Let's Face It:
Causes, treatment and consequences of rare facial clefts

Let's Face It:

Oorzaken, behandeling en gevolgen

van zeldzame aangezichtsspleten

Sarah Lisa Versnel

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GENERAL INTRODUCTION

CHAPTER 1.1

General introduction

Chapter 1.1: General introduction

Rare facial clefts

Pathology

The incidence of a congenital malformation is 1 on 33 live newborn. [1] A congenital malformation can occur in all tissues and all body parts, and can present as an isolated malformation or as a part of a syndrome. Congenital malformations of the skull, face and jaws represent the craniofacial malformations. There are numerous types of congenital craniofacial malformations, which differ in location, pathomorphogenesis and incidence among other things.

Congenital craniofacial clefts, other than just clefts of the lip and palate, are a very rare condition. These 'rare facial clefts' encompass a wide variety of craniofacial dysmorphologies. [2] All facial parts and all tissue-layers of the face can be involved in various degrees of severity. Bone and soft tissues are rarely involved to the same extent. The cleft can occur unilaterally or bilaterally, in the midline of the face or more paramedian or oblique. The affected soft tissue and/or skeletal elements show a disturbed growth-pattern, resulting in more obvious or more severe deformities over the years. This underdevelopment of soft tissue and osseous structures occurs in three dimensions. [3,4]

Other craniofacial malformations, such as encephaloceles, hydrocephaly, craniosynostosis, widow's peak, hypertelorism, choanal atresia, anophtalmia and microphtalmia, coloboma of the iris, or choroids and epibulbar dermoids, have also been reported in this population, as well as associated deformities, such as constriction rings of the limbs, aplasia cutis congenita, club feet, and ectopia vesicae. [5,6]

The first descriptions of this pathology were all case reports. Midline deformities are mentioned in the earliest reports by Schenk (1609) [7] and Bartholinus (1654) [8]. One of the oldest examples of a midline deformity that can still be seen in the museum of the department of anatomy and embryology of Leiden University, was reported in 1765 by van Doeveren. [9] Regarding oblique facial clefts, Laroche was in 1823 the first to differentiate between ordinary cleft lip and clefts of the cheek. [10] In 1864 Pelvet separated oblique facial clefts involving the nose from the other cheek clefts. [11] In 1887 Morian collected 29 cases from the literature and seven of his own, and recognized three different groups of oblique facial clefts. [12] Since then several reviews have been published by Grundberg (1909), Boo-chai (1970)[13], Mazzola (1976) [14], Millard (1977) [15], Kawamoto [16] and Monasterio (2008) [17]. [18]

Classification

Since there is a broad spectrum of possible facial anomalies, multiple attempts have been made to classify facial clefts. Some classifications were based on the position of one cleft in relation to the other, [2,12] or the direction the clefts take (e.g. oronaso-ocular or oro-ocular clefts). [19] Other classifications were according to the period in which the development was disturbed (e.g. primary or secondary clefting) [20], or the area in which the malformations had their origin. [3,21,22] The best known classifications are those by Tessier and van der Meulen. [2,3] Tessier (Figure 1) described an anatomical classification system in 1976, which is now the most widely used classification. The Tessier classification focuses on a topographic description of the facial clefts on the level of soft tissue as well as the underlying osseous structures. It is a practical classification, but it lacks explanation why and how these clefts develop.

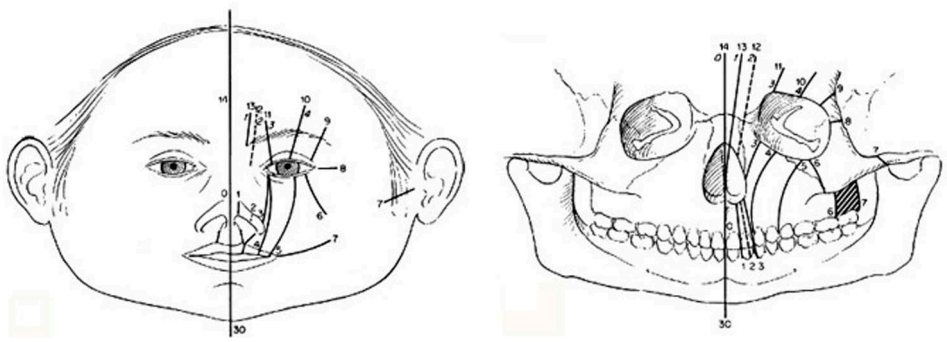

Figure 1. *Tessier classification*

In 1983 van der Meulen developed an embryological classification system based on morphogenesis that explains the mechanism of formation of clefts (Figure 2); however, this classification also has its shortcomings as it is less practical and focuses on osseous structures.

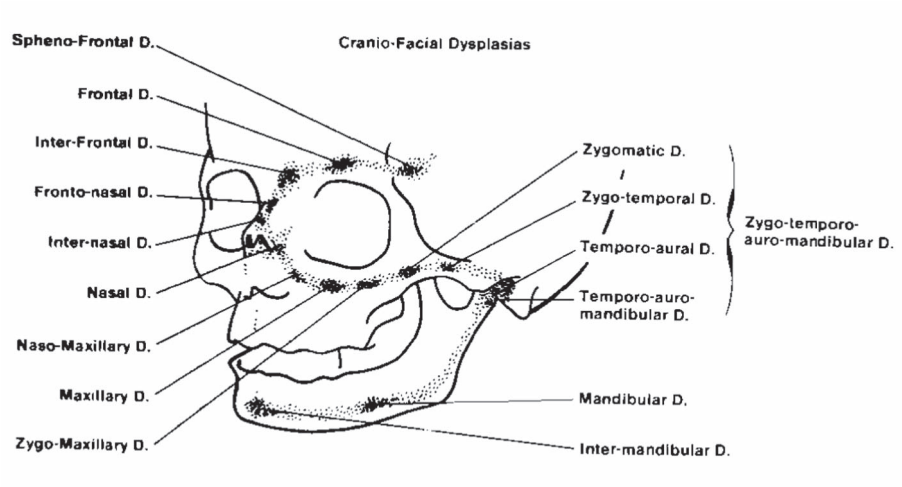

Figure 2. *Van der Meulen classification*

Multiple Tessier or van der Meulen clefts can occur at the same time in one patient. A few specific combinations of cleft types have been given their own name as for example Treacher-Collins syndrome (Tessier cleft 6,7,8). [2,23]

Epidemiology

Since rare facial clefts are a uncommon condition, it is difficult to obtain an accurate incidence of this pathology. One review concluded that the occurrence rate of rare facial clefts ranges from 1.43 to 4.85 per 100.000 births and from 9.5 to 34 per 1000 common clefts (cleft-lip-palate). [16,24] However, the majority of reports are based on small groups and come from various parts of the world; therefore it is difficult to determine its validity. The incidence of rare facial clefts appears to be higher in developmental countries in South-America, Africa and Asia, than in Western countries. In the Netherlands the incidence is estimated at 1 per 400.000 births, when we do not take hemifacial micosomia (Tessier 7) and Treacher-Collins (Tessier 6,7,8) into account; hemifacial microsomia occurs approximately 1 in 4000 births and Treacher-Collins 1 in 50.000. [25]

Causes

The search for the cause of having an 'abnormal' congenital facial appearance has been a conflict between superstition and science over the centuries. In early ages congenital malformations mainly symbolized the power of God or a superior Being. In this context congenital malformations were seen as the herald of mysterious warnings and prophecies, so-called 'omens'. [26] The oldest 'omen-texts' (7th century BC) originate from Babylonian clay tablets of Ashurbanipal's library (Britisch Museum, London):

When a woman gives birth to an infant…
…whose nostrils are absent, the country will be in affliction and the house of the man ruined;
…that has no nose, affliction will strike the country and the master of the house will die;

Cicero also emphasized the predicting role of the congenital malformations in 'De Divinatione'. [26] According to the Bible congenital malformations should be seen as the punishment of God. [27] Many superstitions persisted during the following centuries and throughout the Middle Ages; including astrological (e.g Albertus Magnus) and psychological (maternal impressions and behaviour) explanations. [28] However, also some scarce scientific explanations were given in this period. Probably Hippocrates (460-c–356 BC) was the first to advocate a more observational and scientific explanation for congenital malformations [29]:

…infants become crippled in the following way: where in the womb there is narrowness at the part where in fact the crippling is produced, it is inevitable that the body moving in a narrow place shall be crippled in that part.

In 1575 the French surgeon Ambroise Paré published a book, in which he summarizes the causes of congenital malformations, which include environmental and hereditary causes besides the religious and psychological causes.[30] Later William Harvey (1578-1657) introduces the concept of developmental arrest during embryonic evolution as an explanation for congenital malformations. [31] In the beginning of the 19th century Meckel [32] and father and son Geoffry St. Hilaire laid the foundations of the science of teratology. In the publication of Geoffry St. Hilaire in 1832, the word teratology actually appears for the first time. [33] Since then, the cause of rare facial clefts has remained subject of discussion, and there is still a lack of consensus and scientific evidence.

The theory of amniotic bands as cause of rare facial clefts, one of the two main theories, was first introduced by Geoffry St. Hiliare and has long been subject of discussion. Multiple arguments against this theory have reduced the number of current proponents of this cause. [5]

The other main theory was that clefts result from developmental disturbance with focal fetal dysplasia as a defect; this idea was advocated by Meckel. [34] Various events such as genetic information, incorrect cell deposition, cell differentiation, cell proliferation, and tissue remodelling can play a role in the pathogenesis and have been suggested as a mechanism for this developmental arrest. [35] For example linear necrosis along the watershed between developing vascular areas [36], diminished arterial supply during development [37], disturbance in migration of neural crest cells [38] or a failure of mesodermal penetration and coalescence between facial processes [39], have been suggested.

In theory these mechanisms may be caused by non-genetic as well as genetic factors. Non-genetic factors have never been identified with certainty, but multifactorial etiology is suggested. Environmental factors, such as radiation, infection, metabolic abnormalities, and certain drugs and chemicals, have been shown to produce clefting in animals. [40-43] In humans influenza A2, toxoplasmosis, abnormal maternal phenylalanine metabolism, anticonvulsants, tretinoin, thalidomide have been associated with increased human craniofacial anomalies. [44-49] In addition hematoma, oligohydramnios and the amniotic rupture syndrome have been proposed as a cause of rare facial clefts. [50-52]

Until recently only a hereditary cause had been found for the patients with Treacher-Collins syndrome; they show an autosomal dominant inheritance pattern. [53] Although the majority of rare facial cleft types seem to be the result of a disruptive process, there are multiple reports in literature that suggests a genetic cause. [54-58] However, in none of these reports the genetic cause was proven.

Treatment

…The love of life is next to the love of our own faces, and thus the mutilated cry for help…

This was Sushruta's motivation in 600 BC for performing a plastic surgical reconstruction of the amputated nose, which was the penalty for adultery. [59,60] The

only earlier medical interventions to restore or enhance one's appearance date from the Egyptians (use of golden inlays), the Phoenicians (false teeth and other prostheses) [28, 61], and the *Edwin Smith Surgical Papyrus* (circa 3000BC) with the first mention of surgical management of facial injury. [62,63] The first operation of a cleft lip was performed by Celsus (20BC), who's plan for reconstruction was followed for centuries. [64] Another famous plastic surgeon worth to be mentioned, was the Italian Gaspare Tagliacozzi (1546-1599) who developed new techniques for total nasal reconstruction [65]:

…we restore, repair and make whole those parts of the face which nature has given, but fortune has taken away, not so much that they may delight the eye but that they may buoy up the spirit and help the mind of the afflicted…

The first corrections of facial deformities were all corrections of cutaneous defects; this was also the case for rare facial clefts. Delpech reported a surgical repair of a nazo-schizis in 1828 by rotation of a trilobed flap. [66] In 1890 Jalaguier described correction of a bilateral oblique facial cleft by rotation of multiple local flaps. [67] These first surgical treatments can be considered as palliative corrections. [26] Another example of these type of corrections, was the treatment of hypertelorism as suggested by Webster and Deming (1950): medial advancement of the eyebrows, modification of epicanthal folds and nasal bifidity. [68]

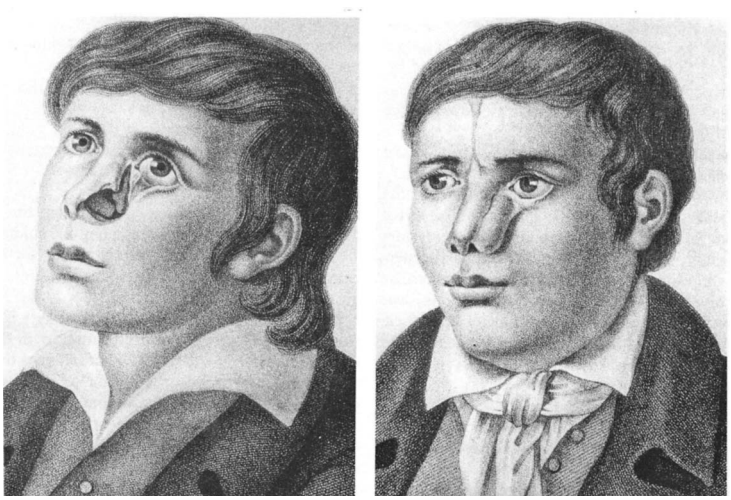

Figure 3. *Delpech 1828: repair of a nasal malformation*

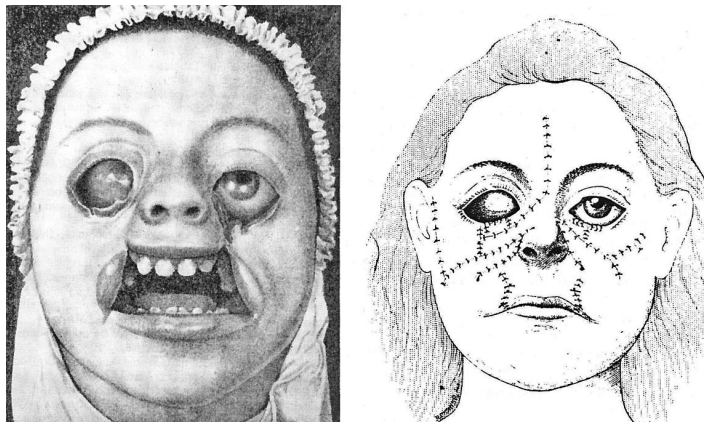

Figure 4. *Jalaguier 1909: repair of oblique facial cleft by a series of flaps*

In early operations, success was mainly defined by closure of the cleft with soft tissue closure and bone grafts. However, over the years surgery evolved towards a more anatomical restoration of the deformed structures. This included the introduction of muscular surgery in the repair of cleft lips and osteotomies. [26] The idea for the Le FORT III osteotomy, for example, was borrowed from facial trauma surgery by Gillies and Harrison. This osteotomy was used to advance the midface in a patient with congenital craniofacial malformations. [69]

In congenital craniofacial surgery there are a few pioneers. The 'Godfather' who was responsible for a breakthrough in craniofacial surgery and the treatment of rare facial clefts, was the Frenchmen Tessier (1917-2008). His new techniques allowed the treatment of many previously inaccessible conditions, including severe birth anomalies affecting the development of the brain, the visual axis, the airway and dentofacial growth. He developed a complex surgical route to release the face from the skull base and bring it forwards with durable stability, thus allowing ocular protection, to prevent blindness, and improve the airway, as well as the patient's facial aesthetic; Tessier developed this technique by working on dry cadaver faces and skulls. In 1964 he carried out the first transcranial orbital translocation for hypertelorism. In 1967 Tessier's craniofacial surgical series was presented at the International Congress of Plastic Surgery in Rome to wide interest, generating the birth of the speciality now known as craniofacial surgery. [70, 71] During the next two decades he developed and demonstrated all the procedures currently associated with craniofacial surgery: transcranial and subcranial correction of

orbital dystopias; correction of Treacher-Collins syndrome; and correction of oro-ocular clefts and hypertelorism. [72-79]

Another surgeon in the hall of fame of treatment of rare facial clefts is van der Meulen. Trained by Tessier himself, he gained an interest for this pathology. In 1979 he described a new technique for correction of hypertelorism: medial faciotomy. [80] He also provided more knowledge regarding the embryology which gave more insight in the pathomorphology which was helpful for surgical treatment of rare facial clefts. [3,5]

The Mexican Ortiz-Monasterio treated many patients with rare facial clefts (largest series in the world) and had a substantial contribution to the treatment philosophy of this pathology. [17,81]

Despite all the experience, there still exists controversy in treatment of rare facial clefts regarding techniques and timing. This is due to several factors: the complexity of the pathology, the rarity of the cases and the lack of good long-term follow-up.

Consequences

What´s in a face?

Feelings attached to physical appearance come from a rich variety of sources, including mythology, legends, fairy tales and other examples from history and contemporary society. The ethos of most of these examples is that especially beauty is all-important. [82] In this, the face is seen as the mirror of the soul (Cicero); with that association that 'what is beautiful is good'. [83] Even very young infants have the ability to categorise on attractiveness, have the same aesthetic perception as adults and prefer to look at attractive faces. [84, 85]

However, there is no compelling evidence for a relationship between personality and facial characteristics, as was also emphasized by Shakespeare [86]:

…There's no art to find the mind's construction in the face…

Despite this, many associations are made between appearance and a person's characteristics. Physical attractiveness is stereotypically strongly associated with sociability, dominance, general mental health, intelligence and physical health. [87, 88] The rating of facial attractiveness decreases, with an increasing severity of the facial disfigurement. [89, 90] As a consequence, patients with abnormal facial characteristics are rated as significant less attractive, but also as less honest, less employable, less

trustworthy, less optimistic, less effective, less capable, less intelligent and less popular. [91] Facial disfigurement has even been called the last bastion of discrimination. [92]

What happens when you look different?

Discrimination of patients with a congenital deformity already was a fact in the earlier days: the Spartans threw deformed newborns from the mountain Taygetus, and in Rome deformed babies were thrown into the river Tiber. [26]

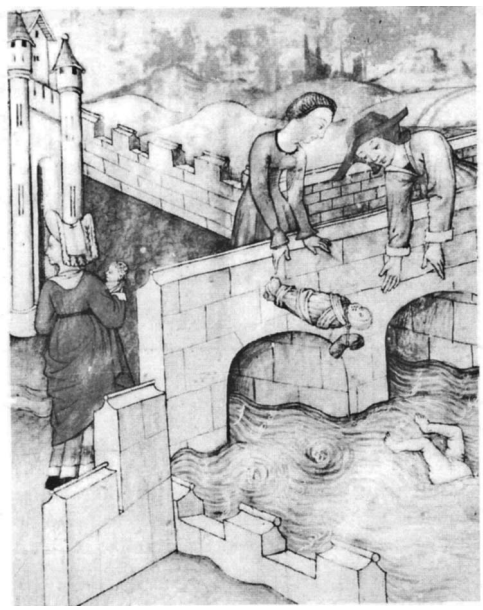

Figure 5. *Child with malformation being thrown into the Tiber*

Another way of dealing with people with deformities, was exclusion from society (within the family, or in the 'caritas' of the church), or displaying them in public (e.g. the circus). [93] In the twentieth century this exhibiting became prohibited. [28]

Nowadays emotional reaction towards people with visible deformities still varies according to education, civilization and religion. Despite the contemporary views that all human beings have the same right to live and that the less capable or less healthy should be cared for, there are still cultures in which babies with congenital deformities are eliminated or isolated from society. [26] Even in our own society an abortus

provocatus can be performed when a cleft lip is diagnosed in utero. On the contrary there are also cultures in which the malformed baby is overprotected and adored.

Facially disfigured people have to cope with all the prejudices and concomitant disapproving reactions from others in their daily life. Like Macgregor (1990) stated [94]:

…In their efforts to go about their daily affairs they are subjected to visual and verbal assault, and a level of familiarity from strangers…which include naked stares, startle reactions, 'double-takes', whispering, remarks, furtive looks, curiosity, personal questions, advice, manifestations of pity or aversion, laughter, ridicule and outright avoidance…

Development of psychosocial problems in this population of patients with facial deformities seems self-evident. Although there is now a considerable amount of literature on this topic, it is patchy and limited in adults. [95] Overall, results are often inconsistent, and difficult to compare due to methodological weaknesses. [96]

Since people are social mammals, there is always an interaction. The fact how other people think of, and react on facially disfigured people, influences thoughts and behaviour of the disfigured themselves; but also the other way around. One of the goals of surgical treatment of congenital craniofacial deformities like rare facial clefts is to give patients a more 'normal' appearance in order to improve acceptance by society and reduce the prejudices and reactions from others to a minimum; prevent the development of psychosocial problems or at least reduce them. An additional goal of surgical treatment is to improve a patient's satisfaction with his own appearance, and with that the way he feels about him/herself. Another way to reduce the development of psychosocial problems in patients with facial disfigurement is to attempt to change others' reactions to disfigurement; increase public awareness and understanding, and ameliorate family support. However, professional psychological support is a more direct and more frequently used intervention to improve psychosocial functioning in disfigured people. Social skills training and cognitive-behavioural therapy (CBT) are the most important approaches in the attempt to help these patients. [97] The limited research that has been performed on the effectiveness of these treatment modalities in patients with visible disfigurement, suggests a positive effect on psychosocial functioning. [98,99] There is however still a need for more knowledge regarding the aspects of psychosocial well-being that should be addressed in psychological treatment of adults with congenital facial deformities. [97]

CHAPTER 1.2

Outline and aims of the thesis illustrated with a case report

Case report

Distraction assisted treatment of a unilateral complex facial cleft: technical note

Versnel SL, Wolvius EB, van Adrichem LNA,
van der Meulen JNM, Ongkosuwito EM, Mathijssen IMJ

Int J Oral Maxillofac Surg. 2009 Jul;38(7):790-4.

Abstract

Unilateral maxillary hypoplasia is a characteristic feature of an oblique facial cleft. This three-dimensional shortage of osseous structures and soft tissue becomes more prominent over the years and is difficult to correct. We describe a 17-year-old boy born with a unilateral nasomaxillary dysplasia and nasal dysplasia (Tessier type 1, 2, 3) who underwent a hemi-Le Fort III distraction with a Rigid External Distraction (RED) system. This distraction, in combination with initial peroperative advancement and retained with elastic traction with a facial mask, achieved a substantial horizontal improvement of the hemi-midface; this resulted in a better projection of the left cheek, infra-orbital rim, nasal ala, and an improved occlusion. However, due to the underdevelopment of maxilla and zygoma in all three dimensions, contour deformities remain. Creating several bone segments for multidirectional distraction would jeopardize vascularization of the bone. Because good long-term planning is essential in these complicated cases, more long-term results need to be assessed. The major reconstructive challenge for this complex pathology continues.

Introduction

In more than 50% of cases, oblique facial clefts (Tessier no. 3, 4 and 5 clefts) present as a unilateral deformity. [81,100,101] Unilateral maxillary hypoplasia is one of their characteristic features. Due to deficient growth of all affected tissues in the cleft area, the subtle hypoplasia of one side of the midface at birth becomes more obvious over the years. This results in a clear unilateral three-dimensional (3D) underdevelopment of hard and soft tissues of the half-sided maxilla, nose and malar region, a deformity that imposes a major reconstructive challenge.

This report describes a hemi-Le Fort III distraction with a Rigid External Distraction (RED) system performed in a 17-year-old boy born with a unilateral nasomaxillary dysplasia and nasal dysplasia (Tessier type 1, 2, 3). Techniques, results after two years, shortcomings and treatment suggestions are discussed.

Patient and surgical technique

Patient

At birth, this patient presented with a unilateral left-sided nasal dysplasia and medial and lateral nasomaxillary dysplasia according to the 'van der Meulen' classification [3]; it is also classified as Tessier type 1, 2 and 3 cleft [2] (Figure 1). There was hypertelorism and left hemi-nasal aplasia with an absent apertura piriformis noted. His left lateral orbital wall and frontal bone showed uncommon retrusion and flattening without evidence of unilateral synostosis of the coronal suture. The orbital floor was hypoplastic and caudally displaced. His premaxilla was lacking on the affected side, and the characteristic retrusion of the maxilla was visible. There was blepharophimosis and exophthalmia of the left eye, together with a coloboma of the upper eyelid, iris and retina. Both his eyebrow and medial eye corner were dysplastic; the latter was in an inferior location. The nasolacrimal apparatus appeared to be absent. In addition, there was dysplastic soft tissue in the midline of the upper lip and a hypoplastic columella. The lateral and central incisor on the affected side were agenetic. Further examination revealed no other congenital anomalies. These facial deformities represent a score of 14 in our scoring list for the severity of congenital craniofacial malformations; a score of zero means no visible facial anomalies. [102]

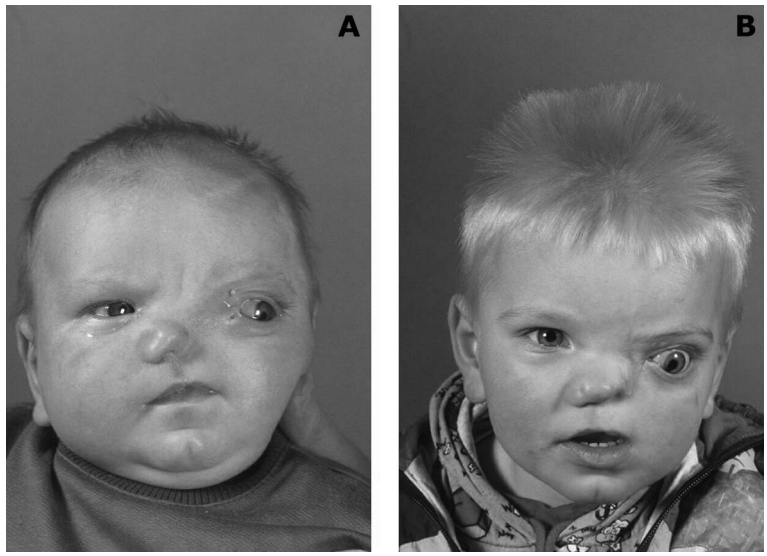

Figure 1. ***(A)*** *Patient at age one year with Tessier type 1, 2 and 3 cleft.*
(B) *Patient at age two years with increased vertical dystopia.*

A total of eight operations were performed. The coloboma was corrected and remnants of the saccus lacrimalis were extirpated. At the age of 2.5 years a medial faciotomy was performed to correct hypertelorism; bone grafts were inserted at both lateral orbital walls. [80] This procedure reduced the inter-orbital distance (IOD) from 25 mm to 15 mm. When the boy was 11 years of age, bone grafts from the tabula externa were placed over the left hypopolastic lateral and infra-orbital walls. The defects in the orbital floor were reconstructed using a rib graft composed of bone and cartilage, which was also used to reconstruct the nasal dorsum in the same procedure. A musculocutaneous flap of the left upper eyelid was transposed to the lower eyelid to correct the ectropion.

The nasal reconstruction was carried out over several operations using an expanded forehead flap, local transposition flaps (cheek, lower eyelid, nose/glabella), and a composed rib graft as mentioned above.

In order to increase the transverse width of the maxilla and to correct the Class III malocclusion, a Surgically-Assisted Rapid Maxillary Expansion (SARME) procedure was combined with orthodontic treatment at the age of 13 years. [103] Due to the collapse of the maxillary halves, a second SARME was carried out two years later.

At the age of 16 years the patient returned to the outpatient clinics of the craniofacial team. Clinically, the left midface was underdeveloped and the exophtalmia and the vertical dystopia of left orbita were more pronounced than at birth. Moreover, the left medial canthus was located more caudally; the lower eyelid lacked support especially on the lateral part, and was accompanied by an insufficient infra-orbital rim. The nasal deformities remaining after earlier interventions were hypoplasia of the left nasal ala and the nasal dorsum. The patient was still in a left-sided class III malocclusion and, despite the two subsequent SARMEs, had a posterior cross bite (Figure 2).

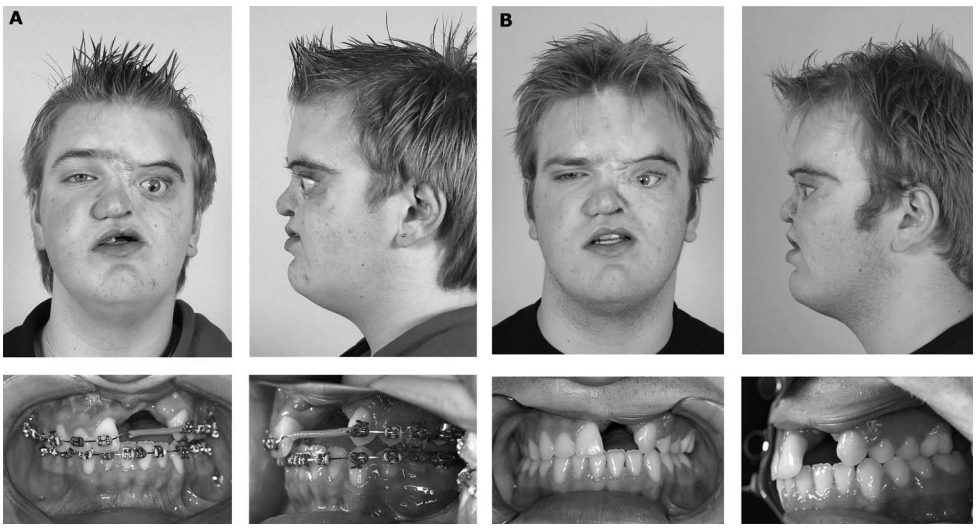

Figure 2. ***(A)*** *Patient (aged 16 years) before hemi-Le Fort III distraction.*
(B) *Patient 24 months postoperatively.*

A 3D-CT scan showed an obvious lack of growth in three dimensions of the left maxilla and a hypoplastic zygoma (Figure 3). With these malformations he scored 10 points on our scoring list.

