Aspects of Hemifacial Microsomia

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Table of contents

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Chapter 1

General introduction

1.1 Introduction

Hemifacial microsomia (OMIM%164210) is a facial birth defect derived from the first and second branchial arches. The phenotype is highly variable and in addition to craniofacial involvement, vertebral, cardiac and central nervous system defects can exist. The high variability and wide range of anomalies has led to a number of names for this condition, including oculo-auriculo-vertebral spectrum, Goldenhar syndrome, oculoauriculovertebral dysplasia, facioauriculovertebral sequence, temporo-auromandibular dysplasia, first arch syndrome, first and second branchial arch syndrome, Goldenhar–Gorlin syndrome, lateral facial dysplasia, unilateral craniofacial microsomia, otomandibular dysostosis, unilateral intrauterine facial necrosis, auriculo-branchiogenic dysplasia, facio-auriculo-vertebral dysplasia, facio-auriculo-vertebral malformation complex and craniofacial microsomia (Hennekam et al., 2010). Gorlin et al. (1963) suggested that it is a continuous spectrum instead of discrete diagnostic entities and used the name oculo-auriculo-vertebral spectrum (OAVS) to include the wide spectrum of characteristics. Throughout this thesis we use the term hemifacial microsomia (HFM). This name covers the region of our interest. First an overview of the broad spectrum of the malformation is provided, and subsequently the focus will be on the craniofacial area.

In the Netherlands, the prevalence of congenital malformations over the period from 1997 to 2007 decreased from 3.94 to 3.75 percent in newborns. This number, however, includes not only craniofacial but all congenital malformations. Craniofacial congenital malformations are relatively rare. For example, even for the most common congenital craniofacial anomalies, namely oral clefts, the prevalence in the same period was 0.24 in 1997 and 0.18 percent in 2007 (Mohangoo and Buitendijk, 2009). The exact prevalence of HFM is unknown for the Netherlands. This is probably due to the wide range of observable characteristics. The reported incidence in the literature ranges from 1:3500 (Poswillo, 1973) to 1:5600 in live births (Grabb, 1965).

1.2 Clinical description

The clinical manifestation includes unilateral deformity of the external ear, underdeveloped ipsilateral half of the face, with epibulbar dermoid and vertebral anomalies. Of the eye defects, coloboma of the upper eyelid is frequent but lipodermoid, blepharophimosis, microphthalmia, anophthalmia, and strabismus also occur. The ear

Figure 1.1   *Clinical representation of Hemifacial Microsomia*

deformities range from preauricular tags of cartilagenous masses, to atresia of the external auditory canal, from anomalies in the size and shape of the external auricle, to anotia. These can be associated with hearing loss. Oral manifestations can include macrostomia, cleft lip, cleft palate, bifid uvula, soft palate malfunction, scissors bite (Stromland et al., 2007) and velopharyngeal insufficiency (Funayama et al., 2007). The ipsilateral facial half of the deformity shows hypoplasia of the facial musculature, aplasia or hypoplasia of the mandibular ramus and condyle combined with maxillary temporal and malar bones which are reduced in size and flattened (Rune et al., 1981). In 10 to 36 percent, bilateral involvement exists, but one side is almost always more severely involved than the other (Cohen et al., 1989). Forty-eight percent of all affected patients has at least one other anomaly, in addition to these principal facial features (Rollnick et al., 1987). These additional malformations can be found in any part or system of the body (Rollnick et al., 1987).

1.3   Classification

The heterogeneity of hemifacial microsomia has led to several classifications of which the most important are SAT, an acronym for Skeletal, Auricular and Soft Tissue (David et al., 1987) and OMENS an acronym for Orbital, Mandibular, Ear, Nerve and Soft tissue (Vento et al., 1991). However these extended classifications are incomplete and do not cover the complete spectrum of hemifacial microsomia. For this study, focusing on the mandibulo-maxillary complex, a less extended classification system was used. HFM was divided into four types, based on the morphology and size of the affected mandible and temporomandibular joint (TMJ) and in relation to treatment options

(Kaban et al., 1998). This four-type classification is based on the three-type system developed by Pruzansky (1969).

In Type I, all mandibular and TMJ components are present and normal in shape but hypoplastic to a variable degree. In Type IIA, the mandibular ramus, condyle, and TMJ are present but hypoplastic and abnormal in shape, while in Type IIB the mandibular ramus is hypoplastic and markedly abnormal in form and location, being medial and anterior. There is no articulation with the temporal bone. In Type III, the mandibular ramus, condyle, and TMJ are absent, the lateral pterygoid muscle and temporalis, if present, are not attached to the mandibular remnant. Functionally, types I and IIa are similar because they have an adequate temporomandibular joint. Types IIB and III are also similar in that a new temporomandibular joint and ramus must be reconstructed.

1.4   Etiology

The etiology of HFM is heterogeneous but has been associated with vascular perturbation and/or neural crestopathy (Hartsfield, 2007). The question of genetic influence was investigated by Kaye et al. (1992), who performed a segregation analysis on 74 families of probands with OAVS anomalies, including 116 parents and 195 offspring. They rejected the hypothesis of no genetic influence. Their data favored autosomal dominant inheritance; recessive and polygenic models were not distinguishable from each other (Kaye et al., 1992). While the underlying pathogenesis of HFM is still unclear, a candidate causal gene has been mapped to 14q32 in one family. Linkage to this region, however, has been excluded in another family, suggesting genetic heterogeneity (Kelberman et al., 2001).

In addition, dysregulation of *BAPX1* was found in several patients. *BAPX1* plays an important role in craniofacial growth (Fischer et al., 2006) and has been found to regulate patterning in the middle ear in mice (Tucker et al., 2004). Epigenetic dysregulation of *BAPX1* likely plays a role in HFM and can explain many of the genetic and phenotypic peculiarities (Fischer et al., 2006). The extremely heterogeneous phenotype even between siblings was again confirmed in a study of a three-generation family with five affected members. The structural variations within the DNA- more specifically, the copy number variations (having an abnormal number of copies of one or more sections of the DNA)- did not differ between affected and normal members.

They found, however, the highest probability (logarithm of the odds of 1.6) of linkage on chromosome 15q26.2-q26.3 but were unable to identify a causative variant suggesting again a complex etiology (Huang et al., 2010).

Etiological heterogeneity, including genetic and non-genetic factors, is possibly the best explanation, making it a challenging task to identify the cause of HFM.

1.5   Craniofacial malformation

Coronal synostosis, in relationship to HFM, has been described (Hennekam et al., 2010). However, while only one patient with HFM and probable coronal synostosis was found in a group of 155 HFM patients, this patient could also suffer from positional plagiocephaly since no radiological confirmation was done (Padwa et al., 1993). A later case report describes a radiologically confirmed coronal synostosis in a HFM case (Terry and Ascherman, 2006). Both studies could not confirm any direct causal relationship and the coronal synostosis may be caused by another mechanism than the one that is related to HFM. HFM is associated with eye defects but also with a possible alteration of size and position of the orbits at the affected side in 15-18 percent of patients (Rahbar et al., 2001; Vento et al., 1991). However, the measurement of the horizontal orbital line (line between Orbitale left and Orbitale right) compared to the vertical reference line between the crista galli and anterior nasal spine, makes it unclear whether the orbits, or the area between the crista galli and anterior nasal spine, are off. Maxillary downward and forward growth on the affected side has been found (Rune et al., 1981; Sarnas et al., 2004). It is unclear to what vertical level the HFM malformation extends. The mandible and maxilla are certainly involved while the orbits, cranial base and calvaria are probably involved.

1.6   Mandibular malformation

One of the most obvious visible characteristics in HFM, is hypoplasia of the mandible and adjacent muscle and soft tissue (Kaban et al., 1998). Some of the muscular structures are also hypoplastic or absent (Grabb, 1965). However, no correlation between skeletal and muscular defects could be proven (Hirschfelder et al., 2004; Huisinga-Fischer et al., 2001; Kane et al., 1997; Marsh et al., 1989; Takashima et al., 2003). Facial nerve dysfunction is found in 22 to 25 percent (Bassila and Goldberg, 1989; Carvalho et al., 1999; Murray et al., 1984; Vento et al., 1991) but in this study they were not able to

differentiate between facial nerve dysfunction and facial muscle weakness, naming both facial nerve dysfunction (Carvalho et al., 1999). The mandibular deformation may relate to a functional abnormality, such as obstructive sleep apnea. Of children with unilateral HFM, 12.5% were found to have sleep apnea (Cohen et al., 1999). The mandibular malformation ranges from an unusual shape of the condyle to absence of the condyle and ascending ramus. The wide range of the mandibular malformation suggests a disturbance in development over a long time period in embryonic development. Normal mandibular development starts in the sixth week and continues until the twelfth week of embryonic development, when the architecture of the mandibular body is complete (Lee et al., 2001). After birth, mandibular skeletal growth continues but it remains unclear whether the malformation worsens until growth ceases (Grayson et al., 1983; Kaban et al., 1998; Kaban, 2009; Kearns et al., 2000; Kusnoto et al., 1999; Melsen et al., 1986; Polley et al., 1997; Rune et al., 1981; Sarnas et al., 2004; Shetye et al., 2006).

1.7   Oral manifestations

The extent of oral anomalies in HFM has not often been studied. However, canting of the occlusal plane is clearly visible (Hennekam et al., 2010) and often a lateral cross-bite exists (Stromland et al., 2007).

In addition to HFM, cleft lip and/ or cleft palate occurs in 7 to 15 percent of the patients (Rollnick et al., 1987). According to a study by Melnick (1980), isolated cleft palate is twice as common as cleft lip with or without cleft palate. Another study found an occurrence of 10 percent, of which 7.5 percent had a unilateral cleft lip or palate and 2.5 percent had a bilateral cleft lip or palate. They did not find any isolated cleft palate in their sample (Fan et al., 2005).

HFM patients without cleft lip or cleft palate may have velopharyngeal insufficiency with reported rates of 33 percent (Luce et al., 1977), 45 percent (Shprintzen et al., 1980) and 14.6 percent (Funayama et al., 2007). Luce et al. (1977) found that these HFM patients with velopharyngeal insufficiency often had more severe soft tissue and skeletal deformities of the maxillary-malar complex compared to the other HFM patients, and Funayama et al. (2007) found a correlation between severity of the mandibular hypoplasia and velopharyngeal insufficiency. This was in contrast to the findings by Sphrintzen et al. (1980).

Macrostomia was found in 23 percent of patients (Fan et al., 2005), 15 percent

(Grabb, 1965), 18 percent (Feingold and Baum, 1978) and in 61 percent of HFM cases (Vento et al., 1991).

Up to five times higher percentages of congenital missing mandibular teeth compared to the normal population (Monahan et al., 2001a) were reported with rates respectively 17.5 percent (Silvestri et al., 1996), 25 percent (Farias and Vargervik, 1998) and 32 percent (Maruko et al., 2001). Whether dental development is disturbed significantly on the affected side is unclear because findings are opposing (Farias and Vargervik, 1988; Loevy and Shore, 1985).

1.8   Treatment and psychosocial impact

Despite developments, the treatment of HFM remains challenging. The treatment goal is improved function and optimal facial symmetry when craniofacial growth is completed (Vargervik et al., 1986). It is impossible to describe one treatment protocol that fits the complete range of HFM. Its heterogeneity leads to a variety and combination of surgical and non-surgical treatment strategies and early and/ or late treatment timing, from birth until late adolescence. In the last century, around 1940, cases were described in which tibia bone was transplanted to replace the missing mandibular part and surgical splints were used to stabilize the result. The problems they encountered were that the children presented had not acquired their full growth and that the bone contact for the transplanted bone was not optimal (Kazanjian, 1940). Both problems have not been solved satisfactorily to date. In general, treatment can include several phases (Vargervik et al., 1986), consisting of a phase with a functional appliance (Kahl-Nieke and Fischbach, 1998; Vargervik et al., 1986), an orthognathic mandibular procedure (or placement of a costochondral graft (Padwa et al., 1998)), a post-surgical treatment to induce bony replacement of the graft, a correction of the distorted maxilla or maxillary alveolar process on the affected side , an orthodontic treatment (Meazzini et al., 2008) and a soft tissue augmentation. Nowadays the orthognathic procedure could be comprised of a maxillo-mandibular correction combined with distraction osteogenesis (Nakajima et al., 2011). However, the use of early distraction osteogenesis for correcting HFM as a single treatment modality lacks statistical evidence (Nagy et al., 2009), and the timing and sequence of the aforementioned treatment phases remain unclear.

Thus, treatment occurs over an extended period of time into adolescence and varies with the severity and type of anomalies and includes ear reconstruction,

orthodontics and surgical interventions (Vargervik, 1996). All these medical procedures and multiple areas of potential impairment may have psychosocial implications for the affected individual and his/her parents or care takers. However, data regarding the psychological implications for children and their parents are limited (Maris et al., 1999b). Understanding psychosocial difficulties is an important part of the total treatment strategy. Most studies were limited by small and diagnostically heterogeneous samples of children with HFM. Standardized behavior checklists and interviews were used, suggesting that children with various craniofacial disorders were often more inhibited, depressed, anxious, introverted, and less socially adept than typical children (Padwa et al., 1991; Pertschuk and Whitaker, 1985; Pillemer and Cook, 1989; Snyder and Pope, 2010). Behavior problems in children with HFM probably exist (Padwa et al., 1991) and also a recent larger report, with 136 children, suggests that these children may have a modestly elevated risk for internalizing behavior problems. These outcomes came from teacher reports; the children's parents did not report differences compared to matched controls (Dufton et al., 2011). Estimates of learning disabilities range from a modest 5 to 15 percent (Gorlin et al., 1963) to 36 percent (Morrison et al., 1992). The occurrence of autism spectrum disorders in more than a third of HFM patients indicates that these problems are common (Johansson et al., 2007). Psychosocial problems may add to parental stress and can influence treatment outcome but this aspect has yet to be studied.

1.9   Imaging tools for clinical evaluation

Individual HFM patients should be evaluated by radiographs to assess skeletal morphology, establish a diagnosis, identify normal or abnormal patterns of growth, monitor presurgical treatment, develop a precise surgical plan, assess the surgical and postsurgical course and monitor subsequent growth (Chirieci, 1983). The most commonly used radiographs to analyze craniofacial growth and development are lateral and posteroanterior cephalograms, oblique mandibular radiographs, and orthopantomograms (OPTs). The cephalometric analysis on a lateral cephalogram consists of a combination of distances and angles, constructed from craniofacial anatomical landmarks (Athanasiou, 1995; Sekiguchi and Savara, 1972; Trpkova et al., 1997). On a posteroanterior cephalogram as well as on a oblique mandibular radiograph, transversal measurements can be performed. Both types of radiographs, however,

have limitations as both methods are affected by a tilt of the head or angulation of the beam (Athanasiou, 1995; Verhoeven et al., 2000). On the posteroanterior cephalogram, inaccuracy of identifying landmarks is a drawback as well. An OPT provides general information on vertical dimensions of craniofacial structures, while a lateral cephalogram results in a more complete view (Geelen et al., 1998; Houston et al., 1986). With respect to accuracy and reproducibility, measurements on lateral cephalograms are reliably performed (Baumrind and Frantz, 1971a; b; Houston, 1983), whereas performing measurements on an OPT seems to be less reliable (Habets et al., 1989; Laster et al., 2005). The panoramic image is affected by both magnification errors and displacement, leading to distortion (Tronje et al., 1981). In addition, the technique is quite sensitive to positioning errors because of a relatively narrow image layer (Tronje et al., 1981). Images of structures within the sharply depicted plane are free of distortion (Kambylafkas et al., 2006). Horizontal measurements have been shown to be particularly unreliable because of the nonlinear variation in the magnification at different object depths, whereas vertical measurements are relatively reliable (Tronje et al., 1981). Absolute measurements or relative comparisons on an OPT should be done with caution, as shifted skull positions affect the panoramic accuracy (Laster et al., 2005). Especially in HFM, certain mandibular landmarks on an OPT can be better identified than on a lateral cephalogram, because the OPT landmarks for left and right do not overlap as they do on the lateral cephalogram (Sekiguchi and Savara, 1972).

As the above makes clear, both two-dimensional imaging techniques used to date have limitations and are not ideal for the study of HFM patients. Growth is three-dimensional and therefore a 3D computed tomography (CT) study would likely show more precise results. Unfortunately the 3DCT technology was not widely available at the start of this retrospective cohort.

1.10   Aims of this thesis

An effective treatment is important for each individual with HFM and several treatment strategies can be applied well into late adolescence. The final results are not only determined by external factors such as the surgical technique, distraction osteogenesis or graft but perhaps even more by the intrinsic factors of a patient such as genetic background, growth and development. Unfortunately, successful results at the end of growth cannot be taken for granted. While understanding intrinsic and extrinsic factors could help to finish treatment successfully from the morphological point of view, the psychosocial well-being of the patient should be taken into account as well. Finally, the psychosocial impact on both parents and patients may be a strong influencing factor in the final result. To summarize, the objectives of the research described in this thesis are:

- To gain further insight into craniofacial growth and treatment timing in HFM.
- To develop a suitable method for measuring and comparing affected and unaffected mandibular sides in HFM.
- To investigate whether dental development is associated with disturbed mandibular development in HFM.
- To study whether parental stress is related to patient characteristics and can be associated with parental cognitive coping in parents of children with HFM.

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Chapter 2

Linear mandibular measurements: Comparison between orthopantomograms and lateral cephalograms

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Abstract

Objective: To investigate the reliability of length measurements of the mandible by comparing orthopantomograms (OPTs) with lateral cephalograms.

Design: Observational study.

Setting: OPTs and lateral cephalograms were taken of 20 human dry skulls. Four orthodontists and four maxillofacial surgeons located landmarks on all radiographs using a computer program for cephalometric measurements. Intraobserver and interobserver variability in locating landmarks was assessed, as well as positioning of the skulls prior to radiography between the x-ray assistants. Magnification differences between the left and right side of the mandible on the OPT were determined for five skulls. Kappa statistics were used to calculate the intraclass correlation coefficient for intraobserver and interobserver differences. An *F* test was used to assess differences between methods and between type of observer.

Results: No significant differences were found in the magnification factor of the left and right side of the mandible. Compared with a lateral cephalogram, the OPT had comparable reliability in measuring mandibular distances condylion-gonion, gonion-menton, and condylion-menton. No significant differences were observed between the x-ray assistants in taking the OPTs and lateral cephalograms or in repositioning the skulls. Significant differences were found between orthodontists and maxillofacial surgeons for landmark measurements.

Conclusion: An OPT is as reliable as a lateral cephalogram for linear measurements of the mandible (condylion-gonion, gonion-menton, and condylion-menton).

2.1   Introduction

Hemifacial or craniofacial microsomia is a complex congenital one-sided deformity of the face and the skull (Cousley and Calvert, 1997; Murray et al., 1984), and its phenotypic expression is highly variable. Clinically, morphological changes such as asymmetrical ramal height, a rotated facial appearance with kinking at the mandibular symphysis, asymmetrical prominence of the lower mandibular border, and canting of the occlusal plane make classification and diagnosis difficult. Several systems are used to classify the affected mandible (Pruzansky, 1969; Vento et al., 1991). Classification into type I, IIa, IIb, and III by Kaban et al. (1988) is widely followed and is based on the severity of the mandibular and temporomandibular joint deformity in anatomy. Different orthodontic and surgical treatment modalities are available to correct asymmetry in severe cases of hemifacial microsomia. Bone transplants, osteotomy, and distraction osteogenesis are used to reshape the affected mandible to a more normal form (McCarthy et al., 2001). Distraction osteogenesis corrects the mandible by increasing its length, and it is assumed to develop the surrounding soft tissue envelope (Murray et al., 1984); this is often considered as the treatment of choice nowadays. In addition, type I and IIa can be treated by osteotomy. However, the treatment modality for type IIb and III is often costochondral reconstruction of the ramus/condyle or temporomandibular joint (Kearns et al., 2000) instead of distraction osteogenesis.

