- O0	81	77	53	72	55
- O1	4	12	22	10	16
- O2	15	11	22	10	14
- O3	0	0	3	8	12
- O4	--	--	--	--	3
P-K classification(%)					
- M0	11	9	0	12	0
- M1	40	30	59	36	26,2
- M2a	22	27	21	19	26,6
- M2b	17	23	18	14	24,5
- M3	10	11	2	19	22,6
Ear (%)					
- E0	34	19	17	12	17
- E1	14	34	12	18	14
- E2	19	27	23	13	13
- E3	33	20	48	57	53
- E4	--	--	--	--	2
Nerve (%)					(n = 283)
- N0	53	76	79	61	56
- N1	8	8	4	7	14
- N2	19	11	6	26	20
- N3	20	5	11	6	10
Soft tissue (%)					
- S0	5	28	24	23	18
- S1	58	45	52	41	43
- S2	28	23	14	27	30
- S3	9	4	10	9	9

Pruzansky-Kaban = Pruzansky-Kaban classification.
The mandible on medical photography of Phenotypic Assessment Tool – Craniofacial Microsomia was not scored by the other studies, because at the time of those studies the mandible was based solely on radiographic images.

Although there was a positive correlation between the score of the mandible on clinical photography (M) of the PAT-CFM and the Pruzansky-Kaban classification, based on radiography ($r = 0,624$; $p < 0.001$; $n = 254$), there was no strong correlation between these variables, and thus these should not be considered as interchangeable components of the PAT-CFM.

Several studies have shown an association between the outcome of the PAT-CFM and the presence of extracraniofacial anomalies. Syndromologists consider an anomaly to be 'associated' if it occurs in 10%-15% of the patients.[6,19] Hennekam et al. described that an association is a pattern of anomalies, of which at least two are morphologic, that occur together more often than would be expected by chance, and in which a causal relationship has not been identified.[30] Extracraniofacial anomalies were diagnosed in 10,5% to 26,1% of the patients with CFM in this study (which is higher than the incidence of 0,001%-1% in live births in the 'healthy' population).[31-33] Statistical analysis showed weak and insignificant correlations among the tested variables; therefore, the term 'association' should be abandoned and replaced with 'correlation' when statistical analysis shows significant findings. Hennekam et al. state that the term 'association' is not durable but might be useful to motivate clinicians to evaluate patients for other, related anomalies.[30]

This study found that structures derived from the first pharyngeal arch are correlated with degree of severity, as are the structures derived from the second pharyngeal arch. These results support the findings by Tuin et al., which reinforces the suggestion that the aetiology involves a disturbed migration of the (cranial) neural crest cells.[9]

Patients diagnosed with an extracraniofacial anomaly have a higher chance of having coexisting extracraniofacial anomalies in other organ systems, as noted by Rollnick and Kaye[28], suggesting a similar pathogenesis of these anomalies.

'Goldenhar syndrome' is often applied to patients with mandibular hypoplasia, epibulbar dermoid and vertebral/spine anomalies; it is regarded by some as a variant and is estimated to represent 10% of the patients with CFM.[28] In this study, this triad was diagnosed only in 3,8% of the patients. There was a very weak positive correlation among the three variables. Analysis of statistical correlations in other studies also failed to substantiate a 'Goldenhar' variant as a distinct entity.[9,17] The term 'Goldenhar syndrome' should therefore be discarded.

It was not possible to identify specific groups of patients with PCA, as all clusters overlapped with at least one other cluster, suggesting that CFM is a continuum of anomalies that coexist in all combinations and degrees of severity. However, many differences were found between patients affected unilaterally and bilaterally. We suggest that patients with unilateral or bilateral CFM be approached more comprehensively.

Patients with bilateral CFM tend to be at the severe end of the spectrum and are also more often diagnosed with extracraniofacial anomalies and/or cleft lip/palate. These results might be explained by the embryogenesis and the default migration of (cranial) neural crest cells.

Conclusion

A large cohort of patients with CFM is presented. Of 955 patients, data on 755 patients were available for in-depth analysis. The demographics showed outcomes similar to those of other cohorts. Using our strict criteria, 12% of the patients were affected bilaterally.

Statistical analyses showed that the structures derived from the first pharyngeal arch correlated more with one another than with the structures derived from the second pharyngeal arch, and vice versa.

Extracraniofacial anomalies were positively, although not strongly, correlated with CFM. Further research is needed to determine a possible correlation is the pathogenesis.

Although phenotypically no specific groups of patients could be identified, patients with bilateral CFM were more severely affected than patients with unilateral CFM. Therefore, these bilaterally affected patients should be approached more comprehensively.

Finally, even patients with a minor clinical presentation should be screened for extracraniofacial anomalies, including cardiac, renal, spinal and vertebral deformities.

Acknowledgements

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CHAPTER

3

Obstructive sleep apnea in Craniofacial Microsomia: a systematic review

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Abstract

Children with craniofacial microsomia (CFM) are at risk of obstructive sleep apnea (OSA). This systematic review provides an overview of the literature on the prevalence of OSA in children with CFM. A search was performed in PubMed, Embase, Cochrane Library, and Web of Science for articles on CFM and OSA. The following data were extracted from the articles: number of patients, patient characteristics, presence of OSA, polysomnography outcomes, and the treatments and outcomes of OSA. We included 16 articles on CFM and OSA, four of which reported the prevalence of OSA (range 7–67%). Surgical treatment was more often described in these patients than conservative treatment. According to the literature, OSA is related to CFM. However, as there have been no prospective studies and few studies have presented objective measurements, no definitive conclusions can be drawn. Prospective studies are needed to determine the prevalence of OSA in patients with CFM.

Introduction

A common problem in children with a craniofacial anomaly is upper airway obstruction. This obstruction may be related to bilateral mandibular hypoplasia, as is the case in children with Robin sequence and Treacher Collins syndrome. The prevalence of upper airway obstruction, and more specifically of obstructive sleep apnea (OSA), in children with Robin sequence and Treacher Collins syndrome is 12.5% and 46%, respectively[1,2]. In the normal population this is 3–4%[3–5].

OSA is one of the clinical manifestations of upper airway obstruction and is characterized by snoring, laboured breathing during sleep, apnea, and excessive daytime sleepiness. Complications of OSA include failure to thrive, pulmonary hypertension, cor pulmonale, and sudden death. Therefore, accurate diagnosis and identification of risk groups is important.

As is the case for Robin sequence and Treacher Collins syndrome patients, craniofacial microsomia (CFM) patients have mandibular hypoplasia as a clinical characteristic. CFM is the result of a disturbance in the embryological development of the first and second pharyngeal arches and is characterized by asymmetric underdevelopment of the facial structures, including the mandible, maxilla, ears, soft tissues, and facial nerves[6,7]. CFM is most often regarded as a unilateral malformation, however the facial structures are involved bilaterally in 10% of cases[8,9] and several recent publications have suggested that the contralateral side is abnormal in most cases as well, although not truly hypoplastic[10,11]. The reported incidence rate ranges from 1 in 3500 to 1 in 20,000[6,12,13], which makes CFM the second most common facial birth defect after cleft lip and palate. CFM in combination with epibulbar dermoid and extra-craniofacial anomalies, such as heart, renal, and vertebral anomalies, is known as Goldenhar syndrome[14–19].

The most typical deformity of CFM is mandibular hypoplasia, which occurs in 89% -100% of cases[20]. The most commonly used classification of mandibular hypoplasia is the classification of Pruzansky modified by Kaban, in which mandibular hypoplasia is classified into four types[21,22]. In type I, the mandibular ramus and temporomandibular joint (TMJ) are of normal shape but small. In type IIa, the mandibular ramus is abnormal in both size and shape, but the deformed TMJ is adequately positioned. In type IIb, the mandibular ramus and TMJ are abnormal in shape, size, and location. Type III deformity consists of an absent ramus, condyle, and TMJ.

As mandibular hypoplasia increases the risk of airway obstruction, patients with CFM are theoretically at risk of airway obstruction. Several authors have stated that patients with CFM should be screened routinely for OSA[20,23,24]. Nevertheless, the exact prevalence of

OSA in CFM and the severity of the pathology on which these statements are based are not mentioned in these expert opinions.

The aim of this review is to provide an overview of the literature regarding CFM and the prevalence and treatment of OSA based on the following key questions: (1) What is the prevalence of OSA in patients with CFM? (2) What are the treatment modalities for OSA reported in patients with CFM? (3) What is known about the follow-up after treatment for OSA in patients with CFM?

Within the group of craniofacial malformation patients, feeding difficulties are often closely related to upper airway obstruction[25]. This topic is described separately in a second article entitled "Feeding difficulties in craniofacial microsomia: a systematic review".

Methods

Search strategy

A search of public domain databases was performed to identify articles focusing on CFM and OSA. The search was conducted in the following databases: PubMed, Embase, Cochrane Library, and Web of Science (all searched up to 27 August 2014). In addition, we performed a manual search of secondary sources including references of the articles initially identified. The goal was to identify all studies addressing CFM in relation to OSA.

The following search terms were used: (((facial[tiab] OR face[tiab] OR hemifacial[tiab] OR orbitocranial[tiab] OR facies[tiab] OR cranial[tiab] OR mandibulofacial[tiab] OR otomandibular[tiab] OR craniofacial[tiab] OR faciocranial[tiab] OR hemimandibular[tiab]) AND (microsom*[tiab] OR asymmetr*[tiab] OR dysosto*[tiab] OR dysplasia[tiab] OR anomal*[tiab] OR deformit*[tiab] OR hypoplasia[tiab] OR syndrom*[tiab] OR malformation*[tiab]) OR (treacher collins[tiab] OR goldenhar[tiab]) OR (oculoauriculovertebral*[tiab] OR facioauriculovertebral*[tiab] OR (auriculo vertebral*[tiab]))) AND (airway obstruction*[tiab] OR obstructive airway *[tiab] OR nocturnal apnea[tiab] OR nocturnal apnea[tiab] OR sleep apnea[tiab] OR sleep apnea[tiab] OR osa[tiab] OR osas[tiab] OR osahs[tiab])) AND publisher[sb].

Data extraction and analysis

Two investigators (C.J.J.M.C and B.I.P.) screened the studies independently. All articles on the prevalence and treatment of OSA in patients with CFM were included. Expert opinions were excluded. The full texts of all articles meeting the inclusion criteria and articles for which the abstract was lacking information were obtained.

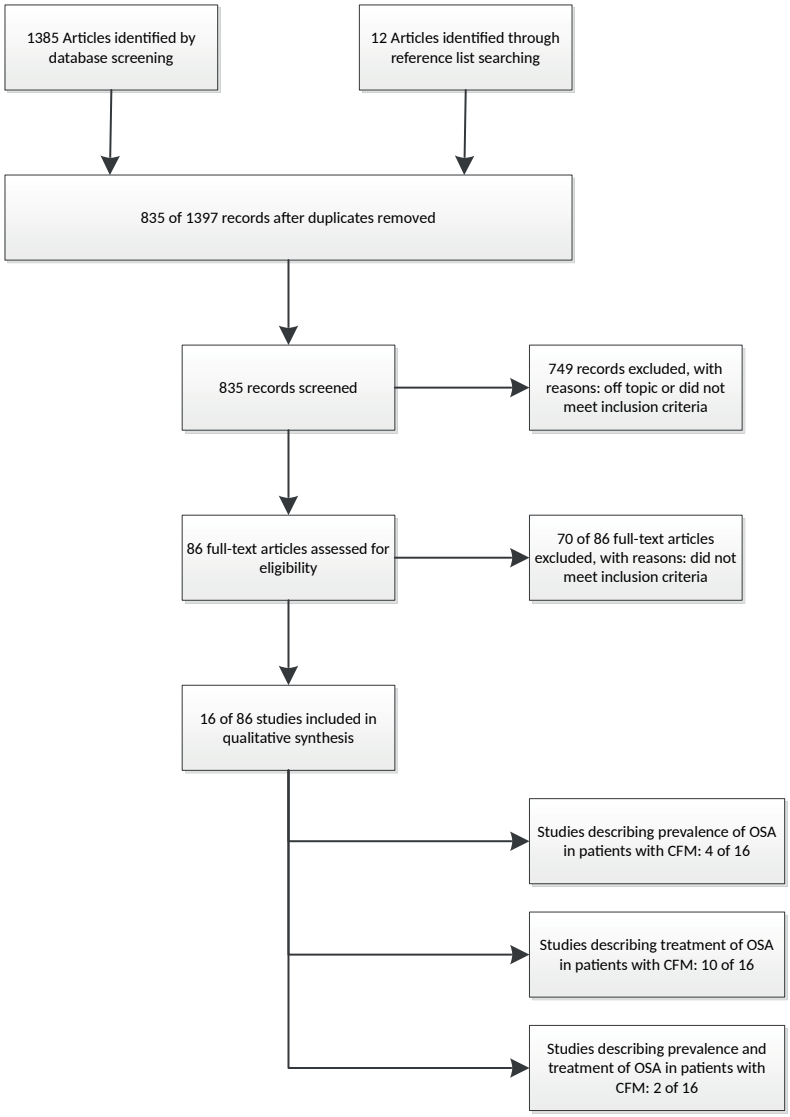
Articles were graded on quality of evidence using the Oxford Centre for Evidence-Based medicine (CEBM) criteria[26]. Data on the number of patients, patient characteristics such as sex, age, and severity of CFM, the presence of OSA, polysomnography outcomes, and the treatment and outcome of OSA were tabulated when available.

Results

Craniofacial microsomia and obstructive sleep apnea

The search retrieved 1385 relevant articles. After removing duplicate articles and including further articles from the manual search of secondary sources, 835 articles were examined based on the title and abstract. A total of 749 articles were then excluded. Of the 86 articles retrieved for further examination, 16 were included in the present analysis (Figure 1).

Figure 1. Data extraction flow chart.



What is the prevalence of OSA in patients with CFM?

Six studies and case series on the prevalence of OSA in CFM were found (Table 1). OSA was defined as complete cessation of airflow for more than two breaths or 10 seconds and hypopnoea as a ≥50% reduction in respiratory airflow accompanied by a decrease of ≥3% in oxygen saturation (SaO_2)[27,28], with a minimum of 30 episodes of obstructive apnoea in a 7-h sleep period[29]. In some cases OSA was not defined at all[30–32]. The prevalence of OSA in these studies varied from 7% to 67% (Table 2).

Table 1. Studies on the prevalence of OSA in CFM meeting the criteria for inclusion.

Reference	CEBM level of evidence	Methodology	Aim of the study
Cloonan et al.[30]	III	Case–control study	To compare sleep outcomes in children with and without CFM
D'Antonio et al.[31]	III	Cross-sectional study	To describe the occurrence and magnitude of pharyngeal and laryngeal anomalies in a population of patients with OAVS
Cohen et al.[27]	III	Retrospective study	To determine the prevalence of OSA in CFM
Luna-Paredes et al.[28]	III	Retrospective study	To determine the prevalence of airway obstruction symptoms in craniofacial anomalies
Sculerati et al.[32]	III	Retrospective study	A delineation of clinical characteristics affecting the airway in craniofacially affected children
Sher et al.[29]	III	Retrospective study	To describe the nasopharyngoscopic findings in patients with craniofacial anomalies

CEBM, Centre for Evidence-Based Medicine; CFM, craniofacial microsomia; OAVS, oculo-auriculo-vertebral spectrum ; OSA, obstructive sleep apnea

Table 2. Summary of the studies on the prevalence of OSA in CFM.

Reference	Method of diagnosis of OSA	No. of patients with CFM	Age, range or mean	Gender, M/F	Severity of CFM	No. of patients with OSA	Outcome of PSG
Cloonan et al.[30]	PSQ, supplemental sleep questions	84/124	5.5–8.5 y	NR	Not possible to deduce	10	NR
D'Antonio et al.[31]	Chart review, PSG	41	6 y 4 m	14/9	NR	5	NR
Cohen et al.[27]	Chart review	38	8 y 3 m	21/17	Not possible to deduce	9	NR
Luna-Paredes et al.[28]	Proactive screening program, cardiorespiratory polygraphy	9	NR	NR	NR	5	AHI: 4.76 (mean)
Sculerati et al.[32]	Chart review	41	NR	NR	NR	9	NR
Sher et al.[29]	PSG	84	Birth to 24 y	NR	NR	6	NR

AHI, apnea–hypopnea index; CFM, craniofacial microsomia; F, female; M, male; m, months; NR, not reported; OSA, obstructive sleep apnea; PSG, polysomnography; PSQ, Paediatric Sleep Questionnaire; y, years

Case–control study on the prevalence of OSA in CFM

Cloonan et al.[30] described the prevalence of sleep disordered breathing (SDB) in children with CFM by studying 124 cases and 349 controls. Parents of children with CFM reported that their child snored more often than did the parents of otherwise healthy controls (29% vs. 17%). Eighty-four of the 124 cases received a supplementary questionnaire regarding history of airway interventions and the use of polysomnography (PSG) to classify the severity of SDB or OSA. A history of airway interventions was more often reported in children with CFM than controls (14% vs. 8%) and more children with CFM had undergone PSG than controls (20% vs. 2%). Of the 15 children with CFM who underwent PSG, 10 were diagnosed with SDB/OSA (67%); of the controls, four out of four were diagnosed with SDB/OSA.

Cross-sectional study on the prevalence of OSA in CFM

D'Antonio et al.[31] evaluated the pharyngeal and laryngeal structure and function in patients with Goldenhar syndrome by physical examination, otolaryngological examination, and video-nasoendoscopy. Nine out of 41 patients (22%) reported symptoms of airway obstruction, of whom five (12%) had OSA documented by PSG (Table 2).

Retrospective studies on the prevalence of OSA in CFM

Cohen et al.[27] found a prevalence of OSA of 24%. Upper airway disorders fell within three categories. Patients in category 1 were asymptomatic for airway disorders, patients in category 2 were suspect for intermittent OSA or had experienced a perioperative apnoeic event, and patients in category 3 had a definite history of OSA. Like Cloonan et al.[30], they found that patients with more severe mandibular and/or extra-craniofacial anomalies had a greater risk of OSA, i.e. 89% of the patients with a category 3 upper airway disorder exhibited a higher incidence of more severe mandibular involvement[27,30].

Luna-Paredes et al.[28] found a prevalence of OSA of 56% in nine patients with Goldenhar syndrome, with OSA ranging from mild to severe.

Sculerati et al.[32] studied 14 patients with Goldenhar syndrome, 12 with CFM, and 15 with microtia. Nine cases required a tracheostomy (22%). The exact diagnosis of the nine tracheostomized cases was not mentioned and the prevalence of OSA was also not mentioned.

Sher et al.[29] evaluated 84 patients with facio-auriculo-vertebral sequence of whom six underwent endoscopy as they had evidence of upper airway obstruction. Five out of six had OSA and one out of six had obstructive awake apnea, defined as a complete or partial cessation of air exchange during wakefulness caused by an observable obstruction in the upper airway.

What are the treatment modalities for OSA reported in patients with CFM?
Twelve studies were found concerning the treatment of OSA in craniofacial anomalies and/or CFM (Tables 3 and 4).

Retrospective studies on the treatment of OSA in CFM
Burstein et al.[33] developed the airway zone concept in order to treat patients with severe OSA refractory to standard medical and surgical treatment. Zone 1 extends from the nares to the velum, zone 2 from the lips to the hypopharynx, zone 3 from the epiglottis to the trachea, and zone 4 from the subglottis to the bronchi. Their goal was to avoid permanent tracheostomy. The four patients with Goldenhar syndrome included in this study all suffered from an obstruction in zone 1 and zone 2 and underwent bony and soft tissue procedures. All patients responded well to skeletal expansion. Both, the preoperative median apnea index, defined as the total number of apneic events divided by the total sleep time and multiplied by 60, and the respiratory disturbance index improved postoperatively (Table 3).

Järund et al.[34] included one patient with Goldenhar syndrome and described the effects of continuous positive airway pressure (CPAP) in patients with craniofacial anomalies and OSA. Clinical characteristics were not given. According to Järund et al.[34], the treatment of OSA with CPAP in children with craniofacial anomalies is superior to early surgery and tracheostomy (Table 3).

All 16 patients in the study of Cohen et al.[35] were considered tracheostomy candidates after conventional medical and surgical treatment of OSA had failed, e.g. tonsillectomy, adenoidectomy, uvulopalatoplasty, and relief of nasal obstruction, or had tracheostomies placed shortly after birth and could not be decannulated by standard protocols. In all cases, external mandibular distraction devices were used. Distraction was started on the third postoperative day and proceeded until the signs and symptoms of OSA resolved. In the patients without tracheostomies, a PSG was obtained preoperatively and postoperatively before removal of the distraction devices. The respiratory disturbance index was defined as the number of apneic and hypopneic events per hour of sleep. Unfortunately, specific clinical characteristics and outcomes could not be deduced for the patients with CFM (Table 3).

Seven of the 25 patients studied by James and Ma[36] were diagnosed with CFM, five bilaterally affected and two unilaterally. Objective data on the airway status of these patients before the tracheostomy were not available. The unilateral cases were treated with a combination of costochondral grafting and osteotomy. The exact treatment of the bilateral cases was not described. All CFM patients were treated successfully and decannulated (Table 3).

Sorin et al.[37] studied five patients with Goldenhar syndrome who underwent upper airway endoscopy before and after mandibular distraction. The results of the pre- and post-surgery airway endoscopy at the level of the oropharynx and supraglottis are shown in Table 5. All of the Goldenhar patients were decannulated and remained tracheostomy-free during the time of the study (Table 3).

Of the 41 patients studied by Sculerati et al.[32], including 14 with Goldenhar syndrome, 12 with CFM, and 15 with microtia, nine cases required a tracheostomy (22%). The diagnosis of the nine tracheostomized cases was not mentioned. Next to craniofacial synostosis syndromes and Treacher Collins syndrome, CFM was the most common craniofacial anomaly associated with tracheostomy (Table 3).

Case reports on the treatment of OSA in CFM

The treatment of patients with CFM or Goldenhar syndrome and OSA was described in five case reports[38–42]. Treatment varied from orthopaedic myofunctional appliances and CPAP to adenotonsillectomy, mandibular distraction, and costochondral reconstruction. In some cases additional treatments were used to successfully treat OSA. Unfortunately, objective outcome measurements were not always reported (Table 4).

What is known about the follow-up after treatment for OSA in patients with CFM?

The follow-up described in these studies varied from several days to 15 years[33,34,36–38,41,42]. All studies described an improvement in the sleep studies performed after both surgical and non-surgical treatment, or an improvement in the clinical symptoms[33,34,36–38,41,42]. However, the outcomes of objective measurements were not reported. Patients who were decannulated as a result of the therapy for OSA were not re-cannulated. Unfortunately, not all studies described the follow-up of the studied patients with CFM specifically.

Table 3. Summary of retrospective studies on the treatment of OSA in CFM.

Reference	CEBM level of evidence[26]	Methodology	Total No. of patients	No. of patients with CFM	Age of total group, mean (range)	Preoperative outcome of PSG	Treatment of OSA	Postoperative outcome of PSG
Burstein et al.[33]	III	RS	28	4	5 y 3 m (18 m to 17 y)	AI: 12 RDI: 22	Skeletal expansion	AI: 1 RDI: 1
Järund et al.[34]	III	RS	21	1	3 y 7 m (1 m to 2 y)	Desat: 23% DI: 32	CPAP	Desat: 11% DI: 5
Sher et al.[29]	III	RS	266	84 (6 patients treated for OSA)	(Birth to 24 y)	NR	2 mandibular advancement, 3 tracheostomy, 1 refused treatment	NR
Cohen et al.[35]	III	RS	16	7	4 y 8 m (14 w to 16 y)	RDI: 7.1 Desat: 30%	Mandibular distraction	RDI: 1.7 Desat: 11%
James and Ma[36]	III	RS	25	7	(12 m to 13 y)	NR	Mandibular distraction	Decannulation
Sorin et al.[37]	III	RS	18	5	2 y 8 m (2 m to 8 y)	NR	Mandibular distraction	Decannulation
Sculerati et al.[32]	III	RS	251	41	4 y 10 m (Birth to 26 y)	NR	Tracheostomy	NR

AI, apnea index; CEBM, Centre for Evidence-Based Medicine; CFM, craniofacial microsomia; CPAP, continuous positive airway pressure; Desat, desaturation; DI, desaturation index; m, months; NR, not reported; OSA, obstructive sleep apnea; PSG, polysomnography; RDI, respiration disturbance index; RS, retrospective study; w, weeks; y, years

Table 4. Case reports on the treatment of OSA in CFM.

Citation	CEBM level of evidence[26]	Methodology	No. of patients	Age	Preoperative outcome PSG	Treatment of OSA	Postoperative outcome PSG
Morris et al.[41]	V	Retrospective CR	1		PSG not possible with capped tracheostomy	Mandibular distraction	AHI: <5 Desat: 0–4%
Hoch and Hochban[38]	V	Retrospective CR	1	4 years	AI: >20 Desat: 8–10%	Nasopharyngeal tube and mandibular distraction	NR
Kourelis et al.[39]	V	Retrospective CR	1	17 years	AHI: 28 Desat: 92%	CPAP	NR
Stellzig et al.[42]	V	Retrospective CR	1	Birth	AHI: not given Desat: <80%	Orthopaedic myofunctional application	NR
McCarthy et al.[40]	IV	Retrospective CS	2	Birth	AHI: 23 Desat: 66%	Adenotonsillectomy	AHI: 3.82

AHI, apnea–hypopnea index; AI, apnea index; CEBM, Centre for Evidence-Based Medicine; CFM, craniofacial microsomia; CPAP, continuous positive airway pressure; CR, case report; CS, case series; Desat, desaturation; NR, not reported; OSA, obstructive sleep apnea; PSG, polysomnography

Table 5. Results of pre- and post-surgery airway endoscopy[37].

Patient	Gender	Distraction age, months	Extent of obstruction of the oropharynx[a]		Extent of obstruction of the supraglottis[a]		Adjunct procedures
			Pre-endoscopy	Post-endoscopy	Pre-endoscopy	Post-endoscopy	
1	F	18	3	1	2	1	Adenoidectomy
2	M	19	3	3	4	3	Adenotonsillectomy, cleft palate repair, fundoplication
3	M	14	4	2	1	1	Adenotonsillectomy, excision suprastomal granuloma
4	F	99	4	3	3	3	Choanal stenosis dilatation, septoplasty
5	M	46	4	3	4	2	Tonsillectomy, sublingual tonsillectomy

F, female; M, male.

[a]The extent of obstruction was 0% (score 1), 1–50% (score 2), 51–75% (score 3), or 76–100% (score 4)

Discussion

The prevalence of OSA in patients with CFM reported in the literature varied from 7% to 67%[27–32]; these prevalence rates are higher than those reported in the normal population, which range from 3% to 4%[3–5]. These results are based on subjective measurements, such as questionnaires (i.e. the Paediatric Sleep Questionnaire), and on the retrospective evaluation of medical charts, or are based on PSG performed in a small proportion of the group of patients studied.

Most studies on the prevalence of OSA in CFM have been based on small numbers. Cloonan et al.[30] were the first to perform a large-scale study to compare sleep outcomes in children with and without CFM[30]. However, PSG was performed to confirm the diagnosis of OSA in only a small proportion of their study group. These patients might not be representative of the total group of patients with CFM studied, which is also the case for the study by D'Antonio et al.[31] To truly give an indication of the prevalence of OSA, all patients should have been screened for OSA with PSG.

As well as a higher prevalence of OSA in CFM, both Cloonan et al.[30] and Cohen et al.[27] found a relationship between the severity of CFM, i.e. the mandibular hypoplasia, and the risk of OSA. However, both studies determined the severity of CFM from photographs and/or medical charts. This gives an idea of the severity and classification of the CFM in patients, but to evaluate and classify mandibular hypoplasia objectively, radiographs, such as orthopantomograms, are needed.

The higher risk of OSA found in several studies might be the result of the (unilateral) mandibular hypoplasia, as is the case in patients with Robin sequence or Treacher Collins syndrome[1,2], causing an obstruction at the level of the oropharynx and supraglottis. Further research is needed to clarify the contribution of additional pharyngeal and/or laryngeal deformities to the obstruction[31,37,43].

Overall, at most these studies suggest a higher prevalence of OSA in patients with CFM, but no definitive conclusions can be drawn.

The treatment modalities described in the studies vary from CPAP to mandibular distraction or reconstruction[29,32–42]. The study populations in those studies that described mandibular distraction or reconstruction comprised patients who were unresponsive to medical and surgical (e.g. adenotonsillectomy) treatment for OSA[33–38,41]. This could have led to a possible bias towards the inclusion of patients with severe OSA. It would be interesting to determine the percentage of patients with CFM and OSA for whom the OSA is refractory to medical and surgical treatment. Furthermore, it would be interesting to

study the specific characteristics of these patients as these have not been described and could provide more information about the patients who are at risk of OSA.

The follow-up ranged from several days to 15 years[33,34,36–38,41,42]. However, almost no information was given about this follow-up period. Patients who were decannulated remained decannulated, but this does not necessarily mean that OSA was absent, and it is not known whether additional treatment was indicated.

With the lack of papers on non-surgical treatment, no criteria can be defined to identify those patients who require surgical treatment. The heterogeneous outcome measurements and the lack of information on follow-up make it impossible to come to a consensus regarding the ideal treatment of OSA in patients with CFM. There is no proof in the literature to support the surgical treatment of OSA as being superior to non-surgical treatment in the long-term.