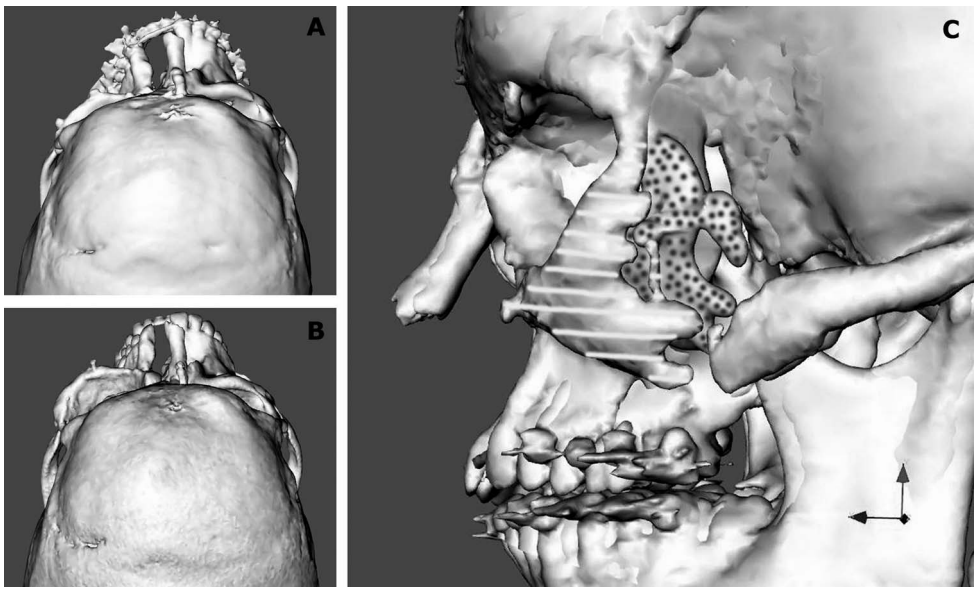

Figure 3. ***(A)*** *3D-CT scan (patient aged 16 years) before hemi-Le Fort III distraction, showing a hypoplasia of the left maxilla and zygoma in three dimensions.*
(B) *3D-CT scan 24 months postoperatively showing considerable improvement of the position of the hemi-midface in sagittal direction.*

At this stage our patient expressed his wish to have greater symmetry in his face. His main complaint was the poor 'filling' of his left cheek. A hemi-Le Fort III distraction was therefore planned to correct the maxillary retrusion. It was clear that not all dimensions of the bony deformity could be corrected with this osteotomy, but major improvement was expected. Soft tissue correction was intentionally postponed until a later stage.

Surgical technique

Based on 3D-CT scanning and a stereolithographic model, the optimal hemi-Le Fort III osteotomy lines were planned with the ideal vector for transposition of the osteotomized bone including slight overcorrection. The osteotomies were performed through the principal coronal and a left upper buccal sulcus incision. After exposure of the left nasal aperture and the transition to the nasal bone, a paranasal osteotomy was performed up to the left medial orbital wall. Subsequently, the orbital floor and the left orbital wall were sectioned according to the standard Le Fort III technique. Laterally, the arcus

zygomaticus was already discontinuous. Next, the pterygomaxillary junction was split and the osteotomy was continued in the inferior plane from lateral to the medial palate. Finally the palate was sectioned through the midline at the level of the cleft.

After mobilization of this hemi-Le Fort III bloc, three wires were attached percutaneously to this complex. One was fixed paranasally to the medial orbital wall. Two wires were attached laterally: one inferior to the body of the zygomatic bone and one superior to the lateral orbital wall. Immediately after closure of the coronal and left maxillary intraoral incision, a Rigid External Distraction device (RED-II System; KLS Martin, L.P., Jacksonville, Florida) was placed. The wires were directly attached to the two horizontal bars located on the left side of the RED frame. The choice for three wires attached to the hemi-bloc was made in order to control the 3D vectors within the active distraction phase (Figure 4).

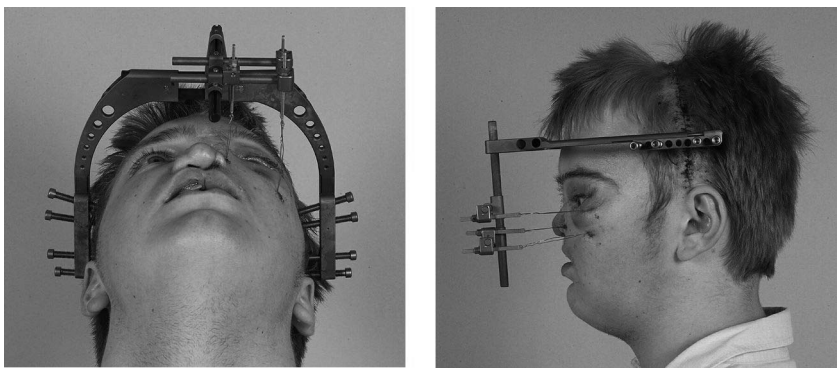

Figure 4. *Patient 2 months postoperatively with the distraction device in place. The vector of distraction is shown.*

The latency period before maxillary distraction was five days. Distraction was then started at a rate of 1 mm per day. After five days, active distraction was ceased as a substantial advancement of the midface of 10 mm had already been obtained per-operatively. Three-and-a-half months later the RED system was removed and a facial mask with fixed appliances and asymmetric elastic traction was used during the night for an additional six months.

Results

Two years postoperatively the advancement of the zygomatic bone and maxilla was clinically sufficient; their position had even been overcorrected (Figure 2). Exophthalmia had disappeared, but had been converted to enophthalmia, which was most prominent laterally. This was the result of impaired function of the left lower eyelid in combination with the position of the lateral infra-orbital rim, which was too far anteriorly and laterally. The lateral canthus was more detached from the eyeball. The left nasal ala had a better projection. Soft tissue filling of the cheek had improved, but remained insufficient.

In a transversal direction the flattening of the lateral orbital wall was less prominent. The occlusion was improved and the cross bite was normalized. The vertical dystopia of the left orbit remained unchanged. Considerable improvement of the position of the hemi-midface in sagittal direction was visible on a 3D-CT (Figure 3). The scans demonstrated that the continuity of the regenerated bone in the distraction gap appeared sufficient at the paranasal area, lateral orbital wall and particularly at the pterygomaxillary plates. The score on the scoring list for craniofacial malformations was now 8.

In our patient the patient's subjective satisfaction with his facial features was measured pre-operatively and postoperatively using the Body Cathexis Scale. [104] The boy's appreciation of his nose, eyes and total face changed from very dissatisfied preoperatively (score1) to neutral (score 3) postoperatively, and of his teeth from very dissatisfied (score1) to satisfied (score 4).

Discussion

With the combination of initial peroperative advancement, distraction and elastic traction with a facial mask, a substantial sagittal improvement of the hemi-midface was achieved. This resulted in a better projection of the left cheek, infra-orbital rim, nasal ala, and an improved occlusion. Good planning was essential to determine the ideal osteotomy lines in the complex anatomy of the unilateral oblique facial cleft; the anatomy of this facial anomaly is too irregular to simply adjust the osteotomy lines as one goes along. A 3D-CT and a stereolithographic model were therefore used for precise planning in addition to traditional lateral and postero-anterior radiographs, cephalometric analysis and dental models.

This technique appears to be a good option for reconstruction of hemi-facial mid-face hypoplasia. No problems or complications were encountered during the whole

process. Vacularization of the bone fragment was not compromised. The pre-operative and postoperative CT scans demonstrated sufficient continuity of the regenerated bone in the distraction gap in the paranasal area and the lateral orbital wall. Especially a continuous bony mass was seen at the pterygomaxillary plates; this could improve the long-term stability of the regenerate.

Despite the substantial improvement in the sagittal plane, the result (according to the planning) was not complete. As expected, the soft tissue increase lagged behind on the osseous expansion and deformities in the vertical plane remained uncorrected.

The 3D shortage of osseous structures and soft tissue in oblique facial clefts, which is the main issue here, becomes more prominent over the years. Due to deficient growth of all affected tissues in the cleft area, growth lags behind compared to the unaffected side and facial asymmetry increases. It is the natural history of this condition rather than the secondary effect of earlier surgical intervention. Significant increase of vertical dystopia and decrease of the prominence of the cheek were seen in this patient before any osseous corrections were performed (Figure 1).

This 3D shortage is difficult to correct. Simultaneous distraction in multiple directions would address the 3D underdevelopment in one stage, but we did not want to put the bone fragment at risk by dividing it in smaller parts due to the expected compromise of vascularization.

Previous correction of the underdevelopment of the osseous structures consisted of onlay of bone grafts and SARME. For correction of the shortage in vertical direction a ribgraft composed of bone and cartilage was placed upon the hypoplastic infra-orbital floor. Cartilage has the advantage of growth potential on the long term. [105]

This case reveals some of the problems and limitations we encountered in the treatment of the complex 3D pathology of an oblique facial cleft. Despite considerable progress in the treatment of oblique facial clefts, few data are available on long-term results. [106] The multiple operations performed in this patient demonstrate once more that good long-term treatment planning is essential. Optimal timing of surgery is essential to reduce relapse and keep the number of re-operations to a minimum. Therefore, to evaluate shortcomings and to optimize planning and techniques, long-term assessments are necessary.

This hemi-Le Fort III procedure, which was performed to ameliorate the osseous framework of the patient's left face, changed the appreciation of his facial features from very dissatisfied to neutral. The current plan for further corrections of the remaining contour deformities is to correct his hypoplastic infra-orbital wall with a bone graft after a retention phase. Surgical treatment of the vertical orbital dystopia is not a current wish

of our patient. If he would reconsider this in the future, several techniques could be used to address this remaining deformity. As planned in advance, filling of the cheek will also be performed in the future to correct the soft tissue shortage, probably by means of lipofilling. The patient's missing teeth will be replaced with dental implants after bone grafting of the alveolar cleft.

In conclusion, in our patient the hemi-Le Fort III procedure achieved substantial improvement of the sagittal position of the affected hemi-midface. However, due to the 3D underdevelopment of maxilla and zygoma, contour deformities remain. Preserving bone vascularization limits optimal correction by creating smaller segments in one stage. Because good long-term planning is essential in these complicated cases, more long-term results need to be assessed. The major reconstructive challenge for this complex pathology continues.

Outline and aims of the thesis

Causes

When the aforementioned patient wants to have children of his own in the future he will ask the inevitable question whether he will pass his congenital anomaly onto his child, and if yes if we could say what the chance is that his child will be affected. It is a question that has risen in this patient population multiple times in the past. This is a difficult matter since there has not been any satisfactory scientific evidence that enables us to give a clear answer to this question (only for patients with the Treacher-Collins syndrome). It is thought that asymmetric rare facial clefts are rather caused by disruptive processes; but in some types of midline clefts there are strong suggestions for a possible genetic cause. In literature several families have been described in which a genetic cause for the rare facial cleft was suspected; this were families with asymmetric clefts and families with midline clefts. [54-58] However, there has not been identified a genetic mutation as cause for the development of a rare facial cleft yet.

Since the population of rare facial clefts of the department of Plastic and reconstructive Surgery of the ErasmusMC included several families with resembling midline clefts and multiple affected family members, a genetic study was conducted in these families. This resulted in the discovery of a new genetic mutation (in the ALX3 homeobox gene) causing this specific type of midline cleft which was called frontorhiny. The results of this study are presented in **CHAPTER 2**.

Treatment

This patient demonstrates that rare facial clefts impose a major reconstructive challenge and that it is difficult to achieve both optimal aesthetic and functional end-results. Often serious asymmetry exists and multiple areas of the face are affected. Due to deficient growth of all affected tissues in the cleft area, the deformities at birth can become more obvious over the years. It can result in clear three-dimensional underdevelopment of hard and soft tissues of the maxilla, zygoma, nose and malar region. Due to this intrinsic impaired growth or growth disturbance by surgical interventions, initial excellent treatment results may turn gradually worse. Determining the right moment of surgical intervention and using the best surgical technique is therefore essential. Various techniques to address this complex pathology have been described in literature [5,73, 101,107-109]; however, evaluation of long-term results has been scarce. Some treatment policies have become general knowledge, but evaluation of long-term results can reveal new details on which techniques give the best results or have the least relapse. It also provides additional information on the aberrant growth patterns. All previous conducted studies are limited by a small number of cases and/ or a relatively short mean period of follow-up. [5,101,106,107,109-117]

The lack of good long-term follow-up is due to the rarity of the pathology and the relatively recent development of craniofacial surgery. The Sophia Children's Hospital in Rotterdam has been treating patients with rare facial clefts since the early seventies, when modern craniofacial surgery was introduced by professor van der Meulen and later on treatment of these conditions was taken over by Michiel Vaandrager. Since they were one of the first treating this pathology, many patients with rare facial clefts from the Netherlands and surrounding countries, as well as some patients from developing countries came to Rotterdam. It resulted in a relatively large population of patients with rare facial clefts who have been treated in Rotterdam. In addition the majority of patients have stayed under treatment during their whole childhood and adolescence, and it is easy to retrieve patients who are lost to follow-up since the Netherlands is a small country. All these factors make that good long-term follow-up is possible; better than in for example countries like Mexico.

Because of the need for more and better long-term follow-up of surgical treatment of rare facial clefts, and the unique population with rare facial clefts in Rotterdam, a study for evaluation of long-term surgical results was conducted. For evaluation of long-term surgical results, a measurement for objective assessment of the congenital facial deformities is necessary. Therefore a scoring list, which also took congenital facial malformations into account, was developed. The development and testing of this

measurement are described in **CHAPTER 3**. New details regarding influence of growth, techniques, timing and difficulties of the pathology, which were revealed by a long-term follow-up study of the oblique and paramedian facial clefts, are described in **CHAPTER 4**. In **CHAPTER 5** guidelines for the treatment of rare facial clefts in the midline are given, based upon long-term experience and follow-up of surgical results.

Consequences

In the presented patient surgical treatment improved satisfaction with his own facial appearance. Does his satisfaction with his facial appearance positively influence his psychosocial functioning? Despite the many operations, his facial appearance is still not completely 'normal'. Does the severity of the residual deformities play a role in the extent of the psychosocial problems? This patient has dealt with his deformity his whole life. Is coping with a facial deformity easier when it is acquired at an adult age?
These were all questions that rose when discussing this patient. It led to the formulation of several main topics:

1. Most patients sustain extensive surgery to improve their facial appearance. However, it is not known how satisfied they are with their own facial appearance after all these corrections.
2. Although one of the goals of treatment for these patients is to establish 'normal'functioning in daily life, it is fairly unclear how successful we are in doing so since assessment of long-term psychosocial impact has remained limited. This knowledge of the long-term psychosocial problems could enable us to give better, and more specific psychological support.
3. Having to deal with a severe facial deformity your whole life is a difficult and challenging task. Is their way of coping different from the way of coping in patients with a facial deformity acquired at an adult age?
4. There are individual differences; not all adult patients react in the same way upon their facial deformity and the treatment. Are there factors which determine the level of satisfaction with their own facial appearance, the extent of the psychosocial burdens or the way of coping? What is the influence of the fact that the facial deformity is congenital and not acquired at an adult age?

On some of these questions there are comments in literature; however there is a lack of good studies to support most of these comments. The majority of studies on psychosocial functioning of congenital facially disfigured people were performed in children and adolescents. In addition most studies were done in patients with a deformity

of a specific facial part (e.g. cleft lip). On top of that the majority of studies had a small sample size, a lack of use of standardized questionnaires or a suboptimal reference group. [96]

Patients with rare facial clefts encompass a variety of deformities from mild to very severe of all facial parts. The fact that almost none of the patients in this group are mentally retarded makes them a suitable study population for the evaluation of the long-term impact of having a severe congenital facial deformity.

To answer all the above questions, a clinical-empirical cross-sectional study consisting of standardized questionnaires and a semi-structured interview, was conducted in the group of adults with a rare facial cleft, a group of adults with facial disfigurement traumatically acquired at adulthood, and a group of adults without any facial disfigurement; these last groups were chosen to evaluate differences and as reference group. Since psychosocial functioning is a broad topic, a careful selection of measures was made. This selection was based on the degree of relevance for this population in combination with the topics of concern for this population mentioned in the literature. In **CHAPTER 6** the level of satisfaction with facial appearance of congenital and of acquired facially disfigured adults is evaluated. In addition, demographic, physical and psychological determinants of this satisfaction are examined. In **CHAPTER 7** social and relational functioning in adults with congenital facial disfigurement is assessed and compared with patients with acquired facial disfigurement. Moreover is explored to what extent dimensions of social and relational functioning are related to satisfaction with facial appearance (SFA), severity of the facial deformity (OS), fear of negative appearance evaluation by others (FNAE), and self-esteem (SE). The use of defense styles (subconscious coping) and the association with SFA, OS, FNAE, and SE are studied in **CHAPTER 8**. **CHAPTER 9** describes the impact of having a severe congenital facial disfigurement on long-term psychological functioning. Differences with the other groups and the relation with SFA, OS, FNAE, and SE are also evaluated.

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CAUSES

CHAPTER 2.1

Frontorhiny, a distinctive presentation of frontonasal dysplasia caused by recessive mutations in the ALX 3 homeobox gene

Twigg SR, **Versnel SL**, Nürnberg G, Lees MM, Bhat M, Hammond P, Hennekam RC, Hoogeboom AJ, Hurst JA, Johnson D, Robinson AA, Scambler PJ, Gerrelli D, Nürnberg P, Mathijssen IM, Wilkie AO

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Abstract

We describe a recessively inherited frontonasal malformation characterized by a distinctive facial appearance, with hypertelorism, wide nasal bridge, short nasal ridge, bifid nasal tip, broad columella, widely separated slit-like nares, long philtrum with prominent bilateral swellings, and midline notch in the upper lip and alveolus. Additional recurrent features present in a minority of individuals have been upper eyelid ptosis and midline dermoid cysts of craniofacial structures. Assuming recessive inheritance, we mapped the locus in three families to chromosome 1 and identified mutations in *ALX3*, which locates at band 1p13.3 and encodes the *aristaless*-related ALX homeobox 3 transcription factor. In total we identified 7 different homozygous pathogenic mutations in 7 families, comprising missense substitutions at critical positions within the conserved homeodomain, nonsense, frameshift and splice site mutations, all predicting severe or complete loss of function. Our findings contrast with previous studies of the orthologous murine gene, which showed no phenotype in *Alx3*$^{-/-}$ homozygotes, apparently owing to functional redundancy with the paralogous *Alx4* gene. We conclude that ALX3 is essential for normal facial development in humans and that deficiency causes a clinically recognisable phenotype, which we term frontorhiny.

Formation of the human face is an exquisitely orchestrated developmental process involving multiple tissue swellings – the frontonasal, medial and lateral nasal, maxillary and mandibular prominences – derived from neural crest. [1] During a critical period between 4 and 8 weeks of human fetal development, these processes must undergo cell proliferation and tissue fusion to form the orbital, nasal and oral structures. [1,2] Disturbance to this developmental sequence causes frontonasal malformation (FNM), a very heterogeneous group of disorders characterized by combinations of hypertelorism, abnormal nasal configuration, and oral, palatal, or facial clefting, sometimes associated with facial asymmetry, skin tags, ocular or cerebral malformations, widow's peak and anterior cranium bifidum. [3-9] Surgical management of FNM often poses substantial challenges.

Most cases of FNM are sporadic and no cause can be identified. However, disruption to development of the fetal face, caused by transient hypovolemia, haemorrhage into facial tissues, amniotic bands, or teratogens, is suspected to contribute to many cases. In addition a marked increase in frequency of monozygotic twinning (with discordance for FNM in the twins) has been noted, suggesting that the twinning process itself may sometimes precipitate the malformation. [10] Genetic causes of FNM are identified in only a minority of cases, with mutations of *EFNB1* (MIM 300035) in craniofrontonasal syndrome (MIM 304110) being the only consistent association. [11,12] No mutation of a specific gene(s) has hitherto been identified in isolated FNM.

We initially identified 3 individuals from 2 families (Subjects 1 and 2 in Family 1, and Subject 3 in Family 2) who shared a similar distinctive facial appearance (Figure 1A and C). Subjects 1 and 2 were siblings (male and female, respectively), born to parents who were not known to be related, but who originated from adjacent valleys in Morocco; the family history elicited from Subject 3, a sporadically affected male from Algeria, was imprecise, but distant parental consanguinity was indicated (Figure 2A). Ethical approval for genetic research and human embryo studies was obtained from the Oxfordshire Research Ethics Committee B (C02.143).

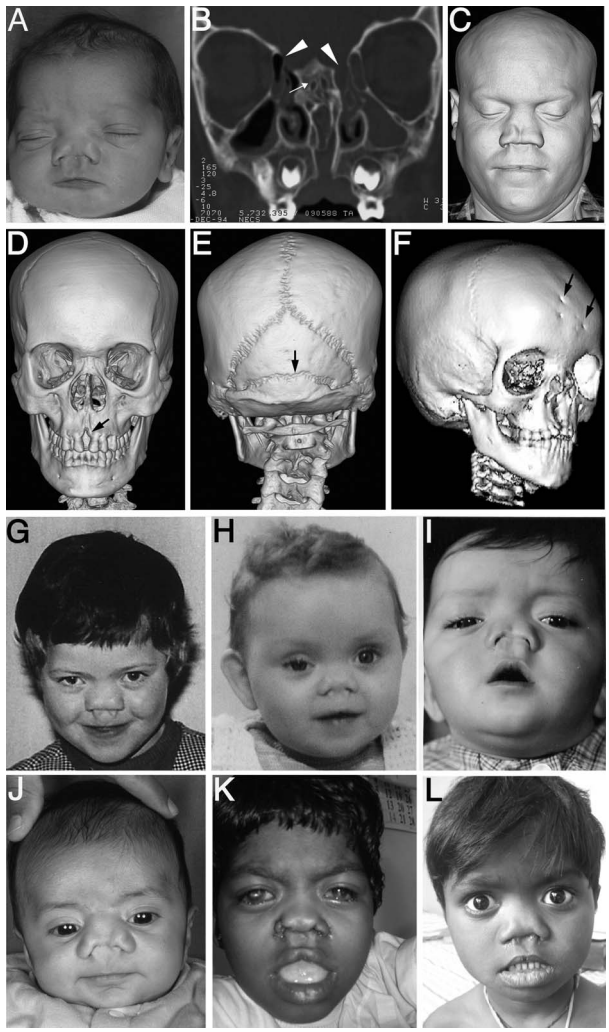


Figure 1. Phenotype of individuals with homozygous ALX3 mutations.

(A, B) *Subject 1. Facial appearance aged 2 days (A). Coronal CT section aged 6 years (B); note broadened dysmorphic ethmoid bone (arrow) and apparent continuities between nasal cavity and brain (arrowheads).* ***(C-E)*** *Subject 3, pre-operative 3-dimensional CT scan aged 30 years. Surface scan* ***(C);*** *anterior and posterior views (D and E respectively), note maxillary diastema (arrow, D) and patent sutures with accessory horizontal suture through the occipital bone (arrow, E).* ***(F)*** *Subject 5, 3-dimensional CT scan aged 5 years. Note maxillary diastema and 5 paramedian defects in frontal bone, corresponding in position to overlying tissue swellings, probably representing congenital dermoid cysts (arrows).* ***(G)*** *Subject 6, facial appearance aged approximately 6 years.* ***(H)*** *Subject 7, facial appearance aged 1 year.* ***(I)*** *Subject 8, facial appearance aged 2 years.* ***(J)*** *Subject 9, facial appearance aged 2 months.* ***(K)*** *Subject 10, facial appearance aged 4 years. The right eye is pthisical due to an infection.* ***(L)*** *Subject 11, facial appearance aged 2 years.*

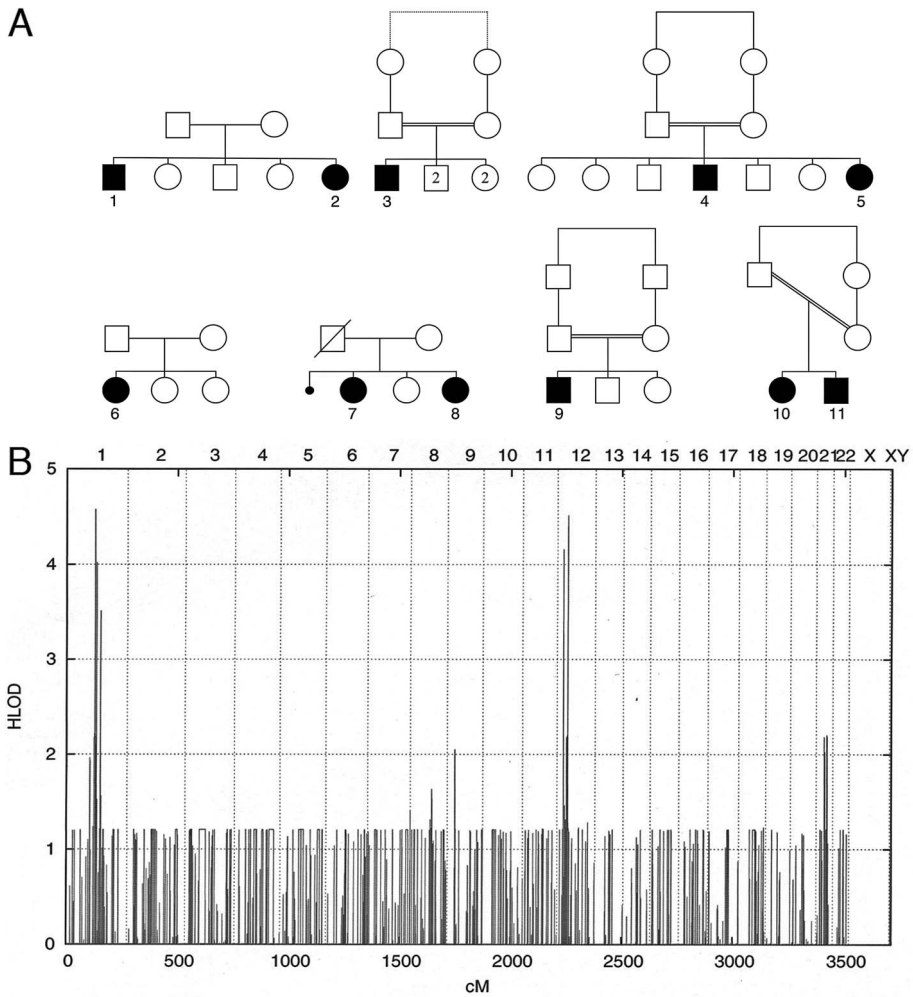


Figure 2. Pedigrees and disease localization.
(A) *Pedigrees of Families 1-7.* ***(B)*** *Whole genome linkage analysis of Families 1 and 2.*

Based on the hypothesis of a shared genetic etiology owing to inheritance of autosomal recessive mutations, we undertook a whole genome linkage analysis using the GeneChip® Human Mapping 250K Sty Array (Affymetrix) using samples from Family 1 (Subjects 1 and 2, both parents, and 3 unaffected siblings) and Subject 3. We assumed recessive inheritance with full penetrance, a disease allele frequency of 0.0001, and

that the parents of affected individuals in Families 1 and 2 were each related as 2nd cousins. Using ALLEGRO software [13] we identified two small regions of the genome that were homozygous in affected individuals and consistent with complete linkage, on chromosomes 1 (maximum heterogeneity LOD [HLOD] score 4.58) and 12 (maximum HLOD score 4.52) (Figure 2B). The chromosome 1 interval, bounded by SNPs rs558370 and rs17671169 that were heterozygous in Subject 3, encompassed 653 kb and 15 genes; the chromosome 12 interval, bounded by SNPs rs776195 and rs9988960 that were heterozygous in Subjects 1 and 2, encompassed 384 kb and 5 genes.

The chromosome 1 interval contained a strong candidate gene, *ALX3* (MIM 606014; related to the *aristaless* gene in *Drosophila*). This gene, located in band 1p13.3, encodes the ALX homeobox 3 transcription factor, a member of the Paired class of homeodomain proteins. [14] Previous studies of the murine orthologue, *Alx3*, had demonstrated strong expression in the frontonasal mesenchyme. [15,16] Although the phenotype of *Alx3*$^{-/-}$ mice was normal, a cleft face occurred when these homozygotes were additionally mutant for the paralogous gene *Alx4*. [16] We amplified each of the 4 exons of *ALX3* (primers and amplification conditions in Table S1) and subjected the products to DNA sequencing and confirmatory restriction digests. This showed that Subjects 1 and 2 were homozygous for a nucleotide substitution (595-2A>T) in the canonical 3' splice acceptor sequence of intron 2; Subject 3 was homozygous for a nucleotide substitution (608A>G) in exon 3, encoding an N203S missense mutation at a very highly conserved asparagine residue in helix III of the homeodomain that directly contacts DNA (Figure 3A, Table 1). [17]

We extended the analysis to additional patients with FNM (Figure 2A). Lees et al. [18] reported 2 siblings from a sibship of 7 (Subjects 4 and 5, Family 3) with a similar phenotype; analysis of samples from this family using the GeneChip® Human Mapping 10K Xba Array (Affymetrix) indicated that Subjects 4 and 5 were homozygous for a 15.9 Mb region on the short arm of chromosome 1, bounded by heterozygous SNPs rs10493874 and rs3908929, and including the *ALX3* gene (data not shown). Both affected individuals were homozygous for the mutation 502C>G in *ALX3*, encoding a L168V substitution in the homeodomain. We identified 4 further different mutations of *ALX3* (all homozygous) in 4 previously unpublished families (Subjects 6-11, Families 4-7) (Figure 3A, Table 1).

We either confirmed that the mutations were heterozygous in both parental samples using restriction digests (Table S1 details those cases where mutant oligonucleotide primers were employed in these digests), or used multiplex ligation-dependent probe amplification (MLPA) to demonstrate that the mutant allele was present in 2 copies in affected individuals (MLPA primers and conditions are listed in Table S2).

