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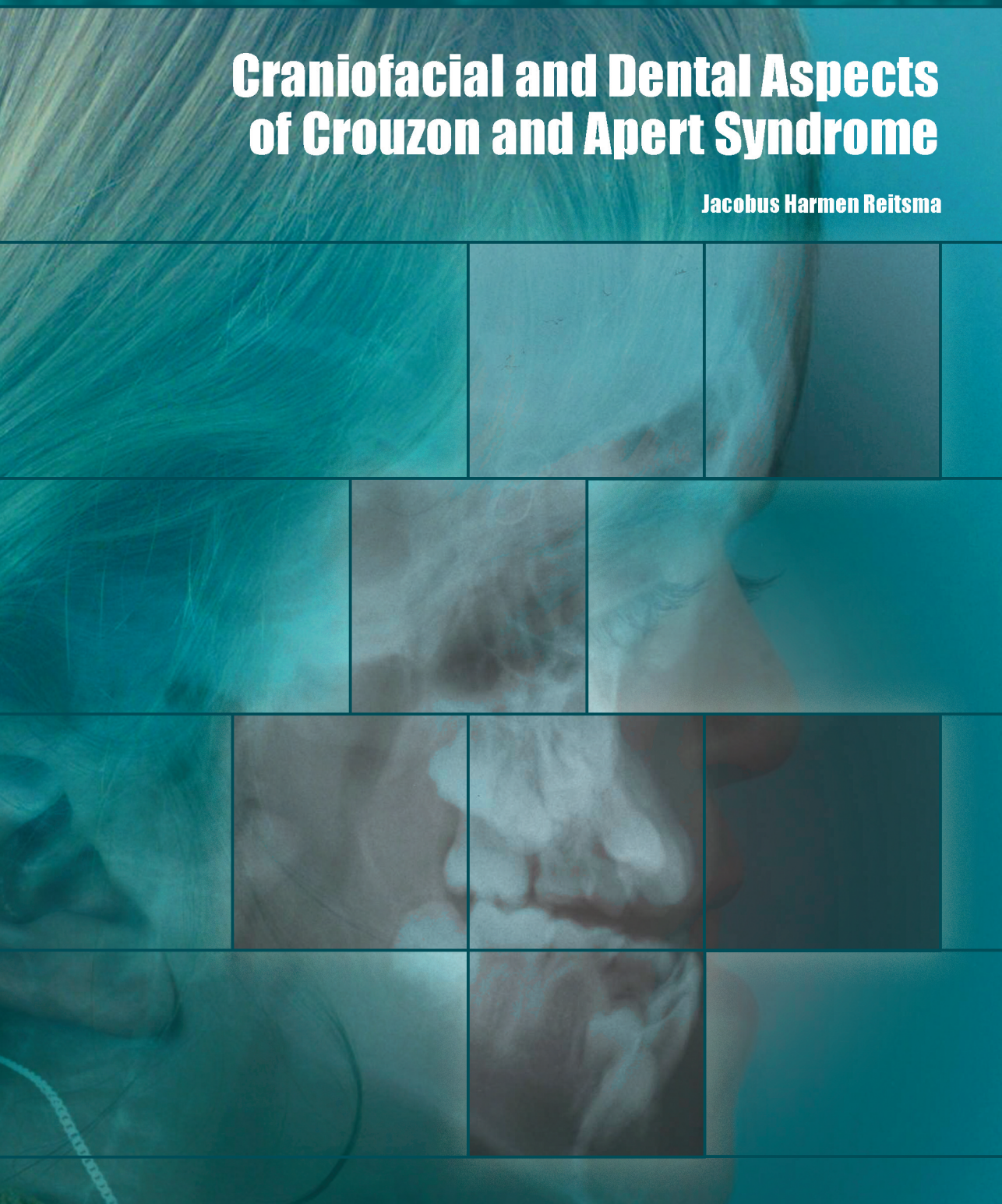
Craniofacial and Dental Aspects of Crouzon and Apert Syndrome

Jacobus Harmen Reitsma



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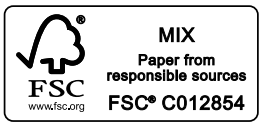

Craniofacial and Dental Aspects of Crouzon and Apert Syndrome

Craniofaciale en dentale aspecten van het syndroom van Crouzon en Apert

Proefschrift

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This thesis is dedicated to my teachers of life

Ynskje Postma-Bijlsma

Douwe Postma

Chapter 1

General Introduction

1.1 Introduction

The cranium of an infant or young child consists of different bony plates intersected by sutures. A calvarial suture is a type of fibrous joint in the cranium. The growth of the cranium is effectuated mainly in the sutures. Two important functions of the calvarial sutures are to secure flexibility of the cranium during passage of a baby through the birth canal, and to facilitate growth and separation of the calvarial bones during intrauterine and perinatal life (Posnick and Ruiz, 2000). It is normal that the calvarial bones are separated by the sutures at the time of birth. Until the age of six years the sutures allow bones of the skull to move. After the age of six years skull growth mostly takes place by apposition of bone at the outer side of the skull and resorption of bone tissue on the inner side of the skull (Herring, 2008).

Premature fusion of one or more sutures in the skull is defined as craniosynostosis (Virchow, 1851; Herring, 2008). The prevalence of craniosynostosis occurs one in 2,000 to 2,500 live births (Cohen and MacLean, 2000). The prevalence of nonsyndromic craniosynostosis at birth is estimated to be three to five per 10,000 births. The prevalence of syndromic synostosis at birth is significantly lower, estimated in the range of 0.15 per 10,000 births (Cohen and MacLean, 2000).

When craniosynostosis is part of a syndrome, different syndromes with craniosynostosis show unique phenotypes, but share clinical features (Cohen, 1986; Gorlin et al., 2001). Initially syndromes were classified on the basis of the clinical findings, but now most of the syndromes are defined according to specific genetic mutations (Glass et al., 1994). Frequently children with craniosynostosis have associated anomalies and conditions including adverse effects on sensory, motoric, cardiovascular and respiratory functions (Cohen and Kreiborg, 1993; Turvey et al., 1996; Anderson et al., 1997; Renier et al., 2000; Bhattacharjee et al., 2009). The Apert, Crouzon, Saethre-Chotzen and Muenke syndromes represent the more commonly identified syndromes with craniosynostosis. These familial craniosynostosis syndromes share many common features, including midface hypoplasia, cranial base growth abnormalities, abnormal facies, and limb abnormalities. A short overview is given of the common syndromes.

1.2 Common craniosynostosis syndromes

The pattern of inheritance in the Crouzon syndrome is autosomal dominant (mainly due to mutations on the fibroblast growth factor receptor 2 (*FGFR2*), and rarely due to the *FGFR1* or *FGFR3* gene). The specific gene mutation for the Crouzon syndrome is found in the third extracellular immunoglobulin domain of *FGFR2* (Reardon et al., 1994; Wilkie et al., 1995). A

mutation of *FGFR3* leads to a Crouzon syndrome with acanthosis nigricans, a skin disorder with velvety hyperpigmentated skin. Even more severe manifestations can be seen, such as stenosis of the choanae and malformation of the brain (Arnaud-López et al., 2007). The prevalence of this manifestation is 1 in 25,000 live births (Reardon et al., 1994). The Crouzon syndrome is characterized by premature fusion of calvarial sutures, midface hypoplasia, shallow orbits, and ocular proptosis. The intelligence of patients with Crouzon syndrome is overall significantly better than the intelligence of patients with Apert syndrome, with a mean IQ of 84 to 92 (Da Costa et al., 2006). The Pfeiffer syndrome is an autosomal dominant syndrome (mutations on the *FGFR1* or *FGFR2* gene) (Muenke et al., 1994; Cornejo-Roldan et al., 1999). Genetically the Pfeiffer and the Crouzon syndrome can often not be distinguished from each other (Rutland et al., 1995). Both syndromes may belong to the same broad spectrum of the same disease (De Jong, 2012). Mutations in *FGFR1* usually give a less expressive phenotype than *FGFR2* mutations in the Pfeiffer patients.

The Apert syndrome is characterized by craniosynostosis, exorbitism, midface hypoplasia and symmetric complex syndactyly of both hands and feet. The reported prevalence is one in 60,000 live births (Cohen and Kreiborg, 1992). Most cases are sporadic, although several cases with autosomal dominant transmission have been reported (mutations on the *FGFR2* gene). The specific gene mutations in Apert syndrome are found between the second and third extracellular immunoglobulin domains of *FGFR2* (Wilkie et al., 1995). 99% of sporadic cases of Apert syndrome are caused by 1 or 2 common mutations in the *FGFR2* gene, *S252W* or *P253R* (Glacer et al., 2003). The heredity of Apert syndrome shows an autosomal dominance in most of the cases (Gorlin et al., 2001). The intelligence varies from near normal to mentally retarded with a mean IQ of 62 to 74 (Da Costa et al., 2006). Apert is the most severe type of syndromic craniosynostosis.

The Muenke syndrome is an autosomal dominant disorder (*P250R* mutation on the *FGFR3* gene) (Glass et al., 1994). It is one of the most commonly found mutations in the human genome, but it does not always result in craniosynostosis (Gorlin et al., 2001). The phenotype of this syndrome may incorporate macrocephaly, uni- or bilateral coronal synostosis, hearing loss and developmental and language delay. The cognitive function seems to be normal with a mean IQ of 93 (Arnaud et al., 2002). The estimated birth prevalence is 1 per 30,000, but is probably higher because not all cases come to medical attention (Carinci et al., 2005).

The Saethre-Chotzen syndrome is an autosomal dominant syndrome with a varying expression (mutations or deletions in the *TWIST* gene) (Brueton et al., 1992; Gripp et al., 2000). In the Saethre-Chotzen syndrome, the coronal sutures can be bilateral or unilateral affected. Other features of this syndrome are upper eyelid ptosis, hypertelorism, strabismus, tear duct stenosis,

brachydactyly, and cutaneous syndactyly of hand and feet. The estimated birth prevalence is around 1 per 25,000 live births (Cohen, 1986; Carinci et al., 2005).

Most syndromes with craniosynostosis show an autosomal dominant inheritance pattern. In these syndromes, often mutations in the gene encoding of the fibroblast growth factor receptor (*FGFR*) or *TWIST* genes are found (Reardon et al., 1994; Wilkie et al., 1995; Meyers et al., 1995; LaJeunie et al., 1999; Cohen and McLean, 2000). Not in all patients with a phenotypically syndromic craniosynostosis can mutations be found. Fusion of two or more cranial sutures without known *FGFR* or *TWIST* gene mutation have been described as complex craniosynostosis (Bannink et al., 2010).

Besides the best known syndromes with craniosynostosis there are many less known syndromic craniosynostosis with a sporadic prevalence, like: craniofrontonasal dysplasia (mutations on *EFNB1* gene), Antley-Bixler syndrome (mutations on *POR* gene), Carpenter syndrome (mutations on *RAB23* gene), Roberts syndrome (mutations on *ESCO2*), Greig syndrome (mutations on *GLI3* gene) or Alagille syndrome (mutations on *JAG1* gene) (Gorlin et al., 2001). Progress has been made in localizing specific genetic pathways related to the pathogenesis of syndromic craniosynostosis in contrast to nonsyndromic craniosynostosis (Persing et al., 1989; Panchal and Uttchin, 2003; Carinci et al., 2005; Sgouros, 2005). The cause of nonsyndromic craniosynostosis however, is still greatly unknown (Sgouros, 2005). Most likely biomechanical factors play a role, as well as other environmental, hormonal and genetical factors leading to cell defects and early suture fusion (Sgouros, 2005).

Although in the majority of cases with craniosynostosis a clinical diagnosis can be made, some cases are not easily distinguished and classified (Cohen and McLean, 2000; Sgouros, 2005). Geneticists, orthodontists, craniofacial surgeons, developmental biologists and pediatricians have described the condition, craniosynostosis in different ways (Virchow, 1851; Bertelsen, 1958; Tessier, 1971; Van der Meulen et al., 1983; Cohen, 1993; David et al., 2009). The contrast between morphological and genetic descriptions may be explained when the pure genetic description of the malformation can be given together with the phenotypic expression (Posnick, 2000).

1.3 Etiology of craniosynostosis

The etiology of craniosynostosis is mostly unknown although there are three main theories (Vermeij-Keers et al., 1983). Craniosynostosis is probably a multifactorial congenital condition.

The first theory, "intrinsic bone malformation", assumes that the origin of pathological synostosis lies within disturbed bone formation early in the pregnancy. The cause can either be genetic, metabolic, pharmaceutical or a mixture.

The second theory, "fetal head constrain", assumes that synostosis starts when the fetal head gets compressed in the pelvic outlet during birth.

The third theory, "intrinsic brain malformation", assumes that disturbed brain formation of the two frontal lobes of the brain is the main issue behind the synostosis. Limited growth of the frontal lobes leads to absence of stimuli for sutural growth, therefore causing premature fusion of the metopic suture (Vermeij-Keers et al., 1983). Considering the literature the first theory is the most probable explanation (Gorlin et al., 2001).

1.3.1 Normal craniofacial growth and development

In the past several theories have been presented and later dismissed with respect to the normal growth of the cranium (Van der Klaauw, 1948 – 1952; Sarnat and Laskin, 1954; Brodie, 1955; Weinmann and Sicher, 1955; Scott, 1959; Sarnat and Wexler, 1966). Later the functional matrix concept influenced the theories of skull growth (Moss and Young, 1960; Moss, 1968; Moss, 1997). According to this concept the growth and development of the skull depend on influences emanating from adjacent functional entities. The morphogenesis of the cranial cartilages and bones is according to this theory controlled by the surrounding functional matrix of the skull. Both the growth of the cranial cartilages and the growth of the sutures (Massler and Schour, 1951; Baer, 1954; Weinmann and Sicher, 1955) can partly be explained by the functional matrix theory (Moss, 1997). The fundamental basis for this hypothesis is that bones do not grow but are grown (Moss, 1997), thus stressing the morphogenetic primacy of function over form. This is in contrast to the current conventional craniofacial growth theories that genetic, rather than epigenetic (non-genetic) factors control such growth. On the other hand, many authors reported observations showing cranial cartilages to function as centers of growth (Sarnat and Laskin, 1954; Sarnat and Wexler, 1966). In contrast to the idea of Moss, it was shown that the sutural area exhibits autonomy of growth and that the growth of the brain has only a limited influence on the growth potential as such in the sutural area (Prahl, 1968; Herring, 2008). The correctness of Moss' theory has not been without doubt (Van Limborgh, 1970; Van Limborgh, 1972). According to Van Limborgh, chondrocranial growth is mainly controlled by genetic factors, while desmocranial growth is mainly controlled by local epigenetic and local environmental factors. Epigenetic factors are determined genetically, but are effective outside the cells and tissues in which they are produced. Local epigenetic factors have a direct effect on the structures (for example, embryonic induction) and general epigenetic factors have an indirect distant influence (for example, sex and growth hormones) (Herring, 2008). Research in animal models has led to the idea that the dura mater plays an important role in determining closure or patency of the suture (Opperman et al., 1994; Slater et al., 2008). Further it appears that the periosteum is not essential in causing closure or patency (Opperman et al., 1994; Slater et al., 2008).

In conclusion: there are many genetic and developmental factors that have contributed to the concept of craniofacial growth and morphology. The major factors are probably the interaction of fusion timing of the various neurocranial and basicranial articulations and an increase in relative brain size. However, other factors such as facial size, facial orientation, and posture may also be important to cranial morphology and variation (Mooney and Siegel, 2002).

1.3.2 Craniofacial growth with premature closure of calvarial sutures

Craniosynostosis demonstrates the importance of sutural growth in skull and facial development (Herring, 2008). Several studies have described skull and facial characteristics in children with various forms of craniosynostosis using cephalometric measurements (Kreiborg et al., 1993; Cohen and Kreiborg, 1994; Avantaggiato et al., 1996). While these measurements provide useful information, it has been difficult to translate the measurements into a global understanding of the growth of the head in patients with craniosynostosis. Knowledge of the craniofacial growth pattern in patients with craniosynostosis may give a better understanding of normal sutural growth and the impact on craniofacial development (Fig. 1.1) (Björk, 1955; Kreiborg and Björk, 1982; Prahl-Andersen, 2005). In syndromic craniosynostosis, multiple sutures in the skull fuse too early and result in a variety of syndromes with affected growth of the head and face.

Estimates of the frequencies of the different types of nonsyndromic synostoses vary. The types, frequencies, and gender ratios of three large series of synostoses have been reviewed by Cohen (Cohen and McLean, 2000). If one includes only the contributions from isolated sagittal, coronal, metopic, and coronal synostoses, then sagittal synostosis occurs most often of all cases, followed by coronal, metopic, and lambdoid synostosis. Due to craniosynostosis normal skull growth is disturbed. In order to accommodate the growing brain, compensatory skull growth results in different cranial deformations: scaphocephaly in case of involvement of the sagittal suture, frontal plagiocephaly in case of one coronal suture, brachycephaly in case of both coronal sutures, trigonocephaly in case of the metopic suture, and plagiocephaly in case of synostosis of one lambdoid suture. Multiple synostoses of cranial sutures are described as complex craniosynostosis.

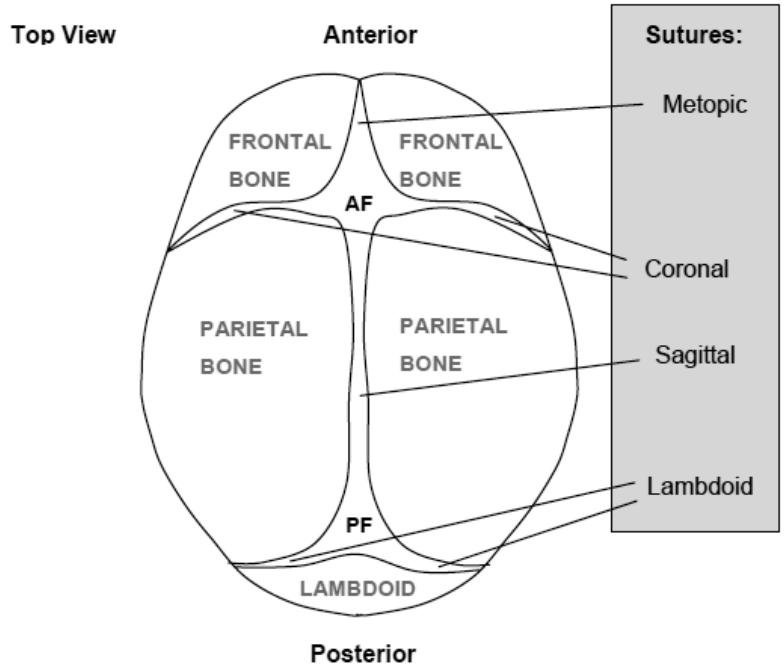

Figure 1.1 *Sutures and fontanelles in the normal newborn skull.*

Craniosynostosis often results in increased intracranial pressure and compensatory intracranial bone resorption and extracranial bone apposition. Inevitably, the restricted sutural growth leads to change in calvarial shape depending on which sutures are obliterated (Renier et al., 2000). The Apert and Crouzon syndromes are the most common and best documented craniosynostosis syndromes and therefore often subject of study (Cohen, 1986; Kreiborg and Cohen, 1998). Of all syndromes with craniosynostosis the Crouzon and Apert syndromes show the most extreme craniofacial malformations. At present, the Saetre-Chotzen, Carpenter and Muenke syndromes are also found to be conditions with similar but far less severe craniofacial malformation (Cohen, 1986; Turvey et al., 1996). Craniofacial growth disturbances in children with Crouzon or Apert syndrome have interested workers in various fields of medicine (Kreiborg and Aduss, 1986; Marchac et al., 1999; Posnick and Ruiz, 2000; Sgouros, 2005; Reid, 2007; Vargervik et al., 2012). The different genetic mutations seen in Crouzon or Apert syndromes express themselves in craniofacial development and morphology. In general this may help to gain a better understanding of clinical findings in craniofacial growth.

Crouzon syndrome: craniofacial malformation

The craniofacial malformation in patients with Crouzon syndrome depends on the order and rate of progression of sutural synostosis. Craniosynostosis usually begins prenatally and is usually complete after two to three years. In some cases, craniosynostosis may be present at birth (Kreiborg, 1981), but the phenotypic features of Crouzon syndrome may not be recognizable at birth; they evolve gradually during the first few years of life (due to pansynostosis). Most often brachycephaly is observed, but scaphocephaly, trigonocephaly or oxycephaly may also be observed. In addition to synostosis in the cranial vault, knowledge about anterior cranial base and facial sutures is scarce (Grayson et al., 1985; Kreiborg et al., 1993). Clinically the midface shows a variable degree of hypoplasia that includes hypoplasia of the orbits, zygomas, and maxilla (Fig. 1.2) (Kreiborg, 1981; Kreiborg and Björk, 1982). Almost no maxillary sagittal growth in patients with Crouzon syndrome can be expected, while some vertical maxillary growth may occur due to the eruption of permanent teeth (Bachmayer et al., 1986; Kreiborg and Aduss, 1986). The mandible has a normal growth rate but may become secondarily deformed due to abnormal cranial base growth resulting in an obtuse gonial angle and relative prognatism (Bu et al., 1989).

Apert syndrome: craniofacial malformation

The craniofacial skeletal abnormalities in the Apert syndrome are present at birth and often show fusion of the coronal sutures bilaterally, and abnormal formation or fusion of the synchondroses in the anterior cranial base and the midfacial sutures (Kreiborg et al., 1993). Extra compensatory growth of the skull is facilitated by the enlarged anterior fontanel that stays open for a relatively long period, compensating for the development of increased intracranial pressure (De Jong et al., 2012a). Fusion of sagittal and lambdoidal sutures may follow after birth. The typical facial appearance is a flat, elongated forehead with bitemporal widening and ocular hypertelorism with proptosis (Fig. 1.3) (Kreiborg and Cohen, 1992). In Apert syndrome earlier closure of sutures, fontanelles and synchondroses is observed than in Crouzon syndrome (Kreiborg, 1993). Moreover, in Apert syndrome the cranial vault takes an turricephalic (tower-like) shape, which is not encountered in Crouzon syndrome (Cohen and Kreiborg, 1996). The synchondroses in the cranial base and the sutures of the upper face are to a variable degree involved, resulting in sagittal midface deficiency (Kreiborg et al., 1993). Furthermore, asymmetric cranial base and an excessively obtuse cranial base angle are more common in Apert than in Crouzon syndrome (Figs. 1.2 and 1.3) (Kreiborg et al., 1993). Facial asymmetry is frequent in both syndromes (Cohen and Kreiborg, 1996). Sagittal maxillary growth may not be expected, while vertical growth occurs with the eruption of teeth (Meazzini et al., 2005). Mandibular growth seems close to normal, although longitudinal data are lacking (Costaras-Volarich and Pruzansky, 1984; Kreiborg and Cohen, 1992).

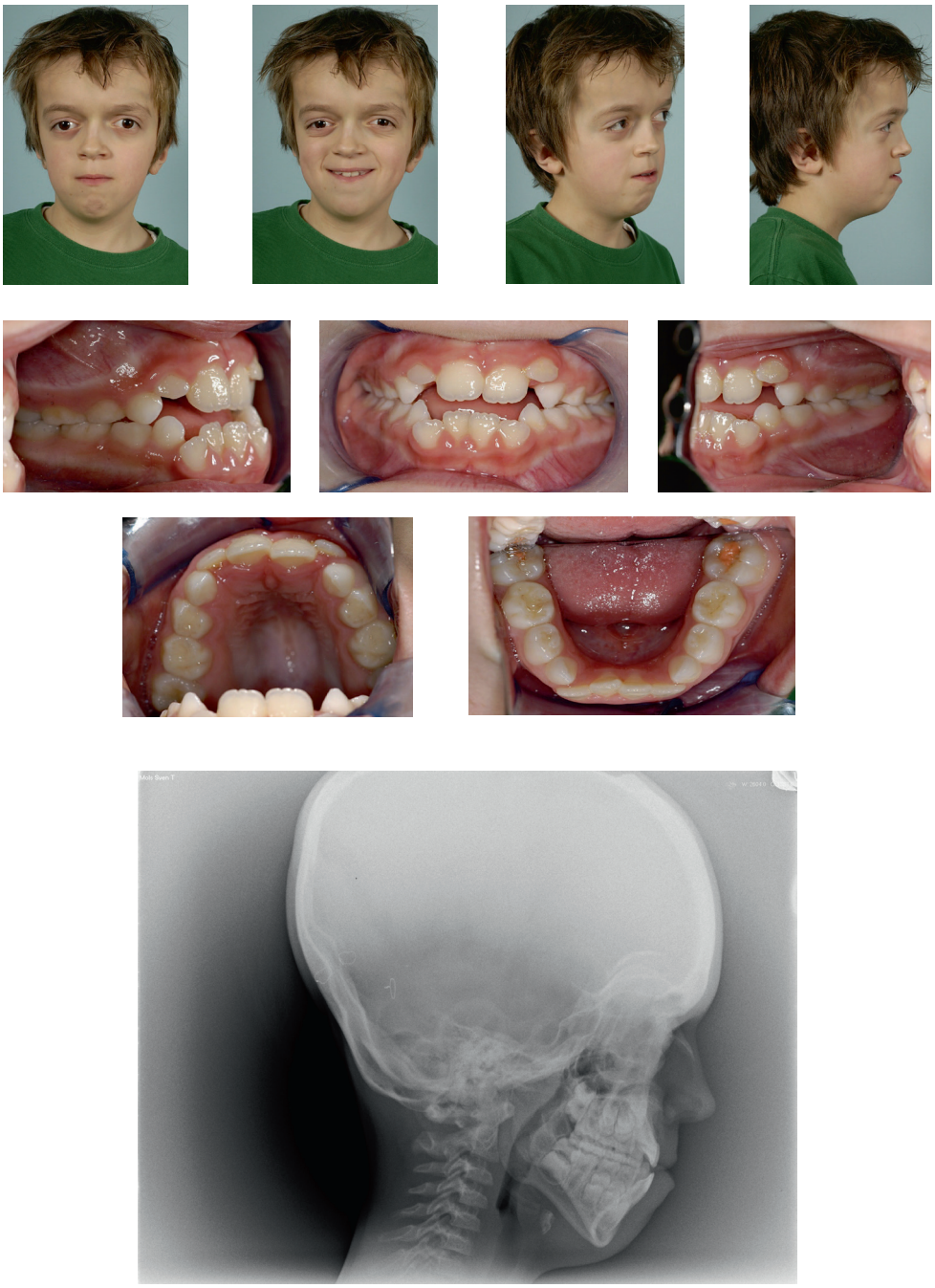

Figure 1.2 *Clinical and radiologic representation of Crouzon syndrome.*

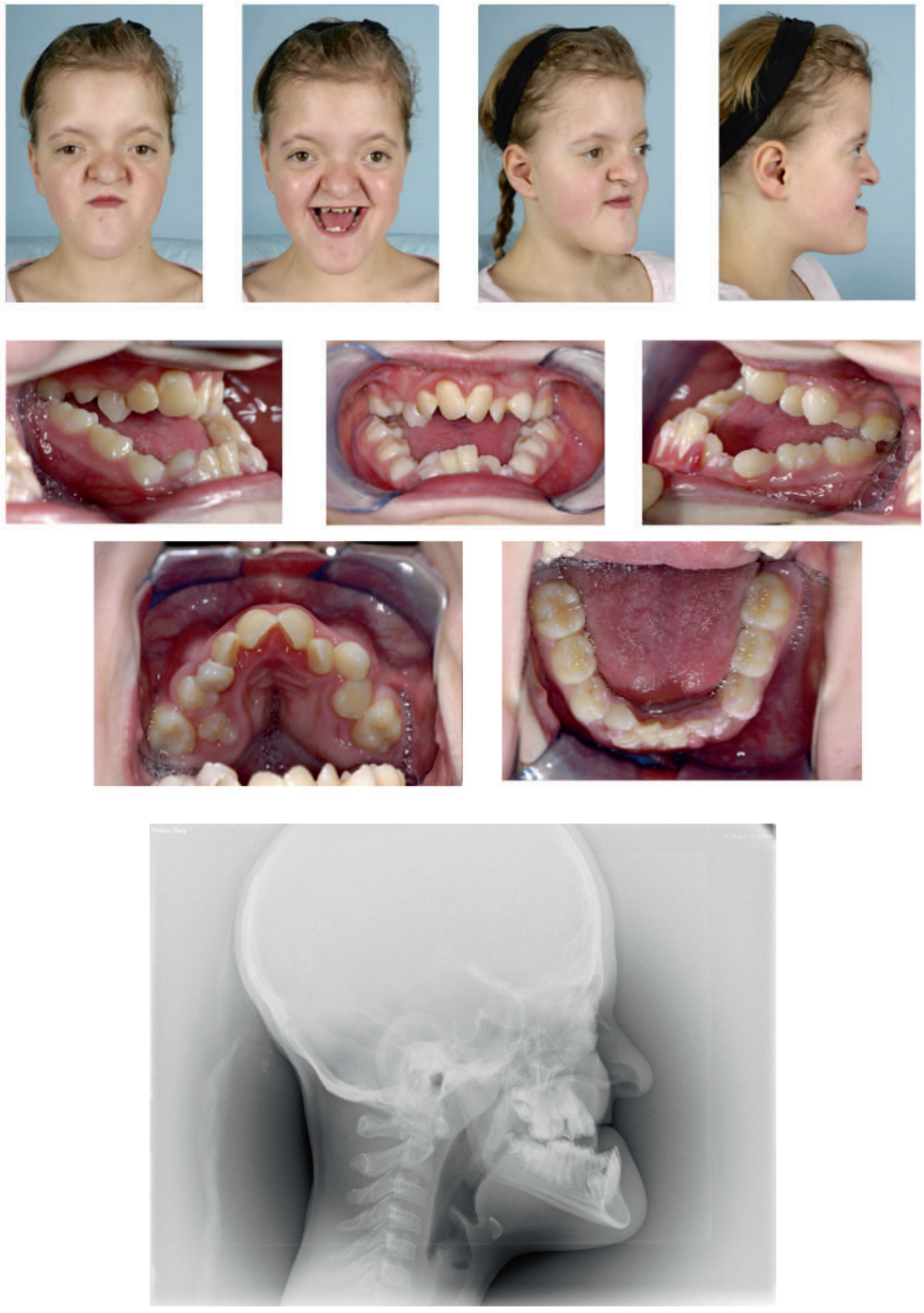

Figure 1.3 *Clinical and radiographic representation of Apert syndrome.*

Oral and dental manifestations in Crouzon or Apert syndrome

The described maxillary hypoplasia results in a shortened anteroposterior and transversal dental arch. An anterior open bite, crowding of mandibular anterior teeth and in a few cases cleft palate is observed. Severe crowding of maxillary teeth and ectopic eruption are the result of lack of growth in the posterior part of the maxilla (Aduss, 1981; Bachmayer et al., 1986; Kreiborg and Aduss, 1986). In patients with Crouzon syndrome there is variation from very mild to very severe oral malformations, while oral characteristics in patients with Apert syndrome are very severe and show less variation.

Specific intraoral characteristics associated with Apert syndrome include a soft palate that is thicker and a hard palate that is shorter than in healthy children (Peterson and Pruzansky, 1974; Marsh et al., 1991). The reported prevalence of cleft palate in Apert syndrome varies from 4% (Letra et al., 2007) to 11% (Peterson and Pruzansky, 1974), and up to as high as 41% (Kreiborg and Cohen, 1992). Maxillary hypoplasia results in irregular positioning and severe crowding of teeth. In Apert syndrome the combination of maxillary hypoplasia and excessive palatal soft tissue decreases pharyngeal space, and the probably normal growing tongue produces an open mouth posture with a protrusive tongue and open bite (Marsh et al., 1991).

Children with Crouzon or Apert syndromes are more likely to have dental anomalies compared to normal children (Cohen, 1986). These dental anomalies can occur with regard to number, shape, size and structure of teeth, timing of development, eruption of teeth and dental occlusion (Cohen and Kreiborg, 1996; Kaloust et al., 1997; Krarup et al., 2005). Dental anomalies tend to be more frequent in Apert syndrome and may reflect the greater complexity of the total clinical manifestation compared to Crouzon syndrome (Cohen and Kreiborg, 1996; Kreiborg and Cohen, 1998). Both syndromes always show severe arch length deficiency with lack of space for the accommodation of the permanent erupting teeth in the upper jaw (Fig. 1.4). However, information about the prevalence of dental agenesis, dental maturation and dental arch development in children with Crouzon or Apert syndromes is scarce.

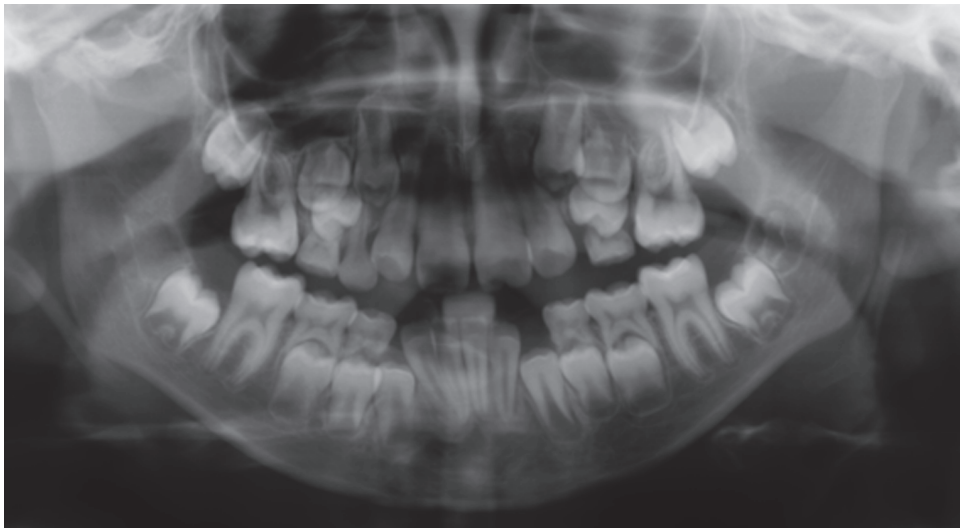

Figure 1.4 *Orthopantomogram of a Crouzon patient with severe space deficiency of maxillary permanent teeth.*

1.4 Functional impairment of patients with Crouzon or Apert syndromes

The Crouzon and Apert syndromes are often severe and functional impairing anomalies. Depending on the number and location of prematurely fused sutures expansion of the cranium is restricted to a varying degree (Reardon et al., 1994; Cohen and MacLean, 2000). A mismatch between intracranial volume versus brain and ventricle volume is thought to be one of the causes of brain abnormalities and elevated intra cranial pressure. However, a raised intracranial pressure is more likely to result from raised cerebrospinal fluid pressure than from a mismatch between intracranial and brain volume, because the majority of patients with craniosynostosis showed a normal or even enlarged intracranial volume (De Jong et al., 2012a). If the increased intracranial pressure is left untreated, brain abnormalities, papilloedema and optic nerve atrophy may develop eventually resulting in possible partial or complete blindness (Reid, 2007). Structural brain lesions may lead to loss of complex cognitive functions, including reduction in mental speed, concentration and overall cognitive efficiency and have influence on behavior (De Jong et al., 2012a; Florisson et al., 2011). The long-term intelligence is within the normal limits in most patients with Crouzon and in some patients with Apert syndrome. In the normal population, 2.3% of the patients have an IQ of ≤ -2 standard deviations. Patients with Crouzon syndrome showed ≤ - 2 sd in 16% and patients with Apert syndrome showed ≤ - 2 sd in 46% of the cases (De Jong, 2012). Recently it was suggested that the combination of the expanding brain and

excess of cerebrospinal fluid might be the driving forces behind compensatory growth of the skull in patients with craniosynostosis (De Jong et al., 2012a). If the increased intracranial pressure is left untreated, brain lesions, papilloedema and optic nerve atrophy may develop eventually resulting in possible partial or complete blindness (Reid, 2007).