To analyze morphology and treatment effects, the most commonly used radiographs are lateral and posteroanterior cephalograms, oblique mandibular radiographs, and orthopantomograms (OPTs). The cephalometric analysis on a lateral cephalogram consists of a combination of distances and angles, constructed from craniofacial anatomical landmarks (Athanasiou, 1995; Sekiguchi and Savara, 1972; Trpkova et al., 1997). Transversal measurements can be performed on both a posteroanterior cephalogram and an oblique mandibular radiograph. Both types of radiographs, however, have limitations in that both methods are affected by a tilt of the head or angulation of the beam (Athanasiou, 1995; Verhoeven et al., 2000). On the posteroanterior cephalogram, the inaccuracy of positioning landmarks is a drawback as well. The analysis on an OPT is mostly done in a qualitative way. An OPT provides global information on vertical dimensions of craniofacial structures, and a lateral cephalogram results in a more complete view (Geelen et al., 1998; Houston et al., 1986). With respect to accuracy and reproducibility, measurements on lateral cephalograms

are reported to be reliably performed (Baumrind and Frantz, 1971a; b; Houston, 1983); whereas, performing measurements on an OPT seems to be less reliable (Habets et al., 1989; Laster et al., 2005). The panoramic image is affected by both magnification errors and displacement, leading to distortion (Tronje et al., 1981). The technique is quite sensitive to positioning errors because of a relatively narrow image layer (Tronje et al., 1981). Images of structures within the sharply depicted plane are free of distortion. Structures outside this plane will appear distorted in the image because of the difference between the velocity of the film and the velocity of the projection of the object on the film (Kambylafkas et al., 2006). Horizontal measurements have been shown to be particularly unreliable because of the nonlinear variation in the magnification at different object depths; whereas, vertical measurements are relatively reliable (Tronje et al., 1981). Absolute measurements or relative comparisons on an OPT should be done with caution, as shifted skull positions affect the panoramic accuracy (Laster et al., 2005).

In hemifacial microsomia, mandibular measurements are especially important because that is where growth is impaired. On an OPT, certain landmarks can be better identified than on a lateral cephalogram because the OPT landmarks for left and right do not overlap as they do on the lateral cephalogram (Sekiguchi and Savara, 1972). This is true not only for hemifacial microsomia but also for other mandibular craniofacial malformation syndromes. However, the reliability of measurements on the OPT has been examined by only two groups (Akcam et al., 2003; Larheim and Svanaes, 1986). Larheim and Svanaes (1986) concluded that vertical measurements on the OPT were reliable, but they did not compare this to measurements on cephalograms. Akcam et al. (2003) compared angular measurements on the OPT to angular measurements on the cephalogram: they found that the OPT can provide information on angular vertical dimensions of the craniofacial structures, but that it is not as reliable as a lateral cephalogram.

The present study therefore investigated the reliability of bilateral mandibular linear measurements using OPTs instead of lateral cephalograms by comparing the reliability of the landmark identification on the OPT and lateral cephalogram and by comparing the effect of positional changes of the skull on the identification of anatomic landmarks and its subsequent cephalometric analysis.

2.2 Materials and methods

Digital lateral cephalograms and OPTs were taken of 20 human dry skulls. The skulls were positioned in an OPT device (SIRONA, Orthophos 3, kV 60, 11.3 seconds, 10 mA) using the Frankfort Horizontal Plane (Orthophos Plus DS Ceph, Sirona, Bensheim, Germany) in a standard configuration defined by the manufacturer. A beeswax mask was used to mimic the normal skin for all procedures done with OPT. The lateral cephalogram device (Philips Oralix, Eindhoven, the Netherlands) was used with the standard settings (kV 75, 24.6 seconds, 0 mA, and filter).

Five landmarks were determined on the OPT and seven landmarks on the lateral cephalogram, as depicted in Figures 2.1 and 2.2 and described in Tables 2.1 and 2.2. Landmarks were traced on a 118-dpi screen with the help of a computerized cephalometric program (Viewbox, v3.1,D. Halazonetis 1995–2006, Athens, Greece) that calculated the final distances. Distance measurements are listed in Table 2.3. Eight observers, four orthodontists and four maxillofacial surgeons (mean experience of 6 years), traced landmarks on 25 OPTs and 25 lateral cephalograms. These 25 cephalograms included five of the same cephalograms in random order to determine intraobserver variability.

To determine the influence of positional changes of the skull among different cephalograms, two x-ray assistants made a lateral cephalogram and an OPT of five skulls. Subsequently, the skulls were repositioned, after which the second lateral cephalogram and OPT were taken. The skulls were repositioned using a stand, the Frankfort horizontal plane, head clamp, and frontal teeth bite according to the manufacturer's instructions. The skulls were tilted anteriorly by 5°. Two observers traced the landmarks on these cephalograms. Intraobserver and interobserver variability was assessed by analyzing the calculated distances statistically.

The difference in magnification error between the left and right of the OPT was calculated using two identical iron bullets with known dimensions placed on both gonial angles of the mandible of the five skulls (Fig. 2.3). For this purpose, both x-ray assistants made five OPTs. Both bullets were measured three times by one observer with an interval of 4 days. For each observer pair, the mean difference and standard deviation between observers were calculated for measurements on the OPT and cephalogram. Correlation between observers was calculated with a variance components analysis using the intraclass correlation coefficient (ICC). The ICC has a value between 0 and
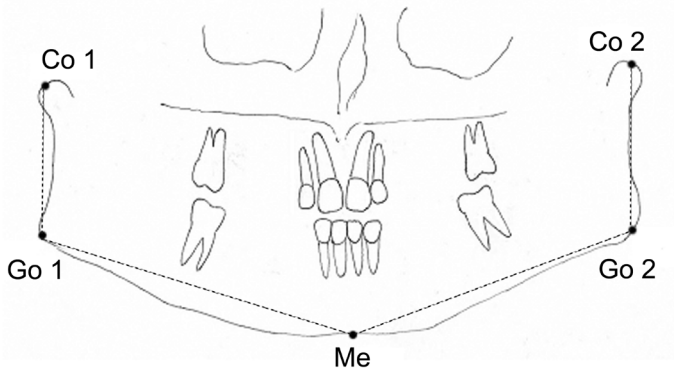
Figure 2.1   *Landmarks and measurements used on orthopantomograms tracings. Co1 = condylion right side; Co2 = condylion left side; Go1 = gonion right side; Go2 = gonion left side; Me = menton. Length measurements from condylion to gonion, condylion to menton, and gonion to menton*

1 and measures the strength of agreement among observers. The ICC is similar to the kappa coefficient. Analogous to kappa, an ICC of 0.61 to 0.80 is interpreted as substantial agreement and an ICC of 0.81 to 1.00 as an almost perfect agreement.

To investigate the variability between the two observer groups, we calculated the ICC from the variances between the orthodontists and maxillofacial surgeons. The ICC can be defined as the ratio of the between-skull variance and the total variance.

The total variance comprises:
- Var(S) = between-skull variance
- Var(O) = between-observer variance
- Var(E) = error-variance

The error E can be interpreted here as the within-observer variability.

Table 2.1   *Landmarks on the mandible used for tracings on the orthopantomogram and lateral cephalogram*

| Number	Abbreviation	Name
1	Co1	Condylion 1
2	Go1	Gonion 1
3	Co2	Condylion 2
4	Go2	Gonion 2
5	Me	Menton
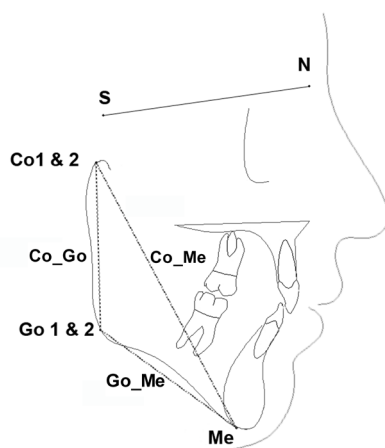
Figure 2.2 *Landmarks and measurements used on lateral cephalogram tracing. Co1 = condylion right side; Co2 = condylion left side; Go1 = gonion right side; Go2 = gonion left side; Me = menton; Na = nasion; S = sella. Length measurements from condylion to gonion, condylion to menton, and gonion to menton*

The ICC of each of the two methods (OPT and lateral cephalogram) was calculated in the same way as the ratio of the between-skull variance to the total variance, whereby the total variance equals the sum of the between-skull variance and the within-skull variance. The within-skull variance = Var (O) + Var (E). In this study, the within-skull variance is based on 16 repeated measurements (four orthodontists, four surgeons, left/right side). To test the null hypothesis that the ICC was the same for both methods, we used an *F* test based on the ratio of the two within-skull variances. The *F* test was done after rescaling the measurements such that the total variance of the OPT and lateral cephalogram measurements was the same.

The ICC difference for observer type was also tested in the same way without rescaling.

Table 2.2 *List of mandibular measurements used for tracings on the orthopantomogram and lateral cephalogram*

Abbreviation	Landmarks Used	Measurement
Co_Go	Condylion-gonion	Ramus length
Co_Me	Condylion-menton	Total length
Go_Me	Gonion-menton	Body length

Table 2.3 *List of landmark definitions from Athanasiou (1995)*

Landmark	Definition
Condylion (Co)	The most superior point on the head of the condylar head (bilateral)
Gonion (Go)	A point on the curvature of the angle of the mandible located by bi-secting the angle formed by lines tangent to the posterior ramus and the inferior border of the mandible
Menton (Me)	The most inferior midline point on the mandibular symphysis, the lowest point on the symphyseal shadow of the mandible seen on a lateral cephalogram

2.3   Results

2.3.1   Magnification error

No significant differences were found between the iron bullets placed at the left and right side in five skulls (p = 0.248), indicating the absence of a left/right magnification error in the OPT and lateral cephalogram measurements.

2.3.2   Intraobserver agreement

The intraobserver agreement was calculated on OPTs and on lateral cephalograms separately for eight observers for the three lengths on both sides: ramus length, total length, and body length measured twice in five skulls. On both the OPT and lateral cephalogram, 85% of the measurements reached an ICC of at least 0.81.
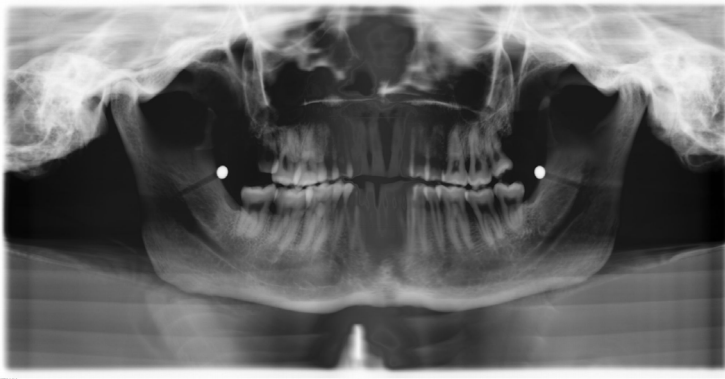

Figure 2.3 *Orthopantomogram with iron bullets placed on the left and right side of the mandible*

2.3.3   Interobserver agreement

Interobserver agreement was calculated for the OPTs as well as for the lateral cephalograms assessed by four orthodontists and four maxillofacial surgeons for the three lengths, ramus length, total mandibular length, and body length, respectively (Tables 2.4 and 2.5).

For ramus length (distance between condylion and gonion: Co-Go), an ICC of at least 0.61 was reached in 96.4% of the OPT measurements and in 82.1% of the lateral cephalogram measurements for ramus length. For total mandibular length (distance between condylion and menton: Co-Me), a substantial measurement (ICC ≥ 0.61) was reached in 89.3% of the OPT measurements and in 67.9% of the lateral cephalogram measurements. For body length (distance between gonion and menton: Go-Me), a substantial measurement (ICC ≥ 0.61) was reached in 67.9% of the OPT measurements and in 64.3% of the lateral cephalogram measurements for body length.

2.3.4   Comparison between OPT and lateral cephalogram

The ICC between lateral cephalogram and OPT was investigated for the orthodontists and maxillofacial surgeons together (Table 2.6; Fig. 2.4). No significant differences were found between the OPT and lateral cephalogram.

2.3.5   Comparison between orthodontists and maxillofacial surgeons

The ICC between orthodontists and maxillofacial surgeons was investigated for the OPT and lateral cephalogram separately (Table 2.7; Fig. 2.5). The average ICC of the orthodontists for the total mandibular length in both methods and for the ramus length on the lateral cephalogram was significantly higher than the ICC of the maxillofacial surgeons. All other ICCs showed no significant differences.

2.4   Discussion

The present study compared mandibular measurements made on skulls with an OPT and lateral cephalogram, as measured by orthodontists and by maxillofacial surgeons, to find a suitable method for measuring growth in hemifacial microsomia patients. Because no hemifacial microsomia skulls were available, skulls with normal anatomy were used. This could have played a role in tracing landmarks since the anatomy in hemifacial microsomia patients is more complex. Also, using skulls with a beeswax mask, to mimic

Table 2.4 *Mean left and right values (in mm) and standard deviations for the distances Condy-lion-Gonion (Co-Go), Condylion-Menton (Co-Me) and Gonion-Menton (Go-Me) on orthopantomograms (OPT). The mean and sd were calculated over 8 observers*

OPT	Left						Right					
	Co-Go		Co-Me		Go-Me		Co-Go		Co-Me		Go-Me	
	mean	sd	mean	sd	mean	sd	mean	sd	mean	sd	mean	sd
1	55.9	1.8	125.0	3.2	89.2	5.3	54.1	4.0	125.2	3.8	89.3	3.3
2	64.2	4.3	121.8	3.5	82.1	4.9	62.0	2.1	119.4	10.8	81.9	4.6
3	62.6	2.9	130.8	2.5	96.1	3.2	60.6	3.8	131.2	2.3	99.9	4.6
4	66.0	3.0	136.5	5.5	90.9	5.5	65.9	3.8	137.5	7.8	109.3	8.8
5	70.3	3.2	130.6	2.0	88.9	3.0	68.2	3.0	132.3	3.5	88.2	3.8
6	63.1	2.4	138.4	4.0	93.9	5.5	59.8	3.1	139.5	3.8	81.2	4.6
7	76.6	4.1	136.0	3.7	90.6	4.4	75.2	3.8	137.4	5.1	86.7	3.0
8	63.8	3.1	142.3	3.6	103.3	1.8	65.5	1.8	144.1	3.2	96.9	2.9
9	65.2	2.3	133.9	3.8	87.2	5.0	60.4	2.7	135.3	3.9	90.6	3.4
10	58.9	2.4	136.7	3.4	96.4	5.4	61.0	3.1	138.1	2.7	96.6	5.6
11	63.8	1.5	123.9	1.0	75.6	2.1	61.9	1.8	124.9	2.7	82.6	4.2
12	66.8	2.4	137.9	2.7	96.9	5.0	62.1	3.2	135.0	9.4	92.5	4.6
13	64.0	1.7	135.5	1.8	95.5	2.1	63.0	2.1	137.3	5.2	98.1	4.1
14	58.1	3.5	132.6	3.1	88.5	5.5	58.7	11.9	134.8	4.0	88.6	5.5
15	57.6	2.5	132.8	4.9	97.4	7.9	54.6	1.4	134.8	4.2	96.2	4.0
16	68.3	3.1	134.1	2.8	84.7	4.9	67.6	2.0	135.7	4.7	85.4	3.7
17	67.3	3.2	148.4	4.1	104.3	6.1	61.1	3.1	151.1	5.4	98.3	5.5
18	64.3	3.5	142.9	1.5	97.6	3.9	75.6	24.2	144.2	2.8	85.7	5.6
19	61.3	2.0	151.5	4.5	111.3	5.1	60.7	2.6	149.9	11.6	107.9	17.5
20	76.2	2.5	133.0	2.6	88.4	2.1	75.6	1.9	134.3	3.0	96.7	14.0
21	57.2	2.9	124.5	3.4	87.9	5.6	55.9	3.5	121.5	9.1	90.4	3.2
22	64.7	2.6	122.3	2.3	82.8	4.5	63.2	2.0	119.3	9.0	80.1	5.4
23	61.7	3.0	130.7	1.3	97.0	3.5	60.2	3.2	131.0	2.3	99.6	4.5
24	65.9	2.5	137.2	5.2	92.1	5.9	65.2	3.6	137.5	6.2	109.8	8.1
25	70.4	2.8	131.0	2.4	89.5	3.4	68.8	3.5	130.8	2.6	88.8	2.9

Table 2.5 *Mean left and right values (in mm) and standard deviations for the distances Condyli-on-Gonion (Co-Go), Condylion-Menton (Co-Me), and Gonion-Menton (Go-Me) on lateral cephalograms. The mean and sd were calculated over 8 observers*

Lateral Cephalogram	Left						Right					
	Co-Go		Co-Me		Go-Me		Co-Go		Co-Me		Go-Me	
	mean	sd	mean	sd	mean	sd	mean	sd	mean	Sd	mean	sd
1	52.4	4.4	110.3	2.1	73.5	3.4	60.9	22.5	110.1	2.1	75.9	3.0
2	58.1	2.7	115.3	2.4	75.8	4.2	58.1	1.2	115.2	2.3	81.9	2.9
3	60.5	2.4	115.8	3.3	78.5	3.2	59.2	3.7	115.6	3.2	81.3	5.3
4	61.1	3.5	123.5	1.7	81.2	2.9	63.6	2.4	123.2	1.7	79.6	2.7
5	69.0	4.4	126.4	5.2	84.8	5.1	69.0	3.4	126.2	5.3	83.2	3.9
6	61.8	2.4	118.9	3.9	70.0	4.0	63.4	4.0	118.9	3.9	73.3	5.0
7	71.1	3.6	123.8	3.5	75.8	4.4	70.2	4.0	123.7	3.5	77.9	4.8
8	64.2	2.2	126.3	3.8	84.8	4.4	64.4	2.5	126.1	3.7	85.6	4.2
9	59.1	2.3	114.7	5.7	68.6	6.2	61.3	3.7	114.5	5.7	72.6	7.7
10	58.9	3.6	119.9	4.0	75.0	4.2	57.2	3.5	119.8	3.9	80.3	3.4
11	66.8	2.5	117.6	1.6	60.9	3.4	63.1	4.9	117.7	1.7	64.8	4.9
12	62.7	1.4	118.3	2.8	76.3	2.8	61.1	0.7	118.3	2.8	80.4	2.8
13	63.3	4.3	123.1	6.3	77.9	6.0	61.4	4.1	123.1	6.2	81.1	5.9
14	54.4	4.2	112.6	4.4	70.6	4.2	53.0	4.3	112.7	4.6	72.8	4.5
15	56.1	2.1	111.6	2.0	71.6	2.4	56.5	1.9	111.6	2.1	70.4	3.0
16	63.1	2.6	123.8	2.0	75.4	2.3	63.3	2.9	123.8	2.1	79.3	3.2
17	62.5	4.8	125.4	4.2	80.3	3.7	62.3	5.2	125.3	4.2	83.7	3.8
18	60.6	1.8	120.8	2.2	73.5	2.3	60.0	2.4	120.6	2.2	74.0	2.7
19	59.7	1.6	122.9	3.0	77.7	4.6	58.2	3.6	122.7	2.8	81.5	4.3
20	74.0	3.0	131.1	3.2	86.5	4.4	78.5	3.9	131.2	3.3	82.6	4.4
21	52.8	3.6	110.4	2.3	72.6	3.6	51.2	4.8	110.3	2.4	75.3	3.7
22	59.4	4.1	115.7	3.1	74.8	3.1	59.1	3.4	115.6	3.2	80.5	5.5
23	59.2	2.8	114.9	4.1	78.2	3.6	59.4	4.7	114.8	4.1	80.6	3.8
24	62.4	3.3	124.2	2.5	80.8	2.8	62.7	2.9	124.2	2.5	79.6	3.9
25	68.3	2.2	126.9	4.5	86.1	4.8	68.5	3.0	126.7	4.5	84.2	3.5

Table 2.6   *Orthopantomogram (OPT) versus lateral cephalogram, average intraclass correlation coefficients (ICC), confidence intervals (CI) and F-tested differences (p-values). Co-Go = condylion-gonion, Co-Me = condylion-menton, Go-Me = gonion-menton*

	Co-Go		Co-Me		Go-Me	
	ICC	CI	ICC	CI	ICC	CI
OPT	0.77	0.61-0.89	0.73	0.58-0.86	0.53	0.44-0.78
Lateral Cephalogram	0.72	0.57-0.86	0.71	0.56-0.85	0.61	0.37-0.73
p-value	0.127		0.343		0.071	

soft tissue, instead of cadavers, probably favors our measurements because real soft tissue can make identification of bony landmarks more difficult.