Table 1. *Mutation details and clinical features of subjects with ALX3 mutation*

Sample ID	Subject	Family no.	Sex[a]	Country of origin	Reported consan-guinity[a]	Exon (intron) no.	Nucleotide change (all homozygous)	Predicted amino acid change	Additional clinical features[a]
4143	1	1	M	Morocco	N	(2)	595-2A>T	*	Cleft palate, bony defect of anterior cranial fossa with recurrent meningitis
4144	2	1	F	Morocco	N	(2)	595-2A>T	*	Cleft palate, convergent squint
4150	3	2	M	Algeria	Y	3	608A>G	N203S	Accessory suture in occipital bone
4179	4	3	M	Ireland	Y	2	502C>G	L168V	R eyelid ptosis, strabismus, choanal stenosis, midline philtral pit connected to dermoid cyst
4180	5	3	F	Ireland	Y	2	502C>G	L168V	Lipoma of corpus callosum, paramedian frontal bone cysts, midline philtral pit connected to dermoid cyst
4254	6	4	F	Netherlands	N	2	547C>T	R183W	R iris coloboma, orbital dystopia
4252	7	5	F	Netherlands	N	2	543T>A	Y181X	R ptosis, scoliosis
4251	8	5	F	Netherlands	N	2	543T>A	Y181X	R ptosis, lumbar lordosis
4295	9	6	M	Turkey	Y	2	578_581delCTGA	T193RfsX137	-
4291	10	7	F	India	Y	2	586C>T	R196W	Rugosity behind external ears
4292	11	7	M	India	Y	2	586C>T	R196W	Bifid tongue, rugosity behind external ears

** splice site mutation. [a] Abbreviations: F, female; M, male; N, no; R, right; Y, yes.*

Table S1. *Primers and amplification conditions for DNA sequencing (ALX3, ALX4 and ALX1) and mutation confirmation (ALX3).*

	Primer sequence 5' → 3'		**Product size (bp)**	**Amplification conditions**
Primer	**Forward**	**Reverse**		
ALX3-1	GGATGGTTCCAGCATTAAGTCAGAG	AGGGGCAAAAAGTTGAGAAATAGGC	422	+ DMSO
ALX3-2	CAAAAGCCCCTGGTTCAGTTGCCATCCTCCC	CCAGATCACTTTCTGGTCACTGTGT-GATAGGGG	437	63°C
ALX3-3	CCCTAGCAGGCTCCTTTCCTCAGGGCTGCCC	CGCTCTCCAGGTTTCTTCAGGCCAGACCTC	280	63°C
ALX3-4	GGGTAGGGAAGTCAGCTCCTGAGGCTA-CAGG	GAGGTGGGCAGCTCATTCTGCAGGTC-CATGC	411	63°C
ALX4-1	AGCCTCCTCGCCTCCCCAAACTCCCAGCC	CCCCAGCACCAGGTGACCCGCACGTGCAC	594	+ DMSO
ALX4-2	CCCCCTGACATTCCCCTTCTCTT	GCTTTACCAGCCTCACTCCCAGGT	417	63°C
ALX4-3	GGGAACAGTTTGCACTGCCTGAA	CTCCTCCAAGGGGCTCATTCTCCA	283	63°C
ALX4-4	GAGCCCCTTCCACACCACACCT	AAACATGGGCGTGGCCCATGGTGTCCC	445	63°C
ALX1-1	GTTTCTGTGCCCCAGGAGCTACGCGACAG	CTCCCTCCCTGCCTGATCAGACCGATCC	352	63°C
ALX1-2	GAGATGAGTTTCACAATCCTGAGAACTGTTG	CAAAATGCACTTATTCAATTATTCTAACACC	434	63°C
ALX1-3	GGGAAAATCACTTACCACATCAAGATACAAG	CAAACCAAATATCCTTTTCTTGATCAGTATTC	368	63°C
ALX1-4	CAGACCACCCAATAGGAGCAAACAATGAAT-AG	CTGGTCTCACTGAATATCTTGACCTTTAGC	573	63°C

Table S1. *Continued*

Mutant oligonucleotide/digests for *ALX3* mutation confirmation				
Subjects 1 and 2				
*Bst*XI digest	GTGATTCAACCTGGGGAGTGACAGCTG-GAGG	GCTTCCGCCACTTGGCTCTGCGGTTCTG-GCCACAGACC	285	63°C
Subjects 4 and 5				
*Alw*NI digest	CGTAACCGCACGACCTTCAGCACATTC-CAGCTGGAGGAG	CCAGATCACTTTCTGGTCACTGTGT-GATAGGGG	200	63°C
Subjects 7 and 8				
*Bst*API digest	GGAGAAGGTCTTCCAGAAAACCCACTATCCT-GCAGTGTA	CCAGAAGAGCCTGTGGCTGCAGCAGAGC	281	63°C

Note.– DNA was obtained from whole blood samples by phenol-chloroform extraction and was amplified in a total volume of 25 µl containing 15 mM TrisHCl (pH 8.0), 50 mM KCl, 2.5 mM $MgCl_2$, 100 µM each dNTP, 0.4 µM primers, and 0.5 units of Amplitaq Gold polymerase (Applied Biosystems) with or without 10% dimethylsulfoxide (DMSO). Cycling conditions consisted of an 8 min denaturation step at 94°C, followed by 35 cycles of 94°C for 30 s, 63°C for 30 s and 72°C for 30s, with a final extension at 72°C for 10 min, unless DMSO was included in the reaction in which case the following cycling was used: 94°C for 8 min, followed by 14 cycles of 94°C for 30 s, 64°C for 40 s with a 0.5°C decrease every cycle, 72°C for 60 s and then 25 cycles of 94°C for 30 s, 58°C for 30 s and 72°C for 1 min, with a final 10 min extension at 72°C. Mutation confirmation in Subjects 1, 2, 4, 5, 7 and 8 was carried out by PCR using the above conditions and indicated mutant primers, followed by restriction digest of 8 µl of PCR product.

Table S2. *MLPA probes for dosage analysis of ALX3, ALX4 and ALX1.*

			Primer sequence 5' ⊠ 3'	
Size (bp)	**Gene**	**Exon**	**5' probe sequence**	**3' probe sequence**
87	*ALX3*	1	gggttccctaagggttggaGCCCTCAACGGCGGCCACTTCTA	CGAGGGCCCCGCGGAAGGTAAGtctagattggatcttgctggcac
90	*ALX4*	2	gggttccctaagggttggaGAGCTCCCTGGGTGAGCCAGAGTT	ACCCCCTGACTCTGACACTGTGGGtctagattggatcttgctggcac
93	*ALX4*	1	gggttccctaagggttggaGCATTTCCCGGAGGCGACAAGTTCG-GCACAACT	TTCCTGTCGGCCGCCGCCtctagattggatcttgctggcac
97	*ALX1*	1	gggttccctaagggttggaGGAGCTACGCGACAGTCTTCCAG-GATT	ATGGAGTTTCTGAGCGAGAAGTTTGCCCtctagattggatcttgctg-gcac
101	*ALX4*	3	gggttccctaagggttggaGAAGGGCCAAGTGGAGGAAGC-GGGAGCGTTT	TGGGCAGATGCAGCAGGTTCGAACCCACtctagattggatcttgctg-gcac
109	*ALX3*	2	gggttccctaagggttggaCGGAGAAGGTCTTC-CAGAAAACCCACTAT	CCTGATGTGTATGCCCGGGAGCAGCTGGCCCTGCGCACtc-tagattggatcttgctggcac
113	*ALX3*	3	gggttccctaagggttggaGGAACCCCTTCACGGCTGCCTATGA-CATCTCTGTG	CTGCCCCGTACTGACAGCCACCCTCAGGTAAGACCCtctag-attggatcttgctggcac
117	*ALX1*	2	gggttccctaagggttggaCAGAGAAGGGAGAGCTGGAT-GAACTTGGGGATAAATGTGATAGCAATGT	ATCCAGCAGTAAGAAACGGAGGCACCtctagattggatcttgctggcac
121	*ALX1*	3	gggttccctaagggttggaCGGAGAAAAAGGGAACGTTATGGC-CAAATACAACAAGC	GAAAAGCCATTTTGCTGCCACCTATGATATATCAGTTTTGCtc-tagattggatcttgctggcac
129	*ALX3*	4	gggttccctaagggttggaGGCCTTCTGAACTGGACCACGT-GATCGGTTGCATGGACCTGCAGAATGAGCTGCCCA	CCTCTTTTTCCATTCCCAGTCGCTCCCAGCtctagattggatcttgctg-gcac
133	*ALX4*	4	gggttccctaagggttggaGTGGAGAAAGCCAGGTGGCCAC-GTTTTTCAGCTTCGCATCCATGATA	AGCTGAAAGCGCTTTCTTGCTCCCGCCCACTCCTCTGCTCT-GCCtctagattggatcttgctggcac
137	*ALX1*	4	gggttccctaagggttggaGAAAAGACTAAATAGGTTTACCATGT-GCCAGTCTCCACAAACCCTGTTTT	AGTAGTAAGGTTTTCTTTTTCTATTGTACAAGTCAAT-GAAATATGtctagattggatcttgctggcac

Note. –Multiplex-ligation-dependent probe amplification was performed using synthetic oligonucleotide probes designed to each exon of ALX3, ALX4 and ALX1 and 3 previously characterized control loci, see MRC-Holland: http://www.mrc-holland.com/pages/indexpag.html. Fragments were analysed by capillary electrophoresis using an ABI 3130 containing POP-7 polymer. Peaks were visualized using Gene Mapper v3.7 (Applied Biosystems). Common PCR primer annealing sequences are shown in lower case, hybridizing sequences are shown in upper case and the 3′ probe sequence is 5′ phosphorylated.

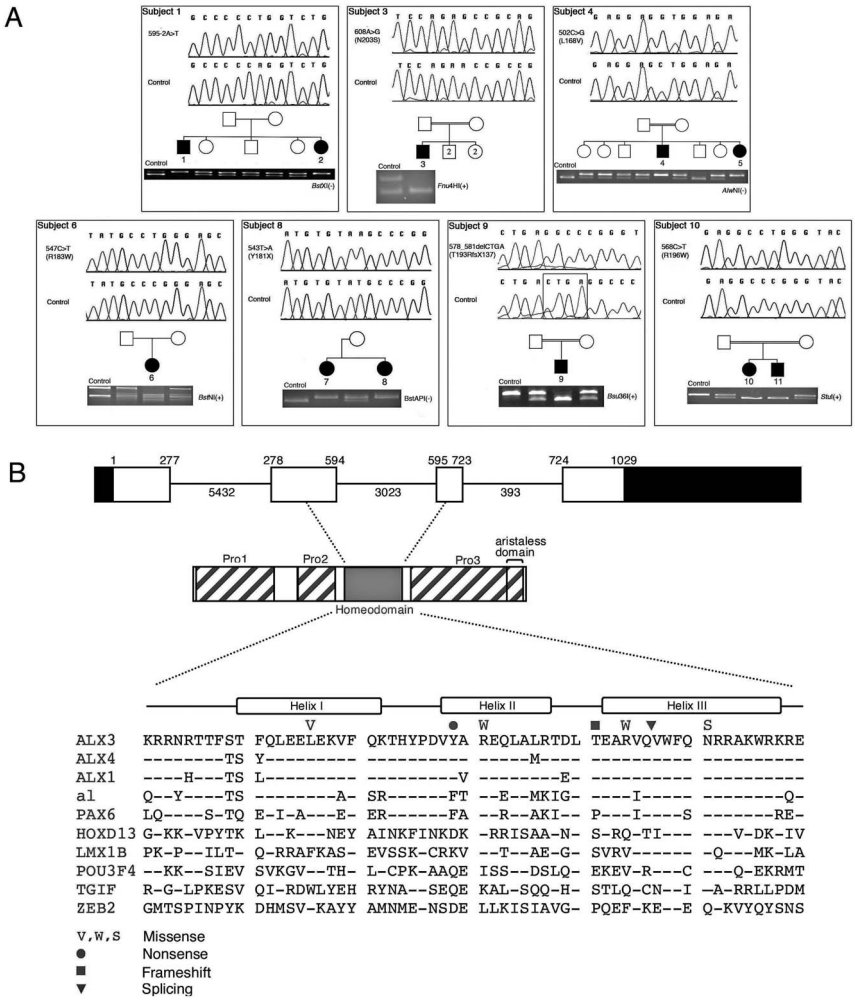


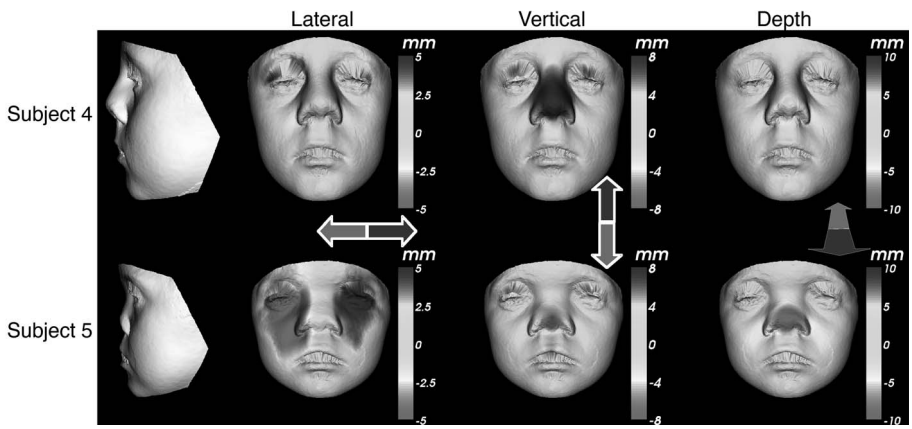
Figure 3. Mutations identified in the ALX3 gene. ***(A)*** *DNA sequence chromatograms (above) and confirmatory restriction digests (below) of the 7 different mutations identified in this work.* ***(B)*** *Cartoon showing (top) genomic organization of ALX3 (numbers above boxes indicate cDNA numbering at exon boundaries, numbers below lines indicate intron sizes), and (middle) domain organization of protein. [19] At bottom is shown the position of individual mutations within the homeodomain of ALX3, compared with other proteins from the Paired class (human ALX4 and ALX1, Drosophila al, human PAX6) and representative examples of increasingly divergent human homeodomain proteins from the other major classes (HOXD13, ANTP class; LMX1B, LIM class; POU3F4, POU class; TGIF, TALE class; ZEB2, ZF class). [20] Dashes indicate residues conserved with respect to human ALX3.*

Although the second linkage signal initially observed on chromosome 12 raises a possible requirement for the digenic inheritance of mutations, both the high rate of phenotype recurrence in siblings (Figure 2A) and the absence of unaffected siblings homozygous for *ALX3* mutations (Figure 3A) argue against this; more likely, the chromosome 12 signal represents a type I error. The genotyping identified 18 individuals heterozygous for an *ALX3* mutation (Figure 3A), none of whom exhibited unusual facial features suggestive of a manifesting carrier state.

The mutations are all consistent with severe or complete loss of DNA binding by the mutant ALX3 protein. The nonsense (543T>A; Y181X), frameshift (578_581delCTGA; T193RfsX137) and acceptor splice site (595-2A>T) mutations are predicted to lead to loss of the DNA-binding helix III of the homeodomain, suggesting complete loss of function (Figure 3B). The other mutations are missense substitutions that occur at some of the most highly conserved residues within the 60 amino acid DNA-binding homeodomain; multiple missense mutations causing loss of function have been reported previously at the equivalent residues of other homeodomain transcription factors. [21,22] The L168V substitution occurs at position 16 in helix I of the homeodomain; this leucine residue, which is conserved in the Paired class, and several other classes of human homeodomain, [20] is buried in the hydrophobic core; [22] an L132V substitution at the equivalent position of the SHOX (MIM 312865) homeodomain showed very weak DNA binding and loss of dimerization. [23] The R183W substitution occurs at position 31 in helix II; this arginine residue is highly conserved in the Paired class, and several other classes of homeodomain, [20] and forms a buried salt bridge with glutamate at position 42 that contributes to the structural integrity of the homeodomain. An equivalent mutation (R298W) was previously described in the homeodomain of HOXD13 (MIM 142989); in vitro studies of several different substitutions of the position 31 arginine have shown severe or complete loss of DNA binding. [24] The 586C>T (R196W) substitution occurs at position 44 in helix III. Although not very highly conserved across homeodomains as a whole, this arginine residue is a common feature in the Paired class, [14] making contact with the paired domain of the protein, as well as DNA. [25] A mutation (R141G) at the equivalent position of the Paired class homeodomain of PHOX2B (MIM 603851) was shown to abolish DNA binding. [26] Finally, the N203S substitution occurs at the position 51 asparagine; this residue directly contacts an adenine base in bound DNA and is one of the most highly conserved residues in the entire homeodomain. [17] Mutations of this asparagine to serine in several different homeodomain-containing proteins showed severely reduced DNA binding. [27] None of the mutations that we

identified was present in the DNA sequences of a minimum of 226 unrelated control chromosomes of north European origin.

We used dense surface modelling [28] to analyse objectively the abnormal facial morphology in Subjects 3, 4 and 5. Whilst this consistently demonstrated maximal tissue deficiency in the midfacial region around the nose and philtrum, the degree of hypertelorism and mid-face hypoplasia was much more marked in Subjects 5 and 3 (not illustrated) compared with Subject 4 (Figure 4). In contrast, Subject 4 showed significant upward displacement of the nose and, to a lesser extent, of the supraorbital region (Figure 4; these differences are also demonstrated in the dynamic morphs in Supplementary videos V1 and V2). These findings and the clinical features are consistent with embryonic tissue disturbance predominantly affecting the frontonasal and medial nasal prominences; [1] the relatively high prevalence of congenital dermoid cysts is consistent with disturbance of fusion of the medial nasal prominences leading to buried ectodermal components.



Figurre 4 Dense surface modelling analysis of Subjects 4 and 5. *Subject 4 (above, postoperative after insertion of nasal silastic strut, aged 10 years) and Subject 5 (below, prior to nasal augmentation, aged 5 years) were compared, in terms of lateral, vertical and depth displacement, to average faces of appropriately age/sex matched controls. Green regions coincide on both patient and average face. Red (blue) regions correspond to displacement of regions of the subject's face right/down/in (left/up/out) more extreme than the scale minimum (maximum). Intermediate colours correspond to displacements on the scale shown. Note that Subject 5 has greater hypertelorism and mid-facial hypoplasia than Subject 4.*

To explore the phenotypic range of *ALX3* mutations, we undertook DNA sequencing of *ALX3* in 14 additional unrelated individuals with various FNMs including 1 reported with possible Pai syndrome (MIM 155145), [29] 1 with oculoauriculofrontonasal syndrome (MIM 601452), [30] 3 with acromelic frontonasal dysostosis (MIM 603671), [31,32] and 9 with miscellaneous combinations of hypertelorism, facial tags, and facial clefting; [6] none of these individuals exhibited *ALX3* mutations. DNA sequencing of *ALX3* in 93 patients with non-syndromic cleft lip and/or palate also gave normal results.

We conclude that the phenotypic range from homozygous loss-of-function of ALX3 appears narrow, and is characterized by the distinctive facial appearance shown in Figure 1; no genotype-phenotype correlation is apparent. The major features characterizing this disorder are hypertelorism, wide nasal bridge, short nasal ridge, splayed nasal bones with bifid nasal tip, broad columella that attaches to the face above the alae, widely separated slit-like nares, long philtrum, prominent philtral ridges sometimes with additional bilateral swellings that run into the nares, and midline notch in the upper lip and alveolus. Additional features present in some patients were upper eyelid ptosis (3 subjects), inclusion dermoids of craniofacial structures, philtral pits or rugose folding behind the ears (2 subjects each), and iris coloboma, strabismus and lipoma of the corpus callosum (1 subject each). Review of skull radiographs or computed tomographic (CT) scans of 5 subjects (1, 3, 5, 6, 8) did not show craniosynostosis; an accessory suture in the occipital bone was present in Subject 3 (Figure 1C). Of clinical significance, Subject 1 had 6 episodes of pneumococcal meningitis, which were associated with rhinorrhea of cerebrospinal fluid and found to be related to multiple defects in the cribriform plate of the ethmoid bone (Figure 1A); Subject 5 had several subcutaneous swellings on the forehead, associated with paramedian foraminae in the frontal bone suggestive of dermoids (Figure 1D). Growth and development have been normal in all subjects, however all have required surgical procedures for improved appearance and function. These have included multiple nasal reconstructions (involving 12 and 13 separate procedures, respectively, in Subjects 8 and 7), ptosis correction (Subjects 6, 7, 8), strabismus correction (Subject 2), excision of dermoid cysts (Subjects 4, 5), cleft palate repair (Subjects 1 and 2), midline cleft lip repair (Subject 5), Le Fort I advancement of maxilla (Subjects 1, 6), Le Fort III advancement and medialization of orbits (Subjects 1, 7) and repair of the anterior cranial base defect and nasal airway reconstruction (Subject 1).

The craniofacial phenotype associated with *ALX3* mutations seems to represent a poorly recognized clinical entity. Subjects 4 and 5 were previously reported, [18] but similar patients are not illustrated in any of the literature classifying the diverse

presentations of FNM. [3-9] Lees et al. [18] drew attention to the resemblance of their siblings to a unique family with a phenotype named craniorhiny (MIM 123050). [33] Although it has not been possible to trace the originally reported craniorhiny family for genetic analysis, three considerations argue that the *ALX3* mutation-positive subjects have a different condition. First, there is differing facial morphology in craniorhiny, with nasal outgrowth being much better preserved; second, craniosynostosis was observed in several individuals with craniorhiny, but is not documented in association with *ALX3* mutations; third, vertical transmission suggesting dominant inheritance was described in craniorhiny, [33] whereas *ALX3* mutations exhibit recessive inheritance. The nasal appearance in our subjects is reminiscent to the family reported by Fryburg et al. (MIM 305645), [34] but the phenotype in that family also showed vertical transmission. A possible match is the proband in the report by Toriello et al. (MIM 164000), [35] who shows a similar nasal appearance to Subject 7, was the offspring of a consanguineous union and had white Dutch ancestry, like Subjects 6-8 in our series. Otherwise, our attempts to identify patients in the literature matching those reported here have, surprisingly, failed. Hence to our knowledge this is a new genetic syndrome of FNM for which we suggest the name frontorhiny. Whilst acknowledging the mixed etymological origin of this term, we believe that it best encompasses the characteristic combination of frontal and nasal malformations in affected individuals (Figures 1 and 4) and the clinical overlap with previously described craniorhiny. [18,33]

As previously noted, *Alx3*$^{-/-}$ mice are phenotypically normal, indicating a greater requirement for ALX3 in development of the frontonasal region in the human compared to the mouse. However both *Alx3* and the paralogous gene *Alx4* are expressed in the frontonasal mesenchyme at embryonic days (E) 9.5-11.5 in the mouse, and mice mutant for three alleles of these 2 genes (either *Alx3*$^{-/-}$;*Alx4*$^{+/lst\text{-}J}$ or *Alx3*$^{+/-}$;*Alx4*$^{lst\text{-}J/lst\text{-}J}$) exhibit facial clefting. [16] This was correlated with increased apoptosis of the developing frontonasal mesenchyme at E10.0, suggesting that the primary defect in combined Alx3/Alx4 deficiency is failure to support normal cell survival in part of the frontonasal process during a critical period of development. In humans, heterozygous mutations of *ALX4* (MIM 605420) cause parietal foramina (PFM2 [MIM 609597]). [36,37] We confirmed by DNA sequencing and MLPA (Tables S1, S2) that there were no mutations or deletions of either *ALX4* or the paralogous *ALX1* gene (MIM 601527; previously termed *CART1*) [38] in the *ALX3*-mutated individuals.

We attempted to compare the expression patterns of *ALX3* and *ALX4* in the frontonasal prominences of human embryos. We were unable to obtain signals above background for *ALX3*, but we observed apparent expression of *ALX4* in the medial nasal

processes of an embryo at Carnegie stage 16, equivalent to ~37 days post fertilization (Figure S1). This excludes a mechanism whereby the abnormal frontonasal phenotype in humans lacking ALX3, compared to mice, is simply attributable to a complete lack of ALX4 expression in the medial nasal process of the human embryo, thus making it entirely dependent on ALX3 expression. Our analysis does not however exclude a more subtle effect involving the relative timing and levels of ALX3 and ALX4 in the developing facial structures.

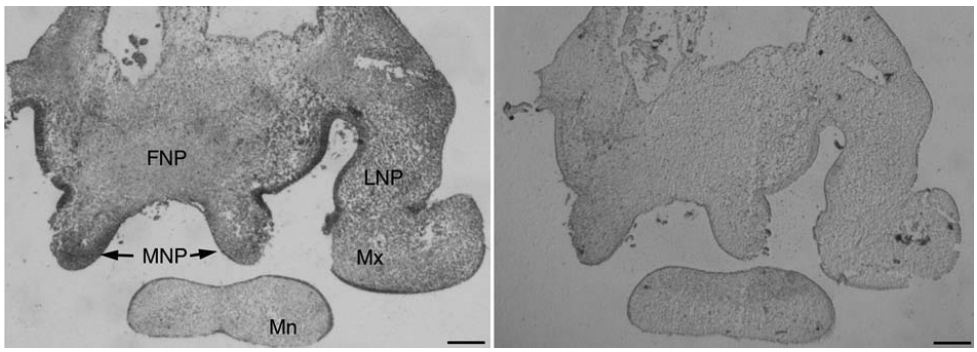


Figure S1. *In situ hybridization analysis of ALX4 in a human embryo at Carnegie stage 16. Coronal sections at the level of the frontonasal process hybridized to an ALX4 antisense probe (left panel) and control ALX4 sense probe (right panel). Arrows in the left panel indicate areas of signal in the medial nasal process. FNP, frontonasal process; MNP, medial nasal process; LNP, lateral nasal process. Mx.maxillary process; Mn, mandibular process. Scale bar: 0,2mm.*

Note. – In situ hybridization analysis of ALX4 was performed, with ethical approval, in human ebryos obtained from the Human Development Biology Resource. Embryos were dissected and fixed in 4% paraformaldehyde, then dehydrated and embedded in paraffin wax. Sections of 7um were cutusing a standard microtome and mounted on Superfrost Plust sides (BDH, Poole, UK). In situ hybridization were performed exentially as described by Wilkinson (Wilkinson DG. In situ hybridization: a practical approach. Oxford University Press, 1992) using digoxidgen in incorporated led riboprobes generated from a pGEM-T Easy vector containing 1294 bp of ALX4 cDNA sequence (nuclectides 1126-2421 numbered from ATG initiation codon, corresponding to 109 bp 3' coding sequence and the remainder 3'untranslated sequence, Genbank accession numbers NM_021926 and AB058691). For antibody detection, slides were incubated with antidigoxigenin antibody conjugated with alkaline phosphatase (diluated 1:1000, containg 2% tetal calf serum). Expression patterns were visualized using the nitro-blue tetrazollurn chloride/5-brorno-4-chicro-3'-indolyphosphat p-toluidine salt saystem (Roche, Welwyn Garden City, UK). Sections were mounted in VectaMount (Vector Laboratories, Burlingarne, CA) and analyzed using a Leica MZFLIII microscope (Leica Microsystems, Milton Keynes, UK) and Openlab software (Perking Elmer, Coventry, UK).

In conclusion, we have identified a recurrent pattern of FNM that is caused by recessive mutations in the homeobox gene *ALX3*. This is the first isolated FNM shown to have a specific genetic etiology, as opposed to arising from a prenatal developmental insult. It is important to recognize this disorder, for which we propose the term frontorhiny, because of its specific implications for diagnostic testing and genetic counselling, and association with congenital dermoid cysts with the potential for transcranial extension. Our work also illustrates the power of homozygosity mapping for identifying rare recessive disease genes using very few samples of uncertain consanguineous origin. [39]

Supplemental Data

Supplemental data comprise two videos and can be found with this article online at http://www.ajhg.org/.
(Video V1 Dynamic morph from average age/sex matched control to Subject 4
Video V2 Dynamic morph from average age/sex matched control to Subject 5)

Acknowledgments

The authors declare no conflict of interest affecting this work. We are very grateful to M. Cunningham, A. Hing, R. Newbury-Ecob, and S. Robertson for additional patient samples analysed in this study, to C. Becker for SNP chip processing, to K. Clarke for DNA sequencing, to M. van den Elzen for help with data collection, to P. Stanier for collaboration on analysis of cleft lip/palate samples and to N. Akarsu for discussions. Human embryonic material was provided by the MRC/Wellcome Trust-funded Human Developmental Biology Resource. This work was supported by the Wellcome Trust (Programme Grant to A.O.M.W.).

Web Resources

Accession numbers and URLs for data presented herein are as follows:

- dbSNP, http://www.ncbi.nlm.nih.gov/SNP/
- GenBank, http://www.ncbi.nlm.nih.gov/Genbank/index.html (for human *ALX3* cDNA reference sequence, accession number NM_006492.2)
- MRC-Holland, http://www.mrc-Holland.com/WebForms/WebFormMain.aspx?Tag=fNPBLedDVp38p\CxU2h0mQ|| (for information on MLPA reagents and methods)
- Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim

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CHAPTER 2.2

Another family with frontorhiny

Twigg SR, Wilkie AO, **Versnel SL**, Mathijssen IMJ

Cleft Palate Craniofac J. 2010 Jul;47(4):430

Letter to the Editor

Sir,

We read with interest the recent report by Rizvi et al. (2010) [1] describing three siblings with median facial clefts, including hypertelorbitism, broad nasal root, cleft of the nose, median cleft of the upper lip, and primary telecanthus. Although the authors suggested that this was caused by "probable" autosomal or X-linked dominant inheritance, the occurrence in siblings of both sexes, with unaffected parents, is much more suggestive of autosomal recessive inheritance.