Another functional problem lies in the severe hypoplasia of the midface causing exorbitism, lagophthalmos, severe malocclusion, poor esthetics and diminished nasal and nasopharyngeal airway space possibly leading to obstructive sleep apnea (OSA) (Posnick and Ruiz, 2000). This means that patients with Crouzon or Apert syndrome can have partial or complete upper airway obstruction, characterized by snoring, apneas during sleep and difficulty in breathing (Bannink et al., 2010). It is highly unlikely that if severe obstructive sleep apnea syndrome (OSAS) is not present early in life it will develop during childhood (Driessen et al., 2013). Besides obstructive components, patients with craniosynostosis can also have a central sleep apnea caused by a temporary absence of a signal from the brain's respiratory center. Without this signal, there is no effort to breath (Cohen, 1986). The newborns with limited nasal airflow may experience difficulty with oral feeding, while breathing through the mouth and eating at the same time (Bhattacharjee et al., 2009).

As children with craniosynostosis get older, the discrepancy between the two jaws becomes accentuated. The skeletal discrepancy between the maxilla and mandible gives functional problems (e.g. feeding, breathing, speaking). Also Crouzon and Apert patients will often require oral surgery. For example, the development and eruption of teeth must be carefully monitored because of the high prevalence of maxillary hypoplasia. Dental crowding is exacerbated as the permanent teeth erupt, often leading to displacement or even impaction of the teeth. Extractions of some deciduous and selected permanent teeth are often needed.

Characteristic malformations and health related problems in Crouzon and Apert syndromes may cause psychological problems that can influence the quality of life of patients with Crouzon and Apert syndromes. Known psychological problems in patients with congenital disfigurements are low satisfaction with appearance, fear of negative appearance evaluation and low self-esteem (Van den Elzen et al., 2012; Versnel et al., 2012). Psychological stress occurs in the period around craniofacial surgery related to: the change in facial appearance; feeding difficulties and removal of external distractor (Bredero-Boelhouwer et al., 2013). Parents can experience stress because they have to make a decision for their child regarding surgical intervention and consequent changing in appearance and feeding problems during treatment (Bredero-Boelhouwer et al., 2013).

1.5 Treatment of midfacial deficiency

Regarding pressing surgical midfacial advancement, timing and type of operations for the correction of the retruded midface show a wide variety (Posnick and Ruiz, 2000; Renier et al., 2000; Panchal and Uttchin, 2003; Prahl-Andersen, 2005; Reid, 2007). Surgical midfacial advancement is pressing at an early age when midface hypoplasia is the main cause of OSA and exorbitism threatening the eyesight (Nout et al., 2008). At this stage (Class III) malocclusion is a relatively minor issue and dealt with later. In the absence of increased intracranial pressure or need to urgently protect the eyes or the airway, the optimal timing of surgery can be a problem. Over time, different surgical reconstructive methods have been developed for the retruded midface (Gillies and Harrison, 1950; Hanson et al., 1977; Tessier; 1971, 1982; Hoffman and Mohr, 1976; Marchac and Renier, 1979. Gillies and Harrison reported the first high midface osteotomy in an attempt to correct morphologic craniofacial deformity (Gillies and Harrison, 1950). The Le Fort III introduced by Tessier demonstrated the feasibility and safety of massive block mobilization of the midfacial segment of the craniofacial skeleton (Tessier, 1971). After this surgical milestone, many surgeons around the world practiced and modified these techniques. Before the introduction of DO, the necessary horizontal advancement of the midface during surgery could not be achieved in one procedure in order to produce satisfactory or acceptable treatment results in the long run. The midfacial soft tissue envelope hindered an unlimited advancement. Unstable treatment results after surgery (sometimes due to continuing mandibular growth) were frequently observed when using these techniques (Marchac and Renier, 1987; Marchac and Arnaud, 1999).

With the introduction of DO as a surgical technique to lengthen the mandible in the early nineties of the last century (McCarty et al., 1992), later advancements with DO became also possible for the retruded midface with less need for second operations (Chin and Toth, 1996; Chin and Toth, 1997; Cohen et al., 1997; Polley and Figueroa, 1997). The distraction device is applied after successful completion of an osteotomy (Polley and Figueroa, 1997), such as Le Fort III osteotomy, monobloc or facial bipartition procedure. Treatment results showed that the often large sagittal movement of the retruded midface seemed to be stable (Iannetti et al., 2006; Hopper et al., 2010; Shetye et al., 2010). Different opinions about post-surgical growth of the maxilla-mandibular complex after midfacial advancement in patients have been published (Pruzansky, 1982; Bachmayer et al., 1986; Kreiborg and Aduss, 1986; Ianetti et al., 2006). Current opinions expect no postsurgical maxillary growth while vertical lengthening of the maxilla may occur with the continued eruption of permanent teeth. Conclusions about possible midfacial post-surgical growth should be made with caution because most studies are based on small numbers of patients and have a short follow-up. Due to the variation in craniofacial

morphology and related functional or psychosocial problems in patients with Crouzon or Apert syndrome, adjustment of treatment protocols for the individual patient is necessary but difficult. Many current treatment protocols recommend to start advancement of the midface in childhood (Adolphs et al., 2012; Medra et al., 2012), but scientific evidence is lacking for beneficial results in the long term. Midfacial advancement in patients treated in childhood needs an overcorrection because the mandible is still growing (Shetye et al., 2010). Predicting the correct amount of overcorrection is difficult, because precise reference data for amount and direction of mandibular growth are lacking for these syndromic patients. In case of distraction at an early age (before skeletal maturity), the advancement is stopped at the point where the OSA is corrected and sufficient peri-orbital projection is accomplished. Ideally, the patients do not need a second major surgical procedure like a monobloc or Le Fort III operation. However, additionally Le Fort I and mandibular osteotomies are usually necessary to correct a malocclusion preferably when facial growth has ceased (Renier et al., 2000). There are functional and psychosocial circumstances in which the choice of surgery in the immature skeleton outweighs the risks of waiting (Sarwer et al., 1999; Reid, 2007; NVCP, 2010). To date, little knowledge exists regarding the craniofacial growth and development in these patients. But the midfacial growth of children with Crouzon or Apert syndrome is always restrained compared to normal development. Therefore surgical intervention may be necessary at one time or another.

Knowledge of timing, amount and variation of facial growth and development in patients with Crouzon or Apert syndrome is fundamental for the timing of any kind of intervention in these patients (Aduss, 1981; Kolar et al., 1988; Panchal and Uttchin, 2003; Sgouros, 2005). Even though efforts have been made, most craniofacial longitudinal growth studies have to deal with a limited number of patients and an insufficient amount of data, due to the rarity of both syndromes (Cohen, 1986). The goal of developmental studies of rare syndromes is to be able to construct an effective multidisciplinary treatment plan. The lack of consensus and evidence based treatment methods regarding the timing and technique used for midfacial reconstruction reflects lack of knowledge of craniofacial morphology and growth and development in syndromic craniosynostosis. Consequently this may imply inconsistencies of the result achieved with any approach to treatment. Therefore growth of developing facial structures should be evaluated in order to favorably alter the trajectory of the abnormal facial growth and development (Prahl-Andersen, 2005).

1.6 General aim

The syndromes of Crouzon and Apert are very similar in their craniofacial manifestations. Patients with these syndromes often reveal severe growth disturbances of nearly all craniofacial regions. The craniofacial morphology in Crouzon and Apert syndromes is somewhat similar, including calvarial deformities, exophthalmos, hypertelorism, and maxillary hypoplasia. In addition, patients with Apert syndrome have syndactyly of hands and feet. Due to the very little craniofacial growth data for both syndromes it has been argued whether craniofacial development in these two conditions is the same or different. In the literature data analysis of both syndromes have often been pooled (Tessier, 1971; Ousterhout et al., 1985). However, Crouzon and Apert syndromes are different disorders and it is reasonably to expect different craniofacial and dental growth and development. The aim of the present study is to gain a better understanding of craniofacial growth and development in patients with Crouzon or Apert syndrome.

Aims:

- To describe and examine vertical and sagittal maxillary facial growth and development of children with Crouzon or Apert syndrome compared with healthy children.
- To describe and examine mandibular asymmetry in children with Crouzon or Apert syndrome compared with healthy children.
- To describe and compare dental age of children with Crouzon or Apert syndrome with healthy children.
- To describe and compare patterns of tooth agenesis in children with Crouzon or Apert syndrome with healthy children.
- To describe and compare dental arch dimensions of children with Crouzon or Apert syndrome with healthy children.
- To evaluate and compare the results of Le Fort III distraction osteogenesis in children with Crouzon or Apert syndrome with age-matched healthy children.

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Chapter 2

Facial Growth in Patients With Apert and Crouzon Syndromes Compared to Normal Children

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Abstract

Objective: To evaluate vertical and sagittal facial growth in children with Apert and Crouzon syndromes and compare it to the growth patterns of a nonsyndromic control group.

Design: Case-control study.

Setting: Department of Orthodontics, Children's Hospital Erasmus Medical Centre, Sophia, Rotterdam, The Netherlands.

Patients, Participants: Sixty-two patients (37 patients with Crouzon syndrome and 25 patients with Apert syndrome) born between 1971 and 2001 (age range 3.9 to 32 years) and 482 nonsyndromic children as a control group.

Interventions: Lateral cephalograms performed prior to any midfacial surgery of 62 patients and 482 nonsyndromic children were traced and horizontal and vertical measurements were digitized.

Main Outcome Measures: Cephalometric measurements of SNA, SNB, ANB, NSMe, and SN/palatal plane angles and lower facial height ratio.

Results: Horizontal measurements for the syndromic groups showed no change in SNA angle during growth. SNA angles were lower in patients with Apert syndrome compared to patients with Crouzon syndrome. The syndromic groups showed smaller values for ANB angles compared to the nonsyndromic group. Vertical measurements showed increased lower facial height ratios for the syndromic groups compared to control subjects. There was an increasing counterclockwise rotation of the palatal plane in relation to the anterior cranial base in syndromic patients. NSMe angles among the three groups were not significantly different.

Conclusions: Based on the growth differences identified, the sagittal and vertical jaw relationships differ in patients with Crouzon syndrome, patients with Apert syndrome, and control subjects. Syndromic patients show aggravation of midfacial underdevelopment and anterior rotation of the mandible.

2.1 Introduction

The prevalence of Apert syndrome is 1 in 100,000 births; Crouzon syndrome is seen more frequently, in 1 in 25,000 births (Cohen, 1986). Genetic mapping of syndromes with craniosynostosis show that mutations in the fibroblast growth factor receptor 2 (*FGFR2*) gene are responsible for most phenotypes seen in these syndromes. The fact that the same mutation can produce a wide range of phenotypic expressions highlights the complexity of anomalous craniofacial developments (Carinci et al., 2005). Midface deficiency is a characteristic feature in Crouzon and Apert syndromes; this skull deformity is caused by premature closure of the cranial sutures.

Previous studies described the midface of Apert and Crouzon syndromes to be deficient in all three planes of space: a sagittal severe midface deficiency compared to the cranial base, a vertically short upper anterior face height, and a reduced maxillary width (Cohen, 1986; Kreiborg and Aduss, 1986; Cohen and Kreiborg, 1996; Posnick and Ruiz, 2000). In contrast to Crouzon syndrome, craniofacial involvement is always clearly identified at birth in Apert syndrome patients, with brachycephaly associated with facial retrusion (Renier et al., 2000). Syndromic midface deficiency is aggravated during growth and development (Reid, 2007). The maxilla grows anteriorly and inferiorly, but this growth is markedly less than that of control subjects (Bachmayer et al., 1986). Two patterns of inferior maxillary growth have been observed. The first shows a symmetrical descent of the anterior and posterior aspects of the palatal plane. The second growth pattern is marked by a descent of the posterior part more than the anterior, which tilts the palatal plane superiorly and anteriorly and in turn affects mandibular growth (Bachmayer et al., 1986). In contrast to the maxilla, the mandible grows more normally in Apert and Crouzon syndromes, exhibiting anterior rotation in relation to the anterior cranial base (Cohen, 1986; Kreiborg and Aduss, 1986; Marsh et al., 1991; Cohen and Kreiborg, 1996; Posnick and Ruiz, 2000).

These two syndromes are different disorders with different craniofacial development (Kreiborg and Cohen, 1998). Patients with Apert syndrome show a more abnormal craniofacial morphology than patients with Crouzon syndrome (Turvey et al., 1996; Kreiborg and Cohen, 1998). Individual variations in facial growth are observed, but prediction of facial growth in individual patients is difficult.

Craniofacial dysmorphology causes increased intracranial pressure, visual impairment, and airway problems. To treat these functional difficulties, surgery of the immature skeleton is often necessary (Bachmayer and Ross, 1986). Surgical treatment to correct the midface deficiency is often performed later in life and is not recommended for the immature skeleton. New treatment possibilities, including craniofacial distraction osteogenesis, may make intervention during early

infancy possible for the retruded midface. However, early surgical interventions are associated with postsurgical relapse and possible inhibition of growth; in these situations, additional surgery is required (Reid, 2007). Treatment of maxillary growth following early intervention is controversial and is based on opinions, anecdotes, and inadequately designed human studies in a small number of patients (Bachmayer et al., 1986). Timing, duration, and the amount of displacement of the retruded midface in the growing child are essential factors affecting the efficacy of treatment. Therefore, craniofacial growth reference data are important for orthodontic diagnosis, orthodontic treatment, and timing of surgical correction of the retruded midface (Prahl-Andersen, 2005).

To predict facial development in patients with Crouzon and Apert syndromes, more information is needed concerning the differences in craniofacial morphology of patients with Apert syndrome, patients with Crouzon syndrome, and normal healthy controls. These data could potentially be used in future research to predict the need for and ideal timing of midfacial surgery. The aim of the present study was to compare normal vertical and sagittal facial growth patterns to those seen in children with Apert and Crouzon syndromes.

2.2 Material and Methods

2.2.1 Patients

Material used in this study consisted of data obtained from 37 patients with Crouzon syndrome (16 girls and 21 boys) and 25 patients with Apert syndrome (17 girls and eight boys) from the Department of Orthodontics of the Erasmus Medical Centre of Rotterdam. Craniosynostosis in syndromes related to the syndrome of Crouzon or Apert was excluded from the study because of difficulty in comparison, insufficient data for patients with Pfeiffer syndrome, and the relatively mild sagittal midface deformity in patients with the Saethre Chotzen, Carpenter, and Muenke syndromes compared to patients with Apert and Crouzon syndromes. Clinical diagnosis of Apert or Crouzon syndrome in all 62 patients had been confirmed genetically. All patients with Apert syndrome had mutations in the gene encoding *FGFR2*. Most patients with Crouzon syndrome had mutations in the gene encoding *FGFR2*; the remainder had mutations in the gene encoding *FGFR3*. The hospital records, craniofacial team assessments, and cephalometric analyses were reviewed retrospectively with approval from the Institutional Review Board at Sophia Children's Hospital, Erasmus Medical Centre.

A total of 177 sets of longitudinal cephalometric data obtained prior to any midface surgery of patients born between 1979 and 2001 (age range 3.9 to 32 years) were collected at regular

time intervals. These data were compared with a large mixed-longitudinal data set from the Nijmegen Growth Study (Prahl-Andersen et al., 1979). This mixed-longitudinal growth study included 482 nonsyndromic children, 4 to 15 years of age. Each child was followed for a period of 5 years. A final measurement was taken at 22 years of age for some control cohorts. The cephalometric data came from existing mixed-longitudinal records obtained between 1971 and 1976. Radiographs were taken annually from 4 to 9 years of age and semiannually from 9 to 15 years of age.

2.2.2 Cephalometric Landmarks and Measurements

Seven cephalometric points situated in the midsagittal plane were identified (Fig. 2.1). Comparison of the three groups was based on six craniofacial measurements (Table 2.1) representing sagittal and vertical jaw relationships and was done using Viewbox software (version 3.1.1.12; dHal Orthodontic Software, Athens, Greece). The cranial base is important and serves as a reasonably stable reference structure in roentgen cephalometric analyses. Two craniofacial measures (S-N and Na-Me) served as reference for comparisons of the six craniofacial measurements (Table 2.6).

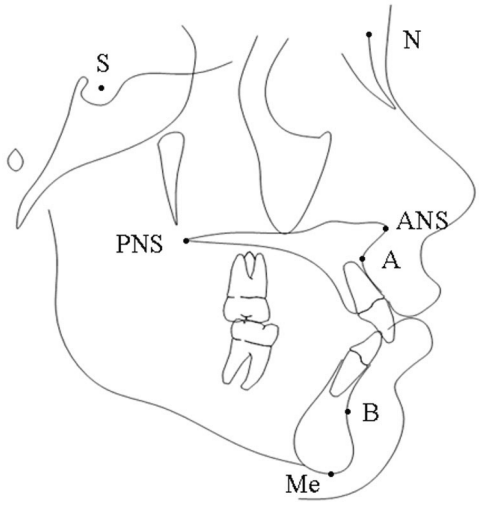

Figure 2.1 *Lateral skull with landmark points. ANS: anterior nasal spine. The anterior tip of the sharp bony process of the maxilla at the lower margin of the anterior nasal opening. Me: Menton. The lowest point on the symphyseal shadow of the mandible seen on a lateral cephalogram. N: Nasion. The most anterior point on the frontonasal suture in the midsagittal plane. PNS: Posterior nasal spine. The posterior spine of the palatine bone constituting the hard palate. Point A: subspinale. The most posterior midline point in the concavity between the ANS and the prosthion (the most inferior point on the alveolar bone overlying the maxillary incisors). Point B: supramentale. The most posterior midline point in the concavity of the mandible between the most superior point on the alveolar bone overlying the mandibular incisors (infradentale) and Pogonion (the most anterior point on the chin). S: Sella. The geometric center of the pituitary fossa.*

Table 2.1 *Description of cephalometric measurements.*

ANS-Me	Represents the lower anterior face height (LFH).
N-Me	Represents the total anterior facial height.
LFH Ratio	The ratio of the lower anterior facial height and the total anterior facial height.
NSMe angle	Measures the angle from nasion to sella to menton.
SN/PP angle	Measures the inclination of palatal plane to the anterior cranial base.
ANB angle	The relative position of points A and B to each other.
SNA angle	The anterior-posterior position of point A to the anterior cranial base.
SNB angle	The anterior-posterior position of point B to the anterior cranial base.

2.2.3 Statistics

2.2.3.1 Assessment of Interexaminer and Intraexaminer Variation

To calculate systematic and random errors, a subsample of 20 randomly selected radiographs was retraced and redigitized by two examiners using Viewbox software; the angular and ratio variables, as listed in table 2.1, were analyzed. Intraobserver duplicate measurement errors were calculated (Fig. 2.1; Table 2.2) according to Dahlberg's formula (Dahlberg, 1940), and reliability coefficients between the first and second digitizing were calculated as Pearson's correlation coefficients. An intraclass correlation coefficient (ICC) was then calculated on the recorded measurements. The same calculations were performed for interobserver errors. Statistical analyses were performed using SPSS (version 15.0, SPSS, Chicago, IL). An ICC value greater than 0.75 represents a high level of reliability, values between 0.4 and 0.75 indicate fair to moderate reliability, and a value less than 0.4 represents poor reliability (Shrout and Fleiss, 1979).

Table 2.2 *Intraobserver and interobserver agreement for digitization of the cephalometric landmarks.*

	Intraobserver reliability n (digitization)	Interobserver reliability n (digitization)
	= 20	= 20
	Correlation coefficient	Correlation coefficient
SNA angle (degrees)	0.921	0.972
SNB angle (degrees)	0.970	0.706
ANB angle (degrees)	0.847	0.872
LFH ratio	0.984	0.742
NSMe angle (degrees)	0.977	0.962
SN/PP (degrees)	0.969	0.65

2.2.3.2 Growth Models

The program MLwiN (version 1.2, Centre for Multilevel Modelling, London, United Kingdom) was used to model growth changes and compare the three groups. Two level models were used, with patients (i) at one level and age (j) nested within patients at the other level. For each *y* variable (craniofacial measurement), a polynomial equation was estimated statistically. The *y* intercept was adjusted (intercept = age - 6) to 6 years of age to reduce the complexity of computations. Average growth curves were estimated between 5 and 15 years of age. Because of expected differences associated with syndrome and gender, separate models were fitted. A cubic model was first fitted for each group, and the highest-order term was checked for statistical significance. If it was not significant, it was removed and a new reduced model was fitted. The initial equation was:

$$y_{ij} = \beta_{0ij}constant + \beta_1 t_{ij} + \beta_2 t_{ij}^2 + \beta_3 t_{ij}^3$$

with

$$\beta_{0ij} = u_{0j} + e_{0ij}$$

where the craniofacial growth measurement *y* was computed by adding the intercept (β_{0ij}) to the products of other fixed coefficients (β_1, β_2, and β_3) multiplied by age (*t*) at each occasion. The u_{0j} and e_{0ij} comprise the random portion of the model and are assumed to have means equal to zero, to be uncorrelated, and to be normally distributed. The level 1 residual e_{0ij} represents within-subject variation, or the "error" term, while the level 2 residual u_{0j} represents, in this case, between-subject variation (Goldstein, 1987).

The polynomial model takes full advantage of each patient's individual longitudinal growth data and statistically evaluates the shape of the curve. Iterative generalized least squares were used to estimate the model's parameters (Goldstein, 1987). Two-level models were also used to estimate the groups' adult stat status at 22 years of age (intercept = age - 22).

2.3 Results

2.3.1 Assessment of Interexaminer and Intraexaminer Variation

ICC values for intraobserver reliability were excellent (Table 2.2). The ICC values for interobserver reliability were fair to excellent (Table 2.2): Fair to good reliability was found for measurements concerning the inclination of the maxilla and point B relative to the cranial base and LFH, and all the other measurements showed excellent reliability.

2.3.2 Growth Models

Control Subjects

Multilevel modeling (Table 2.3; Figs. 2.2 to 2.7) showed that the growth curves ranged from no growth change (constant term only) to complex, third-order changes. The fixed terms of each model were used to estimate the craniofacial values between 5 and 15 years of age. For example, the SNB angle for control boys was 75.95 degrees at 10 years of age, computed as 70.59 + (0.2157 x 4). The linear term 0.2157 (the yearly change) for control boys was multiplied by 4 instead of 10 because the intercept was set to 6 years of age. The SNA angle was not significantly different between boys and girls and did not change significantly over time. The LFH ratio, which also showed no statistically significant gender differences, decreased up to approximately 12 years of age and then increased slightly until age 15. While the SN/PP angle for boys showed no change over time, it increased slightly from 5 to 15 years of age in girls, at which point it approximated the values seen for boys. The SNB angles increased for both genders, but girls displayed a significantly greater yearly increase than boys. The ANB angle of girls decreased steadily (0.18 deg/y), whereas the boys' rate of decrease decelerated over time. Of all the angular measurements, the ANB angle showed the greatest change during growth.

Untreated Patients With Crouzon Syndrome

The patients with Crouzon syndrome showed statistically significant gender differences for all measurements except for the LFH ratio (Table 2.4; Figs. 2.2 through 2.7), which was larger than control values at all ages. The NSMe angle for patients with Crouzon syndrome, which remained constant for girls and decreased slightly for boys, remained within the normal limits seen in the control participants. The SNA angle was significantly smaller in patients with Crouzon syndrome than in controls; the female SNA angle increased slightly, and the male angle remained constant. The SNB angle was larger in patients with Crouzon syndrome than in controls at all ages, with boys increasing at a greater rate than girls. The ANB angle of patients with Crouzon syndrome was significantly smaller than that of controls. The SN/PP angle was significantly smaller for patients with Crouzon syndrome than controls, with this difference remaining constant for boys and increasing for girls.

Table 2.3 *Multilevel models for growing untreated male and female controls.*

Gender	Measurements	Fixed Explanatory Variables*								Between Subjects
		Constant		Linear		Quadratic		Cubic		
		Estimate	SE	Estimate	SE	Estimate	SE	Estimate	SE	SD
Males	SNA	8.023e+1	3.050e-1	-	-	-	-	-	-	3.576e+0
	SNB#	7.509e+1	3.334e-1	2.157e-1	4.847e-2	-	-	-	-	3.228e+0
	ANB	5.293e+0	2.084e-1	-3.347e-1	5.004e-2	2.022e-2	5.465e-3	-	-	2.214e+0
	SN/PP	8.075e+0	2.499e-1	-	-	-	-	-	-	3.082e+0
	NSMe	7.071e+1	2.955e-1	-2.415e-3	6.504e-2	-3.635e-2	1.916e-2	4.031e-3	1.717e-3	3.447e+0
	LFH Ratio	5.928e+1	1.947e-1	-5.004e-1	5.554e-2	-1.875e-3	1.626e-2	3.657e-3	1.453e-3	2.165e+0
Females	SNA	8.048e+1	2.691e-1	-	-	-	-	-	-	3.333e+0
	SNB	7.459e+1	3.017e-1	3.230e-1	3.701e-2	-	-	-	-	3.263e+0
	ANB	5.324e+0	1.776e-1	-1.794e-1	1.670e-2	-	-	-	-	2.095e+0
	SN/PP	8.027e+0	2.363e-1	7.802e-2	2.132e-2	-	-	-	-	2.812e+0
	NSMe	7.070e+1	2.938e-1	9.641e-2	5.481e-2	-1.911e-2	5.807e-3	-	-	3.489e+0
	LFH Ratio	5.883e+1	1.961e-1	-5.089e-1	6.404e-2	2.258e-3	1.754e-2	4.044e-3	1.486e-3	2.224e+0

*Constant = age 6 years; - = not statistically significant.
#SNB10♂ = 7.509e+1 + (2.157e-1 x 4)

Table 2.4 *Multilevel models for growing untreated male and female patients with Crouzon syndrome.*

Gender	Measurements	Fixed Explanatory Variables								Between Subjects
		Constant		Linear		Quadratic		Cubic		
		Estimate	SE	Estimate	SE	Estimate	SE	Estimate	SE	SD
Males	SNA	7.165e+1	1.373e+0	-	-	-	-	-	-	5.675e+0
	SNB	7.630e+1	1.541e+0	6.958e-1	1.413e-1	-	-	-	-	5.925e+0
	ANB	-4.514e+0	1.356e+0	-7.167e-1	1.511e-1	-	-	-	-	4.831e+0
	SN/PP	4.488e+0	1.615e+0	-	-	-	-	-	-	7.041e+0
	NSMe	7.125e+1	1.537e+0	-4.564e-1	1.561e-1	-	-	-	-	5.708e+0
	LFH Ratio	6.369e+1	6.636e-1	-	-	-	-	-	-	2.892e+0
Females	SNA	7.159e+1	1.706e+0	4.334e-2	2.353e-1	-	-	-	-	4.990e+0
	SNB	7.852e+1	1.362e+0	2.880e-1	1.428e-1	-	-	-	-	4.424e+0
	ANB	-7.693e+0	1.723e+0	-	-	-	-	-	-	5.999e+0
	SN/PP	5.792e+0	2.263e+0	-8.928e-1	2.587e-1	-	-	-	-	7.175e-1
	NSMe	6.978e+1	1.405e+0	-	-	-	-	-	-	4.912e+0
	LFH Ratio	6.363e+1	1.298e+0	-	-	-	-	-	-	4.497e+0

Constant = age 6 years; - = not statistically significant.

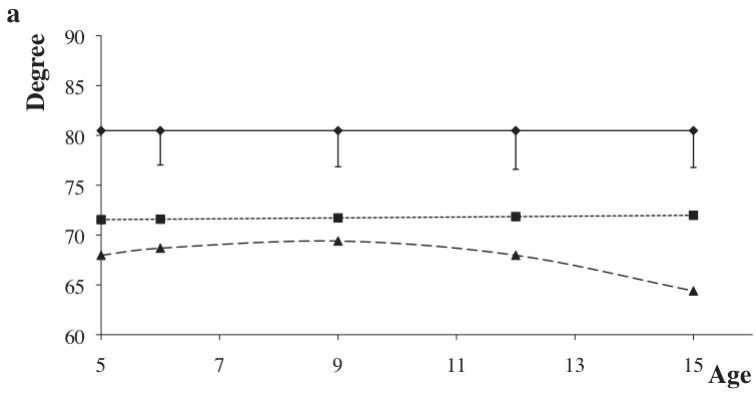

Figure 2.2a girls *SNA angles for untreated patients with Apert (▲) and Crouzon (■) syndrome and control subjects (●).*

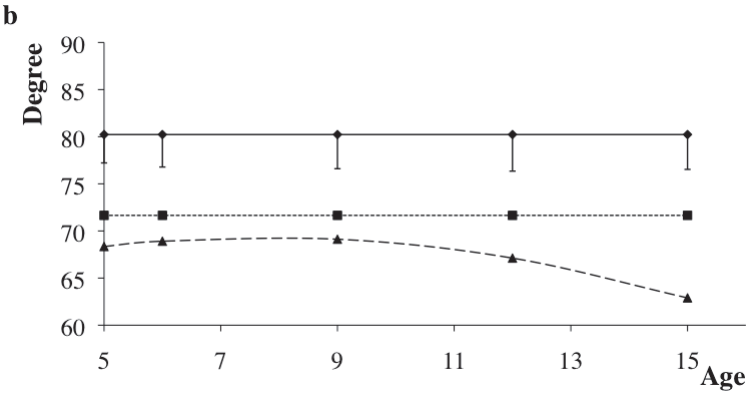

Figure 2.2b boys *SNA angles for untreated patients with Apert (▲) and Crouzon (■) syndrome and control subjects (●).*

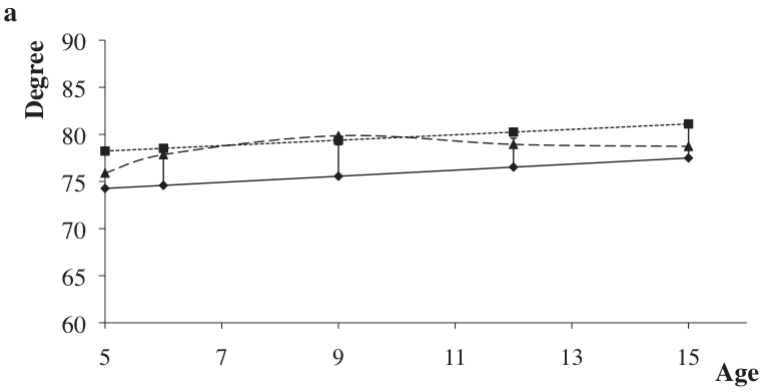

Figure 2.3a girls *SNB angles for untreated patients with Apert (▲) and Crouzon (■) syndrome and control subjects (●).*

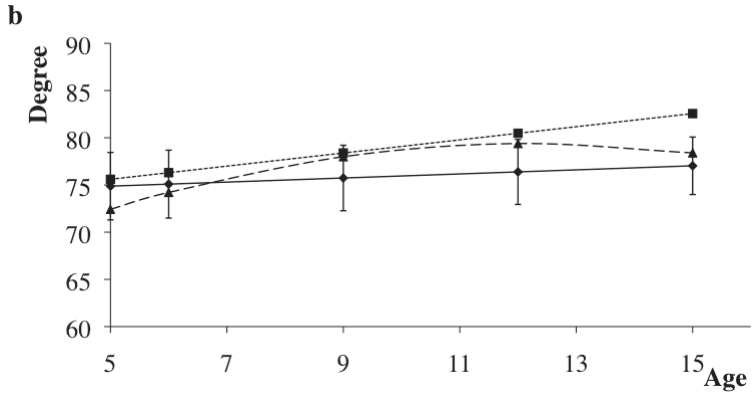

Figure 2.3b boys *SNB angles for untreated patients with Apert (▲) and Crouzon (■) syndrome and control subjects (●).*

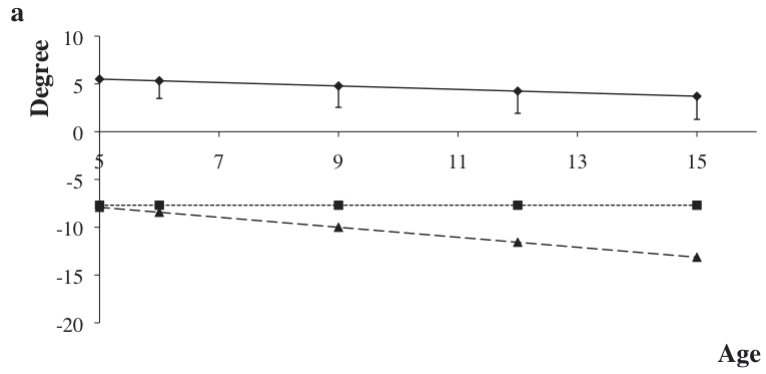

Figure 2.4a girls *ANB angles for untreated patients with Apert (▲) and Crouzon (■) syndrome and control subjects (●).*

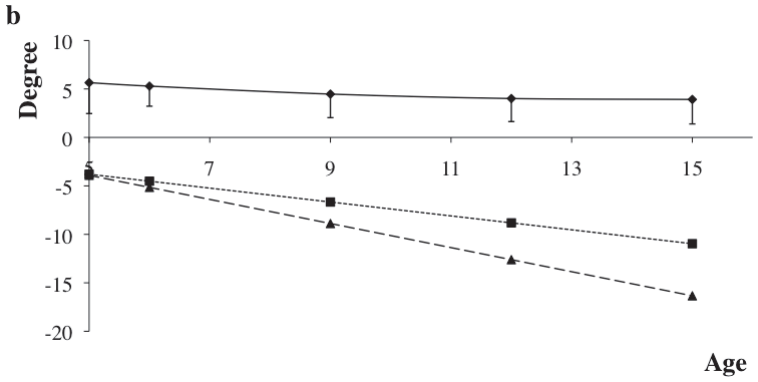

Figure 2.4b boys *ANB angles for untreated patients with Apert (▲) and Crouzon (■) syndrome and control subjects (●).*

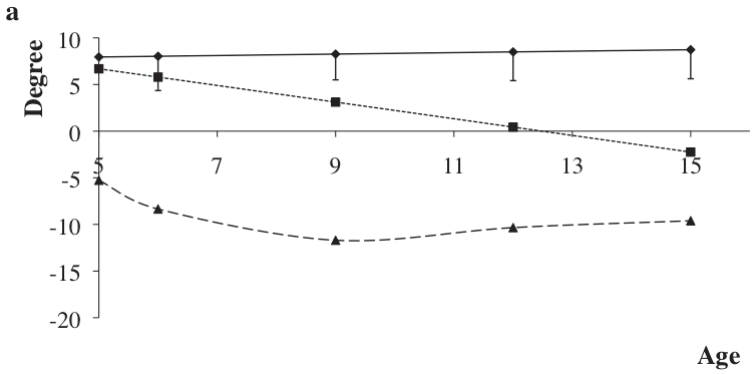

Figure 2.5a girls *SN/PP angles for untreated patients with Apert (▲) and Crouzon (■) syndrome and control subjects (●).*

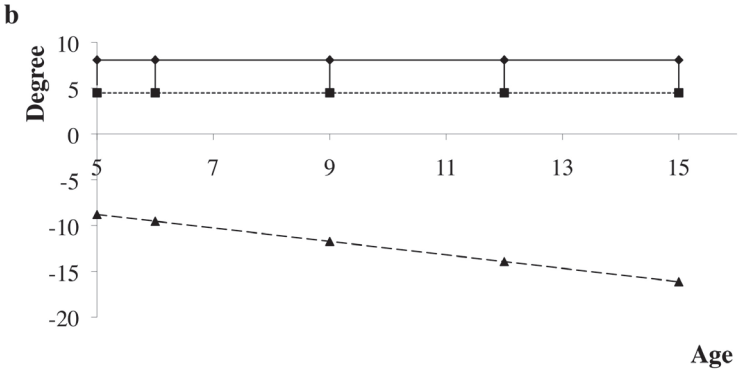

Figure 2.5b boys *SN/PP angles for untreated patients with Apert (▲) and Crouzon (■) syndrome and control subjects (●).*

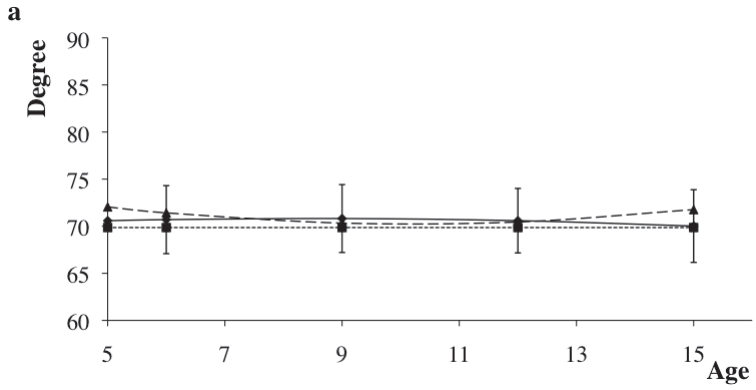

Figure 2.6a girls *NSMe angles for untreated patients with Apert (▲) and Crouzon (■) syndrome and control subjects (●).*

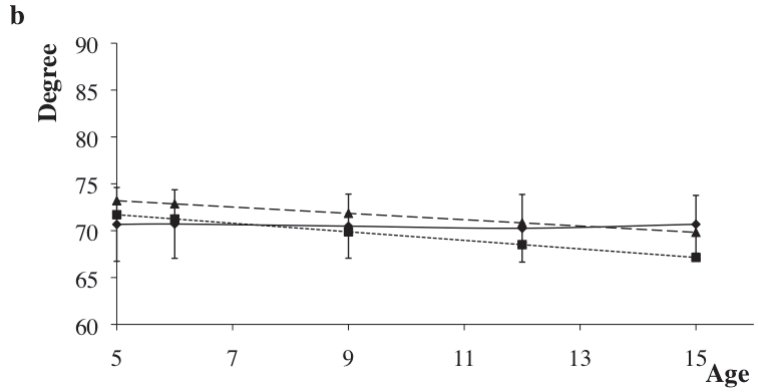

Figure 2.6b boys *NSMe angles for untreated patients with Apert (▲) and Crouzon (■) syndrome and control subjects (●).*

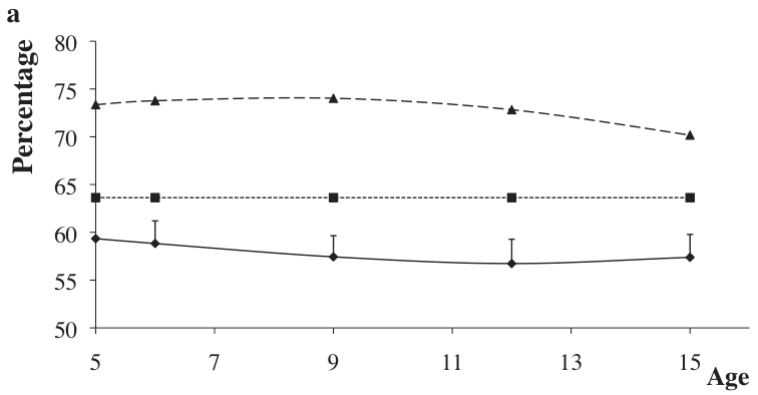

Figure 2.7a girls *LFH ratio for untreated patients with Apert (▲) and Crouzon (■) syndrome and control subjects (●).*

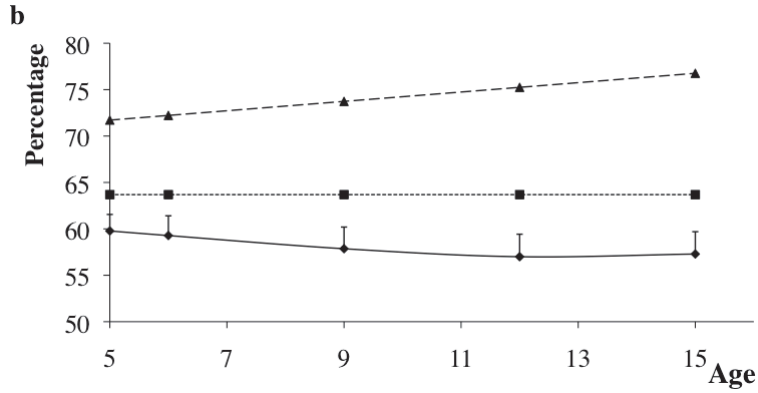

Figure 2.7b boys *LFH ratio for untreated patients with Apert (▲) and Crouzon (■) syndrome and control subjects (●).*

Untreated Patients With Apert Syndrome

Patients with Apert syndrome showed statistically significant gender differences for all measurements except for SNA angle (Table 2.5; Figs. 2.2 through 2.7). SNA angle was significantly smaller than in controls at all ages, with the differences increasing with age. SNB angle in patients with Apert syndrome was significantly larger than SNB angle in control participants, with these differences increasing during childhood and decreasing during adolescence. For both boys and girls, differences in the ANB angle between patients with Apert syndrome and controls increased over time, i.e., the Apert patients developed a more severe Angle Class III malocclusion. The SN/PP angle in patients with Apert syndrome was significantly smaller than the SN/PP angle in controls, with differences increasing between the ages of 5 to 15 years. The NSMe angle for patients with Apert syndrome remained within the limits of the control subjects. The LFH ratio for patients with Apert syndrome was significantly larger at all ages, with differences increasing in boys and decreasing slightly in girls with increasing age.