Very few studies have compared measurements between the OPT and lateral cephalogram. One study concluded that an OPT can provide angles representing vertical dimensions of craniofacial structures, but that measurements are not reliable enough to give accurate additional information compared with a lateral cephalogram (Akcam et al., 2003). Our findings also show that vertical measurements (Co-Go and Co-Me) have a better correlation than a horizontal measurement (Go-Me).

However, our study shows no significant differences between the OPT and lateral cephalogram; although, the measurement Go-Me tends to be better in the lateral cephalogram (p = 0.07). A possible explanation for the same performance of the OPT may lie in the overlap between the right and left condyle in the lateral
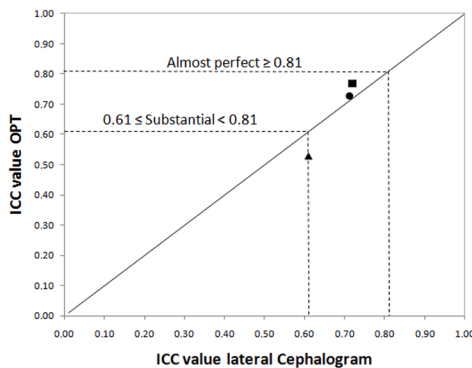

Figure 2.4   *Average intraclass correlation coefficient (ICC) values of orthopantomograms (OPT) versus lateral cephalogram landmark measurements. ▲ = gonion-menton left and right, ● = condylion-menton left and right, ■ = condylion-gonion left and right*

Table 2.7   *Orthodontists versus maxillofacial surgeons, average intraclass correlation coefficients (ICC), confidence intervals (CI) and F-tested differences (p-values) for the orthopantomgram (OPT) and lateral cephalogram. Co-Go = condylion-gonion, Co-Me = condylion-menton, Go-Me = gonion-menton.*

	Co-Go		Co-Me		Go-Me	
OPT	ICC	CI	ICC	CI	ICC	CI
Orthodontists	0.81	0.64-0.91	0.87	0.78-0.94	0.55	0.37-0.75
maxillofacial surgeons	0.80	0.62-0.92	0.65	0.44-0.82	0.55	0.37-0.75
p-value	0.478		0.000*		0.877	
	Co-Go		Co-Me		Go-Me	
Lateral Cephalogram	ICC	CI	ICC	CI	ICC	CI
orthodontists	0.81	0.68-0.91	0.82	0.64-0.92	0.58	0.35-0.78
maxillofacial surgeons	0.68	0.50-0.84	0.66	0.47-0.83	0.61	0.44-0.79
p-value	0.000*		0.000*		0.117	

* p < 0.001

cephalogram (Adenwalla et al., 1988; Sekiguchi and Savara, 1972), which negatively affects measurements involving Co. This may be in contrast to Akcam et al. (2003), who described the occurrence of condylar asymmetry in OPTs, which could lead to less reliable identification of Co on the OPT. According to our study, repositioning of the skull and slight positional changes of the skull had no significant effect on the tracing accuracy of the mandibular landmarks. This means that when a strict protocol is used, measurements can be highly reliable. Iron bullets, taped to both sides of the mandible before imaging, were used to determine the magnification factor in our OPTs.
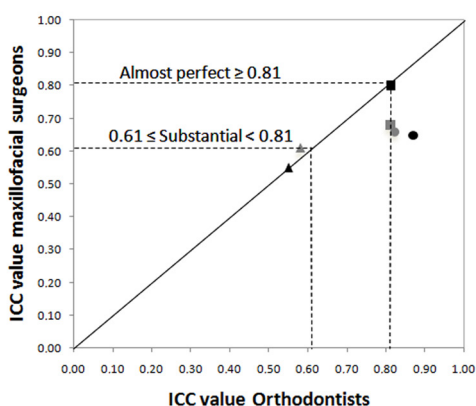

Figure 2.5   *Average ICC values of orthodontists versus maxillofacial surgeons landmark measurements. ▲ = Gonion-Menton left and right, ● = Condylion-Menton left and right, ■ = Condylion-Gonion left and right. light shades = lateral cephalogram, dark shades = OPT*

However, in patients, this could lead to scattering throughout the OPT. Only OPTs made by the same kind of x-ray device and protocol can be used within one study. This makes intercenter studies more difficult.

In the present study, ICCs were used to test reliability. This kind of statistical analysis can clearly reveal differences between methods but does not show the absolute reliability of the method or its precision. In general, the reliability of measurements of a lateral cephalogram is considered accurate enough to measure and analyze growth or treatment results (Geelen et al., 1998; Houston et al., 1986). Growth of the mandible is a complex phenomenon occurring in all three planes of space, and it should ideally be studied on three-dimensional scans or models. In this era, these possibilities are now widely available. However, for growth studies done over the past 20 years, those three-dimensional records were not available. Therefore, most growth studies at this time use two-dimensional records. In our study, maxillofacial surgeons had significantly lower ICC scores than orthodontists. One reason for this difference may be that orthodontists tend to think in terms of tenths of millimeters; whereas, maxillofacial surgeons probably think in larger measures and may have less affinity with tracing than orthodontists. Differences in experience are probably not important in our study, which is in agreement with others (Savage et al., 1987), who report that the experience of the observer (1, 2, or 3 years of experience) in locating landmarks does not influence the landmark identification with replicate identification. Another explanation for these differences could also be that the degree of error depends on individual conceptions of landmark definition and perception of landmark location, rather than on training and experience (Lau et al., 1997). Our study shows no significant differences in the reliability of length measurements between the OPT and lateral cephalogram.

Therefore, the choice of whether to use an OPT or lateral cephalogram will probably depend on the clinician's personal experience; both methods can be equally well used. These findings may offer a simple clinical tool to measure the mandible in patients with hemifacial microsomia. The possibility to roughly estimate mandibular lengthening needed with distraction osteogenesis and to evaluate the effects of treatment will be subject to future research.

In conclusion, measurements of mandibular lengths (such as Co-Go, Co-Me, and Go-Me) on the lateral cephalogram are as effective as on an OPT. These measurements offer a simple clinical tool to measure the length of the mandible.

2.5   Acknowledgments

2.6   References

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Chapter 3

Changes of mandibular ramal height, during growth in unilateral Hemifacial Microsomia patients and unaffected controls

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Abstract

The aim of this study was to design mandibular ramal height growth curves for patients with HFM and compare those with the curves for a Dutch reference population. Two hundred fifty-one pre-operative orthopantomograms (OPTs) from 84 patients with unilateral HFM were used in conjunction with a control set of 2260 OPTs from 329 healthy individuals from the Nijmegen Growth Study (NGS) to determine mandibular ramal distances. For types I/IIa and IIb/III, and for both sides, growth curves were constructed for mandibular ramal height with a linear curve-fitting procedure. This procedure revealed a significant difference between HFM patients and the NGS control group ($p < 0.001$); Both in the mild and severe group mandibular ramal height differed significantly between the affected and non-affected side ($p < 0.001$). Growth was similar between HFM patients and the NGS control group. HFM patients therefore start with a smaller mandible and end with a smaller mandible, but experience growth similar to the Dutch normal population. These growth curves may aid the timing and determination of the combined surgical orthodontic treatment plan for HFM patients.

3.1   Introduction

Hemifacial microsomia (HFM) is an asymmetric unilateral underdevelopment of skeletal, soft-tissue, and neuromuscular structures of the face and skull, which are derived from the first and second branchial arches (Kearns et al., 2000). After cleft lip and palate and craniosynostosis, HFM is the third most common congenital craniofacial anomaly, with an incidence ranging from 1:3500 (Poswillo, 1973) to 1:5600 (Grabb, 1965). The most obvious clinical presentation of HFM is mandibular hypoplasia (Kaban et al., 1998) combined with unilateral or bilateral microtia (Rollnick et al., 1987). The etiology of HFM is heterogeneous but has been associated with vascular perturbation and/or neural crestopathy (Hartsfield, 2007). While the underlying pathogenesis of HFM is still unclear, a candidate causal gene has been mapped to 14q32 in one family; however, linkage to this region has been excluded in another family, suggesting genetic heterogeneity (Kelberman et al., 2001).

Normal mandibular development starts in the sixth week after fertilization and continues until the twelfth week, when the architecture of the mandibular body is complete (Lee et al., 2001). A wide variation in shape, length, and function is observed in patients with HFM. Both unilateral and bilateral expressions can occur, although the unilateral presentation is observed most often (Poswillo, 1973). This variable presentation has led to the introduction of several classification systems (Figueroa and Pruzansky, 1982; Cousley, 1993; Horgan et al., 1995). Pruzansky (1969) developed a system restricted to the anatomy of the mandible and the temporomandibular joint that divides the phenomenon into three types. In 1988, Kaban et al. (1998) expanded this classification to four types by dividing the second Pruzansky class into types IIa and IIb, an adjustment based on the function of the temporomandibular joint and on surgical reconstruction of the mandible.

Patients with HFM types I and IIa retain accurate function and position of the temporomandibular joint; types I and IIa are functionally equivalent. Treatment of these patients can consist of mandibular lengthening by distraction osteogenesis or conventional osteotomy (Meazzini et al., 2005). In type IIb and III patients, both function and position of the temporomandibular joint are inadequate, often requiring reconstruction of the mandible to improve function (James and Ma, 1997). Although the treatment of facial asymmetry in HFM patients has been investigated, the optimal timing of the intervention is unclear (Kaban, et al., 1998; McCarthy et al., 1999;

Honig et al., 2002; Meazzini, et al., 2005; Nagy et al., 2009), likely due to uncertainty regarding preoperative facial growth. Whether or not the condition worsens over time continues to be debated (Rune et al., 1981; Polley et al., 1997; Kaban, 2009), leading to a controversy over the desirability of early or late treatment in HFM (Nagy, et al., 2009). It is widely believed that mandibular asymmetry should be addressed in adolescence; on the other hand, early distraction (which generally takes place at a median age of 4.8 years, but can take place anytime from 2 to 10 years of age) is common practice, and does not change the deficient growth of the distracted bone (Nagy, et al., 2009). Surgical correction seems stable over 5-10 years of follow-up (Shetye et al., 2006). No data are available on long-term development of the mandibular ramal height in HFM in relation to the severity of the mandibular malformation, information that could lead to a more functional perspective on the timing of treatment.

Therefore, knowing the growth potential and expected change of the mandibular ramus is of great importance for improved individual treatment planning. To our knowledge only longitudinal studies with few patients or cross sectional studies exist (Kaban, et al., 1998; Polley, et al. 1997). To gain further insight into the most appropriate intervention timing in HFM patients, this study aimed to design and compare linear ramal height growth curves for children with unilateral HFM in the non-operated mandible and for the Dutch normal population. We hypothesize that no difference exists between the ramal heights of the NGS control group and HFM patients, that no difference exists between the ramal heights of 'severe' and 'mild' HFM patients.

3.2   Materials and methods

3.2.1   *Patients*

Between 1980 and 2005, 84 consecutive patients diagnosed with unilateral HFM or Goldenhar syndrome were seen at the Department of Orthodontics, Erasmus Medical Center Rotterdam, The Netherlands and included in this study. Patients were classified into four types based on the Pruzansky/Kaban classification by a maxillofacial surgeon, a plastic surgeon, and an orthodontist (Table 3.1); a consensus decision was reached in cases of disagreement. The HFM patients were then regrouped into a 'mild' group (I and IIa, 23 and 26 patients, respectively) and a 'severe' group (IIb and III, 25 and 10

patients, respectively). Since patients were diagnosed and treated (or operated on) at different ages (mean age, 9.9 years; standard deviation (SD) = 4.7 years), the number of orthopantomograms (OPTs) varied per patient, with 2.95 mean pre-operative OPTs per patient. The use of human subjects followed an approved protocol and satisfied the requirements of our institutional review board (approval number MEC 2008-258).

3.2.2 *Controls*

Ramal measurements (see below) from HFM patients were compared with OPT measurements from children in the Nijmegen Growth Study (NGS) control group (Table 3.2), a five-year mixed longitudinal study of 482 children (mean age, 10.9 years; age range, 4 to 14 years; SD = 1.7 years) (Prahl-Andersen et al., 1979). Records of 149 boys and 180 girls without HFM were accessed from this database for ramal measurements.

3.2.3 *Ramal measurements*

OPTs of patients during growth were included. OPTs were excluded when surgical intervention had taken place, because surgical intervention can influence growth. Digitized OPTs from film (before 2003) and digital OPTs (from 2003 to the present) were both imported to a cephalometric measurement program (Viewbox version 3.1.1.12, DHAL software, Kifissia, Greece) (Halazonetis, 1994).

One observer performed the measurements according to a method described earlier (Ongkosuwito et al., 2008). The distance between the condylion (Co, the most posterior superior point on the mandibular ramus (Ongkosuwito, et al., 2008)) and the gonion landmark (Go, the constructed point of intersection of the ramus plane and the mandibular plane (Athanasiou, 1995)) is the measured distance for the unaffected side (CoGo), and is called ramal height unaffected side. At the affected side, the condyle is often missing or malformed, so we used the distance (QZ) between a point which is the upper most distal point (Q) of the affected side and a constructed point of intersection of the ramus plane and the mandibular plane (Z) for the affected side in all cases. In cases where ramus plane was unclear or nonexistent, point Z was defined as the lower most distal point. This height QZ is called ramal height affected side.

Table 3.1 *Pruzansky/Kaban classification, number of patients (male/female), and number of orthopantomograms for hemifacial microsomia (HFM) patients and the Nijmegen Growth Study (NGS) control group*

Classification type	Number of patients (male/female)	Number of orthopantomograms
Hemifacial microsomia		
I	23 (13/10)	71
IIA	26 (12/14)	78
IIB	25 (10/15)	66
III	10 (2/8)	36
Total	84 (37/47)	251
Nijmegen Growth Study controls		
Total	329 (149/180)	2260

Table 3.2 *Intra-class correlation coefficients (ICCs) with 95% confidence intervals (CIs) for intra- and inter-observer agreement*

	Inter-observer agreement		Intra-observer agreement	
Measurement	QZ (affected)	CoGo (unaffected)	QZ (affected)	CoGo (unaffected)
ICC	0.973	0.709	0.996	0.943
95% CI	0.928-0.990	0.399-0.874	0.989-0.998	0.863-0.977

3.2.4   Statistics

To calculate intra-examiner reliability, 20 randomly selected OPTs were measured twice by the same observer. To determine inter-examiner reliability, a second observer measured the same 20 OPTs. Intra-examiner and inter-examiner reliabilities were assessed with the intra-class correlation coefficient (ICC) (Landis and Koch, 1977) on the level of measured distances. The ICC Statistical Package for the Social Sciences version 11.5 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. ICC values range from 0 to 1; ICCs of 0.61-0.80 are interpreted as being in substantial agreement and ICCs of 0.81-1.00 indicate almost perfect agreement.

The scores for HFM patients were compared to the NGS control group scores

using a linear curve-fitting procedure to describe the general trend of growth based on a linear function. The function used for the 50th percentile curve of the data was Y = AX+B, in which A stands for increment (mean height over time) and B for the intercept (height at age zero). The following functions were estimated:

1. Control subjects from the Nijmegen Growth Study (NGS) control group (boys and girls together);
2. HFM patients;
3. HFM patients divided into 'mild' (I, IIa) and 'severe' (IIb, III) groups, per affected or unaffected side.

At least two consecutive OPTs were needed to determine the ramal increment. After the estimation, patients with one radiographic measurement were used to improve the earlier established linear curves. The data derived from these OPTs did not directly contribute to the linear curves that represent the ramal increment; their contribution was to the calculations for the intercept, which represents the level of the curve at a given age. The NGS control group score was graphed with the HFM patients' scores, while the 'mild' group and 'severe' group were determined separately.

To ensure that possible measured differences were not caused by an OPT machine difference, ratios of the population means were also calculated, with significance levels determined by Student's paired t-test. The level of significance was established at a p-value of 0.05. The mean ratio (left side versus right side) for the NGS control group ($n = 2260$) was compared to the mean ratio (affected versus unaffected side) for HFM patients ($n = 216$). The mean ratio (affected versus unaffected side) for patients with mild HFM ($n = 148$) was compared to that for patients with severe HFM ($n = 68$).

3.3   Results

The reliability of examiners was tested and, with the exception of the CoGo inter-observer agreement (0.709), all measured distances were nearly perfect (0.81-1.00). All intra-observer ICC values were also within the range of 0.81-1.00 (Table 3.2). Therefore, the following results were not influenced by unreliable measurements.

We started with the null hypothesis that no difference would exist between the ramal heights of the NGS control group and HFM patients. We found significant differences between the NGS control group ramal height and both affected and unaffected ramal heights in HFM patients. A significant difference was also found

within the HFM patients between affected and unaffected ramal heights ($p < 0.001$). No difference was found in increment (curve intercept) between the NGS control group and that of HFM patients, or within the ramal heights of HFM patients (Table 3.3, Figure 3.1).

We hypothesized that no difference would exist between the ramal heights of 'severe' and 'mild' HFM patients. We detected no significant differences between the 'severe' and 'mild' groups (Table 3.4, Figure 3.2).

We also hypothesized that possible measured differences were caused by an OPT machine difference. The ratios between population means of the NGS control group (0.998) and HFM patients (0.821) were significantly different ($p < 0.001$), as were the differences between the population means of the 'mild' (0.888) and 'severe' (0.672) groups ($p < 0.001$). Therefore, we were able to dismiss the hypothesis that the observed differences were caused by an OPT machine difference.

3.4   Discussion

Our starting point was that no difference exists between ramal heights in the NGS control group and HFM patients. We observed a clear ramal height difference between HFM patients (both affected and unaffected sides) and the NGS control group, but the increase over time was in both groups the same (Table 3.3 and Figure 3.1). This significant ramal height difference also occurred within HFM patients between affected and unaffected ramal heights. Furthermore, our results indicate a similar constant increase over time but a clear difference in ramal height between the 'mild' and 'severe' HFM groups (Table 3.4 and Figure 3.2).