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CHAPTER

4

Obstructive sleep apnea in Craniofacial Microsomia: Analysis of 755 patients

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Abstract

A retrospective cohort study was set up to analyse the prevalence and treatment of obstructive sleep apnea (OSA) in relation to the severity of the deformity in patients with craniofacial microsomia (CFM). This study included a population of 755 patients with CFM from three craniofacial centres. Medical charts were reviewed for severity of the deformity, type of breathing difficulty, age at which the breathing difficulty first presented, treatment for OSA, and treatment outcome. In total, 133 patients (17.6%) were diagnosed with OSA. Patients with Pruzansky IIB/III classification or bilateral CFM were significantly more often diagnosed with OSA than unilaterally affected patients of Pruzansky I/IIA classification. The initial treatment of OSA consisted of adenotonsillectomy, tracheotomy, or non-invasive positive pressure ventilation. Thirty-seven patients received more than one treatment (range 1 – 3). In this study, the prevalence of OSA in patients with CFM was higher than the prevalence in the healthy population described in the literature. Although several treatment modalities are available for the treatment of OSA in patients with CFM, treatment should be individualized and based on clinical symptoms, the severity of the deformity, and comorbidities.

Introduction

Craniofacial microsomia (CFM) is a facial anomaly characterized by asymmetric underdevelopment of structures derived from the first and second pharyngeal arches, including the mandible, maxilla, ears, soft tissues and facial nerves[1]. With an occurrence of 1 in 3,500 to 5,000 live births, CFM is the second most common congenital malformation of the head and neck. CFM is most often regarded as a unilateral malformation, however facial structures are involved bilaterally in 10% of cases[2].

CFM is a clinical diagnosis. The dysmorphology of CFM ranges from mild to severe. Several classification systems were designed to define the spectrum of anomalies seen in CFM[1,3,4]. Mandibular hypoplasia can be classified into four types based on the Pruzansky classification, modified by Kaban et al.[5,6]. The O.M.E.N.S. classification of Vento et al.[4] proposes a grading system based on severity and anatomic involvement in each category of the acronym: Orbit, Mandible, Ear, Nerves, and Soft tissue.

Bilateral mandibular hypoplasia is seen in several facial malformations (e.g. Robin sequence, Treacher Collins Syndrome) and can be associated with obstructive sleep apnea (OSA)[7,8]. The term obstructive sleep-disordered breathing (SDB) describes a syndrome of upper airway dysfunction during sleep that is characterized by increased upper airway resistance and pharyngeal collapsibility. Obstructive SDB is associated with snoring and/or increased work of breathing while the patient is sleeping. Obstructive SDB includes a spectrum of clinical entities with variable severity ranging from primary snoring to OSA[9]. OSA is characterized by snoring, laboured breathing during sleep, and periods of complete or partial obstruction. Since OSA is associated with neurocognitive, metabolic, and cardiovascular consequences, accurate diagnosis and identification of at-risk groups is important[10-12].

The prevalence of OSA in lean children without facial malformations is 2,2 – 3,8%[13-17]. However, in patients with mandibular hypoplasia the prevalence of OSA is higher, e.g. 12,5% in patients with Treacher Collins Syndrome[18].

Previous studies on the incidence of OSA in patients with CFM (bilateral and unilateral cases) showed wide variability, from 7 to 67%[19,20]. The results of these studies were based on samples of nine to 124 patients, and OSA was only objectively diagnosed by polysomnography (PSG) in a small proportion of the study groups[20-27]. According to Cohen et al.[22] patients with more severe orbital and mandibular deformities and/or bilateral involvement are at greater risk for OSA. Patients suspected for or diagnosed with OSA also more often had extracranial anomalies. The treatment of OSA in patients with CFM has varied from prone positioning (PP) and non-invasive positive pressure ventilation

to various surgical treatments, such as tracheostomy, (adeno)tonsillectomy ((A)TE) and mandibular distraction osteogenesis (MDO). Both clinical symptoms and respiratory parameters with PSG outcomes have been shown to improve after surgical and non-surgical treatment[19,25,26,28]. So far, no studies have reported long-term results.

The aim of the present study was to retrospectively analyse the prevalence of OSA in patients with CFM in a large group of patients by combining the cohorts of three major craniofacial centers. It was sought to determine the relationship between the severity of CFM and the risk for OSA, as well as analyse the chosen treatment modalities and their respective clinical outcomes.

Materials and Methods

This retrospective study was conducted in a population of patients diagnosed with CFM at the craniofacial centers of Erasmus University Hospital, Rotterdam, the Netherlands; Great Ormond Street Hospital in London, United Kingdom, and Boston Children's Hospital in Boston, United States of America.

Following institutional review board approval, patients diagnosed with CFM were reviewed. As CFM is a clinical diagnosis, patients with clinical and/or radiographic images, i.e. panoramic X-rays and/or computed tomography scans of the head, were included for analysis. Following the identification of patients, a chart review was performed to collect information on age, sex, affected side, severity of the deformity, and presence of breathing difficulties.

All medical charts of patients with CFM and breathing difficulties were categorized as suspected for OSA and were reviewed further for OSA, age at which OSA first presented itself, treatment for OSA, and treatment outcome. The diagnosis of OSA was based on PSG, the presence of a tracheostomy, or was based on the use of treatment for OSA without preceding PSG. The severity of OSA was based on PSG outcomes. When a tracheostomy was present, the severity of OSA was noted to be severe. When the diagnosis of OSA was based on the use of treatment for OSA without a preceding PSG, the severity of OSA was noted to be unknown. When no clinical signs of OSA were found in the medical charts, patients were categorized as not suspected for OSA.

The severity of OSA was determined using the obstructive apnea-hypopnea index (oAHI). For children (0-18 years), OSA was defined as an oAHI ≥ 1 per hour. An oAHI score of 1-5 was defined as mild OSA, a score of 5-24 as moderate OSA, and an oAHI of ≥ 25 as severe OSA, according to Goroza and Guilleminault[29,30]. For adults (age > 18 years), OSA was diagnosed when the apnea-hypopnea index (AHI) was > 5. An AHI of 5 – 15 was defined as mild OSA, 15 – 30 as moderate OSA, and an AHI of > 30 as severe OSA[29,30]. In the case where PSG was performed, but no oAHI was reported, the severity of OSA was drawn from the conclusion of the PSG report. When the oAHI was not available and the conclusion on the chart did not mention the severity of OSA, the result of the PSG was noted as unknown.

The assessment of mandibular hypoplasia in CFM was based on the classification of Pruzansky, modified by Kaban et al.[5,6]The Pruzansky-Kaban classification was scored on both sides in patients with bilateral CFM. However, only the most severe score was used in the analyses.

When radiographic images were not available, the diagnosis of CFM was assessed on clinical pictures with the help of the pictorial global, detailed and radiographic Phenotypic Assessment Tool – Craniofacial Microsomia (PAT-CFM)[31].

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 20.0 for Windows (IBM Corp., Armonk, NY, USA). Descriptive statistics were used. Equality of groups was tested with the Pearson X^2 test. A *P*-value of <0.05 was considered to be statistically significant.

Results

Population

In total, 955 patients were diagnosed with CFM. Clinical pictures and/or radiographic images were available for 755 patients and these patients were included for further analysis (Table 1).

Table 1. Description of the total population.

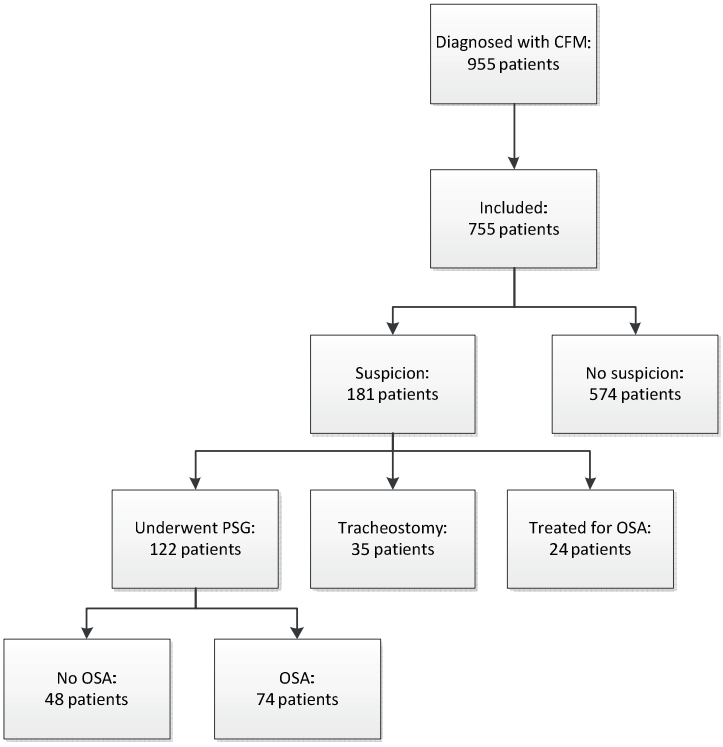
		Obstructive sleep apnea			
		Suspicion		No suspicion	
		No OSA	OSA		Total
Sex	Male	30	71	307	408
	Female	18	62	267	347
Laterality	Unilateral	42	90	537	669
	Bilateral	6	43	37	86
Affected side (UCFM)*	Right	19	50	302	371
	Left	23	40	235	298

UCFM = unilateral craniofacial microsomia.
*In the unilateral cases of craniofacial microsomia.

Presence of Obstructive Sleep Apnea

Of the 755 patients, 181 patients were suspected of having OSA and 574 were not suspected of having OSA. PSG outcomes were found to be negative for OSA in 48 patients suspected of having OSA. In total, 133 patients (17,6%) were diagnosed with OSA: 74 based on positive PSG outcomes, 35 based on the need for a tracheostomy and 24 based on treatment for OSA without a preceding PSG (Figure 1).

Figure 1. Suspected presence and actual presence of OSA in patients with CFM.



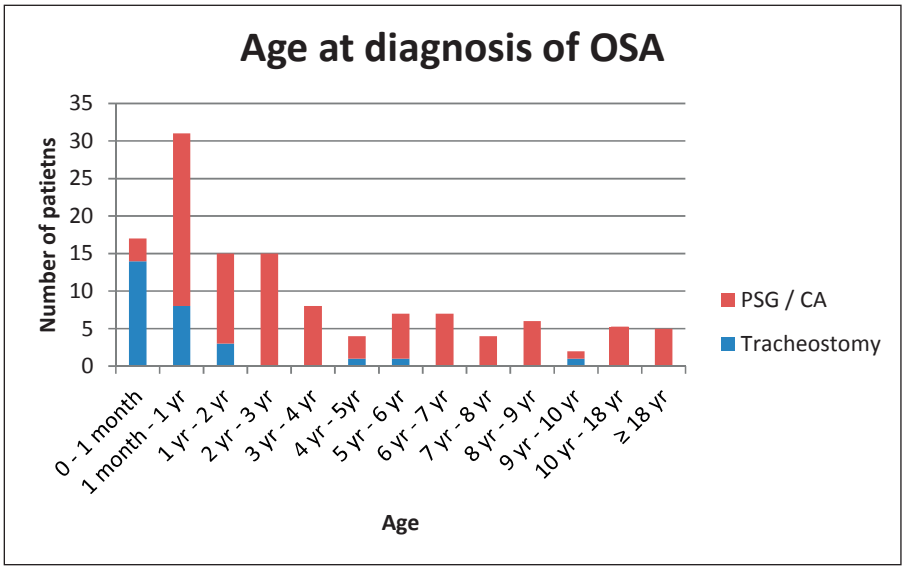
CFM = Craniofacial Microsomia, OSA = obstructive sleep apnea, PSG = polysomnography

Characteristics of patients with Obstructive Sleep Apnea

OSA was diagnosed at a median age of 2,4 years (range 0-25,8 years). OSA was diagnosed before the age of 1 year in 35,3% of the patients (Figure 2).

OSA was significantly more often diagnosed in patients with bilateral CFM than in patients with unilateral CFM (Pearson's $X^2(1)=7,026$, *p=0.008*) (Table 1). Patients with Pruzansky-Kaban IIB/III, both unilateral and bilateral cases, were more often diagnosed with OSA than patients with Pruzansky-Kaban I/IIA (Table 2). Severe OSA was mostly seen in patients with Pruzansky-Kaban IIB/III, in both unilateral and bilateral cases. Of the 11 patients with Pruzansky-Kaban IIB and severe OSA, six patients were diagnosed with unilateral CFM and five patients with bilateral CFM. For the patients with Pruzansky-Kaban III and severe OSA this was 15 patients and nine patients, respectively. When patients with Pruzansky-Kaban III were diagnosed with OSA, 52,5% were diagnosed with severe OSA. Mild OSA was more commonly diagnosed in patients with Pruzansky-Kaban I and IIA, in 30,8% and 50,0% of the cases, respectively (Table 3).

Figure 2. Diagnosis of OSA in CFM according to age.



OSA = Obstructive sleep apnea; yr = year, PSG = polysomnography; CA = clinical appearance.

Table 2. Severity of CFM and the suspected presence and actual presence of OSA.

	OSA suspected clinically						OSA not suspected clinically			
	OSA			No OSA						
Pruz.score	Unilat.	Bilat.	Unilat. & Bilat. (%)	Unilat.	Bilat.	Unilat. & Bilat. (%)	Unilat.	Bilat.	Unilat. & Bilat. (%)	Total (unilat./bilat.)
Pruz. I	10	3	13 (9,3%)	10	1	11 (7,9%)	112	4	116 (82,9%)	140 (132/8)
Pruz. IIA	16	6	22 (15,9%)	5	1	6 (4,3%)	107	4	111 (80,4%)	138 (127/11)
Pruz. IIB	15	10	25 (21,2%)	8	3	11 (9,3%)	77	4	81 (68,6%)	118 (101/17)
Pruz. III	30	16	46 (41,4%)	8	0	8 (7,2%)	50	7	57 (51,4%)	111 (88/23)
Unknown	19	8	27 (10,9%)	11	1	12 (4,8%)	191	18	209 (84,3%)	248 (221/27)
Total	**90**	**43**	**133**	**42**	**6**	**48**	**537**	**37**	**574**	**755 (669/86)**

Pruz. = Pruzansky-Kaban; OSA = obstructive sleep apnea; Unilat. = unilateral CFM patients; Bilat. = bilateral CFM patients.

Table 3. Severity of CFM vs. severity of OSA.

Severity of OSA	Pruz. I Unilat. & Bilat.	Pruz. IIA Unilat. & Bilat.	Pruz. IIB Unilat. & Bilat.	Pruz. III Unilat. & Bilat.	Unknown Unilat. & Bilat.	Total
Mild	4 30,8%	11 50,0%	1 4,0%	4 8,7%	5 18,5%	**25** **(18,8%)**
Moderate	3 23,1%	1 4,5%	4 16%	9 19,6%	5 18,5%	**22** **(16,5%)**
Severe	2 15,4%	3 13,6%	11 44%	24 52,2%	8 29,6%	**48** **(36,1%)**
Unknown	4 30,8%	7 31,8%	9 36%	9 19,6%	9 33,3%	**38** **(28,6%)**
Total	**13**	**22**	**25**	**46**	**27**	**133**

Pruz. = Pruzansky-Kaban classification; Unilat. = unilateral CFM patients; Bilat. = bilateral CFM patients.

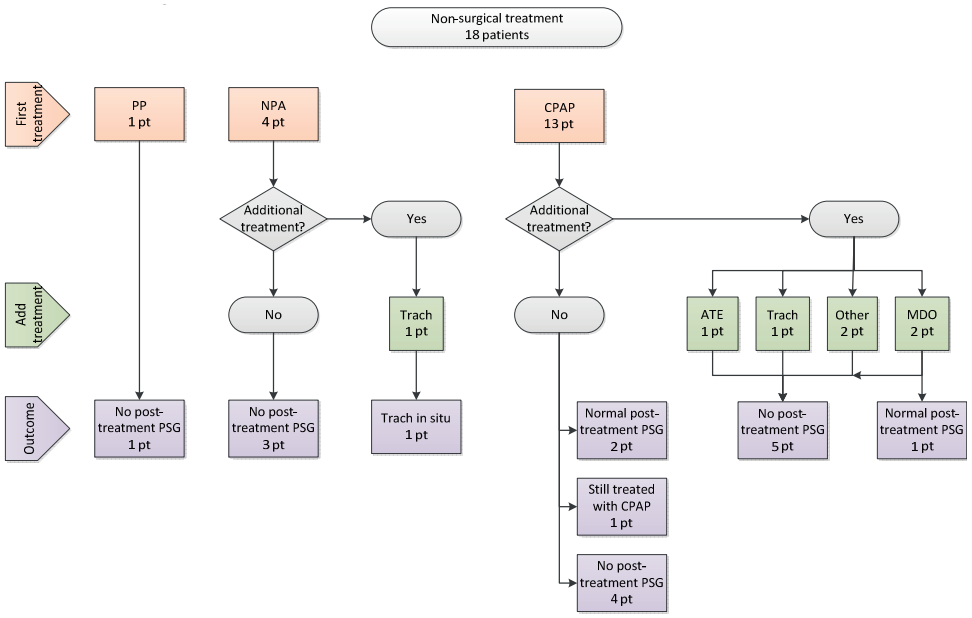
Treatment and follow-up of OSA in patients with CFM

One hundred and two of the 133 patients diagnosed with OSA were treated for OSA. Twenty patients were not treated and 11 patients had an unknown treatment status. Thirty-seven patients received more than one treatment, varying from one to three additional treatments. The median age at first treatment was 2,64 years (range 0-23,9 years). The initial treatment of OSA consisted of ATE (47%), tracheostomy (31%), continuous positive airway pressure (CPAP) (13%), and prone positioning, placement of a nasal pharyngeal airway (NPA), MDO and other treatments, e.g. nasal septum (in 1 to 4%). If additional treatment was indicated, OSA was treated with CPAP and ATE in 16 to 22%, respectively, and MDO was performed in 27% of the patients.

Figures 3, 4 and 5 give an overview of initial and additional treatment for OSA in patients with CFM starting with the first treatment modality; non-surgical, surgical, and tracheostomy.

The first treatment was non-surgical in 18 patients, and consisted of non-invasive positive pressure ventilation in 17 patients and prone positioning in one patient. Prone positioning was started 48 days after birth, after which it was reported by the parents that the complaints of OSA had improved. No further treatment was needed. Four patients were initially treated with a NPA. Additional treatment with a tracheostomy was needed in one of these four patients, which was still *in situ* at time of the study. Seven of the 13 patients who were given CPAP as a first treatment did not receive additional treatment. PSG normalized in two patients and improved in one, who was still treated with CPAP at time of the study (Figure 3).

Figure 3. Non-surgical treatment of OSA in Craniofacial Microsomia.



PP = prone positioning; NPA = nasal pharyngeal airway; No add. Treatment = no additional treatment; Add. Treatment = additional treatment; PSG = polysomnography; Trach = tracheostoma; CPAP = continuous positive airway pressure; ATE = adenotonsillectomy; MDO = mandibular distraction osteogenesis; pt = patient.

A surgery procedure was the treatment of first choice in 84 patients, consisting of ATE, MDO, tracheostomy, or other operations, e.g. nasal septum correction.

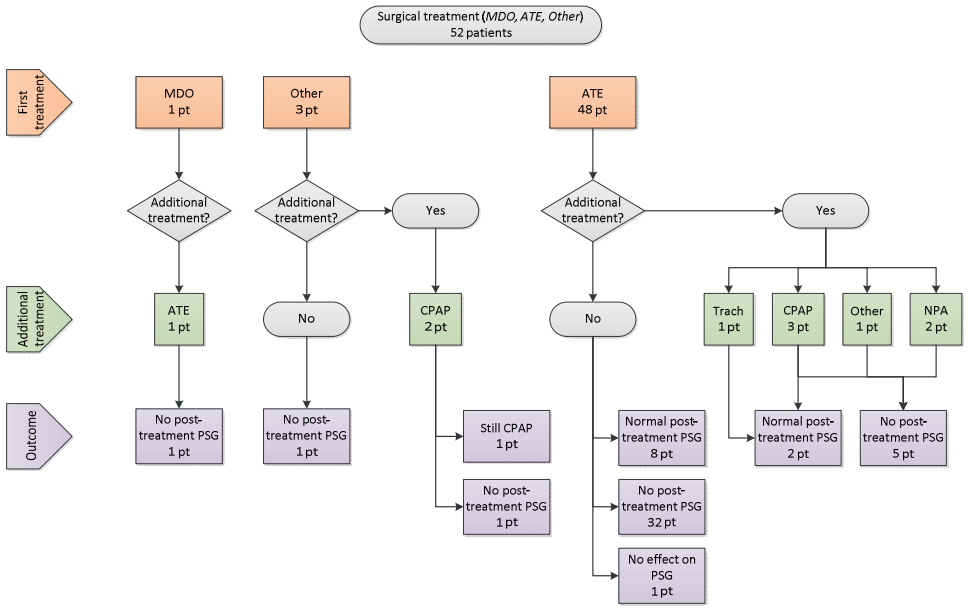
Of the 48 patients who underwent ATE as first therapy for OSA, the treatment outcome was unknown for a total 37 patients and the PSG outcome normalized in 10 patients. However, two of these 10 patients were additionally treated with CPAP or tracheostomy (Figure 4).

In total, 35 patients received a tracheostomy. Tracheostomy was treatment of first choice in 32 patients and given as an additional treatment in three. The tracheostomy was placed before the age of 1 year in 26 patients and after the age of 1 year in six patients, and at a maximum age of 9,28 years. The duration of treatment with a tracheostomy varied from 0,95 to 17,4 years. Six patients still had a tracheostomy at the time of the study and information on insertion and/or decannulation was incomplete for eight other patients, therefore these 14 patients were not included in this calculation.

Of the 32 patients in whom placement of a tracheostomy was the treatment of first choice, 14 patients did not receive further treatment. The post-treatment PSG improved

or normalized in three patients and three other patients were decannulated; the exact treatment outcome was unknown as no post-treatment PSG was performed. At the time of this study, four patients were still being treated with a tracheostomy. The outcome was unknown for four other patients due to loss to follow-up.

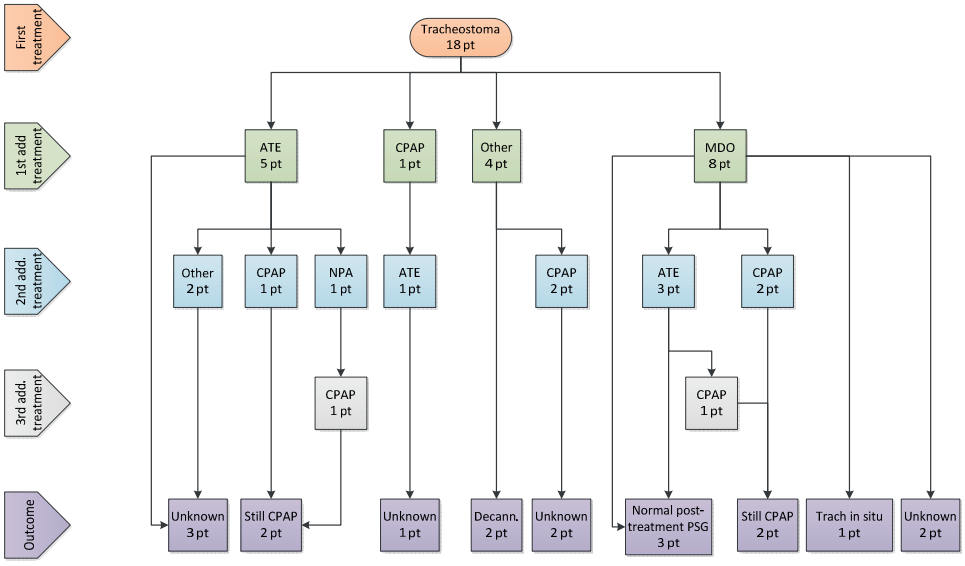
Figure 4. Surgical treatment of OSA in Craniofacial Microsomia.



MDO = mandibular distraction osteogenesis; ATE = adenotonsillectomy; Add treatment = additional treatment; CPAP = continuous positive airway pressure; Trach = tracheostoma; NPA = nasopharyngeal airway; PSG = polysomnography.

Eighteen of the patients who initially had a tracheostomy placed underwent additional treatment. Additional treatment was performed after decannulation in 50% of the patients and with the tracheostomy still in situ in the other 50%. PSG outcomes normalized in three patients. Due to loss to follow-up, the exact treatment outcome was unknown for 10 patients; however two of these patients were successfully decannulated (Figure 5).

Figure 5. Treatment of OSA with tracheostomy and additional treatment.



Add treatment = additional treatment; ATE = adenotonsillectomy; CPAP = continuous positive airway pressure; Other = other treatments, e.g. nasal septum correction; MDO = mandibular distraction osteogenesis; decann. = decannulation; PSG = polysomnography; trach = tracheostoma

Discussion

This study found the prevalence of OSA to be higher in patients with CFM than in the healthy population, where it ranges from 2,2 to 3,8%[13-17]. Overall, OSA was diagnosed in 17,6% of the patients with CFM. The previous literature has reported a prevalence varying from 7 to 67%, in unilateral and bilateral cases. However, the sample sizes of these studies were too small to detect differences in the risk for OSA based on laterality or severity of CFM[19-27].

In total, 755 patients were included in the analysis, both unilateral and bilateral cases. Patients with bilateral CFM more often had complaints suspected to be related to OSA than patients with unilateral CFM, as to be expected according to the previous literature[7,24]. When comparing unilaterally affected patients with bilaterally affected patients, prevalence rates of 13,5% and 50,0% respectively, were found. The more severely affected patients with Pruzansky-Kaban IIB and III showed more severe OSA. The correlation between the severity of CFM and the risk for OSA has been reported previously by both Cloonan et al. and Cohen et al. These studies found that patients with more severe CFM had a greater risk of OSA[20-22]. However, in the study by Cloonan et al.[21] the classification of severity was not based on the Pruzansky-Kaban classification, but was based on medical charts and photographs, whereas Cohen et al. (*n=38*) and Szpalski et al. (*n=62*) studied rather small patient populations[20,22].

In this study, the initial therapy for OSA in CFM consisted of both non-surgical and surgical treatment. Regardless of the severity of OSA, treatment varied from prone positioning and ATE to CPAP and tracheostomy. In patients with mild and moderate OSA, ATE was the first treatment of choice in most patients. Placement of a tracheostomy was done in a considerable number of patients and was the treatment of first choice in 67% of the patients with severe OSA.

In total, 24 patients were proven to be successfully treated:post-treatment PSGs showed improvement or normalization in 19 patients, and five other patients were successfully decannulated. Of these 24 patients, 11 were initially treated with a tracheostomy, 10 with an ATE, and three with CPAP.

CPAP in patients with CFM has rarely been mentioned in the literature, but was considered superior to early surgery and tracheostomy by Järund et al[28]. In the present study, 13 patients received CPAP initially, with 46,2% needing additional treatment; another 13 patients received CPAP following previous therapy for OSA, of which 46,2% still treated with CPAP at the time of this study. It appears that even though it is an effective treatment option for OSA, CPAP for patients with CFM should be individualized based on symptoms

of OSA and comorbidities. CPAP should be considered a treatment option for patients who are ineligible or awaiting additional therapy and/or surgery. However, it should be taken into account that compliance with CPAP, especially in younger patients, is low[32].

Adenotonsillectomy is generally considered to be the first-line treatment option for OSA in children without craniofacial anomalies, with success rates varying from 60 to 85%[33]. Although ATE quite often is performed in patients with craniofacial anomalies, there is limited evidence for its efficacy in patients with craniofacial anomalies[34]. In the present study population, 58 patients were initially or additionally treated with ATE. Objective outcome measurements proved the efficacy of ATE in only 10 patients in this study, but 34 patients did not receive further treatment for OSA following ATE, presumably as the clinical presentation improved and no signs or symptoms of OSA were seen after treatment. These results imply a high success rate of ATE in CFM. This included patients with mild/moderate and severe OSA.

In the literature, MDO is frequently reported as the chosen surgical treatment for OSA[25,35,36] and is found to be successful at preventing tracheostomy in 91,3 to 95,5% of the patients with craniofacial anomalies in which mandibular hypoplasia is a component[35,36]. According to these studies, successful decannulation can be achieved in 80,3% of the patients[35,36]. Although patients with CFM were included in these studies, patient numbers were small, and it was unfortunately not possible to extract data for only the patients with CFM[35,36]. In the present study, MDO did not play a key role in the management of OSA. In total, 11 patients (unilateral) were treated with MDO. Four patients had a normal PSG after treatment with MDO, which makes the success rate 36,4% in this study. These results imply that MDO might not be a successful treatment option for OSA in patients with unilateral mandibular hypoplasia. Further research is needed to support this hypothesis.

Of all patients treated with a tracheostomy, 51,4% were eventually decannulated and/or post-treatment PSG normalized, with or without additional treatment. The treatment of severe OSA with solely CPAP or tracheostomy did often not suffice when compared to patients less severely affected with OSA. This could either be the result of the complicated facial anomalies leading to airway obstruction at different levels, or could mean that normal growth of the mandible in patients affected with severe OSA is not sufficient to overcome these problems without additional treatment. It could also be an indication that a different mechanism or different mechanisms lead to OSA in these patients, e.g. Cohen et al. described neurodevelopmental delay and hypotonia of the pharyngeal muscles in patients with CFM, which could possibly result in collapse of the upper airway[37]. Sufficient monitoring and/or follow-up is needed to confirm this hypothesis.

No post-treatment PSG was performed for 65 patients, possibly as complaints of OSA were reported by the patients or their guardians to have improved. From a clinical perspective, it is thougth likely that treatment was successful in most of these patients, as otherwise they would have returned to the outpatient clinic after their initial therapy for OSA. Improved follow-up in the future could provide greater insight in the pathogenesis of OSA in CFM, which could lead to a treatment algorithm for OSA in CFM.

Regarding the limitations of this study, it should be noted that the medical charts of 52% of the patients with unilateral CFM and 43% of the patients with bilateral CFM did not mention complaints suspicious for OSA. Apparently these patients were not judged as being at risk of OSA in CFM at the time of charting. Such historical changes in clinical awareness represent a confounding factor in studies with a retrospective design. Furthermore, not all patients underwent PSG, and it is stated by Anderson et al that an absence of snoring does not exclude the presence of OSA in patients with mandibular hypoplasia[38]. Therefore, a population-based study including questionnaires and PSG is needed to study both patients with and with symptoms suspicious for OSA.