Comparison of Untreated Patients With Crouzon Syndrome and Untreated Patients With Apert Syndrome

Growing patients with Apert syndrome showed more complex growth changes than patients with Crouzon syndrome (Tables 2.4 and 2.5; Figs. 2.2 through 2.7). The SNA, SNB, ANB, and SN/PP angles were all significantly smaller in patients with Apert syndrome than those with Crouzon syndrome; the differences increased over time for all four angles. The LFH ratio was significantly larger for patients with Apert syndrome than those with Crouzon syndrome. The NSMe angle was larger for patients with Apert syndrome than for patients with Crouzon syndrome; these differences were small but statistically significant.

Comparison of Control Subjects With Untreated Adult Patients With Crouzon and Apert Syndromes

Differences between adult controls and untreated adult syndromic patients were found for SNA, ANB, SN/PP angles, and LFH ratio (Table 2.6). The SNA, ANB, and SN/PP angles showed higher values for controls, while the LFH ratio was larger for syndromic patients. The NSMe and SNB angles were not significantly different between controls and syndromic patients. Patients with Crouzon syndrome had significantly larger SNA angles and smaller values for the LFH ratio than patients with Apert syndrome. Gender differences were observed only for the ANB and SN/PP angles; male patients with Apert syndrome had significantly smaller ANB and SN/PP angles than male patients with Crouzon syndrome. Female patients with Apert and Crouzon syndrome did not differ. The SNB and NSMe angles showed no significant differences between the syndrome groups.

Table 2.5 *Multilevel models for growing untreated male and female patients with Apert syndrome.*

Gender	Measurement	Fixed Explanatory Variables								Between subjects
		Constant		Linear		Quadratic		Cubic		
		Estimate	SE	Estimate	SE	Estimate	SE	Estimate	SE	SD
Males	SNA	6.891e+1	2.277e+0	4.399e-1	4.288e-1	-1.231e-1	5.082e-2	-	-	5.190e+0
	SNB	7.421e+1	1.264e+0	1.658e+0	5.297e-1	-1.325e-1	6.125e-2	-	-	4.569e+0
	ANB	-5.153e+0	1.908e+0	-1.243e+0	1.592e-1	-	-	-	-	4.290e+0
	SN/PP	-9.531e+0	2.120e+0	-7.351e-1	1.878e-1	-	-	-	-	4.593e+0
	NSMe	7.286e+1	1.585e+0	-3.376e-1	1.555e-1	-	-	-	-	3.300e+0
	LFH ratio	7.222e+1	1.340e+0	5.044e-1	1.345e-1	-	-	-	-	2.756e+0
Females	SNA	6.868e+1	9.560e-1	5.967e-1	3.752e-1	-1.192e-1	4.753e-2	-	-	2.400e+0
	SNB	7.785e+1	7.976e-1	1.565e+0	3.052e-1	-3.652e-1	1.090e-1	2.246e-2	9.030e-3	2.440e+0
	ANB	-8.436e+0	1.139e+0	-5.226e-1	1.304e-1	-	-	-	-	3.763e+0
	SN/PP	-8.351e+0	1.444e+0	-2.491e+0	4.009e-1	5.570e-1	1.448e-1	-3.286e-2	1.120e-2	5.081e+0
	NSMe	7.142e+1	9.659e-1	-5.612e-1	1.829e-1	6.658e-2	2.296e-2	-	-	3.578e+0
	LFH ratio	7.377e+1	1.107e+0	3.302e-1	3.080e-1	-8.111e-2	3.881e-2	-	-	3.685e+0

Constant = age 6 years; - = not statistically significant.

Table 2.6 *Multilevel models for untreated control, Crouzon and Apert adults.*

Gender	Measurements	Controls Estimate	SD	Crouzon Estimate	SD	Apert Estimate	SD
Males	SNA	8.127e+1	3.423e+0	6.993e+1	7.085 e+0	5.960e+1	3.586 e+0
	SNB	7.900e+1	3.361 e+0	8.016e+1	5.268 e+0	7.848e+1	2.880 e+0
	ANB	2.291e+0	2.689 e+0	-1.069e+1	4.011 e+0	-1.888e-1	3.685 e+0
	SN/PP	8.498e+0	3.145 e+0	2.220e-1	9.680 e+0	-1.582e+1	3.314 e+0
	NSMe	6.857e+1	3.031 e+0	6.864e+1	4.454 e+0	7.164e+1	4.459 e+0
	LAFH	5.668e+1	2.647 e+0	6.341e+1	2.177 e+0	7.624e+1	3.384 e+0
	SN	7.487e+1	3.239e+0	5.253e+1	3.157e+0	5.547e+1	1. 570e+0
	TAFH	1.197e+2	6.393e+0	9.438e+1	4.229e+0	1.001e+2	5.567e+0
Females	SNA	8.097e+1	3.981 e+0	8.097e+1	3.981 e+0	8.097e+1	3.981 e+0
	SNB	7.808e+1	3.785 e+0	7.808e+1	3.785 e+0	7.808e+1	3.785 e+0
	ANB	2.749e+0	2.610 e+0	2.749e+0	2.610 e+0	2.749e+0	2.610 e+0
	SN/PP	8.600e+0	3.407 e+0	8.600e+0	3.407 e+0	8.600e+0	3.407 e+0
	NSMe	6.855e+1	8.698 e+0	6.855e+1	8.698 e+0	6.855e+1	8.698 e+0
	LAFH	5.694e+1	2.564 e+0	5.694e+1	2.564 e+0	5.694e+1	2.564 e+0
	SN	6.935e+1	2.459e+0	5.108e+1	1.633e+0	5.299e+1	9.689e+1
	TAFH	1.143e+2	5.029e+0	9.584e+1	1.810e+0	1.697e+0	4.137e+0

Constant = age 22 years.

2.4 Discussion

Multilevel modeling is an important tool for the analysis of longitudinal cephalometric data. This model has important advantages compared to other longitudinal statistical analysis procedures. It can describe both individual and average growth curves; it is flexible because it uses polynomials, which can describe growth curves of almost any form. Additionally, the model can handle missing values very easily (without loss of complete cases). Finally, the model can be used with different sample and research designs (Hoeksma and Van der Beek, 1991).

Premature fusion of craniofacial sutures results in midface retrusion in patients with Crouzon and Apert syndromes. Lack of sutural growth of the maxilla and an abnormal remodeling pattern result in a maxilla that is small in three planes of space (Kreiborg and Aduss, 1986). There is almost a complete absence of anterior maxillary displacement in relation to the anterior cranial base during growth (Kreiborg and Aduss, 1986). In this study, patients with Apert syndrome showed smaller SNA angle values compared to patients with Crouzon syndrome (Fig. 2.2; Tables 2.4 and 2.5); this finding is in agreement with other studies (Bachmayer et al., 1986; Kreiborg and Cohen, 1998; Kreiborg et al., 1999). More craniofacial sutures are fused at birth in patients with Apert syndrome, whereas patients with Crouzon syndrome sometimes show open craniofacial sutures.

The synostosis of these sutures for Crouzon patients is often progressive during growth (Renier et al., 2000; Connolly et al., 2004), which might influence sagittal growth in the syndromic patient.

The mandible in patients with Crouzon and Apert syndromes showed an anterior rotation that produced an Angle Class III malocclusion (Figs. 2.3 and 2.4); this increasing mandibular rotation during growth has been reported previously in cross-sectional studies (Bachmayer et al., 1986; Cohen and Kreiborg, 1996; Kreiborg and Cohen, 1998; Kreiborg et al., 1999). The sagittal growth of the mandible for the syndromic groups was similar to that seen in controls (Fig. 2.3). In contrast to the near absence of sagittal growth of the maxilla, the growth rate of the mandible is fairly normal, resulting in a prognathic appearance in relation to the anterior cranial base as a result of retrusion of the midface (Bachmayer et al., 1986; Kreiborg and Aduss, 1986); this growth pattern increases the discrepancy between the maxilla and the mandible (Fig. 2.4). However, controversy exists as to whether the mandible is normal in size and shape (Costaras-Volarich and Pruzansky, 1984; Kreiborg and Aduss, 1986; Bachmayer et al., 1986; Carinci et al., 1994). A reduced mandible would result in a less severe Angle Class III malocclusion.

The palatal plane showed an increasing counterclockwise rotation in relation to the anterior cranial base (Fig. 2.5). Other studies also found a relatively large amount of vertical maxillary growth and virtually no sagittal growth (Bachmayer et al., 1986; Kreiborg and Aduss, 1986; Carinci et al., 1994; Meazzini et al., 2005). Controversy exists concerning vertical maxillary growth following early midfacial surgery (Fearon, 2005; Meazzini et al., 2005). Kreiborg and Aduss showed large vertical maxillary growth in a small maxillary superimposition study (n = 8) using metallic implants (Kreiborg and Aduss, 1986). However, the vertical growth was attributed to remodeling and appositional growth, whereas no sutural growth took place.

Conclusions should be drawn with care for several reasons. First, the low incidence of patients with Crouzon and Apert syndromes makes it difficult to collect data from a large patient population. Most studies evaluating presurgical growth have been cross-sectional in design; only a few studies on craniofacial growth of Crouzon and Apert patients have examined samples larger than 10 patients (Bachmayer et al., 1986; Cohen and Kreiborg, 1996; Kreiborg and Cohen, 1998; Kreiborg et al., 1999). From a statistical viewpoint, the sample size of the present study was not large. However, given the prevalence of these syndromes and in comparison to other studies, the sample size of untreated Crouzon and Apert syndrome patients is acceptable.

Second, the cranial base (basion [Ba]-S-N) in patients with Crouzon and Apert syndromes is reported to be 12% to 15% shorter in all directions, with a shape comparable to that seen in the normal population (Cohen, 1986; Kreiborg and Aduss, 1986). Sagittal shortening of the cranial base is probably caused by diminished growth of the spheno-occipital synchondrosis and sphenofrontal suture. The sphenoid bone, part of the anterior cranial base, is often reduced

because of diminished growth of the sphenooccipital synchondrosis and sphenofrontal suture (Kreiborg et al., 1999). The SN value was significantly smaller for patients with Crouzon and Apert syndromes compared to controls (Table 2.6). A short cranial base means that the mandibular condyle is placed more forward and a skeletal Angle Class III. A relatively more distally placed N will disguise a severe underlying skeletal Angle Class III. Other geometric effects of the used cephalometric points, like the vertical lengths N to A and N to B, will also distort an underlying skeletal discrepancy (Jacobson, 1975; Cohen and Kreiborg, 1996; Posnick and Ruiz, 2000).

Third, the validity of any measurement obtained through a cephalometric radiograph depends largely on the reproducibility of the cephalometric landmarks. Factors such as the quality of the radiographs, the conditions under which they are measured, and the care and skill of the operator will influence the magnitude of identification error. For this reason, it has been suggested that every study should include an assessment of reproducibility, even though standard measurements are used (Houston, 1983). The skeletal morphology of patients with Crouzon and Apert syndromes is different from that of a normal population, but it has been shown that extreme variations in skeletal morphology do not affect the accuracy of cephalometric evaluation (Wah et al., 1995). In a meta-analysis of landmark identification and reproducibility in nonsyndromic patients, it was concluded that 0.6 mm of total error in the x- or y-axis was acceptable (Trpkova et al., 1997). The cephalometric landmarks chosen in this study had even smaller total error for reproducibility in the x- or y-axis (Fig. 2.1; Tables 2.1 and 2.2).

Fourth, intraobserver and interobserver reliability for digitization of cephalometric measurements was sufficient, except for the interobserver reliability measurements of the SN/PP angle. Difficulties in landmark identification for the palatal plane and point A may be a result of tooth germs, erupting teeth, and the radiolucent immature skeleton (Hotz and Gnoinski, 1976).

Finally, early surgical treatment of the midface is sometimes performed because of functional indications or a patient's poor self-image (Reid, 2007). The paucity of data from patients who undergo midfacial surgery at an early age (6 to 9 years of age) and the lack of adolescent data for these syndrome patients may influence the data available in the literature. In this study, the few data from adult syndromic patients were not considered to have much validity; however, it seems that limited growth occurred after 15 years of age.

Given the aforementioned difficulties, caution with the interpretation of cephalometric findings is advised. Multilevel modeling is useful for the construction of growth curves for patients with Apert and Crouzon syndromes to describe and predict development over time for a particular outcome variable. The data for patients with Crouzon and Apert syndrome clearly show growth at adolescence. Therefore, caution with midfacial surgical interventions in growing patients should be exercised because of possible impairment of postsurgical facial growth. The

prediction accuracy for the measurements used in this study might improve with the collection of more data. Individual variations in growth in syndromic patients are observed; however, there is a lack of knowledge concerning the prediction of facial skeletal growth development in the individual patient.

2.5 Conclusion

The craniofacial growth analysis data presented here showed marked and significant differences in sagittal and vertical growth in patients with Apert and Crouzon syndromes. In general, abnormal craniofacial morphology was more severe in Apert syndrome than in Crouzon syndrome. The maxilla in syndromic patients is more retruded and restrained in sagittal than in vertical growth. Fairly normal mandibular growth results in an anterior rotation and a more severe maxillomandibular discrepancy during adolescence. However, vertical maxillary growth is not restrained by growth; therefore a counterclockwise rotation of the palatal plane in relation to the anterior cranial base can be expected.

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Chapter 3

Mandibular Asymmetry in Patients With the Syndrome of Crouzon or Apert

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Abstract

Purpose: The aim of this study was to describe directional and fluctuating mandibular asymmetry in children with Crouzon or Apert syndrome over time.

Patients and Methods: Mandibular asymmetry of children between 7.5 and 14 years of age with the Crouzon syndrome (n = 35) and Apert syndrome (n = 24) were compared with controls (n = 327). From panoramic radiographs, mandibular directional and fluctuating asymmetry was determined for the three groups. Multilevel statistical techniques were used to describe mandibular asymmetry changes over time.

Results: Patients with Crouzon and Apert syndromes showed statistically significant more fluctuating asymmetry for mandibular measures than controls. Between the Crouzon and Apert syndromes, no statistical differences were found in directional and fluctuating asymmetry. The control group showed statistically significant more directional asymmetry than patients with Crouzon or Apert syndrome. Controls showed for condylar-ramal height no change over time for directional asymmetry, while the directional asymmetry for the gonial angle increased. Patients with Crouzon syndrome showed only side dominance for the condylar-ramal height, whereas patients with Apert syndrome did not show dominance for any of the measurements.

Conclusions: Apert and Crouzon syndromes showed developmental instability in contrast to the controls. No statistically significant longitudinal differences were found for both directional and fluctuating asymmetry between Crouzon and Apert syndromes. Findings for fluctuating and directional asymmetry for both syndromes may indicate an inability to cope with genetic and environmental stress during development and treatment compared to nonsyndromic individuals.

3.1 Introduction

Development of facial symmetry in children with premature closure of one or more craniofacial sutures (craniosynostosis) has not been well studied. Facial symmetry is most commonly associated with a state of facial equilibrium, in which there is correspondence in size, shape, and arrangement of facial landmarks on both sides of the face (Peck et al., 1991). Many studies have demonstrated a certain asymmetry of structures as a naturally biological occurring phenomenon (Woo, 1931; Thompson, 1943; Melnik, 1992). Asymmetry is measured as the left minus the right value of a structure. Some authors suggest that a difference of sides between 3-5 percent may be a normal population mean (Skvarilova 1993, Farkas and Cheung 1981). The point where normal asymmetry becomes abnormal cannot easily be defined because no standard outcome measurements for normal and abnormal asymmetry exists (Liukkonen et al., 2005; Kambylafkas et al., 2006). Asymmetry from bilateral structures can be distinguished in two different categories (Fig. 3.1, Table 3.1) (Van Valen, 1962). The first category includes two different types of asymmetry; directional asymmetry and antisymmetry. For directional asymmetry there is a systematic difference, with one side being consistently larger or dominant than the other (Fig. 1a, Table 1) (Van Valen, 1962; Liukkonen et al., 2005). Most individuals are asymmetrical either to the left or right side (>95%). In contrast, antisymmetry is when the left and right side of individuals are almost equally present in a sample. The mean of the total population is centered around zero (Fig. 3.1b, Table 3.1) (Van Valen, 1962). Presumably these two types of asymmetry produce growth discrepancies and have a genetic basis (Van Valen, 1962).

In contrast, fluctuating asymmetry can also occur (Fig. 3.1c) (Van Valen, 1962). Fluctuating asymmetry (the second category of asymmetry), refers to random deviations from perfect symmetry in bilateral structures and is frequently used as a measurement of developmental instability (Van Valen, 1962; Adams and Niswander, 1967; DeLeon and Richtsmeier, 2009; Swaddle, 2003).

The degree of fluctuating asymmetry during growth and medical treatment may reflect developmental instability caused by stress (Van Valen, 1962; Adams and Niswander, 1967; DeLeon and Richtsmeier, 2009; Swaddle, 2003). The amount of stress experienced by individuals during growth may increase by physical impact or mental limitations (Adams and Niswander, 1967; Van Valen, 1962). Both the directional and fluctuating asymmetry of craniofacial structures have been measured (Melnik, 1992; DeLeon and Richtsmeier, 2009).

Table 3.1 *Definition and distribution of directional asymmetry, antisymmetry and fluctuating. L = left side, R = right side*

	Directional asymmetry (DA)	**Antisymmetry (AS)**	**Fluctuating asymmetry (FA)**
Definition	Directional asymmetry is characterized by a symmetry distribution that is not centred around zero but is biased significantly toward either on the left or the right side. DA is frequently used as a measurement of developmental precision and is caused primarily by genetic deviations	Anitsymmetry is a different rare type of DA. AS is characterized by being centred around a mean of zero. However, there is almost a equally distribution of left- and right side population in the same group,	Fluctuating asymmetry is characterized by small deviation from perfect symmetry in bilateral structures. FA is frequently used as a measurement of developmental instability during the growth caused by minor environmental or genetic deviations
Formula	DA = (L – R) / [(L + R) / 2]	AS = (L – R) / [(L + R) / 2]	FA = | L - R | / [(L + R) / 2]
Distribution	The mean of left minus right side is zero, or a small deviation toward either left or right side in normal population	The mean of left minus right side is zero in normal population with non-normal distribution (usually bimodal)	FA is the absolute difference between the left and right side of a character. The differences of the right and left sides having a mean of zero with normal variation
Values	Positive or negative values possible	Positive or negative values possible	Only positive values possible

During growth in normal children, both increases and decreases in directional asymmetry of the mandible have been observed (Melnik, 1992). Dominance of both the left and right sides of the mandible have been described (Vig and Hewitt, 1975; Peck et al., 1991). In normal children with developmental homeostatis, fluctuating asymmetry should be minimal (Fig. 3.1c, Table 3.1). Decreased fluctuating asymmetry indicates that development is relatively stable and unaffected by genetic or environmental distortions over time (Van Valen, 1962; Palmer and Strobeck, 1986; DeLeon and Richtsmeier, 2009). Developmental homeostasis can sometimes be distorted during growth by minor developmental problems, resulting in increased fluctuating asymmetry. Developmental instability during normal growth is small if sufficient homeostasis or buffering occurs (Palmer and Strobeck, 1986).

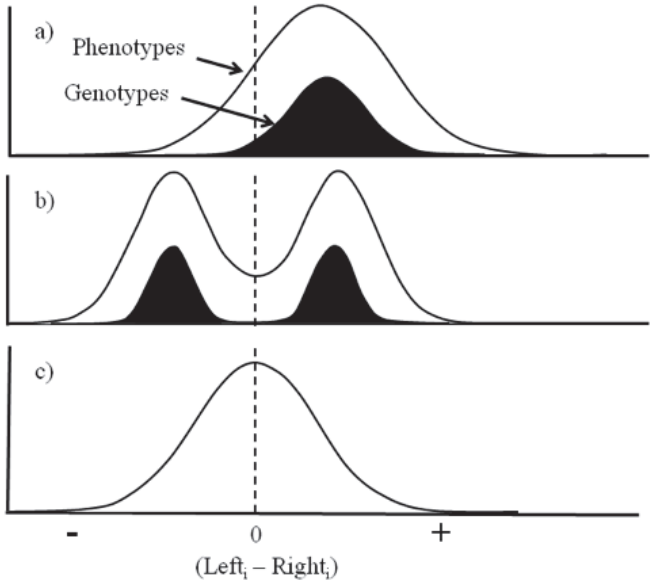

Figure 3.1 *Three types of asymmetry: a) directional asymmetry, b) antisymmetry, c) fluctuating asymmetry (Palmer and Strobeck, 1986).*

Craniosynostosis associated with Crouzon syndrome (1 in 25,000 live births) and Apert syndrome (1 in 60,000 live births) results in severe craniofacial dysmorphology (Cohen and Kreiborg, 1992; Kreiborg and Cohen, 1998; Reardon et al., 1994). The craniosynostosis in these syndromes could indirectly influence the mandibular development and create asymmetries (Costaras-Volarich and Pruzansky, 1984; Boutros et al., 2007). However, limited growth data are available from patients with Crouzon or Apert syndrome due to their very low prevalence (Costaras-Volarich and Pruzansky, 1984; Kreiborg and Cohen, 1998). More information about

asymmetry in patients with Crouzon or Apert syndrome is needed in order to better understand how these patients react to environmental and genetic influences during growth. Therefore, the aim of this study was to evaluate and to describe the development of directional and fluctuating asymmetry in patients with Crouzon or Apert syndrome over time.

3.2 Materials and Methods

Sample preparation and radiographic scans

Panoramic radiographic data of 72 Caucasian patients (age range 3-33 years) with Crouzon syndrome (25 boys and 17 girls) or Apert syndrome (11 boys and 19 girls) were collected from the Craniofacial Center of the Erasmus MC, Sophia Children's Hospital in Rotterdam, The Netherlands. The clinical diagnosis of the syndromes was genetically confirmed (Table 3.2). From these data only radiographs between 7.5 and 14 years of age were selected in order to compare the same age range in nonsyndromic controls. The syndromic patients had undergone various surgical and orthodontic interventions (no mandibular surgical procedures), both prior to the observation period. The panoramic radiographs were taken according to the team protocol. Only radiographs of diagnostic quality, taken before any mandibular surgery was performed, were used. At least two panoramic radiographs from each patient were included. 35 panoramic radiographs were excluded due to poor exposure. This resulted in a sample of 152 panoramic radiographs from 24 patients with Apert syndrome (8 boys and 16 girls) and 35 patients with Crouzon syndrome (18 boys and 17 girls) born between 1970 – 2004. The patients had an average of 2.5 radiographs (min. 2, max. 5, median 2) and the time-interval between the radiographs varied between 6.1 months and 2.2 years. The use of data from human subjects followed an approved protocol and satisfied the requirement of the IRB (approval number MEC-2010-304).

Control panoramic radiographs were obtained from normal children evaluated between 1971 and 1976 who participated in the mixed-longitudinal Nijmegen Growth Study. Only control children with similar ages to the syndromic patients were used as controls (Prahl-Andersen et al., 1979). The controls consist of three mixed-longitudinal cohorts who were followed for 5 years, from 4 to 14 years of age. At the start of the study, the children were 4, 7, or 9 years of age. A total of 2151 panoramic radiographs of 327 children (157 boys and 170 girls, age range 7.5-14 years) were selected. On average 6.5 radiographs (range 2 - 12, median 8) were used for each individual, with a time interval of 6 months between every two radiographs. The control radiographs were collected using a standardized procedure, using different panoramic machines: Philips OrthOralix; Siemens Orthopantomograph and Siemens Orthophos. The magnification

factor varied between 1.28 - 1.33. The conventional panoramic radiographs were scanned and digitized for further analysis.

Table 3.2. *Overview of the diagnostic genetic mutations in patients with Crouzon and Apert syndromes.*

	Apert (n = 30)	Crouzon (n = 42)
FGFR2		
P253R	12	
S252W	18	
A362T		3
C278F		5
C342R		2
C342T		2
C342W		3
C342Y		8
G271V		1
G338R		1
Q289P		3
S267P		3
S354C		2
W290R		4
Y105C		1
Y340H		3
FGFR3		
A391 E		1

3.2.1 Measurements

Twelve landmarks were digitized using Viewbox software (v3.1.1.14, D. Hal 1995-2006, Athens, Greece) (Figs. 2a and 2b). Only angular and ratio measurements were used due to magnification differences. An established method for measuring condylar and ramal asymmetry on panoramic radiographs was used (Habets et al., 1987; Habets et al., 1988). The measurements have been used for quantifying both directional and fluctuating asymmetry (Van Valen, 1962; Melnik, 1992; Liukkonen et al., 2005) (Fig. 2). Condylar-ramal heights and the gonial angles were used to calculate mandibular asymmetry based on the differences between the left (L) and right (R) sides. Directional and fluctuating asymmetry were calculated according to the formulae in table 3.1.

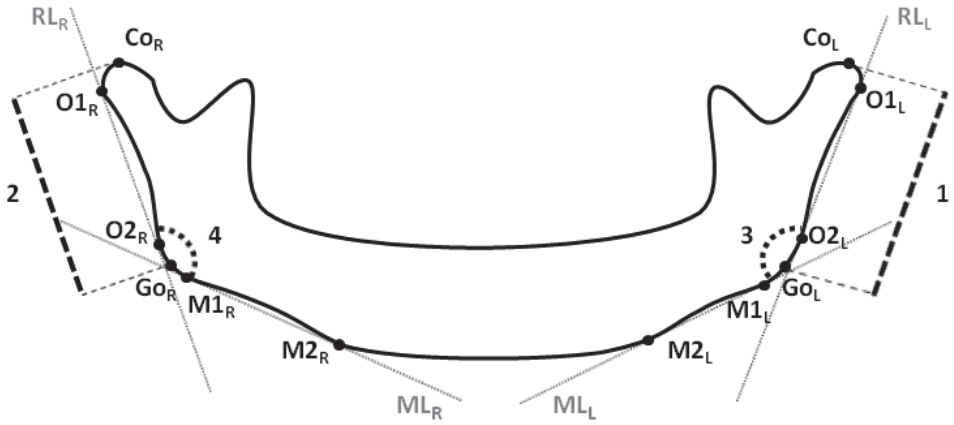

Figure 3.2 *Mandibular landmarks, lines and measurements used for asymmetry (Habets et al., 1987).* ***Landmarks and lines: Co****: most superior point of the condylar image;* ***O1****: most superior point of the condyle;* ***O2****: most lateral point of the ascending ramus;* ***Go****: Gonion; A point on the bony contour of the mandibular angle determined by bisecting the line of the posterior border of the mandibular ramus and the line of the lower border of the mandibular body angle;* ***M1****: most inferior point of the angulus on the tangential line of the lower border of the mandibular body;* ***M2****: most inferior point of the ascending lower border of the mandible;* ***RL-line****: tangential line of the posterior border of the mandibular ramus trough the points O1 and O2;* ***ML-line****: tangential line of the lower border of the mandibular body trough the points M1 and M2.* ***Measurements: 1,2****. Condylar-ramal height left (L) and right (R); the distance between landmarks Condylion and Gonion;* ***3,4.*** *Gonial angle left (L) and right (R); Angle in degrees between tangential line of the posterior border of the mandibular ramus and tangential line of the lower border of the mandibular body*

3.2.2 Statistical Analysis

Intra reliability

One investigator performed all of the measurements. Intra-examiner error for reproducibility of the measurements was determined by retracing panoramic radiographs from 23 syndromic patients (n = 107) and 20 control children (n = 122), with an interval of two weeks between replicates. Interclass correlation coefficients were calculated (Shrout and Fleiss, 1979). For the statistical analyses the SPSS software package (version 15.0, SPSS, Chicago, USA) was used.

Growth Models

Orthogonal polynomials were used to model directional and fluctuating asymmetry over time. The mathematical description of the procedure is given by Grizzle and Allen (Grizzle and Allen, 1969), and extended by Goldstein (Goldstein, 1986). The program MLwiN (version 2.1, Centre for Multilevel Modelling, London, United Kingdom) was used to model growth changes and compare the three groups. For each *y* variable (asymmetry measurement), a polynomial equation was estimated for the patient (i) on the age of measurement (j). For each *y* variable of directional and

fluctuating asymmetry (condylar-ramal height (Co-Go) and gonial angle (Gonang)) a polynomial equation was estimated. The *y* intercept was adjusted to ten years of age (intercept = age 10) to provide a comparison in the middle of the age range and to reduce the complexity of the computations. Average growth curves were estimated between 7.5 and 14 years of age. Due to expected group differences, separate models were fitted for each group. A cubic model was first fitted for each group and the highest-order term was checked for statistical significance, by using the t-test. Statistical significance was determined by the standard errors of the estimates using a 0.05 level for statistical significance. If the term was not significant, it was removed and a new reduced model was fitted. As there were no statistically significant differences between the two sexes, boys and girls were pooled. The initial equation was:

$$y_{ij} = \beta_{0ij}constant + \beta_1 t_{ij} + \beta_2 t_{ij}^2 + \beta_3 t_{ij}^3$$

with

$$\beta_{0ij} = u_{0j} + e_{0ij}$$

The asymmetry growth measurement, *y* was computed by adding the intercept (β_{0ij}) to the products of other fixed coefficients (β_1, β_2, and β_3) multiplied by age (t) at each occasion. The u_{0j} and e_{0ij} comprise the random portion of the model and are assumed to have means equal to zero, to be uncorrelated and normally distributed. The level 1 residual e_{0ij} represents within-subject variation, or the "error" term, while the level 2 residual u_{0j} represents in this case between-subject variation (Goldstein, 1986).

The polynomial model takes full advantage of each patient's individual longitudinal growth data and statistically evaluates the shape of the curve. Iterative generalized least squares were used to estimate the model's parameters (Goldstein, 1986).

3.3 Results

3.3.1 Measurement error

The interclass correlation coefficient for intra-investigator reliability varied from 0.95 to 0.99 for condylar-ramal height and gonial angle, respectively.

3.3.2 Growth models

Controls

The multilevel procedures showed that the growth followed simple models, ranging from constant (i.e. no growth) to linear changes over time. The fixed terms of each model were used

to estimate the values for fluctuating and directional asymmetry between 7.5 and 14 years of age. For instance, the directional asymmetry for the gonial angle in the control group showed ratio 0.00965 at the age of 12 years, computed as 0.00783 + (0.00091 * 2) (Table 3.3b). The linear term 0.00091 (the yearly change) was multiplied by 2 instead of 12 because the intercept was set to 10 years of age.

Multilevel growth models for fluctuating asymmetry in the control group showed no change over time for condylar-ramal height and showed a slight increase for the gonial angle (Figs. 3.3a and 3.3b). For the directional asymmetry, condylar-ramal height showed to have a dominance for the right side and showed no change over time (Fig. 3.4a). However, for the gonial angle, the controls showed an increase of directional asymmetry, with a dominance to the mandibular left side (Fig. 3.4b).