In May 2009 we described a newly defined autosomal recessive syndrome, which we termed frontorhiny, characterized by a distinctive facial appearance with hypertelorism, wide nasal bridge, short nasal ridge, bifid nasal tip, broad columella, widely separated slit-like nares, long philtrum with prominent bilateral swellings, and midline notch in the upper lip and alveolus (Twigg et al. 2009). [2] Homozygous loss-of-function mutations of *ALX3*, encoding the aristaless-related ALX homeobox 3 transcription factor, were identified in all seven families analyzed.

The facial features of the individuals illustrated in the report by Rizvi et al. (2010) bear a striking resemblance to those that we observed in our series of patients with frontorhiny, and the pedigree of their family suggests autosomal recessive inheritance. We would like to suggest that molecular genetic testing of *ALX3* is indicated in this family, and that this would very likely reveal diagnostic mutations in this gene.

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TREATMENT

CHAPTER 3

Measuring surgical outcomes in congenital craniofacial surgery: an objective approach

Versnel SL, Wolvius EB, van Adrichem LN, van der Meulen JN, Ongkosuwito EM, Mathijssen IM

J Craniofac Surg. 2007 Jan;18(1):120-6.

Abstract

Assessment of surgical outcome in congenital craniofacial malformations is necessary to evaluate treatment efficiency since the results of early surgery are influenced by surgical technique and timing. Available outcome measurements all have their limitations, especially for application in congenital craniofacial malformations. Therefore a new outcome measurement was developed, in which each facial unit is scored in a standardized way. For each facial unit, deformities of shape or contour, malposition and soft tissue involvement were evaluated, besides scoring for specific congenital malformations of that area. The final result was tested on pre- and post-operative photographs of patients with rare facial clefts and reliability and validity were demonstrated. The new developed instrument showed the ability to provide quantification of outcome. Because of its properties it can serve as an instrument to compare outcome between techniques, surgeons and centres in a more objective and standardized way.

Introduction

Congenital craniofacial malformations comprise a vast spectrum of diverse cranial and facial deformities that often require complex surgery. The objective of treatment is to create a more normal appearance and restore function. For both functional and psychological indications surgical correction is often undertaken at a very young age. Since the results of early surgery are influenced by surgical technique and timing, a long-term evaluation of surgical outcome is necessary to assess treatment efficiency: To what extent are we able to provide our patients with a more 'normal' appearance with the used techniques?

Although outcome research has become important in medicine, literature on surgical outcome in the field of congenital craniofacial surgery has remained limited. [1] Publications on outcome measurement in aesthetic surgery and cleft (lip-palate) surgery are better represented. They describe two ways of assessment of surgical outcome. Firstly, subjective measurement, like a VAS (Visual Analogue Scale) score on facial attractiveness or facial impairment given by the patient or a panel, is one method of outcome assessment. [2-4] In literature diverse rating systems, numerous compositions of panels and different definitions of outcome are used which makes it difficult to reach consensus and compare results. In general, these articles on subjective surgical outcome state that there is a need for an internationally accepted, standardized objective method to assess surgical outcome. [5,6]

The second method of assessment is objective measurement, like anthropometry. Anthropometry is the oldest and most often used method, especially in evaluation of cleft patients [7-9] and in a few occasions in outcome assessment of aesthetic surgery and facial aging. [10-13] It is objective, but covers only a small range of the pathology as it doesn't take the actual condition of the soft tissue into account, such as coloboma of the eyelid or scars. Especially in congenital craniofacial deformities this poses problems and leads to insufficient assessment. Moreover, there is the problem of altered facial landmarks in congenital deformities, which complicate anthropometric measurements.

Strasser presented a new grading system for objective assessment of surgical outcome in cosmetic surgery, not founded on anthropometry. [14,15] This method is based on the measurement of physical imperfections that are categorised in five headings: malposition, distortion, asymmetry, contour deformity and scar. Although this method is the most comprehensive one since it enables us to measure multiple aspects of facial outcome, it still has its limitations for use in outcome assessment of congenital craniofacial deformities: it doesn't address the specific congenital abnormalities.

Furthermore the distinction that is made between 'noticeable' and 'obvious' in scoring makes the level of objectivity of this method debatable and reliability was not tested.

In conclusion, looking at the available outcome measurements there is a lack of a good instrument for outcome measurement of surgical treatment of congenital craniofacial malformations. There is need for a new objective assessment method for surgical outcome of the total face in these patients. Therefore the current study was performed with the purpose to establish a new instrument through which comparison of operative techniques and quantification of outcome will be possible in the most standardized and objective way.

Here we present our new method for outcome measurement and demonstrate its reliability and validity by testing it on a group of patients with rare facial clefts.

Materials and Methods

Since we are interested in residual deformities after correction of congenital craniofacial malformation, we aimed at measuring impairment of facial anatomical structures. The classification of the World Health Organisation defines impairment as one of the consequences of disease. [16] Strasser's grading system, assessing physical imperfections, can be extrapolated to a measurement for impairment of anatomical structures and is therefore taken as guideline. This list contains five points of attention (malposition, distortion, asymmetry, contour deformity and scars) that were used as starting point and expanded by adding all possible congenital deformities that can occur in a face. The face was divided in several units: forehead including glabella, orbital/peri-orbital zone (2x), nose, mouth/peri-oral region, cheeks/maxilla (2x), chin/mandible (2x). Within each unit a distinction was made between subunits. For the nose we applied regular aesthetic facial units. [17] The other units received a practical subdivision, except for the cheek and chin. (For details see Figure 1)

All facial impairment items including the specific congenital deformities were attributed to each relevant unit. This list was tested and adjusted several times by trial and error to simplify it and some guidelines were added. Introduction of the items shape and soft tissue appeared to be necessary. Because scoring of certain deformities such as heminasal aplasia encompasses malposition, contour deformity and distortion, the item shape was introduced to replace these three items. In the subunit orbit the item malposition was kept as separate item for assessment of orbital dystopia. In the subunits forehead, cheek and chin the distinction between contour deformity and distortion

caused confusion and disagreement in scoring and were therefore joint under contour deformity. For the same reason contour deformity, distortion and malposition of the eyebrow were joint. Introduction of the item soft tissue was necessary to be able to score dysplastic skin present in congenital deformities.

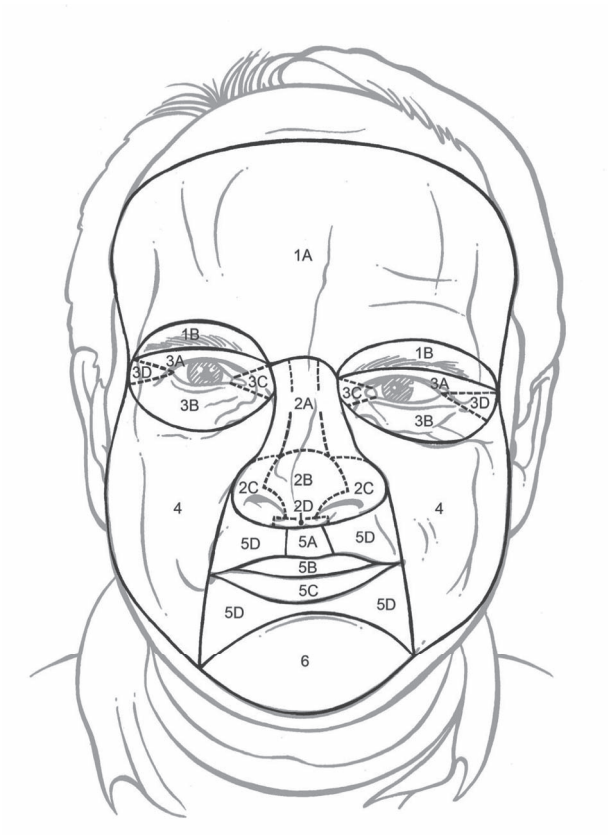

Figure 1. *Facial units and subunits: 1. Forehead/ Glabella (1A Forehead, 1B Eyebrows); 2. Nose (2A Dorsum, 2B Tip, 2C Ala , 2D Columella); 3. Orbital/ Peri-orbital (3A Upper eyelid, 3B Lower eyelid, 3C Medial eyecorner/ canthus, 3D Lateral eyecorner/ canthus); 4. Cheek/ Maxilla; 5. Mouth (5A Philtrum, 5B Upper lip, 5C Lower lip, 5D Peri-oral); 6. Chin/ Mandible.*

Four guidelines were drafted for specific situations. 1) If an aberrant, but not specific deformity of the shape of the orbital/peri-orbital zone is present, like an underdeveloped

lateral orbital wall, this is scored under the item shape as "other". 2) Dystopia of medial/lateral eye corner and eyebrow is not scored separately when there is vertical dystopia. 3) Scoring of a cleft pre-operatively implicates scoring of both contour deformity and dysplastic soft tissue of the involved facial parts. 4) Scoring of heminasal aplasia, implicates scoring of dorsum, tip, ala (unilateral), columella and proboscis (if present).

Two raters performed the testing by grading pre- and postoperative photographs of patients with rare facial clefts. This specific patient group was chosen for its broad range of deformities involving the whole face, making an analysis of most items in the list possible. Ethical approval for conducting this study was granted from the Erasmus Medical Centre Rotterdam local ethics committee.

Scoring of scars within each subunit was subdivided in 'along borders of facial unit' and 'outside borders of facial unit'. Each scored item received 1 point if unilaterally and two points if bilaterally present. The only exception was a scar outside the borders of a facial unit which was graded with 2 points while those along the borders received 1 point. In figure 2, 3 and 4 the method of scoring is demonstrated.

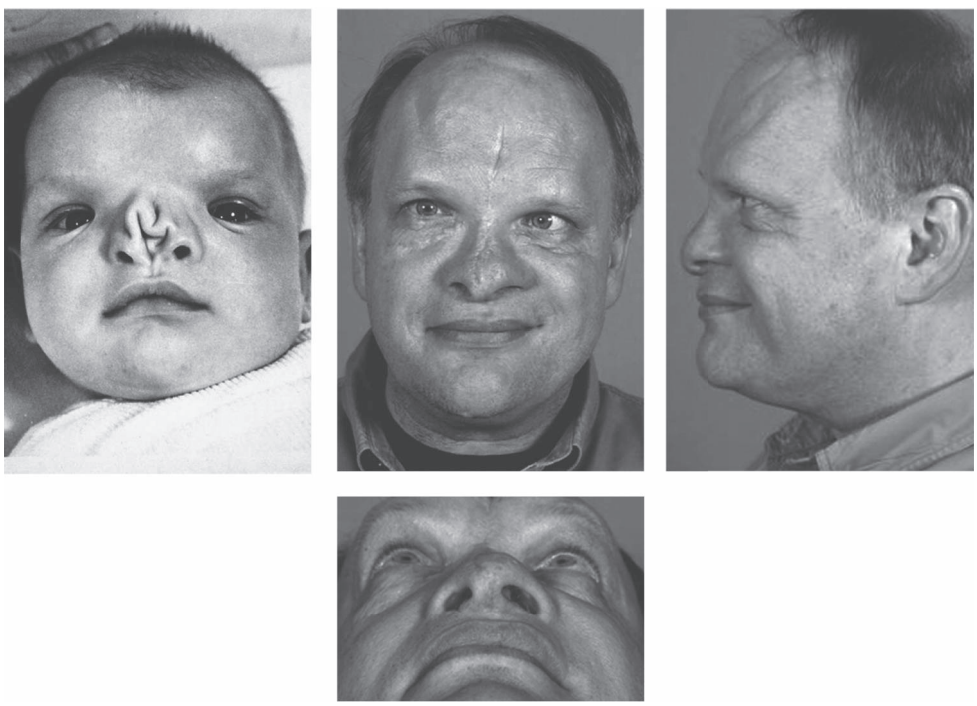

Figure 2. *Pre- and post-operative photographs of patient with rare facial cleft.*

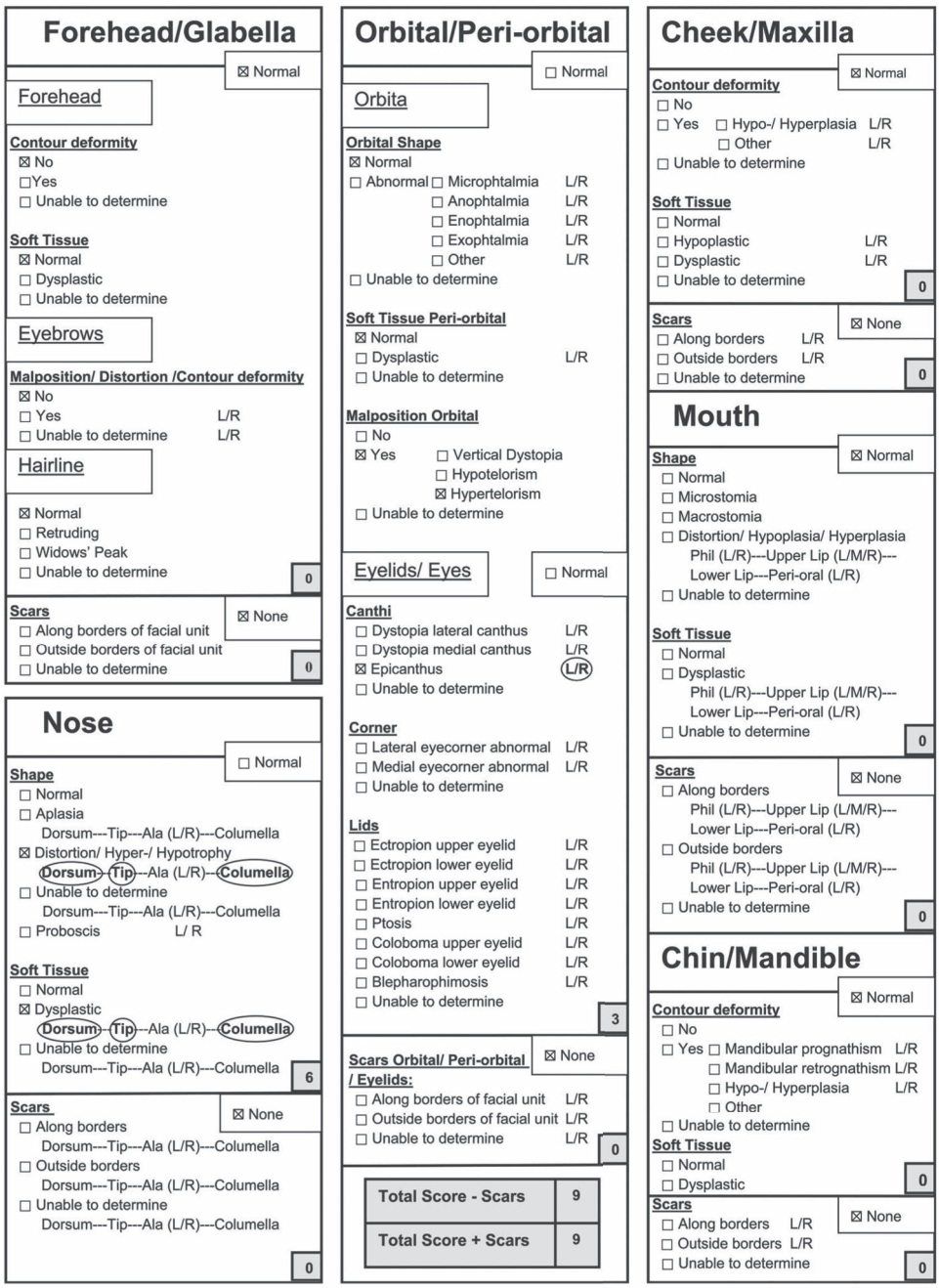

Figure 3. *Scoring of pre-operative impairment with new instrument based on pre-operative photograph in Figure 2.*

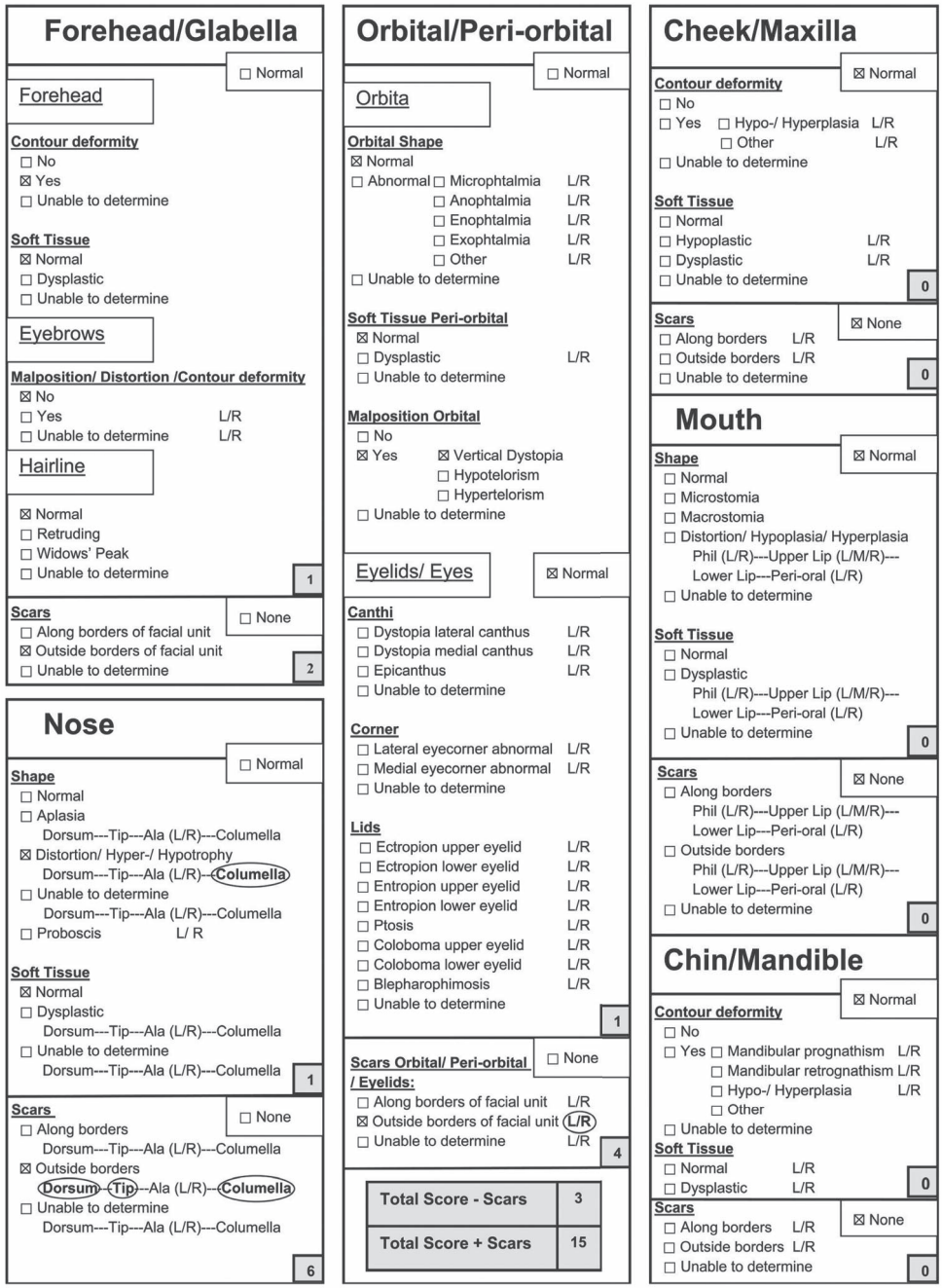

Figure 4. *Scoring of post-operative impairment with new instrument based on post-operative photographs in Figure 2.*

The final outcome measurement obtained through this process, was subsequently tested on reliability. 15 patients suffering from rare facial clefts were chosen at random by an independent person. Pre-operative (infancy) and post-operative (adult age) photographs of these patients were collected. Two raters, familiar with congenital craniofacial pathology (a plastic surgeon and a plastic surgery resident, both not doctor of attendance of the assessed patients), filled out the list for both pre- and post-operative photographs in a random order, and repeated this a few weeks later.

A statistical analysis was performed on the resulting scores. In this analysis patient and rater were treated as random factors. A variance-components analysis was performed, where total variance was decomposed into a between-patients and a within patients component. The latter component was further decomposed into a within-rater and between-rater component. Then the Intraclass Correlation Coefficient (ICC) was calculated as the ratio of the between-patients component to the total variance (sum of between- and within-patients components). An ICC is a statistical measure for reliability of measurements with a value of zero meaning no agreement and a value of one meaning 100% agreement; considering a value above 0.7 a good agreement. Version 11.0 of the computer program SPSS (SPSS Inc, Chicago, Illinois) was used for statistical analysis.

A test on the difference between pre- and post-operative scores of various subunits was done with the Wilcoxon signed ranks test.

Results

Figure 3 and 4 show the final version of our scoring method. Table 1 shows the Intraclass Correlation Coefficient (ICC) per score of subunit for both pre-and post-operative scores (including scores of the scars). In general there was a good to very good agreement in various scores of the subunits between one rater at two different times and between the two different raters (with a lowest ICC of 0.77). The standard errors of the estimated ICC's ranged from 0.31 to 0.37, indicating lack of precision caused by the small sample size (N=15).

Table 1: *Intraclass Correlation Coefficient (ICC) per Score of Subunit for both Pre- and Post-operative Scores*

Subunit	ICC Pre-operative	ICC Post-operative
Forehead	0.94	0.87
Orbit	0.77	0.77
Mouth	0.98	0.87
Nose	0.95	0.90
Cheek	0.77	0.85
Total	0.96	0.85

The results of analysis of the difference between pre- and post-operative scores of various subunits (without the score for scars) are shown in table 2.

Table 2*. Wilcoxon Ranks Test: Difference Between Pre- and Post-operative Scores of the Various Subunits*

Subunit	P-Value	95% Confidence Interval of Median Difference[1]
Forehead	0.72	
Orbit	0.012	(0.50-2.00)
Mouth	0.046	
Nose	0.001	(1.50-2.75)
Cheek	0.26	
Total	0.005	(4.25-7.00)

[1]*According to Hodges-Lehmann*

Some scores of subunits, for example nose (p=0.001) and the total face (p=0.002) demonstrate a significant difference between pre- and post-operative measurement, indicating an unambiguous reduction of impairment. Mean scores of the pre- versus post-operative difference of the various subunits show a different level of improvement for each subunit. The subunits forehead and cheek have a negligible improvement with a mean of respectively 0.2 and 0.1. The range of several subunits, such as forehead (-3.5, 4), orbit (-1, 2.5), mouth (-0.5, 5) and cheek (-0.5, 1) demonstrate the possibility of a negative difference between pre- and post-operative scores, which indicates worsening of the condition.

Discussion

Reliability of developed list

The good ICC for both the scores of the subunits and the total score demonstrates reliability of this test. The high scores show a good level of agreement, which implicates this list is filled out by two persons in almost the same way and leaves little room for differences between raters.

Strasser's MDACS list was used as a starting point because it was the most objective, non-anthropometric assessment method available and is to a certain extent applicable to congenital craniofacial deformities. However it still leaves some room for arguments and reliability is not examined. The distinction between 'noticeable' and 'obvious' in his scoring system remains debatable. That is why we decided to reduce the scorings method to a yes-no option. All the other adjustments made in the list after testing, were done with the purpose to avoid confusion under which item some impairments needed to be scored, thereby increasing the level of agreement and thus reliability.

Although disagreement between raters is reduced to a minimum this way, it will never be completely objective. There are always factors like experience that will influence judgement on whether a certain deformity is present or not. This is why people familiar with congenital craniofacial deformities should fill out this list.

Moreover, there is the issue of quality of the used assessment media. After analysis of the disagreements, the majority could be attributed to the non-optimal quality of photographs. The use of standardised photographs is therefore indicated, including three quarter shots and a view from below for a good assessment of respectively scars and columella. However the best assessment medium will remain the clinical evaluation. [6]

Validity of developed list

The difference between pre-and post-operative scores shows the ability of our list to detect changes in facial deformities. A lower post-operative score of a subunit indicates effect of treatment. In this particular patient group for example the score of the nose decreased in all patients, implicating effective treatment (See also Figure 2, 3 and 4). A higher post-operative score can be caused by the influence of growth, as for example development of vertical dystopia de novo due to intrinsic growth impairment or surgical side-effect (as is seen in the example in Figure 2, 3 and 4). The same post-operative score implicates no change in impairment level, but type of impairment might be of a different kind. With the detailed design of our list we can still distinguish these changes. All the above shows that our list enables us to evaluate the effect of different surgical techniques in a detailed

way and at the same time detect influences of growth on deformities. Furthermore the list provides quantification of outcome, which makes comparison easier. If this list is applied on a uniform group, all having the same dysmorphology/impairment that was treated with one of two different available techniques, the efficiency of both techniques could be compared by applying our method.

The fact that almost all possible congenital facial dysmorphologies are included in the list strengthens its validity. Dysmorphologies like coloboma of the iris and epibulbar dermoid were left out on purpose because they are not treated and thus won't cause differences in pre-and postoperative scores. These untreated deformities disturb true outcome assessment. The latter is also with the case with scoring of scars. By including those in the post-operative score, this score will almost always be higher since scars (=new deformities) are created. Therefore two total scores are determined post-operatively: one total score without points of the scars and one including them (See Figure 4). The first enables us to compare pre- and post-operative results in a 'pure' way. The second gives an overall idea of the severity of residual post-operative impairment and makes it possible to assess location and number of scars placed along or outside the borders of the facial units, which is of importance for the evaluation of the obtained result.

Remarks

In the development of the list we also included the subunit chin/ mandible. Due to the lack of this pathology in our tested population, we were unable to evaluate the scoring of this item. However, since it is based on the same principles, we also expect a reasonable reliability and validity for this item.

Statistical analysis was performed with a small sample size. This reduces the statistical power and causes the estimates to become less precise. In this study statistics were only used as support in the development of the new outcome measurement. The results we show, serve as examples of the possibilities of our list.

To address the above limitations of this study, the list will be applied in larger future studies and different patient groups, together with the use of more raters.

Conclusion

The developed list is a (rather) objective method to measure surgical outcome of congenital (cranio)facial deformities and can be used to assess both surgical techniques and influence of growth. It is more detailed and complete than other existing assessment methods and it provides quantification of outcome. Therefore this list can serve as a

standardized instrument to compare outcome between techniques, surgeons and centres in a more objective way. This list could also be a future outcome measurement for treatment of acquired facial deformities.

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CHAPTER 4

Long-term results after 40 years experience with treatment of rare facial clefts: Part 1- Oblique and paramedian clefts

Versnel SL, van den Elzen MEP , van der Meulen JC, Wolvius E, Biesmeijer CS, Vaandrager JM, Mathijssen IMJ

Submitted

Abstract

Background: Oblique and paramedian rare facial clefts impose a major reconstructive challenge and long-term assessments of the outcomes remain scarce. This study provides new details regarding surgical techniques and timing, influence of growth, and difficulties of this pathology on the long-term; a guideline for surgical treatment is given.
Methods: Twenty-nine adults with an oblique or paramedian facial cleft and surgically treated in the authors' unit between 1969 and 2009, were included. The long-term evaluation was based on series of photographs, 3D-CT's, X-rays, operation data, and was specified per facial area.
Results: The mean number of performed operations per patient was 10.6 (range:1-26). Vertical dystopia is not caused by previous surgery, but by growth deficiencies of the maxilla. In all patients with vertical dystopia, its presence and severity were clear at the age of five, and it should ideally be treated shortly after that age. In mild cases grafting seems sufficient, but in more severe cases orbital translocation is necessary. Costochondral grafts showed the best long-term results in both orbital and nasal reconstructions. Major nose reconstruction is best delayed until adolescence. For an optimal final result in selected cases, correction of midface hypoplasia at adolescence is necessary.
Conclusion: The three-dimensional underdevelopment of the midface region plays a central role in the deformities of most patients, but is complex and difficult to correct. The provided guideline should help to minimize the number of operations and ameliorate long-term results.

Introduction

Oblique (Tessier 3,4,5) and paramedian (Tessier 1,2) [1] rare facial clefts impose a major reconstructive challenge. Often serious asymmetry exists and multiple areas of the face are affected. Due to deficient growth of all affected tissues in the cleft area, the deformities at birth can become more obvious over the years and result in clear three-dimensional underdevelopment of hard and soft tissues of the orbit, maxilla, zygoma, nose and malar region. Due to this intrinsic impaired growth or growth disturbance by surgical interventions, initial excellent treatment results may turn gradually worse. Determining the right moment and using the best technique is therefore essential.

Various techniques to address this complex pathology have been described in literature; [2-7] however, evaluation of long-term results has been scarce. Some treatment policies have become general knowledge, but evaluation of long-term results can reveal new details on which techniques give the best results or have the least relapse. It also provides additional information on the aberrant growth patterns. All previous conducted studies are limited by a small number of cases and/or a relatively short mean period of follow-up. [3-5,7-16]

This study was conducted to evaluate long-term results of surgical treatment of oblique and paramedian rare facial clefts in adults. It includes the evaluation of five cases which have been reported 25 years ago. [3] New details regarding influence of growth, techniques, timing, and difficulties imposed by this specific pathology are discussed. A guideline for surgical treatment is given.

Patients and methods

All patients with a rare facial cleft who had surgical treatment at the Craniofacial Center of the Erasmus Medical Center between 1969 and 2009, were re-evaluated on initial diagnosis. All patients with an oblique or paramedian cleft were included. Patients with craniofrontonasal dysplasia, hemifacial microsomia, macrostomia, pure midline clefts (Tessier 0/14), missing data or photographs, an age less than 16 years or who were deceased, were excluded.