OSA is more prevalent in patients with CFM than in the healthy population, especially in patients with unilateral CFM and Pruzansky-Kaban IIB or III or with bilateral CFM. These patients should be screened for OSA with PSG. Furthermore, clinicians should be aware of the higher risk for OSA in patients with Pruzansky-Kaban I or IIA. Several treatment modalities are available for the treatment of OSA in patients with CFM. However, the treatment of OSA in patients with CFM should be individualized and should be based on clinical symptoms, the severity of the deformity and on comorbidities.

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CHAPTER

5

What are the characteristics of the upper airway in patients with Craniofacial Microsomia?

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Abstract

Purpose: Obstructive sleep apnea (OSA) is a common problem in patients with craniofacial microsomia (CFM); however, the exact pathophysiology in patients with CFM remains unclear. The first aim of this study was to evaluate upper airway volume and morphology in patients with CFM. The second aim was to identify risk factors for the presence of OSA.

Methods: A cross-sectional study was set up and three study groups were identified: *1)* CFM with OSA, *2)* CFM without OSA, and *3)* a control population. Computed tomographic (CT) scans of the head and neck were included and used to create 3-dimensional models. The age-matched control group consisted of patients evaluated for traumatic head injury or epilepsy. Volumetric and morphologic parameters were measured. The results of patients with CFM were compared among the three study groups. Descriptive statistics were computed using the Pearson X^2 test for categorical variables and nonparametric tests for continuous variables. A multiple variable regression model was used to identify risk factors for OSA.

Results: In total, 79 patients with CFM were included, of which 25 patients were diagnosed with OSA. A total of 145 CT scans could be analyzed. In addition, a control population of 88 patients was identified. Oropharynx volume, mean cross-sectional area (CSA), minimal-CSA, and minimal retropalatal area were found to be markedly smaller in patients with CFM compared with the control population. In contrast, in patients with CFM and OSA, minimal retroglossal area, sphericity, and uniformity markedly differed from those in patients without OSA. Sphericity was identified as the main predicting variable of OSA in patients with CFM.

Conclusions: The upper airway of CFM patients is markedly smaller and puts them at risk for developing OSA. Patients with CFM diagnosed with OSA have a markedly smaller CSA behind the base of the tongue and a difference in sphericity.

Introduction

Craniofacial Microsomia (CFM) is a congenital malformation affecting the development of structures deriving from the first and second pharyngeal arches leading to underdevelopment of the mandible, maxilla, ears, and soft tissues.[1, 2] With an incidence of 1 in 3,500 to 5,000 live births, CFM is considered to be the second most common congenital malformation of the head and neck. Most patients are considered to have unilateral involvement of facial structures; however, bilateral malformations are found in 10% of patients.[3] The severity of dysmorphologies found in patients with CFM ranges from mild to severe.

Upper airway obstruction, and more specifically obstructive sleep apnea (OSA), is a common problem in children with craniofacial anomalies such as CFM and might be the result of maxillomandibular or neuromuscular hypoplasia.[4-6] Previous studies documenting the incidence of OSA in patients with CFM reported a wide range of 7 to 67%.[4, 5, 7-14]

The diagnosis of OSA is confirmed by polysomnography (PSG).[15-17] However, PSG does not provide information on the local anatomy resulting in upper airway obstruction. This could be relevant for (surgical) treatment. In previous studies of patients with CFM, different anatomic sites were associated with the presence of OSA. A study by Cohen et al. found patients with mandibular hypoplasia to be at greater risk of OSA.[5] In another study, Burstein et al. suggested that OSA in patients with CFM is caused by airway obstructions above the level of the epiglottal tip [18], and a study by D'Antonio et al. found an association with pharyngeal and laryngeal anomalies.[9] Some theories also focus on nerve or soft tissue deficits resulting in poorly developed muscular tissue, making the upper airway prone to collapse.[13, 19] Although several studies have been performed, the exact pathophysiology of upper airway obstruction in patients with CFM remains unclear and the subject of debate.

Therefore, investigation of the airway using imaging modalities, such as conventional cephalograms[20] or 3-dimensional (3D) computed tomographic (CT) models,[21-30] could help determine the exact localization of upper airway obstructions. Furthermore, comparison of these models with the clinical aspects of patients with CFM, i.e., presence or absence of OSA, could provide more information on the etiology of CFM resulting in upper airway obstructions. In addition, comparing airway measurements could help explain the beneficial effect of surgery on airway obstruction[23-28, 30-33] and help determine what area of the upper airway the surgeon should focus on.

The purpose of this study was to investigate the morphology of upper airway obstruction and upper airway volumes based on 3D CT models in a cohort of patients with CFM. It was hypothesized that patients with CFM would have a markedly smaller airway than the

control population and that patients with OSA also would have a markedly smaller airway than patients with CFM without OSA. The specific aims were to *1)* compare the 3D CT models of patients with CFM to a cohort of patients without CFM, *2)* compare the 3D CT models of patients with CFM with and without OSA, and *3)* compare 3D CT models of patients with unilateral and bilateral CFM.

Materials and methods

Study design

To address the research purpose, the authors designed and implemented a cross-sectional study using CT scans of the head and neck of patients with CFM (study population) and without CFM (control population). After institutional review board approval (Boston X05-08-058; Rotterdam MEC-2013-575; London 14 DS25), all electronic and paper charts of patients with CFM presenting from January 1980 through January 2016 at the department of Plastic and Oral Surgery of Boston Children's Hospital (Boston, MA, United States of America) and the department of Oral and Maxillofacial Surgery of the Erasmus University Hospital (Rotterdam, The Netherlands) were obtained and reviewed.

In addition, all electronic and paper charts of patients without CFM presenting at the emergency department from January 2013 through January 2016 at the Great Ormond Street Hospital (London, United Kingdom) or Erasmus University Hospital for evaluation of traumatic head injury or epilepsy were obtained and reviewed.

The Strenghtening the Reporting of Observational Studies in Epidemiology (STROBE; http://www.strobe-statement.org/) guidelines were used for reporting the results of this study.[34]

Inclusion and exclusion criteria

Patients with and without CFM were eligible for inclusion if they had CT scans partially or completely showing the area of interest (AOI), defined as the head and neck area involving the upper airway, including the paranasal sinuses, ranging from the lower tip of the hyoid bone up to the upper border of the frontal sinuses. CT scans needed to consist of at least 50 slices to be included. If a patient had multiple qualifying scans, then all CT-scans were included and used for analyses.

Patients with CFM were excluded from further analyses if no information on the presence or absence of OSA was available. CT scans of patients with any fractures or swelling to the area of interest were excluded from further analyses.

Study variables

Patients were first categorized according to the primary predictor variable (presence or absence of CFM), leading to a study and control population. Within the study population, the primary predictor variable was presence of OSA. Based on the PSG outcome and reports by primary physicians, patients were categorized as having OSA or not having OSA ('non-OSA'). The secondary predictor variable was laterality of CFM, i.e., unilateral or bilateral CFM. Furthermore, data on severity of CFM, PSG outcomes, and therapeutic

interventions to the area of interest (AOI) were recorded (i.e., adenotonsillectomy or orthognathic surgery).

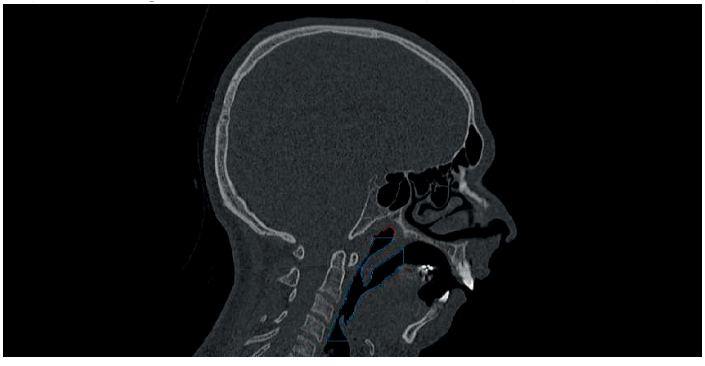
Within the control population, no information on the presence or absence of breathing abnormalities was available. Other variables that were recorded for patients with CFM and the control population were age at time of scanning, sex, and hospital of treatment.

Outcome variables

Mimics 10.01 for Intel X86 (Platform V10.2.1.2, Materialise, Leuven, Belgium) was used to create 3D models of the upper airway from imported CT scans. All CT scans were evaluated for scanning position. All scans were repositioned according to the Frankfurter horizontal plane using the semiautomatic re-slice function to ensure 3D concordance.[35] A threshold of -1024 to -500 Hounsfield units was used to create a mask of the airway, excluding all surrounding tissue. The airway was divided in two parts by creating different masks. Part I (oropharynx) ranged from the most superior aspect of the body of the hyoid bone up to the level of the posterior nasal spine.[36] The anterior border was constructed with a vertical line perpendicular to the posterior nasal spine. Part II (nasopharynx) ranged from the level of the posterior nasal spine to the soft tissue of the posterior skull base measured on the midsagittal view (Figures 1 – 3).

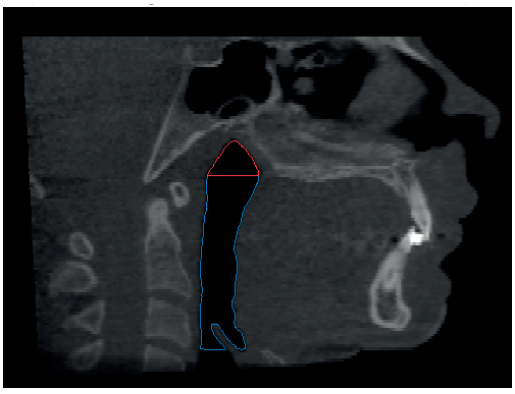
Subsequently, volume in cubic millimeters and surface area in square millimeters were obtained for parts I and II of the upper airway using the Mimics 3D modeling tool, i.e., the primary outcome variable (Figures 4-6). The nasal cavity and ethmoidal sinuses were not measured.

Figure 1. Sagittal 2D view of an OSA patient (male, 16-18 years).



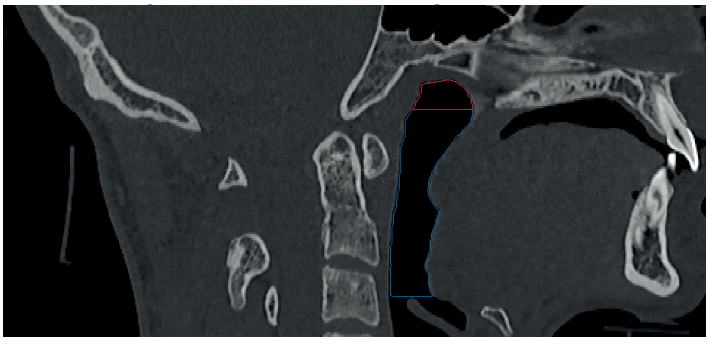
Red = nasopharynx; Blue = oropharynx

Figure 2. Sagittal 2D view of a Non-OSA patient (male, 16-18 years).



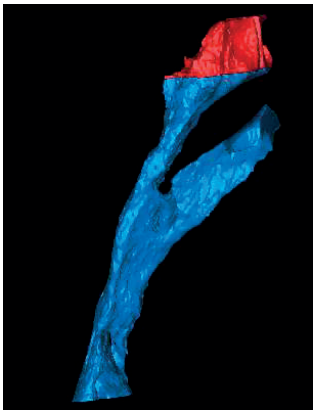
Red = nasopharynx; Blue = oropharynx

Figure 3. Sagittal 2D view of a control group patient (male, 16-18 years).



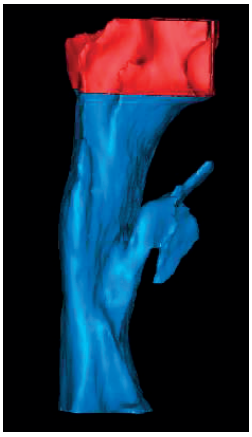
Red = nasopharynx; Blue = oropharynx

Figure 4. D model of an OSA patient (male, 16-18 years).



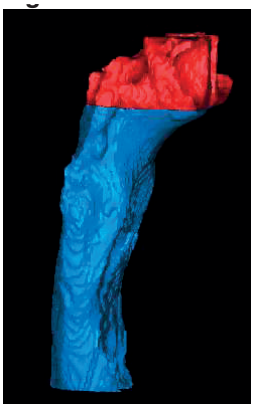
Red = nasopharynx; Blue = oropharynx

Figure 5. 3D model of a Non-OSA patient (male, 16-18 years).



Red = nasopharynx; Blue = oropharynx

Figure 6. 3D model of a control group patient (male, 16-18 years).



Red = nasopharynx; Blue = oropharynx

All scans were measured by one of two authors (Y.P.K. and S.C.S.). A randomly selected set of scans was measured a second time by the same authors after one month. The inter- and intra-observer variabilities were calculated (interclass correlation coefficient: r =0.993, p<0.001; intraclass correlation coefficient: r=0.999, p<0.001).

Morphologic measurements, i.e., secondary outcome variables, were computed solely for the oropharynx model by using the 3D models created in Mimics 10.0.1. Cross-sectional dimensions of the oropharyngeal masks, as proposed by Abramson et al.,[21] were calculated using in-house MATLAB code (MATLAB R2015a, Mathworks, Natick MA). For each of these oropharynx masks, the mean cross-sectional area (CSA), minimal CSA (min-CSA), minimal

retropalatal CSA (min-RP), minimal retroglossal CSA (min-RG), retropalatal-to-retroglossal ratio (RP/RG), sphericity, and uniformity were recorded and used for further analysis (Table 1).[21, 22]

Table 1. Definition of morphologic airway parameters.

Parameter	Symbol	Unit	Dimension	Definition
Volume	VOL	mL	3D	Volume of oropharynx from lower tip of hyoid bone to hard palate
Surface area	SA	mm^2	2D	Surface area of oropharynx
Oropharynx length	L	mm	1D	Length of oropharynx from lower tip of hyoid bone to hard palate
Mean CSA	Mean-CSA	mm^2	2D	Average cross-sectional are of the oropharynx, equal to VOL/*L*
Minimal CSA	Min-CSA	mm^2	2D	Smallest CSA of the oropharynx
Minimal retropalatal CSA	Min-RP	mm^2	2D	Smallest CSA between inferior aspect of soft palate and level of the hard palate
Minimal retroglossal CSA	Min-RG	mm^2	2D	Smallest CSA between lower tip of hyoid bone and inferior aspect of soft palate
Retropalatal to -glossal ratio	RP/RG	N/A	Ratio	Ratio of RP and RG areas, equal to RP/RG
Uniformity	U	N/A	Ratio	Oropharynx uniformity, equal to min-CSA/mean-CSA
Sphericity	Ψ	N/A	Ratio	Measure of how closely the shape of an object approaches that of a perfect sphere equal to: $(\Psi)=[\pi^{1/3} \times (6 \times VOL)^{2/3} / SA$

Morphological parameters are based on proposed measurements[21], CSA = cross-sectional area; RP = retropalatal; RG = retroglossal; N/A = not applicable

Data analyses

Descriptive statistics were computed for the total study population and for the different subgroups using Pearson X^2 test for categorical variables and nonparametric tests for continuous variables. Differences in means between groups were computed. Because several patients had multiple CT scans and use of strictly one CT scan per patient would generate loss of data, random sampling with replacement (bootstrapping) was used to calculate the difference in means and compute the confidence interval (CI) for this difference.[37] A *P*-value for the null hypothesis (i.e., there is no difference between groups)

was computed by inversion of the bootstrap CI. Furthermore, differences of mean values, adjusted for age using a spline with 3 knots, were studied.

Nonparametric tests, i.e., Mann-Whitney *U* test and Pearson X^2 test, were used because the normal distribution of outcomes was not assumed. Furthermore, regression analyses were performed to determine measurements of association for OSA. Statistical analyses were performed using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Amonk, NY, USA) and R 3.5 (Core Team (2016). R: a language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL http://www.R-project.org/). For all analyses, a *P* value less than 0.05 was considered statistically significant.

Results

In total, 491 patients with CFM were identified at the Boston Children's Hospital and the Erasmus University Hospital. Within this group, 79 patients were found to have adequate head and neck CT scans available and documented records stating the presence or absence of OSA. OSA was diagnosed in 25 patients (31.6%); the other 54 patients (68.4%) had no documented OSA. A total of 145 CT scans with a minimum of 1 scan (n = 40) and a maximum of 7 scans (n=1) per patient were included in this study. There were 52 CT scans for patients with OSA (35.9%) and 93 for patients without OSA (64.1%). OSA and non-OSA subgroups did not differ significantly for sex, number of CT scans per patient, and age at time of scanning. Mean time from diagnosis of OSA to the date at which the CT scan was performed was 59.6± 67.4 months. Furthermore, patients with OSA had adenotonsillectomy significantly more often than patients without OSA (P = 0.017) (Table 2).

For the control population, a total of 159 patients were identified to have head and neck CT scans available. After evaluation of exclusion criteria, 88 scans (41 males [46,6%] and 47 females [53,4%] were used for further analyses. The number of scans per age group is presented in Table 2.

Table 2. Characteristics of patients with CFM with and without OSA, and the control population.

	Study population				Control population	p-value
	OSA (n=25)	Non-OSA (n=54)	p-value	Total (n=79)	Total (n=88)	
Sex			0.435			0.196
Male	12	31		43	41	
Female	13	23		36	47	
Number of CT scans (mean)	2.08 ± 1.525	1.72 ± 0.960	0.428	1.84 ± 1.170	1 ± 0.0	<0.01*
Laterality			0.005*			†
Unilateral	17	50		67	-	
Bilateral	8	4		12	-	
Pruzansky-Kaban classification						
1	2	7	0,521	9	-	†
2a	0	10	0,022*	10	-	†
2b	7	18	0,756	25	-	†
3	16	19	0,017*	35	-	†
4	0	0	1,000	0	-	†
Number of CT scans per age group (years)						
0 - 3	4	3	0,230	7	36	0,000*
3 - 5	4	6	0,778	10	5	0,715
5 - 7	8	1	0,001*	9	2	0,171
7 - 10	7	15	0,669	22	8	0,180
10 - 13	5	10	0,830	15	7	0,546
13 - 16	4	10	0,551	14	11	0,497
16 - 18	5	13	0,446	18	12	0,788
18 - 21	12	16	0,392	28	7	0,019*
>21	3	19	0,019*	22	0	0,000*

Continuous variables are expressed as mean ± standard deviation.* = statistically significant. † = p-value could not be calculated since variable was not valid within one column.

Patients with CFM versus the control population

Volumetric and morphologic parameters differed markedly between patients with CFM, including patients with and without OSA, and the control population. The oropharynx volume ($P < 0.01$), surface area ($P < 0.01$), mean CSA ($P < 0.01$), and min-CSA ($P = 0.048$), and min-RP ($P < 0.01$) were significantly smaller in patients with CFM. Sphericity and uniformity were found to be not significantly different between groups (Table 3). When excluding patients with CFM and OSA, these differences remained.

Table 3. Bootstrapped confidence intervals for airway and morphologic parameters in patients with CFM vs. the control population.

	Controls	CFM	Mean diff	95% CI	p-value
Volumes ($mm^{3)}$					
Oropharynx	5450.85	12421.27	6236.61	1455 - 6279	**< 0.01**
Nasopharynx	2480.10	3563.38	915.13	-362.53 – 595.60	> 0.1
Morphologies					
SA (mm^2)	2936.91	5147.50	1957.05	427 - 1764	**< 0.01**
L (mm)	44.97	52.70	6.49	-9.91 – 2.05	> 0.1
Mean-CSA (mm^2)	112.81	231.50	107.17	29.52 – 135.25	**< 0.01**
Min-CSA (mm^2)	55.01	121.24	60.05	0.61 – 64.88	**0.048***
Min-RP (mm^2)	69.78	170.79	94.97	28.74 – 119.93	**< 0.01**
Min-RG (mm^2)	74.76	136.35	53.57	-8.91 – 54.08	> 0.1
RP/RG	1.63	1.36	0.37	-0.52 – 0.47	> 0.1
Sphericity	0.021	0.022	0.0015	-0.0036 – 0.0039	> 0.1
Uniformity	0.41	0.50	0.098	-0.077 – 0.10	> 0.1

Parameters are described as in Table 1, Mean diff: mean difference of Controls minus CFM values independent of age, CI: Confidence Interval, 95% CI: inverted CI by bootstrap of Control minus CFM corrected for age, p-value of 95% CI, *= statistically significant.

Volumetric and Morphologic parameters in patients with CFM

Table 4 presents the volumetric and morphologic parameters of patients with CFM with and without OSA. Volumetric and morphologic parameters showed statistical differences between subgroups. Nasopharynx volume was significantly smaller in patients with OSA (*P*=0.014). In addition, min-RG (*P*=0.048), sphericity (*P*=0.019), and uniformity (*P*=0.023) were significantly smaller in patients with CFM and OSA.

Table 4. Volumetric and morphologic parameters of the airway in patients with CFM with and without OSA.

	OSA	Non-OSA	Mean diff	95% CI	p-value
Volumes (mm^3)					
Oropharynx	11,113.97 ± 10367.14	12,701.81 ± 10336.02	-1587.84	-6249 – 3196	>0.1
Nasopharynx	2732.30 ± 1721.70	3872.91 ± 2378.38	-1140.62	-2091 – -260	**0.014***
Morphologies					
SA (mm^2)	5052.00 ± 3206.21	4969.65 ± 2558.85	82.35	-1506.16 – 1599.56	>0.1
L (mm)	50.66 ± 14.67	51.92 ± 10.49	-1.27	-9.40 – 6.89	>0. 1
Mean-CSA (mm^2)	192.18 ± 141.03	254.06 ± 271.55	-61.88	-149.34 – 8.35	0.086
Min-CSA (mm^2)	93.99 ± 88.82	134.62 ± 101.34	-40.63	-79.04 – 0.19	0.053
Min-RP (mm^2)	145.64 ± 124.66	188.92 ± 160.02	-43.29	-106.14 – 27.72	>0.1
Min-RG (mm^2)	109.13 ± 93.96	147.29 ± 98.18	-38.15	-74.99 – -0.30	**0.048***
RP/RG	1.50 ± 1.43	1.36 ± 1.06	0.13	-0.36 – 0.81	>0.1
Sphericity	0.019 ± 0.007	0.024 ± 0.008	-0.0048	-0.008 – -0.001	**0.019***
Uniformity	0.45 ± 0.18	0.537 ± 0.20	-0.089	-0.16 – -0.005	**0.023***

Volumetric and morphologic parameters are described as in Table 1. Variables are expressed as mean ± standard deviation, Mean diff: mean difference of OSA minus non-OSA values independent of age; CI: Confidence Interval, 95% CI: inverted CI by bootstrap of OSA minus Non-OSA values corrected for age, p-value of 95% CI, *= statistically significant.

Laterality of CFM

The bilateral phenotype of CFM was seen significantly more often in the presence of OSA (Pearson $\chi^2(1)=8.023$, P = 0,005) and patients with OSA had significant higher Pruzansky-Kaban classification scores than patients without OSA (Pearson $\chi^2(3)=8.208$, p = 0,042). Nasopharynx volume was significantly smaller in patients with the bilateral phenotype than in patients with the unilateral phenotype (P=0.001). Min-CSA (P=0.015) and min-RG (P=0.003) were significantly smaller in the bilateral CFM group. Sphericity and uniformity also were significantly smaller with the bilateral phenotype (P=0.003, P=0.000, respectively) (Table 5).

Table 5. Volumetric and morphologic parameters of the airway in patients with unilateral vs. bilateral CFM.

	Bilateral	Unilateral	p-value
Volumes (mm^3)			
Oropharynx	10505.15 ± 12137.76	12273.25 ± 10105.05	0.209
Nasopharynx	1948.21 ± 1361.34	3677.72 ± 2229.35	**0.001***
Morphologies			
SA (mm^2)	4718.66 ± 3780.35	5044.00 ± 2689.99	0.401
L (mm)	47.32 ± 18.93	51.99 ± 11.11	0.254
Mean-CSA (mm^2)	181.60 ± 154.63	235.48 ± 237.07	0.205
Min-CSA (mm^2)	63.85 ± 69.61	125.73 ± 99.32	**0.015***
Min-RP (mm^2)	138.00 ± 131.76	175.96 ± 149.66	0.423
Min-RG (mm^2)	71.74 ± 64.35	140.24 ± 99.01	**0.006***
RP/RG	2.13 ± 2.91	1.31 ± 0.96	0.367
Sphericity	0.015 ± 0.008	0.023 ± 0.008	**0.003***
Uniformity	0.29 ± 0.18	0.53 + 0.18	**0.000***

Volumetric and morphologic parameters are described as in Table 1. Variables are expressed as mean ± standard deviation, *= statistically significant.

When excluding the bilateral cases and solely comparing the patients with unilateral CFM, sphericity was the only parameter that remained significantly smaller in patients with CFM and OSA compared to those without OSA (P=0.049) (Table 6).

Table 6. Morphologic and volumetric parameters in unilateral phenotype CFM patients with and without OSA.

	OSA	Non-OSA	Mean diff	95% CI	p-value
Volumes ($mm^{3)}$					
Oropharynx	11279.59 ± 9256.41	13176.79 ± 9488.13	-1624.07	-7343 - 2817	0.172
Nasopharynx	3220.96 ± 1654.23	4010.18 ± 2315.31	-659.79	-1678.2 – 272.5	0.109
Morphologies					
SA (mm^2)	5211.31 ± 2851.62	5176.05 ± 2423.10	163.94	-1305.9 – 1532.4	0.655
L (mm)	53.30 ± 12.82	53.28 ± 11.17	-0.02	-5.39 – 5.72	0.986
Mean-CSA (mm^2)	193.15 ± 130.71	256.56 ± 247.90	-61.90	-223.70 – 19.82	0.128
Min-CSA (mm^2)	103.82 ± 90.37	138.80 ± 99.06	-32.55	-77.22 – 18.66	0.156
Min-RP (mm^2)	145.31 ± 117.86	189.72 ± 151.80	-42.26	-120.99 – 25.09	0.085
Min-RG (mm^2)	122.07 ± 97.14	153.06 ± 94.31	-27.83	-74.20 – 19.06	0.090
RP/RG	1.31 ± 0.93	1.28 ± 0.93	0.043	-0.37 – 0.43	0.673
Sphericity	0.020 ± 0.007	0.024 ± 0.009	**-0.003**	**-0.007 – 0.001**	**0.049***
Uniformity	0.51 ± 0.15	0.54 ± 0.20	-0.040	-0.097 – 0.053	0.271

Volumetric and morphologic parameters are described as in Table 1. Variables are expressed as mean ± standard deviation, *= statistically significant.

Predicting OSA

After identifying differences in volumetric and morphologic parameters, regression analysis was performed to identify predicting variables for OSA in patients with CFM. A multivariate regression model was used. All variables with significant correlations ($P<0.05$) on bivariate statistics were evaluated for addition to the model (Table 7). The overall model identified sphericity as the main predicting variable for OSA (Odds ratio: 0.19, 95%CI: 0.05 – 0.70, $P=0,012$) (Table 8).

Table 7. Volumetric and morphologic parameters are described as in Table 1.

		OSA	
		Pearson's	**P value**
Demographic parameters	Age group	-0.202	**0.015***
	Sex	0.154	0.065
	Pruzansky-Kaban	0.303	**0.000***
	Laterality	0.405	**0.000***
	ATE	0.291	**0.000***
Volumetric parameters	Oropharynx	-0.097	0.323
	Nasopharynx	-0.277	**0.001***
Morphologic parameters	SA	-0.013	0.893
	L	-0.060	0.540
	Mean-CSA	-0.144	0.144
	Min-CSA	-0.212	**0.030***
	Min-RP	-0.145	0.139
	Min-RG	-0.210	**0.032***
	RP/RG	0.066	0.501
	Sphericity	-0.252	**0.009***
	Uniformity	-0.194	**0.047***

*Statistically significant.

Table 8. Multiple logistic regression model summary for prediction of OSA in CFM patients.

Predictor	**Adjusted Odds Ratio**	**95% CI**	**P value**
Sphericity	0.19	0.05 – 0.70	0.012*

Model summary			
Chi²	**-2 Log Likelihood**	**Accuracy, %**	**P value**
75.12	61.42	84.6	0.000*

Values are adjusted for age group, Pruzansky-Kaban classification, laterality and adenotonsillectomy. *= statistically significant.

Discussion

In this study, the morphology of upper airway obstruction and upper airway volumes based on 3D CT models was studied in a cohort of patients with CFM. It was hypothesized that patients with CFM have a markedly smaller airway than patients without CFM, and that patients with CFM and OSA have a markedly smaller airway than patients with CFM without OSA. The specific aims were to *1)* compare the 3D CT models of patients with CFM with a cohort of patients without CFM, *2)* compare the 3D CT models of patients with CFM with and without OSA, and *3)* compare the 3D CT models of patients with unilateral and bilateral CFM. The results of this study confirmed the hypothesis that patients with CFM have a significantly smaller airway than patients without CFM and that patients with CFM and OSA have a significantly smaller airway than patients with CFM without OSA. In addition, the results of this study showed that although the airway of patients with CFM is smaller than the airway of the normal population, shape and form of the airway between these two groups are comparable, i.e., sphericity and uniformity. When comparing patients with CFM, with and without OSA, there was a marked difference in size behind the base of the tongue and a marked difference in shape and form, i.e., sphericity and uniformity.