Patients with Crouzon syndrome

Fluctuating asymmetry measurements for condylar-ramal height decreased between 7.5 to 14 years of age (Fig. 3.3a). At 10 years of age, statistically significant more fluctuating asymmetry for condylar-ramal height was found compared to controls (Tables 3.3a and 3.4a). Fluctuating asymmetry for the gonial angle did not change during growth (Fig. 3.3b) and no differences with controls were seen at the age of 10 years. For patients with Crouzon syndrome, the condylar-ramal height had a dominance for the right side (Fig. 3.4a) and the directional asymmetry decreased between 7.5 and 14 years of age (Fig. 3.4a). At the age of 10 years the condylar-ramal height showed statistically significant more directional asymmetry compared to the controls ($t = -2.300$, $p<0.05$) (Tables 3.3b and 3.4b). The gonial angle of the patients with Crouzon syndrome showed dominance for the mandibular left side (Fig. 3.4b) and no statistically significant differences were found with controls (Tables 3.3b and 3.4b).

Patients with Apert syndrome

Measurements for fluctuating asymmetry (condylar-ramal height and gonial angle) were statistically significantly higher in Apert patients compared to the controls (Table 3.3a). Measurements for fluctuating asymmetry did not change in the period between 7.5 and 14 years of age (Figs. 3.3a and 3.3b). Patients with Apert syndrome showed no statistically significant directional asymmetry for the condylar-ramal height and gonial angle (Table 3.3b), and these measurements did not change over time (Figs. 3.4a and 3.4b). The controls showed statistically significant more directional asymmetry for gonial angle compared to Apert patients ($t = 2.328$, $p<0.05$) (Table 3.3b). No statistically significant differences were found for the condylar-ramal height between these two groups (Table 3.3b).

Table 3.3a *Fluctuating asymmetry; estimated intercepts and linear coefficient at the age of 10 years in three groups (Crouzon, Apert and Control subjects). * p<0.05; ** p<0.01; *** p<0.001*

Measures	Apert		Crouzon				Controls			
	Intercept		Intercept		Linear		Intercept		Linear	
	Estimate (SE)	t-value	Estimate (SE)	t-value	Estimate (SE)	t-value	Estimate (SE)	t-value	Estimate (SE)	t-value
Condylar-ramal height	**4.244e-2 (5.020e-3)**	**8.454*** **	**4.554e-2 (4.114e-3)**	**11.080*** **	**-5.418e-3 (1.665e-3)**	**-3.254** **	**3.193e-2 (8.737e-4)**	**36.546*** **		
Gonial Angle	**3.468e-2 (5.060e-3)**	**6.854*** **	**2.761e-2 (2.526e-3)**	**10.930*** **			**2.233e-2 (7.588e-4)**	**30.706*** **	**7.302e-4 (2.884e-4)**	**2.532***

Table 3.3b *Directional asymmetry; estimated intercepts and linear coefficient at the age of 10 years in three groups (Crouzon, Apert and Control subjects). * p<0.05; ** p<0.01; *** p<0.001*

Measures	Apert		Crouzon				Control			
	Intercept		Intercept		Linear		Intercept		Linear	
	Estimate (SE)	t-value	Estimate (SE)	t-value	Estimate (SE)	t-value	Estimate (SE)	t-value	Estimate (SE)	t-value
Condylar-ramal height	-1.297e-2 (1.003e-2)	-1.293	**-2.840e-2 (6.507e-3)**	**-4.365*** **	**5.164e-3 (2.248e-3)**	**2.297***	**-1.064e-2 (1.650e-3)**	**-6.448*** **		
Gonial Angle	-4.172e-3 (8.605e-3)	-0.485	3.931e-3 (4.893e-3)	0.803			**7.833e-3 (1.341e-3)**	**5.841*** **	**9.066e-4 (3.885e-4)**	**23.340*** **

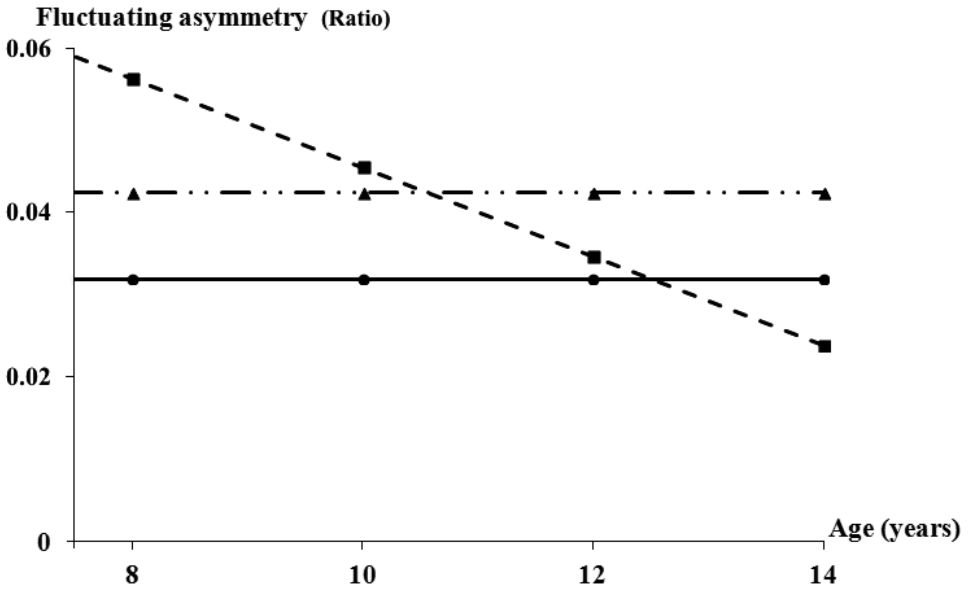

Figure 3.3a *Ratios of fluctuating asymmetry for condylar-ramal height for control subjects (●), patients with the syndrome of Crouzon (■) and Apert (▲).*

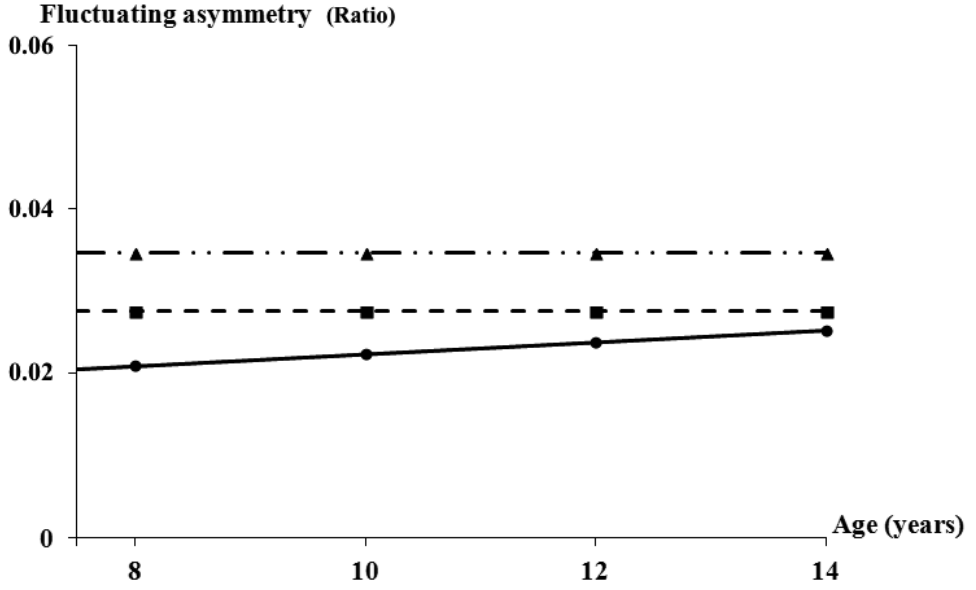

Figure 3.3b *Ratios of fluctuating asymmetry for gonial angle for control subjects (●), patients with the syndrome of Crouzon (■) and Apert (▲).*

Patients with Crouzon syndrome compared with patients with Apert syndrome

Multilevel modelling showed different tendency of growth over time (constant vs linear curves) for patients with Crouzon syndrome compared to patients with Apert syndrome (Figs. 3a and 4a). Although the two groups showed different growth models, no statistically significant differences were found between the two syndromes for either directional or for fluctuating asymmetry (Tables 3.3a and 3.3b).

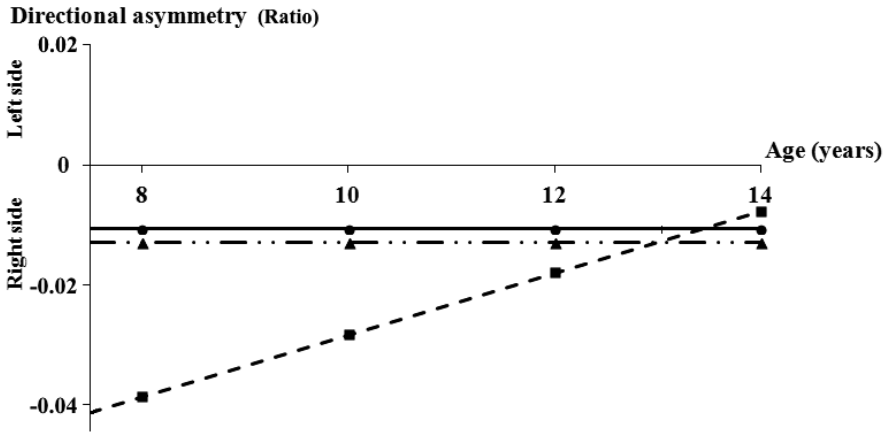

Figure 3.4a *Ratios of directional asymmetry for condylar-ramal height for control subjects (●), patients with the syndrome of Crouzon (■) and Apert (▲).*

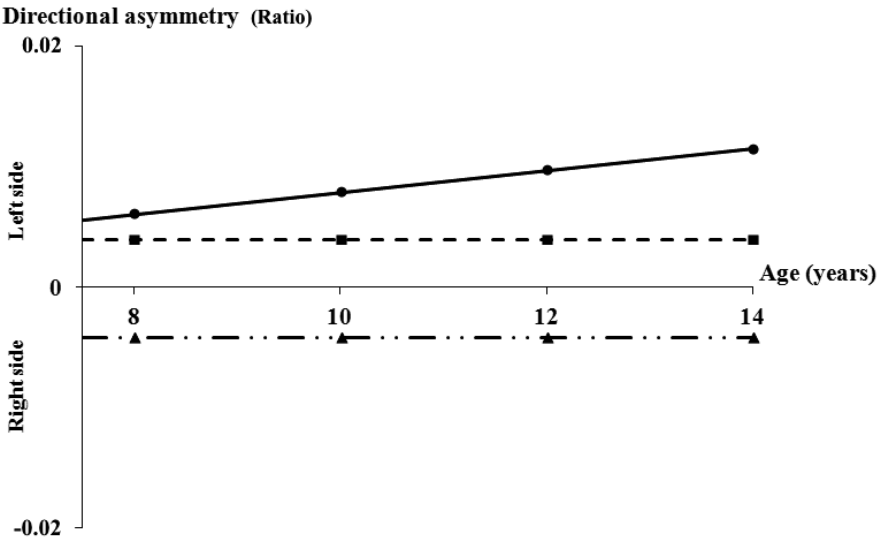

Figure 3.4b *Ratios of directional asymmetry for gonial angle height for control subjects (●), patients with the syndrome of Crouzon (■) and Apert (▲).*

Table 3.4a *Differences in the fluctuating asymmetry between groups (Crouzon, Apert and Control subjects); estimates differences, SE and t-values.* ***** *p<0.05; ** p<0.01; *** p<0.001*

Measures	Apert minus Control Intercept Estimate (SE)	t-value	Crouzon minus Control Intercept Estimate (SE)	t-value	Apert minus Crouzon Intercept Estimate (SE)	t-value
Condylar-ramal height	**1.049e-2 (4.153e-3)**	**2.526***	**8.760e-3 (3.351e-3)**	**2.614***	-1.729e-3 (6.378e-3)	-0.271
Gonial Angle	**1.169e-2 (3.228e-3)**	**3.621****	4.464e-3 (2.568e-3)	1.807	7.394e-3 (5.241e-3)	1.411

Table 3.4b *Differences in the directional asymmetry between groups (Crouzon, Apert and Control subjects); estimates differences, SE and t-values. * p<0.05; ** p<0.01; *** p<0.001*

Measures	Apert minus Control Constant Estimate (SE)	t-value	Crouzon minus Control Constant Estimate (SE)	t-value	Apert minus Crouzon Estimate (SE)	t-value
Condylar-ramal height	-8.7806e-4 (7.2784e-3)	-1.206	**-1.360e-2 (5.913e-3)**	**-2.300***	1.232e-2 (1.114e-2)	1.081
Gonial Angle	**-1.298e-2 (5.575e-3)**	**-2.328***	-4.638e-3 (4.439e-3)	-1.056	-8.271e-3 (9.267e-3)	-0.893

3.4 Discussion

The most important finding in this study was that fluctuating asymmetry was larger in patients with Apert syndrome than in controls and patients with Crouzon syndrome. Increased fluctuating asymmetry for condylar-ramal height and for the gonial angle may imply more developmental instability in patients with Apert syndrome (Table 3.3a, Figs. 3.3a and 3.3b). Previous studies showed increased fluctuating asymmetry in other syndromes or anomalies, such as Down syndrome and cleft lip and palate (Adams and Niswander, 1967; Barden, 1980; Laspos et al., 1997; Kurt et al., 2010). Patients with Crouzon syndrome showed less developmental instability based on condylar-ramal height and gonial angle compared to patients with Apert syndrome (Table 3.3a). Craniofacial discrepancies in both syndromes hardly change with growth and development, probably because of genetic influences (Parsons, 1992). Differences in craniofacial morphology between Crouzon and Apert syndromes showed more severe abnormal growth pattern among the latter group, which concurs with previously reported results (Costaras-Volarich and Pruzansky, 1984; Kreiborg and Cohen, 1998).

Fluctuating asymmetry in growth patients with syndromic craniosynsotosis is influenced by genetic and environmental factors. There is evidence showing that genetic and environmental disturbances contribute to increased fluctuating asymmetry (Parsons, 1992). These patients are confronted with physical, emotional, and social problems, probably partly caused by their craniofacial disfigurement (Campis, 1991; Furlow et al., 1997; De Jong et al., 2012). Also several surgical and other medical interventions like long-term orthodontic treatment during growth could be a major stress factor for these patients. The overall effect may be an explanation for the higher degree of fluctuating asymmetry of the mandible found for patients with Crouzon or Apert syndromes.

Directional asymmetry in a growing patient with syndromic craniosynostosis was expected. A dominant side of a structure can be explained by growth discrepancies due to craniosynostosis and other etiological factors. Etiologic factors that could explain mandibular asymmetry of Crouzon and Apert syndromes include condylar pathologies, functional habits or dental malocclusions (Costaras-Volarich and Pruzansky, 1984; Kreiborg and Cohen, 1998). The controls showed a dominant side (left or right side) for directional asymmetry (Table 3.3b, Figs. 3.4a and 3.4b), which is in line with previous studies (Peck et al., 1991; Melnik, 1992). The Apert and Crouzon syndromes showed a higher degree of directional asymmetry for condylar-ramal height over time compared than the controls. Premature unilateral synostoses of calvarial sutures may explain the directional asymmetry that occurs in these syndromic patients (Cohen and Kreiborg, 1990) and may indirectly influence the growing mandible (Costaras-Volarich and Pruzansky, 1984).

Significantly more directional asymmetry was found for the condylar-ramal height of the patients with Crouzon syndrome than for controls. However, for the other measurements of the syndromic patients, only a tendency of directional asymmetry was found in contrast to controls (Table 3.3b). The small average value of directional asymmetry close to zero could be misleading (Fig. 3.1a). It is reasonable to consider that in Crouzon and Apert syndromes the more rare type antisymmetry may occur (Fig. 3.1b). In contrast to directional asymmetry where the direction of asymmetry is either left or right, antisymmetry shows right- and left-sided bimodal distribution (Fig. 3.1b). Antisymmetry may show a wide range of individual asymmetry in patients. A possible explanation for the present results in this study could be the wide range of asymmetry in patients demonstrated by a large standard error found for both syndromes (Palmer and Strobeck, 1986) (Table 3.3b). However, after analyzing scatterplots for the actual distribution of the results, the syndromic patients showed no bimodal distribution for the condylar-ramal height or for the gonial angle. Further research is needed to study the possible role of bimodal distribution in the facial symmetry of bilateral structures in these syndromic patients. New technological methods like three-dimensional reconstructions of computed tomography (CT) images or laser surface scanning methods could therefore be a helpful tool (DeLeon and Richtsmeier, 2009; Djordjevic et al., 2001).

For reliable and accurate measurements on panoramic radiograph, some recommendations from the literature were used in this study. Reliable vertical and angular measurements were used instead of inaccurate horizontal measurements (Habets et al., 1987; Kambylafkas et al., 2006; Elslande et al., 2008). Ratios instead of absolute values were used to prevent positioning, distortion or magnification errors due to the use of different panoramic x-ray machines (Fig. 3.2) (Habets et al., 1988; Kjellberg et al., 1994). In addition, regarding the adopted statistical methodology, multilevel models offer an important tool for describing longitudinal asymmetry with limited data of rare syndromes like Crouzon or Apert. Both individual and average growth curves can be described; it is a flexible model because it uses polynomials, which can describe growth curves of almost any form (Goldstein, 1986). Conventional procedures, including cross-sectional descriptions and analyses of yearly velocities from two measurement occasions provide less optimal use of the available material. Moreover, other polynomial methods would have required elimination of most of the subjects, due to missing observations, and adjustment of values to exact ages (Goldstein, 1986).

3.5 Conclusion

The following conclusions can be made from this study:
(1) Fluctuating asymmetry in patients with the Apert syndrome was statistically significant higher compared to controls.
(2) No statistically significant differences were found for longitudinal directional and fluctuating asymmetry between patients with Crouzon or Apert syndrome.
(3) Findings of fluctuating and directional asymmetry may illustrate the influence of genetic and environmental factors in growth and development of children with Crouzon and Apert syndromes.

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Chapter 4

Dental Maturation in Children With the Syndrome of Crouzon or Apert

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Abstract

Purpose: Developing teeth are used to assess maturity and estimate age in a number of disciplines. The purpose of this investigation was to study the dental maturation in children with Crouzon or Apert syndrome compared with nonsyndromic controls.

Patients and Methods: Records of 40 children with Crouzon syndrome (18 boys and 22 girls, aged 4.0 to 17.9 years) and 28 children with Apert syndrome (10 boys and 18 girls, aged 3.9 to 15.1 years) were referred to the Department of Orthodontics, Cleft Palate Team and Craniofacial Team, Erasmus MC–Sophia. Data from syndromic children were compared with data from 451 nonsyndromic children (225 boys and 226 girls, aged 2.9 to 16.9 years). From panoramic radiographs, dental maturation was determined for patients with Crouzon and Apert syndromes and compared with data collected from control children. Logistic functions were constructed for dental maturation over time for syndromes and gender.

Results: Statistically significant gender differences in dental maturation scores were found for girls with Crouzon ($P < .05$) and Apert syndrome ($P < .05$). Patients with Apert syndrome demonstrated a significantly delayed dental maturation ($P < .05$), while patients with Crouzon syndrome showed a nonsignificant delay.

Conclusions: Dental maturation in patients with Apert syndrome was more delayed than in patients with Crouzon syndrome. The delay of tooth formation in patients with Crouzon or Apert syndrome suggests a possible common genetic association.

4.1 Introduction

Dental maturity or dental age is a method for biological age determination (Demirjian et al., 1973). Clinicians have studied dental development in relation to chronological age and regard this to be superior to the use of other biological age determinations as indicators for chronological age (Moorrees et al., 1963; Anderson et al., 1976; Nik-Hussein et al., 2011). Developing tooth calcification has been shown to be less susceptible to environmental influences than skeletal development (Prahl-Andersen and Van der Linden, 1972; Prahl-Andersen et al., 1979; Mörnstad et al., 1995; Liversidge, 1999). Identification of key genes for tooth formation may show that disrupted dental development is caused by several independent defective genes, acting alone or in combination with other genes. Exploring these genes involved in different interacting molecular pathways may explain the wide variety in dental development patterns but can also explain their possible association with additional craniofacial anomalies (Wilke et al., 1997; DeMoerlooze et al., 2000; Bachler and Neubüser, 2005; De Coster et al., 2007). This may clarify tooth anomalies seen in patients with craniosynostosis as the genes involved in odontogenesis are also partly involved in craniosynostosis syndromes (De Coster et al., 2007; Nieminen et al., 2011). Mutations in the gene encoding of the fibroblast growth factor receptor (*FGFR*) were found in most syndromes with craniosynostosis (Wilke et al., 1997). The list of genes that are involved in craniosynostosis includes those coding for *FGFR1*, *FGFR2*, and *FGFR3* but also genes encoding transcription factors, such as *MSX2* and *TWIST* (Wilke et al., 1997; Bachler and Neubüser, 2005; Nieminen et al., 2011).

The fibroblast growth factors (*FGFs*) are a family of intercellular signaling molecules that are important factors controlling bone development, growth, remodeling, and repair (De Coster et al., 2007). The *FGF* and the *FGFR* also have been shown to play an important role in tooth formation and regeneration (Kettunen and Thesleff, 1988; Kettunen et al., 2000; Nieminen et al., 2011). The *FGFs Fgf-4*, *-8*, and *-9* have been implicated as epithelial signals regulating mesenchymal gene expression and cell proliferation during tooth initiation and later during epithelial folding morphogenesis and the establishment of tooth shape. *Fgf-10* expression is observed in the presumptive dental epithelium and mesenchyme during tooth initiation, whereas *Fgf-3* expression appeared in the dental mesenchyme at the bud stage. During the cap and bell stage, both *Fgf-3* and *Fgf-10* were intensely expressed in the dental papilla mesenchymal cells both in incisors and molars. *Fgf-3* participates in signaling functions of primary enamel knot. The dynamic expression patterns of different *Fgfs* in dental epithelium and mesenchyme and their interactions suggest existence of regulatory signaling cascades between epithelial and mesenchymal *FGFs* during tooth development (Kettunen and Thesleff, 1988; Miletich and Sharpe, 2003; Lin et al., 2009; Nieminen et al., 2011).

Mutations of *FGFR2* or *FGFR3* are causal to retarded craniofacial growth and development in Crouzon and Apert syndromes (Wilke et al., 1997; Bachler and Neubüser, 2005). The involvement of *FGFR2* in dentogenesis in animal studies may suggest that mutated *FGFR2* genes may influence dental development seen in these syndromes (Wilke et al., 1997). Determining dental maturation of patients with Crouzon and Apert syndromes yields information not only about the general development of the dentition but also about the general development of the individual, thus giving an indication for the involvement of the mutated *FGFR2* or *FGFR3* in the unique growth pattern seen in these syndromes. The aim of this study is to compare dental maturation of patients with Crouzon and Apert syndromes with nonsyndromic Dutch children and to develop new standards for these syndromes.

4.2 Materials and Methods

A retrospective longitudinal design was conducted with data of 96 panoramic radiographs from 28 patients (10 boys and 18 girls) with Apert syndrome and 135 panoramic radiographs from 40 patients (18 boys and 22 girls) with Crouzon syndrome from Erasmus MC Craniofacial Center, Sophia Children's Hospital, in Rotterdam, The Netherlands. The median age at which the panoramic radiographs were taken was 9.2 years for patients with Crouzon syndrome, with a range from 4.0 to 17.9 years. The median age at which the panoramic radiographs were taken was 9.5 years for patients with Apert syndrome, with a range from 3.9 to 15.1 years. The use of data from human subjects followed an approved protocol and satisfied the requirement of the institutional review board (approval MEC-2010-304).

The control group consisted of 451 normal Dutch children (225 boys and 226 girls) included in a previously published study (Leurs et al., 2005). The median age of the controls at which the panoramic radiographs were taken was 7.7 years, with a range from 2.9 to 16.9 years.

The clinical diagnosis of Crouzon or Apert syndrome was confirmed with genetic testing to detect a mutation in the *FGFR2* or *FGFR3* gene.

The subjects for this study had panoramic radiographs taken according to the protocol for treatment planning and treatment of Caucasian patients with Crouzon or Apert syndrome between 1980 and 2011. When one left mandibular tooth was missing, the contralateral right mandibular tooth was used. When mandibular teeth were missing bilaterally, the panoramic radiographs were excluded because no dental maturity score can be determined in these cases. Dental agenesis, identified on radiographs, was verified by analysis of dental records, to exclude premature extractions. Panoramic radiographs with a maturity score of 100 were excluded because the dentition has matured.

4.2.1 Statistical Analysis of Dental Maturity Scores

The dental development scores for patients with Crouzon and Apert syndromes were compared with the scores of control children using a logistic curve-fitting procedure (Leurs et al., 2005). 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 of the mean dental maturation over time and m for mean age at the 50th dental maturation percentile. Several logistic functions were estimated and graphed:

1. For control children (boys and girls), $Y = 100*\{1/(1+ e^{-0.559(x-5.586)})\}$ (Leurs et al., 2005)
2. For patients with Crouzon syndrome (boys and girls)
3. For patients with Apert syndrome (boys and girls)

For dental development to be determined over time, at least two consecutive panoramic radiographs are needed. For logistic curve fitting, at least three measurements are necessary. The patients with one or two radiographic measurements were used to improve the earlier-established logistic curves for estimating the logistic population mean. The data derived from one or two panoramic radiographs do not directly contribute to the calculation of velocity but are substantial to the level of the curve at a certain age. To calculate the 5th and 95th percentiles for the norm logistic curve, the SD was added and subtracted 1.96 times.

4.2.2 Dental Development Scores

The developmental stages of the seven left permanent mandibular teeth were assessed according to the method proposed by Demirjian et al. (1973). Each tooth of the mandible was given a score from A to H. These scores were converted into numbers and summed, referred to as the maturity score (Demirjian et al., 1973). Two examiners were trained by means of a tutorial program, available on CD-ROM (Demirjian, 1993–1994).

4.2.3 Measurement Error

Intra- and interexaminer reliability is expressed by the intraclass correlation coefficient (ICC) for the dental maturity score. To assess intra- and interexaminer reliability, two examiners randomly rescored 35 panoramic radiographs. The ICC is comparable to the kappa coefficient. ICC values range from 0 to 1. An ICC of .61 to .80 is interpreted as substantial agreement and an ICC of .81 to 1.00 as an almost perfect agreement. Calculations were performed with the statistical software package SPSS version 11.5 (SPSS Inc., Chicago, IL).

4.3 Results

4.3.1 Measurement Error

The ICC for intraexaminer reliability was .96 (95% confidence interval [CI], .94 to .99). The ICC for interexaminer reliability was .97 (95% CI, .96 to .99). Both scores indicate high reliability.

4.3.2 Dental Development Scores

Differences in dental development between patients with craniosynostosis and Dutch controls were found. The dental maturation of patients with Apert syndrome is significantly delayed (Table 4.1). Also, patients with Crouzon syndrome had delayed dental maturation scores compared with controls; these differences were not statistically significant (Fig. 4.1; Table 4.1). Compared with the Dutch norm, gender differences were also found. Female patients with Crouzon and Apert syndromes were statistically significantly delayed compared with controls (Figs. 4.1 and 4.2). Dental maturation of male patients with Crouzon and Apert syndromes was less mature than that of control subjects. A slight acceleration occurred between 9 and 12 years of age for male patients with Crouzon syndrome compared with controls.

Female patients with Crouzon syndrome at all ages were less matured than boys, although these differences were not statistically significant (Fig. 4.3). In patients with Crouzon syndrome, male patients showed delayed dental development before 6 to 7 years of age compared with female patients with Crouzon syndrome (Fig. 4.4). From this age on, female patients with Crouzon syndrome were less matured dentally compared with boys.

Table 4.1 *Mean difference for the logistic fits for the syndrome of Crouzon and Apert for gender. N is number of OPTs; mean difference is mean maturity score difference; SD is the standard deviation for the mean difference; SE is the standard error for the mean difference; P-value for mean difference compared to the Dutch control children.*

		N	mean diff	SD	SE	p-value
Crouzon	Boys	81	0.467	1.347	0.1497	N.S.
Apert	Boys	85	-0.347	1.112	0.1206	N.S.
Crouzon	Girls	64	-1.082	1.611	0.2014	p<0.05
Apert	Girls	26	-1.617	0.829	0.1628	p<0.05
Crouzon	Total	145	-0.216	1.655	0.1374	N.S.
Apert	Total	111	-0.645	1.393	0.1120	p<0.05

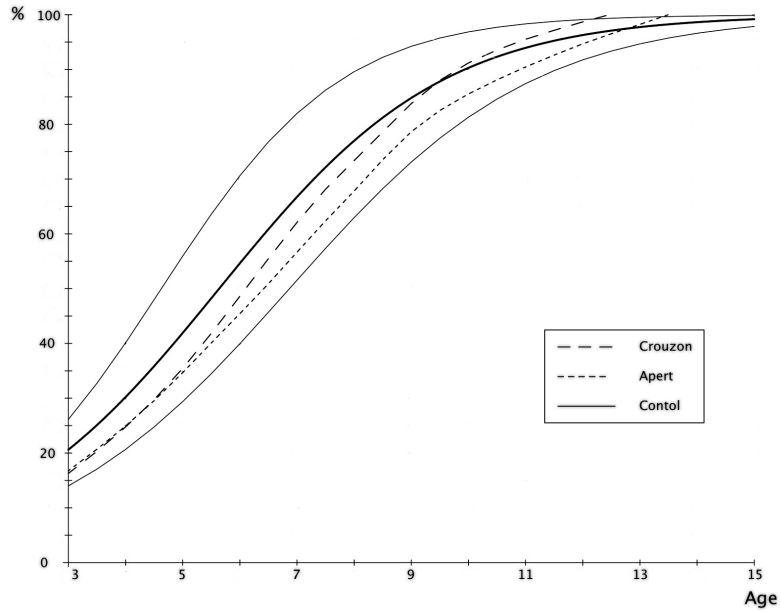

Figure 4.1 *Dental maturation for male controls and male patients with Crouzon and Apert syndromes. The 5th, 50th, and 95th percentile lines for controls are indicated.*

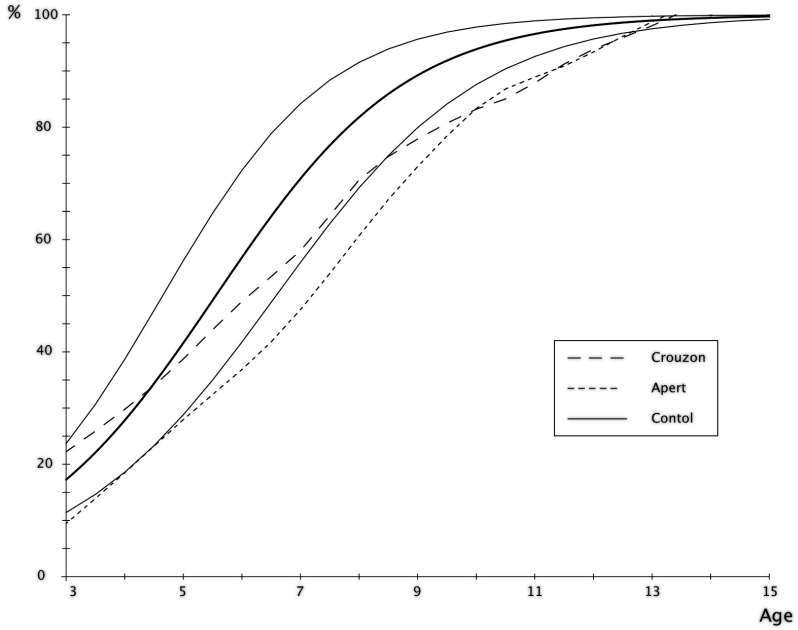

Figure 4.2 *Dental maturation for Dutch female controls and female patients with Crouzon and Apert syndromes. The 5th, 50th, and 95th percentile lines for controls are indicated.*

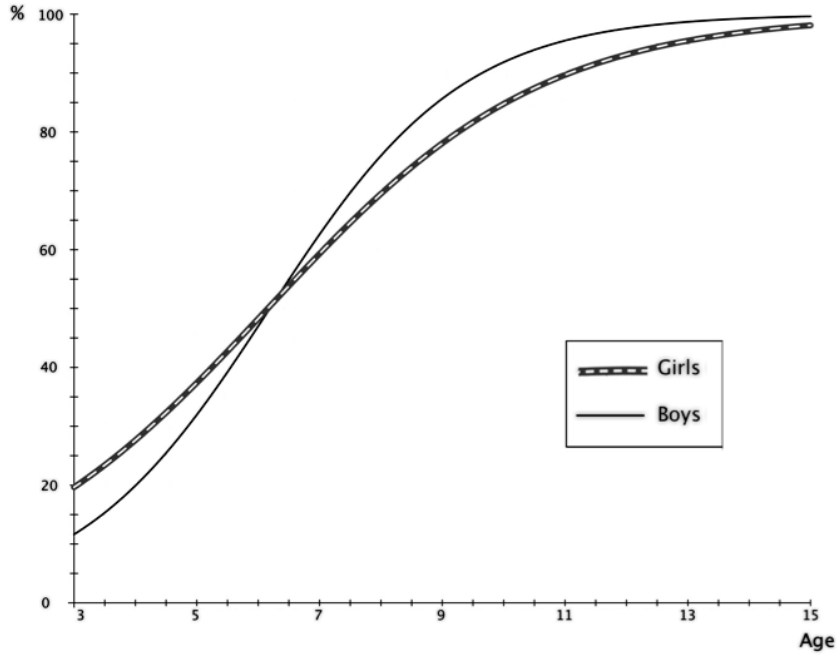

Figure 4.3 *Dental maturation for male and female patients with Crouzon syndrome.*

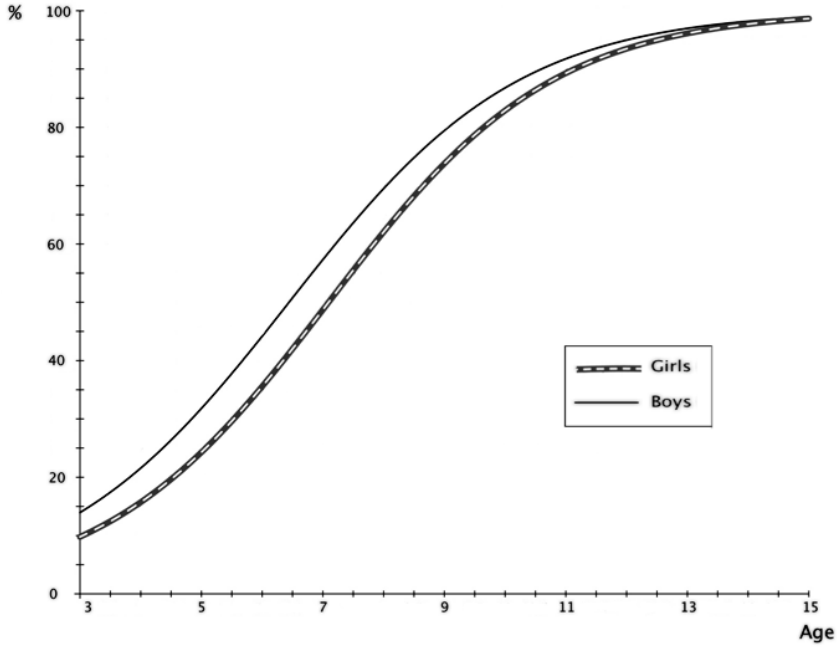

Figure 4.4 *Dental maturation for male and female patients with Apert syndrome.*

4.4 Discussion

The dental maturation in Dutch patients with Crouzon and Apert syndromes was compared with the dental maturation in a nonsyndromic control group of the same ethnicity. In both syndromes, disturbances in the gene expression show abnormal skeletal growth and probably could also have influence on dental development (Wilke et al., 1997; De Coster et al., 2007). The correction of facial deformities in patients with craniosynososis syndromes is complex because of the esthetic and functional difficulties associated with these disorders. Management of these patients requires knowledge and understanding of craniofacial growth and development (Renier et al., 2000). An important role is determining the type and timing of orofacial interventions in which gender- and syndrome specific data for dental maturation may attribute.