We found strong relationships of ramal height and increment between HFM patients and the NGS control group, although our study does have limitations. We were unable to distinguish between boys and girls in the HFM patient group. In normal growth, girls grow differently in comparison with boys, since girls reach their peak height of growth velocity earlier than boys do. Our study contained a limited number of patients from a statistical point of view (Table 3.1), and this may be an important reason that no gender distinctions emerged from the current data. The small number of patients in the current study hinders the collection of sufficient data for each HFM type, especially type III, since type III is a more rare condition (Table 3.1). We regrouped the data into 'mild' (I and IIa) and 'severe' groups (IIb and III) in an attempt

Table 3.3 *Ramal height (mm) and increment (mm) at age 10.5 years for the Nijmegen Growth Study (NGS) control group subjects and both sides for hemifacial microsomia (HFM) patients. Affected sides are designated as 1; unaffected sides are designated as 2. n, number of sides; SD, standard deviation.*

Ramal height (mm)	n_1	n_2	$Mean_1$	SD_1	$Mean_2$	SD_2	p-value
Affected (n_1) versus unaffected (n_2)	41	41	45.97	8.23	55.97	4.29	0.001
Affected (n_1) versus NGS (n_2)	41	318	45.97	8.23	61.01	3.47	0.001
Unaffected (n_1) versus NGS (n_2)	41	318	55.80	4.29	61.01	3.47	0.001
Ramal increment (mm)							
Affected (n_1) versus unaffected (n_2)	41	41	1.34	0.98	1.54	0.64	N.S.
Affected (n_1) versus NGS (n_2)	41	318	1.34	0.98	1.62	0.97	N.S.
Unaffected (n_1) versus NGS (n_2)	41	318	1.53	0.64	1.62	0.97	N.S.

to overcome this shortcoming. This regrouping was done in a similar way as it was done in the Pruzansky/Kaban classification study (Kaban, et al., 1988). The regrouping was based on temporo-mandibular function: the mild group functions well, while the severe group does have functional problems (Kaban, et al., 1988). One of the main difficulties in capturing an increase of the ramal height over time in HFM is to identify reliable landmarks on the affected side. We chose artificial landmarks which show anatomical similarity to condylion and gonion of the unaffected side. This does not mean that these artificial points behave in the same way as Condylion and Gonion. Changes are expected but may explain just a part of the complete growth on the affected side. We have chosen to execute this study from OPTs, since specific mandibular measurements from OPTs can be as accurate as measurements from lateral cephalograms (Ongkosuwito, et al., 2009). Additional two-dimensional (2D) measurements from lateral or posteroanterior cephalograms (Leonardi et al., 2008) were also available, but were considered less useful. Although various other imaging and measuring methods have been used to analyze craniofacial development and asymmetry over time (Kaban, et al., 1998), OPTs were much more available longitudinally than other 2D or three-dimensional (3D) scans or models; preferably, the mandible should be studied in 3D, since growth is a complex phenomenon occurring simultaneously in all three planes of space. Therefore treatment planning such as the maxillo-mandibular driven distraction osteogenesis (Nakajima et al., 2011) should be done in 3D as well (Aboul-Hosn Centenero and Hernández-Alfaro, 2011). However timing of treatment and treatment modality should be carefully chosen,
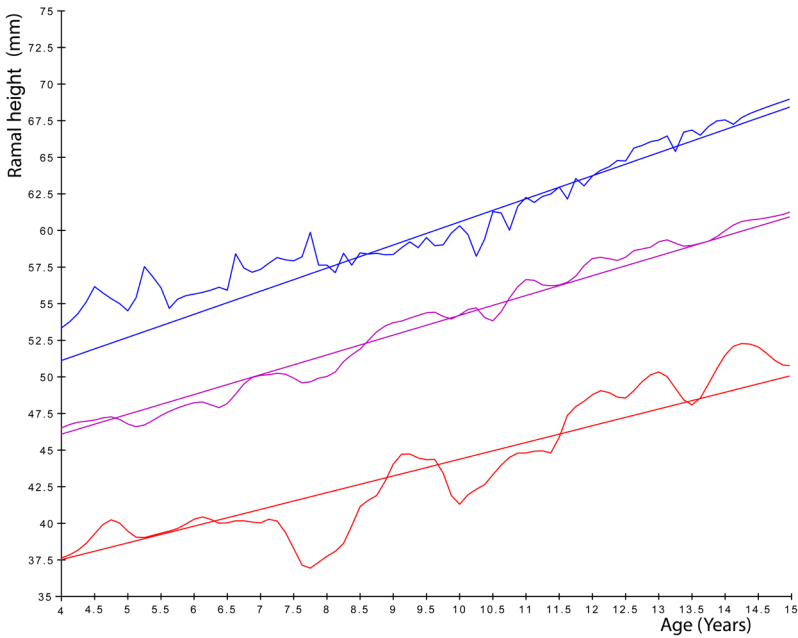
Figure 3.1   *Statistically significant differences in constructed linear growth curves between the ramal height for the Nijmegen Growth Study (NGS) control group (blue) and that of HFM patients (purple and red), and significant differences between the unaffected side (purple) and affected side (red)*

since recurrence for distraction osteogenesis is reported (Meazzini, et al., 2011*).*

The etiology of HFM is diverse and the way environmental factors interact with genetic factors remains unclear. To gain more insight, craniofacial growth studies also remain important (Hartsfield, 2007). Although craniofacial growth has been studied in HFM patients (Rune, et al., 1981; Kaban, et al., 1998; Kusnoto et al., 1999; Shetye, et al., 2006), a clear view of the relationship between mandibular morphological changes and severity is lacking. Some researchers state that unilateral HFM is mainly characterized by the underdevelopment of one side of the mandible, resulting in facial asymmetry (Kaban, et al., 1998). However, a degree of mandibular asymmetry is evident in unaffected individuals, and a clear cut-off for the transition from normal to abnormal has not yet been defined (Liukkonen et al., 2005). Progressive facial asymmetry in HFM patients due to restriction of the growth of the mandible still remains controversial. Kaban et al. (2009) found, based on longitudinal clinical observations, a restricted growth of the
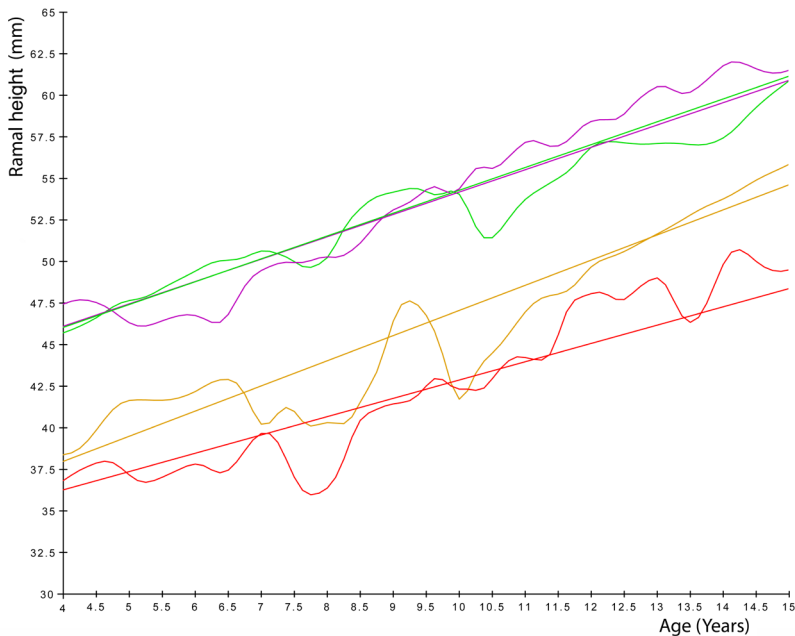
Figure 3.2   *Statistically significant differences in constructed linear ramal growth curves between the unaffected side (green) and the affected side (yellow) in patients with 'mild' hemifacial microsomia (HFM) and the unaffected side (purple) and affected side (red) in patients with 'severe' HFM. No statistically significant differences were observed between the ramal heights for patients with 'mild' (Pruzansky/Kaban I and IIa) and 'severe' (IIb and III) HFM*

mandible, which plays a role in the progressive distortion of both the ipsilateral and contralateral facial skeleton. Polley et al. (1997) concluded that growth of the affected side of the mandible parallels growth of the unaffected side in HFM, and Kusnoto et al. (1999) found that the affected and unaffected sides grew at approximately the same rate regarding both ramal height and body length. Our data support the view that all sides experience the same growth rate, but HFM patients start with a smaller height (Table 3.3, Figure 3.1). We have demonstrated a two-sided underdevelopment phenomenon for HFM patients; the affected and unaffected ramus are both smaller in height but equal in growth to measurements from the reference group (Table 3.3, Figure 3.1).

Similar growth in HFM patients, who start, however, with a smaller mandibular ramal height compared with the NGS control group, suggests that any surgical intervention should be performed at the end of growth. Natural growth may influence whether an individual patient requires distraction osteogenesis or temporomandibular

joint reconstruction at an earlier stage or only at follow-up. Quantitative growth curves (Chvatal et al., 2005) can therefore aid in timing and determining the combined surgical orthodontic treatment plan for HFM patients.

In summary, HFM patients start with a shorter ramal height and end with a shorter ramal height, although growth is the same in HFM patients and controls from the Dutch normal population. In HFM patients, ramal height is smaller on both sides, which means that growth is characterized not simply by unilateral underdevelopment, but by a complex 3D phenomenon.

3.5   Acknowledgments

3.6   References

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Chapter 4

Dental development in Hemifacial Microsomia

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Abstract

Hemifacial Microsomia (HFM) is a congenital disorder marked by facial asymmetry. Whether facial asymmetry accounts for asymmetrical dental development is unknown. There are few data on dental development relative to mandibular development or severity of HFM, or on development over time. We hypothesized that when mandibular development was severely disturbed, local dental development was also affected. We compared dental development scores between affected and non-affected mandibular sides in patients with HFM (n = 84) and compared these data with those collected from Dutch control children (n = 451). Logistic functions were constructed for dental age over time for all four Pruzansky/Kaban types. The results showed a tendency toward delayed dental development in Pruzansky/Kaban types IIb and III at younger ages. The temporary delay of tooth formation in patients with severe forms of HFM and the distribution of agenetic teeth suggest an interaction between mandibular and dental development.

4.1   Introduction

Hemifacial Microsomia (HFM) is a congenital disorder marked by facial asymmetry and ear malformation. The clinical appearance derives from asymmetric unilateral underdevelopment of structures originating from the first and second branchial arches. The causal gene could be mapped to 14q32 in one family but not in another affected family, suggesting genetic heterogeneity (Kelberman et al., 2001). The pathogenesis is still unclear, but HFM has often been associated with some vascular perturbation and/or neural crestopathy (Hartsfield, 2007). Timing, extent, and location of the disturbance vary widely, which could explain the wide spectrum of clinical findings (Loevy and Shore, 1985). In HFM, underdevelopment occurs in facial structures such as the ear, mandible, maxilla, zygoma, temporal bone, fifth and seventh cranial nerves, and associated musculature and soft tissue (Grayson et al., 1983). Orbital malformations vary from minimal malformations to anophthalmia (Jackson, 2004), ear manifestations from a degree of microtia to deafness and deficiency of the external auditory meatus. Multiple auricular appendices are constant findings (Gorlin et al., 1963; Gorlin, 1990). A specific variant of the HFM spectrum is the Goldenhar syndrome. In this syndrome, epibulbar dermoïds and vertebral anomalies are also present (Gorlin et al., 1963).

A classification restricted to the anatomy was developed from one of the earliest studies on mandibular development in HFM (Pruzansky, 1969); in type I, the temporomandibular joint and ramus are well formed but small. In type II, the temporomandibular joint, ramus and glenoid fossa are hypoplastic, malformed and sometimes malpositioned. In type III glenoid fossa, ramus and temporomandibular joint are absent. Later this classification was adjusted into four types by dividing the second type of the Pruzansky classification into type IIa and IIb. This adjustment was based upon the function and surgical reconstruction of the mandible (Kaban et al., 1988).

So far dental development in HFM received relatively little attention (Loevy and Shore, 1985). Whether mandibular asymmetry accounts for asymmetrical dental development remains unclear. Normal mandibular development starts in the sixth week after fertilization and continues until the twelfth week, at which time the architecture of the mandibular body is complete (Lee et al., 2001). Normal dental development starts with the deciduous teeth at 6 weeks of gestation (Nanci, 2007). Dental maturation has been found to be normal when measured at a single age (Loevy and Shore, 1985) but

dental development has not been recorded over time. In contrast, a difference in tooth width was found between HFM patients and non-affected controls, whereby in HFM the first permanent molars on the affected side were smaller than on the non-affected side, while both molars were smaller than in control patients (Seow et al., 1998). A higher incidence of hypodontia was also found in HFM patients (Maruko et al., 2001).

Data are lacking on dental development in relation to mandibular development and the severity of HFM, and on development over time. The aim of our study was to compare dental development between affected and non-affected mandibular sides in patients with HFM and to compare these data to those collected from Dutch control children. We hypothesized that severely disturbed mandibular development was associated with delayed dental development.

4.2   Subjects and methods

4.2.1   Subjects

Eighty four patients (37 boys and 47 girls) diagnosed with HFM or Goldenhar syndrome, between January 1980 and December 2005 at the Erasmus MC Craniofacial Center, Sophia Children's Hospital in Rotterdam, The Netherlands, were included. The use of human subjects followed an approved protocol and satisfied the requirement of our IRB (approval number MEC 2008-258). Only patients with unilateral expression and at least one orthopantomogram (OPT) were included. Patients were subdivided into four groups according to their Pruzansky/Kaban type (Pruzansky, 1969; Kaban et al., 1988; Gorlin et al., 2001). The distributions of patients and mandibular sides are shown in Table 4.1.

OPTs of these patients were taken before any surgical intervention had taken place. The median age at which the OPTs were taken was 10.0 yr with a range from 3.7 to 31 years.

The dental development scores of patients with HFM were compared with those determined from OPTs of 451 Dutch control children (225 boys and 226 girls) included in an earlier published study (Leurs et al., 2005). The median age at which the OPTs were taken was 7.7 yr with a range from 2.9 to 16.9 yrs.

4.2.2 Dental development scores

Dental development was scored from OPTs; 364 OPTs from 84 patients with HFM were used. Dental age was determined for both mandibular sides separately according to the Demirjian method (Demirjian et al., 1973). Each tooth of the mandible (if present) was given a score from A to H according to Demirjian's criteria. These scores were converted into numbers and summed for each mandibular side; this score is referred to as the maturity score (Demirjian, 1993). When two or more mandibular teeth were agenetic on the same side, the OPTs were excluded because no dental maturity score can be determined reliably in these cases. If only one tooth was missing, a mean age was determined from the mandibular teeth present and adjusted for the missing tooth (Table 4.2).

Two examiners were trained using a tutorial program, available on CD-ROM(Demirjian, 1993). To assess intra- and interexaminer reliability both examiners randomly rescored 40 mandibular sides. All of the 364 OPTs were scored by one examiner.

4.2.3 Statistical analysis

Intra-examiner and interexaminer reliability are expressed using the intra-class correlation coefficient (ICC) for the dental maturity score. The ICC is comparable to the kappa coefficient. ICC values range from 0 to 1. An ICC of 0.61-0.80 is interpreted as substantial agreement, and an ICC of 0.81-1.00 as an almost perfect agreement.

Table 4.1 *Patient distribution and measured mandibular sides. The 24 sides that were not measured (numbers in parentheses) were the affected sides of 11 patients (13 %) and the unaffected side of one patient (1.2%)*

Pruzansky/Kaban type	Patients, n		affected sides on available OPTs, n		
	M	F	Affected	Non-affected	Total sides
I	10	13	75	75	150
IIa	12	15	130	131	261
IIb	10	16	113	127	240
III	5	3	22	29	51
Total	84				702(24)

M, males, F, females; OPT, orthopantomogram

Table 4.2 *Number, percentage, and confidence intervals (CIs) of patients with agenetic mandibular teeth*

Pruzansky/ Kaban type	patients without agenesis, n		patients with agenesis, n		95% CI for agenesis	p-value
	n	%	n	%		
I	23	31	0	0		
IIa	25	34	2	7	-0.03:0.18	
IIb	23	31	3	12	-0.02:0.25	
III	3	4	5	63	0.19:1.06	p<0.01
Total (n=84)	74	100	10	12	0.05:0.19	p<0.01

Calculations were performed using the statistical software package SPSS version 11.5 (SPSS Inc., Chicago, IL, USA).

The scores for patients with HFM were compared to the scores for Dutch control children using a logistic curve-fitting procedure (Leurs et al., 2005). The logistic curve describes the general trend of growth based on the growth curve for stature. The function used for the 50th percentile curve of the data was $Y = 100*\{1/(1 + e^{-v\,(x-m)})\}$, in which v stands for velocity (mean dental age over time) and m for mean age at the 50th dental age percentile. Several logistic functions were estimated:

1. For control children (boys and girls together), $Y = 100*\{1/(1 + e^{-0.559(x-5.586)})\}$ (Leurs et al., 2005).
2. For patients with HFM divided into Pruzansky/Kaban types, per affected or unaffected side.
3. For patients with HFM divided into Pruzansky/Kaban types, both sides together.

For dental development over time to be determined, at least two consecutive panoramic radiographs are needed. For logistic curve fitting at least three measurements are necessary. After the estimation the patients with one or two radiographic measurements were used to improve the earlier established logistic curves for estimating the population logistic mean. The data derived from these OPTs do not directly contribute to the calculation of velocity, however, their contribution to calculating the level of the curve at a certain age is substantial.

The Dutch normal score was graphed and a mean for every Pruzansky/Kaban

type was determined. To calculate the 95th and 5th percentiles for the norm logistic curve, 1.96 times the SD was added and subtracted.

To compare the distribution of agenetic mandibular teeth, a one-sample Students' t-test was used.

4.3 Results

4.3.1 Measurement error

The ICC for the intra-examiner reliability was 0.98 (95% confidence interval [CI], 0.97-0.99). The ICC for interexaminer reliability was 0.99 (95% CI, 0.98-0.99). Both scores are considered very high.

4.3.2 Dental development scores

For patients with HFM, the difference in dental development between the affected and non-affected sides for the mean or velocity at the 50th dental age percentile was not significant, with the exception of the mean dental age of patients with Pruzansky/Kaban type III, for whom the affected side showed significantly delayed dental development (Table 4.3). When comparing both sides to the Dutch norm, the mean dental age for patients with Pruzansky/Kaban type I was significantly younger than the norm and that for patients with type IIb and III was significantly older (Table 4.3). It also appeared that catch-up growth occurred for patients affected by types IIa- III. In these types, the velocity was significantly greater than that of the norm (Table 4.3).

These significant differences support the tendency displayed in the graph constructed from the logistic functions showing that patients with Pruzansky/Kaban types IIb and III have delayed dental development early in life, marked by a dental age in the 5th percentile of normal dental age (Figure 4.1).

4.3.3 Distribution of agenetic mandibular teeth

The distributions of agenetic mandibular teeth within patients with Pruzansky/Kaban type III and within the total of missing teeth were significantly different (Table 4.2).

4.4 Discussion

Our aim was to investigate asymmetry of dental age progress and prevalence of hypodontia in patients with HFM and to compare these data to those collected from

normal Dutch children. Dental age assessment by the Demirjian method (Demirjian et al., 1973) is the most precise and accurate method as compared to other dental age estimation methods (Hagg and Matsson, 1985; Maber et al., 2006). We used population-adjusted scores for Dutch children because there are differences between populations (Leurs et al., 2005; Maber et al., 2006).