When comparing of volumetric measurements, no differences were found in oropharynx volume, but nasopharynx volume was smaller in patients with CFM and OSA, although they were often treated with ATE. This finding suggests that patients with CFM and OSA have skeletal deformities at the level of nasopharynx resulting in smaller nasopharynx volume. However, no relevant difference in nasopharynx volume between patients with CFM in general and the control population was seen, probably because patients with CFM without OSA have only mild or no skeletal deformity at the level of the nasopharynx, making this group comparable to the control population. Analysis of the morphologic parameters showed that mean CSA, min-CSA, and min-RP of the oropharynx were smaller in patients with CFM than in the control population. In addition, the min-RG was markedly smaller in patients with CFM and OSA compared with patients with CFM without OSA. Considering these findings, upper airway obstruction in patients with CFM might be explained by the Bernoulli principle. This principle in fluid dynamics states that an increase in velocity will lead to a simultaneous decrease in pressure. Increased velocity in a tubular structure, such as the airway, is often the result of local narrowing within this tubular structure, because a decrease in cross-sectional vector area leads to a higher velocity of airflow. Furthermore, the lack of difference in min-RP and the considerably smaller min-RG in patients with OSA suggest that obstruction of flow will most likely derive from the lower half of the pharynx, behind the base of the tongue.

Sphericity and uniformity of the oropharynx were significantly smaller in patients with CFM and OSA than in those without OSA. Previous studies have suggested that patients

with OSA tend to have a longer anteroposterior axis in relation to the lateral axis, resulting in a more elliptical airway.[21, 38] This difference in shape would affect surrounding muscle function. In the present study, less sphericity was the main predicting variable for OSA in patients with CMF; therefore, these results support the previous finding that the shape of the airway in patients with OSA is less spherical. The significant difference in min-RG between patients with CFM with and without OSA might explain this decrease in sphericity; however, no hard conclusions can be drawn because the authors did not measure the anteroposterior or lateral axis directly.

The idea that the shape of the airway plays an essential role in the development of OSA also is supported by comparison of patients with CFM without OSA with the control population. The airway of patients with CFM without OSA was significantly smaller for certain parameters, e.g., oropharyngeal volume, surface area, min-CSA, and min-RG. Nevertheless, sphericity was found to be similar in these two groups, suggesting a certain threshold in sphericity might need to be exceeded for OSA to become clinically relevant.

Previous studies looking into different types of CFM have suggested that the bilateral phenotype is different from the unilateral phenotype in several aspects.[14, 39] In the present study group, the bilateral phenotype was seen considerably more often in combination with OSA than without. Because of smaller patient numbers, no hard conclusions could be drawn from the comparison between unilaterally and bilaterally affected patients without OSA; therefore, these results were not mentioned in this article. However, the known fact that patients with bilateral CFM are more frequently affected with OSA[14], might indicate a relevant difference in size, shape, and form of the airway in these patients, especially when more severe mandibular hypoplasia is present. Furthermore, multiple morphologic parameters (e.g., min-CSA, min-RG, sphericity, and uniformity) were markedly smaller in patients with bilateral CFM. This could suggest that in unilateral CFM the unaffected side could compensate for the affected side to some extent before airway obstruction occurs, whereas the bilateral phenotype has no reserve for compensation. Furthermore, when comparing only patients with unilateral CFM, sphericity was still significantly smaller in patients with OSA compared with those without. Therefore, sphericity seems to be a determining factor in airway obstruction independent of the phenotype, whereas the differences found in CSA between patients with and without OSA might be caused by the bilateral phenotype.

Previous studies of patients with OSA have shown that (maxillo)mandibular advancement surgery improves sleep quality [26, 40] by creating a broader and shorter airway.[23] Not enough information on the persistence of OSA before and after surgery was available in the present study population to draw conclusions. Nevertheless, the smaller CSA for patients with OSA in the present study population does suggest that this group could benefit from

mandibular advancement surgery (MAS) because it increases cross-sectional dimensions of the airway. Bianchi et al. stated that MAS improves OSA by increasing total upper airway volume.[26] The lack of difference in oropharynx volume in the present study population might be explained by the fact that the flow of air depends on the CSA instead of the total airway volume. Unfortunately, Bianchi et al. did not measure any morphologic parameters such as the CSA.[26]

Conversely, the smaller nasopharynx volume in patients with CFM and OSA also could indicate morphologic differences in this part of the airway, warranting ATE as a treatment for OSA in CFM.

Because patients with bilateral CFM and OSA have notably smaller nasopharyngeal volume and min-RG, they might benefit from both ATE and MAS. Of course, this also depends on the severity of OSA.

This study has a number of limitations. Because all data were collected retrospectively, some information was limited or not available. This could lead to bias or leave confounders undisclosed. For example, information on body mass index (BMI) and body length was not available in this population. Beause a higher BMI[41] and a longer upper airway in relation to total body length [21, 42] are considered to increase the risk of OSA, this could have affected our data. In addition, diagnostic tests for OSA and CT scanning procedures were not standardized, possibly causing differences in the definition of OSA and the precision of the 3D models. Furthermore, to have the radiographic images correspond at best with the clinical findings of OSA at a certain date, it would have been ideal if the time from diagnosis of OSA to the date of the CT scan would have been no longer than six months. Unfortunately, no information was available on the presence or absence of OSA in the control population. This might have influenced the differences found between the patients with CFM and the control group. However, the prevalence of OSA in lean children is 2.2 – 3.8%, meaning that two or three patients might have been affected by OSA in the present control group.[43-47]

Conclusion

The upper airway of patients with CFM and OSA differs from that in those without OSA. Differences in sphericity play a role in the development of OSA in patients with unilateral CFM, whereas a smaller CSA behind the base of the tongue and differences in sphericity put patients with bilateral CFM at higher risk for airway obstruction. Furthermore, the lack of difference in sphericity between patients with CFM without OSA and the control group supports this idea. Moreover, the identification of sphericity as the main predicting variable for OSA in patients with CFM suggests that this group might benefit from treatments such as ATE and MAS.

Future research should look into the effect of growth on volumetric and morphologic measures of the airway in both the normal population and the CFM population. In addition, the effect of therapies such as MAS and ATE on these variables should be studied, which might lead to a better treatment protocol for OSA in CFM.

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CHAPTER

6

Feeding difficulties in Craniofacial Microsomia: a systematic review

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Abstract

Patients with craniofacial microsomia are at higher risk of developing obstructive sleep apnea (OSA), as described in the previous article entitled "Obstructive sleep apnea in craniofacial microsomia: a systematic review". These patients are also more likely to develop feeding difficulties. The present systematic review provides an overview of the literature on the prevalence, treatment, and follow-up of feeding difficulties in children with craniofacial microsomia (CFM). A search was performed in PubMed, Embase, Cochrane Library, and Web of Science for articles on CFM and feeding difficulties. The following data were extracted from the articles: number of patients, patient characteristics, presence of feeding difficulties, and the treatments and outcomes of feeding difficulties. Eight articles on CFM and feeding difficulties were included, two of which reported the prevalence of feeding difficulties (range 42–83%). Treatment mostly consisted of tube feeding. No information regarding follow-up was found in these articles. According to the literature, feeding difficulties are related to CFM. However, as there have been no prospective studies and few studies have presented objective measurements, no definitive conclusions can be drawn. Prospective studies are needed to determine the prevalence of feeding difficulties in patients with CFM.

Introduction

Craniofacial microsomia (CFM) is the result of a disturbance in the embryological development of the first and second pharyncheal arches and is characterized by asymmetric underdevelopment of the facial structures, including the mandible, maxilla, ears, soft tissues, and facial nerves[1,2]. CFM is most often regarded as a unilateral malformation, however the facial structures are involved bilaterally in 10% of cases[3,4] and several recent publications have suggested that the contralateral side is abnormal in most cases as well, although not truly hypoplastic[5,6]. The reported incidence rate ranges from 1 in 3500 to 1 in 20,000[1,7,8], which makes CFM the second most common facial birth defect after cleft lip and palate. CFM in combination with epibulbar dermoid and extra-craniofacial anomalies, such as heart, renal, and vertebral anomalies, is known as Goldenhar syndrome[9–14].

The most typical deformity of CFM is mandibular hypoplasia, which occurs in 89% to 100%[15] of these patients. The severity of mandibular hypoplasia can be classified into four types based on the Pruzansky classification, modified by Kaban[16,17]. Type I is a small mandible with normal morphology. Type IIa is a mandibular ramus abnormal in both size and shape. Type IIb is a mandibular ramus and temporomandibular joint (TMJ) abnormal in size, morphology, and location. Type III deformity consists of an absent ramus, condyle, and TMJ.

Huisinga-Fischer et al.[18] evaluated the relationship between underdevelopment of the masticatory muscles and hypoplasia of the craniofacial skeleton in CFM. Craniofacial bony abnormalities were found to be associated with underdevelopment of the masticatory muscles, which might lead to problems with mastication and therefore feeding difficulties.

Other studies have suggested that sucking efficiency is limited in patients with CFM as a result of mandibular hypoplasia, which restricts the excursion of the mandible. Facial nerve weakness might lead to limited active cheek and lip movements, and anomalies in the structure and function of the tongue might play a role in feeding difficulties in patients with CFM as well[19,20].

Additionally, anomalies at the level of the oropharynx and larynx may play a role in feeding difficulties in patients with CFM, and more specifically in patients with Goldenhar syndrome, as movement of the lateral pharyngeal wall of the affected side is diminished compared to the unaffected side during swallowing. This does not appear to be related to the severity of the facial anomalies[21].

Not only do oropharyngeal and laryngeal deformities, and more specifically Goldenhar syndrome, increase the risk of feeding difficulties in patients with CFM, but extra-

craniofacial anomalies, such as gastrointestinal malformations and congenital heart disease, also have an influence on this risk[22,23].

As previously mentioned, mandibular hypoplasia is the most common deformity in patients with CFM. As well as leading to malocclusion and therefore to feeding difficulties, mandibular hypoplasia can also lead to obstructive sleep apnea (OSA). With a prevalence of 7–67%, as described in the previous review "Obstructive sleep apnea in craniofacial microsomia: a systematic review", patients with CFM are more likely to develop OSA than patients in the healthy population[24–29]. As feeding difficulties are closely correlated to OSA, patients with CFM could, for this reason, be more at risk of feeding difficulties as well[30].

Thus, feeding difficulties in patients with CFM might be the result of underdevelopment of the mandible, facial nerve, and/or masticatory muscles, but could also be the result of lateral pharyngeal wall anomalies or OSA[18–21,30]. Although several studies have stated that feeding difficulties are more likely to occur in patients with CFM, not much is known about the prevalence, treatment, and follow-up of feeding difficulties in patients with CFM.

The aim of this review is to give an overview of the literature regarding CFM and the prevalence and treatment of feeding difficulties based on the following key questions: (1) What is the prevalence of feeding difficulties in patients with CFM and what types of feeding difficulties are reported? (2) How are feeding difficulties treated in patients with CFM?

Methods

Search strategy

A search of public domain databases was performed to identify articles focusing on CFM and feeding difficulties. The search was conducted in the following databases: PubMed, Embase , Cochrane Libary, and Web of Science (all searched up to 12 September 2014). In addition, we performed a manual search of secondary sources including references of the articles initially identified. The goal was to identify all studies addressing CFM in relation to feeding difficulties.

The following search terms were used: (((facial[tiab OR face[tiab] OR hemifacial[tiab] OR orbitocranial[tiab] OR facies[tiab] OR cranial[tiab] OR mandibulofacial[tiab] OR otomandibular[tiab] OR craniofacial[tiab] OR faciocranial[tiab] OR hemimandibular[tiab]) AND (microsom*[tiab] OR asymmetr*[tiab] OR dysosto*[tiab] OR dysplasia[tiab OR anomal*[tiab] OR deformit*[tiab] OR hypoplasia[tiab] OR syndrom*[tiab] OR malformation*[tiab])) OR (treacher collins[tiab] OR goldenhar[tiab]) OR (oculoauriculovertebral*[tiab] OR facioauriculovertebral*[tiab] OR (auriculo vertebral*[tiab]))) AND (dysphagia[tiab] OR ((feeding[tiab] OR swallow*[tiab] OR deglutition[tiab] OR eat*[tiab] OR chew*[tiab] OR masticat*[tiab] OR bite[tiab] OR biting[tiab]) AND (problem*[tiab] OR difficult*[tiab] OR abnormal[tiab] OR disabilit*[tiab] OR disorder*[tiab] OR impair*[tiab] OR normal*[tiab] OR disturb*[tiab] OR unable[tiab] OR unabilit*[tiab])) OR nutrition*[tiab] OR malnutrition*[tiab] OR failure to thrive[tiab]) AND publisher[sb].

Data extraction and analysis

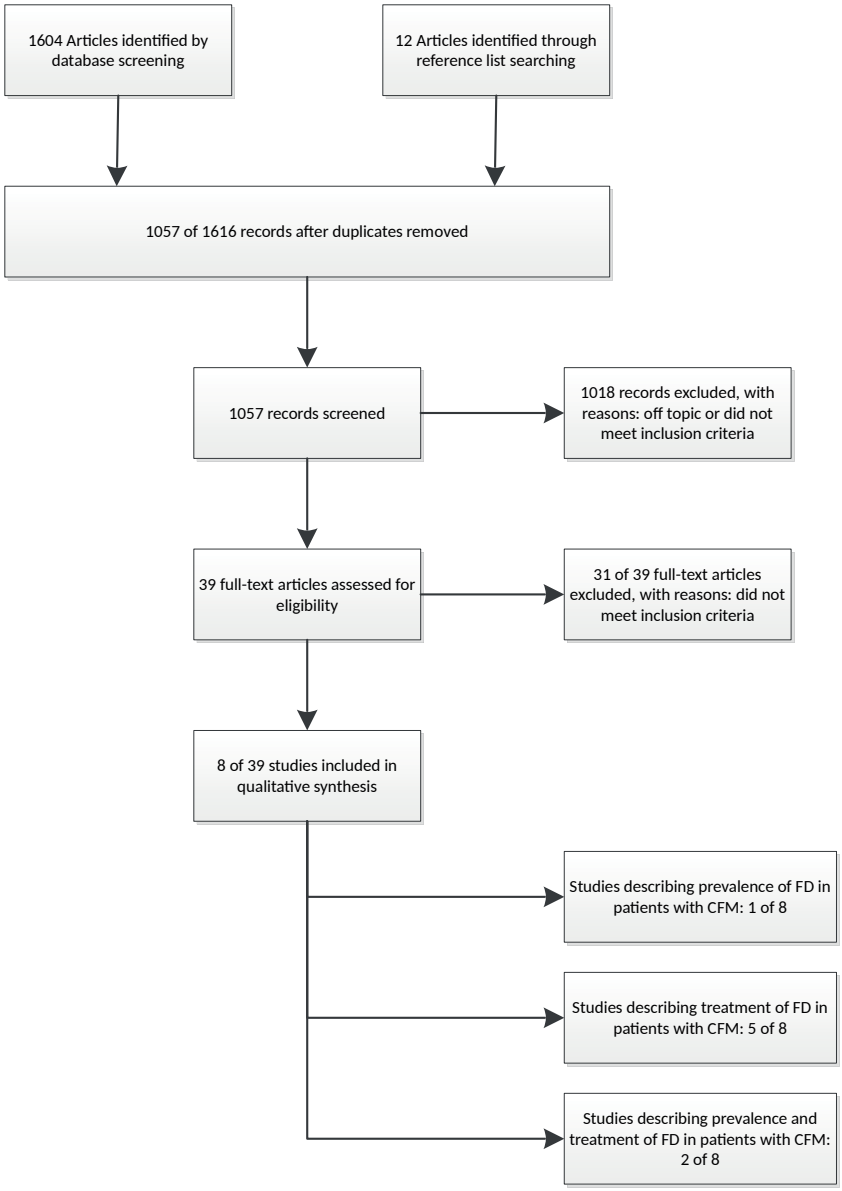
Two investigators (C.J.J.M.C and B.I.P.) selected the studies independently. All articles on the prevalence and treatment of patients with CFM and feeding difficulties were included. Expert opinions were excluded. The full texts of articles that met the inclusion criteria and of articles for which the abstract was lacking information were obtained.

Articles were graded on quality of evidence using the Oxford Centre for Evidence-Based medicine (CEBM) criteria[31]. Data on the number of patients, patient characteristics such as gender, age, and severity of the CFM, and the presence of feeding difficulties were tabulated when available.

Results

The initial search retrieved 1604 articles. After removing duplicate articles and including additional articles identified from secondary sources, 1057 abstracts were assessed. After examination of the title and abstract, 39 articles were retrieved for further examination. Eight articles were included in the analysis (Figure 1).

Figure 1. Data extraction flowchart.



What is the prevalence of feeding difficulties in patients with CFM and what types of feeding difficulties are reported?

Feeding difficulties are strongly related to OSA and could therefore be present more often in patients with CFM. Furthermore, the anatomical deformities in CFM could lead to feeding difficulties as well. The prevalence of feeding difficulties in the studies included varied from 42% to 83%. However, data on the prevalence of feeding difficulties in CFM were scarce and no firm conclusions can be drawn based on these studies (Tables 1 and 2).

Table 1. Studies on the prevalence of feeding difficulties in CFM meeting the criteria for inclusion.

Reference	CEBM level of evidence[31]	Methodology	Aim of the study
Cohen et al.[32]	III	Cross-sectional study	To examine the neurodevelopmental profile of children with Goldenhar syndrome and to determine if physical manifestations are indicative of poor developmental outcomes
Strömland et al.[14]	III	Retrospective study	To survey the systemic and functional defects in patients with Goldenhar syndrome
Shokeir[13]	III	Retrospective study	To delineate the natural history of the disorder

CEBM, Centre for Evidence-Based Medicine; CFM, craniofacial microsomia

Table 2. Summary of the studies on the prevalence of feeding difficulties in CFM.

Reference	No. of patients with CFM	Classification of CFM	Extra-craniofacial malformations	No. of patients with FD and cleft lip and/or palate	Age range	Gender, M/F	No. of patients with FD	Type of FD
Cohen et al.[32]	24	NR	Congenital heart defect, scoliosis, genitourinary abnormality, limb defect	NR	Birth to 57 m	16/8	10	Feeding disturbances, swallowing dysfunction, failure to thrive
Strömland et al.[14]	18	NR	Cardiovascular, respiratory system, gastrointestinal	5	8 m to 17 y	11/7	12	Dysphagia
Shokeir[13]	24	NR	Congenital heart defect, hiatus hernia	6	Birth to 58 y	11/13	20	Incoordination of deglutition, choking spells

CFM, craniofacial microsomia; F, female; FD, feeding difficulty; m, months; M, male; NR, not reported; y, years

Cross-sectional study on the prevalence of feeding difficulties in CFM

Ten of the 24 patients (42%) studied by Cohen et al.[32] were diagnosed with feeding difficulties, mainly caused by a decreased tone in the orofacial musculature. Details of the classification of the CFM were not mentioned.

Retrospective studies on the prevalence of feeding difficulties in CFM

Of the 18 patients included in the study of Strömland et al.[14], 12 reported feeding problems in infancy. Half of the group had complaints such as difficulty chewing and swallowing, and six patients complained of drooling. Oral impairment and orofacial deformities could explain the dysphagia in most cases, but in some cases feeding difficulties were mainly the result of other symptoms affecting the general condition of the patient, e.g. heart defects, breathing difficulties, and gastrointestinal problems[14].

According to Shokeir[13], one of the four major problems in the neonatal period of patients with Goldenhar syndrome is feeding difficulties such as dysphagia and choking due to anatomical deformities at the level of the mandible, larynx, and/or oesophagus, necessitating gavaging, nasogastric feeding, or surgical treatment. Feeding difficulties occurred in 20 of the 24 patients included. For the other four patients, nothing was mentioned regarding feeding difficulties.

How are feeding difficulties treated in patients with CFM?

The treatment of feeding difficulties was described in a few retrospective studies and case reports and mainly consisted of tube feeding. Patient numbers were low and no objective outcome measurements were reported, except in the case series of Clawson et al.[33] Firm conclusions cannot be drawn based on these studies and case reports (Tables 3 and 4). Unfortunately, follow-up of the patients with feeding difficulties was not described in these studies.

Retrospective studies on the treatment of feeding difficulties in CFM

Patients with CFM and feeding difficulties described in these studies most often received tube feeding[13,14]. Nine of the 12 patients described by Strömland et al.[14] received tube feeding. Three patients had a gastrostomy and one a nasogastric tube at the time of examination. Gavaging and surgical treatment, such as gastrostomy and reconstruction of the cleft, was described by Shokeir et al[13]. The type of treatment chosen for each patient and the reasons for this treatment were not reported.

Table 3. Studies on the treatment of feeding difficulties in CFM meeting the criteria for inclusion.

Reference	CEBM level of evidence[31]	Methodology	Aim of the study
Strömland et al.[14]	III	Retrospective study	To survey the systemic and functional defects in patients with Goldenhar syndrome
Shokeir[13]	III	Retrospective study	To delineate the natural history of the disorder
Hoch and Hochban[34]	IV	Retrospective CR	Presentation of a case with CFM
Clawson et al.[33]	IV	Retrospective CS	To discuss the effectiveness of a behavioural-based feeding programme to improve feeding abilities in Goldenhar syndrome
Yokochi et al.[35]	IV	Retrospective CS	Presentation of cases with CFM including videofluorographic finding
Zanardi et al.[36]	IV	Retrospective CR	To describe the treatment of a patient with a severe facial deformity due to CFM
Mellor et al.[37]	IV	Retrospective CS	Presentation of cases

CEBM, Centre for Evidence-Based Medicine; CFM, craniofacial microsomia; CR, case report; CS, case series

Table 4. Summary of studies on the treatment of feeding difficulties in CFM meeting the criteria for inclusion.

Reference	No. of patients with CFM	No. of patients with CFM and FD	Age range, or mean age	Feeding difficulties	Cleft palate in patients with FD?	Treatment of the FD
Strömland et al.[14]	18	12	8 m to 17 y	Chewing, swallowing, drooling, dysphagia	Yes, 5 out of 12	Tube feeding; gastrostomy; nasogastric tube
Shokeir[13]	24	20	Birth to 58 y	Incoordination of deglutition, choking spells	Yes, 5 out of 20	Tube feeding; gastrostomy and reconstruction of cleft
Hoch and Hochban[34]	1	1	Birth	Sucking, failure to thrive	Yes	Tube feeding, reconstruction of cleft, treatment of obstructive sleep apnea
Clawson et al.[33]	3	3	15 m to 42 m	Gastroesophageal reflux, dysphagia	Yes, 2 out of 3	Tube feeding
Yokochi et al.[35]	3	3	2 y to 4 y	Sucking, drooling	Yes, 3 out of 3	Tube feeding
Zanardi et al.[36]	1	1	12 y	Chewing	No	Not further specified
Mellor et al.[37]	3	2	Birth	Not further specified	Yes, 1 out of 2	Tube feeding

CFM, craniofacial microsomia; FD, feeding difficulties; m, months; y, years

Case reports on the treatment of feeding difficulties in CFM

There are several case reports that mention feeding difficulties and the treatment of these feeding difficulties in patients with CFM[33–37].

All patients in the case series of Clawson et al.[33] were dependent on tube feeding and were without significant oral intake upon admission. Outpatient therapy to improve the feeding difficulties had no effect. Data such as weight, height, and calorie intake were collected at admission and discharge from the programme. Treatment consisted of four therapeutic meals a day, oral motor interventions followed by oral feeding, behavioural interventions, and training of caregivers. The results of the treatment are shown in Table 5.

Table 5. Outcomes of a behavioural-based feeding programme[33].

Patient	Average percentage accepts		Average percentage expels		Average percentage mouth clean (swallowing)		Average total grams per meal	
	Admission	Discharge	Admission	Discharge	Admission	Discharge	Admission	Discharge
1	62	94	45	6	18	100	0.7	154
2	30	74	13	15	7	96	1.5	47.7
3	66	98	32	21	3	95	8	114.4

Two patients were completely weaned from tube feeding by discharge. According to this study, oral motor and behavioural interventions are effective in the treatment of feeding difficulties in patients with CFM.

Several other case reports and case series have described patients with CFM or Goldenhar syndrome treated successfully with nasogastric tube feeding. Feeding difficulties consisted of coordination problems in sucking and breathing, dysphagia, and chewing difficulties[34,35,36]. All three cases described by Yokochi et al.[35] had cleft palate, which leads to an obvious bias in the results.

The 12-year-old boy with CFM described by Zanardi et al.[36] complained of several functional problems including difficulty chewing. This was treated with orthodontics, orthognathic surgery with TMJ reconstruction, and a costochondral graft.

Discussion

Data on the prevalence, treatment, and follow-up of feeding difficulties in patients with CFM are scarce. The results of the few studies that have been performed are mostly based on a small number of patients with CFM and the retrospective analysis of medical charts or subjective measurements.

Feeding difficulties in patients with CFM vary from dysphagia to choking and are often treated successfully with a nasogastric tube. In some cases a gastrostomy or cleft lip and/or palate repair is indicated. Most studies and case reports included patients with Goldenhar syndrome, therefore feeding difficulties could have been the result not only of oral malformations, but also of extra-craniofacial malformations, such as gastrointestinal malformations, congenital heart disease, or other respiratory malformations.

As previously mentioned, feeding difficulties in patients with CFM are most often treated with a nasogastric tube. However, whether tube feeding is sufficient for such cases or whether surgery is needed was not described in these studies, and objective outcome measurements were rarely provided. Follow-up was not reported, but the use of a nasogastric tube has been noted to be an effective treatment for feeding difficulties. Refusal of oral intake caused by prolonged therapy with a nasogastric tube can be treated with a behavioural-based feeding programme to improve oral intake, and this has been shown to be effective[33]. However, this programme is not appropriate as an initial therapy for feeding difficulties.

Regardless of the limitations, it may be concluded that feeding difficulties are more often reported in patients with CFM, and specifically patients with Goldenhar syndrome, than in patients without craniofacial anomalies. This could be the result either of the facial anomalies, such as mandibular hypoplasia or underdevelopment of the masticatory muscles, or of extra-craniofacial malformations and/or OSA in the case of patients with Goldenhar syndrome.

Further research should focus on the relationship between the severity of CFM and the risk of feeding difficulties. The identification of the patient groups at risk of feeding difficulties will allow better screening and specific treatment.

A prospective study to determine the exact prevalence, treatment modalities, and follow-up of OSA and feeding difficulties in CFM, and their relationships with the severity of the CFM, is required.

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CHAPTER

Feeding difficulties in Craniofacial Microsomia: a multicenter retrospective analysis of 755 patients

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Abstract

A retrospective cohort study was initiated to analyse the prevalence, risk factors and treatment modalities of feeding difficulties in patients with Craniofacial Microsomia. This study included 755 subjects with Craniofacial Microsomia from three craniofacial centers. Medical charts were reviewed for severity of the deformity, documented feeding difficulties, age at which feeding difficulties first presented and treatment, presence of cleft lip/palate, extracraniofacial anomalies, and obstructive sleep apnea. In total, 199 patients (26,4%) had documented feeding difficulties. Patients with bilateral involvement, Pruzansky-Kaban III classification, cleft lip/palate, or obstructive sleep apnea were significantly more at risk for developing feeding difficulties and significantly more often needed additional feeding via a nasogastric tube than patients without these risk factors.

Introduction

Craniofacial microsomia (CFM) is a malformation affecting both first and second pharyngeal arch derivatives, and is estimated to occur in one of every 3500 to 5000 live births. Although the exact etiopathogenesis of CFM is still unknown, the consequences have been well described and include asymmetric underdevelopment of the mandible, maxilla, ears, temporomandibular joint (TMJ), muscles of mastication and facial nerves. Mandibular hypoplasia is the most common feature of CFM and occurs in 89 – 100 percent of patients with CFM.[1-3]

CFM is a clinical diagnosis with a highly variable phenotype. Although in nearly 90 percent of the cases the facial structures are affected unilaterally, abnormality of the contralateral side is common.[4, 5] Extracraniofacial anomalies have been documented in 35 – 55 percent of patients with CFM, and are mostly seen in the skeletal, circulatory, urogenital and gastro-intestinal tract.[4, 6]

CFM can not only lead to aesthetic problems, but also to functional problems, such as hearing impairment, obstructive sleep apnea (OSA), and feeding difficulty (FD).[7-11] FD has been documented in 42 - 83 percent of patients with CFM and consist of difficulties with suckling and chewing, dysphagia, failure to thrive and incoordination of deglutition.[8, 12-14]

However, previous studies on the prevalence and/or origin of FD in CFM have been small in terms of patient numbers, i.e. 18 to 24 patients, and so definitive conclusions cannot be drawn from the data provided. Therefore, a collaboration between three major craniofacial units was instigated to create a large dataset.

The aim of this study was to retrospectively analyse the prevalence of FD in patients with CFM. The purpose of the study was to (1) determine the associations between the severity of CFM and the risk for FD, and (2) to describe the treatment modalities used and their respective clinical outcomes.

Materials and methods

This retrospective study was conducted in a population of patients diagnosed with CFM at the craniofacial units of Erasmus University Hospital, Rotterdam, the Netherlands; Great Ormond Street Hospital, London, United Kingdom, and Boston Children's Hospital, Boston, United States of America.

Following IRB approval (Rotterdam: MEC-2012-248; London: 14DS25; Boston: X05-08-058) all patient charts diagnosed with CFM were reviewed. As CFM is a clinical diagnosis, patients with clinical and/or radiographic images, i.e. panoramic X-rays and/or CT head scans, were included for further analyses. Following identification of patients, a chart review was performed on information on age, sex, affected side, severity of the deformity, and presence of FD. Although microtia is part of CFM, isolated microtia was not regarded to be CFM, so these patients were excluded.

The severity of mandibular hypoplasia was assessed on panoramic X-rays or on 3D-CT scans, and was based on the Pruzansky-Kaban classification.[15, 16] The Pruzansky-Kaban classification was scored on both sides in patients with bilateral CFM. However, only the most severe score was used in the analyses.

When panoramic X-rays or 3D-CT scans were not available, the diagnosis of CFM was assessed on clinical pictures with the help of the pictorial global, detailed and radiographic Phenotypic Assessment Tool – Craniofacial Microsomia (PAT-CFM).[17] The Pruzansky-Kaban classification was scored as 'unknown' in these patients.

Medical charts of patients with CFM and FD were reviewed for the type of FD, age at diagnosis, treatment of FD, timing of treatment, and treatment outcome. When no information on a history of FD was present, patients were categorized as not having FD. Presence and type of cleft lip/palate and presence of macrostomia were also noted. Furthermore, charts were reviewed for presence of extracraniofacial anomalies, i.e. cardiac and gastro-intestinal anomalies, presence of OSA, and age at time of diagnosis of OSA.