This study showed that the early dental maturation in syndromic patients is severely delayed (Table 4.1). Also, dental maturation in patients with Crouzon and Apert syndromes is abnormally distributed when compared with the nonsyndromic Dutch control group. The development over time at the 50th percentile was delayed compared with normal values (Figs. 4.1 and 4.2). One study in the literature investigated the relationship between dental maturity and Apert syndrome (Kaloust et al., 1997). This study showed a delayed dental maturity in patients with Apert syndrome, with a trend of increasing delay with increased age compared with a control group. The authors suggested a positive correlation between increased age and increased delay, extending equally the general growth of Apert children (Kaloust et al., 1997). However, gender differences were not accounted for.

Remarkable gender differences in dental maturation were found in patients with Crouzon and Apert syndromes. Girls with Crouzon and Apert syndromes showed statistically significant delayed dental maturation compared with boys. A large study of a normal sample (n = 1031) showed independent gender scores of dental maturity, which were always more advanced for girls (Chaillet et al., 2005). Girls were advanced already at 2 years of age until 12 years of age. Acceleration of dental maturation in boys started at 12 to 13 years, at the beginning of their puberty, and continued strongly until 18 years of age (Chaillet et al., 2005). Control Dutch boys and girls in the present study confirmed these findings. Gender differences in dental maturation for patients with craniosynostosis and control subjects (Field et al., 1991; Cohen and Kreiborg, 1993; Chaillet et al., 2005) might be related to variability due to the limited sample size of syndromic patients.

There is evidence to suggest that tooth agenesis is related to dental maturation in patients with Crouzon and Apert syndromes (Kaloust et al., 1997; Lin et al., 2009). Dental maturation of permanent teeth in nonsyndromic children (n = 108) is delayed with dental agenesis (Ruiz-Mealin

et al., 2012), and the severity of dental agenesis affects the magnitude of the delay (Ruiz-Mealin et al., 2012). The prevalence of tooth agenesis in patients with Crouzon and Apert syndromes is much higher than reported for the general population (Polder et al., 2004; Stavropoulos et al., 2011; Stavropoulos et al., 2012). High prevalence of tooth agenesis in patients with Crouzon and Apert syndromes might negatively influence delayed maturation in the present study, although the literature contains no consensus concerning delayed tooth development in patients with dental agenesis (Ruiz-Mealin et al., 2012).

The ability to determine dental maturity is important to those involved in treatment of patients with Crouzon or Apert syndrome (Kaloust et al., 1997). The oral surgeon plays an important role in determining the type and timing of orofacial interventions partly determined by the dental development (Cohen and Kreiborg, 1993; Kaloust et al., 1997). Dental development is particularly useful to the orthodontist when planning the treatment of different types of malocclusions in relation to surgical intervention. Dental maturation may also be of interest to molecular biologists, because genetic mutations may alter dental morphogenesis (Kaloust et al., 1997).

Dental maturity assessed by the Demirjian method (Demirjian et al., 1973) is considered to be the most precise and accurate method (Hägg and Matsson, 1985). Most methods determine dental maturation according to the degree of dental calcification observed in x-rays of the jaws (Schour and Massler, 1941; Garn et al., 1959; Haavikko, 1970; Moorrees et al., 1963; Prahl-Andersen and Van der Linden, 1972; Gustafson and Koch, 1974; Anderson et al., 1976). This is in contrast to Demirjian's method of estimating dental maturity by the development stage of seven teeth in the left side of the mandible.

Further, the method developed by Demirjian et al. (1973) avoids magnification considerations and the need for direct measurements. Therefore, it is one of the simplest, practical, and widely used methods (Garamendi et al., 2005).

After the age of 15 years, the accuracy of Demirjian's age prediction decreases because most subjects reach dental maturity scores of 100. Adding the third molar might increase the possibility of prediction until 18 years of age. However, the high variability of third molar development (Mesotten et al., 2002; Gunst et al., 2003; Chaillet et al., 2005), a 20% chance of third molar agenesis (Polder et al., 2004), and small sample sizes make accuracy of dental maturation at an older age low.

4.5 Conclusion

To calculate the dental maturation for patients with Crouzon and Apert syndromes, scoring can be carried out according to the system of Demirjian et al. (1973). Girls and boys with Crouzon and Apert syndromes were delayed compared with dental maturation in normal Dutch children (Leurs et al., 2005). Gender differences between the syndromes showed that girls with Crouzon and Apert syndromes had a statistically significant less mature dental maturity compared with controls. Dental maturation in patients with Apert syndrome was more delayed than in patients with Crouzon syndrome. The delay of tooth formation in patients with Crouzon and Apert syndromes suggest a possible common genetic association.

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Chapter 5

Patterns of Tooth Agenesis in Patients With the Syndrome of Crouzon or Apert

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Abstract

Purpose: Dental agenesis is the most common anomaly of dental development and can be a component of a congenital syndrome. The purpose of this study was to evaluate the prevalence of agenesis and to describe patterns of tooth agenesis in patients with Crouzon or Apert syndrome compared with nonsyndromic controls.

Patients and Methods: Longitudinal records of 67 patients with Crouzon syndrome (n = 39) or Apert syndrome (n = 28) from the Erasmus Medical Centre were examined. Syndromic patients were compared with patients in a nonsyndromic control group (n = 284).

Results: Prevalence of tooth agenesis in patients with Crouzon syndrome (35.9%) and patients with Apert syndrome (46.4%) was significantly higher than the prevalence in control subjects (27.5%) ($P < .005$). In all groups third molars were the most likely to be agenetic. Tooth agenesis excluding third molars was significantly higher in syndromic patients than in control subjects ($P < .001$). Bilateral agenesis of mandibular second premolars occurred significantly more often in patients with Crouzon and Apert syndrome than in control subjects ($P < .001$).

Conclusions: Tooth agenesis is more prevalent in patients with Crouzon or Apert syndrome than in control subjects. Tooth agenesis and mandibular symmetrical patterns of second premolar agenesis are more prevalent in syndromic patients.

5.1 Introduction

Tooth agenesis, the most common dental anomaly, is described in different ways: congenitally missing teeth, hypodontia (a few teeth are missing), oligodontia (several teeth are missing), and anodontia (all teeth are missing) (De Coster et al., 2009). In this article, the term tooth agenesis encompasses all of these terms. Excluding the third molars, agenesis of permanent teeth in the general population ranges from 3.2% to 7.6% (Polder et al., 2004). The prevalence of tooth agenesis varies per tooth. Third molar agenesis is the most common, with a prevalence around 20% in population studies (Vastardis, 2000; Polder et al., 2004). The teeth with second most prevalence of agenesis are the lateral maxillary incisor or mandibular second premolar (Polder et al., 2004).

Tooth agenesis can be a nonsyndromic trait or a component of an inherited syndrome (Vastardis, 2000; De Coster et al., 2007). Many syndromes are associated with tooth anomalies, which suggests that common molecular mechanisms are responsible for dental and organ development (Bailleul-Forestier et al., 2008). Tooth agenesis has been reported in syndromic craniosynostosis (premature fusion of the craniofacial sutures), such as in patients with Crouzon or Apert syndrome (Cohen and MacLean, 2000; De Coster et al., 2007). These rare syndromes share common clinical features, genetic features, and craniofacial abnormalities (Wilke et al., 1997; Cohen and MacLean, 2000).

Previous studies describing tooth agenesis often use frequencies to describe which individual tooth is missing in a certain population (Polder et al., 2004). This means that only one tooth at the time is addressed and not the overall pattern of absent teeth. The recently introduced Tooth Agenesis Code (TAC) can be used to describe the number and location of missing teeth (Van Wijk and Tan, 2006). TAC scores of different studies could eventually be combined to describe the overall pattern in tooth agenesis for a specific condition. Therefore, the purpose of this study was to evaluate the prevalence of tooth agenesis and to describe patterns of tooth agenesis in patients with Crouzon or Apert syndrome compared with those in nonsyndromic control subjects.

5.2 Materials and Methods

5.2.1 Participants

The sample consisted of 39 patients with Crouzon syndrome (20 boys and 19 girls) and 28 patients with Apert syndrome (10 boys and 18 girls) from the Erasmus MC Craniofacial Center, Sophia Children's Hospital in Rotterdam, The Netherlands. A large mixed-longitudinal data set

from the Nijmegen Growth Study was used as a control group (Prahl et al., 1979). From these data a random selection of 284 nonsyndromic children was made (125 boys and 157 girls).

5.2.2 Design

This study had a retrospective cross-sectional design. Longitudinal standardized panoramic radiographs of sufficient quality taken in the protocol of diagnosis and treatment of these patients between 1980 and 2011 were analyzed. The clinical diagnosis of Crouzon or Apert syndrome was genetically confirmed. Only Caucasian patients with one or more panoramic radiographs were included. Patients and control subjects were between 11 and 22 years old at the time of the panoramic radiograph examination. If a patient showed no third molar on a panoramic radiograph at a certain age, agenesis was scored when the root length of the second molar was at least equal to crown height on a panoramic radiograph (Liversidge, 2008). Chronological age of at least 15.0 years (if available) (Richardson, 1980) was used as third criterion to score third molar agenesis. Third molar agenesis could not always be determined because some of the syndromic patients or control subjects were younger than 15 years, and third molars were still absent. The use of data from human subjects followed an approved protocol and satisfied the requirement of the Institutional Review Board (approval number MEC-2010-304).

5.2.3 Patterns of Tooth Agenesis

The TAC (Van Wijk and Tan, 2006) was used to identify patterns of tooth agenesis. The TAC consists of four numbers (q1, q2, q3, and q4) that describe the number and location of missing teeth in each quadrant. Within each quadrant the teeth are numbered 1 to 8 (Peck and Peck, 1996). Each tooth has a tooth value that can be determined by calculating 2(n-1), in which n = tooth number. TAC values are derived by calculating the sum of tooth values for the missing teeth in each quadrant (Fig. 5.1).

5.2.4 Procedure

Tooth agenesis was diagnosed by one of two authors (E.O. or B.P-A.) based on clinical examination and after studying the panoramic radiographs, plaster casts, and intraoral photographs. All diagnoses were confirmed twice by one author (J.H.R.) by retrospectively studying the patients' dental charts and panoramic radiographs with an interval between the first and second assessment of at least 1 week. In three patients, discrepancies between the authors were identified and discussed until consensus was achieved. Cohen's kappa showed high intraobserver (1.0) and interobserver (0.96) reliability. Both scores are considered very high.

Right upper jaw (Q1)									Left upper jaw (Q2)							
A	18	17	16	15	14	13	12	11	21	22	23	24	25	26	27	28
B	128	64	32	16	8	4	2	1	1	2	4	8	16	32	64	128
A	48	47	46	45	44	43	42	41	31	32	33	34	35	36	37	38
Right lower jaw (Q4)									Left lower jaw (Q3)							

Figure 5.1 *Schematic representation of the human dentition that can be used to determine Tooth Agenesis Code (TAC) values. To calculate TAC values [Q1, Q2, Q3, and Q4], simply calculate the sum of the values associated with the missing elements in each quadrant. A, tooth numbering according to the FDI tooth numbering system (22); B, values associated with missing teeth. FDI, (French) translates World Dental Federation; Q1, quadrant 1; Q2, quadrant 2; Q3, quadrant 3; Q4, quadrant 4.*

5.2.5 Statistical Analysis

The Statistical Package for the Social Sciences (version 18.0; SPSS Inc., Chicago IL) was used for data analysis. TAC values were analyzed using a website that was specifically developed for this purpose (http://www.toothagenesiscode.com). A chi-square test and independent-samples t test were used for statistical analysis.

5.3 Results

5.3.1 Prevalence of Tooth Agenesis and Tooth Agenesis Patterns in Patients with Crouzon Syndrome

Prevalence of tooth agenesis (≥ 1) in patients with Crouzon syndrome, including the third molar, was 35.9% (upper jaw 10.3%, lower jaw 7.7%, upper and lower jaw 17.9%) (Table 5.1). The number of missing teeth ranged from one to six. Patients showing tooth agenesis had an average of 2.8 (SD = 1.3) missing teeth; for the upper and lower jaw the averages were was 1.8 (SD = 0.72) and 1.9 (SD = 0.30), respectively. The most commonly missing teeth were the third molars (TAC value 128), followed by the second premolars (TAC value 16) and lateral incisors (TAC value 2) (Table 5.1). For the upper jaw, four patterns were found in q1 and three in q2 (Table 5.2). The whole maxilla showed seven different patterns. The only symmetrical maxillary pattern was a single bilateral third molar (TAC value 128). For the mandible, five different patterns were found (Table 5.3). Except for one patient (TAC value 16 found in q4), all other patients with agenesis (n = 9) presented symmetrical patterns of one single tooth.

Table 5.1 *Patterns of missing teeth in each quadrant for each sample.*

Crouzon syndrome

TAC	Tooth type	q1		q2		q3		q4		Total
		n	%	n	%	n	%	n	%	n
1	I_1	0	0	2	20	2	22.2	2	20	6
2	I_2	0	0	1	10	1	11.1	1	10	3
16	P_2	1	12.5	0	0	4	44.4	5	50	10
20	P_2+C	1	12.5	0	0	0	0	0	0	1
128	M_3	5	62.5	7	70	2	22.2	2	20	16
144	M_3+P_2	1	12.5	0	0	0	0	0	0	1
Total		8	100	10	100	9	100	10	100	37

Apert syndrome

TAC	Tooth type	q1		q2		q3		q4		Total
		n	%	n	%	n	%	n	%	n
2	I_2	1	11.1	0	0	0	0	0	0	1
16	P_2	1	11.1	2	28.6	5	62.5	5	71.4	13
128	M_3	6	66.7	5	71.4	2	25.0	1	14.3	14
144	M_3+P_2	0	0	0	0	1	12.5	1	14.3	2
192	M_3+M_2	1	11.1	0	0	0	0	0	0	1
Total		9	100	7	100	8	100	7	100	31

Control subjects

TAC	Tooth type	q1		q2		q3		q4		Total
		n	%	n	%	n	%	n	%	n
2	I_2	3	7.0	2	5.0	1	2.4	1	2.3	7
4	C	2	4.8	3	7.5	0	0	0	0	5
16	P_2	0	0	1	5.0	4	9.8	6	14.0	11
24	P_2+P_1	1	2.4	1	5.0	0	0	0	0	2
128	M_3	34	81.0	32	80.0	36	87.8	34	79.1	136
130	M_3+I_2	2	4.8	1	5.0	0	0	0	0	3
144	M_3+ P_2	0	0	0	0	0	0	2	4.6	2
Total		42	100	40	100	41	100	43	100	166

5.3.2 Prevalence of Tooth Agenesis and Tooth Agenesis Patterns in Patients with Apert Syndrome

Prevalence of tooth agenesis (≥1) in patients with Apert syndrome, including the third molar, was 46.4% (upper jaw 14.3%, lower jaw 10.7%, upper and lower jaw 21.4%) (Table 5.1). The number of missing teeth ranged from one to six. Patients who showed tooth agenesis had an average of 2.6 (SD = 1.5) missing teeth. For the upper and lower jaw the averages were 1.3 (SD = 0.43) and 1.7 (SD = 0.47), respectively. The most commonly missing teeth were the third molars (TAC value 128), followed by the second premolars (TAC value 16). For the upper jaw, four unilateral patterns of agenesis were found in the first quadrant (q1) and two patterns in the second quadrant (q2) (Table 5.2). The maxilla showed six different patterns (Table 5.2). Half of these maxillary patterns showed a symmetrical single tooth pattern of agenesis. Agenesis of the third molars (TAC value 128; 63.6%) was found bilaterally or unilaterally in q1 (Tables 5.1 and 5.2). For the lower jaw, three patterns were found in the third quadrant (q3) and fourth quadrant (q4) (Table 5.3). The mandible showed nine different patterns of agenesis. In six patients a symmetrical mandibular pattern of a single tooth was found. In all of these patients the mandibular agenesis was found in the second premolars and third molars (TAC values 16 and 128).

5.3.3 Prevalence of Tooth Agenesis and Tooth Agenesis Patterns in Control Subjects

The prevalence of tooth agenesis (≥1) in control subjects, including the third molar, was 27.5% (upper jaw 8.8%, lower jaw 10.6%, upper and lower jaw 8.1%) (Table 5.1). The number of missing teeth ranged from one to seven. Patients who had tooth agenesis had an average of 2.2 (SD = 1.4) missing teeth. For the upper and lower jaw the averages were 1.6 (SD = 0.48) and 1.4 (SD = 0.50), respectively. The most commonly missing teeth were the third molars, followed by the second premolars and upper lateral incisors. Five agenesis patterns were found in q1 and six in q2 (Table 5.2). In the maxilla, 11 different patterns were found. In 64.6% of the symmetrical patients a single bilateral tooth symmetry was found in TAC value 128 (n = 28) and TAC value 2 (n = 3). Of the patients with agenesis, 88.5% was found in the lateral incisors or third molars (TAC value 2 or 128). Unilateral patterns of agenesis were found in q3 (n = 3) and q4 (n = 4) (Table 5.3). The mandible showed eight different patterns of agenesis, most often in the second premolars and third molars (TAC values 16 and 128).

Table 5.2 *Maxillary patterns of tooth agenesis for patients with the syndrome of Crouzon, Apert and control subjects.*

TAC values	Corresponding missing teeth	Apert			Crouzon			Control		
		q1	q2	q1 & q2	q1	q2	q1 & q2	q1	q2	q1 & q2
1	I_1					1 (9.1%)				
2	I_2	1 (7.7%)						1 (2.1%)		2 (4.2%)
4	C								1 (2.1%)	2 (4.2%)
16	P_2		1 (7.7%)	1 (7.7%)	1 (9.1%)					
128	M_3	2 (15.4%)		4 (30.8%)		2 (18.2%)	4 (36.4%)	7 (14.6%)	5 (10.4%)	26(54.2%)
130	M_3+I_2									1 (2.1%)
20.1	C+P_2 (q1) and I_1 (q2)						1 (9.1%)			
24.16	P_1+P_2 (q1) and P_2 (q2)									1 (2.1%)
128.2	M_3 (q1) and I_2 (q2)						1 (9.1%)			
128.24	M_3 (q1) and P_1+P_2 (q2)									1 (2.1%)
130.128	M_3+I_2 (q1) and M_3 (q2)									1 (2.1%)
144.128	M_3+P_2 (q1) and M_3 (q2)						1 (9.1%)			
192.128	M_3+M_2 (q1) and M_3 (q2)			1 (7.7%)						
Total		3	1	6	1	3	7	8	6	34

Table 5.3 *Mandibular patterns of tooth agenesis for patients with the syndrome of Crouzon, Apert and control subjects.*

TAC values	Corresponding missing teeth	Apert			Crouzon			Control		
		q3	q4	q3 & q4	q3	q4	q3 & q4	q3	q4	q3 & q4
1	I_1						2 (20%)			
2	I_2						1 (10%)			1 (1.9%)
16	P_2	1 (7.7%)	1 (7.7%)	4 (30.8%)		1 (10%)	4 (40%)		1 (1.9%)	4 (7.5%)
128	M_3	1 (7.7%)		1 (7.7%)			2 (20%)	10(18.9%)	11(20.8%)	23(43.4%)
144	M_3+P_2			1 (7.7%)						
16.128	P_2 (q1) and M_3 (q2)									1 (1.9%)
144.128	M_3+P_2 (q1) and M_3 (q2)									2 (3.8%)
Total		2	1	6		1	9	10	12	31

5.3.4 Comparison of Patients With Crouzon and Apert Syndrome With Control Subjects

Differences between control subjects and patients with Crouzon and Apert syndrome were found in the prevalence of tooth agenesis. Prevalence of agenesis including the third molar was significantly higher in that patients with Apert syndrome ($\chi^2[1] = 4.4$; $P = .035$), but no difference was found for patients with Crouzon syndrome compared with control subjects ($\chi^2[1] = 1.2$; $P = .27$). The prevalence of agenesis, excluding the third molar, among patients with Crouzon syndrome (23.1%) and Apert syndrome (25.0%) was significantly higher than that for control subjects (6.0%) ($\chi^2[2] = 23.8$; $P < .001$). The mean number of missing teeth was significantly higher in patients with Crouzon syndrome compared with control subjects ($t[315] = 2.51$; $P = .013$). Among patients with tooth agenesis, symmetrical maxillary patterns were found more frequently in control subjects than in patients with Crouzon or Apert syndrome, ($\chi^2[2] = 3.23$; $P = .019$). Symmetrical mandibular patterns were found more frequently in patients with Crouzon and Apert syndrome than in control subjects, but these differences were not statistically significant ($\chi^2[2] = 5.04$; $P = .081$) (Tables 5.2 and 5.3). In syndromic patients, agenesis of a bilateral second mandibular premolar occurred significantly more often in syndromic patients than in control subjects ($\chi^2[2] = 24.62$; $P < .001$).

5.4 Discussion

5.4.1 Prevalence of Tooth Agenesis

The prevalence of agenesis among patients with Crouzon and Apert syndromes was significantly higher than in control subjects and was in agreement with an earlier finding that these syndromes are associated with tooth agenesis (Bailleul-Forestier et al., 2008). The prevalence of third molar agenesis in the present study is very similar to that found in other studies (Kazanci et al., 2010; Celikoglu et al., 2011). Third molar agenesis in patients with Apert syndrome was statistically significant higher than that for control subjects. Third molar agenesis might correlate with an increased prevalence of other missing teeth (Celikoglu et al., 2011). In addition, agenesis of the third molars exhibited maxillary lateral incisor microdontia more frequently and showed higher prevalence of other dental anomalies than in control subjects (De Coster et al., 2009; Celikoglu et al., 2011).

Previous reports (Garn et al., 1962; Gravely, 1965) suggested that the upper age limit for third molar agenesis is 13 years. Additionally, some studies reported that third molar development was as late as age 14 or 15 years (Richardson, 1980). Besides age, third molar agenesis can also be predicted from second molar formation. The probability of a third molar crypt developing

decreases as the adjacent second molar root matures. When the root of the second molar is halfway, it is very unlikely for individuals to develop a third molar crypt at a later stage (Liversidge, 2008).

In this study, the prevalence of agenesis, excluding third molars, in control subjects was within the same range as found in other studies (Polder et al., 2004), whereas the prevalence found in patients with Crouzon or Apert syndrome showed much greater prevalence. The second most commonly absent tooth was the mandibular second premolar in all groups, although the prevalence was significantly higher in patients with Crouzon and Apert syndrome than in control subjects.

5.4.2 Patterns of Tooth Agenesis

Among patients with tooth agenesis, a trend of symmetrical maxillary patterns was found more often in control subjects than in patients with Crouzon or Apert syndrome (Tables 5.1 and 5.2). In contrast, symmetrical mandibular patterns were found significantly more frequently in patients with Crouzon or Apert syndrome compared with control subjects (Tables 5.1 and 5.3). This finding is surprising as tooth agenesis was shown to be more or less equally distributed between maxilla and mandible in each of the three groups. Prevalence of bilateral mandibular second premolar agenesis was significantly higher in syndromic patients than control subjects. In two patients, a combination of TAC values were found, whereas all other symmetrical patterns in mandible or maxilla were combinations of missing bilaterally single teeth (Tables 5.2 and 5.3). Although sample sizes are small, it might suggest that there are common molecular mechanisms of the same genetic defect for tooth agenesis and syndromic development (De Coster et al., 2007).

Two Swedish studies also revealed higher prevalence of tooth agenesis in patients with Crouzon syndrome (42.3%; n = 26) (Stavropoulos et al., 2012) or Apert syndrome (34.8%; n = 23) (Stavropoulos et al., 2011), although third molars were excluded. A variety of patterns, mainly asymmetric, were found for patients with Crouzon syndrome (Stavropoulos et al., 2012) in contrast to the mainly symmetrical patterns found in this study. In contrast, the other Swedish study showed mainly symmetrical dental agenesis patterns in patients with Apert syndrome (Stavropoulos et al., 2011). Bilateral tooth agenesis patterns were found for second mandibular premolars and lateral maxillary incisors in patients with Apert syndrome (Stavropoulos et al., 2011). However, in this study the prevalence of maxillary incisors in patients with Apert syndrome was very low (Table 5.1). It was also apparent that in the Swedish study agenesis occurred in either the maxilla or mandible and not in both arches (Stavropoulos et al., 2011). The prevalence of the second mandibular premolar agenesis was in agreement with this study. Ethnic population differences and the number of patients might explain differences found in this study and the Swedish studies.

5.5 Conclusion

- Prevalence of agenesis excluding the third molar is significantly higher in syndromic patients than in control subjects.
- Tooth agenesis including the third molar is more prevalent in patients with Apert syndrome than in patients with Crouzon syndrome and control subjects.
- Symmetrical maxillary patterns of tooth agenesis were found more often in control subjects than in syndromic subjects.
- Symmetrical mandibular patterns of tooth agenesis seem to occur more often in patients with Crouzon or Apert syndrome often than in control subjects.
- Prevalence of bilateral tooth agenesis of second mandibular premolars is higher in syndromic patients than in control subjects.

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Chapter 6

A Longitudinal Study of Dental Arch Morphology in Children With the Syndrome of Crouzon or Apert

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Abstract

Objective: The aim of this study was to compare changes in dental arch morphology between patients with Crouzon syndrome or Apert syndrome and controls.

Patients and Methods: Children between 4 and 14 yr of age with Crouzon syndrome (n = 40) or Apert syndrome (n = 28) were compared with nonsyndromic controls (n = 457) in terms of arch widths, depths, and length dimensions. Multilevel statistical modeling techniques were used to evaluate changes over time.

Results: Dental arch dimensions were found to be smaller in patients with Crouzon syndrome or Apert syndrome compared with control subjects. Maxillary intercanine width for patients with Apert syndrome were increased, whilst other arch width variables showed no change. Patients with Crouzon syndrome showed increases in maxillary intercanine width, whilst intermolar width showed no change over time.

Conclusions: Dental arch dimensions in syndromic patients were thus found to be consistently smaller than in control subjects between 4 and 14 yr of age, implying that patients with Crouzon syndrome and Apert syndrome had a diminished growth potential.

6.1 Introduction

Longitudinal reference data of dental arch dimensions during childhood and adolescence in patients with Crouzon syndrome or Apert syndrome are scarce. Such data would make it easier to predict abnormal tooth movement and help the often challenging orthodontic treatment planning in these patients. Children born with Crouzon syndrome or Apert syndrome suffer from a marked craniofacial skeletal deformity that may also affect the overlying soft tissues and underlying structures. Crouzon syndrome is characterized by shallow orbits, ocular proptosis, a variable degree of maxillary hypoplasia, and a Class III malocclusion. Patients with Apert syndrome have a craniofacial appearance comparable with that of patients with Crouzon syndrome, but the deformity has generally been characterized as more severe. The premature closure of craniofacial sutures (craniosynostosis), seen in both syndromes, indirectly influences tooth eruption and dental arch dimensions (Cohen and Kreiborg, 1996; Kreiborg, 1981; Kreiborg and Björk, 1982). Dental arches in the syndromic patients are often distorted because the morphology of the dental arch is determined by the supporting basal maxillary and mandibular bones (Kreiborg and Björk, 1982; Costaras-Volarich and Pruzansky, 1984). Craniosynostosis severely decreases dental arch dimensions as a result of the lack of maxillary growth, which might be expected to produce tooth size arch discrepancies in patients with Crouzon syndrome or Apert syndrome (Kreiborg and Cohen, 1998). Increased prevalence of dental agenesis and delayed dental maturation in Crouzon syndrome or Apert syndrome may decrease dental arch dimensions even more (Reitsma et al., 2013; Stavropoulos et al., 2011; Stavropoulos et al., 2011a).

The development of the human dentition is normally a continuous process (Moorrees, 1959). Individual variation in dental arch dimensions may be explained by the supporting bone, genetic background, tooth movement, oral habits, dental caries, periodontal disease, oral musculature, age, or gender (Moorrees, 1959; Buschang et al., 1987; Thilander, 2009; Moorrees et al., 1969). The maxilla and mandible are consistently larger in boys than in girls (Thilander, 2009; Moorrees et al., 1969; Ward et al., 2006). Knowledge of these kinds of change of different variables affecting dental arch dimensions may be useful for individualized predictions of dental arch development (Buschang et al., 1987).

Dental arch dimensions change during the period of intensive growth and less so in adulthood (Ward et al., 2006; Bishara et al., 1996; Carter and McNamara, 1998). Intercanine width, intermolar width, dental arch depth, and arch length are the dental arch dimensions most often described (Thilander, 2009; Bishara et al., 1996). In healthy children, width dimensions in both arches remain static between 3 and 5 yr of age (Moorrees et al., 1969; Ward et al., 2006; Bishara et al., 1996). The intercanine width increases between 6 and 10 yr of age, associated

with the eruption of the permanent incisors and canines (Moorrees, 1959; Prahl-Andersen et al., 1979). From 10 to 11 yr of age, the maxillary intercanine width increases up to the age of 16 yr, whilst the mandibular intercanine width decreases between 10 and 16 yr of age (Thilander, 2009; Moorrees et al., 1969; Prahl-Andersen et al., 1979). The mandibular intermolar width increases between 9 and 14 yr of age and remains constant after 14 yr of age (Moorrees, 1959, Ward et al., 2006, Prahl-Andersen et al., 1979). These changes in width are related to the growth period and to the timing and direction of eruption of the permanent teeth (Ward et al., 2006). The maxillary and mandibular arch lengths decrease between 9 and 14 yr of age and remain constant after the age of 14. The main causes of these changes are the closure of posterior interproximal spaces as a result of the replacement of the deciduous molars with the permanent premolars, lingual tipping of the anterior teeth, and the interproximal contacts made by the permanent teeth (Moorrees et al., 1969). In the early mixed dentition, the dental arch depth increases with the eruption of the permanent incisors in a proclined position. In the late mixed dentition, the dental arch depth decreases owing to the mesial drift of the first molars into leeway spaces and sometimes because of incisor crowding (Moorrees, 1959; Bishara et al., 1997).

To date, the dental features of patients with Crouzon syndrome and Apert syndrome have been poorly described and characterized. They have been reported mainly in isolated case reports (Dalben et al., 2006). Longitudinal dental arch measurements of patients with Crouzon syndrome or Apert syndrome are currently lacking. It is essential to provide information on the dental arch changes and, more importantly, on the variability in the observed changes. It is particularly important to have a better understanding of the sagittal and transversal growth changes that occur between primary and late mixed dentitions in the maxillary and mandibular arches in both syndromic and nonsyndromic children.

Therefore, the aim of this study was to investigate longitudinal changes in dental arch dimensions during the growth of patients with Crouzon syndrome or Apert syndrome.

6.2 Material and methods

6.2.1 Patient sample

Between 1980 and 2007, all Caucasian patients diagnosed with Crouzon or Apert syndrome with available dental casts were used from the Erasmus Medical Center Rotterdam, the Netherlands. Data from patients, 4 -14 yr of age, with Crouzon syndrome (18 girls and 22 boys) or Apert syndrome (16 girls and 12 boys) were obtained from the Department of Orthodontics, Sophia Children's Hospital, Erasmus MC, in Rotterdam, the Netherlands. The clinical diagnosis of the

syndromes was genetically confirmed. Dental casts of patients with Crouzon syndrome or Apert syndrome were transformed into digital models (Ortho-Proof, Nieuwegein, The Netherlands). The impressions and the wax bite were scanned using a Flash CT scanner (model FCT-1600; Hytec, Los Alamos, NM, USA) at 160 kV with a voxel resolution of 0.05 mm.

Patients were diagnosed early and most often had a fronto-orbital advancement or cranial remodeling between 6 and 12 months after birth to prevent brain and optic nerve damage. As patients were diagnosed and treated (or operated on) at different ages, only patients who had no previous surgical midfacial advancement, orthodontic treatment, or extractions of permanent teeth were selected. Syndromic data were analyzed and compared with a longitudinal data set from the Nijmegen Growth Study (Prahl-Andersen et al., 1979). This longitudinal growth study comprised a total of 457 Dutch nonsyndromic children (241 girls and 216 boys) between 4 and 14 yr of age. The sample selection was based on longitudinal records, with no malformed, extracted teeth, no previous orthodontic treatment, and all points to be measured being clearly identifiable. In the present study, the prevalence of dental agenesis of permanent teeth, excluding third molars, occurred in patients with Crouzon syndrome (maxilla 12.8%; mandible 20.5%), Apert syndrome (maxilla 14.3%; mandible 25.0%), and healthy children (maxilla 3.5%; mandible 3.2%). In patients with dental agenesis, only dental casts with the remaining primary teeth were used. This resulted in 70 dental casts [median (range) = 2 (1–5)] from 40 patients with Crouzon syndrome, 64 dental casts [2 (1–6)] from 28 patients with Apert syndrome, and 3.667 dental casts [9 (1–12)] from 486 healthy children. The hospital records of the syndromic patients were retrospectively reviewed after ethical approval from the Institutional Review Board at Sophia Children's Hospital, Erasmus Medical Centre (MEC-2010-304).

6.2.2 Outcome variables

To examine the morphological changes of dental arches, eight measurements (Fig. 6.1) were taken, four in the mandible and four in the maxilla. One investigator made all the measurements for further statistical analysis.

(i) Intercanine width, measured as the distance between the cusp tips of deciduous and permanent canines. In the case of attrition, the measuring point was determined as the middle of the facet.

(ii) Intermolar width, measured as the distance between the center point of the occlusal surface of the right and left first permanent molars. Intermolar width was measured from the first appearance of permanent first molars between 7 and 14 yr of age.

(iii) Arch depth, measured as the perpendicular distance from the labial surface of the central incisors to the mesial surface of the first permanent molar or the distal surface of the second deciduous molar or permanent second premolar.

(iv) Arch length, the sum of the right and left distances between the mesial surface of the first permanent molars or the distal surface of the second deciduous molar or permanent second premolar and the interproximal contact point of the central incisors or the midpoint of the central diastema when present.

6.2.3 Intra- and inter-reliability

Measurements on 20 randomly selected dental casts were repeated after 2 months to determine the intraclass correlation coefficient (Shrout and Fleiss, 1979). The inter-reliability was tested by two examiners on the same selected dental casts.

6.2.4 Growth models

The data were analyzed using multilevel modeling of longitudinal data (Goldstein, 1987). Multilevel models are statistical models of parameters that vary at more than one level. A multilevel model attempts to model all the components in a hierarchy of nested effects (Goldstein, 1987). The program, MLwiN (version 1.2; Centre for Multilevel Modelling, London, UK), was used to model growth changes and compare the three groups. For each *y* variable (the dental arch measurement), a polynomial equation was estimated for the child (i) on the age of the measurement (j). The *y* intercept was adjusted to 10 yr of age (intercept = age - 10) to provide a comparison in the middle of the age range. Average growth curves were estimated mathematically. Owing to expected differences associated with the syndromes, separate models were fitted. Multiple tests for each variable were run for the separate groups and for possible differences between groups. Despite multiple testing, it was decided not to correct alpha because the accompanying reduction in statistical power would not be beneficial given the relatively small sample sizes of the syndromic groups. A cubic model was first fitted for each group and the highest-order term was checked for statistical significance; if it was not statistically significant ($P < 0.05$) it was eliminated and the lower-order model was tested. The initial equation was:

$$y_{ij} = \beta_{0ij}constant + \beta_1 t_{ij} + \beta_2 t_{ij}^2 + \beta_3 t_{ij}^3$$

with

$$\beta_{0ij} = u_{0j} + e_{0ij}$$

The dental arch measurement, *y*, was computed by adding the intercept (β_{0ij}) to the products of other fixed coefficients (β_1, β_2, and β_3) multiplied by age (*t*) at each occasion. u_{0j} and e_{0ij} comprise the random portion of the model and are assumed to have means equal to zero, to be uncorrelated, and normally distributed. The level 1 residual, e_{0ij}, represents within-subject variation, or the 'error' term, whilst the level 2 residual, u_{0j}, represents, in this case, between-

subject variation (Goldstein, 1987). The fixed parameters from the different models for the various groups were used to construct growth curves for the different dental arch measurements. Initial multilevel modeling showed no gender differences for syndromic patients, in contrast to healthy children. Therefore, the data from all boys and girls were pooled. The polynomial model takes full advantage of each patient's individual longitudinal growth data, easily handles missing data, and statistically evaluates the shape of the curve. Iterative generalized least squares were used to estimate the model's parameters (Goldstein, 1987).