The series of photographs of all patients were collected. Details on performed operations were retrieved from the patient's medical chart; also when operated in other hospitals. For evaluation of the osseous structures 3D-CT's and X-rays of the patients were used when available. Final surgical results were assessed based on severity of the

initial and the remaining facial deformities, using the Versnel et al. scoring list, [17] and based on the need for revisional surgery, using the Whitaker et al. classification. [18]

Results

Twenty-nine adults had an oblique (N=22), or paramedian rare facial cleft (N=7). Twenty patients were female. The mean age at time of follow-up was 32.1 years (SD 11.3, range 17-61). Eighteen patients had a unilateral cleft.

In general

The mean numbers of performed operations per patient and per facial area are shown in Table 1. Twenty-two patients had had operations in another hospital prior to referral. In none of the presented cases major complications were seen.

The majority of the long-term results were not as good as expected. Initially good results deteriorated over time. Patients without previous surgery in another hospital, showed better results; mainly due to better positioning of scars and superior aesthetic outcome of nose and orbital region.

At time of follow-up, nine patients were still under treatment and six restarted their treatment in consequence of their participation in our research project.
In 24 patients the scores on the Versnel et al. scoring list decreased, indicating a decrease of the facial deformities. Three patients were assessed as a category I, 18 patients as category II and six patients as a category III according to the Withaker Classification.

Eyes and orbits

Soft tissue

Local flaps gave good initial results for coloboma correction. However, only a minority remained stable over time; in the majority it resulted in shortage of skin or an ectropion (Figure 1). For correction of the lower eyelid the cheek flap was superior (Figures 1, 2, 3, 4, 5), while the forehead flap showed tissue mismatch especially regarding thickness (Figure 2). Correction of the lateral canthus/corner of the eye was done in 19 patients; seven patients needed one or more redo's (mean:1.7, range:1-5). Correction of the medial canthus/corner of the eye was performed in 20 patients, of which 16 had one or more redo's (mean:3.2, range:1-8). Microphtalmia was never corrected completely (Figure 3). In six patients a dacrocystorhinostomia was performed; multiple adults complained of tearing eyes.

Table 1. *Performed operations*

	Patients (n)		Performed operations (n)		Age at first operation (years)	
	Affected	**Operated**	**Mean**	**R**	**M**	**R**
Total number of operations	29	29	10.6	1-26		
Eyes and orbits	27					
Total		25	4.6	1-9		
Soft Tissue		22	4.3	1-9	2.0	0-30
Hypertelorism	17	14	1.1	1-2	5.5	0-30
Bony framework		20	2.2	1-4	5.0	0-30
Vertical dystopia	15	10	1.4	1-3	7.5	0-30
Nose	28					
Total		26	6.2	1-20		
Soft Tissue		26	5	1-15	3	0-28
Bony framework		21	3	1-9	14	0-41
Maxilla, palate and lips	25					
Total		16	2.6	1-6		
Soft Tissue		10	2.7	1-6	3	0-28
Bony framework		12	2.1	1-4	14.5	0-23

M= median, R= range

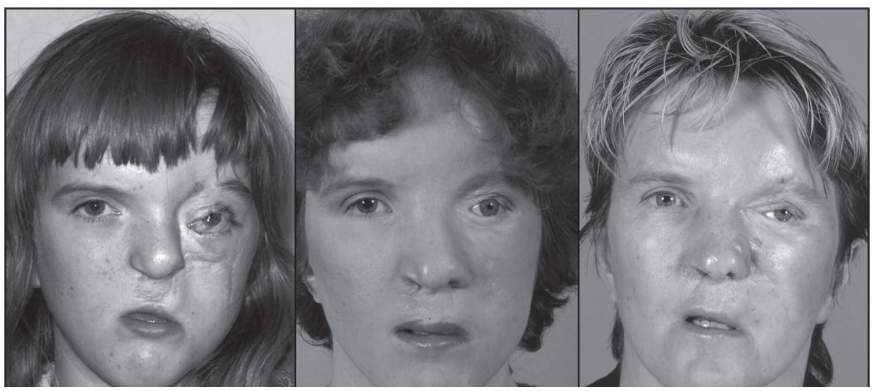

Figure 1.a.-1.c.: *Monolateral medial maxillary dysplasia. (Patient 1 in Table 2)*

***Figure 2.a.-2.c*:** *Monolateral maxillary dysplasia. The initial forehead flap was replaced by a cheek flap. (Patient 10 in Table 2).*

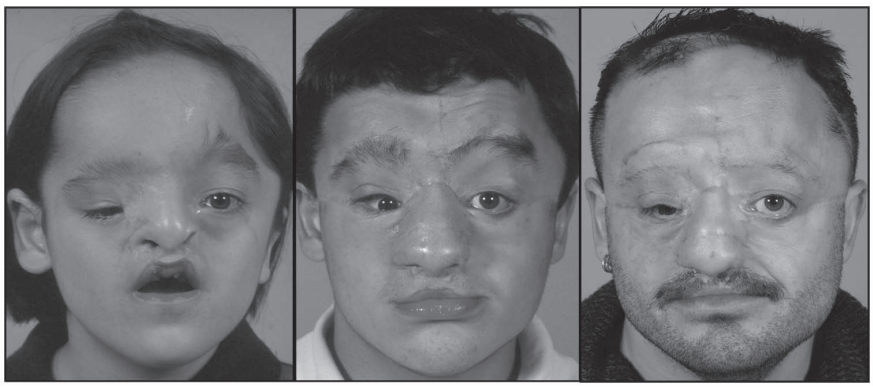

***Figure 3.a.-3.c*:** *Bilateral complete nasomaxillary dysplasia. (Patient 12 in Table 2).*

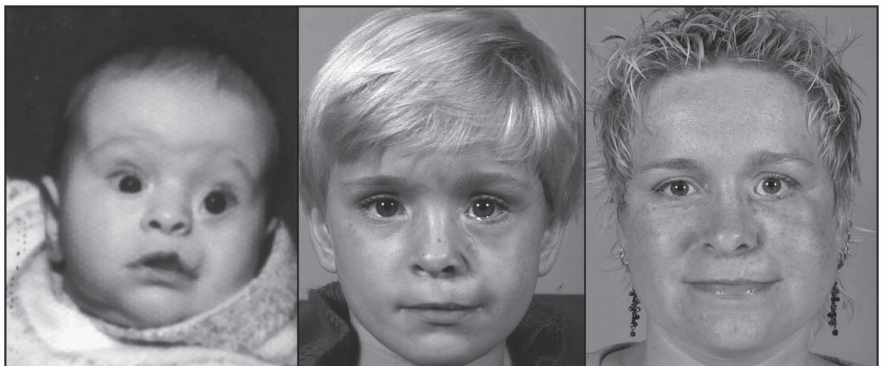

Figure 4.a.-4.c.: *Medial maxillary dysplasia. A cheek flap and grafting of the orbital floor (2 times) gave stable results over time. In adulthood lipofilling was performed. (Patient 9 in Table 2)*

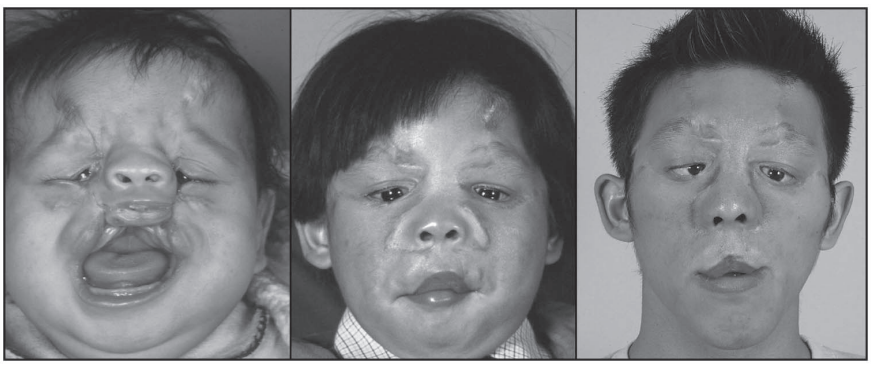

Figure 5.a.-5.c.: *Bilateral medial maxillary dysplasia.*

Correction of hypertelorism

Seventeen patients had hypertelorism at birth, and in 14 patients hypertelorism correction was performed: six medial faciotomies according to van der Meulen, [19] eight orbital box osteotomies. All the medial faciotomies were performed at an age under four. The mean reduction in interocular distance overall was 15.2 mm (range:6-25). Six patients had an obvious residual hypertelorism after the correction due to insufficient primary correction. In two of these patients, who both had orbital box corrections, a second hypertelorism correction was performed. Medial faciotomy often was the technique with the best results. No relapse was seen after hypertelorism correction in the remaining

eight patients, implying that growth had an insignificant influence on results of early hypertelorism corrections.

Bony framework

Fifteen patients had vertical dystopia (Table 2). Nine of them had it at birth and six developed the vertical dystopia later; in all patients, vertical dystopia was overt at the age of four. In three patients (Table 2: patient 4,6,14) with congenital dystopia who had no early operations in the orbital zone, the dystopia worsened up to the age of five years and then remained stable. The severity of dystopia could not be predicted in hind sight by the type of cleft. All patients who developed vertical dystopia had an oblique cleft involving the maxilla, but not every patient with a maxillary cleft developed vertical dystopia. In all patients with dystopia and a unilateral cleft, the unaffected side still developed normally. When patients with a bilateral cleft developed vertical dystopia, they did not have identical clefts on both sides; the most affected side had more hypoplasia of the midface resulting in a lower position of the orbit/globe. Previous surgery seemed not to have an influence; in patients with previous bilateral hypertelorism corrections, the unaffected side developed normally. Vertical hypoplasia of the midface was present on the affected side in all patients with vertical dystopia.

In 10 patients the vertical dystopia was corrected: five patients received a graft in the orbital floor, three an orbital elevation, and two a combination of the two techniques. Grafting of the orbital floor appeared insufficient for correction of severe vertical dystopia, independent of age at time of placement (Figures 1,2); it only reduced the dystopia from severe to mild (Table 2: patient 1,10,15). Only in mild dystopia grafts gave stable and sufficient results on the long-term (Figure 4, Table 2: patient 8,9). Patients who had an orbital elevation at an age older than four years, had no relapse of the vertical dystopia (Table 2: patient 5, 11). Four of the 10 corrected patients had no final residual vertical dystopia, and in four other patients the correction reduced the dystopia from severe to mild. Also in 12 of the 29 patients one or more grafts for reconstruction of the medial, lateral or superior orbital walls were necessary. In the majority of orbital grafts iliac crest and/or skull grafts were used; however, over the years costochondral grafts, which showed more stability over time, became first choice.

Table 2. *Characteristics of patients with vertical dystopia*

Patient	Cleft type[1] dystopia side	Cleft type[1] other side	Age visibility VD	Severity[2] Early VD	Age (yrs) 1st corr.	Type[3] 1st corr.	Relapse after 1st corr.	Age (yrs) 2nd corr.	Type[3] 2nd corr.	Severity[2] Final VD
1	2,3,4,5,10	2	0	S	17	2	1	18	2	M
2	1,2,3	-	3	M	-	-	-	-	-	M
3	3,10,11,7	7	0	M	0	3	1	-	-	M
4	3,11	2,12	0	M	-	-	-	-	-	S
5	2,3,11	2,12	3	M	5	3	0	-	-	0
6	1,2,3, 11	-	1	S	-	-	-	-	-	S
7	3,11	2	3	S	3	1	1	9	3	M
8	3,4	0,2,3	0	M	23	2	0	-		0
9	4	-	0	M	2	2	1	6	2	0
10	3,4	-	0	S	6	2	1	29	2	M
11	2,3,11	-	0	S	30	1	0	-	-	0
12	2,3,4,11	2,3,11	4	M	-	-	-	-	-	M
13	0,2,3,4, 10,11	-	0	M	3	1	1	-	-	S
14	3,4	-	0	M	-	-	-	-	-	M
15	2,3,4	-	1	S	10	2	1	16	1	M

VD=vertical dystopia, corr.=correction; [1)] According to the Tessier classification; [2)] M=mild, S=severe, 0=no vertical dystopia; [3)] 1=orbital translocation, 2=graft, 3=orbital translocation + graft

Nose

Soft Tissue

Many local closures and flaps were used, including redistribution of nasal dorsum skin, forehead flaps, and L-incisions. Initially the majority of these techniques showed good results. However, on the long-term the affected parts lagged behind and the soft tissue of the local closures and forehead flaps appeared insufficient; L-incisions on the contrary showed good results. Many corrections and redo's of the alae were performed (range:1-7); in 16 patients without a graft and in five patients with a graft. The use of a graft improved the shape of the ala on the long-term only when placed after the age of 15 years and with sufficient overlying soft tissue (unaffected by the cleft). Experience with alar grafting in childhood was very limited.

Bony framework

In 50% of these patients the dorsum of the nose was reshaped by using a graft (costochondral, skull, composite) at a mean age of 13 years (range: 2-28). Over time 42% needed a redo. In 85% of the nasal dorsum corrections a costochondral graft was used as final graft with a median age of 19 years (range:4-28) at time of placement. Time showed that once a costochondral graft had been used for correction of the nasal dorsum (after the age of 10 years), no reoperation had to be performed.

Maxilla, palate and lips

Soft tissue

On the long-term, local closure and local flaps appeared insufficient for correction of soft tissue deformities of the midface; it also caused bad scarring and the appearance of 'patchwork'. Cheek flaps showed stable results with scars in borders of the facial units, and were reusable; seven patients received a cheek flap, and in five patients it was necessary to advance the cheek flap a second time due to new shortage.

Bony framework

Fifteen patients had an obvious hypoplasia of the midface region at birth, while it became clear over the years in 10 others. Seven patients underwent maxillary advancement (oseotomy/distraction) (mean:1.9 operations, range:1-2) for correction of osseous midface hypoplasia. The median age at time of the first operation was 16 years (range:13-19). In this group a Le Fort I correction was performed nine times (three redo's), a Le Fort II once, and a Le Fort III four times. All the Le Fort III corrections were performed at adolescence and one of them was done unilaterally. [16] Eighteen

patients received bone grafts for correction of the zygoma and maxilla at a median age of 11 years (range:0-23). The majority of these grafts (50% iliac crest, 23% skull) appeared insufficient. All 25 patients had a residual hypoplasia at an adult age, due to an incomplete correction of the 3D-defect. The restricted vertical height of the maxilla was often the most problematic to correct and resulted in malocclusion (Figure 2).

Discussion

Patients

This is a unique group of patients with a rare facial cleft since it only consists of adults whose treatment started at a young age. Classification remained challenging as paramedian and oblique facial clefts presented in the majority of cases as multiple clefts. [20,21] At adulthood in most patients the facial deformities had improved, but in many patients there was still an indication for surgical intervention.

Treatment considerations

A large total number of operations was performed. Numerous patients had been operated previously in non-specialized centers, and because the reconstruction had not always been performed correctly (e.g. extensive scarring, patchwork, insufficient nose reconstructions and eyelid corrections), operations had to be redone. As a consequence optimal final aesthetic results were difficult to achieve. Therefore, it is very important to have a long-term plan to optimize end results and limit the number of operations. The large number of operations was also due to the learning curve which led to additional operations; e.g. forehead flap used in childhood in the early days, was later rejected.

The actual timing of corrections is often based on severity and nature of the deformity with consideration of functional problems, growth, mental burden for the patient and wishes of patients and/or parents. However, previous conducted studies show that the intensity of the psychological burden for patients caused by the deformity is not directly related to the severity of the deformity. [22] In addition, the intermediate results in these patients often still show severe deformities and patients may still be teased or looked at. Furthermore there is a major influence of intrinsic growth deficiencies on early reconstructions in this patient group. It is therefore in some cases better to wait with major reconstructions and give them a chance on an optimal result at adulthood. Although it is difficult to convince the patient and parents, it prevents that all good options will already have been used. There is a lot of controversy about the staging of

the repair of soft tissue and osseous structures: some advocate simultaneous correction, [2,3,8,23] some address the soft tissue first, [4,11,24] others start with establishing a skeletal foundation. [20,25,26] The only generalization made in the literature is immediate reconstruction of the lower eyelid when the cornea is exposed. [4,10,12, 27, 28]

Based on a long-term experience, the following treatment guidelines were developed.

Age < 1 year: Peri-orbital soft tissue correction with cheek flap

As is general knowledge, good initial positioning of scars is important for optimal long-term surgical results. The cheek advancement flap (with tissue expansion in wide clefts [10,13,20,26,29]), is best used for correction of the lower eyelid or cheek deficiencies. [3,4] When correcting the medial part of the lower eyelid, the cheek flap should be placed high up at the medial canthus (Figure 6: see A); at an older age further transposition of the flap is possible. For coloboma's local flaps can be used. When the cleft affects the medial canthal area, attention should be directed towards identifying the canalicular lacrimal system. [30] It is best to preserve as much as possible of the original system and reposition this; often a distended lacrimal sac is found lateral to cleft which can be brought into the nose. Later reconstruction might be indicated if both the upper and lower canalicular system are hypoplastic.

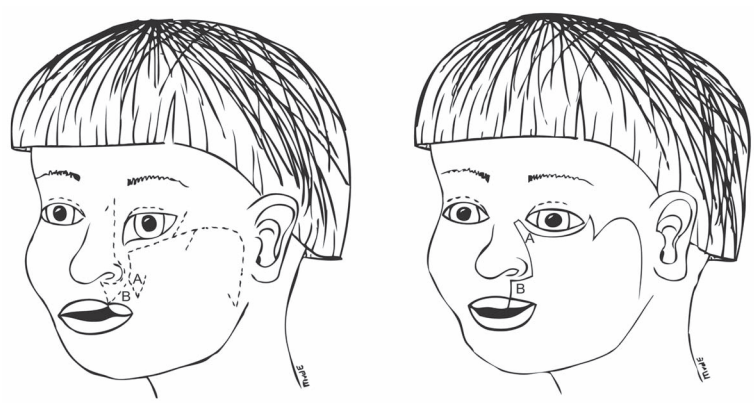

Figure 6. *With this technique optimal use of the cheek flap is possible. Lowering/ partial failure of the cheek flap can be caused by gaining suboptimal length initially, by performing an insufficient medial canthopexy, or by growth deficiency of the maxilla.*

Age > 4 years: Re-use of cheek flap, medial faciotomy, graft in orbital floor for mild vertical dystopia, minor nose reconstruction

Corrections of the medial canthus are required more frequently than corrections of the lateral canthus, because the majority of patients have a cleft involving the medial corner of the eye. Repositioning of the medial canthus is best performed at the same time as the definitive positioning of the orbitae, and is preferably done with a bone anchor. [31]

Growth of the affected osseous parts in patients with an oblique facial cleft is very unpredictable, but in all patients with vertical dystopia, its presence and severity were clear at the age of five. It is thought that dystopia correction with bone grafting at an early age might limit the increase in vertical dystopia; [4,10] however, a few patients with early bone grafting still developed severe vertical dystopia. Moreover, the statement of others that early bone grafting disturbs growth of the maxilla can be discarded after the results of this study. [32] The theory that surgery has no influence, but that intrinsic growth deficiencies of the maxilla cause vertical dystopia, was already advocated by van der Meulen based on pathomorphological findings. [21] In view of the good results in nose and orbital reconstruction, we advise to use costochondral grafts, as they demonstrate less resorption. Ideally treatment of vertical dystopia should not be performed before the age of five, but soon after this age; this is in accordance with facial growth studies. [33] In mild cases grafting might be sufficient, but in more severe cases orbital translocation, preferably towards the age of 10, will be necessary; this last technique caused no growth disturbance in our population. It is important to stay above the tooth buds with the osteotomy; therefore it is best performed towards maturation of the maxilla. Ectropion occurs frequently after correction of vertical dystopia; therefore simultaneous correction of the lower eyelid with a cheek flap should be performed in most cases.

When sufficient soft tissue is initially present in a nose with hypoplastic subunits, only minor reconstructions with local flaps should be performed. These early corrections are best performed with placement of the scars within the borders of the facial units and with a flap that is reusable. Redistribution of nasal soft tissue with an L-incision is a technique which takes these two aspects into account (like the cheek flap). [34] It is a very important principle; once scars have been wrongly placed, it is very difficult to correct them. Some authors prefer to perform a total nose reconstruction before the child enters school, [20] and others advise to wait. [35] However, the intrinsic growth deficiencies cause underdevelopment of the nasal skeleton on the long-term, resulting in shortness of the forehead flap placed in childhood, which cannot be elongated later

on. Therefore in facial clefts the forehead flap should best be preserved for patients of 16 years or older.

Age > 6 years: Hypertelorism correction, orbital evaluation for severe vertical dystopia

Hypertelorism corrections through medial faciotomies can be performed at the age of four to six years. Relapse of hypertelorism after correction appears to be very rare. It is stated in literature that medialization of the medial orbital walls and hemifacial rotation do not interrupt midfacial growth. [20] Likewise, the disturbance in midfacial growth in this study is caused by intrinsic factors, and not by interference of surgical corrections. The choice between orbital box osteotomy and medial faciotomy is based on the associated malformations of the maxilla, palate, and alveolar bow. Orbital box osteotomy is also best performed towards the age of 10 years

Age > 16 years: Final corrections

Advancement of the midface is often necessary due to a 3D-underdevelopment of the midface over the years. It should ideally be performed at skeletal maturity as part of an orthognathic treatment plan.

The goal should be to reconstruct the nose in three operations. Therefore we advocate performing a definite/major nose reconstruction after the age of 16 years as described above. Two additional reasons for postponing until adolescence are: growth of the nasal skeleton/dorsum is completed at this age (36), and advancement of the hypoplastic maxilla can be performed. The latter is indeed necessary for a good final result, since it forms the fundament for the nose and influences its projection.

A forehead flap (with tissue expansion) can be used for nose reconstruction. For the dorsum we prefer a costochondral graft, also when performed in childhood (after the age of 10 years). Simultaneously a correction of the ala with a cartilage graft can be performed.

Conclusion

The three-dimensional complex underdevelopment of the midface region plays a central role in the deformities of most patients with oblique and paramedian facial cleft, but has unpredictable growth impairment and is difficult to correct. It is important to minimize the total number of operations and improve long-term results, which can be achieved

by postponing some reconstructions till after childhood and use the best techniques. The provided guidelines for treatment should help to ameliorate final results.

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CHAPTER 5

Long-term results after 40 years experience with treatment of rare facial clefts: Part 2 – Symmetrical median clefts

van den Elzen MEP, **Versnel SL**, Wolvius EB, van Veelen M-LC, Vaandrager MJM, van der Meulen JC, Mathijssen IMJ

Submitted

Abstract

Background: Median facial clefts are reconstructive challenges, requiring multiple operations throughout life. Long-term results are often still far from ideal and could be improved. Due to surgical intervention and diminished intrinsic growth potential, surgical results may change from initially good into a progressively disappointing outcome. If, however, the ideal timing and type of surgery is known, in combination with the intrinsic growth potential, the results can be ameliorated. A guideline for surgical treatment is given.

Methods: Twenty patients with a pure symmetrical median cleft were evaluated on intermediate and long-term surgical results. The final result was scored based on severity of the initial and the remaining facial deformities, and the need for revisional surgery.

Results: The long-term surgical outcome was initially good for each of the affected facial parts and the face in general, but worsened over time, especially in the zone of the nose. An adequate and stable result of hypertelorism correction was observed for both the orbital box osteotomy and medial faciotomy, even when performed at a young age.

Conclusions: The intrinsic growth restriction is mainly localized in the central midface. This leads to a complex and often unpredictable growth of the maturing face. It makes it difficult to achieve perfect reconstructions. Caution with surgical interventions of the nose at a young age is required. Once the face has matured, a midface advancement and secondary nose correction should be considered for satisfactory projection. Early referral to a specialized center is essential.

Introduction

Rare facial clefts of the midline (also known as Tessier 0-14) [1] are a major reconstructive challenge. In contrast to rare facial clefts of an oblique (Tessier 3, 4 & 5) or paramedian (Tessier 1, 2) type, they are purely symmetrical. Although this seems to make reconstruction easier, long-term results are often still far from ideal. Good initial results can deteriorate over time due to restricted growth during the maturation of the face. In our opinion this could be ameliorated.

The pathology mainly consists of hypertelorism, hypoplasia of the nose and midface, sometimes in combination with a median cleft lip and palate or an encephalocele. In literature multiple methods to classify and treat this multifaceted pathology are defined, however, they barely speak about diminished growth potential while the face matures. [1-5] Previous studies on surgical results are usually based on small cohorts and lack a long-term follow-up. [6-8] If, however, the ideal timing and type of surgery is known, and considered together with the intrinsic growth potential, surgical results will improve and become more stable over time.

This review of a cohort of patients with midline clefts was conducted to evaluate the long-term surgical outcome. The effect of diminished growth potential in the affected facial parts and consequent ideal timing and techniques for surgical treatment are presented. A guideline deducted from these data is provided.

Patients and methods

Nearly all patients with rare facial clefts in the Netherlands are treated by our Craniofacial Center and followed up throughout adulthood. All patients with a pure symmetrical median cleft, who had surgical treatment between 1969 and 2009, were selected and included in this study. Patients under the age of 16 were included only for evaluation of their facial growth, but excluded for the assessment of long-term surgical results. Other absolute exclusion criteria were; cerebral craniofacial dysplasias, involvement of an oblique or paramedian facial cleft, patients with craniofrontonasal dysplasia (EFNB1 mutation) and missing data or photographs.

The complete series of photographs of all patients were collected. Details on performed operations were retrieved from the patient's medical chart; also when operated in other hospitals. For evaluation of the osseous structures 3D-CT's and X-rays of the patients were used when available. Final surgical results were assessed based on

severity of the initial and the remaining facial deformities, using the Versnel scoring list [9], and based on the need for revisional surgery, using the Whitaker classification. [10-11]

Inner- Outer Canthal Distance Ratio

Because preoperative CT-scan or radiographic image was not available for all patients, a measurement of the initial bony hypertelorism could not be obtained. Since standardized photographs of all included patients were available, a soft tissue ratio was made dividing the inner by the outer canthal distances (IOCD ratio).

Results

General

Twenty patients (13 women, seven men) were included, out of a total of 123 patients with a rare facial cleft. At time of follow-up, five patients were under the age of [16] and still under treatment. The average age at inclusion was 27 (range 2-52). The mean years of follow-up of the adult patients was 25.7 (range 12-42).

Three patients had a basal encephalocele, one a frontonasal encephalocele and one a bicoronal synostosis. Six patients were diagnosed with frontorhiny based on an ALX-3 mutation. [12]

The mean number of operations is shown in Table 1. Four patients underwent one or more surgical procedures elsewhere prior to their referral to our institution and had a higher number of operations (mean 10.7, range 3-14), than patients operated solely at our institution (mean 7.6 range 1-15). One of the patients died 45 days after surgery, due to a cascade of complication. This was one of the first patients treated at our craniofacial center, 34 years ago. Other major complications, such as loss of vision or death were not observed afterwards.

The initial outcome of these patients was very satisfactory; however, the majority of the long-term results deteriorated over time, especially in the zone of the nose.

In twelve patients the scores on the Versnel et al. scoring list decreased (Table 2). The Whitaker score revealed nine patients with a category I, seven with a category II and three patients with a category III.

Table 1. *Performed operations*

	Patients (n)		Performed operations (n)		Age first operation (years)	
	Affected	**Operated**	**Mean**	**R**	**M**	**R**
Total number of operations	15	15	7.6	1-15	2.0	1-36
Eyes and orbits	15					
Total		8	3.8	1-8		
Soft tissue		8	3	1-8	12.0	1-27
Hypertelorism		8	1	1	6.5	1-19
Bony framework		6	3,3	1-5	13.5	6-20
Skullbase		1	1	1	2.0	6
Nose	13					
Total		13	11.5	4-30		
Soft tissue		10	6.6	1-19	6.5	1-20
Bony framework		13	5.4	2-11	4.0	1-20
Maxilla, oral cavity and lips	7					
Total		5	3.3	1-7		
Soft tissue		4	2.8	1-6	10.0	4-44
Bony framework		5	2.2	1-4	15.0	10-44

M= median, R= range

Table 2. *Versnel score (objective severity of facial deformity)*

	Scars	**Mean**	**SD**	**Range**
Pre-surgery	Not present	6.6	2	3-9
Post-surgery	Excluded	5.4	3.3	1-12
	Included	9.2	4.7	2-21

SD= standard deviation

Eyes and orbits

Soft tissue

Patients had few periorbital operations. Tightening of the levator palpebrae muscle was performed in three patients, and an additional reconstruction of the tarsal fold in one. Other periorbital soft tissue procedures were correction of epicanthal folds (n=1), a

medial canthopexia (n=3) and a lateral canthopexia (n=4). Two out of three patients with a prior medial canthopexia had one or more reoperations. Two out of four patients with a lateral canthopexia had one reoperation.

Correction of hypertelorism

All patients had a variable degree of hypertelorism. Surgical correction was performed in eight patients: five orbital box osteotomies and three medial faciotomies according to van der Meulen. [13] The mean IOCD ratio was 0.45 in the non operative patient group and 0.52 in the operated group prior to surgery. The orbital box osteotomies were performed at an age ranging from one to 19 years, the medial faciotomy at an age ranging from one to seven years. Both techniques corrected the hypertelorism adequately. Only one case was re-operated two years later for a residual telecanthus after an orbital box osteotomy. No other corrections for hypertelorism were indicated on the long-term. The mean difference between IOCD ratio measured shortly after the correction of the hypertelorism, and measured at the most recent photograph was 0.0013. So, the result of both techniques remains very stable over time (Figure 1). In addition, none of the patients developed a vertical dystopia of the orbits after correction of their hypertelorism, or a distortion of their teeth. In three patients a post-operative temporal hollowing was seen after an orbital box osteotomy.

Bony framework

An onlay bone graft was carried out in four patients, all at the time of hypertelorism correction; bilaterally for the orbital floor (n=1), bilaterally on the lateral walls (n=2) and bilaterally on the medial walls (n=1). Bone grafts were derived from the skull, costal arch and iliac crest.