In these patients with HFM we found no significant difference between dental development of the affected and non-affected side. We also did not find progressive development over time (any differences in velocity) between affected and non-affected sides. Neither did we find a difference in any other velocity pointing to the absence of a progressive developmental effect over time. This means that asymmetric progression of dental development probably does not occur. However, when both sides were considered together, the data differed significantly from that for the Dutch norm. In Pruzansky/Kaban types IIb and III dental development was significantly later than the norm. However the development over time was at the 50th percentile faster than the norm, suggesting the presence of a dental development catch-up phenomenon.

Table 4.3 *Logistic fits between sides and for both sides considered together. Velocity is mean maturity score over time; mean is mean maturity score at the 50th dental age percentile. The deviation is the mean standard deviation of the maturity percentage over time*

Pruzansky/ Kaban type	Side	(n)	Velocity	Mean	Standard deviation	p-value
I	affected side	75	0.577	5.380	8.155	
	non-affected side	75	0.580	5.307	7.219	
	both sides	150	0.575	5.334[‡]	7.690	p<0.05[‡]
IIa	affected side	130	0.628	5.460	5.600	
	non-affected side	131	0.610	5.501	5.794	
	both sides	261	0.617[‡]	5.476	5.703	p<0.05[‡]
IIb	affected side	113	0.686	6.084	4.610	
	non-affected side	127	0.633	6.087	5.659	
	both sides	240	0.658[‡]	6.085[‡]	5.207	p<0.05[‡]
III	affected side	22	0.550	6.494[†]	12.610	p<0.05[†]
	non-affected side	29	0.669	6.115	8.712	
	both sides	51	0.630[‡]	6.244[‡]	10.565	p<0.05[‡]
Dutch Norm	both sides	902	0.559	5.586	6.424	

†P-value for mean and velocity between sides ‡P-value for mean and velocity compared to the Dutch control children

The distribution of our sample population with HFM could have influenced our results. In our sample, the ratio of boys to girls was almost 1:1, which is in agreement with some earlier reports (Seow et al., 1998; Maruko et al., 2001), but differs from an earlier reported ratio of 3:2 (Grabb, 1965). The number of patients with agenetic mandibular teeth (n = 10; 12%) agrees with a previously reported rate of 17.5% (Silvestri et al., 1996). However, more recent studies reported rates of 25% (Farias and Vargervik, 1998) and 32% (Maruko et al., 2001). The frequencies of Pruzansky/Kaban types for types IIa (32.1%) and III (9.5%) were approximately the same as those reported in other studies; however, the frequencies of type I (41.6% in our study versus 27.4%) and type IIb (14.4% versus 31.0%, respectively; Grabb, 1965; Maruko et al., 2001) differed from previously reported values. Data for patients with HFM are difficult to obtain because the incidence is low, ranging from 1 in 3500 (Poswillo, 1973) to 1 in 5600 newborns (Grabb,
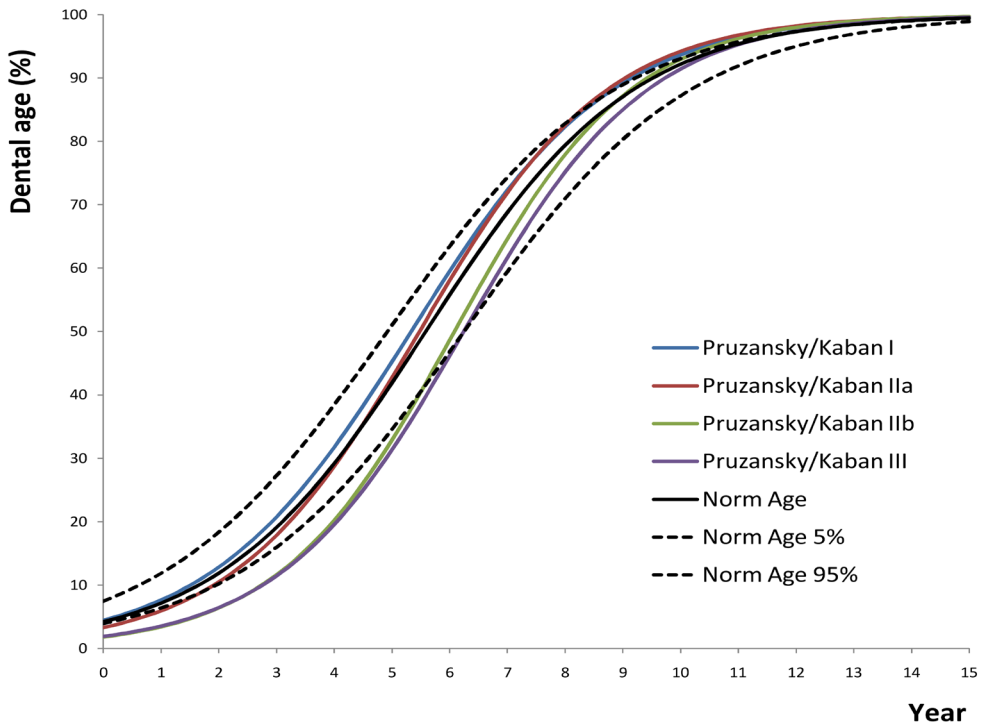

Figure 4.1   *Dental ages for Dutch control children (n=451) and patients with Pruzansky/Kaban types I (n=23), IIa (n=27), IIb (n=26), and III (n=8) according to the maturity score (Demirjian's method). The 5th, 50th, and 95th percentile lines are indicated*

1965). The low incidence makes it very difficult to collect sufficient data per severity type, especially for type III. During analysis, data for girls and boys were combined in order to attain sufficient statistical power. This was allowed since the difference between Dutch control boys and girls in the logistic curve at the 50th percentile was 0.01 (SD ± 0.03). Because there was sizable variation in the measurements taken for patients with HFM, larger sample sizes for each of the Pruzansky/Kaban types are needed to reach statistical significance.

For normal odontogenesis, the presence and interaction of normal neural crest ectoderm and of neural crest derived mesenchymal cells is required. Disturbances in the odontogenic process can produce abnormal or incomplete dental development (Shafer et al., 1983). The disturbance of mandibular growth in HFM can occur over a relatively long period of time (6-12 weeks after fertilization), which probably leads to a wide range of dental developmental disturbances ranging from delayed dental development to hypodontia. In normal development, regionally restricted expression of homeobox-containing genes is responsible for patterning of the skeletal and probably of the dental elements. Mandibular teeth also derive from the first branchial arch and originate from both the ectoderm and the underlying ectomesenchyme (Cobourne and Sharpe, 2003). Development of the jaw and teeth is a complex process involving many interacting factors and is not yet fully understood. For example, disruption of Msx-1 expression during early stages of neurulation in mice produced hypoplasia of the maxillary, mandibular, and frontonasal prominences, eye anomalies, and somite and neural tube abnormalities (Foerst-Potts and Sadler, 1997). Genes encoding for the *msx*, *dlx*, and *lhx* transcription factor families are all necessary for the progression of tooth development beyond the initiation stage (Thesleff, 2006).

Because the development of the facial skeleton and that of the teeth are spatially and temporally related, we hypothesized that a disturbance in one process would affect the other. The distribution of hypodontia in our sample supports this hypothesis since more teeth were agenetic in the patients with more severe types of Pruzansky/Kaban. This hypothesis was also supported by the tendency illustrated in Figure 4.1, which shows that both Pruzansky/Kaban types IIb and III are associated with early delayed development as compared to Pruzansky/Kaban type I, type IIa, and the Dutch norm. These results suggest that surgical treatment at a later age would be more favorable for dental development especially for patients with Pruzansky/Kaban type IIb or III. The

risk that dental development will be arrested or delayed, decreases after the age of 5.5 years.

In summary, no significant asymmetry in dental development between affected and nonaffected hemimandibles of patients with HFM was detected. Patients with Pruzansky/Kaban types IIb and III showed a delay in development as compared to patients with types I and IIa and the Dutch norm. This tendency toward dental developmental delay at a young age and the different distribution of hypodontia found in this study are suggestive of an early interaction between mandibular and dental development.

4.5 Acknowledgements

4.6   References

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Chapter 5

Craniofacial morphology in unilateral Hemifacial Microsomia

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Abstract

Hemifacial microsomia (HFM) is a complex three-dimensional congenital condition that is characterized by mandibular hypoplasia and unilateral or bilateral microtia; although, other facial structures may be affected. Little is known about craniofacial growth and morphology in patients with HFM; therefore, we examined 75 HFM patients in a longitudinal study. We hypothesized that the growth of several facial structures on both sides of HFM patients would be different compared to Dutch controls. We determined patients with HFM had more retruded mandibles and maxillae and a more vertical morphology compared to the reference population. In addition, there was a more retruded and vertical pattern on the affected side compared to the unaffected side and in patients with a severe condition compared to those with a mild condition. Individual HFM growth curves showed very high inter-variability, further strengthening the need for individualized treatment plans that consider all three dimensions and the severity of the condition.

5.1 Introduction

Hemifacial microsomia (HFM) is a three-dimensional craniofacial condition that changes over time (Kaban, 2009). The most obvious clinical presentation of HFM is mandibular hypoplasia combined with unilateral or bilateral microtia (Kaban et al., 1998; Rollnick et al., 1987). Both musculature and the facial skeleton are involved, but the degree of bony and muscular malformation appeared unrelated (Huisinga-Fischer et al., 2001). However, closer clinical inspection revealed asymmetry of the soft tissue and facial skeleton that involved the maxilla and orbit (Poon et al., 2003). There is downward growth of the naso-maxillary region on the affected side, which is probably restricted or influenced secondarily by the small mandible (Rune et al., 1981). This has not directly been associated with any known etiological factor for HFM or any defect in gene regulation affecting the maxilla directly.

The etiology of HFM is still unclear; although, it is heterogeneous and has been primarily associated with vascular perturbation and/or neural crestopathy (Hartsfield, 2007). Skeletal mandibular defects develop early, probably within the first 10 or 12 weeks of gestation (Hartsfield, 2007). Muscular defects may also originate from an event in early embryonic development, deriving from a defect in the communication between the cranial neural crest and cephalic myogenic mesodermal cells (Heude et al., 2011). Recently, studies in mice showed inactivation or the allelic reduction of *Edn1, Ednra, Dlx5, Dlx6, Gsc, Pitx1,*and *Gbx2* all resulted in a proximal defect of the developing mandible or of the middle and external ear, (Gitton et al., 2010) which is also characteristic of HFM. However, combined maxillary and mandibular pathologies are rarely associated and might correspond to earlier defects in the differentiation of cephalic neural crest cells (Gitton et al., 2010).

From a clinical perspective, the phenotype is highly variable in the extent of the deformity (Rune et al., 1981). Patients with a milder form may show more normal craniofacial growth; while, there may be limited growth in patients who have a severe form. It is unclear whether or not the mandibular growth condition worsens over time, which is likely due to the high variability (Kaban, 2009; Polley et al., 1997; Rune et al., 1981). Even less is known about maxillary growth; therefore, it is still uncertain if early or late surgical treatment is best in HFM (Nagy et al., 2009).

Further insight into the growth and most appropriate treatment time in HFM is needed; therefore, this study aimed to design craniofacial linear growth curves for the

non-operated mandible in children with unilateral HFM and for Dutch controls. The hypotheses to be tested were: a) no difference in craniofacial growth exists between HFM patients and normal Dutch children. b) no difference exists between the `mild' and `severe' types of HFM.

5.2   Subjects and methods

5.2.1   Subjects

Between 1980 and 2005, 75 consecutive patients (39 girls and 36 boys) diagnosed with unilateral HFM or Goldenhar syndrome were seen at the Department of Orthodontics, Erasmus Medical Center Rotterdam, The Netherlands and were included in this study. Patients were classified into four types based on the Pruzansky/Kaban classification (Kaban et al., 1988) by a maxillofacial surgeon, plastic surgeon, and an orthodontist. A consensus decision was reached in cases of disagreement. The HFM patients were then divided into a 'mild' group (I and IIa, 24 and 22 patients, respectively) and a 'severe' group (IIb and III, 23 and 6 patients, respectively). Functionally, patients with types I and IIa are similar because they have an adequate temporomandibular joint; while, patients with types IIB and III are also similar in that a new temporomandibular joint and ramus must be constructed (Kaban et al., 1998). The distribution of girls over the four types was 9 (I), 12 (IIa), 14 (IIb), and 4 (III); while, the distribution of boys was 15 (I), 10 (IIa), 9 (IIb), and 2 (III). Patients were diagnosed early, had their first follow up around four years of age, and were treated (or operated on) at various ages. The number of lateral cephalograms (cephalograms) varied per patient, with a mean of 2.72 pre-operative cephalograms per patient (range 4 to 29 years, mean 10.0 years, and standard deviation (sd) 5.0 years). This study of human subjects followed an approved protocol and satisfied the requirements of our IRB (approval number MEC 2008-258).

5.2.2   Controls

For controls, the records of 232 boys and 254 girls without HFM were accessed from the Nijmegen Growth Study (NGS), a five-year mixed longitudinal study of 482 children. We used cephalograms taken at ages 4 to 14 years; the mean age was 11.61 years (sd 3.21 years) for boys and 11.41 years (sd 2.97 years) for girls. There was a total of 2524 cephalograms used (Prahl-Andersen et al., 1979).

5.2.3   Craniofacial measurements

Cephalograms of growing patients were included unless surgical intervention had taken place, as the surgery may influence growth. Digitized cephalograms from film (before the year 2003) and digital cephalograms (from 2003 until 2010) were imported to a cephalometric measurement program (Viewbox version 3.1.1.12, DHAL software, Kifissia, Greece). Thirteen measurements (Table 5.1) were performed by one experienced observer according to (Athanasiou, 1995). In HFM patients, the landmark Articulare and the landmark Gonion can't always be found on the affected side. In those cases, the angle between the ramus and the corpus mandibulae (Ar-Go-Me) cannot be established; therefore, the most distal and upper point (Z) and the most distal and lowest point (Q) on the affected side of the mandible were used to construct this angle (Z-Q-Me).

5.2.4   Statistics

To calculate the intra-examiner reliability, 20 randomly selected lateral cephalograms were measured twice by the same experienced observer. Intra-examiner reliabilities were assessed with the intra-class correlation coefficient (ICC) for the level of measured distances (Landis and Koch, 1977). ICC values range from 0 to 1; ICC values of 0.61-0.80 are interpreted as substantial agreement and values of 0.81-1.00 indicate almost perfect agreement.

The measurements for HFM patients were compared to those for the NGS control group using a procedure that started with the creation of individual curves. Subsequently, these individual curves were combined via a curve-fitting procedure into one combined curve. If too much individual variation existed, no combined curve was created, but values for a certain point in time were estimated using these individual curves. The linear function used for the individual patient data was $Y = AX+B$, in which A represents the increment (mean length over time) and B the intercept (length at age zero). The procedure was used for the control subjects from the NGS (boys and girls together), the affected or unaffected side of HFM patients, and HFM patients in the 'mild' (I, IIa) and 'severe' (IIb, III) groups. The results were then compared using a two sided student's t-test. The Statistical Package for the Social Sciences version 18.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis.

Table 5.1 *Definitions of measurements for the controls and unaffected sides of hemifacial microsomia (HFM) patients (except where noted)*

Measurement	Definition
Position of the maxilla	Angle between Sella-Nasion and Nasion-point A (SNA).
Position of the mandible	Angle between Sella-Nasion and Nasion-point B (SNB).
Relation between the maxilla and mandible	Angle between Nasion-point A and Nasion-point B (ANB).
Palatal plane angle	Angle between Sella-Nasion and Anterior nasal spine-Posterior nasal spine (SN to ANS-PNS).
Occlusal plane angle	Angle between Sella-Nasion and the occlusal plane. The anterior point of the occlusal plane is formed by a constructed point, the midpoint of the incisor overbite in occlusion. The posterior point is formed by a constructed point, the midpoint of the mesial cusps of the upper and lower first molars and the mean between both sides.
Mandibular plane angle	Angle between Sella-Nasion and Gonion-Gnathion (SN to Go-Gn).
Mandibular plane angle (affected side, HFM)[#]	Angle between Sella-Nasion and point Q-Gnathion. Point Q is the most distal and lower point on the mandible.
Angle between ramus and corpus mandibulae	Angle between Articulare-Gonion and Gonion-Mention (Ar-Go-Me).
Angle between ramus and corpus mandibulae (affected side, HFM)[#]	Angle between point Z-point Q and point Q-Menton, in which Z is the most distal and upper point on the mandible and point Q is the most distal and lower point on the mandible.
Angle between the upper incisor and palatal plane	Angle between the upper incisor and Anterior nasal spine-Posterior nasal Spine (upper incisor to ANS-PNS).
Angle between the upper incisor and skull base	Angle between the upper incisor and Sella-Nasion (upper incisor to SN).
Angle between the lower incisor and mandibular plane	Angle between the lower incisor and Gonion-Gnathion (lower incisor to Go-Gn).
Angle between the upper and lower incisor	Angle between the upper incisor and lower incisor.

[#] *These measurements refer to the affected sides of HFM patients only.*

5.3 Results

5.3.1 Intra-observer reliability

The ICC for intra-observer reliability, in the HFM patients, showed almost perfect agreement (ICC; 0.82-0.97, Table 5.2) for almost all distances, with the exception of the occlusal plane angle (0.79) and the angle of the lower incisor to mandibular plane (0.76). The intra-observer reliability for measurements on the affected side showed almost perfect agreement (ICC; 0.96).

5.3.2 Craniofacial measurements

The combined linear curve fitting of all individual HFM curves did not lead to a reliable curve. As a result, values were estimated for HFM patients at 9 years of age by using the individual growth and intercept. For all craniofacial measurements except two, HFM patients differed significantly from the reference population (Table 5.3). HFM patients showed a significantly more retruded mandible and maxilla in relation to the skull base and a more retruded mandible in relation to the maxilla when compared to the Dutch reference population. In addition, the mandibular angles showed more vertical

Table 5.2 *Intra-class correlation coefficients (ICCs) with 95% confidence intervals (CIs) for intra-observer agreement*

Measurements	ICC	95 % CI
SNA	0.93	0.83-0.97
SNB	0.94	0.86-0.98
ANB	0.94	0.85-0.98
SN line to palatal plane (°)	0.82	0.61-0.93
SN line to occlusal plane **(°)**	0.79	0.54-0.91
SN line to GoGn line (°)	0.97	0.92-0.99
SN line to Go1Gn line (°)	0.96	0.90-0.98
ArGo line to GoMe line (°)	0.96	0.90-0.98
ZGo1 line to Go1Me line (°)	0.96	0.91-0.97
Upper incisor to palatal plane (°)	0.92	0.80-0.97
Upper incisor to SN line (°)	0.93	0.83-0.97
Lower incisor to GoGn line (°)	0.76	0.50-0.90
Upper to lower incisor **(°)**	0.92	0.80-0.97

Table 5.3   *Craniofacial configuration comparisons at 9 years of age for hemifacial microsomia (HFM) patients and the control subjects from the Nijmegen Growth Study (NGS) and for the unaffected versus affected side in HFM patients.*

HFM versus controls	HFM N	controls N	HFM Mean	SD	Controls Mean	SD	*p*-value
skeletal							
SNA	204	1621	79.34	4.41	80.31	3.42	0.01
SNB	204	1604	74.08	5.52	76.31	3.55	0.001
ANB	204	1587	5.26	3.97	3.80	2.44	0.001
SN line to palatal plane (°)	204	1616	8.41	4.58	8.51	3.27	N.S.
SN line to GoGn line (°)	204	1625	38.38	9.17	33.76	5.32	0.001
SN line to Go1Gn line (°)	204	1625	42.88	9.44	33.76	5.32	0.001
SN line to occlusal plane (°)	204	1463	20.96	8.27	17.61	4.83	0.001
ArGo line to GoMe line (°)	204	1615	131.87	8.82	129.94	5.48	0.01
ZGo1 line to Go1Me line (°)	204	1615	139.23	12.27	129.94	5.48	0.001
dental							
Upper incisor to palatal plane (°)	204	1448	102.00	12.72	108.93	5.96	0.001
Upper incisor to SN line (°)	204	1452	93.60	14.94	100.28	6.37	0.001
Lower incisor to GoGn line (°)	204	1446	95.38	8.43	84.98	6.31	0.001
Upper to lower incisor (°)	204	1390	132.63	16.85	130.83	8.90	N.S.