6.3 Results

6.3.1 Measurement error

The intraclass correlation coefficient values for intraobserver reliability varied from 0.897 to 0.984 for dental arch measurements. The intraclass correlation coefficient values for interobserver reliability varied from 0.875 to 0.988. An interclass correlation coefficient value larger than 0.75 represents a high level of reliability (Fleiss, 1986).

6.3.2 Nonsyndromic control subjects

Multilevel statistical/mathematical modeling showed that the growth curves ranged from linear changes to second-order changes. The second-order changes or quadratic coefficient of the model refers to changes in growth velocity. The fixed terms of each model were used to estimate the dental arch values in subjects between 4 and 14 yr of age (Table 6.1). For example, the mandibular intermolar width for control subjects was 42.20 mm at 12 yr of age, computed as 41.30 + (0.4514 x 2). Note that the linear term 0.4514 (the yearly change) for control subjects was multiplied by two instead of by 12, because the intercept had been set to 10 yr of age. The multilevel statistical models showed statistical group differences for 18 of the 24 variables evaluated (Table 6.2). The multilevel models of the control subjects showed that mandibular and maxillary intermolar widths (Fig. 6.2) followed linear patterns of growth between 4 and 14 yr of age (i.e. the widths increased by approximately the same amounts each year). All of the other arch dimensions followed quadratic growth curves, with rates of growth increasing initially and then decreasing. Maxillary intercanine width increased 6 mm; and mandibular intercanine width increased approximately 4 mm between 4 and 12 yr of age, and then decreased slightly (Fig. 6.3). Arch depths increased slightly during the first 4 yr, and decreased between 8 and 14 yr of age (Fig. 6.4). Maxillary arch length increased between 4 and 12 yr of age, and then decreased slightly (Fig. 6.5a); mandibular arch length increased, with little or no change after 12 yr of age (Fig. 6.5b).

Table 6.1 *Multilevel models for untreated control, Crouzon and Apert children.*

Measures	Control						Crouzon						Apert			
	Constant		Linear		Quadratic		Constant		Linear		Quadratic		Constant		Linear	
	Estimate	SE	Estimate	SE	Estimate	SE	Estimate	SE	Estimate	SE	Estimate	SE				
Maxillary intermolar width (mm)	4.432e+1	4.376e-2	2.776e-1	2.427e-2			4.027e+1	6.382e-1					3.758e+1	1.015e+0	9.274e-1	1.991e-1
Mandibular intermolar width (mm)	4.130e+1	1.178e-1	4.514e-1	1.195e-2			4.012e+1	8.212e-1					3.870e+1	9.842e-1		
Maxillary intercanine width (mm)	3.188e+1	9.463e-2	6.214e-1	1.266e-2	-2.655e-2	3.007e-3	2.979e+1	6.209e-1	4.163e-1	1.374e-1			2.502e+1	6.157e-1		
Mandibular intercanine width (mm)	2.630e+1	8.490e-2	1.991e-1	1.141e-2	-8.682e-2	2.824e-3	2.309e+1	5.016e-1	6.092e-1	1.126e-1			2.097e+1	8.423e-1		
Maxillary arch depth (mm)	2.841e+1	9.806e-2	-3.337e-1	1.181e-2	-7.524e-2	2.855e-3	2.259e+1	5.113e-1					2.356e+1	7.167e-1		
Mandibular arch depth (mm)	2.354e+1	1.015e+0	-5.163e-1	1.040e-2	-4.793e-2	3.717e-3	2.352e+1	3.452e-1	-4.312e-1	8.127e-2	-6.763e-2	2.395e-2	2.210e+1	4.555e-1	-6.811e-1	8.369e-2
Maxillary arch length (mm)	9.786e+1	2.341e-1	1.621e-0	-5.491e-2	-6.448e-1	1.390e-2	6.783e+1	1.160e+0					6.585e+1	1.468e+0	-8.645e-1	3.379e-1
Mandibular arch length (mm)	8.840e+1	2.459e-1	9.081e-1	4.525e-2	-1.813e-1	1.778e-2	6.690e+1	8.739e-1	-6.687e-1	1.924e-1	-1.363e-1	5.735e-2	6.500e+1	1.035e+0	-9.391e-1	1.720e-1

Table 6.2 *Comparison between multilevel models for untreated control, Crouzon and Apert children. * bold indicates statically significant difference.*

Measurements	Difference Control vs Crouzon						Difference Control vs Apert				Difference Crouzon vs Apert			
	Constant		Linear		Quadratic		Constant		Linear		Constant		Linear	
	Estimate	SE	Estimate	SE	Estimate	SE	Estimate	SE	Estimate	SE	Estimate	SE	Estimate	SE
Maxillary intermolar width (mm)	**-4.096e+0**	**5.319e-1**					**-7.584e+0**	**1.119e+0**	**9.135e-1**	**2.576e-1**	1.262e+0	1.419e+0		
Mandibular intermolar width (mm)	**-1.358e+0**	**5.540e-1**					**-2.841e+0**	**8.031e-1**			1.4273e+0	1.285e+0		
Maxillary intercanine width (mm)	**-1.954e+0**	**4.332e-1**	**-2.5759e-1**	**7.865e-2**			**-4.553e+0**	**4.843e-1**			**-3.657e+0**	**8.022e-1**		
Mandibular intercanine width (mm)	**-2.649e+0**	**3.596e-1**	**1.887e-1**	**5.463e-2**			**-3.872e+0**	**4.319e-1**			-8.798e-1	9.036e-1		
Maxillary arch depth (mm)	**-5.140e+0**	**4.163e-1**					**-7.523e+0**	**1.302e+0**			9.512e-1	8.556e-1		
Mandibular arch depth (mm)	-1.850e-1	4.137e-1	1.300e-1	6.555e-2	3.949e-3	2.063e-2	**-1.358e+0**	**5.540e-1**			**-1.005e+0**	**5.353e-1**	**4.285e-1**	**1.004e-1**
Maxillary arch length (mm)	**-2.075e+1**	**1.068e+0**					**-2.734e+1**	**1.488e+0**	**-4.244e+0**	**3.344e-1**	3.936e-1	1.767e+0		
Mandibular arch length (mm)	**-2.176e+1**	**1.273e+0**	**-1.964e+0**	**3.470e-1**	**4.311e-1**	**1.015e-1**	**-1.949e+1**	**1.426e+0**	**-3.977e+0**	**3.242e-1**	**-1.030e+0**	**1.286e+0**	**6.142e-1**	**2.273e-1**

6.3.3 Crouzon syndrome patients

Compared with the controls, patients with Crouzon syndrome followed entirely different (simpler) growth patterns for six of the eight variables measured; only mandibular arch depths and lengths followed the same quadratic pattern of the controls. The mandibular and maxillary intermolar width (Fig. 6.2) for patients with Crouzon syndrome showed no change over time, whereas mandibular and maxillary intercanine widths increased (Fig. 6.3). The intercanine and intermolar widths of the dentition in patients with Crouzon syndrome were statistically smaller at 10 yr of age compared with those of control subjects (Tables 6.1 and 6.2). The growth model for mandibular arch depth for patients with Crouzon syndrome was not statistically different from that for control subjects (Fig. 6.4 and Tables 6.1 and 6.2). Maxillary arch depth showed no change at the given age range; these variables were statistically smaller than in control subjects. Maxillary and mandibular dental arch lengths measured for patients with Crouzon syndrome were statistically smaller than in control subjects (Fig. 6.5). Dental arch length did not change in the maxilla, but it decreased slightly in the mandible.

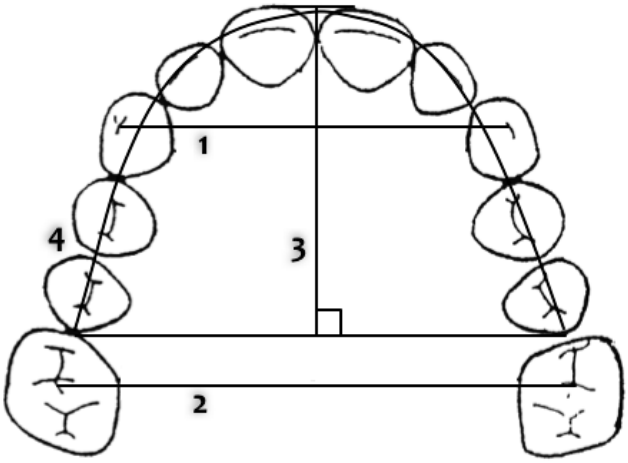

Figure 6.1 *Diagram showing dental arch measurements. (1) Intercanine width. (2) Intermolar width. (3) Arch depth. (4) Arch length.*

6.3.4 Apert syndrome patients

Compared with the controls, the growth patterns of patients with Apert syndrome were entirely different for all variables measured. Patients with Apert syndrome showed no change over time for mandibular intermolar width (Fig. 6.2a), or for maxillary and mandibular intercanine width variables (Fig. 6.3). The maxillary intermolar width increased between 7 and 14 yr of age (Fig.

6.2b). All width variables were statistically smaller than in control subjects. Dental arch depth in the maxilla decreased over time, whilst mandibular dental arch depth showed no change over time (Fig. 6.4). The arch depth in the maxilla was statistically smaller than in control subjects at 10 yr of age, whilst the mandibular arch depth showed no difference. Maxillary and mandibular arch lengths in syndromic patients were statistically smaller than in control subjects and decreased slightly from 4 to 14 yr of age (Fig. 6.5 and Tables 6.1, 6.2).

6.3.5 Comparison of patients with Crouzon syndrome and Apert syndrome

Growth curves for patients with Crouzon syndrome showed changes ranging from constant to acceleration, while those for patients with Apert syndrome ranged from constant to linear (Table 6.1). The mandibular arch depth, arch length, and maxillary intercanine width were all statistically smaller in patients with Apert syndrome than in patients with Crouzon syndrome (Table 6.2). Mandibular intercanine and intermolar width, maxillary intermolar width, arch depth, and arch length showed no statistical differences (Table 6.2).

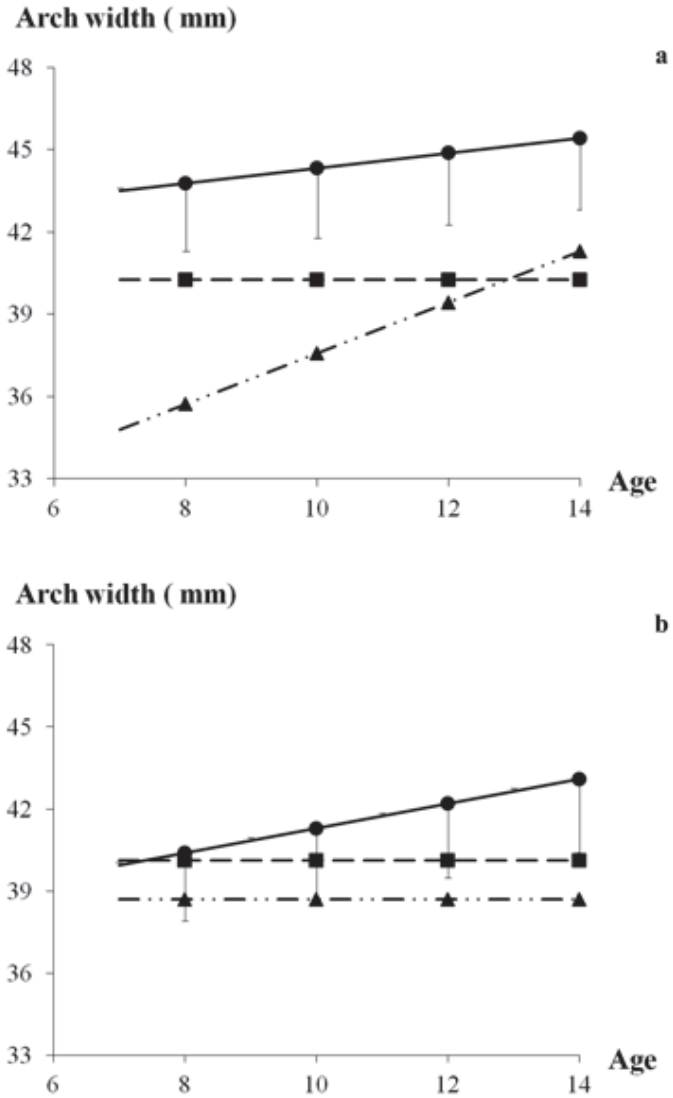

Figure 6.2 *Growth curves of mean maxillary (a) and mandibular (b) intercanine width for male and female control subjects (SD) (●), and for patients with Crouzon syndrome (■) and Apert syndrome (▲).*

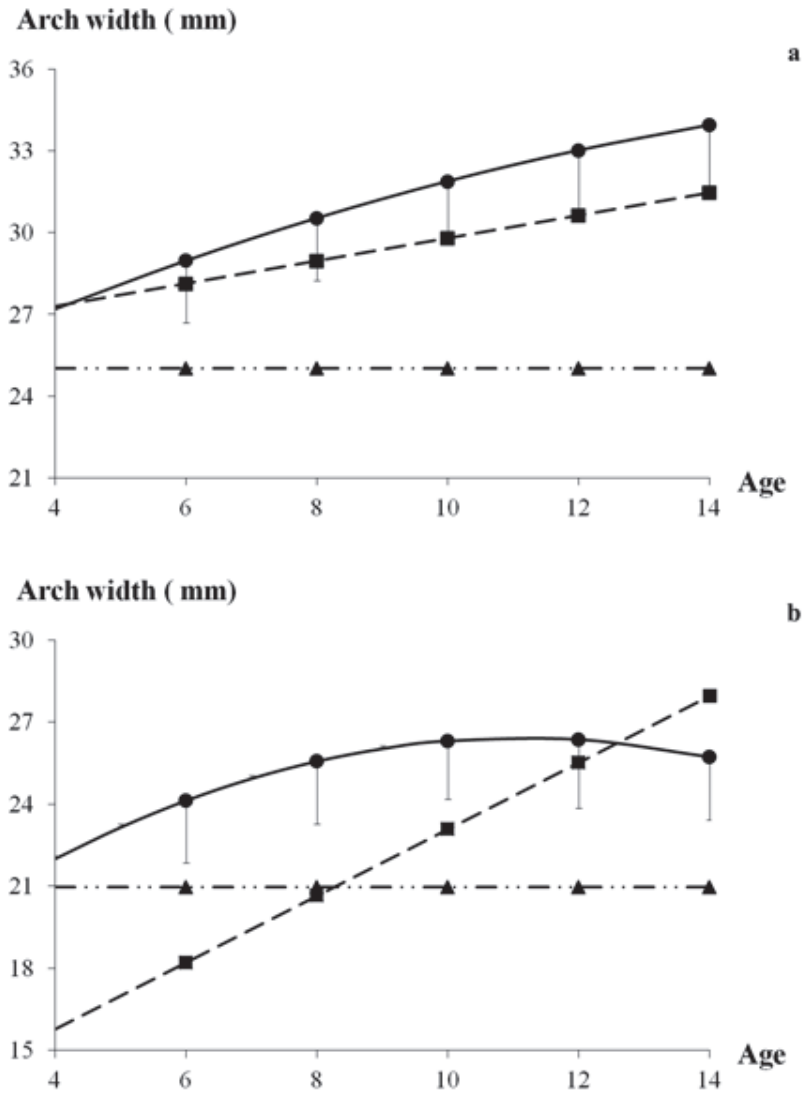

Figure 6.3 *Growth curves of mean maxillary (a) and mandibular (b) intermolar width for male and female control subjects (SD) (●), and for patients with Crouzon syndrome (■) and Apert syndrome (▲).*

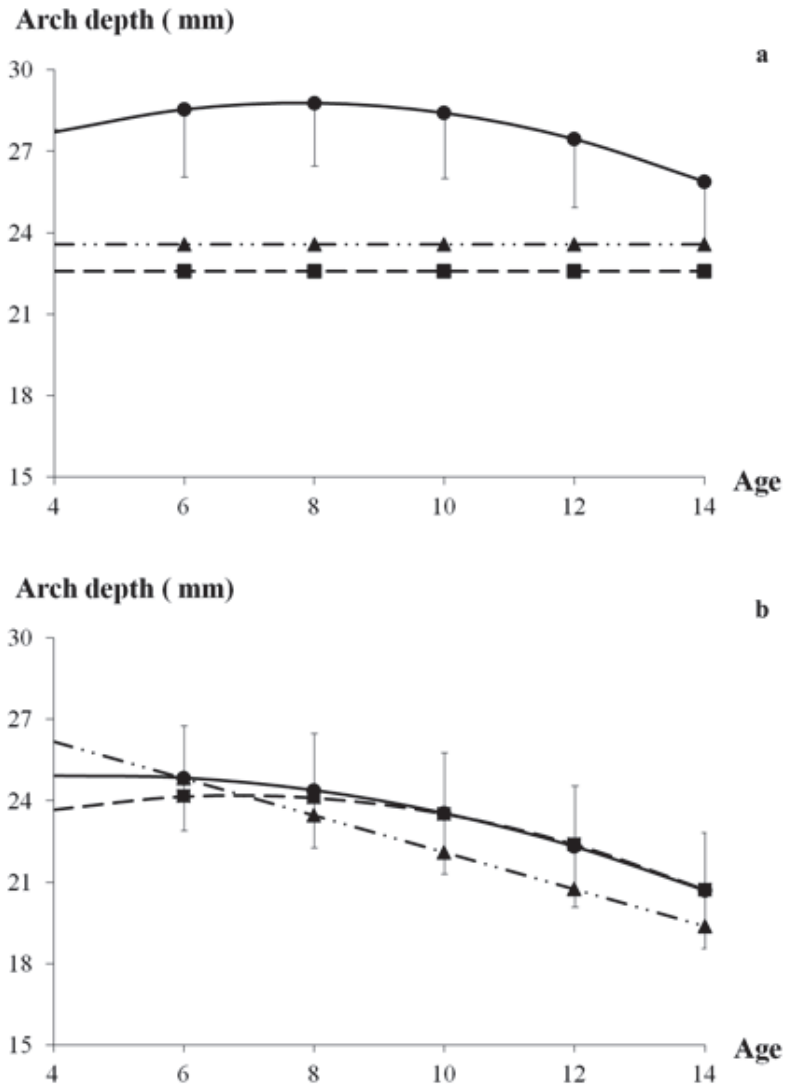

Figure 6.4 *Growth curves of mean maxillary (a) and mandibular (b) arch depth for male and female control subjects (SD) (●), and for patients with Crouzon syndrome (■) and Apert syndrome (▲).*

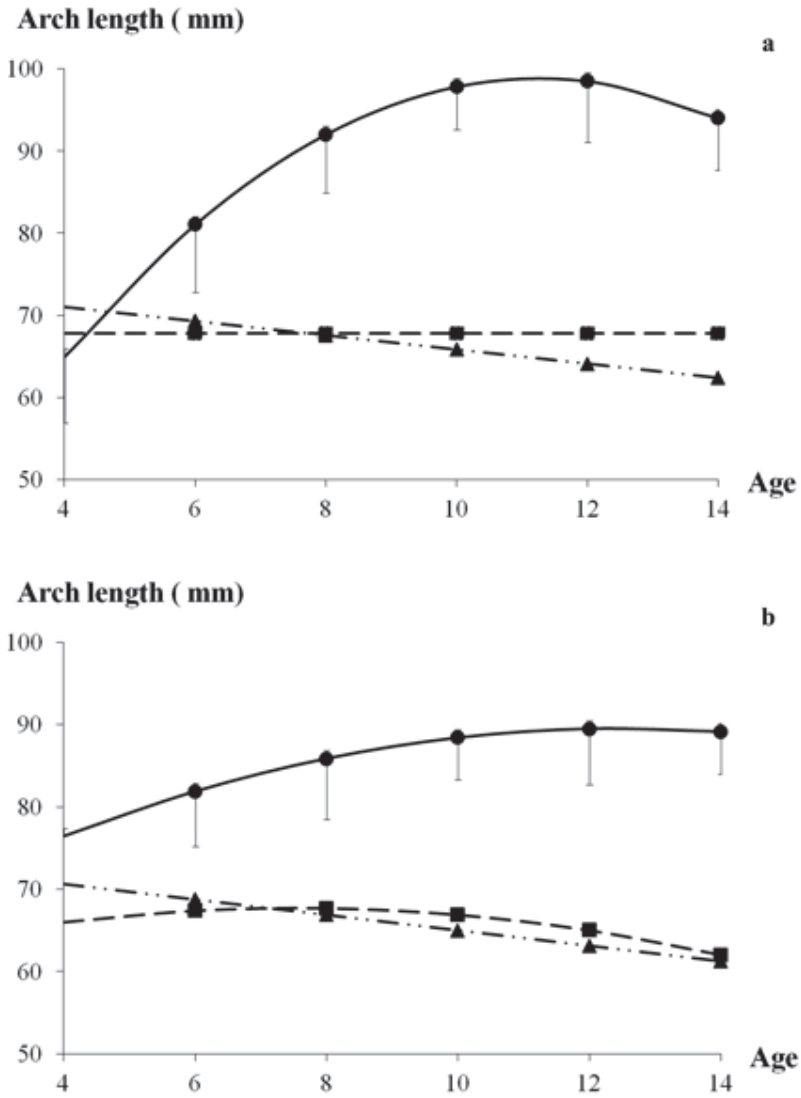

Figure 6.5 *Growth curves of mean maxillary (a) and mandibular (b) arch length for male and female control subjects (SD) (●), and for patients with Crouzon syndrome (■) and Apert syndrome (▲).*

6.4 Discussion

Multilevel models offer an important tool for describing longitudinal dental arch changes with limited data in rare syndromes such as Crouzon or Apert. Both individual and average growth curves can be described; it is a flexible model because it uses polynomials, which can describe growth curves of almost any form and they do not require complete longitudinal data or observations taken at the same time points (Buschang et al., 1989). Moreover, traditional polynomial methods would have required elimination of most of the subjects as a result of missing observations and adjustment of values to exact ages (Buschang et al., 1989, Goldstein, 1986). Conventional procedures, including cross-sectional descriptions and analyses of yearly velocities from two measurement occasions, would have provided less illustrative and informative results.

It is important, when analyzing longitudinal dental arch changes of small samples of syndromic subjects, to compare these outcomes with a representative large sample of unaffected individuals. To our knowledge, this is the first study to analyze longitudinal data of dental arch changes in patients with Crouzon syndrome or Apert syndrome with the aid of multilevel modeling. Abnormal arch development in syndromes where ceased growth does not reach its full potential is very easily picked up compared with normal arch development. In patients without any surgical or orthodontic treatment in the midface or mandible, or dental extractions, Crouzon or Apert syndrome showed a higher prevalence of dental agenesis, excluding third molars, compared with healthy controls (Reitsma et al., 2013; Stavropoulos et al., 2011; Stavropoulos et al., 2011a). Dental agenesis may account for smaller dental arch dimensions in syndromic patients. When dental agenesis occurred, the remaining primary teeth were used to calculate dental arch dimensions. Maxillary lateral incisors and mandibular second premolars were the most frequently missing teeth in all three groups (Reitsma et al., 2013; Stavropoulos et al., 2011; Stavropoulos et al., 2011a), although were more prevalent in syndromic patients. The arch development changes, in control subjects, for dental arch width, in the literature (Moorrees, 1959; Thilander, 2009; Moorrees et al., 1969; Bishara et al., 1996; Bishara et al., 1997). Arch width and depth increases have been previously reported to occur between 4 and 14 yr of age (Bishara et al., 1997, Moorrees and Reed, 1965; Moyers et al., 1976). Importantly, approximately 73% of the total maxillary intercanine width increases, and 84% of the total maxillary intermolar width increases occurred between 6 and 9 yr of age (Bishara et al., 1997, Moorrees and Reed, 1965; Moyers et al., 1976). The increases of dental arch widths, particularly the intermolar width, were more likely to be related to dental eruption than to growth.

Patients with Crouzon syndrome exhibited severe constriction of dental arch development, especially during the transition from primary to permanent dentition. In contrast to normal

development, arch dimensions for dental arch width, depth, and length in patients with Crouzon syndrome hardly changed with growth and transition from primary to permanent dentition (Figs 6.1-6.4). Premature fusion of craniofacial sutures in patients with Crouzon syndrome influences growth and development of the maxilla and mandible (Kreiborg and Cohen, 1998; Marsh et al., 1991; Reitsma et al., 2012), with major consequences for the development of the dentition and the occlusion. The limited craniofacial growth potential explains the changes in dental arch measurements seen in these patients (Kreiborg and Cohen, 1998; Cohen and Kreiborg, 1993).

Patients with Apert syndrome tended to have smaller arch dimensions than patients with Crouzon syndrome. Longitudinal dental arch changes between Crouzon and Apert syndrome differ, and the corresponding values for patients with Apert syndrome were even smaller than for those with Crouzon syndrome (Table 6.2). Although both syndromes share clinical features, differences in craniofacial growth and development have been observed (Costaras-Volarich and Pruzansky, 1984; Reitsma et al., 2012). A more abnormal growth pattern was seen in patients with Apert syndrome, which was confirmed by earlier reports (Tables 6.1, 6.2) (Kreiborg, 1981; Kreiborg and Cohen, 1998, Avantaggiato et al., 1996). The premature arrest of maxillary sutural growth in Crouzon syndrome had usually already occurred during the first years of life (Kreiborg, 1981) and is probably earlier and more severe in Apert syndrome. The maxillary intermolar width in patients with Apert syndrome showed an increase over time, although the measurements were much smaller compared with those for control subjects. This increase in intermaxillary arch width may be related to ectopic eruption of maxillary first molars in a transversally reduced maxilla (Kreiborg and Cohen, 1992). Maxillary dental arch depths measured in syndromic patients were smaller than in control subjects and showed no change over time (Fig. 6.4). Besides space deficiency for the permanent canines, the frequent mesial eruption of the maxillary first molars might be related to the small maxillary dental arch depth. This may result in first molar retention and resorption of the distal root of the adjacent primary molar and its premature loss, aggravating the space deficiency.

A Class III skeletal relationship caused by retruded midfacial growth in patients with Crouzon syndrome or Apert syndrome is associated with maxillary posterior crossbites. Although upper and lower dental arch width dimensions in both syndromes were severely reduced (Fig. 6.2), the upper arch was relatively smaller. In patients with craniosynostosis, transverse discrepancies are usually the result of maxillary constriction. In these cases, the suture fusion is not limited to the skull and cranial base but may also involve facial sutures and cartilages. Maxillary constriction may be part of the pathophysiology of obstructive sleep apnea (Luna-Paredes et al., 2012). Subjects with maxillary constriction have increased nasal airway resistance and resultant mouth breathing (Langford et al., 2003). An abnormal muscular balance, such as a low tongue posture, seen

in patients with Crouzon or Apert syndrome, may contribute to the underdevelopment of the maxillary arch dimensions (Kreiborg and Cohen, 1998). The direction of eruption of mandibular teeth could therefore be influenced by the narrow hypoplastic maxilla, leading to a more lingual direction of tooth eruption than normal and thereby enhance the already decreased mandibular arch width dimensions (Krarup et al., 2005).

Because of the complexity of the functional and structural abnormalities, the care of a patient with craniosynostosis should be managed and treated by a multidisciplinary team of experts. The focus in such a center is on general oral health needs, orthodontic and surgical management, as well as psycho-social needs, which should give better overall treatment results. Different types of intervention are often necessary to prevent brain damage, possible blindness, or obstructive sleep apnea (Oberoi et al., 2012).

The lack of maxillary growth and development caused by craniosynostosis in these syndromes results in crowding, impaction, premature loss of primary teeth, delayed tooth eruption, and ectopic eruption. These oral features are found in both arches, but are more severe in the maxilla (Cohen and Kreiborg, 1996; Reitsma et al., 2012). Probably, the mandible is indirectly influenced by the absence of primary and secondary displacement of the bones of the maxillary complex and the cranial base. The goal of orthodontic treatment in the mixed dentition is to resolve issues related to aberrant eruption of the permanent teeth. Knowledge about the sequence of tooth eruption in patients with Crouzon or Apert syndrome is necessary for dental and orthodontic management. In a future study, dental maturation may be better predicted by assessing mineralization and eruption stages. It should be stressed that better prediction of dental arch dimensions might be expected using the multilevel method in a relatively small, but well-defined, group, although some variation was left unexplained in this study. Extreme small arch dimensions in these patients require early intervention and referral to a specialized team.

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Chapter 7

Craniofacial Stability in Patients With Crouzon or Apert Syndrome After Le Fort III Distraction Osteogenesis

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Abstract

Objective: Le Fort III osteotomy with distraction osteogenesis (DO) is used to improve the retruded midface in patients with Crouzon or Apert syndrome. This study aimed to evaluate sagittal and vertical preoperative and postoperative cephalometric changes of DO of the midface in patients with Crouzon or Apert syndrome.

Design: Population-based case-control study.

Patients and Methods: Records of patients with the syndrome of Crouzon (n = 6) or Apert (n = 7) were compared, before and after Le Fort III DO, with a nonsyndromic untreated control group (n = 486).

Main Outcome Measures: Sagittal and vertical cephalometric maxillary landmarks and measurements were used to predict and measure midface advancement and rotation after Le Fort III DO. Cephalograms were taken before surgery (T0), 4 months after surgery at removal of the distraction device (T1), and 1 year after removal of the distraction device (T2).

Analysis: Z scores were performed to compare cephalometric measures of syndromic patients with control subjects.

Results: Cephalograms of 13 patients with Crouzon syndrome (n = 6) or Apert (n = 7) (age range 8.2 to 19.8 years) were evaluated. Treatment changes (T1-T2) showed statistically significant maxillary advancement, with no significant differences between the patients with the Crouzon or Apert syndrome.

Conclusions: DO of the midface in patients with Crouzon or Apert syndrome seems to be stable in the sagittal direction after follow-up. Although Crouzon and Apert differ after DO, anteroposterior craniofacial dimensions were significantly improved and were closer to patterns of normal subjects.

7.1 Introduction

Patients with Crouzon or Apert syndrome have similar, but not identical, craniofacial morphologies (Kreiborg and Aduss, 1986; Kreiborg and Cohen, 1998). Various surgical treatment methods have been developed for the advancement of the midface for these patients (Marchac and Arnaud, 1999; Panchal and Uttchin, 2003; Figueroa and Polley, 2007; Pelo et al., 2007; Allam et al., 2011). Conventional treatment of such anomalies includes Le Fort III osteotomies, which have been associated with heavy blood loss, relatively long operation time, and a risk for infection (Sloan et al., 1997; Cheung et al., 2006; Shetye et al., 2010; Allam et al., 2011). The postoperative patients' discomfort after such osteotomies can be great. Lethality of patients after conventional Le Fort III osteotomy has also been reported (Sloan et al., 1997). Moreover, relapse after Le Fort III osteotomy may occur, but it is unpredictable (Panchal and Uttchin, 2003; Meazzini et al., 2005; Iannetti et al., 2006). The nonvascularized grafts that are often used to bridge the operated gap are a risk for morbidity and infection; vascular grafts are technically difficult (Iannetti et al., 2006).

Currently, Le Fort III distraction osteogenesis (DO) is the most used treatment modality in these patients (Swennen et al., 2001; Figueroa and Polley, 2007; Shetye et al., 2010; Allam et al., 2011). Benefits of DO compared to conventional surgery include no morbidity of donor areas, the absence of postsurgical bone gaps and no need for bone grafts, less intraoperative bleeding, the possibility of increased volume of the soft tissues, and the possibility to achieve bigger and better corrections (Swennen et al., 2001; Meazzini et al., 2005; Iannetti et al., 2006; Figueroa and Polley, 2007). Under optimal conditions DO leads to the generation of bone and stretching of surrounding soft tissues (De Bastiani et al., 1987). Therefore, Le Fort III DO is currently the treatment of choice for the severe underdeveloped midface of patients with Crouzon or Apert syndrome. However, long-term evaluation for this procedure is needed (Figueroa et al., 2004; Fearon, 2005; Meazzini et al., 2005; Iannetti et al., 2006; Figueroa and Polley, 2007; Shetye et al., 2007; Hopper et al., 2010; Shetye et al., 2010; Allam et al., 2011).

The timing of surgical correction of the midface advancement in growing patients is controversial. Surgical intervention of the midface before puberty shows deterioration of the final result due to the continued growth of the lower jaw (Reid, 2007). Surgical overcorrection is proposed in order to avoid extra surgery later in life (Swennen et al., 2001). The prediction of the final outcome in younger children is difficult because the prediction of an individual's mandibular growth pattern is difficult. The pubertal growth spurt, which occurs around 14 years of age for boys and is larger, longer, and later than for girls, further complicates predictions (Tanner et al., 1983). Due to the lack of studies, controversy also exists about further maxillary growth following early midfacial surgery (Fearon, 2005; Meazzini et al., 2005). Nevertheless, accurate estimates

of the timing and amount of midface displacement that are necessary for growing children are essential for efficient and effective treatment outcomes (Prahl-Andersen, 2005).

The primary aim of this study was to evaluate the sagittal and vertical changes of the midface after Le Fort III external DO in patients with Crouzon or Apert syndrome compared to normal growing children. The secondary aim was to determine whether DO results in normalization of the midface and evaluate these findings after a 1-year follow-up.

7.2 Materials and Methods

7.2.1 Study Design and Sample

From 1985, standardized patient records of craniofacial patients were kept at the Department of Orthodontics of the Erasmus Medical Centre Rotterdam, The Netherlands. From this group, a total of 62 patients with Crouzon or Apert syndrome, patient records were retrospectively reviewed for the period of 1985 to 2010. The clinical diagnoses of the patients with Crouzon or Apert syndrome were genetically confirmed.

All 13 consecutive patients treated with Le Fort III external DO were studied. The Le Fort III DO procedure was used since 2003. Older patients who underwent a second midface advancement by a Le Fort III DO after a previously first surgical midface advancement, were excluded. Other methods of treatment to improve the retruded midface (e.g., monoblock advancement, Le Fort III with internal distraction devices, Le Fort III midface advancement) were excluded.

The data of the patients were compared with a large mixed-longitudinal dataset from the Nijmegen Growth Study (Prahl-Andersen et al., 1979). This mixed-longitudinal growth study comprised 486 nonsyndromic children. All cohorts were followed for a period of 5 years, from 4 to 14 years of age. At the start of the study, the children were 4, 7, or 9 years of age. A final measurement was taken at 22 years of age for a few cohorts.

The hospital records of the patients, the craniofacial team assessments, and cephalometric analyses were retrospectively reviewed after exemption approval from the Institutional Review Board at Sophia Children's Hospital, Erasmus Medical Centre (MEC-2010-304).

7.2.2 Surgical Procedure

All patients underwent a Le Fort III distraction osteotomy. After the osteotomy and mobilization of the midface, a RED (rigid external distraction) device was placed (Fig. 7.1). The RED device was used in all patients using a custom maxillary palatal heavy wire frame bonded to the upper molars. In nine cases, the RED device was additionally secured to the maxilla with subcutaneous

suspension wires as the point of traction of the distraction force. Active midfacial advancement was started after a latency period of 5 days, at a rate of 1 mm per day, until the desired orbitozygomatic position was obtained. The RED device was removed under local anesthesia, after a 3-month retention period. After this period, a protraction facemask was used for 3 to 6 months at nighttime for retention.

Figure 7.1 *Fixation of the halo-frame of the RED II system parallel to the Frankfurter horizontal plane. This patient with the syndrome of Apert underwent a Le Fort III osteotomy.*

7.2.3 Data Collection

Lateral cephalograms were used to assess the changes in position of the midface at the end of the consolidation period immediately after device removal. Only cephalograms of good quality, taken before distraction (T0), at the end of the consolidation period immediately after device removal (T1), and 1 year after removal of the distraction device (T2) were used. The pretreatment cephalograms were taken within 1 month prior to surgery. One patient was excluded from the study because of previous midface advancement with Le Fort III DO, resulting in 13 patients for

further analysis. Comparison of the three groups was based on six craniofacial measurements (Table 7.1) representing the sagittal and vertical jaw relationships. Viewbox software (version 3.1.1.12; dHal Orthodontic Software, Athens, Greece) was used to calculate the measurements.