Skullbase

Three patients, all under the age of 16, were born with a basal encephalocele. Before the age of one year they underwent a cranialization of the cele (Figure 2). In one ALX-3 case a congenital bone defect of the lamina cribrosa was closed with a graft derived from the skull and periosteal flap. This operation was performed at the age of six when the patient had suffered multiple episodes of meningitis. [12]

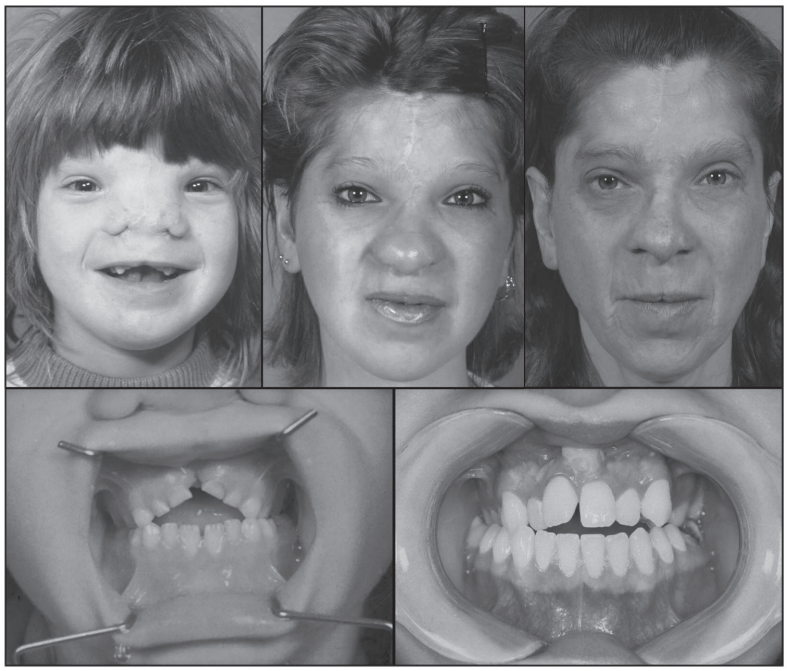

Figure 1.a.-1.c. *Female patient at the age of four, nineteen and forty. Hypertelorism was corrected with a medial faciotomy according to van der Meulen at the age of seven. A stable long-term result is shown.*
Figure 1.d.-1.e. *A clear keel-shaped maxilla is shown prior to a medial faciotomy, post surgery only a mild maxillary hypoplasia is present.*

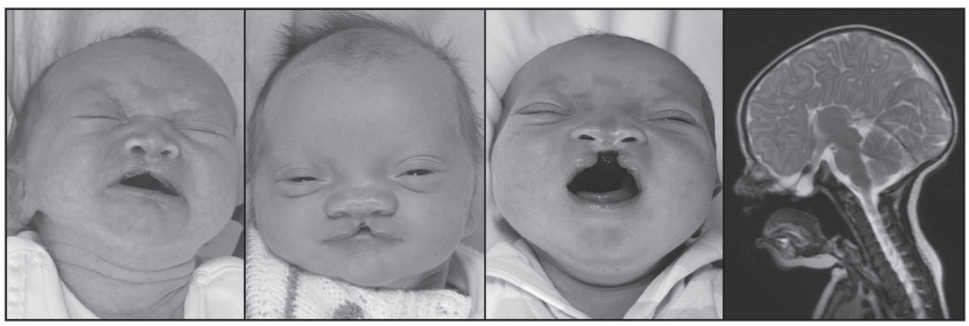

Figure 2.a.-2.c. *Three male patients with basal encephalocele, all aged less than a month. Patients had a typical notch or true cleft at the center of their upper lip.*
Figure 2.d. *MRI illustrating the skull base defect and brain herniation.*

Nose

Soft tissue

Most operations were performed to correct the shortage of skin, especially after insertion of a dorsal graft. The forehead flaps (n=4) were performed at an adult age, and remained stable over time. Following hypertelorism correction, the abundant local skin was rearranged which corrected the soft tissue of the nose. Long term results of these local flaps were sufficient. A free unvascularised temporal fascia flap was successfully applied to improve the contour of the nasal dorsum (n=2). If an incision was planned on the midline of the nose, the scar continued to be very striking. Furthermore, local corrections of the columella were performed (n=8, mean 1.8), a tissue expander was implanted for expansion of the nasal soft tissue (n=3), and corrections of the nasal alae were performed (n=4, mean 2.8).

Bony framework

Sixteen patients had one or more operations for reconstruction of their nose (mean age first surgery: 4.4 years, range 0-19). All 16 patients had either a bone or costochondral graft implanted. Grafts were placed in the septum (mean 1.0), in the columella (mean 1.8), the tip (mean 1.7) and dorsum (mean 2.2). Looking specifically at the grafts placed in the nasal dorsum, the bone graft was most frequently used (n=10), harvested from the iliac crest or skull. If a first reconstruction (mean age 9.3 years) was done with a bone graft, an average of 2.6 operations were necessary to complete the reconstruction. With an initial costochondral graft (mean age 8.8 years), an average of 0.75 additional operations were required. After implantation of a graft, most additional operations were performed to correct the shape and contour of the nasal dorsum, placement and refinement of a columellar strut, or soft tissue and scar touch-ups.

Maxilla, palate and lip

Soft tissue

Closure of the cleft lip was carried out in one patient. A cleft palate was seen in two adult patients. Both of them underwent closure of the cleft palate and obtained an alveolar bone graft as well.

Bony framework

Ten patients had clear intraoral pictures, and could be evaluated. A keel-shaped deformity was observed in four patients at first presentation. A high arched palate was observed in six patients before surgery, as well as a rather narrow alveolar ridge in

three. A maxillary hypoplasia was seen frequently prior to surgery in as much as eight cases. A Le Fort I operation with distraction was performed in two patients. One case had previously undergone a medial faciotomy. The ages at time of the Le Fort were 17 and 44 years. A Le Fort III advancement was performed in two (one with distraction) at the ages of 15 and 19. One patient underwent a SARME (Surgically Assisted Rapid Maxillar Expansion). Moreover, all patients underwent extensive orthodontic therapy for better alignment of their teeth. After surgical treatment a keel-shaped deformity was observed very mildly in two cases, a high arched palate in seven, and a rather narrow alveolar ridge in three. Although maxillary hypoplasia was seen very frequently prior to surgery, this was unusual thereafter and seen only in two cases (Figure 1). Overall, growth potential was evidently absent or diminished at the site of the cleft, resulting in an hour-glass alike deformity; a 3-dimensional underdevelopment in the midface.

Complications

A total of eight complications were observed; one death, three abscesses, two perforations of the dorsal graft through the skin of the nasal tip, one leakage of cerebral spinal fluid following Le Fort III with distraction, one displacement of a tissue expander. Cause of death in the one patient that died was a myocardial infarction, 45 days after surgery. She also suffered from a bronchopneumonia, two subcutaneous abscesses in the nasal area and the temporal fossa, and a necrosis of the frontal brain tissue. One of the patients with a basal encephalocele developed a short period of diabetes insipidus after reconstruction of the anterior skull base, which was adequately treated with medication.

Discussion

Patients

Nearly all patients with rare facial clefts in the Netherlands are treated by our team and followed up throughout adulthood. For that reason the selected population is unique for its number and mean years of follow-up. Looking at the objective aesthetic outcome, the facial appearance improved in the majority of the patients. As is shown by the Whitaker score, the large majority of patients were treated adequately. Nevertheless, indication for further surgical interventions was present in many cases. In most cases, objective indications for minor improvement remain but often the patient is satisfied or tired of all previous operations and wants to end the long period of medical treatment.

Patients who were primarily treated at our center had better aesthetic results, with a lower number of operations, demonstrating the impact of gaining experience. Overall, the mean number of operation sessions was relatively high (mean 7.6, range 1-15). This was due to learning curve and exploration of new and improved techniques, since some of these patients were the first for whom craniofacial surgery was available.

Treatment considerations

The most essential procedures that were performed are the correction of the hypertelorism, the reconstruction of the nose and correction of the midface. Concerning the first, we conclude that the results of the medial faciotomy as well as the orbital box osteotomy were good and stable over time, apparently there is a good growth potential of bone in this region. There was a tendency to perform a medial faciotomy in case of a more extensive hypertelorism with a more pronounced maxillary deformity, and an orbital box osteotomy for the milder cases. [4,14-15] The fact that the deformities are of a symmetrical type adds to the good long term results of hypertelorism correction, probably because effect of the correction can be estimated more accurate in these patients. Once again this study demonstrates that vertical dystopia is not caused by a correction of hypertelorism. [2] As this is common in patients with an oblique facial cleft, the cause of the vertical dystopia must be a growth restriction within the osseous structures itself, rather than a direct effect of surgical intervention. [16] Therefore, it is safe to perform these operations at a relatively young age, taking the position of the developing tooth buts in account. [17-18]

Reconstructing the nose is the most challenging aspect of patients with a median facial cleft, especially the nasal dorsum and projection of the nose, as well as the positioning of the scars. [19] In contrast to the oblique facial clefts, the nostrils are not affected, and the shortage of skin is less of a problem. [20] The relative surplus of skin is regularly excised through a midline incision on the dorsum of the nose, at the same session as the hypertelorism correction. Although this skin occasionally consists of a different quality, rearrangement of the present skin provides a sufficient initial coverage of skin on the nose.(4) This is strengthened by the fact that a relatively small number of patients received a forehead flap. As a result, however, scars are very visible in most cases. Perhaps these scars can be avoided. One forehead flap at an adult age might be preferable over the multiple scars derived from local flaps. [3,15,20] Alternatives are available in the form of a L-incision or tissue expansion. [4,19,21-23] Concerning the projection of the nose, the majority of patients received multiple grafts for reconstruction of the dorsum. Costochondral grafts gave the most stable result. [24-25] To create an adequate projection of the nose, a correction of the midface is frequently required by

a Le Fort advancement. [26] Because of the lack of growth potential in the zone of the nose, good initial results consequently deteriorate over time as the rest of the face grows. A correction of the earlier reconstruction is almost inevitable to keep the face aesthetically balanced. [14]

Looking specifically at the midface, a special pattern of growth is observed in these patients. There is an absent or diminished growth potential at the site of the cleft, resulting in an hour-glass deformity; a 3-dimensional underdevelopment in the midface. [2,19] Therefore, the maxillary hypoplasia is most likely the result of an intrinsic growth restriction and not induced by previous surgery (Fiure 3). [16-17,27-28] Thus, growth of the maxilla, orbital zone and alveolar arch in sagittal direction should not be expected and consequently should be anticipated on during surgery.

Taking these conclusions into account, we provide a guideline for time and type of surgery. Planning of the incisions is important in these reconstructions. A suboptimal planning or poor executed operation reduces the alternatives to accomplish an optimal result at the end. Before starting any treatment, a plan for all future surgeries should have been developed, since reconstructions usually consists of a multiple staged operations adapted for every patient individually.

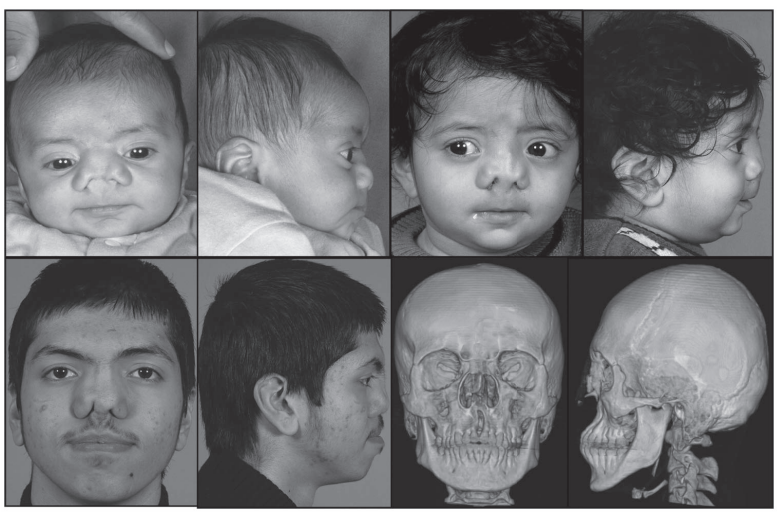

Figure 3.a.-3.h. *Male patient with Frontorhiny (ALX3 mutation), aged two months, one year and 17 years. The single surgical intervention was reconstruction of nasal dorsum at the age of one. A clear underdevelopment of the maxillary region and restricted growth in the nasal area is shown. Patient is scheduled for a Le Fort II advancement and consecutive reconstruction of his nasal septum, dorsum, tip, and alar rims.*

Age <1 year: Correction of skull base defects, closure of lip and palate

Patients with a midline cleft should be screened for skull base defects. Basal encephaloceles are corrected before the age of one year, regarding the risk of nasal obstruction, cerebral spinal fluid leakage and developing meningitis. [29-32] Close observation by a pediatrician is essential because of the possibility of hormonal disorders, and the possibility of leakage of cerebrospinal fluids. [33-34] Similar to current treatment protocols, closure of a cleft lip is performed around the age of three months and a cleft palate at the age of nine months.

Age 4-10 years: Hypertelorism correction, costochondral graft nasal dorsum

The choice between orbital box osteotomy and medial faciotomy is primarily based on the associated deformity of the alveolar ridge. A medial faciotomy is preferred in case of maxillary involvement [4,14-15] and at a younger age. An orbital box osteotomy is recommended towards the age of 10 years.

A cartilage graft for reconstruction of the nasal dorsum has proven to give the most stable result over time. [24-25]

Age >16 years: Le Fort I or III, secondary correction nasal dorsum, final corrections

A Le Fort I, II or III advancement is part of a combined orthodontic surgical treatment plan and preferably performed at the age of 18 years or older. Early corrections may result in an under correction at later age due to the growth restriction which requires additional surgery at skeletal maturity. A Le Fort I to III advancement should therefore be postponed whenever possible. [26] A correction of the earlier nose reconstruction is almost inevitable to keep the face aesthetically balanced. [14] In case of midfacial hypoplasia an adequate projection of the nose cannot be achieved before a Le Fort advancement is performed. Final correction of the nose should therefore be postponed after adequate correction of its base.

Conclusion

Direct referral to a specialized center benefits the number of operations. Experience can be gained in this matter, which will lead to better surgical results. The intrinsic growth restriction at the site of the cleft and its adjacent structures makes the result of reconstruction of the face difficult to predict and anticipate on. Early reconstructions will

lead to the need for reoperations due to aesthetic and functional misbalance, once the face has matured. We do not proclaim abstention from early surgery, but intervention should always be deliberated. Well placed incisions at a young age should be reusable during future surgical intervention. The provided guidelines and insight in restricted growth potential should be taken into account when planning actual but also future operations.

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CONSEQUENCES

CHAPTER 6

Satisfaction with facial appearance and its determinants in adults with severe congenital facial disfigurement: a case-referent study

Versnel SL, Duivenvoorden HJ, Passchier J and IMathijssen IMJ

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Abstract

Background: Patients with severe congenital facial disfigurement have a long track record of operations and hospital visits by the time they are 18 years old. The fact that their facial deformity is congenital may have an impact on how satisfied these patients are with their appearance. This study evaluated the level of satisfaction with facial appearance of congenital and of acquired facially disfigured adults, and explored demographic, physical and psychological determinants of this satisfaction. Differences compared with non-disfigured adults were examined.

Methods: Fifty-nine adults with a rare facial cleft, 59 adults with a facial deformity traumatically acquired in adulthood, and a reference group of 201 non-disfigured adults completed standardized demographic, physical, and psychological questionnaires.

Results: The congenital and acquired groups did not differ significantly in the level of satisfaction with facial appearance, but both were significantly less satisfied than the reference group. In facially disfigured adults, level of education, number of affected facial parts and facial function were determinants of the level of satisfaction. High fear of negative appearance evaluation by others (FNAE) and low self-esteem (SE) were strong psychological determinants. Although FNAE was higher in both patient groups, SE was similar in all three groups.

Conclusion: Satisfaction with facial appearance of individuals with a congenital or acquired facial deformity is similar and will seldom reach the level of satisfaction of non-disfigured persons. A combination of surgical correction (with attention for facial profile and restoring facial functions) and psychological help (to increase SE and lower FNAE) may improve patient satisfaction.

Introduction

Reconstruction of rare facial clefts is complex and challenging. Since they can encompass deformities in all facial units and with a different degree of severity, they represent a large spectrum of congenital facial deformities. [1] Surgical treatment aims at restoring facial function and creating a more 'normal' appearance, and often spans an interval of at least 18 years. At this age most patients have undergone multiple operations and many more hospital visits.

To assess the effect of the reconstructive process, patients' satisfaction with their facial appearance is an important outcome criterion. Whereas once considered a 'soft indicator', evaluation of patient satisfaction has become integrated into healthcare quality management. [2] In addition, studies on adult patients with predominantly mild facial disfigurements found a close relationship between satisfaction with facial appearance and psychosocial functioning, indicating more relevance for using this outcome measurement. [3-10]

A patient's satisfaction with facial appearance after reconstruction is determined by many factors. The fact that the rare facial cleft deformity is congenital might be of influence, but evidence is scarce. [11,12] Studies on other possible determinants of satisfaction with facial appearance among different populations produced conflicting results .

The first aim of this study was to explore the level of satisfaction with facial appearance of adults treated for a rare facial cleft by comparing them with patients with traumatic-acquired facial disfigurement at an adult age, and with non-facially-disfigured subjects. Secondly, to identify demographic, physical and psychological determinants for the level of satisfaction after reconstruction in adult facially disfigured persons. For this, candidate-determinants were studied in a combined population of patients with a rare facial cleft and with a traumatic facial disfigurement; these results were compared with the reference group without facial disfigurement. The third aim was to evaluate whether these determinants differ between the three groups.

Materials and methods

Study populations

Patients with rare facial cleft

Of the 123 patients with an extensive rare facial cleft operated between 1969 and 2009, 75 were invited to participate.

Hemifacial microsomia and mild facial clefts were excluded. The remaining 48 patients were excluded when they met one or more of the following criteria: deceased (four), incomplete data (nine), age under 18 years [32], mentally retarded (one), blind (one), or not able to understand Dutch (one).

Patients with an acquired facial deformity

A reference group of patients with an acquired facial deformity due to facial trauma at an adult age with a minimum follow-up time of two years after initial reconstruction was recruited. The same exclusion criteria were applied as for the rare facial cleft population. In addition, all patients with an additional visible congenital craniofacial disfigurement were excluded.

Reference group without facial disfigurement

For the reference group, persons without any congenital or acquired visible deformity were recruited in the waiting rooms of five randomly selected general practitioner (GP) practices in Rotterdam. Again, the exclusion criteria were the same as those applied for the rare facial cleft population.

Design and procedure

This clinical cross-sectional study was approved by the local Medical Ethics Committee (MEC-2006-121).

An explanatory letter, a patient information form, the questionnaires, an informed consent form were mailed to the participants. The patients were given one month to consider their decision. Patients who did not return their questionnaire within one month were contacted again. When participation was refused, the motive for declining was asked.

Subjects in the reference group received the same package and were asked to complete the questionnaires at home. Signed informed consent was obtained from all participants.

Assessments

Demographic information

The questionnaire provided data on age, gender, nationality, marital status, occupational and educational level, and medical condition.

Visual Analogue Scale

The visual analogue scale (VAS) was a 100-mm continuous line that is horizontally visualised and anchored by word descriptors at the poles: "very dissatisfied" at the left and "very satisfied" at the right pole. With this self-report device the magnitude of satisfaction with the appearance of the total face (Facial-VAS) was measured. The patients had to mark the location on the line that adequately represented their perception of their current appearance. The VAS is a frequently used measure and it has shown reliability and validity in studies on facial appearance. [5,13] The internal consistency reliability of the Facial-VAS in this study, determined with a VAS of the nose and of the zone of the eyes, was considered good (Crohnbach's alpha: 0.84).

Body Cathexis Scale

To measure satisfaction with facial appearance, a modified version of the Body Cathexis Scale (BCS), [14] the Facial-BCS, was constructed. The original BCS measures level of satisfaction with one's own body; it comprises 46 items with a five-point response scale. Because the 'Face-subscale' of this original BCS does not cover all important facial parts and functions, extra facial parts and functions were added by an expert panel. These missing facial parts and functions were assessed by evaluation of a semi-structured interview with all patients and an analysis of the photographs of all patients. The adjusted scale was piloted in 20 volunteers. Previous studies have used modified versions of the original BCS. [15,16] A validated Dutch version of the original BCS is available. [17]

Different subscales were used for facial appearance, facial function, and the body. They all demonstrated a good internal consistency reliability (Cronbach's alpha: BCS facial appearance: 0.90, BCS facial function: 0.83, BCS body: 0.77, BCS total: 0.94)

Rosenberg Self-esteem Scale

The Rosenberg Self-Esteem Scale (RSES) is a ten-item self-report inventory measuring self-esteem on a four-point Likert scale. [18] Internal consistency, discriminant and convergent validity have been reported; [19] a validated Dutch version is available. [20]

Fear of Negative Appearance Evaluation Scale

The 6-item Fear of Negative Appearance Evaluation Scale (FNAES) is a self-report measure, assessing apprehension about appearance evaluation. The FNAES is reported to have good internal consistency and a similar convergent validity with measures of body image in the field of eating disorders. [10] The English version was translated to Dutch according to recommendations for adequate translation methods. [21]

Clinical appearance

Two experts independently scored which facial parts were affected in both the congenital and the traumatic-acquired group. This scoring was based on pre-operative and postoperative photographs, as well as on clinical notes from the patient's medical chart. The experts were a plastic surgeon and a plastic surgery resident, both familiar with congenital craniofacial pathology.

Statistical analyses

Version 14.0 of SPSS for Windows was used for statistical analysis. As measures of central tendency for metric variables the mean and/or median were used, and as measures of dispersion, the standard deviation and/or interquartile range (IQR) were used. For categorical variables, percentages were calculated as a measure of central tendency. Unpaired t-tests (two-tailed) were performed to compare means between groups. Differences in categorical variables between groups were analysed using a Fisher-exact test. Associations between the measures of satisfaction were examined using Pearson's product-moment correlation. Multivariate analyses of covariance (MANCOVA) were conducted to compare means between the three groups with adjustment for mean age and gender. MANCOVA, with additional adjustment for mean number of affected facial parts, was used to compare means between the two patient groups. To identify determinants of satisfaction with facial appearance, multiple linear regression analysis was used. The variables were entered in three blocks: demographic, physical and psychological characteristics. As a measure of relative importance of the individual determinants, the standardized regression coefficient (ß) was estimated. In the regression analysis the Facial-VAS score was used as outcome variable. This was preferred to the BCS facial appearance score because the VAS assesses more than the sum of the facial parts; it also takes the relative importance and proportions into account. All tests were performed at p=0.05 level of significance (two-sided) and, if necessary, adjustment was made for multiple testing.

Results

Of the 75 facial cleft patients, 59 (79%) participated in the study. The remaining 16 patients did not participate for the following reasons: eight did not respond to the letters (four of them lived abroad), three were very dissatisfied with the treatment they received (which they experienced as very traumatic), two had talked to the media about their disfigurement and had no wish to discuss it again, and for three patients it was psychologically too difficult to be confronted with their disfigurement.

Demographic characteristics

Table 1 presents the characteristics of the study groups. There was a significant difference between the congenital and the acquired patients for gender, age, and number of affected facial parts; there was also a significant difference between the congenital patients and the reference group for age. Therefore, in order to make an unbiased comparison of the groups, statistical adjustment was made for the variables gender, age and, if indicated, number of affected facial parts.

The level of satisfaction in both the congenital and acquired patient groups was significantly lower than in the non-disfigured reference group. The mean Facial-VAS score after additional adjustment for number of affected facial parts was 4.64 for the congenital group and 4.40 for the acquired group (p=0.65). The percentage of patients dissatisfied with facial appearance (when taking the mean value of the reference group as the average level of satisfaction with facial appearance) is shown in Figures 1 and 2.

In the two patient populations, the lines reflecting the cumulative percentage distribution of the level of satisfaction were almost identical. The Pearson correlation coefficient for the relation between the scores of Facial-VAS and BCS facial appearance was r=0.66 (p=0.0001). In the combined group of congenital and acquired patients the Facial-VAS score had the highest correlation with the BCS scores of the profile of the face (r=0.65, p=0.0001), the nose (r=0.64, p=0.0001) and the eyes (r=0.47, p=0.0001).

Determinants of satisfaction with facial appearance

Table 3 shows all evaluated candidate-determinants of satisfaction with facial appearance in the patients group and in the reference group. Demographic and physical determinants in the patient group were level of education, number of affected facial parts, and the function of the face. Self-esteem (SE) and fear of negative appearance evaluation (FNAE) were important psychological determinants.

Table 1. *Demographic characteristics*

				P-values[2] for differences between groups	
	Congenital (*C*) N=59	**Acquired (*A*) N=59**	**Reference (*R*) N=201**	***C* vs. *A***	**C vs. *R***
Gender (%)				0.01	0.44
Male	32.2	58.6	38.5		
Female	67.8	41.4	61.5		
Age (years)				0.01	0.001
Mean	34.05	43.07	43.75		
SD	12.92	14.59	17.14		
Min-Max	18-74	18-84	18-79		
Education level (%)				0.68	0.34
Primary school [1]	35.1	27.6	25.5		
High school [1]	47.4	55.2	51.5		
Postgraduation[1]	17.5	17.2	23.0		
Dutch nationality (%)	89.8	84.5	91.0	0.42	0.80
Working/ studying (%)	78.0	72.4	65.5	0.53	0.08
Partner (%)	47.5	72.4	72.5	0.01	0.01
Number of affected facial parts				0.001	0.001
Mean	6.60	4.04	0.00		
SD	2.36	2.38	0.00		

[1] % represent column percentages; [2] p-values corrected for multiple testing, α= 0.025

Satisfaction with facial appearance

Table 2 presents mean scores for satisfaction with facial appearance.

Table 2. *Satisfaction with facial appearance*

							P-values[2] for differences between groups	
	***C* N=59**		***A* N=59**		***R* N=201**		***C* vs. *A***	***C* vs. *R***
	$\hat{\mu}$[1]	$\hat{\sigma}$	$\hat{\mu}$[1]	$\hat{\sigma}$	$\hat{\mu}$[1]	$\hat{\sigma}$		
Facial BCS (Score range 1-5)	3.40	0.54	3.47	0.54	3.87	0.54	0.63	0.001
Facial VAS (Score range 0-10)	4.19	2.24	4.72	2.23	6.80	2.23	0.30	0.001

$\hat{\mu}$=mean, $\hat{\sigma}$=standard deviation; [1] adjusted for mean values of age and gender; [2] corrected for multiple testing, α= 0.025

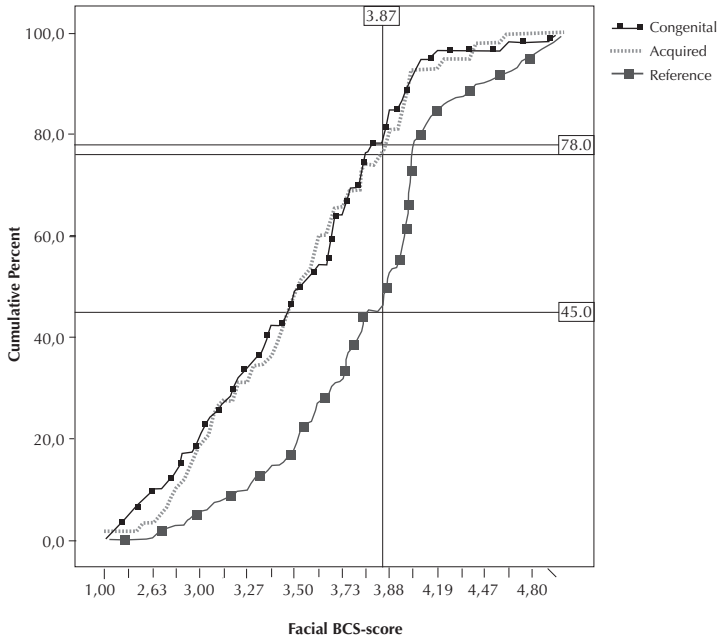

Figure 1. *Cumulative percentage distributions of the level of statisfaction with Facial BCS.*

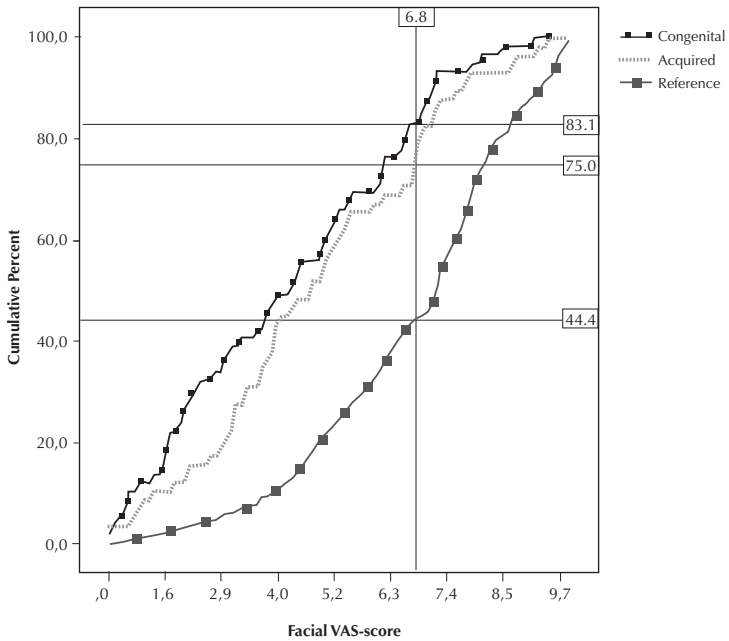

Figure 2. *Cumulative percentage distributions of the level of statisfaction with Facial VAS.*

Patients with facial disfigurement were more satisfied with their facial appearance when they had high SE and low FNAE. These two psychological determinants accounted for almost 43% of the variance; this was substantially more than the demographic and physical determinants. Considering the magnitudes of ß, FNAE and the function of the face had the highest values. In the non-disfigured reference group the function of the face, SE and FNAE were also significant determinants, although their contribution to the level of satisfaction with facial appearance was lower than that in the patient group.