Severity of FD was scored as 'mild', 'moderate' and 'severe' and was based on type of treatment:

a) Mild FD applied to patients who were able to feed orally, regardless of minor adjustments to the type of food or feeding vehicle (e.g. use of a Habermann nipple), eat pureed or solid foods, consultation of a speech and language therapist.
b) Moderate FD applied to patients who were fed orally, but were also dependent on additional tube feeding.

c) Severe FD applied to patients who received only tube feedings, i.e. nasopharyngeal, percutaneous, or parenteral feeding.

Statistical analysis

Statistical analyses were performed using Statistical Package for Social Sciences (SPSS) version 24.0 for Windows (2011, SPSS Inc., Chicago, IL, USA). Descriptive statistics were used. Equality of groups was tested with the Pearson χ^2 test. A *P*-value of <0.05 was considered to be statistically significant.

Results

Population

There were 955 patients with CFM, of which 755 had clinical and/or radiographic images available, and were therefore included for further analyses. Patient characteristics of the included patients are shown in Table 1.

Characteristics of patients with Feeding Difficulties

FD was diagnosed in 199 of the 755 patients (26%); 92 with mild FD, 25 with moderate FD and 82 with severe FD. FD was diagnosed at a median age of 2.9 months (range 0-25.3 years) and in 60% of the patients before the age of 6 months. A total of 62 patients (31.2%) had cleft lip/palate.

Of the patients with bilateral CFM, 49.0% had FD. FD was significantly more often diagnosed in patients with bilateral CFM than in patients with unilateral CFM (Pearson's χ^2 (1) = 25,267; p<0,001). Furthermore, patients with cleft lip/palate were significantly more often diagnosed with FD than patients without cleft lip/palate (Pearson's χ^2 (1) = 47,084; p<0,001). Patients with macrostomia did not have a significantly higher risk for FD than patients without macrostomia (Pearson's χ^2 (1 = 1.169; p=0,280) (Table 1).

Table 1. Description of the total population.

		Feeding difficulties		
		No	**Yes**	**Total**
Total		556	199	755
Sex	Male	312	96	408
	Female	244	103	347
Laterality	Unilateral	512	157	669
	Bilateral	44	42	86
Affected side (UCFM)*	Right	291	80	371
	Left	221	77	298
Cleft lip/palate	No	498	137	635
	Yes	58	62	120
Macrostomia	No	437	149	586
	Yes	119	50	169
Extracraniofacial anomalies	No	443	85	528
	Yes	113	114	227
Obstructive sleep apnoea	No	503	119	622
	Yes	53	80	133
Pruzansky- Kaban classification	I	114	26	140
	IIA	110	29	139
	IIB	82	36	118
	III	56	55	111
	Unknown	194	53	247

UCFM = unilateral craniofacial microsomia.
*In the unilateral cases of craniofacial microsomia.

Extracraniofacial anomalies were diagnosed in 180 patients, of which 50.0% were also diagnosed with FD. FD was significantly more often diagnosed in patients with extracraniofacial anomalies than in patients without extracraniofacial anomalies (Pearson's χ^2 (1) = 69.172; p<0.001). Additionally, patients with OSA were significantly more often diagnosed with FD than patients without OSA (Pearson's χ^2 (1) = 94.978; p<0.001). Of the 133 patients diagnosed with OSA, 80 patients (60.2%) were also diagnosed with FD.

More severe mandibular hypoplasia was also associated with a significantly higher risk for FD (Pearson's χ^2 (3) = 34.929; p<0.001). Of the patients with a Pruzansky-Kaban III classification 50.0% had FD, whereas patients with a Pruzansky-Kaban I classification were less likely to have FD (19.0%). However, patients with more severe mandibular hypoplasia were not significantly more severely affected with FD (Pearson's χ^2 (6) = 10.792; p=0,095) (Tables 1 and 2).

Table 2. Severity of mandibular hypoplasia, including patients with and without cleft lip/palate, and presence of mild, moderate, and severe feeding difficulties.

		No FD	Mild FD	Moderate FD	Severe FD	Total
Mandibular hypoplasia	**Pruz-Kab I**	114 (20.5%)	14 (15.2%)	1 (4%)	11 (13.4%)	140
	Pruz-Kab IIa	110 (19.8%)	16 (17.4%)	5 (20.0%)	8 (9.8%)	139
	Pruz-Kab IIb	82 (14.7%)	20 (21.7%)	2 (8%)	14 (17.1%)	118
	Pruz-Kab III	56 (10.1%)	18 (19.6%)	10 (40.0%)	27 (32.9%)	111
	Pruz-Kab unknown	194 (34.9%)	24 (26.1%)	7 (28.0%)	22 (26.8%)	247
Total		556 (100%)	92 (100%)	25 (100%)	82 (100%)	755

FD = feeding difficulties; Pruz-Kab = Pruzansky-Kaban classification.

Patients with Mild Feeding Difficulties

In total, 92 patients were diagnosed with mild FD, of which 16 patients were also diagnosed with cleft lip/palate. Patients with CFM and cleft lip/palate are described separately. The remaining 76 patients were diagnosed with FD at a median age of 12.0 months (range 0 – 25.3 years). A total of 24 patients (26.1%) were also diagnosed with OSA. Symptoms of mild FD were linked to oral-motor dysfunction, including difficulties with swallowing, suckling, and chewing, as well as restricted mouth opening. Sixty-nine patients (90.8%) had unilateral CMF and seven patients (9.2%) had bilateral involvement.

Treatment of mild FD involved using different types of feeding bottles/nipples, pureed foods, anti-reflux medication, and/or speech- and language therapy.

Patients with Moderate Feeding Difficulties

Twenty-five patients were fed both orally and via a tube. Fourteen patients (56.0%) were also diagnosed with OSA. Cleft lip/palate was diagnosed in eight patients; these patients are described in detail separately. Of the remaining 17 patients, FD were diagnosed at the median age of 0.93 months (range 0 – 5.8 years). Eleven (64.7%) patients had unilateral CFM and six (35.3%) had bilateral CFM. Moderate FD was most frequently diagnosed in patients with Pruzansky-Kaban III mandibular deformities.

Patients received tube feeding for a median duration of 11.7 months (range 1.1 month – 16.4 years). Four patients underwent a gastrostomy and three patients still received tube feedings at the time of this study.

Adjustment of oral feeding consisted of using different types of feeding bottles/nipples, pureed foods, anti-reflux medication, and/or speech- and language therapy.

Patients with Severe Feeding Difficulties

A total of 82 patients were solely fed via tube or parenteral feedings. Forty-two patients (51.2%) were also diagnosed with OSA. Patients with cleft lip/palate are described separately. Of the remaining 44 patients, 32 patients (72.7%) had unilateral CFM and 11 patients (27.3%) had bilateral CFM.

The diagnosis of severe FD was made at the median age of 1.3 months (range 0 – 13.9 years). Parenteral feeding was given to four patients for a median duration of 6 days (range 3 – 183 days) and was always followed by tube feedings. In total, 11 patients underwent a gastrostomy. Patients received tube feeding for a median duration of 7.1 months (range 2 days – 12.9 years). Five patients were still receiving tube feedings at the time of this study.

Complaints from parents and/or patients mostly applied to difficulties in swallowing and/or reflux. No information was available on the transition from tube feedings to oral intake. Like moderate FD, severe FD were also more frequently diagnosed in patients with a Pruzansky-Kaban III mandibular deformity.

Cleft lip/palate and Feeding Difficulties

Of the 199 patients with FD, 62 patients (31.2%) had cleft lip/palate. These patients were diagnosed with FD at a median age of 0.62 months (range 0.00 – 14.2 years). In total, 45 patients (72.6%) had unilateral CFM and 17 had bilateral CFM (27.4%). Patients with cleft lip/palate were significantly more severely affected with FD than patients without cleft lip/palate (Pearson's χ^2 (3) = 17.462; p<0,001). Of the four patients with cleft lip (CL) or cleft lip alveolus (CLA) who had FD, one patient (10%) was severely affected. Of the 58 patients with a cleft palate – i.e. cleft lip alveolus palate (CLAP) and cleft palate (CP) – and FD, 37 (64%) had severe FD (Table 3). Patients with CFM and cleft palate were diagnosed significantly more often with severe FD than patients with CFM without a cleft (Pearson's χ^2 (2) = 19.662; p<0,001) (Table 4).

Moderately affected patients needed tube feeding for at least 4.1 months and for a maximum time of 6.5 years (median 13.1 months). Severely affected patients were tube fed for a median duration of 19.5 months (range 0.1 months – 18.1 years). Difficulty swallowing was the major complaint of patients and/or their parents.

Table 3. Type of cleft lip/palate and the presence of feeding difficulties.

	Feeding difficulty				
Cleft type	**No**	**Mild**	**Moderate**	**Severe**	**Total**
- CL	6	2	0	0	8
- CLA	0	1	0	1	2
- CLAP	25	6	5	15	51
- CP	27	7	3	22	59
Total	58	16	8	38	120

CL = cleft lip; CLA = cleft lip alveolus; CLAP = cleft lip alveolus palate; CP = cleft palate

Table 4. Presence of cleft lip/palate and the presence of mild, moderate and severe feeding difficulties.

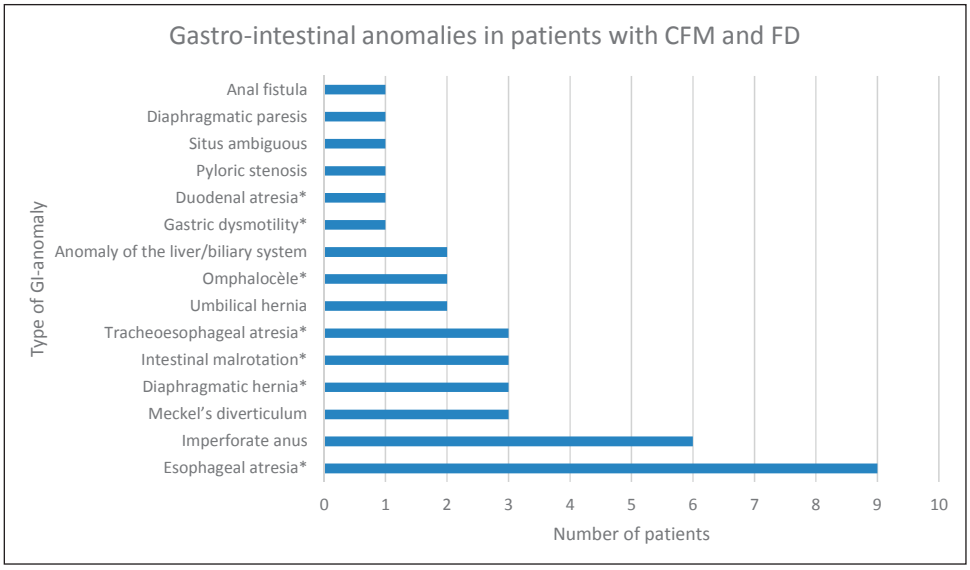
		Mild FD	**Moderate FD**	**Severe FD**	**Total**
CFM with cleft palate*	**Yes**	13 (17.1%)	8 (32.0%)	37 (45.7%)	58
CFM without cleft palate	**No**	76 (85.4%)	17 (68.0%)	44 (54.3%)	137
Total		89	25	81	195

FD = feeding difficulty; CFM = craniofacial microsomia
*including patients with cleft lip alveolus palate and patients with cleft palate.

Extracraniofacial anomalies and Feeding Difficulties

Extracraniofacial anomalies were present in 45.2% of the patients with FD. Cardiac anomalies were diagnosed in 38.2% and gastro-intestinal anomalies (GI anomalies) were diagnosed in 15.6%. Patients with cardiac anomalies had significantly more severe FD (Pearson's χ^2 (2) = 11.377; p=0,003) than patients without cardiac anomalies. Patients with GI anomalies also had significantly more severe FD (Pearson's χ^2 (3) = 8.409; p=0,015) than patients without GI anomalies. However, in the 22 patients diagnosed with a GI anomaly, the type of GI anomaly played an important role in the development of FD and could have been the causative factor. Types of GI anomaly are shown in Figure 1. Eight patients were affected with two different types of GI anomaly.

Figure 1. Gastro-intestinal anomalies in patients with craniofacial microsomia and feeding difficulties.



GI-anomaly = gastro-intestinal anomaly.
*gastro-intestinal anomaly that might also lead to feeding difficulties without the presence of facial anomalies.

Obstructive Sleep Apnoea and Feeding Difficulties

Of the 199 patients diagnosed with FD, 80 patients (40.2%) were also diagnosed with OSA. The median age at which the diagnosis of FD in patients with and without OSA was made was 3.0 months and 2.9 months, respectively. Of the patients with OSA, 31 patients (38.8%) had bilateral CFM and 48 patients (61.2%) had unilateral CFM. In the patients without OSA the figures were 108 (90.8%) and 11 patients (9.2%), respectively. Patients with OSA and moderate FD needed tube feeding for a median duration of 1.9 years (range 0.1 – 16.4 years), whereas patients without OSA and with moderate FD needed tube feeding for a median duration of 0.6 years (range 0.2 – 16.3 years). Additionally, patients with OSA and severe FD needed to be tube fed for a median duration of 1.4 years (range 0.02 – 15.6 years), whereas patients affected with severe FD without OSA needed to be tube fed for a median duration of 1.0 year (range 0.01 – 18.1 years). Patients with OSA and FD were significantly more severely affected with FD than patients without OSA (Pearson's χ^2 (2) = 14.361; p=0.001). Furthermore, patients with OSA had a significantly higher Pruzansky-Kaban classification than patients without OSA (Pearson's χ^2 (3) = 12.278; p=0.006) (Tables 5 and 6).

Table 5. Severity of feeding difficulties and the presence of obstructive sleep apnea.

		Mild FD	Moderate FD	Severe FD	Total
OSA	**Yes**	24 (30.0%)	14 (17.5%)	42 (52.5%)	80
	No	68 (57.1%)	11 (9.2%)	40 (33.6%)	119
Total		92	25	82	199

FD = feeding difficulties; OSA = obstructive sleep apnea.

Table 6. Severity of mandibular hypoplasia and the presence of obstructive sleep apnea in patients with feeding difficulties.

		No OSA	OSA	Total
Mandibular hypoplasia	**Pruz-Kab I**	18 (15.1%)	8 (10.0%)	26
	Pruz-Kab IIa	19 (16.0%)	10 (12.5%)	29
	Pruz-Kab IIb	23 (19.3%)	13 (16.3%)	36
	Pruz-Kab III	20 (16.8%)	35 (43.8%)	55
	Pruz-Kab unknown	39 (32.8%)	14 (17.5%)	53
Total		119	80	199

OSA = obstructive sleep apnea; Pruz-Kab = Pruzansky-Kaban classification.

Discussion

In this multicenter study the prevalence of FD in patients with CFM was 26.4%, which is lower than the 42 – 83% reported in the literature.[8, 12-14] However, we found a considerable number of patients with moderate to severe FD. Risk factors for FD were cleft lip/palate, OSA and Pruzansky-Kaban III mandibular deformity. Also, several patients had extracraniofacial anomalies, which increased the risk for FD. The results of this study are based on a large number of patients (*n*=755) and may be more representative than the results of previous studies with a smaller number of patients in which a higher prevalence of FD was reported.

Some important risk factors for the development of FD should be noted. First, we found that patients with bilateral CFM were significantly more at risk for developing FD than patients with unilateral CFM. Additionally, patients with more severe mandibular hypoplasia were also significantly more at risk for developing FD than patients with less severe mandibular hypoplasia. These results are in line with previous studies and can be explained by the underdevelopment of facial structures.[4, 6, 9, 10, 18, 19].

FD was more common in patients with other craniofacial anomalies, and was more severe in these patients. A possible explanation of severe FD in patients with CFM and a cleft lip/palate might be the fact that there is limited active cheek and lip movements during feeding, which limits mouth opening and sucking efficiency. With an additional cleft palate, it is more difficult to generate negative pressure and more difficult to swallow the bolus.[20, 21]

We found that 40% of the patients with FD also had OSA, and these patients were significantly more severely affected with FD than patients without OSA. However, it is also suggested in patients without OSA that specific craniofacial features seen in CFM, such as hypoplastic masticatory and/or pharyngeal muscles and abnormal orofacial muscle tone, play a more important role in the pathogenesis of FD than the presence of OSA. Additionally, these craniofacial anomalies could also lead to OSA.

Extracraniofacial anomalies, which were present in 45% of the patients with FD, might be an additional risk factor for FD. In this group, severe FD was more common. For patients with GI anomalies, these results could partly be explained by the type of GI anomaly, because in several patients the type of GI anomaly could play a more important role in developing FD than the presence of facial anomalies.

A considerable number of patients with FD (53.8%) required a prolonged time of tube feeding, with a median duration of 1.3 years. This can have serious psychosocial

consequences and can be stressful for both patient and parents.[22] Furthermore, most of the patients who received tube feeding in the first few months after birth complained of difficulties with swallowing. Because FD (e.g. chewing problems and/or mouth opening restriction) might also develop later in life when oral feeding begins, it is recommended that clinicians inform parents and/or patients about this problem. Mild FD is diagnosed in most cases around the age of 1 year when eating solid foods begins. Chewing difficulties are more prominent in these patients than swallowing difficulties.

Screening and treatment of FD should preferably begin early in life. Therefore, the authors recommend that all patients with CFM are screened for FD before the age of 1 year by a speech and language therapist. Conservative treatment consists of modification of bottles and/or nipples, supplemented breastmilk/increased caloric concentration of the formula, and antireflux medication. In patients with bilateral CFM, a Pruzanksy-Kaban III classification, OSA, cleft lip/palate, or extracraniofacial anomalies, additional surgical therapy might be indicated. These patients could, for example, benefit from cleft lip/repair or mandibular distraction osteogenesis. However, a detailed description of these surgical therapies and their positive effect on FD lies beyond the scope of this article. After the age of 1 year special attention to FD in patients with CFM is still needed, and patients should be monitored by a feeding specialist on a regular basis.

A number of limitations of this study should be addressed. The medical charts of 51.7% did not mention complaints suggesting the presence of FD. This could be the result of a lack of awareness among medical staff for the risk of FD in CFM at the time of charting, and may have resulted in an underestimate of the number of patients with FD. However, parents mostly pay a lot of attention to the feeding habits of their children, so it was assumed when nothing was mentioned that no problems existed in most cases. Furthermore, we feel that the classification developed by our group to describe the severity of FD is clinically relevant, easy to use, and easy to interpret. Another limitation of this study is the lack of data on the duration of the complaints, and on what role the speech and language therapist could play. As for other craniofacial anomalies, it is expected that the speech and language therapist could play an essential role in both prevention and treatment of FD in patients with CFM.

Conclusion

In almost one out of four patients with CFM, feeding difficulties occur due to their craniofacial anomalies. Risk factors for FD are bilateral CFM, a Pruzansky-Kaban III mandibular deformity, cleft lip/palate, presence of OSA, and extracraniofacial anomalies.

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CHAPTER

Evaluation of swallow function in patients with Craniofacial Microsomia: a retrospective study

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Abstract

Craniofacial microsomia (CFM) is characterized by underdevelopment of the structures derived from the first and second pharyngeal arches resulting in aesthetic, psychological, and functional problems including feeding and swallowing difficulties. The aim of this study is to gain more insight into swallowing difficulties in patients with CFM. A retrospective study was conducted in the population of patients diagnosed with CFM at three major craniofacial units. Patients with feeding difficulties and those who underwent video fluoroscopic swallow (VFS) studies were included for further analyses. The outcome of the VFS-studies was reviewed with regard to the four phases of swallowing. In our cohort, 13.5% of the 755 patients were diagnosed with swallowing difficulties. The outcome of the VFS-studies of 42 patients showed difficulties in the oral and pharyngeal phase with both thin and thick liquids. Patients with more severe mandibular hypoplasia showed more difficulties to form an appropriate bolus compared to patients who were less severely affected. This is the first study to document swallowing problems in patients with CFM. Difficulties were seen in both the oral and pharyngeal phases. We recommend routine screening for swallowing issues by a speech and language therapist in all patients with CFM and to obtain a VFS-study in patients with a type III mandible.

Introduction

Craniofacial microsomia (CFM) is a complex and heterogeneous condition characterized by underdevelopment of structures derived from the first and second pharyngeal arches including the orbit, mandible, ear, facial nerves, facial soft tissues, and muscles[1, 2]. The most striking feature, mandibular hypoplasia, is present in 89 to 100% of the patients. With an incidence of 1:3000 to 1:5000 live births, CFM is believed to be the second most common craniofacial anomaly following cleft lip and palate[2-4].

The facial anomalies seen in CFM may not only lead to aesthetic and psychological problems, but also to functional issues such as breathing and feeding difficulties (FD)[5, 6]. FD are seen in 42 – 83% of the patients with CFM and include problems with suckling, chewing, failure to thrive, and swallowing[5, 7-9].

Feeding and swallowing are complex neuromuscular functions that are dependent upon volitional and reflexive activities of a significant number of oropharyngeal muscles and nerves that form the oropharyngeal apparatus. Reflexive activities play a dominant role up to six months in healthy infants [10-13].

Normal swallowing is divided into four phases that proceed seamlessly from one to another for which adequate neuromuscular coordination is necessary. During the four phases of swallowing, (i.e., preparatory, oral, pharyngeal and esophageal), the bolus is formed and transported into the stomach via the oropharynx and esophagus [10, 14-17]. To evaluate the different phases of swallowing, a videofluoroscopic swallow study (VFS-study) can be used, which is considered to be the gold standard [18-20]. With this imaging technique, all four phases of swallowing can be assessed using pellets of different consistencies, e.g., thin liquids, thick liquids, purees, and solids.

Swallow difficulties (SD) can result from a wide variety of functional or structural deficits of the oral cavity, pharynx, larynx, or esophagus[10]. SD in CFM might be the result of mandibular hypoplasia, possible underdevelopment of the oropharyngeal apparatus, and/or decreased innervation of the masticatory and pharyngeal muscles [7, 11, 21]. Furthermore, swallow dysfunction might be aggravated by cleft lip and/or palate, which is present in 15.9% of the patients with CFM [22-24].

The aim of this study is to document the incidence of SD in patients with CFM and gain more insight into SD in patients with CFM by studying the outcomes of VFS-studies at three major craniofacial units.

Materials and methods

A retrospective study was conducted in the population of patients diagnosed with CFM at the craniofacial units of Erasmus MC, Rotterdam, The Netherlands; Great Ormond Street Hospital in London, United Kingdom; and Boston Children's Hospital in Boston, United States of America. Following IRB approval (Rotterdam: MEC-2013-575; London: 14DS25; Boston: X05-08-058), medical charts were reviewed for information on sex, affected side, severity of the deformity according to the Pruzansky-Kaban classification [4, 25], presence of FD and type of FD, presence of cleft lip and/or palate, cleft repair, presence of tracheostomy, reports of performed VFS-studies, and available clinical pictures and/or radiographic images (i.e., panoramic X-rays and/or CT head scans). Patients with and without cleft lip/palate were independently analyzed.

Charts of patients with documented FD were reviewed for type of FD, i.e., swallow difficulties. FD were clinically determined by the treating physician. Patients clinically diagnosed with SD who had undergone a VFS-study were included for further analyses. The criteria used to determine SD are described in Table 1.

Table 1. Criteria to determine swallow difficulties.

Criteria Swallow Difficulties
Sucking and swallowing incoordination
Weak suck
Excessive gagging
Recurrent coughing during feeds
Recurrent pneumonia
Nasopharyngeal reflux
Desaturation during feeds
(Risk for) aspiration during feeds

Original reports of all VFS-studies were collected. Incomplete reports of the VFS-studies and VFS-studies performed following mandibular reconstruction were excluded. The first VFS-study per patient was used for (statistical) analyses. Information was collected on the number of performed VFS-studies; indication; age at time of the first VFS-study; positioning, seating and imaging view during the VFS-study; nutritional route at time of the VFS-study, (i.e., fully oral, oral in combination with a nasogastric tube, or completely fed by a nasogastric tube); and utensils used (e.g., bottle, spoon, nipple). When patients were fully fed via a nasogastric tube at time of the VFS-study, the VFS-study was nevertheless fully orally assessed. Information on the outcome of the VFS-studies regarding the four

phases of swallowing was collected. Impairment of the oral phase included impaired bolus formation and premature spill of the bolus into the pharynx. Premature spill of the bolus into the pharynx was defined as progression of the bolus over the tongue base into the pyriform sinus in the absence of purposeful oral transfer before the initiation of swallowing.[26] Bolus formation was tested with all four consistencies, whereas premature spill into the pharynx was only evaluated with thin and thick liquids. Impairment of the pharyngeal phase included delayed swallow trigger, post-swallow stasis, nasopharyngeal reflux, laryngeal penetration, and aspiration. Laryngeal penetration is defined as food/liquid passing the laryngeal inlet above the level of the vocal folds, whereas aspiration is defined as food/liquid passing the laryngeal inlet below the vocal folds, with or without the trigger for cough.[26] The esophageal phase included data on adequate movement of the bolus into the esophagus. Gastroesophageal reflux was not studied. The pharyngeal phase was evaluated using pellets with different consistencies, i.e., thin liquids, thick liquids, puree, and solids. [10, 14-16, 27, 28]

Severity of mandibular hypoplasia in CFM was scored on panoramic X-rays or on CT scans according to the Pruzanksy-Kaban classification. In patients with bilateral CFM, the Pruzansky-Kaban classification was scored on both sides of the patient; however, for analyses the most severe score was used.

Statistical analysis

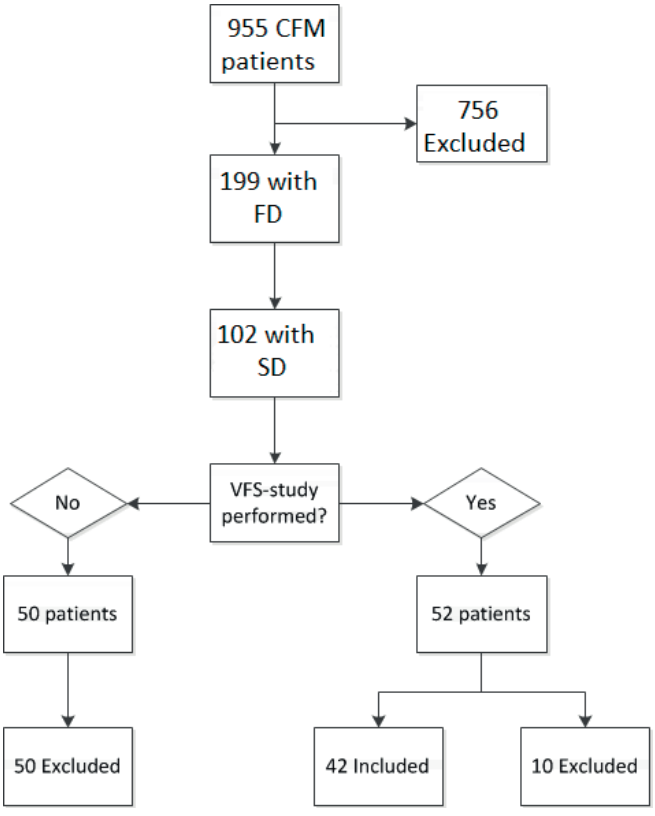
Statistical analyses were performed using Statistical Package for Social Sciences (SPSS) version 20.0 for Windows (2011, SPSS Inc., Chicago, IL, USA). Descriptive statistics were used. Equality of groups was tested with the Pearson χ^2 test and Fisher's Exact test. A *P*-value of <0.05 was considered statistically significant.

Results

Population

Of the 955 patients diagnosed with CFM, clinical pictures and/or radiographic images were available in 755 patients, who could be further reviewed and analyzed. In total, 199 patients were diagnosed with FD, of which 102 patients were diagnosed with SD. Of these patients, 51.0% had undergone a VFS-study. As there were no clinical concerns for aspiration, 50 patients did not undergo a VFS-study. Ten patients were excluded since the first available VFS-study was done following mandibular reconstruction. A total of 42 patients were included. Indications for the VFS-study were to assess function and safety of swallowing (*n*=36), including the risk for (silent) aspiration (*n*=4), or in case of excessive gagging and vomiting (*n*=2) (Figure 1).

Figure 1. Inclusion and exclusion of patients with CFM and VFS-studies.



CFM = Craniofacial Microsomia, SD = swallow difficulties, FD = feeding difficulties, VFS-study = videofluoroscopic swallow study

Characteristics of the VFS study group

The study group consisted of 24 (57.1%) males and 18 (42.9%) females. In total, 31 (73.8%) patients were unilaterally and 11 (26.2%) patients were bilaterally affected. The Pruzansky-Kaban classification could be assessed in 31 patients, in which most patients were classified as Pruzansky-Kaban III (Table 2).

Table 2. Description of the included population.

	No. of patients
Sex	
- Male	24
- Female	18
Laterality	
- Unilateral CFM	31
- Bilateral CFM	11
Affected side*	
- Right side	19
- Left side	12
P-K classification	
- P-K I	9
- P-K IIA	5
- P-K IIB	6
- P-K III	11
- Unknown	11
Cleft lip/palate	
- Cleft palate	8
- Cleft lip and palate	4
- Submucous cleft	1
- No	29
Tracheostomy during VFS-study	
- Cuffed	4
- Uncuffed	2
History of tracheostomy	4
No tracheostomy	32

CFM = craniofacial microsomia, P-K classification = Pruzansky-Kaban classification
*In the unilateral cases of craniofacial microsomia.

Cleft lip/palate was diagnosed in 13 patients (31.0%); at time of the VFS-study cleft lip/palate was repaired in seven patients and unrepaired in three. In another three patients, the status of cleft lip/palate repair remained unknown.

Six out of 42 patients had a tracheostomy at time of the VFS-study (Table 2).