7.2.4 Outcome Variables

Seven cephalometric landmarks situated in the midsagittal plane were identified and digitized (Fig. 7.2). To identify the same nasion at T0, T1, and T2, the landmark 'N' was located at the nasofrontal suture, above the surgical cut of the Le Fort III osteotomy. This alternative landmark point N recorded on the presurgical lateral cephalogram was relocated as a reconstructed N point on the subsequent lateral cephalograms by superimposition on sella and cranial base structures. The primary horizontal and vertical measurements of anterior maxillary position were the SNA and SN/PP angles, respectively (Table 7.1).

Four secondary craniofacial measurements (SNB angle, ANB angle, NSMe angle, and LFH ratio) were used to describe relative craniofacial changes following Le Fort III DO.

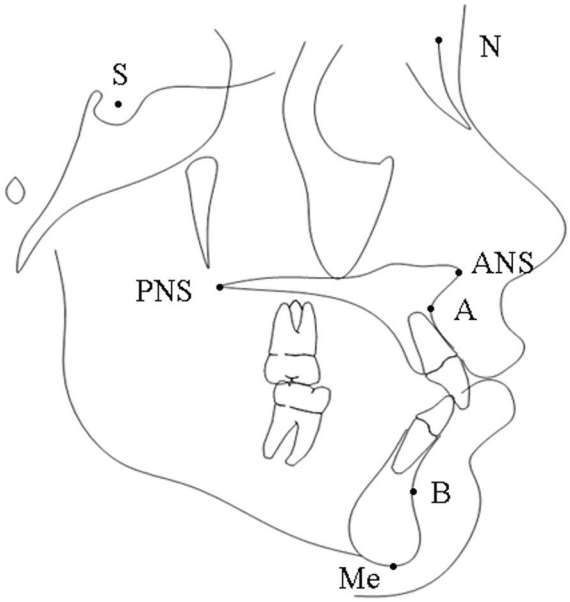

Figure 7.2 *Lateral Skull with landmark points. ANS: anterior nasal spine. The anterior tip of the sharp bony process of the maxilla at the lower margin of the anterior nasal opening. Me: Menton. The lowest point on the symphyseal shadow of the mandible seen on a lateral cephalogram. N: Nasion. The most anterior point on the frontonasal suture in the midsagittal plane. PNS: Posterior nasal spine. The posterior spine of the palatine bone constituting the hard palate. Point A: subspinale. The most posterior midline point in the concavity between the ANS and the prosthion (the most inferior point on the alveolar bone overlying the maxillary incisors). Point B: supramentale. The most posterior midline point in the concavity of the mandible between the most superior point on the alveolar bone overlying the mandibular incisors (infradentale) and Pogonion (the most anterior point on the chin). S: Sella. The geometric center of the pituitary fossa.*

Table 7.1 *Description of primary predictor variables*

ANS-Me	Represents the lower anterior face height (LFH).
N-Me	Represents the total anterior facial height.
LFH Ratio	The ratio of the lower anterior facial height and the total anterior facial height.
NSMe angle	Measures the angle from nasion to sella to menton.
SN/PP angle	Measures the inclination of palatal plane to the anterior cranial base.
ANB angle	The relative position of points A and B to each other.
SNA angle	The anterior-posterior position of point A to the anterior cranial base.
SNB angle	The anterior-posterior position of point B to the anterior cranial base.

7.2.5 Predictor Variables

Quantitative data of patients with the Crouzon syndrome (n = 6) and Apert (n = 7) were compared with an age, sex, and ethnic grouped matched nonsyndromic standards, derived from the mixed-longitudinal dataset from the Nijmegen Growth Study (Prahl-Andersen et al., 1979).

7.2.6 Data Analysis

Due to the heterogeneity of the sample, the cephalometric measurements of the patients with Crouzon or Apert syndrome were transformed into z scores using the following formula: z score = (X –M) /SD, where X is the subject's cephalometric measurement taken at a given age, M is the mean value of the control data at the same age and sex, and SD is the standard deviation of the control data at the same age and sex.

7.2.7 Assessment of Interexaminer and Intraexaminer Variation

To calculate the systematic and random errors, a subsample of 20 randomly selected radiographs was retraced and redigitized by two examiners with a 3-month interval. The statistical analyses of the data were carried out with SPSS (version 15.0, SPSS, Chicago, IL). Intraobserver duplicate measurement errors were calculated according to Dahlberg formula (Dahlberg, 1940), and reliability coefficients between the first and second digitizing were calculated as Pearson correlation coefficients. An interclass correlation coefficient value greater than 0.75 represents a high level of reliability. Values between 0.40 and 0.75 indicate a fair to moderate level of reliability, and a value less than 0.40 represents a poor level of reliability (Shrout and Fleiss, 1979).

7.3 Results

A total of six patients with the Crouzon syndrome (three girls and three boys; mean age at the time of surgery 13.2 years) and seven patients with Apert syndrome (six girls and one boy; mean age at the time of surgery 15.4 years) satisfied the inclusion criteria (Table 7.2). The mean distraction time was 26 (± 12) days (range 11 to 54 days). The distractor was in place for a mean of 114 (± 17) days, including the latency and distraction period.

Table 7.2 *Intraobserver and interobserver agreement for digitization of the cephalometric landmarks.*

	Intraobserver reliability n = 20 Correlation coefficient	Interobserver reliability n = 20 Correlation coefficient
SNA angle (degrees)	0.921	0.972
SNB angle (degrees)	0.970	0.706
ANB angle (degrees)	0.847	0.872
LFH ratio	0.984	0.742
NSMe angle (degrees)	0.977	0.962
SN/PP (degrees)	0.969	0.652

The analysis of the cephalometric data prior to treatment (T0) showed that the syndromic patients and the control subjects differed significantly (Tables 7.3 through 7.8). The SNA, ANB, and SN/PP angles were significantly smaller in the syndromic patients, and the LFH ratio was significantly larger than control values. The SNB angle, the sagittal position of the mandible, for the Crouzon patient was significantly larger than the angle for the control subjects; there was no significant difference in the SNB angle between the Apert patients and control subjects. The pretreatment NSMe angles of the patients with Crouzon or Apert syndrome were not significantly different from the control subjects (Table 7.7).

The immediate postsurgical midfacial advancement, measured by the SNA angle, showed values that closely approach the values of the control subjects (T1, Table 7.3). Treatment changes (T0-T1) were statistically significant for all of the sagittal measurements, with no significant differences between the patients with Crouzon or Apert syndrome (Table 7.3). The SNA and ANB angle increased significantly and the SNB angle decreased significantly during treatment. None of the immediate postdistraction (T1) sagittal measurements were significantly different from the control averages.

Table 7.3 *Changes in sagittal measures of SNA angle. Mean values, NGO control values and standard deviations (SD) and probability scores for sagittal pretreatment (T0), immediate post-distraction (T1), and one year after removal of the distraction device (T2) of patients with the syndrome of Apert and Crouzon. * = significant (p<.05) difference from control mean. ** = significant (p<.05) change over time.*

Variance	Syndrome	T0			T1			T2			T1-T0	T2-T1	T2-T0
		Value (SD)	Control NGO value (SD)	Prob.	Value (SD)	Control NGO value (SD)	Prob.	Value (SD)	Control NGO value (SD)	Prob.	Prob.	Prob.	Prob.
SNA	Apert	64.69* (5.48)	80.56 (3.69)	<0.01*	77.16 (6.91)	80.61 (3.67)	0.17	78.64 (8.86)	80.62 (3.67)	0.29	<0.01**	0.34	<0.01**
	Crouzon	70.14* (2.61)	80.39 (3.81)	<0.01*	82.16 (8.09)	80.40 (3.83)	0.32	83.31 (8.22)	80.40 (3.83)	0.22	<0.01**	0.38	<0.01**
	Total	67.17* (5.03)	80.48 (3.74)	<0.01*	79.37 (7.57)	80.49 (3.74)	0.38	80.73 (8.58)	80.50 (3.76)	0.48	<0.01**	0.36	<0.01**

Table 7.4 *Changes in vertical measures of SN/PP. Mean values, NGO control values and standard deviations (SD) and probability scores for sagittal pretreatment (T0), immediate post-distraction (T1), and one year after removal of the distraction device (T2) of patients with the syndrome of Apert and Crouzon. * = significant (p<.05) difference from control mean. ** = significant (p<.05) change over time.*

Variance	Syndrome	T0			T1			T2			T1-T0	T2-T1	T2-T0
		Value (SD)	Control NGO value (SD)	Prob	Value (SD)	Control NGO value (SD)	Prob	Value (SD)	Control NGO value (SD)	Prob	Prob	Prob	Prob
SN/PP	Apert	-11.39* (8.46)	8.50 (2.77)	<0.01*	-10.89* (7.51)	8.50 (2.77)	<0.01*	-14.80* (9.11)	8.49 (2.76)	<0.01*	0.43	0.07	0.10
	Crouzon	-0.15* (7.78)	8.31 (3.24)	<0.01*	-1.38* (5.69)	8.31 (3.23)	<0.01*	-2.57* (1.26)	8.32 (3.25)	<0.01*	0.35	0.36	0.23
	Total	-7.86* (10.87)	8.41 (3.21)	<0.01*	-8.12* (9.09)	8.41 (3.21)	<0.01*	-11.07* (10.56)	8.41 (3.20)	<0.01*	0.47	0.18	0.15

The vertical measurements did not change significantly with the treatment (Tables 6 through 8). At the end of treatment (T1), LFH was significantly larger and the SN/PP was significantly smaller than the control values. Only NSMe showed a difference between the syndromes after treatment; patients with Crouzon syndrome did not differ significantly from controls, whereas the patients with Apert syndrome showed statistically significant larger values.

After the follow-up period (T2), the sagittal measurements of the syndromic patients and control subjects were not significantly different (Table 7.3). The midface showed a counterclockwise rotation of the palatal plane (SN/PP angle) relative to the cranial base during follow-up, which was even more evident than during activation (T0-T1). In terms of the vertical measurements, the SN/PP and NSMe angles decreased significantly between T1 and T2 (Tables 7.4 and 7.7). Both angles became smaller in patients with Apert syndrome, but not in patients with Crouzon syndrome. At the end of the follow-up (T2), the SN/PP angle and LFH ratio for syndromic patients were significantly smaller and larger, respectively, than the control values.

The overall treatment effect (T0-T2) showed statistically significant increases of the SNA and ANB angles. The SNA increased 13.178 for patients with Crouzon syndrome and 13.958 for patients with Apert syndrome; the corresponding ANB angles improved 14.25° and 14.48°. The changes that occurred for the other measurements were not significantly different from control values at T2 (Tables 7.4, 7.5, 7.7, and 7.8).

7.3.1 Assessment of Interexaminer and Intraexaminer Variation

The intraclass correlation coefficient values varied from 0.847 to 0.984 for cephalometric measures, which indicates high reliability. The interclass correlation coefficient values showed sufficient reliability values for SNB angle, LFH ratio, and SN/PP, while the other measures showed high reliability.

Table 7.5 *Changes in sagittal measures of SNB angle. Mean values, NGO control values and standard deviations (SD) and probability scores for sagittal pretreatment (T0), immediate post-distraction (T1), and one year after removal of the distraction device (T2) of patients with the syndrome of Apert and Crouzon. * = significant (p<.05) difference from control mean. ** = significant (p<.05) change over time.*

Variance	Syndrome	T0			T1			T2			T1-T0	T2-T1	T2-T0
		Value (SD)	Control NGO value (SD)	Prob	Value (SD)	Control NGO value (SD)	Prob	Value (SD)	Control NGO value (SD)	Prob	Prob	Prob	Prob
SNB	Apert	78.35 (4.79)	77.39 (3.44)	0.39	76.72 (3.97)	77.44 (3.43)	0.42	77.51 (4.12)	77.72 (3.53)	0.48	0.31	0.44	0.37
	Crouzon	80.28 (2.71)	77.08 (3.37)	0.17	77.27 (3.76)	77.14 (3.36)	0.48	79.28 (4.62)	77.34 (3.35)	0.28	0.18	0.29	0.36
	Total	79.23 (4.15)	77.24 (3.40)	0.28	76.97 (3.72)	77.30 (3.40)	0.46	78.39 (4.26)	77.56 (3.45)	0.41	0.25	0.37	0.36

Table 7.6 *Changes in sagittal measures of ANB angle. Mean values, NGO control values and standard deviations (SD) and probability scores for sagittal pretreatment (T0), immediate post-distraction (T1), and one year after removal of the distraction device (T2) of patients with the syndrome of Apert and Crouzon. * = significant (p<.05) difference from control mean. ** = significant (p<.05) change over time.*

Variance	Syndrome	T0			T1			T2			T1-T0	T2-T1	T2-T0
		Value (SD)	Control NGO value (SD)	Prob	Value (SD)	Control NGO value (SD)	Prob	Value (SD)	Control NGO value (SD)	Prob	Prob	Prob	Prob
ANB	Apert	-13.56 (4.94)	3.73 (2.48)	<0.01*	0.53 (6.27)	3.70 (2.49)	0.10	0.92 (8.21)	3.55 (2.53)	0.15	<0.01**	0.40	<0.01**
	Crouzon	-10.21 (3.04)	3.96 (2.35)	<0.01*	4.81 (5.10)	3.94 (2.36)	0.36	4.04 (3.78)	3.84 (2.48)	0.47	<0.01**	0.38	<0.01**
	Total	-11.98 (4.08)	3.84 (2.42)	<0.01*	2.54 (5.97)	3.81 (2.43)	0.30	2.36 (6.51)	3.67 (2.51)	0.30	<0.01**	0.49	<0.01**

Table 7.7 *Changes in vertical measures NSMe angle. Mean values, NGO control values and standard deviations (SD) and probability scores for sagittal pretreatment (T0), immediate post-distraction (T1), and one year after removal of the distraction device (T2) of patients with the syndrome of Apert and Crouzon. * = significant (p<.05) difference from control mean. ** = significant (p<.05) change over time.*

Variance	Syndrome	T0			T1			T2			T1-T0	T2-T1	T2-T0
		Value (SD)	Control NGO value (SD)	Prob	Value (SD)	Control NGO value (SD)	Prob	Value (SD)	Control NGO value (SD)	Prob	Prob	Prob	Prob
NSMe	Apert	71.41 (4.73)	70.03 (3.72)	0.36	72.74 (3.43)	69.99 (3.72)	0.23	70.35 (3.80)	69.79 (3.79)	0.44	0.36	0.28	0.41
	Crouzon	69.19 (3.89)	70.18 (3.53)	0.39	71.56 (3.81)	70.15 (3.52)	0.34	67.76 (4.40)	70.06 (3.50)	0.25	0.25	0.15	0.35
	Total	70.35 (4.29)	70.10 (3.63)	0.47	72.18 (3.50)	70.06 (3.63)	0.28	69.09 (4.09)	69.90 (3.65)	0.41	0.31	0.21	0.38

Table 7.8 *Changes in vertical measures of LFH ratio. Mean values, NGO control values and z-scores and standard deviations (SD) for sagittal pretreatment (T0), immediate post-distraction (T1), and one year after removal of the distraction device (T2) of patients with the syndrome of Apert and Crouzon. * = significant (p<.05) difference from control mean. ** = significant (p<.05) change over time.*

Variance	Syndrome	T0			T1			T2			T1-T0	T2-T1	T2-T0
		Value (SD)	Control NGO value (SD)	Z-score (SD)	Value (SD)	Control NGO value (SD)	Z-score (SD)	Value (SD)	Control NGO value (SD)	Z-score (SD)	Z-score (SD)	Z-score (SD)	Z-score SD
LFH	Apert	74.78 (1.93)	56.83 (2.45)	<0.01*	72.34 (2.86)	56.83 (2.45)	<0.01*	73.96 (4.42)	56.85 (2.47)	<0.01*	0.16	0.27	0.34
	Crouzon	64.69 (5.76)	57.15 (2.45)	<0.01*	64.80 (2.63)	57.12 (2.47)	<0.01*	64.02 (2.09)	57.03 (2.41)	<0.01*	0.49	0.42	0.43
	Total	70.14 (6.60)	56.98 (2.45)	<0.01*	68.89 (4.72)	56.96 (2.46)	<0.01*	69.31 (6.12)	56.94 (2.44)	<0.01*	0.30	0.41	0.38

7.4 Discussion

This study evaluated sagittal and vertical changes of the midface after Le Fort III external DO in patients with Crouzon or Apert syndrome. Maxillary advancement in patients with these syndromes showed statistically significant improvement at removal of the RED device and after 1-year follow-up. The sagittal craniofacial measurements for both syndromes showed values closer to normal after treatment. Maxillary sagittal advancement using Le Fort III DO has been shown to be a successful treatment for the severely retruded midface (Figueroa et al., 2004; Fearon, 2005; Prahl-Andersen, 2005; Iannetti et al., 2006; Figueroa and Polley, 2007; Shetye et al., 2007; Hopper et al., 2010; Shetye et al., 2010; Allam et al., 2011).

No change was seen during the follow-up period. Relapse has been previously reported shortly after distractor removal (Cheung et al., 2006). The amount of early relapse can be important for the prediction of the amount of necessary overcorrection. In this study, a cephalogram was not taken before the removal of the distraction device in order to prevent unnecessary radiation. Although 1 year post surgery is a short retention period, others (Shetye et al., 2007; Hopper et al., 2010; Shetye et al., 2010) have also found that sagittal movement of the midface by Le Fort III DO is stable 1 year later. Statements regarding long-term stability should not be relied upon in studies with a short follow-up because most patients are still in active orthodontic treatment, which may influence surgical treatment results positively. Although most studies have to deal with a small number of patients with Crouzon or Apert syndrome, long-term stability after Le Fort III DO consistently shows successful stable advancement (Swennen et al., 2001; Figueroa et al., 2004; Figueroa and Polley, 2007; Pelo et al., 2007; Hopper et al., 2010).

Presurgical sagittal measurements showed midfacial retrusion in the syndromic patients, with greater retrusion among Apert than Crouzon patients. This difference could be due to the fact that more craniofacial sutures are prematurely fused at birth in Apert than Crouzon syndrome patients. Patients with Crouzon syndrome sometimes show some open craniofacial sutures at birth (Renier et al., 2000). The synostosis of the sutures in the Crouzon patients is often progressive during postnatal growth (Renier et al., 2000; Connolly et al., 2004) and causing the variation of sagittal facial growth in syndromic patients.

The midface showed a counterclockwise rotation of the palatal plane in the syndromic patients. This suggests that, during forward traction of the midface, the posterior part of the maxilla extruded more than the anterior part. This may cause an undesirable posterior rotation of the mandible, lengthening of the total anterior face height, and often an increase of the anterior open bite, although not statistically significant (Fig. 7.3b). However, the fact that the SNB and SN/PP angles of the syndromic patients decreased and the LFH ratio did not change suggests that the

midface came forward, and vertical control was maintained (Fig. 7.3a). After the follow-up period the patients with Apert syndrome showed the largest increase in the SN/PP angle (Table 7.4). A continuation of vertical maxillary growth after surgery has been reported for the syndromic patients (Bachmayer et al., 1986; Meazzini et al., 2005; Shetye et al., 2007; Shetye et al., 2010). This also makes it important to avoid extrusion of the maxilla and to maintain the vertical height of the midface during the Le Fort III DO.

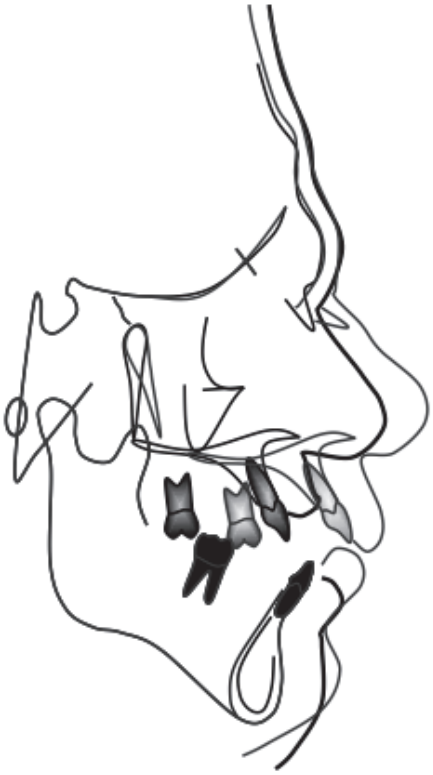

Figure 7.3a *Drawing showing surgical midfacial movement in a patient (15.2 years) with the syndrome of Apert, with superimposition tracing on the anterior cranial base. The black line represents the patient before the Le Fort III osteotomy, and the red line represents the patient 1 year and 4 months after surgery.*

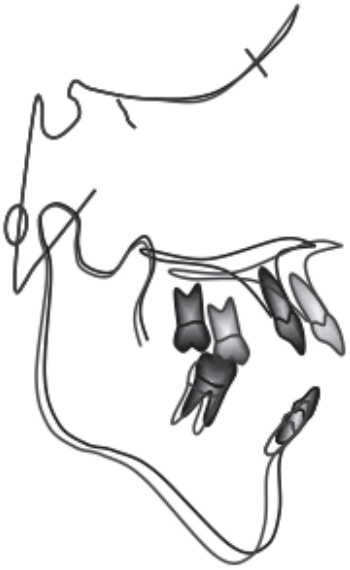

Figure 7.3b *Theoretical situation of the patient where extrusion of the midface is causing posterior rotation and lengthening of the face.*

Various degrees of counterclockwise palatal plane rotation have been previously reported with DO (Shetye et al., 2007; Hopper et al., 2010; Shetye et al., 2010; Allam et al., 2011). Variation in palatal plane rotation during DO is probably attributable to the direction of force by the external device relative to the center of resistance of the Le Fort III segment (Hopper et al., 2010).

The cranial base, Ba-S-N, for patients with Crouzon and Apert syndromes has been reported to be 12% to 15% shorter than in nonsyndromic patients, with a shape comparable to the normal population (Kreiborg and Cohen, 1998; Allam et al., 2011). The distance SN was significantly smaller for patients with Crouzon and Apert syndromes compared to controls (Reitsma et al., 2012). A short anterior cranial base means a more forward placed mandibular condyle and a positional Angle Class III. In addition, a more distally placed point N also increases the likelihood of an Angle Class III. Other geometric effects of the used cephalometric points, like the vertical lengths of N to A and N to B, may also distort an underlying skeletal discrepancy (Jacobson, 1975; Kreiborg and Cohen, 1998; Posnick and Ruiz, 2000). These geometric effects should be kept in mind when making comparisons between syndromic patients and the controls.

Although the facial morphology of patients with Crouzon and Apert syndromes is different from a normal population, it has been shown that extreme variations in facial morphology do not affect the accuracy of cephalometric evaluation (Wah et al., 1995). Six cephalometric measurements were used to describe the sagittal facial morphology of patients with Crouzon or Apert syndrome. In a meta-analysis on landmark identification and reproducibility in nonsyndromic patients, it was concluded that 0.6 mm of the total error in the x- or y-coordinate was acceptable (Trpkova et al., 1997). The cephalometric landmarks chosen in this study had even lower total error for reproducibility in the x- or y-coordinate.

The sagittal growth rate of the mandible in syndromic patients is fairly normal, resulting in a prognathic appearance due to a retrusion of the midface and the short anterior cranial base (Costaras-Volarich and Pruzansky, 1984; Bachmayer et al., 1986; Kreiborg and Aduss, 1986). Previous research (Costaras-Volarich and Pruzansky, 1984; Bachmayer et al., 1986; Kreiborg and Aduss, 1986; Kreiborg and Cohen, 1998) showed a reduced mandibular body and anterior cranial base lengths for patients with Crouzon or Apert syndrome. These aspects influence the SNB angle and, in combination with the individual growth potential of the lower jaw, makes it difficult to estimate the success of midfacial advancement in surgical cases. When the midface is extruded, the mandible might be expected to show a posterior rotation (Tables 7.5 and 7.7; Fig. 7.4).

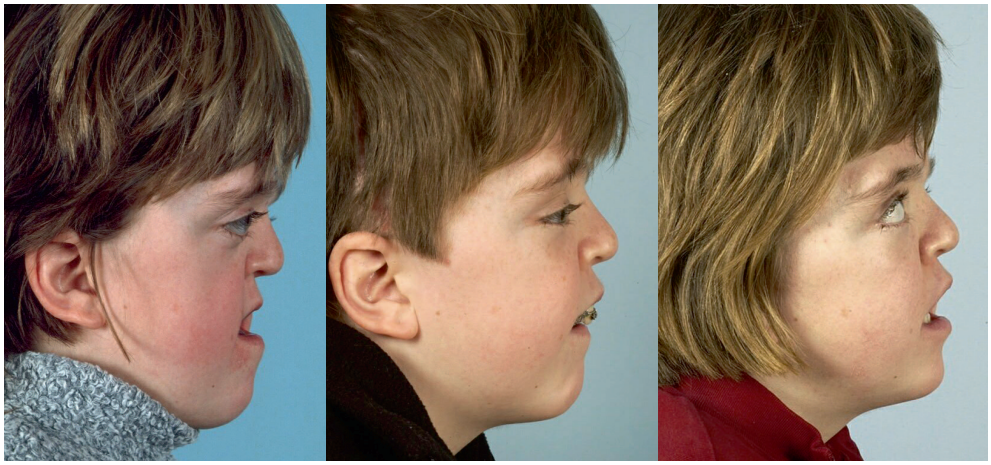

Figure 7.4 *a: Standardized profile photographs of a patient with Apert syndrome: before distraction (T0). b: Standardized profile photographs of a patient with Apert syndrome: 1 year after removal of the distraction device (T1). Standardized profile photographs of a patient with Apert syndrome: 1 year after removal of the distraction device (T2).*

7.4.1 Treatment Timing

Treatment in patients younger than 13 years of age was performed for functional, psychological, and social considerations. Young adult patients older than 13 years of age were treated at an older age because DO was not available at that time. It has been recommended to surgically overcorrect the midface in patients younger than 15 years of age, whereby the necessity for secondary Le Fort III procedures could be reduced (Meazzini et al., 2005; Shetye et al., 2010). However, the final positioning of the maxilla at this age does not guarantee that the maxillary-mandibular relationship will be normal later in life because the amount and timing of mandibular growth is difficult to estimate in syndromic patients (Reitsma et al., 2012). Overcorrection during childhood to adult norms may give a distorted facial appearance. Extreme overcorrection can be difficult for both the children and their parents. The facial appearance changes during the distraction process from abnormal to normal to abnormal once again. From the psychological perspective, it is recommended not to distract to the final normal adult midface position (Shetye et al., 2007). The aim of the surgeon for Le Fort III DO is an adequate positioning of the inferior parts of the orbits and zygomata. When correction is aimed at the relationship between the upper and lower dental arches, often inadequate positioning of the orbits will occur. Therefore, the current protocol aims to correct both inferior orbits, zygomata, and, if possible, the occlusion during Le Fort III DO, monoblock DO, or facial bipartition DO. For the orthodontist this may not always create an ideal occlusion. Although efforts have been made to reach this goal, the treatment result may unfortunately need secondary corrections later in life.

After surgical correction of the midface, the orbits and zygoma should be in a normal position. For control subjects the overall cranio-orbito-zygomatic skeleton is greater than 85% of its adult size at the age of 5 years. This explains the frequent finding of recurrent exophthalmos in patients with Apert or Crouzon syndromes after a total midface osteotomy with advancement has been performed during early childhood (Waitzman et al., 1992). The orbital region showed the greatest dysmorphology in the entire craniofacial complex for patients with Crouzon syndrome. The intercanthal, binocular, and eye fissure lengths all tended to be greater than average (Kolar et al., 1988). For control subjects, additional growth increments after maturation of the orbit continue until adolescence, but only a fraction of a millimeter (Waitzman et al., 1992). The skeletal maturation of the orbit is an important factor for the timing of midface advancement in patients with a retruded midface. However, the growth pattern of the orbital region for patients with craniosynostosis remains unknown. Therefore, the decision for surgical midfacial advancement should not rely solely on growth data of nonsyndromic subjects.

The indication and timing of surgical treatment of patients with craniosynostosis still remains controversial. A general trend is seen to perform midfacial advancement in early childhood (Marchac and Arnaud, 1999; Renier et al., 2000; Swennen et al., 2001; Panchal and Uttchin, 2003). Research shows that the incidence of complications using halo-frames is higher in children compared to adults (Baum et al., 1989). By contrast, limited information about incidence rates of complications in craniofacial patients is available. This is remarkable since this patient category might be even more prone to developing complications (Nout et al., 2006). A functional indication for midfacial advancement is ocular proptosis, while palliation of obstructive sleep apnea is a controversial indication because long-term results are not present (Iannetti et al., 2006).

Finally, a literature review of DO of the craniofacial skeleton showed a lack of long-term data, especially regarding skeletal relapse (Swennen et al., 2001). Relapse factors and prediction of the result of DO surgery remain unknown. Long-term data are needed to quantify soft tissue changes and facial growth and development after maxillary DO. Such data are essential to perfect the timing of midfacial DO for patients with Crouzon or Apert syndrome.

7.5 Conclusions

1. Le Fort III external DO improved the position of the midface in patients with Crouzon or Apert syndrome are significantly improved in the sagittal direction 1 year and 4 months postoperatively.
2. Vertical dimensions of the midface were difficult to correct during treatment in patients with Crouzon or Apert syndrome, and these should be taken into consideration during DO treatment.
3. From a growth perspective, surgical intervention and Le Fort III DO can be considered from 10 to 12 years of age. Taking the individual growth maturation and pubertal growth spurt into consideration, postponement of treatment for a few years may be advisable.

7.6 References

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Chapter 8

General Discussion

8.1 Introduction

Standardized longitudinal data of patients with Crouzon or Apert syndrome are very important for quantifying and describing their abnormal craniofacial growth and development and the morphological variation. In general, many craniofacial anomalies are characterized by complex deviations in the shape and configuration of facial hard and soft tissue structures. Longitudinal reference data are urgently needed for treatment planning in terms of timing, type of surgery, amount of surgical overcorrection, orthodontic guidance and evaluation of treatment results. New methods of data collection have made longitudinal evaluation, defining, locating and comparing of anatomical structures and landmarks complex. For example, definitions of landmarks used in 3D are largely adapted from their 2D definitions and have been shown to be less precise (Hassan et al., 2011). Discrepancies may result from differences in how the landmarks are viewed in 2D images (in a single tomographic plane) and 3D images (in multiple planes). That is why a comparison between 2D and 3D images should be undertaken with great caution. There is no evidence that 3D-CT analysis of the normal skull is more reliable than conventional cephalometric methods (Hassan et al., 2011). However, conventional cephalometrics are inadequate for assessing patients with severe asymmetric craniofacial syndromes; therefore, 3D-CT cephalometrics are indicated in these patients (Fourie et al., 2012).

For several disciplines dealing with craniofacial anomalies knowledge of longitudinal craniofacial development and dental development is important for the choice and timing of treatment. In the following, the general and specific research aims described in Chapter 1 are addressed in relation to findings in this thesis. In addition, the clinical relevance of the findings and future perspectives regarding the study of craniofacial growth and development in patients with Crouzon or Apert syndrome will be explored.

8.2.1 Facial development in Crouzon or Apert syndrome

Patients with Crouzon or Apert syndrome showed unique longitudinal craniofacial growth patterns (Chapters 2 and 3). The patients showed increased mandibular asymmetry, increased lower facial height ratios, decreased transversal dimensions, increased inclination of the palatal plane, a more retruded midface, and a more protruded mandible compared with control subjects. The craniofacial measurements showed that patients with Apert syndrome had a more severe abnormal craniofacial growth pattern, morphology and mandibular asymmetry compared to patients with Crouzon syndrome (Chapters 2 and 3). Differences in craniofacial growth between the syndromes may imply the necessity of different treatments, different treatment timing, and type of any kind of intervention in both syndromes (Reardon et al., 1994).

From early childhood maxillary dimensions are very small with minimal changes over time in both syndromes (Chapters 2 and 3). Marked craniofacial deformities are present at birth in Apert syndrome, while in Crouzon syndrome craniofacial deformities are often milder (Kreiborg and Cohen, 1998). The results of this study support previous reports (Costaras-Volarich and Pruzansky, 1984; Cohen and Kreiborg, 1996; Kreiborg and Cohen, 1998) indicating significant differences in sagittal and vertical craniofacial patterns in children with Crouzon or Apert syndrome compared to controls. A more abnormal craniofacial morphology in patients with Apert syndrome than in those with Crouzon syndrome has been found (Cohen and Kreiborg, 1992; Cohen, 1993; Kreiborg and Cohen, 1998; Cohen and McLean, 2000; Sgouros, 2005). Patients with Crouzon and Apert syndromes exhibit severe constriction of midfacial development. With the continuous growth of the mandible the midfacial malformation increases. Premature fusion of calvarial sutures in patients with Crouzon and Apert syndromes influence growth and development of the maxilla and indirectly the mandible, with severe consequences for the developing maxillary-mandibular complex (Costaras-Volarich and Pruzansky, 1984; Cohen and Kreiborg, 1996; Kreiborg and Cohen, 1998). The ceased sutural growth potential may also explain the changes in dental arch measurements seen in these patients.

Asymmetry is common in Apert and Crouzon syndromes (Cohen, 1986) whereas mild asymmetries are found in normal children (Palmer and Strobeck, 1986). Abnormal craniofacial development is often characterized by strong asymmetries. In the case of craniosynostosis developmental differences between the two opposing sides of the skull and growth compensation in all other calvarial sutures and synchondroses create asymmetry (Cohen, 1986). The increased degree of asymmetry of the face in syndromes with craniosynostosis (Kreiborg and Cohen, 2010) is related to differences in the bilateral onset of sutural area closure (Kreiborg et al., 1993). In addition, asymmetry in the midface has impact on the mandible, because the mandible is influenced during growth of the base of the skull at the side of temporomandibular joint. The mandible normally adapts to the maxilla, but also the other way around, the maxilla may adapt to the mandible (Laspos et al., 1997). In the literature a wide range of differences of mandibular ramal heights and mandibular morphology in Crouzon and Apert syndromes was found (Costaras-Volarich and Pruzansky, 1984; Bu et al., 1989). Therefore, it is reasonable to expect maxillomandibular skeletal asymmetry to be inherent to syndromes with craniosynostosis (Pelo et al., 2011). For instance, asymmetry of the mandible was primarily located in the region of the ramus and condyle in a dry skull in Crouzon syndrome (Kreiborg and Björk, 1981). But the normal variation in directional asymmetry of the lower jaw was more evident in controls than in patients with craniosynostosis (Chapter 3). The average value of directional asymmetry showed a possible misleading value, close to zero (Chapter 3, Fig. 3.1b), being the direction of asymmetry

is either left or right. The incidence of directional asymmetry tended to be higher in patients with Apert syndrome than in patients with Crouzon syndrome. The mandibular asymmetry may also be influenced by occlusal interference such as malpositioned teeth, dental crossbites caused by a constricted maxillary arch in growing syndromic children (Chapter 5) (Pelo et al., 2011). Abnormal initial tooth contact causes subsequent mandibular displacement in maximum intercuspation and possible growth adaptations.

Asymmetry can also be measured as fluctuating asymmetry. Fluctuating asymmetry is a measurement of minor developmental deviations and developmental instability over time (Chapter 3, Fig. 3.1b) (Van Valen, 1962; Adams and Niswander, 1967; DeLeon and Richtsmeier, 2009). It is reasonable to expect developmental instability in patients with syndromic craniosynostosis. Increased fluctuating asymmetry is an expression of environmental and genetic disturbances of an otherwise symmetrical phenotype and may imply pathology (Van Valen, 1962; Palmer and Strobeck, 1986; Parsons, 1992; Furlow et al., 1997). In contrast to directional asymmetry, the increased degree of fluctuating asymmetry (Chapter 3) demonstrates a higher developmental instability in patients with Crouzon or Apert syndrome compared to normal children. Fluctuating asymmetry is an important indicator for a population's state of adaptation and coadaptation to environmental and genetic influences (Palmer and Strobeck, 1986). This is logically less in patients with craniosynostosis (DeLeon and Richtsmeier, 2009).