HFM: unaffected versus affected	unaffected N	affected N	unaffected Mean	SD	Affected Mean	SD	*p*-value
ArGo line to GoMe line (°) compared to ZGo1 line to Go1Me line (°)	204	204	131.87	8.82	139.23	12.27	0.001
SN line to GoGn line (°)	204	204	38.38	9.16	42.88	9.43	0.001

configurations for both the affected and unaffected sides in the HFM patients compared
N, number of cephalograms; SD, standard deviation.

to the Dutch reference population; while, no significant differences could be found in the palatal plane angle between the populations. The vertical configuration also differed significantly between the affected and unaffected side in HFM patients (Table 5 .3). In addition, upper incisors were significantly less proclined and lower incisors

were significantly more proclined in HFM patients compared to the Dutch reference population.

Significant differences were found to exist between `mild' and `severe' HFM patients. `Mild' HFM patients were more similar to the Dutch reference population than the `severe' HFM patients (Table 5.4); while, `severe' patients showed a more retruded position of both the maxilla and mandible, had a bigger sagittal difference between the two jaws, and a more vertical configuration compared to the Dutch reference population. Dental cephalometric variables did not differ with the severity of the condition.

5.4   Discussion

Our aim was to construct craniofacial growth curves for HFM patients and compare them with a Dutch reference population. Measurements from cephalograms were used and the affected and unaffected sides and `mild' to `severe' conditions were also compared in HFM patients. The inter-patient variability was high in the HFM group; therefore, no curves could be constructed. Craniofacial values at 9 years of age were estimated by interpolation of individual growth data, which is probably a more accurate way to make population estimations from individual HFM patient growth data than using the average values at 9 years. It might have been possible to construct growth curves if our study group had been larger, but data were limited due to the low incidence of HFM, which ranges from 1 in 3500 to 1 in 5600 newborns (Grabb, 1965; Poswillo, 1973). None of the published studies on HFM had more than 75 patients, as in our longitudinal study (Kaban et al., 1988; Kearns et al., 2000; Polley et al., 1997; Rune et al., 1981; Sarnas et al., 2004). Kaban et al. (1998) had a study group of 67 patients, but it was a cross-sectional study and patients were divided into two groups, mild and severe, and according to deciduous, mixed, and permanent dentition. To our knowledge, our study comprises the largest longitudinal group of HFM patients published so far.

In the present study, HFM patients showed retrusion of both the maxilla and the mandible compared to the Dutch reference group with the mandible more affected than the maxilla. We determined this morphology became more distinct in HFM patients as the condition became more severe by comparing mildly affected sides with severely affected sides. This trend also occurred for vertical relationships, which became more distinct with the severity. We hypothesize that our data indicate the maxilla follows

Table 5.4 *Craniofacial configuration comparisons at 9 years of age for patients with 'mild' and 'severe' hemifacial microsomia (HFM)*

HFM: Mild versus Severe	Mild N	Severe N	Mild Mean	SD	Severe Mean	SD	*p*-value
skeletal							
SNA	124	80	80.26	3.68	77.96	5.10	0.001
SNB	124	80	75.51	4.73	72.00	6.12	0.001
ANB	124	80	4.75	3.51	5.96	4.21	0.05
SN line to palatal plane (°)	124	80	7.16	4.34	10.33	4.44	0.001
SN line to occlusal plane (°)	124	80	18.72	7.60	24.35	8.53	0.001
SN line to GoGn line (°)	124	80	35.96	9.17	42.11	8.20	0.001
SN line to Go1Gn line (°)	124	80	39.49	9.00	48.38	8.37	0.001
ArGo line to GoMe line (°)	124	80	130.22	9.09	134.44	8.15	0.01
ZGo1 line to Go1Me line (°)	124	80	136.03	11.10	144.57	13.45	0.001
dental							
Upper incisor to palatal plane (°)	124	80	101.55	13.24	102.71	12.08	N.S.
Upper incisor to SN line (°)	124	80	94.40	15.40	92.38	14.65	N.S.
Lower incisor to GoGn line (°)	124	80	94.96	8.94	95.89	8.18	N.S.
Upper to lower incisor (°)	124	80	134.67	18.15	129.62	14.50	0.05

the mandible in growth and severity. This means that the asymmetry in the maxilla is probably caused indirectly by the process that leads to an affected mandible. Song et al. (2009) indicated that the deviation in HFM patients may only be related to the maxillary alveolar process itself rather than to the shape of the maxillary sinus. They compared maxillary sinuses and did not find statistically significant differences between the affected and unaffected sides in their group of Pruzansky type I patients (Song et al., 2009). However, the height of the maxillary alveolar process is also influenced by the eruption and development of teeth (Bondarets and McDonald, 2000). We assume the diminished height of the maxillary alveolar process may be a result of slower eruption and development in the upper jaw due to the confined space of the lower jaw, rather than due to etiological factors primarily working on the maxilla. Our results show the maxillary and mandibular alveolar processes are affected and both should be addressed. This finding provides scientific evidence for treatment strategies that treat the upper and lower jaw together.

Progressive facial asymmetry in HFM patients due to growth restriction of the mandible remains controversial. Kaban et al. (2009) found, based on longitudinal clinical observations, restricted growth of the mandible, which plays a role in the progressive distortion of both the ipsilateral and contralateral facial skeleton. In contrast, both Polley et al. (1997) and Kusnoto et al. (1999) concluded that growth of the affected side of the mandible parallels growth of the unaffected side in HFM. Our data show HFM cases tend to be more vertical and more retruded than controls as the severity increases. Therefore, there are conflicting findings on facial asymmetry and more studies may be necessary to elucidate this.

HFM is a complex 3D phenomenon and future research should extend to a combined approach that takes into account all involved bony structures as well as the soft tissue envelope, dental development (Ongkosuwito et al., 2010) and perhaps neural involvement. The association and organization between these complex units provide measures of covariation that infer developmental and/or functional relationships called morphological integration (Richtsmeier and Deleon, 2009) and may lead to a better understanding of growth and surgical impact. The potential to study morphological integration is now broader and a combined approach to study HFM in three dimensions is nearly possible with recent developments in three dimensional imaging. Digital dental models can be integrated into cone beam CTs with lesser radiation doses than conventional 3dCTs, which than can be integrated into stereophotograms leading to an overall view of all involved structures (Rangel et al., 2008). This study showed that an individual patient approach is always needed. Growth curves should be estimated for each individual patient to determine the best treatment age from a growth perspective; in addition, all three dimensions should be evaluated and the severity of the condition should be taken into account.

5.5 Acknowledgments

5.6   References

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Chapter 6

Parental stress in parents of a child with Hemifacial Microsomia: the role of child characteristics and parental coping strategies

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Abstract

Objectives. Hemifacial microsomia (HFM) is a congenital facial malformation visually characterized by a hypoplastic or totally absent ear, an off-centre chin, and an asymmetric mandible and maxilla. Aim of this study was to examine the stress levels of parents of children with HFM and investigate the relationship of this stress to child characteristics (i.e., appearance, feeding problems, speaking problems, hearing problems, learning difficulties, and psychosocial problems) and cognitive coping strategies (i.e., acceptance, rumination, and positive reappraisal).

Methods. Parents with a child (ages 3–19) with HFM (N = 31) were recruited through the Department of Orthodontics from the Erasmus-MC Sophia Children's Hospital, Rotterdam, The Netherlands. The adapted and shortened Dutch version of the parental stress index (NOSI-K) was used to measure parental stress, and the cognitive emotion-regulation questionnaire (CERQ) was used to measure cognitive coping strategies. Pearson correlations were calculated, and a multiple regression analysis was performed.

Results. Child appearance did not have a strong significant relationship with parental stress; however, child learning difficulties and psychosocial problems were significantly associated with parental stress. The hierarchical multiple regression analysis (MRA) confirmed the association between learning difficulties and increased parental stress. Acceptance and positive reappraisal both had significant correlations with parental stress. The MRA confirmed the association between acceptance and increased parental stress.

Conclusions. The results suggest that problems other than the characteristic malformation of the child's face in HFM have a greater influence on parental stress. Pearson correlations suggest that all three cognitive coping strategies may be important but that learning difficulties of the child and the parental coping strategy of acceptance affect parental stress the most. These results may be important in the search for the keys to a more targeted tailoring of intervention for parents with high levels of parental stress.

6.1   Introduction

Hemifacial microsomia, or HFM, is a congenital facial malformation that affects approximately one in every 5,000 to 6,000 births (Monahan et al., 2001). It is characterized by asymmetric underdevelopment of the structures originating from the first and second branchial arches. The most obvious visible signs are a hypoplastic or totally absent ear, an off-centred chin, and an asymmetric mandible and maxilla (Fearon and Johnson, 2005). Although the medical aspects of HFM and its treatment have been well reported, data regarding the psychological implications for children and their parents are limited (Maris et al., 1999). The vast majority of available research has focused on children with orofacial clefts (OFCs) and a wide range of craniofacial anomalies (CFAs) (Endriga and Kapp-Simon, 1999). Within OFC research, a lack of a specific patient reported outcome questionnaires exists, although almost 30 non-specific questionnaires have been used. A specific questionnaire is needed instead of a general applicable questionnaire, to address the distinct domains or characteristics of the patients studied (Klassen et al., 2012). Caution should be exercised when applying evidence based on a group of different types of CFAs, to HFM. In a population of 136 children with HFM, their teachers suggested that children with HFM have a modestly elevated risk for internalizing behaviour problems, lower social competency, and less peer acceptance (Dufton et al., 2011). Also trends towards higher anxiety, lower self-concept scores in 16 children (Pertschuk and Whitaker, 1985), and behavioural problems in 11 children (Maris et al., 1999) have been found in paediatric cohorts with HFM. However, another sample of 12 children with HFM showed that they were well adjusted (Padwa et al., 1991).

Available studies all highlight, raising a child with a CFA often is very demanding for parents and may cause stress. When an infant with a CFA is born, parents endure feelings of shock, grief, disbelief, worry, and other types of psychological distress (Benson and Gross, 1989; Drotar et al., 1975; Endriga and Kapp-Simon, 1999; Speltz et al., 1990). An extremely difficult period for parents is infancy, during which stress, confusion, and emotions are high because parents receive the infant's diagnosis and have to cope with multiple medical appointments (Endriga and Kapp-Simon, 1999). They must adapt to the functional differences that can affect hearing, feeding, and speaking (Lockhart, 2003; Speltz et al., 2000). A wide variety of learning problems was identified in CFA patients but was not studied in depth (Kapp-Simon, 1998). Parental stress might

also arise from various psychosocial problems of a child with HFM (Collett and Speltz, 2007; Hunt et al., 2007) and the acceptance of the child's appearance (Sarimski, 1998). Parental stress can be a powerful predictor of children's later psychosocial adjustment (Goldberg et al., 1997); therefore, an intervention programme for parental stress may be important. Traditionally, the management of stress has been studied from a stress-coping perspective (Lazarus and Folkman, 1984), either behavioural or cognitive coping (Garnefski et al., 2001). Behavioural coping may be relevant because avoiding social situations leading to less frequent interpersonal behaviour (van den Elzen et al., 2012) or seeking surgery, seem practical approaches for diminishing parental stress caused by the congenital anomaly. Therefore, cognitive coping styles that refer to conscious mental strategies that individuals use may be more relevant for handling the intake of emotionally arousing information (Garnefski et al., 2001). Cognitive therapy can affect these strategies; therefore, the current study examines only cognitive coping styles.

Based on the literature, we selected three cognitive coping strategies to examine: rumination, acceptance, and positive reappraisal (Lazarus and Folkman, 1984). Rumination refers to thinking about the feelings and thoughts associated with having a child with a congenital malformation, and the cognitive strategies it characterizes may play an important role in the emotional adjustment to stress. Rumination is significantly related to reporting of more emotional problems like depression, anxiety, and distress (Garnefski et al., 2003; Kraaij et al., 2003; Nolen-Hoeksema, 2000). Acceptance, which refers to thoughts about acceptance of having a child with a congenital malformation, may be related to more parental stress in HFM. Several studies have shown that acceptance of and self-resignation to what has happened form an important coping strategy (Lazarus and Folkman, 1984). A recent study among parents whose children have Down syndrome found that a lack of acceptance is significantly related to more parenting stress (Norizan and Shamsuddin, 2010). Finally, positive reappraisal refers to thoughts of attaching a positive meaning to having a child with a congenital malformation and may play a role in parents with a child with HFM. Positive reappraisal in terms of personal growth as a coping strategy is inversely related to emotional well-being (Garnefski et al., 2003; Garnefski and Kraaij, 2006; King et al., 2000; Kraaij et al., 2003; van der Veek et al., 2009).

Cognitive coping thus may play a key role in the adjustment of parents to the stressful event of having a child with a facial anomaly such as HFM, but its role in

this context has not been studied earlier. The current work had three aims. The first was to examine which child characteristics (i.e., aberrant appearance, feeding problems, speaking problems, hearing problems, learning difficulties, and psychosocial problems) are related to higher levels of parental stress. Our second objective was to analyse whether the parental cognitive coping styles of rumination, acceptance, and positive reappraisal can be associated with parental stress. Finally, our third aim was to examine whether significant relationships can be found between parental stress and the cognitive coping strategies, after controlling for the child characteristics.

6.2   Method

6.2.1   Sample and procedure

The institutional review board gave ethical approval for this cross-sectional study (approval number MEC-2009-315). Participants were contacted through the Department of Orthodontics from the Erasmus-MC Sophia Children's Hospital, Rotterdam. Addresses of 59 couples or single parents rearing a child with HFM, ages 3–19, were collected. A package was sent to these parents, containing a letter to introduce the objectives and the procedures of the study, an informed consent form, a questionnaire, and a prepaid envelope. Parents were allowed to decide who would fill out the questionnaire, which was expected to take approximately 30 to 45 minutes. As an incentive, all parents were informed that a book token valued at 10 Euros would be given to all who returned a completed questionnaire. If they wanted to receive this book token, participants were asked to write their address on an added address label that would be separated from the questionnaire to ensure their anonymity. After approximately 7 weeks, and again after 12 weeks, participants were called to be reminded of the study.

A total of 34 questionnaires were completed for a response rate of almost 60%. Three participants did not fill out a considerable proportion of the questionnaire. Table 6.1 shows the sociodemographic characteristics of the sample.

6.2.2   Instruments

6.2.2.1   Parental stress

To measure parental stress, the NOSI-K (Nijmeegse Ouderlijke Stress Index Korte versie (De Brock et al., 1992)) was used, which is the adapted and shortened Dutch version of the Parental Stress Index (Abidin, 1990). This questionnaire is regularly used in studies

on parents of children with various disabilities and measures stress experienced within the parenting role. The NOSI-K consists of 25 statements, measured by a 6-point Likert scale, ranging from 'totally disagree' (1) to 'totally agree' (6). Examples of questions are, "Raising this child brings me far more difficulties than I had expected", and "It is not always easy to accept my child as he/she is". All 25 items were summed, giving a parental stress scale with high scores reflecting a high level of parental stress. The NOSI-K has been found to have good psychometric properties, with a good internal validity, and reliability coefficients ranging from 0.92 to 0.95 (Asscher et al., 2007; De Brock et al., 1992). The reliability coefficient in the present study was 0.97.

6.2.2.2 *Child characteristics*

Two questions were formulated regarding the appearance of the child, both measured with a 5-point Likert scale: (1) "To what extent do you think the anomaly of your child is visible?" (ranging from 'not visible' to 'very visible'), and (2) "To what extent do you experience that bystanders look at your child with HFM?" (ranging from 'not at all' to 'very much'). Scores were averaged, and together they formed the appearance scale. The Cronbach's alpha was 0.85.

6.2.2.3 *Additional child problems*

The additional problems, namely hearing, speaking, feeding, learning, and psychosocial problems, were measured with the following five questions: (1) "To what extent does your child have nutrition problems?"; (2) "To what extent does your child have trouble speaking?"; (3) "To what extent does your child have hearing problems?"; (4) "To what extent does your child have learning difficulties?"; and (5) "To what extent does your child have psychosocial problems (like feeling gloomy, being aggressive, withdrawal from social occasions, etc.)?"
All of these questions were measured on a 5-point Likert scale, ranging from 1 (not at all) to 5 (very much).

6.2.2.4 *Cognitive coping strategies*

The cognitive emotion-regulation questionnaire (CERQ; (Garnefski et al., 2001; 2002)) was adapted specifically to coping with a child with HFM and used to measure the three subscales: rumination (referring to thinking about the feelings and thoughts associated

with having a child with HFM), acceptance (referring to thoughts of accepting having a child with HFM), and positive reappraisal (referring to thoughts of attaching a positive meaning to having a child with HFM). Each subscale consists of four items, measured on a 5-point Likert scale. A sum score over the four items was calculated (ranging from 4 to 20). Research has shown that the subscales have good internal consistencies, with alphas ranging from 0.67 to 0.81 (Garnefski et al., 2001; 2002). Furthermore, the CERQ has been shown to have good factorial validity, good discriminative properties, and good construct validity (Garnefski et al., 2002). Also in the present study, the alpha-reliabilities of the subscales appeared to be good, with alpha coefficients of 0.92 for rumination, 0.85 for acceptance, and 0.86 for positive reappraisal.

6.2.3   *Statistical analysis*

The means and standard deviations of all variables were calculated. Pearson correlations were calculated to study the bivariate relationships between the variables. To study the variance explained by the child characteristics and the cognitive coping scales and to see whether the cognitive coping strategies of the parents significantly added to the regression model, we used a hierarchical multiple regression analysis (MRA; method: enter) after controlling for the child characteristics. The child characteristics were entered in the first block, and the cognitive coping strategies were entered in the second block. To preserve the power of the study, only the variables with significant Pearson correlations were entered in the regression analysis. The Statistical Package for the Social Sciences version 18.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis.

6.3   Results

6.3.1   *Preliminary analyses*

Table 6.2 presents the means and standard deviations for all the variables. A total of 93.5% of parents reported that their child had few or no feeding problems at all (M = 1.19; SD = 0.654). Therefore, this question seemed irrelevant for the studied group and was excluded from further analyses.