All VFS-studies were performed in an upright position in a tumble forms feeder seat. Lateral view was standard. The oral and pharyngeal phase was tested in 41 and 42 patients, respectively. At time of the VFS-study, 25 patients were fully orally fed, six patients were nasogastric tube dependent, and 11 patients were fed both orally and via a nasogastric tube. Patients with cleft lip/palate were significantly more often fed using a nasogastric tube at time of the VFS-study than patients without cleft lip/palate (Pearson's χ^2 (2)=6,499, *p=0.039*) (Table 3).

Table 3. Current nutritional route in patients with and without cleft lip/palate at time of the VFS-study.

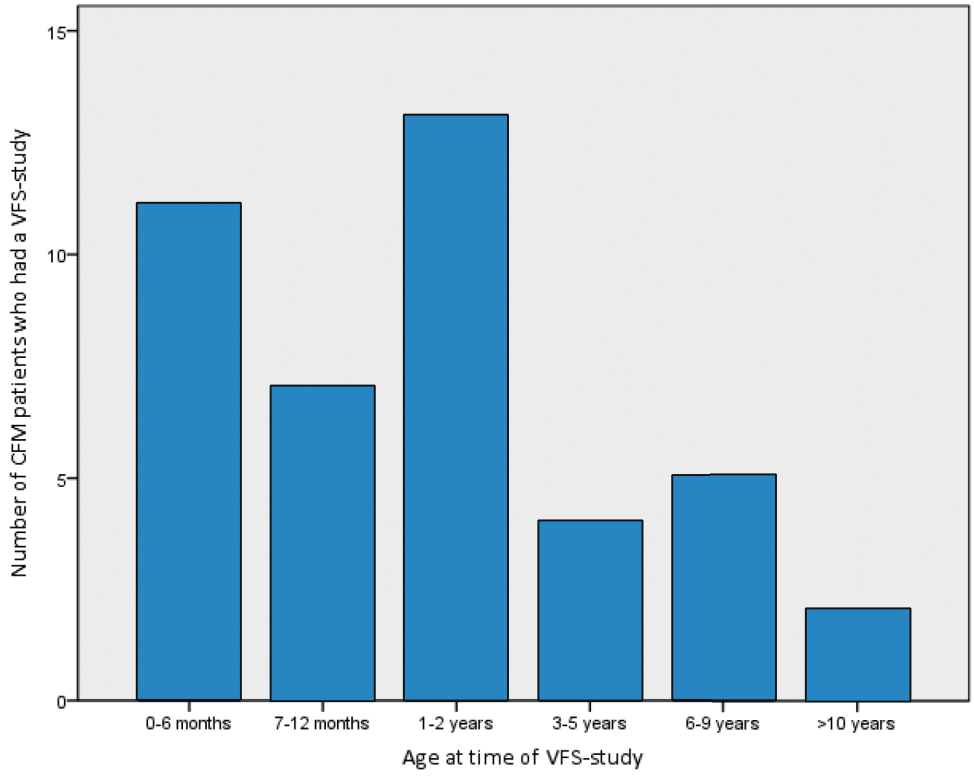
		Current Nutritional Route			
		Oral	**Oral & NG tube**	**NG tube**	**Total**
Cleft lip/palate					
-	No	21	5	3	29
-	Yes	4	6	3	13
Total		25	11	6	42

NG tube = nasogastric tube

Overall, the median age at time of the VFS-study was 1.15 years (range 0.02 – 26.26). A VFS-study was performed in 26.2% of patients before the age of 6 months. There were no (significant) differences between patients younger and older than six months regarding clinical features, such as severity of CFM, presenting symptoms and indication for a VFS-study.

The majority of patients younger than six months showed problems in all phases of the VFS-study; most problems were seen in the bolus formation (62.5%), nasopharyngeal reflux (75%), and aspiration (62.5%). Patients younger than six months were significantly more often diagnosed with nasopharyngeal reflux than patients older than six months (Pearson's χ^2 (1)=7,529, *p=0.011*). The group of patients older than 6 months (*n*=31) showed mostly inappropriate bolus formation (55%), delayed/variable swallow trigger (47.4%), and post-swallow stasis (47.1%) (Figure 2 and Table 4).

Figure 2. Age at time of first videofluoroscopic swallow study in patients with CFM.



VFS-study = videofluoroscopic swallow study.

Table 4. Outcome of the VFS-study before or after the age of 6 months.

	Age at time of VFS-study		
	< 6 months	**> 6 months**	**Total**
Oral Phase			
- Inappropriate bolus formation	5 out of 8 (62.5%)	11 out of 20 (55.0%)	16 out of 28 (57.1%)
- Premature spill into the pharynx	4 out of 8 (50.0%)	3 out of 16 (18.7%)	7 out of 24 (29.2%)
Pharyngeal Phase			
- Delayed/variable swallow trigger	4 out of 7 (57.0%)	9 out 19 (47.4%)	13 out of 26 (50.0%)

Table 4. Outcome of the VFS-study before or after the age of 6 months.

	Age at time of VFS-study		
	< 6 months	**> 6 months**	**Total**
- Post-swallow stasis	3 out of 7 (42.9%)	8 out of 17 (47.1%)	11 out of 24 (45.8%)
- Nasopharyngeal reflux	6 out of 8 (75.0%)	4 out of 20 (20.0%)	10 out 28 (35.7%)
- Laryngeal penetration	4 out of 7 (57.0%)	4 out of 19 (21.2%)	8 out of 26 (30.8%)
- Aspiration	5 out of 8 (62.5%)	5 out of 21 (23.8%)	10 out of 29 (34.5%)

*Numbers do not add up due to unknown outcome of VFS-study

The videofluoroscopic swallow study in CFM patients without cleft

The oral phase (Table 5)

Appropriate bolus formation was mostly seen with the use of puree (78.9%, *n*=15). Inappropriate bolus formation was mostly seen with the use of thin (48.0%, *n*=12) or thick (47.1%, *n*=8) liquids. Premature spill into the pharynx was seen when both thin liquids (27.3%, *n*=6) and thick liquids (23.5%, *n*=4) were given.

Table 5. Oral phase of VFS-study.

Oral phase / **Consistencies**	**Thin**		**Thick**		**Puree**		**Solids**	
Bolus Formation	n	%	n	%	n	%	n	%
Appropriate	12	48,0	9	52,9	15	78,9	6	60,0
Inappropriate	12	48,0	8	47,1	3	15,8	4	40,0
Noncompliance	1	4,0	--	--	1	5,3	--	--
Total	25	100,0	17	100,0	19	100,0	10	100,0
Premature spill into pharynx	n	%	n	%				
No	16	72,7	13	76,5	N/A	N/A	N/A	N/A
Yes	6	27,3	4	23,5	N/A	N/A	N/A	N/A
Total	22	100,0	17	100,0				

N/A = not applicable

The pharyngeal phase (Tables 6, 7, 8, 9)

The pharyngeal phase included swallow trigger, post-swallow stasis, nasopharyngeal reflux, laryngeal penetration, and aspiration. Overall, and regardless of the consistency used, swallow trigger was tested in 26 patients of which in total 13 patients (50.0%) showed an abnormal swallow trigger. However, when the consistency used was taken into account, delayed swallow trigger was seen in 10.0-33.3 % of the patients; the thinner the consistency the more delayed the swallow trigger. Overall, post-swallow stasis was diagnosed in 45.8% of the tested patients (*n*=24), but was mostly seen when thick liquids (35.7%, *n*=5) and puree (35.3%, *n*=6) were given.

The highest incidence of nasopharyngeal reflux and laryngeal penetration was seen with the use of thin liquids (40.0%, *n*=10) and thick liquids (35.3%, *n*=6), and was not seen with the use of solid pellets.

Overall, aspiration was diagnosed 34.5% of the patients (*n*=29), regardless of the consistency used. Aspiration was especially seen when thin liquids were used (38.5%, *n*=10), and three of these patients showed silent aspiration.

Table 6. Results swallow trigger (pharyngeal phase) of VFS-studies.

Pharyngeal phase / **Consistencies**	**Thin**		**Thick**		**Puree**		**Solids**	
Swallow trigger	n	%	n	%	n	%	n	%
Timely	13	54,2	11	68,8	16	84,2	9	90,0
Variable	2	8,3	1	6,3	--	--	--	--
Delayed	9	33,3	4	25,0	2	10,5	1	10,0
No initiation	--	--	--	--	1	5,3	0	0
Total	24	100,0	16	100,0*	19	100,0	10	100,0

*Numbers do not add up due to rounding numbers.

Table 7. Results post swallow stasis (pharyngeal phase) of VFS-studies.

Pharyngeal phase Consistencies	**Thin**		**Thick**		**Puree**		**Solids**	
Post-swallow stasis	n	%	n	%	n	%	n	%
Yes	6	27,3	5	35,7	6	35,3	3	30,0
No	16	72,7	9	64,3	11	64,7	7	70,0
Total	22	100,0	14	100,0	17	100,0	10	100,0

Table 8. Results post swallow stasis (pharyngeal phase) of VFS-studies.

Pharyngeal phase Consistencies	**Thin**		**Thick**		**Puree**		**Solids**	
Nasopharyngeal reflux	n	%	n	%	n	%	n	%
Yes	10	40,0	6	35,3	3	15,8	N/A	N/A
No	15	60,0	11	64,7	16	84,2	10	100
Total	25	100,0	17	100,0	19	100,0	10	100
Laryngeal penetration	n	%	n	%	n	%	n	%
Single episode	2	8,3	--	--	--	--	N/A	N/A
Multiple	5	20,8	4	23,5	1	5,3	N/A	N/A
No	17	70,8	13	76,5	18	94,7	10	100
Total	24	100,0	17	100,0	19	100,0	10	100

N/A = not applicable.

Table 9. Results of aspiration and airway protection (pharyngeal phase) of VFS-studies.

Pharyngeal phase / **Consistencies**	**Thin**		**Thick**		**Puree**		**Solids**	
Aspiration	n	%	n	%	n	%	n	%
Yes	10	38,5	5	27,8	1	5,0%	N/A	N/A
Micro-aspiration	2	7,7	1	5,6	--	--	N/A	N/A
Silent aspiration	3	11,5	2	11,1	--	--	N/A	N/A
Not further specified	5	19,2	2	11,1	1	5,0	N/A	N/A
No	16	61,5	13	72,2	19	95,0	10	100
Total	26	100,0	18	100,0	20	100,0	10	100,0

N/A = not applicable.

The Pruzansky-Kaban classification and the risk for swallow difficulties (Tables 10 and 11)

Inappropriate bolus formation was significantly more often diagnosed in patients with Pruzansky-Kaban III classification than in patients with a lower Pruzansky-Kaban classification (Pearson's $\chi^2(3)=10{,}708$, $p=0{,}013$). However, severe and less severely affected patients were comparably affected in the pharyngeal phase. Furthermore, the outcome of the VFS-studies performed in patients with bilateral CMF (n=9) was not significantly different from patients with unilateral CFM (n=20).

Table 10. Pruzansky-Kaban classification of included patients and outcome of the tested phases of the VFS -studies.

	P-K I n = 5	**P-K IIA n = 5**	**P-K IIB n = 4**	**P-K III n = 10**	**P-K Unknown n =5***	**Total**
Oral phase						
- Inappropriate bolus formation	2	2	0	9	3	16
- Premature spill into the pharynx	0	3	0	2	2	7
Pharyngeal phase						
- Delayed/variable swallow trigger	2	4	0	4	3	13
- Post-swallow stasis	1	4	0	4	2	11
- Nasopharyngeal reflux	0	2	0	5	3	10
- Laryngeal penetration	1	3	0	1	3	8
- Aspiration	0	2	2	3	3	10

*Not included in statistical analyses.
P-K = Pruzansky-Kaban classification.

Table 11. Laterality of craniofacial microsomia and outcome of the tested phases of the VFS -studies.

	Unilateral CFM	Bilateral CFM	Total
Oral phase			
- Inappropriate bolus formation	10	6	16
- Premature spill into the pharynx	5	2	7
Pharyngeal phase			
- Delayed/variable swallow trigger	10	3	13
- Post-swallow stasis	6	5	11
- Nasopharyngeal reflux	7	3	10
- Laryngeal penetration	5	3	8
- Aspiration	6	4	10

CFM = Craniofacial Microsomia.

Current nutritional route and the risk for swallow difficulties (Table 12)

Twenty-one patients were fully orally fed at the time of the VFS-study, five orally in combination with a nasogastric tube and three solely via a nasogastric tube. Current nutritional route did not significantly correlate with the outcome of the VFS-studies in this study.

Table 12. Nutritional route and outcome of the tested phases of the VFS-studies.

	Oral n = 21	Oral & tube n=5	Tube n=3	Total
Oral phase				
- Inappropriate bolus formation	11	5	0	16
- Premature spill into the pharynx	6	1	0	7
Pharyngeal phase				
- Delayed/variable swallow trigger	8	3	2	13
- Post-swallow stasis				
- Nasopharyngeal reflux	6	3	2	11
- Laryngeal penetration	8	2	0	10
- Aspiration	6	2	0	8
	8	2	0	10

The videofluoroscopic swallow study in CFM patients with cleft

Table 13 shows the VFS-study findings of CFM patients with repaired cleft lip/palate at time of the VFS-study (*n*=7). The oral phase and pharyngeal phase was affected in these patients.

The oral phase was affected in 4 patients; 4 patients showed 'inappropriate bolus formation' and 4 patients showed 'premature spill into the pharynx'. Six out of 7 patients had problems with timing of swallowing, 4 patients showed post-swallow stasis, and 4 showed nasopharyngeal reflux. Laryngeal penetration was seen in 3 patients, but aspiration only in one patient.

Table 13. Overview oral and pharyngeal phase in CFM patients with repaired cleft lip/palate.

CFM patients with repaired cleft (lip) palate	**n**
Oral phase (*n* = 6)	
- Inappropriate bolus formation	4
- Premature spill into the pharynx	4
Pharyngeal phase (*n* = 7)	
- Delayed/variable swallow trigger	6
- Post-swallow stasis	4
- Nasopharyngeal reflux	4
- Laryngeal penetration	3
- Aspiration	1

CFM = craniofacial microsomia

Discussion

By combining the data of three major craniofacial centers, the medical charts of 755 patients were analyzed. In our cohort, 13.5% of the patients were diagnosed with a swallowing disorder, necessitating a VFS-study in 50.9% of these patients. In total, 42 VFS-studies were included for analysis.

The majority of CFM patients with SD, who did not need further examination in the form of a VFS-study, are most likely affected with clinically less relevant SD since there were no clinical concerns for aspiration according to the medical charts. The SD of these patients might resolve by developing compensatory mechanisms and/or by offering smaller volumes with the use of simple adjustments, e.g., Habermann nipple, Dr. Brown's bottle.[22] The indication for a VFS-study was made by their physician based on clinical symptoms; however, the exact criteria used in the three institutions remain unclear.

In healthy infants reflexive activities play a key role in swallowing during the first six months of life as the brain is still developing. [22] In this study, a considerable number of patients (26,2%) had undergone a VFS-study before the age of six months and showed most difficulties in the pharyngeal phase, i.e., nasopharyngeal reflux, laryngeal penetration, and aspiration. Nasopharyngeal reflux, which is considered to be a pathological entity after the age of three months, was diagnosed in a considerable number of patients, i.e., in both patients younger and older than six months.[29, 30] As our results are based on patients without cleft lip/palate, it is suggested that the presence of nasopharyngeal reflux in our cohort could be the result of velopharyngeal insufficiency or a neurological disorder. [30, 31]

The majority of the patients were evaluated after the age of six months (75.6%). Difficulties of bolus formation, timing of swallow trigger, and post swallow stasis were seen in a relatively smaller number of patients after the age of six months. Inappropriate bolus formation, mostly seen in patients with type III mandibular deformities, is likely the result of anatomical anomalies leading to ineffective lip closure, tongue movements/incoordination, or muscle weakness, which was also concluded by Huisinga-Fischer.[21] Yet, it is impossible to rule out differences in innervation and muscle function as (part of the) cause for these problems.[7, 22, 23]

In the newborn infant, the pharynx follows a gentle curve from the nasopharynx to the hypopharynx. Growth results in increased anteroposterior dimension of the nasopharynx and an increased angle between the nasopharynx and oropharynx, gradually up to 90 degrees.[16, 22, 32] Difficulties of the pharyngeal phase were seen in a greater number of patients before the age of six months than after the age of six months. Nasopharyngeal reflux and difficulties with laryngeal penetration and aspiration occurred more often

before the age of six months. Delayed swallow trigger and post-swallow stasis occurred equally in patients younger and older than six months. Moreover, premature spill into the pharynx was seen after the age of six months in a smaller number of patients. Even though the nature of triggering the pharyngeal phase of swallowing is relatively unknown, and although the oral and pharyngeal cavities are anatomically apart, it is known that their function is integrated.[14, 33, 34] In these infants, a significant part of the problems might resolve over time. To support this theory, follow-up of VFS-studies is essential to compare the findings over time within this patient group.

A substantial number of patients (31.0%) of the studied cohort also had a cleft lip/palate. FD and SD seen in these patients might be more complicated in the presence of other craniofacial anomalies.[22, 35] Therefore, patients with CFM and repaired cleft lip/palate were analyzed separately in this study. Like patients without cleft lip/palate, not only difficulties were seen in bolus formation and timing of the swallow trigger, but also in the pharyngeal phase. Kaufman et al. found that abnormalities seen in the pharyngeal phase cannot be explained by presence of cleft lip/palate and might be the result of hypoplasia of the pharyngeal muscles, which is part of the anomalies seen in CFM.[7, 11, 35] From this study, it cannot be concluded that patients with CFM and cleft lip/palate have more severe SD than those without cleft lip/palate. However, patients with CFM and cleft lip/palate are more frequently NG-tube dependent, which influences development of normal swallowing. However, it should be taken into account that these NG-tube depending patients might be more prone to have SD as a result of the additional anatomical deformities caused by cleft. With regard to the SD, these patients should be seen as a different entity.

Aspiration was tested in all patients and overall diagnosed in 34.5% of the patients (including 4 patients with silent aspiration), regardless of the consistency used, but specifically with thin liquids. This could partly be explained by inappropriate bolus formation which is more frequently seen in patients with CFM and difficulties with timing of swallowing. Whereas patients before the age of six months showed aspiration in 62.5% of the cases, aspiration was seen in 23.8% of the cases after the age of six months. It is expected that aspiration might resolve when patients have developed compensating mechanisms forming appropriate boluses later in life. Moreover, some studies that analyzed SD in patients with Robin Sequence – a disorder characterized by micrognathia, glossoptosis, and upper airway obstruction – showed that the difficulties seen were proportional to the degree of airway obstruction seen in these patients.[36] Upper airway obstruction is also seen in patients with CFM and therefore it cannot be excluded that a component of airway problems in these infants might (also) play a role in the etiology of SD in CFM.[6]

Limitations

Accuracy of VFS-study interpretation is critical and findings from VFS-studies can be discussed from a variety of viewpoints. Since there is limited research on the interpretation of VFS-study findings in the pediatric population - no criterion-referenced outcome of VFS-study exist for this age group - the results of this study are based on the radiologist' experience and expertise. A more objective and validated scale for adults does exist for interpreting VFS-study findings: a modified barium swallowing tool used for quantification of swallowing impairment (MBSImp).[37] With concerns to penetration and aspiration: a Penetration- Aspiration Scale according to Rosenbek (an 8-point scale) exists for adults.[38, 39] The criteria used in these scales are congruent to the VFS-study findings used in this study; however, not all criteria used were identical. Therefore, this study could not benefit from these scales.

To perform the VFS-study, different consistencies were used as a bolus, but no data on the volume of the bolus were available. Literature shows that as bolus size increases, the pharyngeal transit time, laryngeal closure, and elevation increases [40, 41]. However, the included VFS-studies were performed in large craniofacial centers with experienced physicians and the VFS-studies were performed in a standardized setting. Bolus formation can best be imaged with ultrasound and the VFS-studies are ideally performed in a standardized setting and examined by an experienced radiologist.[22] To gain more insight in the pathogenesis of SD in CFM, all patients with SD should undergo a VFS-study because it permits visualization of bolus flow in relation to structural movement throughout the upper aerodigestive tract in real time. In this study, the severity of SD was not included as it was not the aim of the study. The main question is whether a child can swallow safely and successfully.

For clinicians, treatment of FD and SD should preferably be started early in life. Therefore, it is recommended to have all patients with CFM screened for SD by a speech and language therapist and to perform a VFS-study in patients with a type III Pruzansky-Kaban classification or with a high risk for SD after screening by a speech and language therapist. This study shows a trend between the severity of CFM and the outcome of VFS-studies: more severely affected patients show more difficulties with bolus formation and in the pharyngeal phase than less severely affected patients. Possibly, a combination of neuromuscular deficits and anatomical anomalies causes SD seen in patients with CFM.

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CHAPTER

9

The effect of cleft lip and palate in Craniofacial Microsomia on breathing, feeding and swallowing

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Abstract

Objective: To determine the influence of cleft lip/palate on breathing, feeding and swallowing in patients with craniofacial microsomia.

Design: a retrospective analysis of medical charts.

Setting: Tertiary centers.

Patients, Participants: all patients diagnosed with craniofacial microsomia at the craniofacial units of Erasmus University Hospital, Rotterdam, The Netherlands; Great Ormond Street Hospital, London, The United Kingdom; and Boston Children's Hospital, Boston, The United States.

Main outcome Measure: Patient characteristics, presence of cleft lip/palate and the severity of craniofacial microsomia were studied. In addition, presence, severity and treatment of obstructive sleep apnea, feeding difficulties and/or difficulties swallowing were noted. The results of patients with craniofacial microsomia and cleft lip/palate were compared to the results of patients with solely craniofacial microsomia.

Results: In total, of 755 patients diagnosed with craniofacial microsomia 120 patients had co-existing cleft lip/palate. In these 120 patients obstructive sleep apnea was present in 35.0%, feeding difficulties in 51.7% and swallowing difficulties in 28.3%. In patients with solely craniofacial microsomia this is 14.3%, 21.6%, and 10.7% respectively. Obstructive sleep apnea was treated both non-surgical and surgical. Feeding difficulties were treated by adjustment of the bottle/nipple or with placement of a nasogastric tube.

Conclusions: Patients with craniofacial microsomia and cleft lip/palate are significantly more often diagnosed and more severely affected with obstructive sleep apnea, feeding difficulties and swallowing difficulties than patients with craniofacial microsomia without cleft lip/palate. Therefore, treatment of first choice of functional difficulties in these patients is more often surgical than in patients with craniofacial microsomia without cleft lip/palate.

Introduction

With an incidence of 1:5600 live births, craniofacial microsomia (CFM) is regarded to be the second most common congenital anomaly of the head and neck following cleft lip and palate.[1] CFM is a clinical diagnosis with a widely heterogeneous phenotype and is the result of a developmental disorder of the first and second pharyngeal arches.[2] This primarily leads to asymmetrical underdevelopment of the skull base, the ear, orbit, maxilla, mandible, temporomandibular joint (TMJ), facial soft tissues and nerves (Vth and VIIth).[3-5] The most characterizing feature of CFM is mandibular hypoplasia which occurs in 89 to 100 percent of the patients with CFM.[6]

Other craniofacial anomalies may be seen in patients with CFM, including epibulbar dermoids, ear tags, macrostomia and cleft lip/palate (CL/P).[7] CL/P is diagnosed in 7 to 15.9% of the patients with CFM.[1, 7-9] Previous reports describe that side and severity of labiopalatal clefting correlate with the severity and predominant side of CFM, which suggests a causative link between CFM and CL/P.[9] When compared to patients with CL/P, patients with both CFM and CL/P have a different anatomic distribution of labial clefting. The left-to-right-to-bilateral ratio for labial clefting is 2:2:1 in patients with CFM and CL/P, whereas this distribution is 6:3:1 in patients without additional craniofacial anomalies. Moreover, patients with CFM are less likely to have isolated cleft palate than patients with non-syndromic CL/P.[9, 10]

Patients with CL/P are more likely than non-cleft patients to have sleep-disordered breathing (SDB). SDB encompasses a spectrum from primary snoring to obstructive sleep apnea (OSA).[11] Previous reports documented that 22 to 65% of the patients with CL/P have SDB.[12-14] However, some studies show an increase in symptoms of airway obstruction following CL/P repair, suggesting that surgery initiates SDB and OSA. In the literature, there is uncertainty as to whether OSA correlates with CL/P itself or is a complication after palatoplasty or pharyngeal flap.[13, 15]

The prevalence of feeding difficulties (FD) in patients with CL/P is increased compared to the general population. CL/P can lead to feeding and swallowing difficulties including insufficient suction, nasal regurgitation, choking and reduced airway protection and as a result, more chest infections and malnutrition.[16] Consequently, poor feeding and failure to thrive is frequently seen in this group of patients.[17]

It is known that patients with CFM are also at increased risk levels for OSA, feeding and swallowing difficulties, compared to the general population.[18-22] However, the exact relationship between CL/P in patients with CFM and its influence on breathing, feeding and swallowing difficulties is unclear and has not been described in previous literature.

Based on our clinical experience and our previous research reports regarding CFM it was hypothesized that patients with CFM and co-existing CL/P are more severely affected with functional difficulties and possibly are more prone to refractory functional difficulties. It is possibly important for clinicians to know if patients with CFM and co-existing CL/P should be seen and treated as a specific group of patients requiring more (specific) medical care.

Therefore, the aim of this study was to analyze the characteristics of patients with CFM and CL/P in a cohort of 755 patients with CFM diagnosed at three major craniofacial centers and to determine if functional problems in patients with CFM are negatively influenced by the presence of CL/P.

Materials and methods

Following IRB approval, this retrospective study was conducted in a population of patients diagnosed with CFM between January 1986 and January 2016 at the craniofacial units of Erasmus University Hospital, Rotterdam, The Netherlands (MEC-2013-575); Great Ormond Street Hospital in London, United Kingdom (14DS25); and Boston Children's Hospital in Boston, United States of America (X05-08-058).

Patients with clinical and/or radiographic images, i.e. panoramic X-rays and/or CT scans of the head, and medical history were included for further analyses. Patients with isolated microtia, i.e., without mandibular hypoplasia on radiologic images, and patients diagnosed with other craniofacial syndromes that include craniofacial hypoplasia (e.g., Treacher Collins syndrome) were excluded.

Following identification of all patients with CFM, a chart review was performed on information for age, sex, affected side, severity of the deformity according to the Pruzansky-Kaban classification, presence of CL/P and macrostomia, and presence of functional problems, (i.e., OSA, FD and swallowing dysfunction). When applicable, age at which these functional problems originally presented and type of feeding/breathing/swallowing difficulties were noted. When no information on functional problems was present, patients were categorized as not having one of these functional problems. Cleft lip/palate was categorized as cleft lip (CL), cleft lip and alveolus (CLA), cleft lip, alveolus and palate (CLAP) and cleft palate (CP).

CFM patients with CL/P suspected for OSA were reviewed further for OSA, age at which the patient first presented with OSA, treatment, and treatment outcome for OSA. The diagnosis of breathing difficulties resembling OSA was made by polysomnography (PSG), the presence of a tracheostomy, or other treatment for OSA without a preceding PSG. Patients with solely subjective snoring complaints were not observed as having OSA. The severity of OSA in those patients who underwent a PSG was determined using the obstructive apnea–hypopnea index (oAHI).[23] An oAHI score of 1-5 was defined as mild OSA, a score of 5-24 as moderate OSA and an oAHI of ≥ 25 as severe OSA.[23] Patients with a tracheostomy were classified as having severe OSA.

Medical charts of patients with CFM, CL/P and FD were reviewed for the type of FD, e.g., difficulties swallowing, difficulties suckling, chewing, restricted mouth opening, age at diagnosis, treatment of FD, timing of treatment and treatment outcome. Severity of FD was scored as 'mild', 'moderate' and 'severe' and was based on type of treatment.[21]

The criteria used to determine swallowing difficulties (SD) were; sucking and swallowing incoordination, weak suck, excessive gagging, recurrent coughing during feeds, recurrent pneumonia, nasopharyngeal reflux, desaturation during feeds, and (risk for) aspiration during feeds. When SD were diagnosed, charts of these patients were additionally reviewed for reports of performed videofluoroscopic swallow-studies (VFS-studies). All original reports of all VFS-studies were collected and information on the number of performed VFS-studies, indication, age at time of the first VFS-study, nutritional route at time of the VFS-study (i.e. via a nasogastric tube, fully orally or orally in combination with a nasogastric tube). When patients were fully fed via a nasogastric tube at time of the VFS-study, the VFS-study was nevertheless fully orally assessed. Furthermore, information on the outcome of VFS-studies regarding the oral and pharyngeal phases of swallowing was collected.

Evaluation of the oral phase included 'bolus formation' and 'premature spill into the pharynx'. 'Bolus formation' was tested with all four consistencies, whereas solely thin and thick liquids were used to evaluate 'premature spill into the pharynx'. Evaluation of the pharyngeal phase included 'delayed swallow trigger', 'post-swallow stasis', 'nasopharyngeal reflux', 'laryngeal penetration', and 'aspiration'. The pharyngeal phase was evaluated using pellets with different consistencies, i.e., thin liquids, thick liquids, puree, and solids. Incomplete reports or reports of VFS-studies performed following mandibular reconstruction were not included. All VFS-studies were performed in an upright position in a tumble forms feeder seat and lateral view was standard. For statistical analyses only the first VFS-study per patient was used. The same definitions as described by Van de Lande & Caron et al. were used for 'premature spill into the pharynx', 'laryngeal penetration' and 'aspiration'.[22]

Severity of mandibular hypoplasia was assessed on panoramic X-rays or on 3D CT scans. Assessment of mandibular hypoplasia in CFM is based on the classification of Pruzansky, modified by Kaban et al.[24, 25]. In this classification system, Type I mandibles are smaller in size with normal dimensions and position of the condyle and ramus. Type IIA mandibles are smaller in size with decreased overall dimensions, but with normal position of the condyle and ramus. Type IIB mandibles are smaller in size with decreased overall dimensions of the condyle and ramus, in addition the temporomandibular joint is malformed and displaced. In Type III mandibles, the ramus, condyle and TMJ are absent. The Pruzansky-Kaban classification was scored on both sides in patients with bilateral CFM, using the most severely affected side in our analyses.