Table 3. *Determinants of satisfaction with facial appearance*

Population	Group factor	R^2	Candidate- determinant	ß	P
Celft and Acquired group	Demographic	0.11	Group	-0.09	0.36
			Gender	0.11	0.28
			Age	0.01	0.91
			Nationality	0.05	0.56
			Partner	0.02	0.85
			Level of education	0.27	0.01
	Physical	0.35	Number of affected facial parts	-0.22	0.01
			Physical condition	-0.04	0.65
			Satisfaction with body	-0.13	0.20
			Function of face	0.57	0.001
	Psychological	0.43	Self-esteem	0.23	0.02
			Fear of negative appearance evaluation	-0.48	0.001
			Psychological condition	-0.07	0.42
Reference group	Demographic	0.03	Gender	0.10	0.21
			Age	-0.09	0.24
			Nationality	0.10	0.17
			Partner	0.04	0.63
			Level of education	-0.02	0.78
	Physical	0.16	Physical condition	0.08	0.26
			Satisfaction with body	0.04	0.68
			Function of face	0.38	0.001
	Psychological	0.20	Self-esteem	0.25	0.01
			Fear of negative appearance evaluation	-0.24	0.01
			Psychological condition	-0.10	0.18

Differences in determinants between the groups

The mean group scores of SE, FNAE and function of the face are shown in Table 4. The level of SE in the three groups is similar, but FNAE is significantly higher in the two patient groups.

Table 4. *Differences in determinants between the groups*

							P-values[2] for differences between groups	
	***C* N=59**		***A* N=59**		***R* N=201**		***C* vs. *A***	***C* vs. *R***
	$\hat{\mu}$[1]	$\hat{\sigma}$	$\hat{\mu}$[1]	$\hat{\sigma}$	$\hat{\mu}$[1]	$\hat{\sigma}$		
Fear of Negative Appearance Evaluation (Score range 6-30)	17.39	6.18	15.50	6.12	12.78	6.10	0.16	0.001
Rosenberg Self-esteem	29.61	5.84	30.45	5.79	31.04	5.75	0.45	0.10
BCS Function Face (Score range 1-5)	3.53	0.51	3.51	0.51	3.90	0.50	0.71	0.001

$\hat{\mu}$=mean, $\hat{\sigma}$=standard deviation; [1] adjusted for mean values of age and gender;[2] corrected for multiple testing, α= 0.025

Discussion

Satisfaction with facial appearance

In patients with congenital and acquired disfigurement the level of satisfaction with facial appearance was similar, even when accounting for the number of affected facial parts. As expected and in line with previous studies, it was lower than in persons without facial disfigurement. [3,5,7,8,22] It is striking, however, that 44% of the non-disfigured subjects reported to be dissatisfied with their facial appearance.

The similarity between the level of satisfaction among the congenital and acquired groups is unexpected. Adaptation of body image after surgical correction is thought to be more challenging for patients with an acquired deformity than for patients with a congenital disfigurement; however, evidence for this assumption is limited. [11,12] Also, one study on hemi-facial palsy contradicts this assumption. [23]

Although outcome studies generally recommend to administer measures for body image [24] they have not yet shown significant differences in studies on facially

disfigured persons, not even when using the facial subscale. [12] For this reason, together with the fact that satisfaction with facial appearance was the dimension of body image of interest, [25] satisfaction with facial appearance was explored and not total body image. The validity of the BCS facial appearance was demonstrated by the substantial correlation with the Facial-VAS.

The high correlation between the Facial-VAS score and the BCS score of the facial profile in the congenital and acquired groups shows that the facial profile was valuable for the patients, besides the nose and the eyes.

Determinants of satisfaction with facial appearance

The level of education, number of disfigured facial parts, function of the face, self-esteem (SE), and fear of negative appearance evaluation (FNAE) in the congenital and acquired groups were important determinants for the level of satisfaction with facial appearance. The higher the level of education, the more satisfied the patients were. A possible explanation for this could be that persons with a higher level of education might better understand that a 'normal' appearance is difficult to achieve and therefore have more realistic expectations or are more likely to accept their disfigurement. It is suggested that, in children, intelligence is an important protective factor against maladjustment to facial disfigurement. [26]

Neither gender and age, nor nationality and having a partner were determinants of satisfaction with facial appearance. The relevance of these factors with respect to satisfaction with facial appearance have shown inconsistent results. [5,7,27-30]

The more disfigured the facial parts, the less satisfied a patient was. The number of affected facial parts, however, is not related to the severity of the facial deformity (an affected nose can have just a scar or be totally disfigured).

The higher a patient's satisfaction with the function of the face, the higher the satisfaction with facial appearance was. This supports the idea that, during correction of the facial deformity, not only the appearance but also the function of the facial parts should be adequately addressed.

The psychological determinants accounted for a substantial part of the variance of the level of satisfaction among the patients. Others also linked SE to satisfaction with facial appearance. [29,31,32] This relationship seems to be bidirectional: increasing satisfaction with facial appearance through surgery increases SE and by increasing SE satisfaction with outcome increases. On the contrary, the FNAE construct has not previously been linked to satisfaction with facial appearance; however, it has been linked to body image (i.e., body size and shape). [10]

Although the physical and psychological determinants of satisfaction with facial appearance in the non-disfigured reference group correspond to those in the patients group, they account for a less substantial part of the level of satisfaction.

Differences in determinants between the groups

In the present study, the similar level of SE between the congenital and the reference group is partly supported, [7,30,32-34] but also partly contradicted [3,6,28,35,36] by others. However, most of these latter studies were performed in children and adolescents with a cleft-lip-palate. Only a few were conducted among adults with congenital facial disfigurements. [3,6,28,30] Only one study was performed in patients with a large degree of residual deformity (hemifacial microsomia and orbital hypertelorism) and reported a significantly lower level of SE in the patients than in the matched control group. [3] However, when comparing the scores on the Rosenberg Self-Esteem Scale of the latter patients (mean=32.00, SD=6.26) with that of a measured level of SE in a non-disfigured population in the USA (mean=32.21, SD=5.01), [20] the mean levels of SE in these two groups is almost identical. In our reference group the mean score of SE (mean= 31.04, SD=5.47) is very similar to the level measured in a non-disfigured population in the Netherlands (mean=31.60, SD=4.48). [20] Other studies reporting a lower level of SE in Chinese populations among patients, [6,28] also presented debatable results regarding SE levels in the control groups.

Due to methodological deficits and inconsistencies it is difficult to draw definite conclusions about all these results. Some previous conclusions are based on preliminary studies or studies with low response rates. In addition the choice of a control or reference group may make an important difference; e.g. if matched case controls are used, which factors should be controlled for? The present study shows that the level of education should be controlled for.

Generally, it appears that adult facially disfigured people do not have a lower level of SE. Perhaps they compensate for the deficits they recognize in themselves by placing greater emphasis on other qualities, [12] or perhaps they adapt their goals and values thereby keeping their SE at a good level.

In our study, the fact that the congenital and acquired groups had a higher FNAE than the reference group suggests that FNAE is increased by facial disfigurement. This is supported by the idea that those affected are acutely aware of the reactions of others and may become excessively preoccupied with their appearance and the effect it has on others. [37] An earlier study reported a higher level of general Fear of Negative Evaluation (FNE) in adults with congenital facial deformities than a control group.

[6] FNE is related to FNAE, in that both constructs assess cognitive aspects of social anxiety; the main difference is that FNAE is concentrates more on the impact of facial appearance.

Clinical implications

Patients of the congenital and acquired group should be screened for SE and FNAE. Despite the fact that psychological support for patients with congenital deformities has been advocated in previous studies, [38] in most clinics it is not sufficiently applied in daily practice. Parents can have difficulties with admitting their child has problems or are just not sufficiently aware of it. For this reason and the fact that SE is mainly formed during childhood and adolescence, it is important to screen at an early age. The involvement of the parents is important; moreover since the parent's feelings about their child's defect are thought to be paramount in the development of the child's self-esteem and self-image. [39]

Methodological limitations

In this study, the limited number of patients restricted the number of determinants that could be evaluated. Because SE and social anxiety are considered the most commonly cited as being central to adjustment to disfigurement, [40] SE and FNAE (i.e. the cognitive affective aspect of social anxiety) were selected for evaluation in our study. This does not preclude, however, that other factors (e.g. depression and expectations) might be of relevance.

It was difficult to find patients in whom the acquired facial deformities matched the extent of those with congenital deformities; therefore, matching the number of affected facial parts was impossible.

As at least six of the 16 non-participants were dissatisfied with treatment or had psychological problems, outcomes of the congenital group may be worse than presented here. Nonetheless, a participation rate of 79% is considered good.

Conclusion

Patients with facial disfigurement should be screened for low SE and high FNAE. A combination of surgical correction (with attention paid to facial profile and restoring facial functions) and psychological help (to increase SE and lower FNAE) may improve patient satisfaction on the long term.

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CHAPTER 7

Social and relational functioning of adults with congenital or acquired facial disfigurement

Versnel SL, van den Elzen MEP, Hovius SER, Passchier J, Duivenvoorden HJ, Mathijssen IMJ

Submitted

Abstract

Purpose: 1) Evaluate whether patients with severe congenital facial disfigurement differ from patients with acquired facial disfigurement and from people without facial disfigurement regarding different dimensions of social and relational functioning; 2) explore to what extent dimensions of social and relational functioning are related to satisfaction with facial appearance (SFA), severity of the facial deformity, fear of negative appearance evaluation by others (FNAE), and self-esteem (SE) ; 3) identify which dimensions of social and relational functioning should be addressed in psychological treatment.

Material and methods: Fifty-nine adults born with a rare facial cleft, 59 patients with a traumatically acquired facial deformity in adulthood, and a reference group of 120 non-facially-disfigured adults, completed standardized physical, social, relational and demographic questionnaires.

Results: Social and relational functioning did not differ between congenital and acquired facially disfigured people. The congenital and acquired group differed from the normal reference group on the behavioral dimensions by displaying a decrease in frequency of interpersonal functioning. SE was a strong predictor for all dimensions of social and relational functioning. SFA and FNAE were good predictors for the cognitive-affective dimensions, but not for the behavioral dimensions.

Conclusion: Avoiding stress caused by stigmatisation, fear of negative evaluation and uncertainty about the reactions of others, forms the base of avoidance behavior in facially disfigured people. Although the avoidance leads to a reduced stress level, it also leads to ego constriction. Improving a patient's SE or SFA, and reducing FNAE can contribute to an amelioration of social and relational functioning. Psychological treatment should concentrate on social skills and dysfunctional cognitive-affective processing.

Introduction

Feelings attached to physical appearance come from a rich variety of sources, including mythology, legends, fairy tales and other examples from history and contemporary society. The ethos of most of these examples is that especially beauty is all-important. [1] In this, the face is seen as the mirror of the soul (Cicero); with that association that 'what is beautiful is good'. [2] Even very young infants have the ability to categorise on attractiveness, have the same aesthetic perception as adults and prefer to look at attractive faces.

Physical attractiveness is stereotypically strongly associated with sociability, dominance, general mental health, intelligence and physical health. [3,4] The rating of facial attractiveness decreases, with an increasing severity of the facial disfigurement. [5,6] As a consequence, patients with abnormal facial characteristics are rated as significant less attractive, but also as less honest, less employable, less trustworthy, less optimistic, less effective, less capable, less intelligent and less popular. [7] Facial disfigurement has even been called the last bastion of discrimination. [8]

It is difficult for facially disfigured people to adequately cope with these prejudices and concomitant disapproving reactions from others. Previous conducted studies have shown that problems with social interactions are the main concern in this population. [9-14] Therefore, it is not surprising that, in comparison with non-disfigured, physically impaired patients display more inhibition on social behavior. Moreover, they tend to withdraw from peers and are more probable of being disliked by peers. The adopted different coping behaviors, to hide or compensate for their disfigurement, often makes them unsociable, which gives rise to an interference with personal relationships, work life and leisure activities. [9-11,13,15,16]

However, scientific research on social and relational functioning of congenital facially disfigured adults is limited; the majority of studies were performed in children and adolescents. Secondly, most studies were done in patients with a deformity of a specific facial part. Thirdly, the majority of the studies had a small sample size, a lack of use of standardized questionnaires or not optimal reference group. Overall results on social and relational functioning were inconsistent, and difficult to compare due to methodological weaknesses.

Studies on adults with acquired facial deformities are even more scarce. [17] In addition, all these performed studies have methodological weaknesses like very small sample sizes, again infrequent use of standardized questionnaires, low response rate and lack of relevant control groups. Moreover, only two studies have distinguished congenital from acquired facial deformities. [18,19]

It is thought that persons with an acquired facial disfigurement have more problems to adjust to their facial disfigurement than persons with a congenital facial deformity. [19-21] Patients with a congenital facial deformity have been confronted with the consequences of their deformity their whole lives and, therefore, have had more time to get used to the situation and finds ways to cope. Patients with an acquired deformity on the contrary have had less time to deal with the sudden change in reactions from others and within themselves.

Multiple factors might be involved regarding the extent to which a facial disfigurement affects social and relational functioning. These factors can be extra-personal components such as cultural (for example the disfigurement is a punishment from God), general awareness and tolerance in society (e.g. in the old days people were seen as a monster) or family (support and upbringing). Especially, family may have a great impact on the social and relational functioning of the patient during upbringing. [22]

Even more important are the intra-personal components since they are more susceptible to change or treatment. Examples are the severity of the disfigurement, the dissatisfaction with facial appearance, fear of negative appearance evaluation and self-esteem.

Social response towards individuals with milder defects is less predictable than that towards severely disfigured individuals. There is some speculation that milder disfigurements cause as much, if not more anxiety, than severe disfigurement. It is the unpredictability that is thought to raise anxiety levels. [23-26]

Patients with a facial disfigurement and dissatisfaction with their facial appearance have been associated with greater loneliness, fewer close friends and are less likely to belong to a club or society. [13,15,16,27] Fear of negative appearance evaluation is a cognitive-affective aspect of social functioning. Compared to a non-disfigured population, people with a facial disfigurement have a greater fear of negative appearance evaluation in general. [28] The relation with other dimensions of social and relational functioning has not been assessed in facially disfigured people. Self-esteem is related to social functioning. It has not been investigated whether this relation is similar for the different dimensions of social and relational functioning.

The dimensions of social and relational functioning can be divided into general social functioning (group functioning) and interpersonal functioning. In addition, a difference can be made between cognitive-affective and behavioral aspects.

Cognitive-behavioral interventions have often been used to treat problems related to facial disfigurement. Previous studies have demonstrated the effectiveness of these cognitive-behavioral interventions. [19,29] However, the effectiveness of the various components of such interventions remains unclear.

The objectives of this study were to 1) evaluate whether patients with severe congenital facial disfigurement differ from patients with acquired facial disfigurement and people without facial disfigurement regarding different dimensions of social and relational functioning; 2) explore to what extent dimensions of social and relational functioning are related to satisfaction with facial appearance, severity of the facial deformity, fear of negative appearance evaluation by others, and self-esteem; 3) identify which dimensions of social and relational functioning should be addressed in psychological treatment.

Materials and methods

Study populations

Patients with a congenital deformity

For the congenital group patients with a rare facial cleft were recruited. Since they can encompass deformities in all facial units in a different sequence and with a different degree of severity, they represent a large spectrum of congenital facial deformities. [30, 31]

Seventy-five out of the 123 patients with an extensive rare facial cleft who were operated on their facial clefts between 1969 and 2009 at the department of Plastic and Reconstructive Surgery of the Erasmus University Medical Center or Sophia Children's Hospital, Rotterdam, the Netherlands, were invited to participate in this study.

Patients with hemifacial microsomia and mild facial clefts were excluded. The other 48 patients were excluded because they met one or more of the following removal criteria: deceased (four), incomplete data (nine), age under 18 years, mentally retarded (one), blind (one), and insufficient command of the Dutch language (one). Another study using this patient sample has been reported. [32]

Patients with an acquired facial deformity

The acquired group was recruited from the patient population of the same department. From all patients who suffered from facial disfigurement due to facial trauma at an adult age, patients were selected with a minimum follow-up time of 2 years after the first

operation. This was done because after that period it could be expected that the physical and/or psychological consequences of that trauma were stabilized. Patients who had suffered from personal assault were excluded. In addition, the same exclusion criteria as in the rare facial cleft population were used and also all patients with an additional visible congenital disfigurement were excluded. 104 patients were invited to participate in this study.

Reference group without facial disfigurement

Patients from several general practitioner practices in Rotterdam and employees of the Erasmus University Medical Centre without any congenital or acquired visible deformity were recruited by posters. Again, the exclusion criteria were similar to those used in the rare facial cleft group.

Design and procedure

A clinical-empirical cross-sectional study was designed and conducted. Ethical approval was received from the board of the Medical Ethical Committee of the Erasmus University Medical Centre Rotterdam (MEC-2006-121).

After the home addresses of the patients with congenital or acquired craniofacial deformities were retrieved, a cover letter, a patient information form, questionnaires, an informed consent form to sign, and a stamped return envelope were sent by mail. They had a month to consider their decision and could withdraw from the study at any moment. Patients, who did not return their questionnaires within one month, were contacted again. When someone refrained from participation, his or her motive was asked. The individuals of the reference group without facial disfigurement were recruited in the waiting room of five randomly selected general practitioner practices in Rotterdam, the Netherlands, and employees of the Erasmus University Medical Center. These participants were given the same package as was sent to the patients with facial disfigurement and were asked to complete the questionnaires at home.

Assessments

Demographic information

This questionnaire provided data on age, gender, having children, having a partner, and educational level.

Fear of Negative Appearance Evaluation

The Fear of Negative Appearance Evaluation Scale (FNAES) is a six-item self-report questionnaire, assessing apprehension about appearance evaluation. [33] It is the most recent modification of the Fear of Negative Evaluation Scale, which is a measure of the cognitive aspects of social anxiety. [34] The FNAES is sensitive to emotional distress and helps to determine the magnitude of the distress over their negative appearance, avoidance of evaluative situations and the expectation that others would evaluate themselves negatively. The FNAES is reported to have good internal consistency and a similar convergent validity with measures of body image in the field of eating disorders. [33] This scale was translated fully according to recommendations for good translation. [35]

Social Avoidance and Distress

The Social Avoidance and Distress Scale (SADS) is a 28-item questionnaire measuring social avoidance and subjective distress. Having a high score for SADS indicates avoiding social interactions more, a preference to work alone, to be less talkative, more worrying and less confident about social relations. [34] Although the SADS is one of the most widely used self-report measure for assessing the magnitude of social anxiety, yet it is not a diagnostic tool for a social phobia or any other anxiety disorder. The SADS has proved to have a good reliability, validity and adequate test-retest reliability. [34,36-38] The English version was translated into Dutch fully according to recommendations for good translation methods. [35]

Family functioning

The 12-item General Functioning subscale of the McMaster Family Assessment Device (FAM) was designed to assess family functioning as it was in childhood. The questionnaire investigates the six family functioning domains: problem solving, communication, roles, affective responsiveness, affective involvement and behavioral control. It has shown good reliability and validity. [39] In this study the patient was the only family member that completed this self-report questionnaire with a four-point Likert Scale. It was translated fully according to recommendations for good translation. [35]

Interpersonal Behavior

The Scale for Interpersonal Behavior (SIB) was designed for clinical assessment concerning the state of assertiveness: the probability of the response or performance ('F': symbolising frequency or behavioral aspects), and the degree of discomfort or

distress ('S': representing cognitive-affective aspects). The SIB comprises 50 items scored twice (once in terms of frequency of occurrence of behaviors and once in terms of degree of discomfort). The 50-item version of SIB appears to be four dimensional for both behavioral (F) and cognitive-affective aspects (S); (1) display of negative feelings (FNEG/ SNEG), (2) expression of and dealing with personal limitations (FLIM/ SLIM), (3) initiating assertiveness (FASS/ SASS) and (4) praising others and the ability to deal with compliments (FPOS/ SPOS). The SIB has demonstrated good reliability and good validity, and has proven to be a sensitive measure of change. [40-42] As this scale was originally devised in the Netherlands, no translations had to be made.

Satisfaction with facial appearance

The Visual Analogue Scale (VAS) is usually a 100-mm continuous horizontal line with descriptors at the ends: "very dissatisfied" at the left, and "very satisfied" at the right.

This self-report device was used to measure the degree of satisfaction with facial appearance (SFA). The patients had to mark on the line what their perception of their own appearance was. It has shown to be highly associated with the Body Cathexis Scale. [28] The VAS is a frequently used measure and it has shown reliability and validity in studies on facial appearance. [43,44]

Self-esteem

The Rosenberg Self-Esteem Scale (RSES) is a 10-item self-report measure that assesses self-esteem on a four-point Likert-scale. [45] It is the most widely used measure for assessing self-esteem. Good internal consistency and validity have been reported. [46] A validated Dutch version was used. [47]

Severity of facial disfigurement

Two experts independently scored the severity of facial disfigurement in each patient of both the congenital and traumatic acquired group by using the Versnel et al. scoring list for facial disfigurement; this is a scoring list with an objective scoring approach. [48] Recent post-operative standardised photographs of all patients were used. The experts were two plastic surgery residents, both familiar with congenital craniofacial pathology. If scores differed, the average score was calculated.

Statistical analysis

The mean was used as measure of central tendency for metric variables, and the standard deviation was used as measure of dispersion. Percentages were calculated for categorical

variables as a measure of central tendency. T-tests for independent observations were performed to compare means between groups. A Fisher-exact test was used or analysis of differences on categorical variables between groups. Analyses of covariance (ANCOVAs) were conducted to compare means between the three groups with adjustments for mean age, gender and education level. ANCOVA with additional adjustment for severity of the facial deformity was used to compare means between the two patient groups. The magnitudes of the effects/differences were calculated by dividing the mean differences by the pooled standard deviations of the pertinent groups. Associations of the measures of social functioning with self-esteem (SE), fear of negative appearance evaluation (FNAE), satisfaction with facial appearance (SFA) and severity of the facial disfigurement (OS) were examined using the method of multiple linear regression analysis (procedure ENTER). As a measure of relative importance of the previous individual predictors, the standardized regression coefficient (ß) was calculated. As outcome variable the scores of the social and relational questionnaires were used. The tests were done at p=0.05 level of significance (two-sided) and with adjustment for multiple testing if indicated. Version 17.0 of the computer program SPSS was used for statistical analysis.

Results

Fifty-nine (79%) of the 75 facial cleft patients participated. The other 16 patients refused for several reasons: eight did not respond (four lived in another country), for three patients treatment had been traumatic and they were very dissatisfied with the results, two had had interviews with the media about their disfigurement and did not want to talk anymore, and for three patients it was emotionally too difficult to discuss their disfigurement.

Of the 104 trauma patients 59 (57%) participated. The majority of non-participants did not respond and could not be contacted.

Demographic characteristics

Characteristics of the two patients groups and the reference group are shown in Table 1. The congenital patients differed statistically significant from the acquired patients on gender, age, having a partner and whether they had children of their own. There was only a significant difference on the level of education between the congenital patients and the reference group. As a consequence of these findings, all analyses were statistically adjusted for gender, age and education level.

Table 1. *Demographic characteristics*

	Congenital (*C*) N=59	Acquired (*A*) N=59	Reference (*R*) N=120	P-values[2)] for differences between groups	
				C vs. *A*	*C* vs. *R*
Gender (%)				0.01	0.73
Male	32.2	58.6	29.4		
Female	67.8	41.4	70.6		
Age (years)				0.01	0.21
Mean	34.05	43.07	36.65		
SD	12.92	14.59	16.43		
Min-Max	18-74	18-84	18-79		
Education level (%)				0.68	0.04
Primary school [1)]	35.1	27.6	17.2		
High school [1)]	47.4	55.2	59.5		
Postgraduation[1)]	17.5	17.2	17.2		
Partner (%)	47.5	72.4	60.7	0.01	0.09
Children (%)	27.1	60	38.5	0.001	0.14
Severity facial deformity				0.001	-
Mean score	13.90	6.44	-		
SD	7.65	5.0	-		

[1)] % represent column percentages; [2)] p-values corrected for multiple testing, α= 0.025 (two-tailed)

The severity of facial disfigurement was significantly higher in patients with a congenital facial disfigurement compared to the patients with an acquired facial disfigurement.

Differences between the groups

Table 2 shows no significant differences between the congenital and acquired group on social functioning; even after additional adjustment for the severity of the facial disfigurement.

Table 2. *Differences between groups on social and relational questionnaires*

	C **(N=59)**		***A*** **(N=59)**		***R*** **(N=120)**		**P-values**[2)]				
	$\hat{\mu}$[1)]	$\hat{\sigma}$	$\hat{\mu}$[1)]	$\hat{\sigma}$	$\hat{\mu}$[1)]	$\hat{\sigma}$	***C*** **vs.** ***A*** [1)] [3)]		**SMD**	***C*** **vs.** ***R*** **SMD**	
SADS	17.59	4.29	19.36	4.37	18.40	4.25	.06	.22	-.41	.21	-.19
FAM	23.90	7.08	24.66	7.05	23.60	6.82	.57	.18	-.11	.67	.04
FNEG	2.71	.64	2,71	.66	2.99	.63	.99	.84	.00	.01	-.44
FLIM	3.32	.63	3.40	.63	3.53	.61	.62	.78	-.13	.04	-.34
FASS	3.00	.66	3.14	.66	3.21	.64	.29	.88	-.21	.048	-.32
FPOS	3.14	.76	2.98	.77	3.09	.77	.36	.10	.21	.71	.07
SNEG	2.14	.83	2.13	.85	2.13	.81	.92	.58	.01	.99	.01
SLIM	1.82	.68	1.74	.70	1.68	.67	.75	.70	.12	.19	.21
SASS	2.11	.80	1.97	.82	1.96	.79	.43	.80	.17	.20	.19
SPOS	1.95	.80	1.93	.80	1.88	.78	.85	.44	.03	.57	.09
FNAE	18.02	6.38	15.87	6.48	14.09	6.29	.19	.28	.33	.001	.62
SE	31.81	5.16	32.32	5.33	33.23	5.13	.64	.48	-.10	.07	-.28
SFA	4.28	2.19	4.67	2.24	6.98	2.19	.54	.43	-.18	.001	-1.23

C*=Congenital group,* ***A****=Acquired group,* ***R****=Reference group,* $\hat{\mu}$ *=mean,* $\hat{\sigma}$ *=standard deviation;,* ***SMD****=Standardized Mean Difference,* ***SADS****=Social Avoidance and Distress Scale,* ***FAM****=General Functioning subscale of the McMaster Family Assessment Device,* ***FNEG/SNEG****=behavioral/cognitive-affective aspects of display of negative feelings,* ***FLIM/SLIM****=behavioral/cognitive-affective aspects of expression of and dealing with personal limitations,* ***FASS/SASS****=behavioral/cognitive-affective aspects of initiating assertiveness,* ***FPOS/SPOS****=behavioral/cognitive-affective aspects of praising others and the ability to deal with compliments,* ***FNAE****=Fear of Negative Appearance Evaluation,* ***SE****=Self-esteem,* ***SFA****=Satisfaction with Facial Appearance;* [1)] *adjusted for mean values of age, gender and education level;* [2)] *corrected for multiple testing,* α*= 0.025 (two-tailed;* [3)] *with additional adjustment for severity of the disfigurement.*

Comparing the congenital group with the reference group demonstrates that they did not differ significantly on scores of the SADS and FAM. Looking at the specific questions of the FAM, the congenital facially disfigured patients indicated to have more difficulties to talk about fears and worries and more difficulties to take decisions, in comparison with the reference group.

No differences were seen between the congenital and the acquired group on the SIB. However, a significant difference was observed between the congenital group and the reference group on the behavioral aspects of SIB including reporting their negative feelings (FNEG), expressing their personal limitations (FLIM), and initiating assertiveness (FASS). Remarkably, all groups scored analogously on displaying positive feelings, both in cognitive-affective and in behavioral aspects.

Compared to the reference group, a significant higher score on FNAES was seen in the patients with congenital facial deformities. Patients with a congenital or acquired facial deformity were significantly less satisfied with their facial appearance compared to persons without a facial deformity.

Predictors of social and relational functioning

As can be seen in Table 3, SE is a significant predictor for all dimensions of social functioning: the higher the SE the better the social functioning. Its predictive value is less strong for the behavioral aspects of the SIB, than it is for the other dimensions of social functioning. In both the behavioral and the cognitive-affective aspects, SE has the highest predictive value for initiating assertiveness. Also FNAES has a significant predictive value for the dimensions of social functioning, except for the behavioral aspects FNEG, FLIM and FPOS. The higher the FNAES the more problems are encountered with social functioning. In the cognitive-affective aspects of the SIB, FNAES has the highest predictive value for initiating assertiveness. Satisfaction with facial appearance (SFA) appears to be a significant predictor for the dimensions of social functioning, but accounts for a low explained variance (especially for the behavioral aspects of social functioning). The more satisfied patients are with their facial appearance, the better their social functioning is. The highest predictive value of SFA is seen for the cognitive-affective aspects of displaying positive feelings. All relations were comparable in the normal reference group, but the predictive value of all the predictors was less.