6.3.2   *Main analysis*

6.3.2.1   *Bivariate relationships*

Table 6.3 presents the Pearson correlations among the variables. There was no evidence

Table 6.1   *Sociodemographic characteristics of the sample*

Characteristics of the parent	Mean (SD; range) or N (%)
Sex	
Male	9 (29)
Female	22 (71)
Age	43.9 (5.6; 33–56)
Nationality	
Dutch	30 (96.8)
Other	1 (3.2)
Biological parent	
Yes	30 (96.8)
No	1 (3.2)
Partner is also biological parent	
Yes	22 (71.0)
No	5 (16.0)
No partner involved (widowed/single parent)	4 (12.9)
Educational level	
Primary school	11 (35.5)
High school	4 (12.9)
Post-graduation	16 (51.6)
Work	
Employed	23 (74.2)
Unemployed	8 (25.8)
Characteristics of the child	
Sex	
Boy	22 (71)
Girl	9 (29)
Age	11.8 (4.6; 3–19)
Severity of HFM (Pruzansky classification[a])	
Type I or Type IIa	20 (64.5)
Type IIb or Type III	8 (25.8)
Unknown	3 (9.7)

[a]*A classification of severity based on the anatomy of the skeletal forms of the mandible and temporomandibular joint (Kaban et al., 1988; Pruzansky, 1969). Type I and Type IIa are functionally similar in that they have an adequate joint. Types IIb and III both require a newly constructed joint and ramus.*

of multicollinearity. From the child characteristics, the appearance of the child had no strong relationship with parental stress (Pearson correlation, 0.067). Learning difficulties and psychosocial problems of the child were significantly associated with parental stress (Pearson correlations of 0.705 and 0.633, respectively). For the variables of hearing and speaking problems and their association with parental stress, a trend was observed (p between 0.05 and 0.10).

Regarding the coping strategies, acceptance and positive reappraisal both had positive significant correlations with parental stress (Pearson correlations of 0.496 and 0.541, respectively). The variable rumination also showed a trend towards a positive correlation with parental stress (Pearson correlation, 0.333).

6.3.2.2 *Multivariate relationships*

To study the impact of the child characteristics and cognitive coping strategies on parental stress, a hierarchical MRA was performed with the variables with significant Pearson correlations entered (Table 6.4). Learning difficulties and psychosocial problems were entered in the first block, and acceptance and positive reappraisal were added in the second block.

The results showed that parents who reported more learning difficulties for their child with HFM had significantly higher parental stress scores. Also, using acceptance, more intensively, as a coping strategy was related to more parental stress. In the MRA, no significant relationships were found between parental stress and the variables of psychosocial problems and positive reappraisal. Regarding the variable psychosocial problems, a trend was visible in the first block, but this trend dissolved when the cognitive coping strategies were entered into the second block.

The amount of variance explained by learning difficulties and psychosocial problems of the child was 51%. Acceptance and positive reappraisal added significantly 18% of variance ($F(2,26) = 9.07$; $p < 0.01$), giving a total for explained variance of 69%.

6.4   Discussion

Studies on psychosocial outcome with HFM are limited by the number of patients with HFM and number of studies. This study is the first to explore the relationships between child characteristics, parental cognitive coping strategies and parental stress.

Parental stress was significantly related to psychosocial and learning problems.

Table 6.2   *Descriptives and reliability coefficients of study variables*

	Descriptives		Cronbach's alpha
	M	SD	α
Parental stress	40.14	22.71	0.97
Child characteristics			
Appearance	2.129	0.957	0.85
Speaking problems	1.45	0.961	-
Hearing problems	2.39	1.256	-
Learning difficulties	1.65	0.985	-
Psychosocial problems	1.65	1.082	-
CERQ[a] subscales			
Acceptance	7.48	3.70	0.85
Rumination	5.45	2.25	0.92
Positive reappraisal	9.39	4.27	0.86

[a]*CERQ is the cognitive emotion-regulation questionnaire.*

Remarkably, we found that the appearance of the child as seen from a parent's perspective was the only variable that had a low correlation with parental stress. Speaking and hearing problems had non-significant Pearson correlations with parental stress, but for these variables, a trend was visible and this may be important. Surprisingly, feeding problems were reported by 94% of the parents as non-existent, in contrast to other studies (Stromland et al., 2007). Perhaps HFM patients become accustomed to their oral situation after some time.

The joint influence of all the variables in the MRA of the child characteristics showed that only learning difficulties were significantly associated with parental stress. Parents of a child with more learning difficulties reported a significantly greater level of stress than parents whose child had few or no learning difficulties. This result has also been found in groups of parents with children with severe learning difficulties alone (Quine and Pahl, 1992). For the variable psychosocial problems, a trend was observable. These findings may imply that it is not the HFM in itself, with the characteristic malformation of the face, but additional problems such as learning or psychosocial problems that are related to parental stress. The effects on parents of additional factors may be as great as—if not greater than—the effects of factors that are related specifically to the child's craniofacial appearance (Pope et al., 2005; Speltz et al., 1990).

The cognitive coping strategies of acceptance and positive reappraisal were significantly correlated with parental stress, and there was a visible trend for rumination. When studying their joint impact on parental stress, accepting remained a significantly related variable in the MRA. Positive reappraisal had less effect, with a non-significant outcome.

Acceptance and positive reappraisal are positive coping mechanisms, and it is unclear why these mechanisms seem to lead to more stress in parents of children with HFM. For the coping strategy of acceptance, an inverse association has more often been found (Kraaij et al., 2002; van der Veek et al., 2009). An explanation may be that acceptance might also reflect a passive giving up (Kraaij et al., 2002). However, the child with HFM is constantly developing and growing. One hypothesis might be that at a certain point in time, parents cope with their child with acceptance and/or positive reappraisal, but later on they start worrying after specific occurrences such as an unexpected outcome of a hospital visit. Perhaps unexpected growth, development, or future surgery may lead to more worry and thus increased parental stress. Further research is needed for a better understanding of the relationships between parental stress and these coping strategies.

Finally, when studying the joint impact on parental stress, the cognitive coping strategies were of significant importance and added 18% of variance to the already 51% variance explained by the child characteristics.

Table 6.3 *Pearson correlations among all variables*

	1.	2.	3.	4.	5.	6.	7.	8.
1. Parental stress	-							
2. Appearance	0.067	-						
3. Speaking problems	0.337[†]	0.098	-					
4. Hearing problems	0.324[†]	0.428[*]	0.513[**]	-				
5. Learning difficulties	0.705[**]	0.121	0.316[†]	0.438[*]	-			
6. Psychosocial problems	0.633[**]	0.432[*]	0.159	0.178	0.660[**]	-		
7. Acceptance	0.496[**]	0.081	0.208	0.001	0.103	0.127	-	
8. Rumination	0.333[†]	-0.152	-0.067	-0.123	0.120	0.109	0.677[**]	-
9. Positive reappraisal	0.541[**]	0.199	-0.25	-0.004	0.200	0.326[†]	0.625[**]	0.425[*]

$**p < 0.01$; $*p < 0.05$; † = p between 0.05 and 0.10.

6.4.1   Limitations and suggestions for future research

When interpreting the results from the present study, several limitations need to be taken into account. First of all, the cross-sectional design means that inferences about cause and effect relationships are impossible. Prospective studies are necessary to give insight into the potential bi-directional relationships. Future research should focus on why the cognitive coping strategies of acceptance and positive reappraisal have unexpected positive relationships with parental stress. Possible underlying mechanisms should be studied, such as having more intrusive thoughts that cause a higher level of distress in parents. Second, all measures were self-reports, which could have introduced bias into the data in both directions. A study by Dufton et al. (2011) showed that parents did not report any differences compared to their unaffected controls but that teachers did. The wide age range of HFM children in this study could show how specific occurrences may affect parental stress but our study was limited because of the sample size to just two main variables, child characteristics and cognitive coping strategies. However, both explained 69% of the impact on parental stress.

6.5   Conclusions

The results of this study suggest that characteristic malformations in HFM are not the most influential factors in parental stress. Positive reappraisal and psychosocial problems

Table 6.4   *Hierarchical multiple regression analysis with the selected significant variables on parental stress*

	Parental stress	
	Block 1	Block 2
	β	β
Learning difficulties	0.51**	0.50**
Psychosocial problems	0.30†	0.20
Acceptance		0.30*
Positive reappraisal		0.19
R^2_{adj}	0.51	0.69
df	(2,28)	(4,26)
F	16.89***	17.85***

***p < 0.001; **p < 0.01; *p < 0.05; †p between 0.05 and 0.10.

are among the findings of significant interest. Parents of children with HFM often report that functional problems are non-existent, in contrast to the doctors' opinion, and perhaps a certain denial may lead to psychosocial issues. This model, including child characteristics and cognitive coping strategies, accounts for a rather large proportion of the variance, indicating that cognitive coping strategies are highly important in explaining parental stress. An intervention programme for parents and their child with HFM should include parental cognitive coping strategies.

The non-visual characteristics of HFM may help to identify parents with high levels of stress more than the visual malformations of HFM will.

6.6   Acknowledgements

6.7 References

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Chapter 7

General discussion

7.1 Introduction

The aim of this research project was to gain further insight into those external and internal factors related to HFM patients that can influence treatment and treatment results. Our objectives as formulated in paragraph 1.10 were:

- To gain further insight into craniofacial growth and treatment timing in HFM.
- To develop a suitable method for measuring and comparing affected and unaffected mandibular sides in HFM.
- To investigate whether dental development is associated with disturbed mandibular development in HFM.
- To study whether parental stress is related to patient characteristics and can be associated with parental cognitive coping in parents of children with HFM.

In this general discussion, we will first consider methodological issues concerning the data collection, including imaging tools, and quality of life measurements. Subsequently, we will continue with the clinical implications of the findings of this study and conclude with the future perspectives.

7.2 Methodological considerations

7.2.1 Sample

The patient sample that we used for the radiological studies in this thesis was collected over several decades, between 1980 and 2005. We used 84 consecutive patients with a unilateral expression of HFM in our study on ramal mandibular height and dental development on OPTs. Seventy-five patients were included in the study on craniofacial morphology on lateral cephalograms. From a statistical point of view, the study group may seem small, but from a prevalence perspective, this is a large group followed over a long period of time. Nevertheless, a much larger group is needed to reach a definitive answer on questions posed. A multicenter study is superior for collecting a larger sample. Such a study could have a prospective rather than a retrospective design and would give better insight in the complete HFM spectrum and, would distinguish better amongst the four types of the Pruzansky/Kaban classification. In the present study, we had to combine type I and IIa patients into a 'mild' and type IIb and III into a 'severe' group in order to handle the data statistically. Although based on function (Kaban et al., 1988), the combination of types into two groups prevented us from a detailed analysis of the four different Pruzansky/Kaban types and thus from further insight into the

heterogeneity of HFM.

The sample for the study on parental stress was not the same as for the studies mentioned previously. For our questionnaire on parental stress in HFM, we asked 59 couples or single parents rearing a child with HFM, aged 1.5 to 19 years, to participate and almost 60 percent of the questionnaires were completed and returned. Children with HFM who were older than 18 at the start of the study were considered adults and their parents were excluded. Patients between 1.5 and 4 years of age were not included in the radiographic study but their parents were included in the sample on parental stress.

The wide age range of HFM children in this study could have introduced bias caused by the differences in parental stress between parents of children who had already undergone surgery and those who had not. The same may be the case for changes of parental stress during the psychosocial development of children with HFM, but the sample size prevented a detailed further analysis. We limited, therefore, our study to just two main variables. However, both child characteristics and cognitive coping strategies explained 69% of the impact on parental stress.

7.2.2   *Controls*

Records of control children without HFM were taken from the Nijmegen Growth Study (NGS), a mixed longitudinal study of 482 children from 4 to 14 years of age (Prahl-Andersen et al., 1979). The NGS is the most extensive study in the Netherlands on craniofacial growth and dental development in Dutch children, executed according to a strict protocol for inclusion and longitudinal follow-up. The study was conducted in the 1970's which means that a cohort effect may be present between the NGS and our study group. For medical ethical reasons, however, it is no longer possible to collect cephalometric data on a current group of healthy children. Nowadays, three-dimensional imaging techniques that do not require radiation exposure could fill this gap.

7.2.3   *Craniofacial measurements*

Facial soft tissue (skin, connective tissues, fat and muscles), the facial skeleton (bone and cartilage) and the dentition are the three important tissue groups to be considered. Together with other structures, such as the superficial musculo-aponeurotic system, the skeleton and dentition support the facial soft tissue surfaces (Plooij et al., 2011).

In this thesis we focused on the dentition and its bony surrounding structures in HFM patients. We realize that dental development and craniofacial growth are three-dimensional processes, and that HFM is a very heterogeneous malformatin three planes of space, leading to a highly variable clinical picture. Therefore, theoretically, the best way to study HFM would be a three dimensional examination.

Three dimensional CT scans show a superior quality for studying bony structures compared to other imaging modalities such as magnetic resonance imaging (MRI) (Ahmad and Branstetter, 2008; Alberico et al., 2004). However, the radiation dose is still relatively high for a multislice CT scan or cone beam CT (CBCT) compared to 2D cephalograms or OPTs. It implies that executing a longitudinal study with these techniques should be carefully considered and advantages should outweigh the disadvantages (van Vlijmen et al., 2012).

So until now, long term growth studies have been based on readily available radiographic examinations, such as OPTs and lateral cephalograms which are made as part of the routine clinical protocol. Many cephalometric analyses are available for analyzing craniofacial growth, but analyses for facial asymmetry as found in HFM are less common. The reason is that each type of radiograph has its disadvantages, keeping in mind that HFM is a 3D malformation. To enable a 3D interpretation of 2D measurements to a certain extent, measurements should be distinguished in the horizontal and vertical plane. On lateral cephalograms measurements in a 2D horizontal plane may be hindered by overprojection, making the distinction between left and right anatomical sides difficult. In postero-anterior cephalograms there is a lower accuracy because of head positioning or distortion in OPTs. We tried to find a reliable measurement method to evaluate craniofacial morphology and dental development on these radiographs by selecting cephalometric measurements that were the most reliable and the least affected by the problems mentioned.

We found that specific mandibular length measurements performed on an OPT can be as reliable as on a lateral cephalogram. This was also confirmed in a study by Hazan-Molina et al. (2011) who concluded that mandibular length (Gonion-Menton Go–Me) and ramal height (Condylion-Gonion;Co–Go) measurements on OPT, can be used as an alternative to lateral cephalograms (Hazan-Molina et al., 2011). Ramal height (Co-Go) can be an important indicator in mandibular asymmetry. Identification of Co is more difficult on a lateral cephalogram compared to an OPT because of the

overprojection. Another indicator of mandibular asymmetry can be gonial angle. The gonial angle measurement on an OPT and a lateral cephalogram shows a comparable accuracy (Mattila et al., 1977; Shahabi et al., 2009). On a lateral cephalogram we were able to measure the asymmetry between affected and unaffected sides by using the mandibular angle compared to skeletal base (Sella-Nasion plane).

Vertical length measurements of maxillary left versus maxillary right side have not often been reported. The reason is that on a 2D image, it is difficult to find a reproducible and reliable measurement that represents these vertical measurements well enough. Angular measurements may give an indication of the asymmetry on a postero-anterior cephalogram, but run often into a low reproducibility (Athanasiou, 1995; Leonardi et al., 2008; Pirttiniemi et al., 1996).

Despite the shortcomings of 2D images, the cephalometric measurements we have chosen are sufficiently reproducible and reliable to study longitudinally facial asymmetry in HFM.

7.2.4   *Quality of life: Parental stress and cognitive coping*
Quality of life (Qol) is defined as an individual's perception of his position in life in the context of the culture and the value system where he lives, and in relation to his goals, expectations, standards and concerns. It is a broad ranging concept, incorporating in a complex way a person's physical health, psychological state, level of independence, social relationships, personal beliefs and relationship to salient features of the environment WHQol Group (1996). Qol as a conceptual framework in oral clefts can be divided into physical health, psychological health and social health (Klassen et al., 2012).

Psychological health has been studied in children with craniofacial disorders, suggesting that they are more inhibited, depressed, anxious, introverted and less socially adept than typical children (Padwa et al., 1991; Pertschuk and Whitaker, 1985; Pillemer and Cook, 1989; Snyder and Pope, 2010). This may lead to avoidance behavior, caused by stigmatization, and uncertainty about the reactions of others. Although avoidance conduct leads to a reduced stress level, it also leads to restricted social behavior with less frequent personal interaction (van den Elzen et al., 2012).

Social health has not been studied often. It includes the concepts: social function, peer relations, school function, family function and social support (Klassen et al., 2012). We focused on parental stress, as it can be a powerful predictor of children's

later psychosocial adjustment (Goldberg et al., 1997). Traditionally, the management of stress has been studied from a stress-coping perspective (Lazarus and Folkman, 1984). This perspective has frequently served as the model for research into parental stress and coping in families of children with disabilities (Hassall et al., 2005). A modification of this stress-coping model is the distinction between behavioral and cognitive coping (Garnefski N, 2001). The Nosi-K questionnaire is aimed at cognitive coping and was validated for 12 to 16 year old, normal functioning, secondary school children (Garnefski N, 2001). It is necessary to adjust these kinds of questionnaires so that they specifically address the unique characteristics or conditions of the patients studied. The reason that no specific instrument exists for orofacial clefts or HFM or other CFA groups probably reflects the complexity involved in developing a suitable questionnaire or other instrument (Klassen et al., 2012). Further research is needed to develop suitable instruments for CFA patients in general, and HFM patients in particular to get better insights into social health of these specific patient categories.

7.3   Clinical implications

The complexity of HFM has led to a variety of treatment protocols that have not been substantiated by sound scientific data. Early treatment of HFM patients has been advocated for many years, based on the assumption that HFM has a progressive nature (Kaban et al., 1981; Kaban et al., 1998; Kaban, 2009). However, no definitive evidence was found to support this assumption (Nagy et al., 2009). On the contrary, the evidence for the opposite is probably stronger, as this comes from two prospective studies (Polley et al., 1997; Rune et al., 1981). We also showed in our longitudinal study that the mandible starts small but shows a growth pattern until the end of growth that does not worsen over time. The mandible showed a more vertical growth pattern (measured at gonial angle and the angle between Sella-Nasion and Gonion-Gnathion) and was also more retruded than in the reference population. Both the affected and unaffected mandibular side were smaller than in the reference population. Steady growth with absent or altered condyles, may point into the direction that mandibular growth in HFM patients may be a result of remodeling and not of condylar growth or a combined situation, which would explain the retruded and vertically inclined mandible (Enlow and Hans, 1996).

In the smaller HFM mandibles compared to controls, we found that delay of dental development occurred and with increasing severity, according to the Pruzansky/

Kaban type, the delay in early life was more pronounced. The distribution of agenetic teeth showed the same tendency. Both affected and unaffected sides of HFM patients were delayed compared to the control group. Since development of the mandible and the teeth are spatially and temporally related, we hypothesized that a disturbance in one would affect the other. The finding that delay in dental development was found at the affected and unaffected side suggests that not only the confined space plays a role, but that additional general factors may play a role. This makes it less likely that a local vascular perturbation is the main cause of the pathogenesis. The early role and mutual interaction of neural crest cells is a more probable cause.

The extent to which the maxilla or midface is involved in HFM is unclear. The difficulty in measuring the vertical dimensions of the maxilla contributes to that. Several studies report that treatment of the asymmetric maxilla is often necessary (Ko et al., 2004; Meazzini et al., 2005; Nakajima et al., 2011; Scolozzi et al., 2006; Trahar et al., 2003). Our study showed that the maxilla was involved to a lesser extent than the mandible, however, we were not able to quantify the amount of asymmetry in the maxilla. As the maxillary involvement seemed more limited, we hypothesized that the asymmetry in the maxilla is probably caused indirectly by the process that leads to an affected mandible and that the degree of maxillary asymmetry is not independent from the mandible. Song et al. (2009) indicated that the facial deviation in HFM patients may only be related to the maxillary alveolar process itself rather than to the shape of the maxillary sinus. The height of the maxillary alveolar process is influenced by the eruption and development of teeth (Bondarets and McDonald, 2000). We assumed that the diminished height of the maxillary alveolar process may be a result of slower eruption and development of maxillary teeth due to the confined space caused by the underdeveloped mandible, rather than due to etiological factors primarily working on the maxilla.