When OPTs or 3D CT scans were not available, the diagnosis of CFM was assessed on clinical pictures with the help of the pictorial global, detailed and radiographic Phenotypic

Assessment Tool – Craniofacial Microsomia (PAT-CFM).[26] The PAT-CFM by Birgfeld is based on the OMENS-Plus classification and was used to classify the severity of CFM.

Statistical analysis

Statistical analyses were performed using Statistical Package for Social Sciences (SPSS) version 24 for Windows (2011, SPSS Inc., Chicago, IL, USA). Descriptive statistics were used to describe sex, laterality and diagnostic criteria. Equality of groups was tested with the Pearson χ^2 test. A *P*-value of < 0.05 was considered to be statistically significant.

Results

Characteristics of the population

In total, 955 patients were diagnosed with CFM in three participating craniofacial centers. Clinical pictures and/or radiographic images were available in 755 patients; these patients were included for further analyses. Of the 755 included patients, 120 patients (15.9%) were also diagnosed with CL/P. CL/P was more likely to occur in patients bilaterally affected with CFM (27.9%) than in patients unilaterally affected with CFM (14.3%)(Pearson $\chi^2(1) = 10{,}431$, p=0.001). The severity of mandibular hypoplasia and the presence of macrostomia did not significantly differ between the CL/P group and the non-CL/P group (p=0.098 and p=0.609, respectively). Table 1 shows the characteristics of the CFM patients with and without CL/P.

Table 1. Patient characteristics in craniofacial microsomia, with and without cleft lip/palate.

		CL/P (%) Yes	No	Total	P-value
Sex	**Male**	71 (17.4)	337 (82.6)	408 (100)	0.22
	Female	49 (14.1)	298 (85.9)	347 (100)	
Laterality of CFM	**Unilateral**	96 (14.3)	573 (85.7)	669 (100)	0.001*
	Bilateral	24 (27.9)	62 (72.1)	86 (100)	
Side when unilateral CFM	**Left**	42 (14.1)	256 (85.9)	298 (100)	0.31
	Right	54 (14.6)	317 (85.4)	371 (100)	
P-K classification	**I**	21 (0.15)	119 (85.0)	140 (100)	0.098
	IIa	17 (12.1)	124 (87.9)	141 (100)	
	IIb	24 (18.8)	104 (81.2)	128 (100)	
	III	28 (23.1)	93 (76.9)	121 (100)	
Macrostomia	**Yes**	29 (17.2)	140 (82.8)	169 (100)	0.609
	No	91 (15.6)	495 (84.4)	586 (100)	
Type of cleft	**CL**	8	N/A	8	
	CLA	2	N/A	2	
	CLAP	51	N/A	51	
	CP	59	N/A	59	
Presence of OSA	**Yes**	42 (31.2)	91 (68.4)	133 (100)	0.001*
	No	78 (12.5)	544 (87.5)	622 (100)	
Presence of FD	**Yes**	62 (31.2)	137 (68.8)	199 (100)	0.001*
	No	58 (10.4)	498 (89.6)	556 (100)	
Presence of VFS-study	**Yes**	13	29	42	
	No	107	606	713	

CL/P = cleft lip/palate; CFM = craniofacial microsomia; P-K classification = Pruzansky-Kaban classification; CL = cleft lip; CLA = cleft lip alveolus; CLAP = cleft lip alveolus palate; CP = cleft palate; N/A = not applicable; OSA = obstructive sleep apnea; FD = feeding difficulties; VFS-study = videofluoroscopic swallow study; *significant.

Obstructive sleep apnea

Out of 120 patients with CL/P, 42 patients (35%) were diagnosed with OSA, versus 91 patients (14.3%) of the patients without CL/P. OSA was in patients with CFM and CL/P, diagnosed at a median age of 16.7 months (range 0.0 – 25.5 years). Patients with CL/P were significantly more likely to develop OSA than patients without CL/P (Pearson X^2 = 39,591, $p < 0.001$, see Table 1). Furthermore, patients diagnosed with CL/P were more likely to develop severe OSA than patients without CL/P (Pearson's $\chi^2(1) = 26{,}647$, $p < 0.001$). Patients with cleft palate, i.e., CLAP and CP, were more likely to develop (more severe) OSA ($p < 0.001$, Pearson's $\chi^2(1) = 17{,}029$). Thirty-seven of the 42 patients diagnosed with OSA were diagnosed with CLAP or CP (Table 2).

Table 2. Severity of obstructive sleep apnea in craniofacial microsomia, with or without cleft lip/palate.

		Severity of OSA					
		Mild	**Moderate**	**Severe**	**Unknown severity**	**No OSA**	**Total**
Cleft type	**CL**	1 (12.5%)	1 (12.5%)	2 (25.0%)	0 (0.0%)	4 (50.0%)	8 (100%)
	CLA	0 (0.0%)	0 (0.0%)	1 (50.0%)	0 (0.0%)	1 (50.0%)	2 (100%)
	CLAP	1 (2.0%)	2 (3.9%)	8 (15.7%)	2 (3.9%)	38 (74.5%)	51 (100%)
	CP	5 (8.5%)	5 (8.5%)	9 (17.6%)	5 (8.5%)	35 (59.3%)	59 (100%)
	No cleft	18 (2.8%)	14 (2.2%)	28 (4.4%)	31 (4.9%)	544 (85.7%)	635 (100%)
	Total	25 (3.3%)	22 (2.9%)	48 (6.4%)	38 (5.0%)	622 (82.4%)	755 (100%)

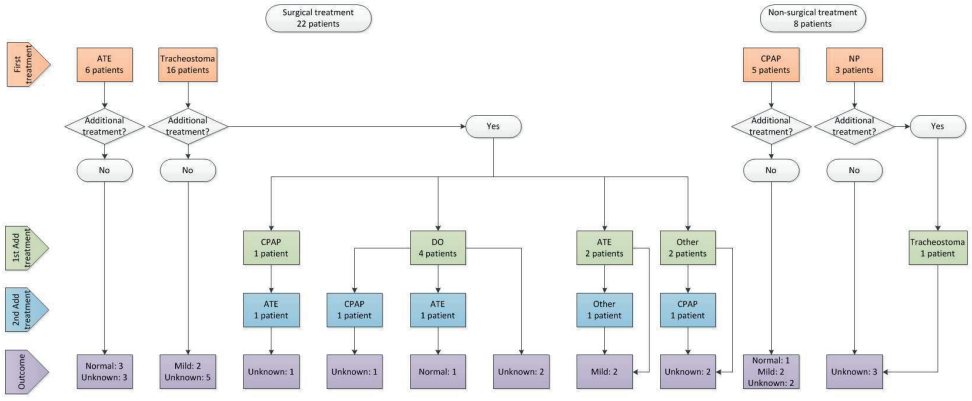
OSA = obstructive sleep apnea; CL = cleft lip; CLA = cleft lip alveolus; CLAP = cleft lip alveolus palate; CP = cleft palate.

CFM patients with CL/P were not significantly more often diagnosed with higher Pruzansky-Kaban IIB or III scores. In two patients OSA was diagnosed directly following primary cleft palate repair. In the other 35 patients OSA was diagnosed before cleft palate repair or more than several months following cleft palate repair.

Thirty patients were treated for OSA, both non-surgical and surgical. Non-surgical therapy consisted of placement of a nasopharyngeal airway (NPA) or continuous positive airway pressure (CPAP). Surgical therapy consisted of adenotonsillectomy (ATE) or placement of a tracheostomy. The initial treatment consisted of NPA (10.0%), CPAP (16.7%), ATE (20.0%), or tracheostomy (53.3%). Ten patients needed additional treatment, consisting of

mandibular distraction osteogenesis (MDO) (40.0%), ATE (20.0%), nasal septum correction (20.0%), CPAP (10%), or placement of a tracheostomy (10.0%). Figure 1 gives an overview of the initial treatment, additional treatment and outcome for OSA in patients with CFM and CL/P. The twelve patients not treated for OSA, were all diagnosed with mild OSA or the severity of OSA was unknown.

Figure 1. Treatment of obstructive sleep apnea in patients with Craniofacial Microsomia and cleft lip/palate.



ATE = adenotonsillectomy, CPAP = continuous positive airway pressure, NP = nasal prong, DO = mandibular distraction osteogenesis.

Feeding difficulties

Sixty-two (51.7%) of the 120 CFM patients with CL/P were diagnosed with FD at a median age of 0.62 months (range 0.0 – 14.2 years). In the group of 635 patients without CL/P this was 137 (21.6%). Difficulties swallowing was the most common feeding difficulty (n=34, 54.8%). Patients with CFM and CL/P were significantly more likely to have a feeding difficulty than the CFM patients without CL/P (Pearson's $\chi^2(2) = 47.824$, $p < 0.001$) (Table 1). Furthermore, CFM patients with CL/P were more severely affected with FD than CFM patients without CL/P (Pearson's χ^2 (3) = 17.462; $p < 0.001$). In the CL/P group with FD, 38 patients suffered from severe feeding difficulties (62.0%). This was a significantly higher percentage than in the non-CL/P group, in which 44 patients (32.1%) suffered from severe feeding difficulties (Pearson's $\chi^2(1) = 49{,}769$, $p < 0.001$). Of the patients with CFM and CL/P who were severely affected with FD, 97.4% had a cleft palate, i.e. CLAP or CP (Table 3).

Table 3. Severity of feeding difficulties in patients with craniofacial microsomia with and without cleft lip/palate.

	Feeding difficulties (%)				
Cleft type	**No**	**Mild**	**Moderate**	**Severe**	**Total**
- **CL**	6 (75)	2 (25)	0	0	8
- **CLA**	0	1 (50)	0	1 (50)	2
- **CLAP**	25 (49)	6 (11.8)	5 (9.8)	15 (29.4)	51
- **CP**	27 (45.8)	7 (11.8)	3 (5.1)	22 (37.3)	59
- **No cleft**	498 (78.4)	76 (12.0)	17 (2.7)	44 (6.9)	635
Total	556	92	25	82	755

CL = cleft lip; CLA = cleft lip alveolus; CLAP = cleft lip alveolus palate; CP = cleft palate.

Out of 38 CL/P patients with severe feeding difficulties, 36 patients received nasopharyngeal or percutaneous tube feeding, and 2 patients received parenteral feeding. In the non-CL/P group, 44 patients were solely fed via tube or parenteral feedings. Twenty-nine patients received nasopharyngeal or percutaneous tube feeding, four patients received parental feeding and 11 patients underwent a gastrostomy.

For severe FD, the duration of tube feeding was significantly longer in the patient group with CL/P than in the group without CL/P. These patients were tube fed for a median duration of 19.5 months (range 0.1 months – 18.1 years) and 7.1 months (range 2 days – 12.9 years), respectively. For moderate FD no significant difference was found. The median duration of tube feeding in the CL/P group was 13.1 months (range 4.1 months – 6.5 years), whereas in the non-CL/P group this was 11.7 months (range 1.1 months – 16.4 years).

Difficulties swallowing

Of the 34 patients with swallowing difficulties (28.3%), 19 patients with CFM and CL/P underwent a VFS-study (55.9%). Of the patients without CL/P, 68 patients (10.7%) were diagnosed with swallowing difficulties, of which 42,6% underwent a VFS-study. The VFS-studies of six patients were excluded as the reports were incomplete. Three of the remaining 13 patients underwent a VFS-study before the age of six months. In none of these three patients, palate repair had taken place before the VFS-study. CL/P was repaired in seven patients and unrepaired in three. In another three patients, the status of CL/P repair remained unknown. At time of the VFS-study, four patients were fully orally fed,

three patients were nasogastric tube dependent, and six patients were fed both orally and via a nasogastric tube (NG-tube).[22]

The oral phase was tested in all 13 patients with CFM and CL/P. 'Bolus formation' was evaluated in all 13 patients, whereas 'premature spill into the pharynx' was evaluated in 12 patients. Appropriate bolus formation was mostly seen with the use of puree in patients with and without CL/P in 60.0 and 78.9%, respectively. Patients with CL/P had more difficulties forming an appropriate bolus when using thick liquids or solids. For patients without CL/P, this was seen with the use of thin or thick liquids. For both, patients with and without CL/P, 'premature spill into the pharynx' was mostly seen with the use of thin liquids. Of the CFM patients with CL/P, 46.2% was diagnosed with 'inappropriate bolus formation', and 50.0% with 'premature spill into the pharynx'. Both, 'inappropriate bolus formation' and 'premature spill into the pharynx' were not significantly more often diagnosed in patients with CL/P than in patients without CL/P (Pearson χ^2 (1) = 0.431, p= 0.511, and Pearson χ^2 (1) = 1.505, p=0.220 respectively) (Table 4).

Table 4. Results of the oral phase in patients with craniofacial microsomia, with and without cleft lip/palate.

	Bolus Formation		**Premature spill into the pharynx**	
	Appropriate	**Inappropriate**	**No**	**Yes**
CL/P				
- **Yes**	7	6	6	6
- **No***	12	16	17	6
Total	19	22	23	12

CL/P = cleft lip/palate. *The oral phase was not in all 29 patients with craniofacial microsomia without cleft lip/palate tested.

The pharyngeal phase was also tested in all 13 patients with CFM and CL/P. Overall, and regardless of the consistency used, 10 patients CFM and CL/P (76.9%) were diagnosed with an 'abnormal swallow trigger'. Patients with CL/P were not significantly more often diagnosed with 'abnormal swallow trigger' than patients without CL/P (Pearson (1) = 2.973, p=0.085) (Table 5). However, depending on the consistency used (i.e., thin or thick liquids), patients with CFM and CL/P had a delayed swallow trigger in 50.0 – 66.7%, and patients with CFM without CL/P in 10.0 to 33.3%.

Table 5. Results of the pharyngeal phase in patients with craniofacial microsomia, with and without cleft lip/palate.

	Swallow trigger		Post-swallow stasis		Nasopharyngeal reflux		Laryngeal penetration		Aspiration	
	Timely	**Abnormal**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**
CL/P										
- **Yes**	3	10	5	7	7	6	8	5	9	4
- **No**	14	13	14	11	18	10	19	8	19	10
Total	17	23	19	18	25	16	27	13	28	14

CL/P = cleft lip/palate.

Post-swallow stasis was evaluated in 12 patients and diagnosed in 58.3% of the patients with CL/P. Post-swallow stasis was not more often seen in patients with CL/P than in patients without CL/P (Pearson χ^2 (1)=0.667, p=0.414) (Table 5). However, when thin liquids or solids were used, more patients with CL/P were diagnosed with post-swallow stasis than patients without CL/P.

Nasopharyngeal reflux was diagnosed in six out of 13 (46.2%) patients with CFM and CL/P. Nasopharyngeal reflux was also not more frequently diagnosed in patients with CL/P than in patients without CL/P (Pearson χ^2 (1)=0.407, p=0.524) (Table 5). The highest incidence of nasopharyngeal reflux was seen with the use of thin and thick liquids, 33.3% in patients with CL/P and 40.0% in patients without CL/P.

Laryngeal penetration was seen in five of the 13 (38.5%) tested patients and not more frequently diagnosed in patients with CL/P than in patients without CL/P (Pearson χ^2 (1)=0.312, p=0.576) (Table 5). The highest incidence of laryngeal penetration was also seen with the use of thin and thick liquids; 28.6% in patients with CL/P and 35.3% in patients without CL/P. Laryngeal penetration did not occur when solids were used as pellets.

Like the other variables, aspiration was not significantly more often seen in patients with CL/P (30.8%) than without CL/P (34.5%) (Pearson χ^2 (1)=0.056, p=0.813) (Table 5). In the group of patients with CL/P aspiration was mostly seen when thick liquids (50.0%) were used, compared to 9.1% when puree was used.

Bilateral CL/P

Fourteen patients had bilateral CL/P, of which 9 patients (64%) had a Pruzansky-Kaban type IIb or type III mandible. Out of 14 patients with bilateral CL/P, 5 patients (36%) had OSA, of which three patients had severe OSA. Feeding difficulties were diagnosed in seven patients (50%) with bilateral CL/P; three patients had severe feeding difficulties. Swallowing difficulties were reported in three patients.

Discussion

In our study population, 15.9% of patients with CFM were also diagnosed with CL/P. This study showed that patients with CFM and CL/P are at higher risk for developing (severe) OSA and feeding difficulties than CFM patients without CL/P. It is known that patients with CFM are more at risk for developing OSA than the healthy population.[18, 19] CL/P has especially been associated with OSA following palatoplasty or in patients with Robin sequence.[27, 28] According to the current study, the prevalence of OSA in patients with both CFM and CL/P is significantly higher than in CFM patients without CL/P (35.0% vs. 14.3%). Palate repair did not play a relevant role in the risk for developing OSA in the study population. Furthermore, CFM patients with CL/P have more severe OSA than CFM patients without CL/P. The exact underlying mechanism for developing OSA more often and more severely in CFM patients with CL/P cannot be explained by a more severe phenotype.

CFM patients with CL/P were not significantly more often diagnosed with a Pruzansky IIB/III mandible than CFM patients without CL/P, which was also confirmed by one of our previous studies.[7] Especially patients with cleft palate are more at risk for developing (severe) OSA. Possibly, there is a difference in the anatomy of the oral cavity leading to a narrower airway. For clinicians it is important to be aware of the additional risks for OSA in patients with both CFM and CL/P. Screening for OSA at a young age is recommended and should not only be performed when palatal repair is considered.

Interestingly, concerning the treatment for breathing difficulties a tracheostomy was placed in 53.3% of the patients with CFM and CL/P, compared to 22.2% in CFM patients without CL/P, whereas in patients with CFM without CL/P, ATE was the treatment of first choice (58.3%) while only 20.0% of the CFM patients with CL/P underwent ATE. The initial presentation might prelude further treatment and for example children with a tracheostomy will not get an ATE in addition to the tracheostomy.

Clinicians play an important role in informing patients and their parents/caregivers on differences in treatment, and treatment duration. Placement of a tracheostomy has greater implications for patients and their parents/caregivers than performing an ATE, not only physically, but also psychosocially.

FD in CFM patients and in non-syndromic CL/P have been described in the literature. It is known that CL/P contributes to the development of feeding difficulties during the early years of life.[20, 21, 29, 30] However, information on FD in the CFM population with CL/P is scarce. The present study also showed that CFM patients diagnosed with CL/P are at higher risk for developing FD and it seems that the anomalies seen in CFM and CL/P are compounding

factors regarding FD. Reasons for the increased FD might be the limited active cheek and lip movement, restriction in jaw excursion (as a result of underdevelopment of the facial musculature and facial nerve due to CFM), and difficulties generating negative pressure or ineffective posterior transfer of the bolus (as a result of CL/P).[31]

Patients with bilateral CL/P were not significantly more diagnosed with (severe) feeding difficulties than patients with unilateral CL/P. These results should lead to more awareness among clinicians and especially among speech- and language therapists. Patients with both CFM and CL/P and their parents/caregivers might need more support with regards to feeding. In addition, tube feeding can have psychosocial consequences, which should also be taken into account as patients with both CFM and CL/P require tube feedings for a longer period of time.

In our cohort of patients with CFM and CL/P, 54.8% of the patients were diagnosed with a swallowing disorder, necessitating a VFS-study in 55.9% of these patients. Previously, in CFM patients without CL/P swallowing difficulties were diagnosed in 13.5%.[22] The VFS-studies included for further analyses showed difficulties swallowing in both the oral and pharyngeal phase. These difficulties were not significantly more often diagnosed in CFM patients with CL/P than in CFM without CL/P. It should be noted that CL/P was not repaired in all patients at time of the VFS-study. Although not statistically significant, when looking more closely into different food consistencies used in these VFS-studies, a few differences were notable. Especially the use of thin and thick liquids caused most swallowing difficulties in patients with CFM and CL/P.

Limitations

Due to the retrospective nature of this study not all medical charts mentioned complaints suggesting functional difficulties. This could be the result of a lack of awareness of the risk for OSA, FD and SD in patients with CFM and CL/P. Consequently, this may have led to an underestimate of the number of patients with functional difficulties. However, most parents are aware of feeding and sleeping habits of their children and will report any difficulties, so it was assumed when nothing was documented that no functional difficulties existed.

Furthermore, there was little documentation regarding functional difficulties following cleft palate repair. This limits us in drawing conclusions about the effects of cleft palate repair. However, the majority of the invasive treatments for functional difficulties given in CFM patients with CL/P started before CL/P repair. In other words, information about the effect of cleft palate repair would not have changed our conclusion about the functional difficulties in patients with CFM and CL/P.

In addition, the conclusions regarding the results of the VFS-studies are based on a limited number of patients and hard conclusions cannot be drawn. However, the results do indicate that clinicians should be aware of swallowing difficulties and should consider performing VFS-studies in these patients.

Conclusion

Patients with CFM and CL/P are at higher risk of developing OSA and feeding difficulties than patients with CFM without CL/P. The importance of early diagnosis of these functional problems is shown in the different types of initial treatment and duration of treatment. We recommend that clinicians be aware of the additional risks for patients with CFM and CL/P.

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CHAPTER

10

General discussion and future perspectives

The aim of this thesis was to study two essential functional problems in patients with craniofacial microsomia (CFM), obstructive sleep apnea and feeding difficulties. We hypothesized that *1)* patients with CFM were more at risk for developing obstructive sleep apnea as a result of mandibular hypoplasia, and *2)* that these patients were more at risk for feeding difficulties as a result of underdevelopment of the facial structures, or as a result of obstructive sleep apnea. Functional difficulties in CFM were first assessed in two systematic reviews.

The systematic reviews that were performed showed that not much was known regarding obstructive sleep apnea and feeding difficulties in CFM. The number of patients in the reviewed studies were–small and risk factors for developing OSA and FD were hardly described. Therefore, datasets of three craniofacial centers were combined leading to a database of 755 patients with CFM, which made it possible to retrospectively study the general population, its phenotype and specific patient groups. In addition, obstructive sleep apnea, feeding and swallowing difficulties in CFM could be analyzed, including their risk factors. A cross-sectional study was performed to identify the level of obstruction in patients with obstructive sleep apnea using CT-scans obtained from all three craniofacial centers.

In the general discussion of this thesis, the main findings of the studies described in the previous chapters will be discussed against the background of the literature, followed by clinical recommendations and future perspectives.

Our study population

The basic characteristics of our study population, e.g. male-female ratio, laterality, and distribution of Pruzansky-Kaban type I, IIA, IIB and III, were in line with previous literature (chapter 2).[1-7] Principal component analysis showed that it was not possible to identify specific groups of patients within the whole range of heterogeneous CFM patients and it became clear that the term 'Goldenhar syndrome' should be abandoned. 'Goldenhar syndrome' is often applied to patients with mandibular hypoplasia, epibulbar dermoid and vertebral/spine anomalies; it is regarded by some as a variant and is estimated to represent 10% of the patients with CFM.[2] In our study this triad was present in only 3.8% of the patients and there was a weak positive correlation among the three variables. Analysis of statistical correlations in other studies also failed to substantiate 'Goldenhar syndrome' as a distinct entity (chapter 2). [4, 8]

CFM seems to be a gradual spectrum of anomalies, in which structures of the first pharyngeal arch are correlated to other structures derived from the first pharyngeal arch.

The first pharyngeal arch gives rise to the mandible, maxilla, zygoma, trigeminal nerve, muscles of mastication, the inner ear and part of the external ear. In addition, structures of the second pharyngeal arch are correlated to other structures derived from the second pharyngeal arch, i.e. the facial nerve, stapes, styloid process, portions of the hyoid bone, facial musculature, and majority of the external ear. This was also suggested by Tuin et al. (chapter 2).[8]

Although no specific groups could be identified, it was found that bilaterally affected patients were more severely affected than unilaterally affected patients and it is therefore advised to approach patients with bilateral CFM more comprehensively (chapter 2).[1]

Extracraniofacial anomalies, i.e. vertebral, cardiac and renal anomalies, were found in 35% of all patients with CFM, which is considerably higher than the incidence of up to 2% in a non-affected population.[9-11] In addition, extracraniofacial anomalies were significantly more often seen in patients with bilateral CFM than in patients with unilateral CFM (chapter 2). A study specifically looking into extracraniofacial anomalies in CFM by Renkema et al.[12] found a prevalence of 46% extracraniofacial anomalies in CFM. This study looked into all body tracts, and not only at vertebral, cardiac and renal anomalies, which might explain the higher prevalence of extracraniofacial anomalies. Extracraniofacial anomalies were seen in the vertebrae (28%), central nervous system (11%), the circulatory tract (21%), the gastro-intestinal tract (9%), and the urogenital tract (11%). Anomalies of the respiratory tract were scarce with a prevalence of 3%. Overall, the findings of chapter 2 should raise awareness among caregivers to screen for extracraniofacial anomalies and difficulties next to craniofacial anomalies in patients with CFM. Patients bilaterally affected with CFM should be screened by a paediatrician or geneticist for extracraniofacial anomalies, even those presenting with a mild phenotype.[1]

The exact etiology of CFM is still unknown, yet it is thought that CFM is caused by an alteration in the development of the first and second pharyngeal arches during the first six weeks of development.[13-15] During these first six weeks, neural crest cells migrate into the first and second pharyngeal arches, which leads to the formation of ectomesenchyme. Ectomesenchyme is necessary for the formation of facial structures. A defect in the generation or migration of neural crest cells has been suggested to be the origin of deformities found in CFM.[16-18] Additionally, abnormal migration of neural crest cells has also been found to form the basis of anomalies or defects of the vertebrae, central nervous system, cardiovascular tract and urogenital tract.[19-21] The knowledge of extracranial anomalies in CFM could possibly contribute to better understanding of the etiology. The higher number of CFM patients with extracraniofacial anomalies might be explained by a defect in the migration of neural crest cells. A recent study by Zhang et al.[22] addressed this theory and identified, via a genome wide association study, eleven

genes correlated with the pathogenesis of CFM. The candidate genes found by Zhang et al.[22] all played a role in the development of facial structures and all participated in neural crest cell formation, migration and differentiation.[22] Future research should focus on the genetic basis for CFM by additional genome wide association studies, but also by whole-genome sequencing. Better understanding of the etiopathogenesis could lead to early detection and treatment.

Obstructive sleep apnea

A systematic review of the literature revealed a prevalence of 7 to 67% of OSA in patients with CFM (chapter 3).[23] Despite the large spread in prevalence, which can most likely be explained by selection bias, differences in sample size and the prevalence of OSA in CFM is higher than in the general population which is 2.2 – 3.8%.[24-28] The outcome of our systematic review was mainly based on studies with small patient numbers and on questionnaires such as the pediatric sleep questionnaire. A small proportion of the patients with CFM underwent a polysomnography in these studies, however, the selected cases for analyses might not have been representative for the entire population of patients with CFM and may have caused a selection bias. Although the diagnosis or severity of CFM in these studies was mainly based on clinical photographs or documentation in medical charts, mandibular hypoplasia was suggested as a possible cause for OSA in patients with CFM (chapter 3).[29-34]

Treatment of OSA in CFM was described in several studies, both non-surgical and surgical.[33-39] Non-surgical treatment options such as a nasopharyngeal tube, use of an orthopaedic myofunctional application or continuous positive airway pressure (CPAP) were mentioned by a few.[38, 40-42] Described surgical treatment options were adenotonsillectomy (ATE), mandibular distraction osteogenesis (MDO), or placement of a tracheostomy tube.[33-37, 39] Regarding the effect of MDO as a treatment option for OSA, Burstein et al. showed that all patients responded well to MDO based on post-operative PSG outcomes, whereas in the study by Cohen et al. clinical signs and symptoms improved, however no post-operative PSG results were given (chapter 3).[35, 36] Unfortunately, it remained unclear which patients benefitted the most from which treatment. Furthermore, due to lack of patient information and follow-up it remained unclear which patients were prone to refractory obstructive sleep apnea. Therefore, based on the results of this systematic review it was not really possible to come to a treatment algorithm for OSA in patients with CFM.

In our cohort of 755 patients with CFM, OSA was diagnosed in 17.6% of the patients. The prevalence of OSA was based on three different criteria; (1) results of a polysomnography, (2) treatment for OSA by ATE, without a polysomnography, and (3) the severity of breathing

problems necessitating a tracheostomy tube (chapter 4). Using these criteria there was a risk of over- or underestimating the number of patients diagnosed with OSA. Due to the fact that in our studies a large number of patients were included, we feel that our study seems to be more representative than the reports of small series of patients reported in previous literature.[43]

Combining the data of three craniofacial centers made it also possible to identify groups at risk for developing OSA. Especially bilaterally affected patients and/or patients with Pruzansky-Kaban IIB or III mandibles were significantly more at risk for developing OSA than patients unilaterally affected and/or with I or IIA mandibles (chapter 4).[43] It was hypothesized that airway obstruction in CFM mainly resulted from airway collapse at the level of the mandible, i.e. at the level of the base of the tongue. To test this hypothesis all CT-scans of CFM patients with and without OSA were converted into 3D-models, which made it possible to measure volumes of the oro- and nasopharynx and to study the morphologic features of the oropharynx (chapter 5). The airway of patients with CFM was significantly smaller on key parameters than the airway of the control population, i.e. oropharynx volume, minimal cross-sectional area and retropalatal area. Among patients with CFM, with and without OSA, significant differences were found on minimal retroglossal area, sphericity and uniformity. These results suggest that OSA in CFM is caused by an obstruction at the level behind the base of the tongue in which (the degree) of mandibular hypoplasia might play an essential role. Furthermore, what also distinguishes patients with CFM and OSA from those without OSA is the difference in sphericity and uniformity of the airway. Most likely this is the result from the previously mentioned obstruction behind the base of the tongue. Unfortunately, our study was not designed to study or support this hypothesis.[44] To investigate this a sleep endoscopy might be helpful. With a sleep endoscopy it is possible to evaluate the upper airway in the supine position during a sleep-like state. [45-47] In addition, a sleep endoscopy can identify various levels of upper airway obstruction, which might be useful in patients with craniofacial anomalies in whom OSA is often a result of multi-level obstruction.[48, 49] The severity of obstruction might be determined by the Sleep Endoscopy Rating Scale (SERS) proposed by Lam et al.[50], especially because it has been demonstrated that there is a significant correlation between the SERS and the severity of OSA.