8.2.2 Differences in dental findings in Crouzon or Apert syndrome

The indication of delayed dental development before seven years of age in both syndromes was pronounced (Chapter 4, fig. 4.2). Dental development in syndromic patients was delayed compared to control subjects, and small differences between patients with Crouzon and Apert syndrome were found (Chapter 4). Hypodontia seems related to delayed dental development (Cohen and McLean, 2000; Ruiz-Mealin et al., 2012). Increased prevalence of tooth agenesis and delayed dental development were found in both syndromes (Chapter 5). In healthy children the most prevalent type of tooth agenesis is third molars followed by mandibular second premolars or maxillary lateral incisors. Although the prevalence of tooth agenesis was much higher in syndromic patients, the same pattern of agenesis of third molars followed by second mandibular premolars and maxillary lateral incisors was found both in syndromic children as in healthy children. The mutated *FGFR2* gene may be involved in the pathogenesis of dental agenesis. Expression of the signaling molecules that bind to *FGFRs*, the *FGFs*, have been observed during all stages of dental morphogenesis (Thesleff, 1998). Failure in the function of *FGFs* in the dental epithelium and/or in the underlying mesenchyme during tooth development may result in dental agenesis (De Coster et al., 2009). Consequently, certain patterns of agenesis can be linked to specific gene mutations,

also in nonsyndromic children. The recently introduced Tooth Agenesis Code (TAC) was used to describe the number and location of missing teeth (Van Wijk and Tan, 2006). More symmetrical patterns of tooth agenesis were found in Crouzon and Apert syndrome than in healthy children (Chapter 4). Analyzing large numbers of subjects with the same gene mutations may show similar TAC codes that are typical for specific gene mutations (Coussens et al., 2007; Coussens et al., 2008). This also may reveal the relation between increased fluctuating asymmetry and increased patterns of symmetrical tooth agenesis seen in for example cleft lip and palate (Laspos et al., 1997; DeLeon and Richtsmeier, 2009; Bartzela et al., 2010). Specific TAC codes may be used as biomarkers linked to specific gene mutations.

Dental arch morphology was very abnormal in patients with Crouzon or Apert syndrome. Children with Apert syndrome had smaller arch dimensions than children with Crouzon syndrome (Chapter 6). The dental arch dimensions showed hardly any change from primary dentition to mixed permanent dentition in both syndromes (Chapter 6). Dental arch dimensions of normal children remained relatively stable during primary dentition (Moorrees et al., 1969; Prahl et al., 1979). The normal children showed continuous growth and development, particularly during the transitional period from primary to mixed dentition to accommodate the permanent teeth. The premature arrest of maxillary sutural growth in patients with craniosynostosis clarifies the small maxillary intermolar and intercanine dimensions (Chapter 6). The maxillary intermolar width in patients with Apert syndrome showed an increase over time but were much smaller compared to control subjects. This increase in intermaxillary arch width may be related to ectopic eruption of maxillary first molars as the second maxillary premolars often show palatal eruption in a transversally reduced maxilla. Clinically, reduced dental arch dimensions of the upper and lower jaw result in severe crowding in the mixed and permanent dentition (Kreiborg and Cohen, 1992). The limited sutural growth potential seen in these patients explain the very small longitudinal changes in upper dental arch measurements for both syndromes (Chapters 2, 3 and 6).

Well-aligned teeth and coordinated dental arches are needed as a prerequisite basis for midface surgical reconstructive procedures in patients with syndromic craniosynostosis. Extractions of some deciduous and selected permanent teeth are often needed and should be determined by the pediatric dentist and the orthodontist together (Vargervik et al., 2012).

8.3 Clinical implications

Apert and Crouzon syndromes are different disorders, and the craniofacial and dental development is not the same. The craniofacial morphology are distinct at all ages between both syndromes. The role of the orthodontist in an interdisciplinary craniofacial team consists of the observation and management of (abnormal) growth and dental development from infancy to adulthood. In most team settings, the orthodontist takes care of growth data (e.g. dental and cephalometric radiographs, computed tomography (CT) scans, cone-beam CT (CBCT) scans, dental casts, photographs, height and weight measurements, and for some patients, handwrist radiographs) and thus plays an important role in the timing and planning of jaw reconstructive and facial surgical procedures. It is suggested that a detailed growth analysis, as described in the present study, can provide a rational basis for treatment planning in individual patients with Crouzon or Apert syndrome. In craniofacial teams standardized data collection of all patients is important in order to gain accurate information about growth and development of rare syndromes. The often used cephalometric norm values are difficult to use as guideline for adequate positioning of the inferior parts of the orbits and zygomatic bone during surgery (Chapter 7), because the anatomy of the orbit is distorted due to syndromic factors and sometimes previous surgical intervention. Normative cephalometric values can not be used directly as templates or surgical goals for syndromic patients.

Management of individuals with syndromic craniosynostosis requires a team of experienced specialists and extends over the entire growth period from infancy to adulthood. An interdisciplinary craniofacial team can be expected to house the experience, knowledge, skills and organizational logistics to provide the highest level of care. Midfacial advancements with several surgical techniques are common in different published treatment protocols (Renier et al., 2000; Perlyn et al., 2009; Sant'Anna et al., 2010; Shetey et al., 2010). Some protocols describe a midfacial advancement combined with a mandibular set-back osteotomy (Hohoff et al., 2007; Stavropoulos et al., 2012). This procedure may increase a present obstructive sleep apnea in these patients (Bannink et al., 2010). It should be kept in mind that the length of the mandible is significantly shorter than normal (Costaras-Volarich and Pruzansky, 1984) and anteriorly positioned in the face, because the cranial base is short in Crouzon and Apert patients (Chapter 2). The question of timing for restoring abnormal morphology early in the patient's life is still a problem.

There are differing opinions on the best timing for midface surgical advancement in patients with midface hypoplasia. This is in part due to variations in each patient's medical, physical, and developmental needs as well as the acknowledgment that various interdisciplinary teams will have different treatment philosophies. Obstructive sleep apnea or severe exorbitism are pressing

indications for early midface advancement. The orthodontist facilitates the dentition for tooth eruption in severe crowding, prepares surgical prediction tracings and splints as needed, and provides long-term follow-up with appliances and treatment (Kreiborg et al., 1999; Kreiborg and Aduss, 1986). The orthodontist and surgeon would ideally plan a midface advancement only once, both for practical/technical and psychological reasons, and still achieve a normal position of the midface. Although desirable, this goal may not be achievable due to impaired midfacial growth in syndromic patients. Since surgery does not restore the innate lack of growth potential, patients operated on before the completion of skeletal growth will often require repeated surgical procedures. The cooperation between orthodontist and surgeon is critical not only to plan midface and jaw procedures, but also to prevent dental injuries that could result in irreversible tooth damage or loss, especially in infants and children in the deciduous and transitional dentition stages (Santiago et al., 2005; Sant'Anna et al., 2010).

Implicit in the choice of treatment made by the surgeon is the understanding that the first adapted procedure often provides the best opportunity for a good surgical outcome (Shetye et al., 2010; McCarthy et al., 2012). To achieve a good or excellent surgical outcome is more challenging if crucial tissues are surgically malpositioned or damaged. An experienced surgeon and an interdisciplinary team are even more important when contemplating surgical revision after a previous suboptimal outcome (McCarthy et al., 2012).

In the case of no acute indication for surgical intervention it is advisable before any maxillary surgery is undertaken in young children with Crouzon or Apert syndrome and wait with surgical intervention after the skeletal growth has stopped. Even more important, patients with craniosynostosis exhibit a higher chance developing psychosocial problems and irrational expectations when a Le Fort III is performed between 12 and 18 years of age (NVPC, 2010). Preferably a Le Fort III should not be performed during this period (NVPC, 2010). Greater utilization of two- or three-dimensional imaging techniques may improve the standardization and accuracy of growth analysis, and treatment planning. Considering the high rate of oral anomalies in patients with Crouzon or Apert syndrome, observation and knowledge of the extent of the oral abnormalities is important. This information is important for the orthodontic treatment, to guide dental eruption, management of space and choice of the often needed extractions in these patients.

Delayed dental development is a problem for the orthodontist, because surgical intervention starts often in childhood between 6 and 12 years of age with an early midface advancement with or without a facial bipartition. At this time retention of orthodontic braces on permanent teeth can be difficult or is impossible, because the first permanent molars are often unerupted, due to severely delayed dental development. Dental arch morphology in the permanent dentition is

very abnormal in patients with Crouzon or Apert syndrome. Children with Apert syndrome have smaller arch dimensions than children with Crouzon syndrome. Without orthodontic intervention no normal arch development will occur and at this time the choice is to expand the upper jaw orthodontically or possibly surgically. The already clinically, reduced dental arch dimensions in the primary dentition of the upper and lower jaw may therefore result in even more severe crowding in the mixed and permanent dentition. At this time, between 12 and 15 years of age a new decision or evalution should be made to create well aligned arches in preparation for the final ideal operatively obtained occlusion (at the age of 18 years or older). Knowledge of dental and craniofacial development is important for any kind of intervention. The orthodontist and the surgeon should inform other team members when craniofacial interventions are planned. It is important when circumstances permit to prepare dental arch dimensions before surgical intervention and coordinate this treatment with other team members. The orthodontist should have sufficient experience with presurgical orthodontic treatment in patients with craniofacial anomalies are fundamental. Knowledge of normal and abnormal dental and craniofacial growth and development.

Consensus on timing and type of intervention and experience in treatment of craniosynostosis are important on the effects of growth and intervention. The physicians and other involved specialists should be able to monitor and plan surgical interventions in patients, performing the planned procedures, and establish adequate follow-up for evaluating the results. Disappointing or unexpected results as well as deviations from the protocols should be reported and hopefully lead to re-evaluation of the guidelines over time (Marchac and Renier, 1996; NVPC, 2010; Shetye et al., 2010). Evidence-based knowledge about the optimal care for children with craniosynostosis is rare. Unfortunately, at the moment prospective randomized clinical trials are not feasible to conduct due to small sample sizes and ethical issues.

8.4 Statistical data analysis

In this thesis statistical multilevel modeling has been used. Multilevel models are statistical models of parameters that vary at more than one level. The units of analysis are usually individuals (at a lower level) who are nested within contextual/ aggregate units (at a higher level). These models can be seen as generalizations of linear models (in particular, linear regression), although they can also extend to non-linear models (Goldstein, 1986). It can describe both individual and average growth curves; it is flexible because it uses polynomials, which can describe growth curves of almost any form. Additionally, the model can handle missing values very easily (without loss

of complete cases). Finally, the model can be used with different sample and research designs (Hoeksma and Van der Beek, 1991). While the lowest level of data in multilevel models is usually an individual, repeated measurements of individuals may also be examined. As such, multilevel models provide an alternative type of analysis for univariate or multivariate analysis of repeated measures. The initial equation was:

$$y_{ij} = \beta_{0ij}constant + \beta_1 t_{ij} + \beta_2 t_{ij}^2 + \beta_3 t_{ij}^3$$

with

$$\beta_{0ij} = u_{0j} + e_{0ij}$$

The e_{0ij} refers to the random errors of prediction for the level 1 equation. At level 1, both the intercepts and slopes in the groups can be either fixed (meaning that all groups have the same values, although in the real world this would be a rare occurrence), or non-randomly varying (meaning that the intercepts and/or slopes are predictable from an independent variable at level 2), or randomly varying (meaning that the intercepts and/or slopes are different in the different groups), and that each have their own overall mean and variance. Arguments for choosing a rondom intercept model in this thesis: the groups are not unique entities; the groups are regarded as a sample from a population; the number of values in the study is small relative to the values of the variable as it appears in the population it is drawn from (Goldstein, 1986).

Most measurements contain some error component. This may be due to observer error when measuring distances on radiographs. When variables in statistical models contain relatively large components of such error the resulting statistical interferences can be very misleading. To prevent large measurement errors the measures of the observer, first digitizing of landmarks were practiced and reviewed by an expert, and second reliability tests were performed. In the current study assessment of goodness of the model fit in the multilevel modeling procedure was performed; scatter plots were used to check for outliers; models were checked for significance and statistics procedures were performed under guidance of an expert. Some of the growth curves showed cubic statistically significant multilevel models. Cubic models showing four waves, although tested significant, explains the complexity involved in fitting the data. With an increased number for modeling of the data a quadratic or linear model seems to be more realistic for growth models (Goldstein, 1986).

In chapter 4 a different longitudinal statistical procedure and control group were used compared to the other studies. Nonsyndromic logistic curve-fitting procedures were used instead of multilevel modeling. This procedure treats data as independent observations. A consequence of failing to recognize hierarchical structures is that standard errors of regression coefficients will be underestimated, leading to an overstatement of statistical significance. In contrast to the other

studies, the date of birth of the control group is more comparable with the syndromic groups to decrease the effect of a possible secular trend.

8.5 Considerations and recommendations for future research

In the future, longitudinal 3D measurements before and after surgery may contribute to the study of facial growth and development and treatment implications in Apert and Crouzon syndromes. In order to prove that the quality of care is improving, comparisons of results over time, are imperative. This will become more difficult in the near future because centers may change the method of record taking from 2D to advanced computerized 3D equipment. All the outcome variables in this study are two-dimensional. In the near future it can be expected that two-dimensional pictures like photographs or cephalograms will be replaced by three-dimensional images, but at the start of data collection in many studies this technology was not available. Especially in patients with craniosynostosis, three-dimensional images can give new insights because asymmetry of the different parts of the face can better be evaluated. However, limited 3D longitudinal reference data for Crouzon or Apert syndrome are available yet (Cerovac et al., 2002).

At present, it still is a utopia for clinicians to be able to predict growth reliably in patients with craniosynostosis, to prevent or reduce relapse in surgical and orthodontic intervention and to manipulate the growth potential. Attempts should be made to integrate longitudinal data for patients with craniosynostosis into the prediction of individual craniofacial growth and development. The recent introduction of three-dimensional records will eventually lead to a virtual head of the patient which can be used for case analysis and treatment planning. The introduction of digital dental models at the end of the 20th century, 3D digital data sets, combining the bone, soft tissues, and the dentition, have gained increasing interest (Rangel et al., 2008). Integrating different types of X-rays, 2D or 3D photographs or composite tracings, life-like 3D models provide a tool for identification of areas of deformities, levels of asymmetry and relative relationships between different components of the face. Combining and integrating all available data in Europe with new imaging 3D techniques into a longitudinal data set should make craniofacial growth prediction possible even in syndromic patients.

The results in this thesis confirm the necessity and advantage of the use of protocolized standardized (rare) data for patients with Crouzon or Apert syndrome in order to be able to predict craniofacial growth and development. Most craniofacial centers now store their digital images on servers or a picture archiving and communications system (PACS). The PACS is an electronic and

ideally filmless information system for acquiring, sorting, transporting, storing, and electronically displaying medical images. With proper and secure access to data protection for privacy and legal issues, these digital longitudinal data can be readily accessed from inside or outside the institution in real time, permitting the use of a large file of longitudinal data from which to create a database of craniofacial measurements of rare syndromes like Crouzon or Apert.

8.6 References

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Chapter 9

Summary

In **Chapter 1**, the influence of craniosynostosis on the facial morphology of patients with Apert or Crouzon syndrome and the developmental changes over time are described and discussed in general. The syndromes of Crouzon or Apert are complex congenital anomalies. Both anomalies are associated with numerous problems. The consequent treatments introduced to solve the problems unfortunately may create additional handicaps. Research has elucidated many aspects of these problems, psychosocial well-being of the affected individuals and recently the genetic factors suspected of causing craniosynostosis have been reported. Research of the craniofacial growth and development including morphology of untreated syndromic patients is limited because of the low prevalence, early surgical midfacial intervention and a short follow-up. The focus of this study was dentofacial growth and development. Midfacial treatment modalities and protocols differ in timing found in the literature. This problem is related to insufficient evidence based knowledge of craniofacial growth in both syndromes. Surprisingly, detailed information about longitudinal craniofacial growth and development of syndromic patients is remarkably scarce. It was the aim of this study to evaluate and describe the craniofacial and oral development in growing patients with craniosynostosis. The patients were all treated in the craniofacial team at Erasmus Children's University Hospital in Rotterdam, The Netherlands. The Craniofacial Team coordinates and provides multidisciplinary specialty care for children with congenital defects of the head and neck. A multidisciplinary craniofacial team may be expected to house the experience, knowledge, skills and organizational logistics to provide the highest level of care.

In **Chapter 2** the craniofacial growth pattern in patients with Crouzon or Apert syndrome was analyzed in detail and compared with a sample of unaffected normal subjects. Multilevel modeling was used to analyze growth changes and compare the three groups. Significant differences in the sagittal and vertical dimensions within the syndromic groups showed an increased lower facial height, increased inclination of the palatal plane, retrusion of the maxilla, and proposition of the mandible compared with the controls. Overall, the patients with Apert syndrome had a more severe abnormal craniofacial morphology than did the patients with Crouzon syndrome.

In **Chapter 3** directional and fluctuating asymmetry in Crouzon or Apert syndrome compared with unaffected controls was described. Both measurements showed that the Apert syndrome had more directional and fluctuating asymmetry over time followed by the Crouzon syndrome and controls.

In **Chapter 4** the prevalence patterns of tooth agenesis were described in patients with Crouzon or Apert syndrome compared with nonsyndromic controls. Dental agenesis is the most common anomaly of the dentition and can be a component of a congenital syndrome. Tooth agenesis of third molars and lower second premolars is more prevalent in the syndrome of Crouzon and Apert than in control subjects. Mandibular symmetric patterns of tooth agenesis are also more prevalent in syndromic patients.

In **Chapter 5** dental maturation in children with Crouzon or Apert syndrome were compared with nonsyndromic controls. Logistic development curves for dental age over time were constructed. Significant gender differences in dental maturation scores were found for girls with Crouzon or Apert syndrome. Patients with Apert syndrome demonstrated a significantly delayed dental maturation, while patients with Crouzon syndrome showed non-significant delay. The delay of tooth formation in patients with Crouzon or Apert syndrome suggests a relationship between craniosynostosis and dental maturation.

In **Chapter 6** changes in dental arch morphology were compared in patients with Crouzon or Apert syndrome and controls. Multilevel statistical techniques were used to evaluate dental arch changes over time for the three groups. Dental arch dimensions were statistically significant smaller in patients with Crouzon or Apert syndrome than in controls. Maxillary intermolar arch width in patients with Apert syndrome increased, while all other arch width measurements showed no change. Patients with Crouzon syndrome showed increase in maxillary intercanine width, while intermolar width showed no increase over time. Maxillary arch depth showed no change over time and was statistically significant smaller in syndromic patients than in controls. The mandibular and maxillary arch lengths decreased only slightly over time. From this study it can be concluded that dental arch dimensions in syndromic patients are consistently smaller than in control subjects between 4 and 14 years of age. Also dental arch dimensions of patients with Crouzon or Apert syndrome showed diminished increase from 4 to 14 years of age.

In **Chapter 7** the effect was evaluated of Le Fort III osteotomy with distraction osteogenesis (DO) on the retruded midface in patients with Crouzon or Apert syndrome. One year after removal of the distraction device no statistically significant difference of the surgical maxillary advancement was found for both syndromes. From this study it could be concluded that DO of the midface in patients with Crouzon or Apert syndrome seems to be stable in the sagittal direction after one year follow-up. Although Crouzon or Apert syndromes differ in craniofacial characteristics, anteroposterior craniofacial dimensions were significantly improved and were closer to normal after treatment.

In **Chapter 8** the general aims of this thesis are discussed in relation to the main results. It can be concluded that:

1. Children with Crouzon and Apert syndromes showed retarded craniofacial growth, decreased craniofacial dimensions and facial asymmetry.
2. It appeared that most craniofacial dimensions from early childhood are abnormal small and hardly change over time.
3. The lack of craniofacial growth potential explains the differences in dental arch dimensions seen in these patients.

4. Delayed dental development and increased agenesis of teeth are part of both syndromes and may be related to the genetic background.

Although the syndrome of Crouzon and Apert show similarities in their craniofacial growth and development they are two distinct syndromes with more severe growth and development deficiencies in the Apert syndrome. Regarding the implementation of the findings of the present study, it should be mentioned that individual and overall growth should be monitored in advance to the decision regarding timing of any kind of treatment and discussed with the patient and the parents. Surgical midfacial advancement performed at early childhood may often need secondary midfacial surgery later in life because the mandible grows continually until adulthood.

Management of cleft lip and palate and craniofacial deformities has recently been focused on interdisciplinary approach with several recommendations in the literature. Cleft lip and palate and craniofacial teams have evolved across the globe over the last 40 years in order to provide coordination between different professionals involved in the care of patients with clefts and craniofacial deformities. Hopefully, an interdisciplinary care system with each member of the team involved in a coordinated treatment approach should give the best possible treatment outcome. The mission for the future will be the national implementation of the recommendations from this study and to urge craniofacial centers to (re)evaluate their treatment protocols. The use of protocolized standardized data for patients with Crouzon or Apert syndrome gathered at these national centers should be pooled in order to confirm the necessity and advantage of the used treatments and to predict craniofacial growth and development. International intercenter studies are necessary!

Chapter 10

Samenvatting

In **hoofdstuk 1** wordt de invloed besproken van craniosynostose op de aangezichtsmorfologie bij patiënten met het syndroom van Crouzon en Apert, waarbij ook de veranderingen tijdens de groei en ontwikkeling worden beschreven. Het syndroom van Crouzon en Apert zijn ernstige aangeboren afwijkingen. Beide afwijkingen hebben meerdere functionele problemen. Bij de behandeling van deze functionele problemen kunnen ook bijkomende ongemakken ontstaan. Wetenschappelijk onderzoek verklaart aspecten van deze problemen, zoals psychosociale aspecten van patiënten en vrij recent de genetische factoren die craniosynostose veroorzaken. Wetenschappelijk onderzoek naar aangezichtsgroei en ontwikkeling bij chirurgisch onbehandelde patiënten is zeer schaars door de lage prevalentie, de vaak vroege chirurgische interventie in het middengezicht en de korte vervolgperiode. Het doel van dit onderzoek was de dentale en de aangezichtsgroei en ontwikkeling te beschrijven. Er zijn veel verschillende behandelingsprotocollen voor het aangezicht beschreven. Dit probleem is gerelateerd aan onvoldoende wetenschappelijke onderbouwing van de craniofaciale groei in beide syndromen. Het is echter opmerkelijk dat gedetailleerde kennis omtrent longitudinale craniofaciale groei en ontwikkeling van syndromale patiënten zeer schaars is. Het doel van deze studie is om de craniofaciale en orale groei te evalueren en te beschrijven bij patiënten met craniosynostoses. De patiënten werden behandeld in het craniofaciale team van het Erasmus Medisch Centrum te Rotterdam. Het craniofaciale team coördineert en voert multidisciplinaire zorg uit bij kinderen met aangeboren afwijkingen aan het gezicht en de nek. Van een multidisciplinair team mag verwacht worden dat zij expertise, kennis, behandelvaardigheiden en organisatie heeft om zo de kwalitatief hoogst mogelijke patiëntenzorg te geven.

Hoofdstuk 2 beschrijft het craniofaciale groeipatroon bij patiënten met het syndroom van Crouzon en Apert vergeleken met normale kinderen. Statistische multilevel modeling technieken werden gebruikt om de groeiverandering te analyseren en deze te vergelijken tussen de drie groepen. Significante verschillen voor sagittale en verticale dimensies werden gevonden bij de syndromale groepen en deze lieten een vergrootte onderste aangezichtshoogte, een toegenomen inclinatie van het palatinale vlak, een toegenomen retrusie van de maxilla en een toegenomen propositie van de mandibula vergeleken met een controle groep. Patiënten met het Apert syndroom hebben een meer abnormale craniofaciale morfologie dan patiënten met het Crouzon syndroom.

In **hoofdstuk 3** wordt de directionele en de fluctuerende asymmetrie bij het syndroom van Crouzon en Apert vergeleken met een niet aangedane controle groep. De metingen lieten zien dat tijdens de groei het Apert syndroom meer directionele en fluctuerende asymmetrie hadden gevolgd door het Crouzon syndroom en vervolgens de controle groep.

In **hoofdstuk 4** wordt het prevalentie patroon beschreven van tandagenesie bij patiënten met het syndroom van Crouzon en Apert vergeleken met een niet syndromale controle groep. Tandagenesie is de meest voorkomende afwijking in de dentitie die een onderdeel kan zijn van een aangeboren syndroom. Tandagenesie van derde molaren en tweede premolaren in de onderkaak komen meer voor bij het syndroom van Crouzon en Apert dan bij een controle groep. Symmetrische patronen van tandagenesie in de onderkaak zijn meer prevalent bij syndromale patiënten.

In **hoofdstuk 5** werd de tandontwikkeling bij kinderen met het syndroom van Crouzon en Apert vergeleken met een niet-syndromale controle groep. Daarvoor werden logistische ontwikkelingscurves geconstrueerd voor tandontwikkeling. Significante geslachtsverschillen in tandontwikkeling werden gevonden bij meisjes met het syndroom van Crouzon en Apert. Patiënten met het Apert syndroom lieten een significant vertraagde tandontwikkeling zien, terwijl patiënten met het syndroom van Crouzon geen verschil in tandontwikkeling lieten zijn met de controle groep. De vertraagde tandontwikkeling bij patiënten met het syndroom van Crouzon en Apert suggereert een relatie tussen craniosynostose en tandontwikkeling.

In **hoofdstuk 4** worden veranderingen in tandboog morfologie vergeleken tussen patiënten met het syndroom van Crouzon en Apert met een controle groep. Statistische multilevel technieken werden gebruikt om de veranderingen in de tijd van de tandboog tussen de drie groepen te vergelijken. Tandboogdimensies waren significant kleiner bij patiënten met het syndroom van Crouzon en Apert dan bij de controle groep. De tandboogbreedte in de bovenkaak bij patiënten met het Apert syndroom namen toe, terwijl alle andere breedte metingen van de tandboog geen verandering lieten zien. Patiënten met het Crouzon syndroom lieten een toename zien van de tandboogbreedte tussen de bovenhoektanden, terwijl de boogbreedte tussen de molaren geen verandering liet zien. De boogdiepte in de bovenkaak liet geen verandering zien en de gevonden warden waren significant kleiner bij syndromale patiënten dan bij de controle groep. De booglengte in de onder- en bovenkaak nam af tijdens de groei. Uit deze studie blijkt dat de tandboogdimensies bij syndromale patiënten kleiner zijn dan een controle groep in de leeftijd tussen 4 en 14 jaar. Daarnaast lieten tandboogdimensies beperkte toename zien in de leeftijd tussen 4 en 14 jaar.

In **hoofdstuk 7** werd het effect van een Le Fort III osteotomie met distractie osteogenese geëvalueerd op het teruggevallen middengezicht bij patiënten met het Crouzon en Apert syndroom. Een jaar na verwijdering van het distractie apparaat waren geen significante verschillen gevonden na chirurgische bovenkaak voorwaartse verplaatsing in beide syndromen. Uit deze studie kan worden geconcludeerd dat distractie osteogenese van het middengezicht bij patiënten met het Crouzon en Apert syndroom stabiel lijkt in de sagittale dimensie na een

vervolgtijd van 1 jaar. Ondanks dat het Crouzon en Apert syndroom verschillen in craniofaciale kenmerken, verbeterden de sagittale craniofaciale dimensies significant. De sagittale waarden na de behandeling lagen dicht bij de waarden van de controle groep.

In **hoofdstuk 8** worden de uitkomsten in relatie tot het algemene doel van dit proefschrift besproken. De uitkomsten van dit proefschrift bevestigen dat:

1. Kinderen met het Crouzon en Apert syndroom lieten een vertraagde craniofaciale groei, en kleine craniofaciale dimensies en faciale asymmetrie zien.
2. Het blijkt dat bepaalde craniofaciale dimensies van de kindertijd zijn abnormaal klein en nauwelijks verandering tijdens de groei.
3. Het gebrek aan craniofaciale groei potentiaal verklaart de verschillen in tandboog dimensies bij syndromale patiënten.
4. Vertraagde tandontwikkeling en het meer voorkomen van tandagenesie zijn beide onderdeel van het syndroom van Crouzon en Apert en kunnen gerelateerd zijn aan de genetische achtergrond.

Hoewel het syndroom van Crouzon en Apert vergelijkbare craniofaciale groei en ontwikkeling lieten zien, zijn beide syndromen verschillend met meer ernstige groei- en ontwikkelingsdeficiëntie bij het syndroom van Apert. Bij de integratie van de resultaten in dit proefschrift moet de individuele en de algemene syndromale groei betrokken worden voor de behandeling en de bespreking van het behandelplan met de patiënt en zijn of haar ouders/verzorgers. Bij een voorwaartse chirurgische verplaatsing van het middengezicht tijdens de kindertijd is vaak een tweede chirurgische ingreep in het middengezicht nodig, omdat de onderkaak blijft groeien tot volwassenheid van de patiënt.

De behandeling van schisis en craniofaciale afwijkingen heeft tegenwoordig een multidisciplinaire benadering welke ook wordt ondersteund door wetenschappelijk onderzoek. Schisis- en craniofaciale teams zijn de laatste 40 jaar ontstaan voor een goede samenwerking tussen verschillende professionals in de patiëntenzorg van schisis en craniofaciale afwijkingen. Een interdisciplinaire benadering van patiëntenzorg vraagt van elk teamlid een goede samenwerking, waardoor het best mogelijke behandelresultaat mag worden verwacht. Een doel voor de toekomst is de nationale realisatie van de aanbevelingen uit dit proefschrift en het aanzetten van craniofaciale centra tot (her-) evaluatie van behandelprotocollen. Het gebruik van geprotocolleerde gestandaardiseerde data van patiënten met het syndroom van Crouzon en Apert bijeengebracht uit de nationale centra kunnen zo onderling worden vergeleken om de behandelnoodzaak van gebruikte behandeltechnieken te bevestigen en de craniofaciale groei en ontwikkeling te voorspellen. Bij voorkeur zijn studies tussen internationale behandelcentra noodzakelijk!

Publications

Curriculum Vitae

PhD Portfolio

Acknowledgements

Publications

1. Mandibular Asymmetry in Patients With the Syndrome of Crouzon or Apert. Elmi P, Reitsma JH, Buschang PH, Wolvius EB, Ongkosuwito EM. Cleft Palate Craniofac J. (submitted)

2. Dental Maturation in Children With the Syndrome of Crouzon and Apert. Reitsma JH, Balk-Leurs IH, Ongkosuwito EM, Wattel E, Prahl-Andersen B. Cleft Palate Craniofac J. 2013; doi: 10.1597/13-071.

3. A Longitudinal Study of Dental Arch Morphology in Children With the Syndrome of Crouzon or Apert. Reitsma JH, Elmi P, Ongkosuwito EM, Buschang PH, Prahl-Andersen B. Eur J Oral Sci. 2013; 121: 319-327.

4. Patterns of Tooth Agenesis in Patients With the Syndrome of Crouzon of Apert. Reitsma JH, Ongkosuwito EM, van Wijk AJ, Prahl-Andersen B. Cleft Palate Craniofac J. 2014; 51: 178-183.

5. Craniofacial Stabillity in Patients With Crouzon or Apert Syndrome After Le Fort III Distraction Osteogenesis. Reitsma JH, Ongkosuwito EM, Buschang PH, Adrichem LN, Prahl-Andersen B. Cleft Palate Craniofac J. 2013; 50: 561-569.

6. Facial Growth in Patients with Apert and Crouzon Syndromes Compared to Normal Children. Reitsma JH, Ongkosuwito EM, Buschang PH, Prahl-Andersen B. Cleft Palate Craniofac J. 2012; 49: 185-193.

7. Oligodontia: treatment plan and therapy. Reitsma JH, Meijer HJ, van Oort RP. Ned Tijdschr Tandheelkd. 2005; 112: 325-329. Dutch.

Curriculum Vitae

The author is a farmers son born on June the 25th, 1981 in Dokkum, The Netherlands. He finished secondary school in 1999 at the 'Dockinga College' in Dokkum, The Netherlands. The following year he started his dental education at the Rijksuniversiteit Groningen, Groningen, The Netherlands, which he completed in June 2005. From August 2005 to 2006 he started working as a dentist in a private practice in London, United Kingdom and also worked as researcher at the Department of Orthodontics in orthodontic materials at the University Medical Centre Groningen (UMCG). In 2006 he started the full-time orthodontic training program at the Department of Orthodontics at the Academic Centre for Dentistry Amsterdam (ACTA), which he completed in 2010. In 2010 he also received the diploma of Membership in Orthodontics from the Royal College of Surgeons of Edinburgh. Until November 2013 he combined working in several orthodontic practices with the research in this thesis, before starting an orthodontic practice in Groningen, The Netherlands.

PhD Portfolio

Name PhD student:	J.H. Reitsma
Erasmus MC department:	Department of Orthodontics
PhD Period:	2008-2013
Promotors:	Prof. Dr. E.B. Wolvius, Prof. Dr. P.F. van der Stelt
Supervisors:	Em. Prof. Dr. B. Prahl-Andersen, Dr. E.M. Ongkosuwito

1. PhD training

	Year	Workload
Research skills		
Introduction to data analysis and regression analysis, ACTA	2006-2007	2.0
Introduction to multilevel modeling, Baylor, Texas, USA	2009, 2012	1.4
Specific courses		
Basiscursus stralingsbescherming deskundigheidsniveau 4A/M voor medisch specialisten (variant kaakchirurgie/ orthodontie), ACTA	2009	1.0
Presentations		
Facial growth in patients with Apert and Crouzon syndromes compared to normal children. 7th International Orthodontic Congress, Sydney	2010	1.4
Poster presentation		
Craniofacial stability in Crouzon and Apert patients one year post Le Fort III distraction. European Orthodontic Congress, Portoroz	2010	1.4
Oral presentation		
A longitudinal study of dental arch morphology in children with the syndrome of Crouzon or Apert. European Orthodontic Society, Reykjavik	2013	1.4

Poster presentation		
Growth and development in patients with congenital craniosynostosis. Department of orthodontics, Baylor University	2009, 2012	1.5
(Inter)national conferences		
Najaarsvergadering Vereniging voor Orthodontisten	2008-2010	3.0
European Orthodontic Congress	2008-2010 2013	4.0
Biennial Symposium Surgical Orthodontics	2009	1.0
2nd International Conference on Ectodermal Dysplasia	2009	0.7
International Orthodontic Congress	2010	1.0
American Orthodontic Congress	2010, 2011	2.0
Seminars and workshops		
Introduction to evidence based orthodontics, ACTA	2008	1.0
Gezichtschirurgie: Schisis, cranio-faciale afwijkingen, brandwonden en aangezichtswondgenezing, operaties bij schisis patienten. Academisch Medisch Centrum Amsterdam	2009	0.5
3D diagnosis and virtual treatment planning of cranio-maxillo--facial deformity. Eindhoven	2010	1.0
Workshop: symptomen en syndromen, ACTA	2010	0.5

2. Teaching activities

Lecturing		
Craniofacial growth and development. dental students, ACTA	2008-2010	2.0
Supervising postgraduate orthodontic student		
Supervising Poejan Elmi, postgraduate orthodontic student ACTA. Retrospective research, statistics and article writing	2010-2013	3.6

3. Other activities

Treasurer European Postgraduate Students Orthodontic Society	2010-2011	2.0

One ECTS stands for around 28 working hours (including preparation, self-study, examinations etc.)

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Why is it that I spend so much time writing my thesis and less than one day writing my acknowledgements if the latter is so much more often read than the former? I find myself facing a fast-moving deadline. This has however no effect on the gratitude I feel towards all those who have helped me on my way, shared with me their knowledge, their time, their friendship and their patience. So if you haven't already done so, please go back and read chapter 8 to see all those who made this thesis possible.

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