The heterogeneity of HFM and evidence found for a non-progressive worsening of the growing facial skeleton in HFM leads to the conclusion that surgical correction of the deformity needs to be delayed until growth has ceased. This may have psychosocial implications for the patient and his or her parents because they will be confronted with a visible facial deformity far into puberty. The treatment will start, in early adolescence, but treatment outcome may not always be what the patient and the parents expect and have hoped for over the years. The child with HFM will have to

cope with these problems and we assumed that this could be quite a difficult task for parents to manage and cope. Parental stress can be a powerful predictor of children's later psychosocial adjustment (Goldberg et al., 1997) and therefore it is important to understand the way parents cope.

We found that parental stress may not be influenced as much by the characteristic malformations in HFM as it is by positive reappraisal and psychosocial problems. HFM patients experience no impediment by their appearance, nor do they experience functional problems. It seems that intrinsic child characteristics and the way parents cope with their child are far more important than the way the child looks. Therefore a good evaluation of the non-visual child characteristics early in life and before any surgery has commenced is important, because these child characteristics could influence the patient's satisfaction at the end of the complete treatment. This makes good communication between parents, treating doctors and psychosocial workers important.

7.4   Conclusions and future perspectives

Several aspects of HFM were studied in this thesis. We were surprised to find that parents with high levels of stress may be better identified by psychosocial problems of their child rather than by visual characteristics of their child with HFM. For that reason, it is important to collect information about the social health status of HFM patients. Future studies should aim at development of better measurements of Qol specific to the problems of children with HFM that are more clinically meaningful and psychometrically sound.

Craniofacial and mandibular skeletal growth in HFM interact with the developing dentition and surrounding facial soft tissue. Follow-up studies, utilizing three-dimensional imaging techniques, will provide a better understanding of the craniofacial morphology of HFM. The use of 2D cephalograms is still important in longitudinal follow-up because of the low radiation dose, but the 3D nature of HFM supports the use of techniques such as CBCT to gain further insight into the condition of HFM, especially into the growth and development of the maxilla. Non-invasive digital 3D stereophogrammetry could contribute to a better insight into the soft tissue condition of the anomaly. The soft tissue envelope in HFM has not been studied well but is an important part of the anomaly as is orofacial function. Soft tissue asymmetry

of the face, mandibular movement, effectiveness of chewing and smile esthetics are topics that need further attention.

In the meantime, it is inevitable to treat our patients with HFM according to clinical treatment protocols and treatment modalities for which there is no evidence so far.

HFM is a complex heterogeneous malformation with a low incidence. This stresses the need to follow, evaluate and treat these patients in a limited number of interdisciplinary teams. Patients should be monitored and evaluated for growth, development and timing of treatment but also for psychosocial factors. Team treatment should eventually lead to more adequate treatment protocols but in the case of HFM, the individual variation in patients should be taken into consideration.

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Chapter 8

Summary

Hemifacial microsomia (HFM) is a facial birth defect derived from the first and second branchial arches and has a wide spectrum of characteristics. Its etiology is heterogeneous and unclear, but has been associated with vascular perturbation and/or neural crestopathy. Next to craniofacial involvement, vertebral, cardiac and central nervous system defects can exist. The clinical manifestation includes unilateral deformity of the external ear, underdeveloped ipsilateral half of the face, with epibulbar dermoid and vertebral anomalies. The ipsilateral facial half of the deformity shows hypoplasia of the facial musculature, aplasia or hypoplasia of the mandibular ramus and condyle combined with maxillary temporal and malar bones which are reduced in size and flattened.

The treatment goal in HFM is improved function and optimal facial symmetry when craniofacial growth is completed. Treatment occurs over an extended period of time into adolescence and varies with the severity and type of anomalies and includes ear reconstruction, orthodontics and surgical interventions. Therefore, suitable examination tools are necessary, to get a better understanding of the processes that take place. All these medical procedures and multiple areas of potential impairment may have psychosocial implications for the affected individual and his/her parents or care takers. Parental stress can influence the interaction between child and parents. Understanding psychosocial difficulties is an important part of the total treatment strategy.

Treatment results are not only determined by external factors such as the surgical technique, but perhaps even more by the intrinsic factors of a patient such as genetic background, growth and development. Understanding intrinsic and extrinsic factors could help to finish treatment successfully from the morphological point of view. However, the psychosocial well-being of the patient is also important and psychosocial impact on parents and patients may be a strong influencing factor in the final result. Therefore the objectives as outlined in **chapter 1** are:

- To develop a suitable method for measuring and comparing affected and unaffected mandibular sides in HFM.
- To gain further insight into craniofacial growth and treatment timing in HFM.
- To investigate whether dental development is associated with disturbed mandibular development in HFM.
- To study whether parental stress is related to patient characteristics and can be associated with parental cognitive coping in parents of children with HFM.

To meet these objectives we started to examine and compare measurements done on two often used two-dimensional radiographs, the orthopantomogram and lateral cephalogram. Growth of the HFM mandible is a complex phenomenon occurring in all three planes of space, and it should be studied three-dimensionally. In this era, these possibilities are now widely available, but in growth studies done over the past 20 years, those three-dimensional records were not available. Therefore, most growth studies at this time use two-dimensional records. Especially in children with HFM, it is important to distinguish between affected and unaffected mandibular side. To distinguish between sides, an orthopantomogram (OPT) is as significantly reliable as a lateral cephalogram for linear measurements of the mandible (condylion-gonion, gonion-menton, and condylion-menton) (**Chapter 2**). These findings may offer a simple clinical tool to measure the mandible in patients with hemifacial microsomia.

In HFM patients, the mandibular ramal height on both sides was significantly smaller compared to the normal population and the ramal height in severe HFM patients was significantly smaller than in mild patients. HFM patients start with a smaller mandible and end with a smaller mandible, but experience a growth pattern similar to the Dutch normal population. Patients with HFM do not experience progressive facial asymmetry due to a growth restriction of the mandible (**Chapter 3**).

Chapter 4, describes a study that was designed to investigate, whether severely disturbed mandibular development is associated with local dental development in HFM patients. We constructed logistic development curves for dental age over time. We found a tendency toward delayed dental development in severe HFM patients at younger ages. The temporary delay of tooth formation in patients with severe forms of HFM and the distribution of agenetic teeth suggest an early interaction between mandibular and dental development.

Besides the development of the mandible in HFM patients, little is known about craniofacial growth and morphology in patients with HFM. We found that patients with HFM had more retruded mandibles and maxillae and a more vertical morphology compared to the reference population. In addition, there was a more retruded and vertical pattern on the affected side compared to the unaffected side and in patients with a severe condition compared to those with a mild condition (**Chapter 5**).

The psychosocial implications that HFM has on the patient and his or her parents have not been studied well. To adjust to the stressful event of having a child

with a facial anomaly such as HFM, cognitive coping strategies of the parents may play a key role. In **chapter 6** we describe a study into parental stress in relationship to the child characteristics and the parental cognitive coping strategies. We found that the child learning difficulties and cognitive coping strategies of the parents had significant correlations with parental stress. Therefore intervention programs for parents of a child with HFM should include parental cognitive coping strategies.

The future perspectives for research into complex malformations like HFM, should be that the 3D nature of the deformity should be studied in 3D and supports the use of techniques such as cone beam CTs to gain further insight. Future studies should not only focus on morphological skeletal and soft tissue characteristics but also on functional changes, such as mandibular movement, esthetics during smiling or the effectiveness of chewing. It is also important to collect more insight into the psychological background of the interaction between parents and child. Researchers should use specific questionnaires that address the distinct domains of HFM instead of more general questionnaires. The way parents cope and the strategies they use may affect the final end result of the treatment as part of the quality of their child's life (**chapter 7**).

Chapter 9

Samenvatting

Hemifaciale microsomia (HFM) is een aangeboren afwijking van het gelaat ten gevolge van een aanlegstoornis van de 1e en 2e kieuwboog en kent een breed spectrum aan kenmerken. De etiologie is heterogeen en nog onduidelijk, maar wordt in verband gebracht met een vasculaire verstoring en/ of neurale buis afwijking. Naast craniofaciale (aangezichts) afwijkingen, komen defecten aan de wervels, het hart en het centrale zenuwstelsel voor. Het klinisch beeld bestaat uit een enkelzijdige afwijking van het uitwendige oor, een onderontwikkelde aangedane gezichtshelft met epibulbair dermoid en wervelafwijkingen. De aangedane gezichtshelft kan een onderontwikkeling vertonen van de aangezichtsspieren. Daarnaast kan zowel de ramus als de condylus van de onderkaak aan de aangedane zijde onderontwikkeld of afwezig zijn in combinatie met een hypoplastische bovenkaak, temporaal bot en jukbeen.

Het lange termijn behandeldoel voor de patiënt met HFM is een verbeterde functie en optimale gelaatssymmetrie op het moment dat de aangezichtsgroei voltooid is. De behandeling vindt plaats over een lange periode, tot ver in de puberteit en wisselt naar gelang de ernst en het type van de afwijking. De behandeling kan een oor reconstructie inhouden, maar ook een orthodontische en chirurgische interventie. Om die redenen, zijn er passende onderzoeksmethoden nodig om een beter begrip te krijgen van de processen die plaatsvinden. Al deze medische procedures en de mogelijke beperkingen van HFM zouden kunnen leiden tot psychosociale gevolgen voor de patiënt en zijn ouders of verzorgers. Kennis hebben van de psychosociale problematiek is daarom een belangrijk onderdeel van de totale behandelstrategie.

Behandelresultaten worden niet alleen bepaald door externe factoren, zoals de chirurgische techniek, maar misschien wel meer door de intrinsieke patiënt factoren zoals genetische achtergrond, groei en ontwikkeling. Beide factoren kunnen invloed hebben op het uiteindelijke behandelresultaat. Het psychosociale welzijn van de patiënt is hierin een belangrijke factor en de psychosociale invloed op ouders en patiënten kan een duidelijk stempel op het eindresultaat drukken. De doelstellingen zijn daarom als volgt (**hoofdstuk 1**):

- Het ontwikkelen van een bruikbare methode voor het meten en vergelijken van aangedane en niet aangedane zijden van de onderkaak in HFM.
- Het verkrijgen van een beter inzicht in craniofaciale groei en het behandeltijdstip in HFM.
- Het onderzoeken of tandontwikkeling geassocieerd is met verstoorde

onderkaaksgroei in HFM.

- Het bestuderen of er een relatie bestaat tussen zowel ouderlijke stress en kenmerken van het kind met HFM, als ouderlijke stress en cognitieve verwerkingsprocessen door ouders met een kind met HFM.

Om een antwoord te geven op de vraagstellingen, zijn we begonnen met twee verschillende tweedimensionale röntgenbeelden te vergelijken, namelijk het orthopantomogram (OPT) en het laterale cephalogram. Groei van de HFM onderkaak is een ingewikkeld proces dat in drie dimensies plaatsvindt en dus in drie dimensies bestudeerd zou moeten worden. Thans bestaat er de mogelijkheid om driedimensionaal onderzoek te doen, echter de groeistudies die gedaan werden over de laatste 20 jaar, hadden deze mogelijkheid nog niet. Voor deze studies werd gebruik gemaakt van tweedimensionale beelden. Juist bij kinderen met HFM is het belangrijk om onderscheid te maken tussen de aangedane en niet aangedane onderkaakszijde. Daarvoor blijkt een OPT significant even betrouwbaar te zijn als een laterale cephalogram wanneer lineaire metingen van de onderkaak worden uitgevoerd (condylion-gonion, gonion-menton, and condylion-menton) (**hoofdstuk 2**). Deze bevindingen kunnen een eenvoudige klinische methode vormen om de onderkaak van patiënten met hemifaciale microsomie te meten.

In HFM patiënten, bleek de ramus hoogte van de onderkaak beiderzijds, significant kleiner te zijn vergeleken met de normale bevolking en dezelfde hoogte was in ernstig aangedane HFM patiënten significant kleiner dan in mild aangedane patiënten. HFM patiënten starten met een kleinere onderkaak en eindigen ook met een kleinere onderkaak. Zij hebben een mandibulair groeipatroon dat gelijk is aan de normale Nederlandse bevolking. Patiënten met HFM laten geen progressieve gezichtsasymmetrie zien, die te wijten zou zijn aan groei beperking van de onderkaak (**hoofdstuk 3**).

Hoofdstuk 4, beschrijft het onderzoek naar de vraagstelling of een ernstig verstoorde ontwikkeling van de onderkaak een verband heeft met de lokale tandontwikkeling in HFM patiënten. Daarvoor werden logistische ontwikkelingscurves geconstrueerd voor tandontwikkeling in de tijd. We vonden een tendens richting vertraagde tandontwikkeling in ernstig aangedane jonge HFM patiënten. De tijdelijke vertraging van tandvorming in patiënten met een ernstige vorm van HFM en de verdeling van agenetische gebitselementen doen vermoeden dat er een vroege interactie bestaat tussen tand- en onderkaaksontwikkeling.

Buiten de onderkaaksontwikkeling, is er weinig bekend over craniofaciale groei

en morfologie in patiënten met HFM. We vonden dat patiënten met HFM een meer terugliggende onder- en bovenkaak hadden en dat deze een verticalere opbouw hadden in vergelijking met de normale bevolking. Verder bleek de aangedane zijde een meer terugliggend en verticaal groeipatroon te vertonen dan de niet aangedane zijde. Dit bleek ook te gelden wanneer de ernstig aangedane patiënt werd vergeleken met de mild aangedane (**hoofdstuk 5**).

De psychosociale implicaties van HFM op patiënt en ouders zijn onvoldoende bestudeerd. Voor het aanpassen aan de stressvolle gebeurtenis van het krijgen van een kind met een aangezichtsafwijking, zoals HFM, kan een grote rol zijn weggelegd voor verwerkingsstrategieën door de ouders. In **hoofdstuk 6** beschrijven we een studie naar ouderlijke stress in relatie tot zowel kenmerken van het kind als de ouderlijke cognitieve verwerkingsprocessen.

Toekomstige uitgangspunten voor onderzoek naar complexe aandoeningen, zoals HFM, zouden rekening moeten houden met de driedimensionale aard van de afwijking door deze in 3D te bestuderen door middel van moderne technieken, zoals de conebeam CT. Een vervolg onderzoek zou zich niet alleen op morfologie van het skelet en de weke delen moeten richten maar ook op functionele veranderingen, zoals beweging van de onderkaak, esthetiek gedurende lachen en de effectiviteit van kauwen. De nadruk zou ook gelegd moeten worden op de onderlinge psychologische relatie tussen ouders en kind. Onderzoekers zouden specifieke vragenlijsten moeten gebruiken die de verschillende domeinen van HFM bevragen in plaats van algemeen toepasbare vragenlijsten. De manier waarop ouders verwerken dat zij een kind hebben met HFM en de strategie die zij daarvoor gebruiken kunnen het eindresultaat van de behandeling van hun kind beïnvloeden en daarmee, de kwaliteit van leven van hun kind (**hoofdstuk 7**).

List of publications

List of publications

Reitsma JH, Ongkosuwito EM, Buschang PH, Adrichem LN, Prahl-Andersen B. Craniofacial stability in patients with the Syndrome of Crouzon and Apert after Le Fort III distraction osteogenesis. *Cleft Palate Craniofac J* doi.org/10.1597/12-013.

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van der Meulen JJ, Willemsen J, van der Vlugt J, Nazir PR, Hilling D, Mathijssen IM, Ongkosuwito E, van Adrichem LN, Vaandrager MJ, Hovius SE; Dutch Craniofacial Unit (2009). On the origin of bitemporal hollowing. *J Craniofac Surg* 20(3):752-6.

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The reproducibility of cephalometric measurements: a comparison of analogue and digital methods. Eur J Orthod. 2002 Dec;24(6):655-65.

PhD Portfolio

PhD Portfolio

Name PhD student: E.M. Ongkosuwito
Erasmus MC department: Department of Orthodontics.
PhD period: 2006-2012
Promotors: Prof. dr. S.E.R. Hovius & Prof.dr. A.M. Kuijpers-Jagtman

	Year	Workload (ECTS)
1. PhD training		
Research skills		
Erasmus MC Summer program:		
regression analysis	2002	0.7
advanced statistical models in epidemiology	2002	0.7
topics in meta-analysis	2004	0.7
clinical trials	2004	0.7
Postinitieel masteronderwijs Epidemiologie VU:		
Multilevel analyse	2005	0.9
Erasmus MC:		
BROK (Basiscursus Regelgeving en Organisatie Klinisch onderzoek)	2010	1.0
Specific courses		
Basiscursus stralingsbescherming deskundigheidsniveau 4A/M voor medisch specialisten (variant kaakchirurgie/ orthodontie)	2010	1.0

Presentations

5th International Congress of Maxillofacial and Craniofacial Surgery, *oral presentation*	2006	0.5
Najaarscongres Vereniging van Orthodontisten (VvO), *oral presentation*	2007	0.5
Drie studieclubs, *oral presentations*	2008,2009	1.5
San Juan, Puerto Rico. Outcomes on the Island: The four dimensions of Hemifacial Microsomia, American Cleft Palate- Craniofacial Association (ACPA), *oral presentation*	2011	1.0

(Inter)national conferences

Bilbao 8th European Craniofacial Congress	2007	1.0
UK, Chester The Craniofacial Society of Great Britain and Ireland	2008	1.0
Nijmegen, 2nd Int. Conference on Ectodermal Dysplasia	2009	0.7
Brazilië, Fortaleza Int. Congress Cleft Palate and Related Craniofacial Anomalies	2009	1.0
Najaarsvergadering Nederlandse Vereniging voor Schisis en Craniofaciale afwijkingen	2006-2012	1.7
Najaarsvergadering Vereniging van Orthodontisten	2006-2009, 2012	2.3
Annual meeting American Cleft Palate- Craniofacial Association (ACPA)	2006, 2007, 2011,2012	4.0

Seminars and workshops

USA, Washington Orthodontic clinical course Alan Bagden	2009	1.0
Training HKZ/ISO certification orthodontie	2010	1.4
USA, San Francisco 3D hands on course Invivo	2011	1.0

Reviewing Papers

American Cleft Palate Craniofacial Journal (10 papers)	2007-2012	2.0
American Journal of Orthodontics and Dentofacial Ortho-pedics (2)	2010	0.4
Orthodontics and Craniofacial Research (1)	2010	0.2

	Year	Workload (ECTS)
2. Teaching activities		
Lecturing		
Orthodontische en chirurgische aspecten bij kinderen met extreme congenitale afwijkingen van het aangezicht. Orthodontisten in opleiding	2007	0.3
Orthodontie in craniofaciale groei en chirurgie, 3e jrs geneeskunde studenten	2006-2012	1.0
Supervising		
Geneeskunde studenten, artikel internationaal tijdschrift (2)	2008-	2.0
3. Other activities		
Penningmeester Nederlandse Vereniging voor Schisis en Craniofaciale Afwijkingen (NVSCA)	2006-2012	
Lid commissie Richtlijnontwikkeling update de medische begeleiding van kinderen met Downsyndroom	2010	1.0
Lid commissie Richtlijnontwikkeling Behandeling en zorg voor craniosynostose.	2010	1.0
One ECTS stands for around 28 working hours (including preparation, self-study, examinations etc.).		