The findings of the study described in chapter 5, might also be of importance for future treatment protocols. As previously mentioned, treatment of OSA in patients with CFM has not been extensively described in previous literature. In our study cohort, several treatment options were discussed, both non-surgical and surgical. The retrospective nature of our study did not allow us proposing a treatment protocol. However, our retrospective study can be a start and could provide a guideline for clinicians treating patients with CFM and OSA.

The results of our retrospective study showed that patients with less severe mandibular hypoplasia, i.e. Pruzansky-Kaban classification I and IIa, were less often and less severely affected with OSA (chapter 4). When OSA is diagnosed in young patients, initially non-surgical treatment options will be considered, e.g. prone positioning, nasal pharyngeal airway, oxygen, continuous positive airway pressure (CPAP). The use of CPAP has extensively been described in previous literature, and in our cohort 13 percent of patients with OSA was treated with CPAP. To our opinion, CPAP is a good treatment option and can be used when awaiting surgery.[51]

Possibly, patients with Pruzansky-Kaban classification I and IIa, outgrow their breathing difficulties as they get older and therapy can be stopped.[52] OSA can also become evident in older children if adenotonsillar hypertrophy becomes obvious. Adenotonsillectomy (ATE) at this age is the surgical therapy of first choice.

Patients with more severe mandibular hypoplasia, i.e. Pruzansky-Kaban IIb or III, or bilaterally affected with CFM, are often more severely affected with OSA (chapter 4). In these patients non-surgical treatment can relief symptoms. However, OSA will not resolve over time or in case of severe OSA surgical treatment is indicated depending on the age of the child. In young infants with severe OSA placement of a tracheostomy may be needed. In older children MDO at the age of 2-3 years has to be considered. These patients are not likely to outgrow their breathing difficulties.

Overall, based on the findings in our study it is our thought that patients with CFM and severe OSA might benefit from a combination of therapies. It is important to diagnose the level(s) of obstruction in order to tailor appropriately and on an individual level non-surgical and surgical therapy.[47, 53]

Feeding difficulties

As with OSA, a systematic review regarding feeding difficulties (FD) in CFM was performed.[54] The results of this review showed that feeding difficulties were described in 42-83% of the patients with CFM and were mostly the result of oral impairment or orofacial deformities (chapter 6).[55-57] Difficulties with swallowing, with chewing and choking were the most frequently described types of feeding difficulties.[58-60] According to Cohen et al. decreased muscle tone could possibly play a role in these feeding difficulties as well, whereas Strömland et al. also raised awareness for feeding difficulties as a result of other symptoms affecting the general condition of the patient, i.e. extracraniofacial anomalies.[55, 57] However, limited data on the studied population was available and results were based on small sample sizes. Discussed treatment options were placement of a nasogastric tube

and cleft lip/palate repair in case of a co-existing cleft. Unfortunately, the indication for treatment, treatment outcome and follow-up were not described in any of the studies (chapter 6).[40, 58-61]

When looking into feeding difficulties in our cohort of 755 patients, we found that 26.4% of all patients were diagnosed with feeding difficulties (chapter 7).[62] The most often encountered feeding difficulties in this group were related to oral motor dysfunction, e.g. difficulties swallowing, suckling, chewing, and restricted mouth opening. Most patients were diagnosed with feeding difficulties before the age of 1 year and a significant number of patients with severe FD needed tube feeding (53.8%).

In total, 51.3% of the patients with feeding difficulties had difficulties with swallowing. Additional videofluoroscopic-studies (VFS-studies) showed nasopharyngeal reflux and inappropriate bolus formation as important features (chapter 8).[63] Nasopharyngeal reflux might be explained by velopharyngeal insufficiency or neurological disorders in these patients. Previous studies have looked into problems of the central nervous system and/or developmental disorders, e.g. neuropsychomotor delay, in patients with CFM. A systematic review by Renkema et al. combined these studies and found a prevalence for anomalies of the central nervous system and neuropsychomotor delay of 2 – 69% and 17 – 73%, respectively.[64] The wide range of these prevalence rates might be explained by the small number of patients included in some of these studies. The exact correlation between CFM and CNS problems or neuropsychomotor delay has not been clarified thus far, and although the prevalences show a wide spread, it seems to be a significant problem in patients with CFM leading to several other functional difficulties, including feeding difficulties.

Inappropriate bolus formation was mostly seen in patients with more severe mandibular hypoplasia (chapter 8), a group of patients with a less developed oropharyngeal apparatus, i.e. hypoplasia of masticatory and pharyngeal muscles. Neuropsychomotor delay could play a role in these patients as well.[55, 64]

Aspiration was seen in 35.4% of the patients who underwent a VFS-study (chapter 8). Inappropriate bolus formation due to orofacial anomalies and/or chewing difficulties might play a role in this higher risk for aspiration. Unfortunately, it remains unclear to what extent problems of the central nervous system and/or psychomotor delay play a role in the risk for aspiration.

Several risk factors for developing feeding difficulties were identified, i.e. bilateral CFM, presence of a Pruzansky-Kaban type III mandible, obstructive sleep apnea, presence of cleft lip/palate, and presence of extracraniofacial anomalies such as in the gastro-intestinal

system (chapter 7). Bilaterally affected patients and patients with more severe mandibular hypoplasia show more underdevelopment of the facial structures, e.g. facial musculature and pharyngeal musculature, and might therefore have higher risk of feeding difficulties. Based on our systematic review and our retrospective study it can be concluded that the cause of feeding difficulties in patients with CFM seems to be multifactorial (chapters 6 and 7). It is likely that a combination of orofacial malformations, presence of extracraniofacial anomalies, presence of OSA, and problems of the central nervous system all lead to feeding difficulties in patients with CFM. To what extent and in what way these factors play a role is yet to be studied.

Treatment of feeding difficulties in our cohort consisted of anti-reflux medication, adjustment of feeding bottles and nipples, and placement of a nasogastric tube (chapter 7). In total, 53.8% of the patients with feeding difficulties necessitated tube feeding for a median duration 1.3 years. The role of the nutritionist, speech and language therapist and the pediatrician is hardly described in any research, but should not be underestimated. Pediatricians have to counsel and screen for symptoms affecting the general condition of patients, i.e. heart defects, breathing difficulties, gastro-intestinal problems and developmental behavior. Speech and language therapy have to play an essential role in screening for feeding difficulties, in some countries this is done by a feeding specialist or dietician. In case of feeding difficulties speech and language therapy have to be the first step to improve oral-motor behavior and swallowing difficulties. When patients need tube feeding, a speech and language therapist has to be involved as well for the follow-up of oral-motor behavior and detection of early swallowing difficulties. Close cooperation between the pediatrician and speech and language therapist is at any time required for the treatment of feeding difficulties in patients with CFM.

Cleft lip / palate in craniofacial microsomia

As hypothesized, patients with both CFM and cleft lip / palate (CL/P) were significantly more often and more severely affected with OSA and FD than patients without CL/P (chapter 9).

In contrary to what was expected, severity of mandibular hypoplasia and palatal closure did not seem to play a role in the risk for developing OSA in these patients, and it was thought that the combination of anatomical deformities might lead to a narrower airway. However, at what level and to what extent remained unclear.

When looking into feeding difficulties, it was thought that the anomalies seen in CL/P added up to the anatomical deformities seen in CFM. For example, patients with CFM show

limited active lip and cheek movement during feeding, in combination with CL/P this will lead to more difficulties generating negative pressure which will result in problems with breast and bottle feedings.[65] In our analysis the VFS-studies showed that both the oral and pharyngeal phase were affected, however the numbers of patients were too small to draw conclusions. Most importantly, clinicians should be aware of the additional risks of patients with both CFM and CL/P. According to our studies, these patients should be seen as a different subgroup (chapter 9).

Future perspectives and recommendations

CFM can be characterized by a spectrum of craniofacial and extracraniofacial anomalies with a high prevalence of breathing and feeding difficulties. The hypothesis is that CFM is a result of a disturbance in neural crest cell migration, but the exact etiopathogenesis of CFM has to be further elucidated. This should preferably be done by genome wide association studies and whole-genome sequencing, which is currently being carried out in one of the craniofacial centers (Great Ormond Street Hospital, University College London, London).

Future studies have to look more closely into anomalies of the central nervous system as it was hypothesized that the consequences of these anomalies on sleep apnea, feeding difficulties and swallowing difficulties might be underestimated.

It can be recommended that collaboration with other craniofacial centers has to be expanded in order to build a larger database of patients and to be able to answer research questions and to share and improve clinical care.

Prospective studies will be needed to describe functional difficulties, such as breathing, feeding, swallowing, and speech, in more detail and to come to a uniform treatment protocol. Both, short-term and long-term follow-up studies are needed to evaluate these protocols and to improve care.

In conclusion

According to this thesis, CFM is a gradual spectrum of anomalies in which no specific groups could be identified and the term 'Goldenhar syndrome' should be abandoned.

This thesis also underlines that there should be more awareness by clinicians for functional difficulties, such as breathing and feeding difficulties, in patients with CFM. In addition,

a multidisciplinary approach is essential for screening, monitoring and treating these patients.

Due to the high prevalence of breathing disorders all patients with CFM should be screened for OSA. Patients with Pruzansky-Kaban IIb or III mandibles and/or bilaterally affected should undergo a polysomnography.

Various treatment options are available for OSA and depending on the age of the child and the severity of OSA, non-surgical and surgical treatment options should be considered. To come to optimal treatment it is necessary to have knowledge of the level of obstruction. Sleep studies performed in a standardized way could be the solution for diagnosing the level(s) of upper airway obstruction in patients with CFM and OSA.

Furthermore, it can be recommended that all patients with CFM have to be screened for feeding difficulties preferably by a speech and language therapist. On indication, i.e. patients with Pruzansky-Kaban III mandibles or patients with a high risk for swallowing difficulties according to the speech and language therapist, a VFS-study should be performed. When diagnosed, it is also the speech and language therapist who plays an essential role in the first steps of treatment. Due to the possible multifactorial nature of feeding difficulties in patients with CFM, there should be a close cooperation between the speech and language therapist and the paediatrician.

Patients with both CFM and CL/P are more severely affected with functional difficulties and have to be seen as a different subgroup. These patients possibly require more attention and specialized care by a multidisciplinary team than patients solely diagnosed with CFM.

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Summary

Chapter 1 provides the reader with a general introduction into craniofacial microsomia, the second most common congenital craniofacial anomaly following cleft lip/palate and provides the aims and outline of this thesis. Craniofacial microsomia is characterized by underdevelopment of the facial structures, i.e., the orbit, mandible, ears, facial nerves and soft tissues. Next to aesthetic difficulties, patients with craniofacial microsomia are also at risk for developing functional difficulties such as obstructive sleep apnea and feeding difficulties. To study these functional difficulties in a large cohort of patients a collaboration between three major craniofacial centers was initiated. The participating hospitals included Erasmus University Hospital, Rotterdam, The Netherlands; Great Ormond Street Hospital, London, The United Kingdom; and Boston Children's Hospital, Boston, Massachusetts, The United States of America.

Chapter 2 describes the characteristics of patients diagnosed with craniofacial microsomia in these three craniofacial centers. It was found that craniofacial microsomia is a gradual spectrum of anomalies in which bilaterally affected patients tend to be at the severe end of the spectrum. Phenotypically no specific groups of patients could be identified and the term 'Goldenhar syndrome' should be abandoned. Furthermore, structures derived from the first pharyngeal arch correlated in severity to other structures derived from the first pharyngeal arch, whereas structures derived from the second pharyngeal arch were correlated in severity to other structures derived from the second pharyngeal arch. Furthermore, extracraniofacial anomalies were positively, not strongly, correlated with craniofacial microsomia.

In **chapter 3** the results of a literature study on the prevalence and treatment of obstructive sleep apnea in craniofacial microsomia were described. According to the literature, obstructive sleep apnea is diagnosed in 7 – 67% of the patients and treatment consisted of both non-surgical and surgical treatment options. As non-surgical treatment options prone positioning and continuous positive airway pressure (CPAP) were mentioned. Surgical treatment mostly consisted of adenotonsillectomy, mandibular distraction osteogenesis, or placement of a tracheostomy tube. Some authors advocated treatment with CPAP, whereas others showed positive results with mandibular distraction osteogenesis. Unfortunately, patient characteristics and the severity of obstructive sleep apnea were only scarcely discussed in these articles. In addition, treatment outcome and follow-up were also rarely described and therefore no hard conclusions could be drawn.

The retrospective study to the prevalence and treatment of obstructive sleep apnea in our cohort of 755 patients was described in **chapter 4.** In total, 17,6% of the patients was diagnosed with obstructive sleep apnea. This prevalence was based on *(1)* results of a polysomnography, *(2)* treatment for OSA without a preceding polysomnography, and *(3)* the severity of breathing problems necessitating placement of a tracheostomy tube.

Patients with bilateral craniofacial microsomia or more severe mandibular hypoplasia were more likely to develop obstructive sleep apnea than unilaterally affected patients and/or patients with less severe mandibular hypoplasia. In addition, these patients were also more severely affected with obstructive sleep apnea than unilaterally affected and/or less severely affected patients. Treatment consisted of non-surgical and/or surgical therapies, i.e., prone positioning, placement of nasopharyngeal airway, adenotonsillectomy, mandibular distraction osteogenesis and placement of a tracheostomy tube.

To define the level of airway obstruction in patients with craniofacial microsomia CT scans of the upper airway of patients with and without OSA were compared with a control group. These results are presented in **chapter 5**. Patients with craniofacial microsomia have a significantly smaller airway than patients without craniofacial microsomia, and patients with craniofacial microsomia and obstructive sleep apnea have a significantly smaller airway than those without obstructive sleep apnea. In addition, the results of this study showed that although the airway of patients with craniofacial microsomia (without OSA) is smaller than the airway of the normal population, sphericity and uniformity of the airway between these groups is comparable. When comparing patients with craniofacial microsomia, with and without obstructive sleep apnea, it was found that there was a significant difference in size behind the base of the tongue and a significant difference in sphericity and uniformity.

Chapter 6 gives a systematic overview of the literature on feeding difficulties in craniofacial microsomia. According to literature feeding difficulties were present in 42-83% of the patients and mostly the result of oral impairment or orofacial deformities. Difficulties swallowing, chewing and choking were the most frequently described types of feeding difficulties. Decreased muscle tone and presence of extracraniofacial anomalies were thought to cause these feeding difficulties. Discussed treatment options were placement of a nasogastric tube and cleft lip/palate repair in case of a co-existing cleft. Unfortunately, the indication for treatment, treatment outcome and follow-up were not described in any of the studies.

In **chapter 7** the results of our retrospective study on feeding difficulties in our cohort of 755 patients were described. Feeding difficulties were diagnosed in 26.4% of the patients. Patients with bilateral involvement, Pruzansky-Kaban III classification, cleft lip / palate, extracraniofacial anomalies or obstructive sleep apnea were more at risk for developing feeding difficulties and significantly more often needed additional feeding via a nasogastric tube than patients without these risk factors. The most common types of feeding difficulties were choking, difficulties chewing and difficulties swallowing.

Therefore, a retrospective study on videofluoroscopic swallow studies in craniofacial microsomia was performed to gain more insight into these swallowing difficulties.

The outcomes were described in **chapter 8**. Of 755 studied patients, 13.5% was diagnosed with swallowing difficulties. The outcome of the VFS-studies of 42 patients showed difficulties in the oral and pharyngeal phases with both thin and thick liquids. Patients with more severe mandibular hypoplasia showed more difficulties to form an appropriate bolus compared to patients who were less severely affected.

Chapter 9 describes the influence of the presence of cleft lip / palate in craniofacial microsomia on breathing, feeding and swallowing. This study showed that patients with a combination of these diagnoses were not only significantly more often affected with obstructive sleep apnea, feeding difficulties and swallowing difficulties than patients solely diagnosed with craniofacial microsomia. Treatment of first choice of functional difficulties is also more often surgical, whereas the treatment of first choice in patients without cleft lip / palate is mostly non-surgical.

Finally, in **chapter 10**, the limitations of the studies that were carried out and recommendations for clinicians were formulated. Based on this thesis, patients with craniofacial microsomia should be screened for obstructive sleep apnea and feeding difficulties. Special attention should be reserved for patients with Pruzansky-Kaban IIb or III mandibles,bilaterally affected patients, and patients also diagnosed with cleft lip / palate.

Nederlandse samenvatting

Hoofdstuk 1 geeft de lezer een inleiding in craniofaciale microsomie en beschrijft de doelstellingen en de hoofdlijnen van dit proefschrift. Craniofaciale microsomie is na schisis de meest voorkomende aangeboren craniofaciale afwijking. Deze afwijking wordt gekenmerkt door onderontwikkeling van de aangezichtsstructuren, zoals de oogkas, onderkaak, oren, aangezichtszenuwen, en de weke delen. Naast esthetische problemen lopen patiënten met craniofaciale microsomie ook risico op het ontwikkelen van functionele problemen, zoals obstructief slaap apneu en voedingsproblemen. Om deze functionele problemen in een groot cohort patiënten te bestuderen, werd een samenwerking tussen drie grote craniofaciale centra opgezet. De deelnemende ziekenhuizen zijn het Erasmus Medisch Centrum, Rotterdam, Nederland; Great Ormond Street Hospital, Londen, Verenigd Koninkrijk; en Boston Children's Hospital, Boston, Massachusetts, de Verenigde Staten.

Hoofdstuk 2 beschrijft de kenmerken van patiënten met craniofaciale microsomie, die werden geïncludeerd in de drie craniofaciale centra. Het bleek dat craniofaciale microsomie een geleidelijk spectrum is van afwijkingen, waarbij de bilateraal aangedane patiënten meestal tot de ernstig aangedane patiënten behoren. Op basis van uiterlijke kenmerken konden geen specifieke groepen patiënten worden geïdentificeerd en de term 'Goldenhar-syndroom' is dan ook geen specifieke entiteit binnen craniofaciale microsomie. De studie in hoofdstuk 2 toonde ook aan dat afwijkingen aan de structuren die ontstaan uit de eerste kieuwboog in ernst correleerden met afwijkingen van andere structuren ontstaan uit de eerste kieuwboog. Structuren die waren afgeleid van de tweede kieuwboog waren op hun beurt weer gecorreleerd in ernst met andere structuren afgeleid van de tweede kieuwboog. Ten slotte werd geconstateerd dat extracraniofaciale afwijkingen een positieve correlatie hadden met craniofaciale microsomie.

In **hoofdstuk 3** werden de resultaten beschreven van een literatuuronderzoek naar de prevalentie en behandeling van obstructief slaap apneu bij patiënten met craniofaciale microsomie. Volgens de literatuur werd obstructief slaap apneu bij 7 tot 67% van de patiënten gediagnosticeerd en bestond de behandeling uit zowel niet-chirurgische als chirurgische behandelingen. Als niet-chirurgische behandelingsopties werden buikligging en ‘continuous positive airway pressure’ (CPAP) genoemd. Chirurgische behandeling bestond meestal uit adenotonsillectomie, mandibulaire distractie osteogenese of plaatsing van een tracheostoma. Sommige auteurs pleitten voor behandeling met CPAP, terwijl anderen positieve resultaten van mandibulaire distractie osteogenese beschreven. Echter, de kenmerken van de onderzochte patiënten en de ernst van de ademhalingsproblemen werden in deze artikelen niet tot nauwelijks besproken. Bovendien werden behandelresultaten en de follow-up niet beschreven en daarom konden geen harde conclusies worden getrokken op basis van de reeds verschenen literatuur.

De resultaten van de retrospectieve studie naar de prevalentie en behandeling van obstructief slaap apneu in ons cohort van 755 patiënten werd beschreven in **hoofdstuk 4**. In totaal werd 17,6% van de patiënten gediagnosticeerd met obstructief slaap apneu. Deze prevalentie was gebaseerd op *(1)* resultaten van een polysomnografie, *(2)* behandeling voor obstructief slaap apneu, niet voorafgegaan door een polysomnografie, en *(3)* de ernst van ademhalingsproblemen waarvoor plaatsing van een tracheostoma noodzakelijk was. Patiënten met bilaterale craniofaciale microsomie of patiënten met meer ernstige mandibulaire hypoplasie hadden meer kans op het ontwikkelen van obstructief slaap apneu dan unilateraal aangedane patiënten en / of patiënten met minder ernstige mandibulaire hypoplasie. Bovendien hadden de bilaterale casus of ernstig aangedane patiënten ook ernstiger obstructief slaap apneu dan de unilateraal aangedane en / of minder ernstig aangedane patiënten. Behandeling bestond uit zowel niet-chirurgische als chirurgische therapieën, buikligging, plaatsing van een nasofaryngeale luchtweg, adenotonsillectomie, mandibulaire distractie osteogenese, en plaatsing van een tracheostoma.

Om het niveau van luchtwegobstructie bij patiënten met craniofaciale microsomie te bepalen, werden CT-scans van de bovenste luchtwegen van patiënten met en zonder OSA vergeleken met een controlegroep. Deze resultaten worden getoond in **hoofdstuk 5.** Patiënten met craniofaciale microsomie hebben een significant kleinere luchtweg dan patiënten zonder craniofaciale microsomie. Patiënten met craniofaciale microsomie en obstructieve slaap apneu hebben een significant kleinere luchtweg dan patiënten zonder obstructief slaap apneu. Bovendien toonden de resultaten van deze studie aan dat, hoewel de luchtweg van patiënten met craniofaciale microsomie zonder OSA kleiner is dan de luchtweg van de normale populatie, de uniformiteit en sfericiteit van de luchtweg tussen deze groepen vergelijkbaar is. Bij het vergelijken van patiënten met craniofaciale microsomie met en zonder obstructief slaap apneu, werd gezien dat er een significant verschil in volume achter de tongbasis was en een significant verschil in uniformiteit en sfericiteit.

Hoofdstuk 6 geeft een overzicht van de literatuur over voedingsproblemen bij craniofaciale microsomie. Volgens de literatuur waren voedingsproblemen aanwezig bij 42-83% van de patiënten en meestal het gevolg van de orofaciale afwijkingen. Moeilijkheden met slikken, kauwen en verslikken waren de meest beschreven voedingsproblemen. Verminderde spiertonus en aanwezigheid van extracraniofaciale afwijkingen werden verondersteld deze voedingsproblemen te veroorzaken. Als behandelingsopties werden sondevoeding en sluiting van de lip en/of het verhemelte bij patiënten die ook schisis hadden genoemd. Helaas werden de indicatie voor behandeling, de behandel uitkomsten en de follow-up in geen van de onderzoeken beschreven.

In **hoofdstuk 7** werden de resultaten van ons retrospectief onderzoek naar voedingsproblemen in ons cohort van 755 patiënten beschreven. Voedingsproblemen werd bij 26,4% van de patiënten gediagnosticeerd. Patiënten met bilaterale betrokkenheid, classificatie van Pruzansky-Kaban III, schisis, extracraniofaciale afwijkingen of obstructief slaap apneu liepen meer risico op het ontwikkelen van voedingsproblemen en hadden significant vaker extra voeding via een sonde nodig dan patiënten zonder deze risicofactoren. De meest voorkomende soorten voedingsproblemen waren verslikken, problemen met kauwen en slikproblemen. Daarom werd een retrospectief onderzoek uitgevoerd naar de slikstudies bij patiënten met craniofaciale microsomie om hier meer inzicht in te verkrijgen.

De uitkomsten hiervan werden beschreven in **hoofdstuk 8**. Van alle 755 patiënten had 13,5% slikproblemen. De resultaten van de slikstudies bij 42 patiënten toonden afwijkingen in de orale en faryngeale fase met zowel dunne als dikke voedingsmiddelen. Patiënten met meer ernstige mandibulaire hypoplasie vertoonden meer problemen in vergelijking met patiënten die minder ernstig waren aangedaan.

Hoofdstuk 9 beschrijft de invloed van de aanwezigheid van schisis bij patiënten met craniofaciale microsomie op ademhalingsproblemen, voedingsproblemen en slikproblemen. Deze studie toonde aan dat patiënten met een combinatie van deze diagnoses significant vaker last hadden van obstructief slaap apneu, voedingsproblemen en slikproblemen dan patiënten die uitsluitend de diagnose craniofaciale microsomie hadden. Behandeling van eerste keuze van functionele problemen bij deze patiënten was ook vaker chirurgisch, terwijl de behandeling van eerste keus bij patiënten zonder schisis meestal niet-chirurgisch is.

Ten slotte werden in **hoofdstuk 10** de beperkingen van de uitgevoerde onderzoeken en aanbevelingen voor clinici geformuleerd. Op basis van dit proefschrift werd geconcludeerd dat screening op obstructief slaap apneu en voedingsproblemen bij alle patiënten met craniofaciale microsomie aangeraden is. Speciale aandacht moet worden besteed aan patiënten met Pruzansky-Kaban IIb of III, bilateraal aangedane patiënten of patiënten die ook zijn gediagnosticeerd met schisis.

List of publications

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International Journal of Oral and Maxillofacial Surgery.2014 Mar;43(3):286-95. PMID:24332589

PhD Portfolio

1. PhD training

	Year	Workload (Hours/ECTS)
General courses		
- BROK 'Basiscursus Regelgeving Klinisch Onderzoek'	2012	0.9 ECTS
- Biomedical English Writing and Communication	2012	10 ECTS
- Methodologie van patiëntgebonden onderzoek en voorbereiding van subsidieaanvragen	2012	1.0 ECTS
- Integrity Course (Erasmus MC)	2013	0.5 ECTS
- Herregistratie BROK 'Basiscursus Regelgeving Klinisch Onderzoek	2015	0.5 ECTS
- Integrity Course (Erasmus MC)	2015	0.5 ECTS
Specific courses (e.g. Research school, Medical Training)		
- Introduction to Clinical Research by NIHES	2012	5 ECTS
- Biostatistics for Clinicians by NIHES	2012	5 ECTS
- Sleep Course by the University Hospital Antwerp	2013	1 ECTS
- 'Open Clinica' Course by the Erasmus MC	2013	1 ECTS
- Introduction to data-analysis by NIHES	2015	5 ECTS
Seminars and workshops		
- Literature search course (Erasmus MC)	2012	0.1 ECTS
- Endnote (Erasmus MC)	2013	0.1 ECTS
- VENI-Masterclass	2018	0.1 ECTS
Presentations & (Inter)national conferences		
- X World Congress on Sleep Apnoea, Rome, Italy	2012	3 ECTS
- European Society of Paediatric Neonatal Intensive Care congress, Rotterdam	2013	1 ECTS
- Refereeravond Keel-, Neus- en Oorheelkunde	2013	0.5 ECTS
- National conference of the Dutch Society of Oral and Maxillofacial Surgery (NVMKA) (attendance)	2012 - 2019	6 ECTS
- European Society of Paediatric Neonatal Intensive Care congress, Rotterdam, The Netherlands	2013	1 ECTS
- Sleep & Breathing, Berlin, Germany	2013	1 ECTS
- Biennial Congress of the European Society of Craniofacial Surgery, Paris, France	2014	2 ECTS
- International Society Craniofacial Surgery, Tokyo, Japan	2015	3 ECTS
- Biennal Congress of the European Society of Craniofacial Surgery, Athens, Greece	2018	1 ECTS
Other		
- United Nations Public Speaking	2016	0.5 ECTS
- Organisatie en bijwonen 'Research meetings dept. of Oral and Maxillofacial Surgery'	2012 - 2017	3 ECTS
- Inventarisatie Wetenschappelijk onderzoek	2012 - 2017	3 ECTS

2. Teaching

	Year	Workload (Hours/ECTS)
Lecturing		
- Weekly seminars for medical and dental students	2016 – 2019	2 ECTS
- Onderwijs OK-assistentes	2018	0.1 ECTS
Supervising practicals and excursions, Tutoring		
- Supervising medical and dental students in the outpatient clinic and operation theatre	2017 - 2019	6 ECTS
Supervising Master's theses	2014 - 2019	40 ECTS
- L.S. van de Lande		
- Y.P. Klazen		
- S.C. Schaal		
- B.D.P.J. Maas		
- C. van Poucke		
- M.N. Gribova		
- R. van de Wijdeven		
- R.W. Renkema		
- L.M. Beelen		
- W. Rooijers		
- A. Pelouto		
- C.A.A. Beaumont		
- E.E.C.M. Elsten		
- T. Houwen		
- M.J. Schreuder		
- H. Galema		
- A. Sahtoe		
- I. van Beelen		
- T. Khosnaw		
Other		
- N/A		

Curriculum vitae

Curriculum Vitae

Linda Caron was born on the 25th of April 1987 in Breda, The Netherlands. She graduated high school at Monseigneur Frencken College in Oosterhout in 2005 and started her study Medicine in that same year at the Erasmus University in Rotterdam. During her studies she became a member of the Surgical Anatomy-student team and took part as a student and lecturer in the Erasmus Anatomy Research Project (EARP), which led to a special interest in the anatomy of the Head and Neck region. Her master thesis in her final year of Medical School was conducted at the departments of Surgical Anatomy and Oral- and Maxillofacial surgery under supervision of prof. dr. G.J. Kleinrensink and dr. M.J. Koudstaal. After graduating Medical School in December 2011 she worked full-time as a researcher at the department of Oral- and Maxillofacial surgery before she went on with her dentistry studies at the Radboud University Nijmegen in September 2013. She started her training in Oral- and Maxillofacial surgery at the Erasmus University Hospital in Rotterdam in September 2016. At present she is in her third year of training, which she will finish in September 2020.

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Dankwoord

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