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Table 3. *Predictors of the different social and relational aspects*

Population	Questionnaire	R^2	Candidate-Predictor	ß	P
Cleft-Acquired	SADS	.31	SFA	.33	.001
		.36	FNAE	-.41	.001
		.51	SE	.59	.001
		.24	OS	-.17	.10
	FAM	.18	SFA	-.29	.01
		.24	FNAE	.39	.001
		.31	SE	-.49	.001
		.08	OS	-.01	.97
	FPOS	.07	SFA	.26	.02
		.05	FNAE	-.20	.07

Table 3. *Predictors of the different social and relational aspects*

Population	Questionnaire	R^2	Candidate-Predictor	ß	P
		.09	SE	.29	.01
		.05	OS	-.15	.20
	FNEG	.04	SFA	.19	.09
		.03	FNAE	-.18	.10
		.06	SE	.25	.19
		.03	OS	-.15	.20
	FASS	.07	SFA	.23	.04
		.03	FNAE	-.11	.32
		.10	SE	.29	.01
		.06	OS	-.15	.18
	FLIM	.12	SFA	.23	.03
		.12	FNAE	-.24	.02
		.18	SE	.36	.001
		.12	OS	-.18	.10
	SPOS	.14	SFA	-.35	.01
		.18	FNAE	.43	.001
		.29	SE	-.55	.001
		.05	OS	.09	.43
	SNEG	.09	SFA	-.24	.02
		.20	FNAE	.43	.001
		.34	SE	-.59	.001
		.05	OS	.02	.90
	SASS	.13	SFA	-.29	.01
		.18	FNAE	.38	.001
		.39	SE	-.62	.001
		.06	OS	.05	.70
	SLIM	.16	SFA	-.25	.02
		.30	FNAE	.48	.001
		.46	SE	-.65	.001
		.11	OS	.03	.81

OS=Severity of the facial disfigurement

Discussion

Differences between groups

Congenital vs. acquired

Not many differences could be demonstrated in social and relational functioning between congenital and acquired facially disfigured people. Therefore, the assumption that having a congenital or an early acquired facial disfigurement beneficially influences adjustment regarding social and relational functioning can be discarded. [19] The fact that the congenital group had more time to get used to the situation and adjust, does not mean they cope better with social and relational situations. Patients with acquired deformities at an adult age tend to have more social support, which might be of help in dealing with these situations or might benefit from a better self-image prior to the facial disfigurement. [49]

The only difference was that patients with a congenital deformity appeared to have significantly less partners and children of their own in proportion to patients with an acquired deformity. This can be explained by the fact that patients with an acquired facial deformity already had a partner before the trauma occurred. Patients in the congenital group have significantly less children because they less frequently have a partner or they are afraid to pass their deformity on to their children (although a genetic cause is not always proven).

Congenital vs. normal reference

Behavioral dimensions

A clear difference on behavioral aspects of interpersonal functioning was seen between the congenital facially disfigured group and the group without disfigurement. More specifically, patients in the congenital group less frequently reported their negative feelings (FNEG), expressed their personal limitations less frequently (FLIM), and less often initiated assertiveness (FASS). Remarkably, the groups behaved analogously regarding the frequency of expressing positive feelings. This could be explained by the fact that expressing positive feelings is far less threatening compared to the other aspects of behavioral functioning; no negative reactions from others are to be expected. It is often the uncertainty how others will react, which causes more distress and confrontations are therefore avoided. [26]

On the contrary, no significant difference was found in the level of social avoidance and distress between the congenital and normal reference group. This was supported

by some former studies, [50] but in contrast with others in which scores of SADS were higher in patients with a facial disfigurement. [51]

The difference in the scores of the behavioral aspects of interpersonal functioning on one hand and social avoidance and distress on the other hand could be attributed to the fact that the SADS does not have the power to differentiate between the cognitive-affective components and the behavioral components. As a result of the latter it is difficult to adequately interpret the scores. This has to be ascribed to the ambiguity of the item formulation. Although SADS scores both avoidance and distress, it does not specify for the frequency of the avoidance and does not interrogate distress in particular. In addition the SADS is more focussed on group functioning than interpersonal functioning in particular. For these reasons the SADS might not be the ideal questionnaire to evaluate social functioning in this population. In addition this questionnaire has been developed in a student group. The SIB might be more suitable for a more detailed analysis of social and relational functioning.

Moreover, the congenital and normal reference group did not significantly differ on family functioning. Since not much is known about family functioning in patients with a disfigurement or other handicap, or how it can be assessed most accurately, it is hard to draw firm conclusions on the meaning of this finding. However, it seems confirm with the sparse findings in literature in which a normal psychological functioning of mothers and a normal mother-child relationship is reported. [52,53] It must be remarked that large discrepancies can exist in perceptions of family functioning reported by parents, dependents, and other household residents. [53] Since this was a one-sided assessment (only by the patient), interpretation of these data should be done with some precaution. Looking at specific questions, the congenital facially disfigured patients reported more difficulties to talk about fears and worries and difficulties to take decisions. This could be caused by the difficulties parents have coping with the deformity of their child. It is difficult for the majority of them to determine what is best for the child. In addition, some parents demonstrate avoidance behavior which can result in having difficulties to talk about the problems or take good decisions; even guilt might play a role. Good maternal adjustment and perceptions are important for a child's adaptation to craniofacial disfigurement. [52]

In the literature information about marital status and number of offspring of people with a congenital facial deformity is sparse; although few report a larger percentage of patients with a congenital facial deformity to remain single, marry at an older age or have children of their own less or later in life. [54-56] In our study also students

were included in the normal reference group, which may explain the lower number of marriages and children of their own in this group.

Cognitive-affective dimensions

No significant differences in the cognitive-affective aspects of interpersonal functioning were observed between the congenital group and the normal reference group; this is in contrast with the scarce reports in literature. It might be attributed to the fact that they avoid confrontations more frequently and, by consequence, do not experience more stress. This fear-avoidance model is based on a model of exaggerated pain perception and applicable on patients with a facial disfigurement. [57,58] The model suggests that the avoidance of stressful events, as is present in disfigured people, is phobic in nature. This concept is also known as 'ego constriction', a process to avoid psychological pain triggered from an external stimulus by restricting activity in that specific area. [59] Above all, non-facially affected adults avoid social situations and feel distressed in social situations too.

As is seen in a previous study using the same sample of congenital patients, fear of negative appearance evaluation was higher in people with a disfigured facial appearance in comparison with the reference group, which is not really surprising. [28]

With regards to self-esteem, the congenital disfigured group did not differ from the normal reference group. This is not what would be expected, but patients tend to shift in qualities that determine their level of self-esteem; this has been discussed in an article on the same congenital population. Possibly, they place greater importance on other qualities than their physical appearance, or adapt their standards thereby keeping their self-esteem at a good level. [28]

Furthermore, as expected, patients with facial disfigurement were significantly less satisfied with their facial appearance. [13,21,28,60] When an associated congenital malformation is present, there is a tendency for more serious school and conduct problems. [61] It should be noted that this specific deformity is not necessarily related with mental retardation; this is an additional reason that this group was chosen as the congenital group.

Predictors of social and relational functioning

The predictive value of self-esteem, fear of negative appearance evaluation and satisfaction with facial appearance was significant for the dimensions of social and relational functioning, except for the behavioral aspects of interpersonal functioning. Self-esteem seemed to be the strongest predictor for the dimensions of social functioning.

Fear of negative evaluation, from which fear of negative appearance evaluation is derived, has been associated with social functioning in one study on patients with visible disfigurement. [62] Self-esteem is thought to play an important role in social relationships. [63] In this study the predictive value of self-esteem on social functioning appeared stronger in patients with facial disfigurement compared to patients without facial disfigurement.

In both the behavioral and cognitive-affective aspects of interpersonal functioning, self-esteem and fear of negative appearance evaluation had the highest predictive value for initiating assertiveness. Initiating assertiveness implies showing initiative; this is easier with a high self-esteem and no fear of negative appearance evaluation.

The severity of the facial deformity was not a significant predictor for the dimensions of social and relational functioning. This is in accordance with previous conducted studies. They show no relationship between the severity of the disfigurement and the level of distress. [19,64] The theory that the response to a major disfigurement is rather predictable and thereby open for anticipation, and that a response to a fairly minor disfigurement is less easily and more erratically interpreted (which may induce fortification of anxious feeling and tension), can therefore be discarded. The fact the face is always visible in social contact, and deformities therefore always noticed, could be an explanation for these results.

Methodological limitations

A methodological limitation of this clinical-empirical study was that it is questionable whether the patients in this study adequately represent the target population. It is plausible to assume that the most courageous patients entered the study. Therefore, selection bias may be there. The participation rate (79%) in the congenital group can be considered high. Since at least six of the 16 non-participants were dissatisfied with treatment or had psychological problems, outcomes of the congenital group could be worse. The participation rate of the traumatically acquired group is low (57%), but relatively high when compared with other studies in literature. Furthermore, this study is cross-sectional of character. It is of utmost clinical interest to design and conduct an observation study of longitudinal nature; this in order to evaluate the impact of upbringing, surgical treatment and/or psychological treatment on the different aspects of social and relational functioning.

Besides that, our reference group consisted of both patients from several general practitioners and employees of the Erasmus University Medical Centre. Among the last mentioned group the number of students was relatively large, which might bias the

findings. The significant differences in baseline characteristics between the congenital and acquired facially deformed group were statistically adjusted in all analyses.

Clinical implications

Avoiding stress caused by stigmatisation, fear of negative evaluation and uncertainty about the reactions of others, forms the base of avoidance (coping strategy) behavior. Although the avoidance leads to a reduced stress level, it also leads to ego constriction. This is a result of dysfunctional cognitive-affective information processing, directly resulting in a suboptimal and restricting social and relational behavior. Although the cognitive-affective dimensions of the interpersonal functioning seem to be normal and similar to patients without facial deformities, this is to all probability the basis of the problem; since they avoid confrontations more frequently, they do not experience more stress. If this dysfunctional process can be adapted, a more extensive social and relational behavior can be expected; psychological treatment should be on cognitive-affective coping in daily social functioning. Both patients with congenital and acquired facial deformities experience these problems, so both groups should be offered psychological interventions.

Improving a patient's self-esteem, reducing the fear of negative appearance evaluation or a patient's satisfaction with his/her facial appearance can contribute to an amelioration of social and relational functioning. Surgical corrections of the deformities can also help to improve social and relational functioning by improving satisfaction with facial appearance and with that self-esteem; a correlation between self-esteem and satisfaction with facial appearance has been demonstrated in previous studies. [28] Objective improvement of the deformity is insufficient for improvement of social and relational functioning since there is no direct relation. It is therefore important to respect patient's wishes regarding treatment, but besides that clearly let the patient know what the limitations of the surgical treatment are and be sure that their expectations are realistic. Unrealistic expectations, meaning magic expectations or too high expectations, can lead to dissatisfaction with facial appearance post-operatively. Pre-operative psychological intervention is therefore preferred to reduce post-operative dissatisfaction.

The effectiveness of treating people with a disfigurement is relatively underexposed in literature. Some work has been done in workshops with social interaction skills training, which led to a long term improvement of reduced social avoidance and distress and improved confidence. Self-help instructions in addressing the social difficulties

of facially disfigured people seemed helpful. [19,29] Psychological treatment should concentrate on social skills and cognitive-affective dimensions in social functioning.

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CHAPTER 8

Defense mechanisms in congenital and acquired facial disfigurement; a clinical-empirical study

van den Elzen MEP, **Versnel SL**, Mathijssen IMJ, Duivenvoorden HJ

Submitted

Abstract

Background: It is of clinical interest to investigate the degree to which patients with a facial disfigurement utilise defense styles. Objectives of this study were 1.) Do the levels of defense mechanisms differ in patients with or without a facial disfigurement? 2.) Which defense mechanisms have differential qualities between congenital and acquired facial disfigurement? 3.) Are the defense mechanisms of patients with a facial disfigurement associated with: objective severity of the disfigurement, self-esteem, fear of negative appearance evaluation and satisfaction with their appearance?

Methods: Fifty-nine adults born with a rare facial cleft and 59 patients with a facial deformity acquired at an adult age, operated at a single institution, completed standardized questionnaires. A reference group of 141 adults without facial disfigurement was recruited.

Results: There was a significant difference between the group with and the group without a disfigurement on immature defense styles, meaning that the disfigured group used the immature style more frequently. There was a trend, albeit statistically insignificant, for the non-disfigured group to use more of the mature defense styles. No difference was seen on any individual defense mechanism. Looking at the predictor variables, only self-esteem seemed to have the power to differentiate the mature and the immature defense styles within our disfigured groups.

Conclusion: The fact that a low self-esteem comes with utilisation of immature defense styles suggests that professional help may be indicated for these patients. To our belief, it is less difficult to enhance self-esteem than to reduce immature defense styles and mechanisms.

Introduction

Since a person's face cannot be neglected during encounters, conversations or other usual daily activities, patients with a facial deformity are confronted with disapprovals and prejudices on a regularly basis. They have to live with the stigma of being less sociable, intelligent, honest, trustworthy, effective and above all less attractive. [1-3] In previous conducted studies, it was shown that ratings of facial attractiveness decrease as the severity of the disfigurement increases. [4] Despite of all this, their self-esteem is not seriously lowered, yet their fear of negative appearance evaluation and social avoidance behaviour is substantial. [1] (Unpublished data Versnel et. al 2010) In addition, self-perceived (satisfaction with) facial appearance is negatively associated with the level of participation in social events. [5] (Unpublished data Versnel et. al 2010) An earlier study showed that patients with a congenital or acquired facial disfigurement avoided social interactions and the concomitant psychological pain and thereby avoiding cognitive-affective stress situations. This phenomenon is also known as ego constriction. (6)(Unpublished data Versnel et. al 2010) Having an acquired facial deformity is considered as tougher than living with a congenital facial deformity. [7,8] However, this assumption can no longer be justified since recent data showed that both the extent of the facial deformity as the time span living with the deformity was not of influence on the level of social and relational functioning. [9,10] (Unpublished data Versnel et. al 2010) Therefore, it is of great clinical interest to get insight into the way they deal with their disfigurement.

The conscious approach deals with coping styles, while the unconscious approach concerns the defense mechanisms. [11,12] In this study we focussed on the unconscious approach; in casu the defense mechanisms. Sometimes we ask ourselves in retrospection why we acted in a certain way, and we may conclude that our behaviour was a result of an unconscious process, a defense mechanism. Defense mechanisms may be defined as an unconscious, rigid, maladaptive repetition of earlier patterns in which the reality is misrepresented. The definition originated from the field of psychoanalysis. Psychoanalysis resulted in personality-theory and clinical practice using a theory about clinical phenomena. Defense mechanisms are considered to be of fundamental value for adequately managing internal and external conflicts. [13] In psychodynamics Sigmund Freud was the first to conceptualize defense mechanisms which were considered to protect the ego against anxiety, while Vaillant operationalised defense mechanisms in concrete terms. [14,15] Anna Freud states that the use of rigid defense mechanisms disturbs adaptive functioning. [15] She also postulates that personal growth and maturation

implies maturation of defense mechanisms. The psychoanalytic personality-theory about normal development states that different styles of defense develop during the natural course of development of a person, in which maturation is part of the process. Early in this developmental phase, the defense styles are mainly immature, later on these mechanisms change into mature defense styles. These immature defenses styles remain available during life, even when mature styles have been developed. Mature defense mechanisms (sublimation, humour, anticipation and suppression) are best summarized as the recognition of the threat, but the concomitant pain is controlled until the threat can be dealt with. Concerning the immature defense mechanisms (projection, passive aggression, acting out, etc.) the occurrence of the threat is denied or the responsibility is transferred. In neurotic defense mechanisms, localised in between the mature and immature defense mechanisms, (undoing, altruism, idealisation and reaction formation) the event is recognised, the responsibility is accepted, but the meaning is inverted. [16]

Predominantly, mature defenses are associated with better mental and physical health; in contrast, immature defenses are associated with mental illness and greater psychopathology. [17,18] It is plausible that patients with facial disfigurement utilize defense mechanisms more and in another manner than individuals without facial disfigurement. The degree to which the patients with facial disfigurement availed themselves from defense mechanisms is yet unknown. Therefore, objectives of this study were 1.) Do the levels of defense mechanisms in patients with a facial disfigurement differ from patients without a facial disfigurement? 2.) Which defense mechanisms have differential qualities between congenital and acquired facial disfigurement? 3.) Are the defense mechanisms of patients with a facial disfigurement associated with the following variables: objective severity of the disfigurement, self-esteem, fear of negative appearance evaluation and satisfaction with their own facial appearance?

Material and Methods

Study sample

Patients with a congenital deformity

Seventy-five out of the 123 patients with an extensive rare facial cleft who were operated on their facial clefts between 1969 and 2009 at the department of Plastic and Reconstructive surgery of the Erasmus Medical Centre or Sophia Children ‘s Hospital, Rotterdam, the Netherlands, were invited to participate in this study. Since they can

cover deformities in all facial units in a different sequence and with a different degree of severity, they represent a large spectrum of congenital facial deformities.
Hemifacial microsomia and mild facial clefts were excluded. The remaining 48 patients were excluded because they met one or more of the following criteria: deceased (n=4), incomplete data (n=9), age under 18 years (n=32), mentally retarded (n=1), blind (n=1), and insufficient command of the Dutch language (n=1). Total number of patients meeting our criteria and participating in this study was 59.

Patients with an acquired facial deformity

These patients were recruited from the same department as the patients with a congenital deformity. From all patients who suffered from facial disfigurement due to facial trauma at an adult age, patients were selected with a minimum follow-up time of 2 years after initial reconstruction, as it was expected that the physical and/or psychological consequences would be stabilized. The exclusion criteria applied to the patients with congenital deformity are the same as used for the patients with an acquired facial deformity. Furthermore, all patients with an additional visible congenital disfigurement were excluded. A total of 59 patients met our criteria and participated in this study.

Reference group without facial disfigurement

In order to get insight into the psychological sequelae of having a facial disfigurement, we have decided to introduce a reference group without a facial disfigurement. Therefore, we have recruited a reference group of 141 persons, consisting of adults and their partners (n= 72) and psychology students (n= 69).

Design and procedure

All patients received a cover letter, a patient information form, questionnaires, and an informed consent form to sign. They had a month to consider their decision and could withdraw from the study at any moment. A clinical-empirical cross-sectional study was designed and conducted. Ethical approval was received from the board of the Medical Ethical Committee of the Erasmus Medical Centre Rotterdam. (MEC-2006-121).

Instruments

Defense Style Questionnaire

Defense Style Questionnaire (DSQ-42) was constructed as an instrument for evaluating oneself on defense style. [18] The assumption was that conscious representations of unconscious defense processes can be identified by self-observation. [18] The

questionnaire administered was the Dutch version of DSQ consisting of 42 items (DSQ-42). [19] An extra type of defense mechanism 'repression' was presumed, which was not in the previous versions. The two newly added items concerning repression were; 'I hardly remember anything from my primary school time' and 'If something unpleasant happened to me, the next day I've sometimes forgotten what is was about'. This DSQ-42 represents all 21 defense mechanisms, each represented by two items; acting out, altruism, anticipation, autistic fantasy, denial, devaluation, displacement, dissociation, humour, idealisation, isolation, passive aggression, projection, rationalisation, reaction formation, somatisation, splitting, sublimation, suppression, undoing and repression. The DSQ-42 was translated into Dutch, and back translated by a native speaker, not knowing about the original English version of the DSQ. The answer categories of the questionnaire are of the Likert-type. Defense mechanisms were hierarchically classified into three defense levels, in accordance with psychodynamic theory and according to maturity level: mature, neurotic and immature. [14,20] The individual defense scores are calculated by the average of the two items for each given defense mechanisms, and the style scores are calculated by the average of the scores of the defenses under each style. Each item was evaluated on a scale from 1 to 9, where 1 indicates "fully disagree" and 9 indicates "fully agree". The original DSQ was deemed valid for measuring groups of defense mechanisms but not for measuring individual defense styles. The DSQ-40 has been validated for three levels of defense styles, covering 20 individual defense mechanisms. The internal consistency of the questionnaire and criterion validity was investigated. [18]

Objective Severity of Facial Disfigurement

Two experts independently scored the objective severity of facial disfigurement (OSFD) in each patient of both the congenital and traumatic acquired group by using the Versnel et al. quantified scoring list for facial disfigurement. The higher the score, the more units of hard and/or soft tissue are deformed. [21] Recent post-operative standardised photographs of all patients were used. The experts were two plastic surgery residents, both familiar with congenital craniofacial pathology. If scores differed, the average score was calculated. This scoring list has proved to have a good validity and reliability. [21]

Self-esteem

The Rosenberg Self-Esteem Scale (RSES) is a 10-item self-report inventory measuring self-esteem on a four-point Likert-scale. [22] It is the most widely used measure for

assessing self-esteem. Good reliability and validity have been reported. A validated Dutch version is available. [23]

Fear of Negative Appearance Evaluation Scale

The six-item Fear of Negative Appearance Evaluation Scale (FNAES) is a self-report measure, assessing fear about appearance evaluation and of the cognitive aspects of social anxiety. [24,25] The FNAES is sensitive to emotional distress and helps to determine the magnitude of the distress over their negative appearance, avoidance of evaluative situations and the expectation that others would evaluate themselves negatively. [25,26] The FNAES has been found to have good internal consistency as a measure of reliability, and a good validity. [24-26] This scale was translated fully according to recommendations for good translation. [24]

Satisfaction with facial appearance

Satisfaction with the patients' own facial appearance (SFA) was measured using the Visual Analogue Scale (VAS), this is usually a 100-mm continuous line that is horizontally visualised and anchored by word descriptors at the extremes: "very dissatisfied" at the left and "very satisfied" at the right. The patients had to mark the location on the line that they felt represented their perception of their current appearance. It has shown to be highly associated with the Body Cathexis Scale. [27] The VAS is a frequently used measure and it has shown reliability and validity in studies on facial appearance. [28,29]

Statistical analyses

As measure of central tendency for continuous data we have used the mean, including the standard deviation as a measure of dispersion. In case of categorical data the percentages were calculated. To compare the group of patients with a congenital facial disfigurement to the patients with an acquired facial disfigurement and the reference group, we have applied analysis of variance (ANOVA) for independent observations. When we have adjusted for gender and age, we have used analysis of covariance (ANCOVA) for independent observations. Furthermore, we have used the method of linear regression analysis. As a measure of individual performance of the predictor variable, the standardised regression coefficient (ß) was estimated, including the corresponding 95% confidence intervals (95% CI). All the analyses were adjusted for gender and age. As a measure of model performance we have decided to present the determination coefficient (R^2) symbolising the variance explained by the selected predictor variables, adjusted for confounding. The level of statistical significance was

fixed at 0.05 (two-tailed). For statistical analysis we have used the Statistical Package for the Social Sciences (SPSS) for Windows, version 15.

Results

General characteristics

The study population comprised 19 (=32.2%) males in the congenital facial disfigurement group, 34 (=58.6%) males in the acquired group and 63 (=58.6%) in the reference group. The mean age of the acquired group was significantly higher than the congenital and the non-disfigured group. The means of the objectively assessed severities of their facial deformities (OSFD) of the patients in the congenital and acquired group had a significant difference, with the congenital disfigured group being the most severely affected (p-value <0.001). Self-esteem (SE) was about equally distributed between both groups, as was fear of negative appearance evaluation (FNAE) and satisfaction with their own facial appearance (SFA) too.

Table 1. *Descriptive data*

	Congenital		Acquired		Non-disfigured		Testing values			
	Mean	SD	Mean	SD	Mean	SD	F	df_{num}	df_{denom}	p-value
Age[1]	34.05	12.92	43.07	14.59	34.01	12.36	10.86	2	255	<0.001
OSFD[2]	11.71	5.07	3.99	5.10	d.n.a.		59.74	1	98	<0.001
FNAE[2]	17.62	7.04	15.67	6.98	d.n.a.		2.10	1	112	0.16
SFA[2]	4.51	2.15	4.92	2.21	d.n.a.		0.96	1	113	0.34
SE[2]	31.50	5.78	32.45	5.83	d.n.a.		0.73	1	112	0.40

[1)]= ANOVA; [2)]= ANCOVA (covariates; gender and age), adjusted means; d.n.a.= did not apply

Defense styles

Looking at the three levels of defense styles (mature, neurotic and immature), the group with a facial disfigurement significantly differed from the non-disfigured group on immature defense styles, meaning that the disfigured group utilized more often the immature style. Besides that, there was a trend for the non-disfigured group to use more of the mature defense styles in comparison with the disfigured group. However, this was an insignificant finding.

Table 2. *Defense styles disfigured group vs. non-disfigured group*[1]

	Disfigured		Non-disfigured						Testing values			
	Mean	SD	Mean	SD	p-value	ß	95% CI		F	df_{num}	df_{denom}	p-value
Mature defense style	6.35	0.91	6.11	1.04	0.07	-0.12	-0.25	0.01	3.23	1	230	0.08
Neurotic defense style	4.08	0.83	4.00	0.95	0.28	-0.07	-0.2	0.06	1.17	1	232	0.29
Immature defense style	3.33	0.85	3.60	0.92	0.04	0.13	0.00	0.26	4.16	1	232	0.04

1)= ANCOVA (covariates; gender and age), adjusted means

Table 3. *Defense styles congenital group vs. acquired group*[1]

	Congenital		Acquired						Testing values			
	Mean	SD	Mean	SD	p-value	ß	95% CI		F	df_{num}	df_{denom}	p-value
Mature defense style	6.02	0.94	6.20	1.13	0.83	0.02	-0.18	0.23	0.05	1	89	0.83
Neurotic defense style	4.05	1.05	3.97	0.86	0.45	0.08	-0.13	0.3	0.58	1	91	0.46
Immature defense style	3.64	0.92	3.57	0.93	0.42	0.09	-0.12	0.3	0.67	1	91	0.42

1)= ANCOVA (covariates; gender and age), adjusted means

Comparing the group of patients with an acquired deformity to the group of patients with a congenital deformity, no difference of significance was seen on any individual defense mechanism. Looking at specific defense mechanisms of the group of patients with a facial disfigurement in comparison with the scores of the non-disfigured group, a difference of significance was found between the score on the following defense mechanisms: sublimation ($p<0.05$), rationalisation (p-value <0.005), projection (p-value <0.001), denial (p-value <0.02), passive aggression (p-value <0.01), anticipation (p-value <0.003) and displacement (p-value <0.02).

Evaluating the power of our predictor variables to differentiate between the three defense styles, the objectively assessed severity of the facial disfigurement (OSFD) did not show a significant differential power. Within our disfigured groups, self-esteem (SE) seemed to have the power to differentiate the mature and the immature defense styles. The fear of negative appearance evaluation (FNAE) did not seem to have a significant differential power, neither did the satisfaction with their own facial appearance (SFA).

Table 4. *Differential power of joint selected variables on Defense styles*[1]

outcome variable:						
OSFD	**ß**	**t-value**	**p-value**	**95% CI**		**R^2**
Mature defense style	0.02	0.21	0.84	-0.17	0.21	
Neurotic defense style	0.11	1.01	0.32	-0.10	0.32	<0.01
Immature defense style	-0.04	-0.35	0.73	-0.25	0.17	
SE	**ß**	**t-value**	**p-value**	**95% CI**		**R^2**
Mature defense style	0.22	2.21	0.03	0.02	0.41	
Neurotic defense style	-0.18	-1.61	0.11	-0.40	0.04	0.26
Immature defense style	-0.34	-2.95	<0.01	-0.56	-0.11	
FNAE	**ß**	**t-value**	**p-value**	**95% CI**		**R^2**
Mature defense style	-0.05	-0.48	0.84	-0.25	0.15	
Neurotic defense style	0.14	1.16	0.32	-0.09	0.37	0.09
Immature defense style	0.20	1.68	0.73	-0.03	0.43	
SFA	**ß**	**t-value**	**p-value**	**95% CI**		**R^2**
Mature defense style	0.07	0.63	0.53	-0.15	0.28	
Neurotic defense style	-0.06	-0.46	0.64	-0.30	0.19	0.07
Immature defense style	-0.23	-1.80	0.08	-0.47	0.02	

[1)] *= Corrected for age and gender*

Discussion

The disfigured patients appeared to differ from the non-disfigured patients on immature defense styles, in that the disfigured patients had a higher level of immature defense styles, specifically on projection, denial and passive aggression. To our belief, within this category of immature defense mechanisms, these defense mechanisms are of a relatively high level. Furthermore, the disfigured patients did not differ from the reference group on mature and neurotic defense styles. Nevertheless, they did differ on the following specific defense mechanisms: sublimation, rationalisation, anticipation and displacement. On all these defense mechanisms the disfigured patients scored unfavourably, which is in line with what may be clinically expected.

In our previous studies we concluded that in general, patients with a facial disfigurement have an avoiding behaviour. To our belief, this avoidance is of phobic nature. Fear of psychosocial difficulties is worse than the psychosocial difficulties themselves. [30] (Unpublished data Versnel et. al 2010) Therefore, patients with a facial disfigurement may act similar on defense styles as the patients with a social phobia. Many earlier studies investigated whether patients with various psychopathologies could be differentiated by their defense styles. [18] Literature shows that in particular immature defenses styles are related to depressive state, [31] panic disorders, [31,32] social anxiety disorders [33] and personality psychopathology. [34] Whereas neurotic and immature defenses are associated with social phobia, anxiety disorders, [31] panic disorders, obsessive compulsive disorders. [18,19,31-42] The expected predominant defense style of the patients with a facial deformity would be immature, probably combined with a neurotic defense style.

Looking at other somatic disorders and their associations with defense styles, the only data found were derived from studies concerning patients with inflammatory bowel disease. Since data were not compared to a reference group, these data could not be used. [36,41] Previous research has demonstrated that more mature defenses are significantly associated with better adjustment and consequently better mental and physical health. [17,18]

On the whole, patients with immature defense styles are associated with mental and physical illnesses and greater symptomatology, as expected. [17,18,43,44] If we apply these conclusions to the patient in our population with a facial deformity, the conclusion may be justified that these patients are at risk for having or developing mental illnesses and perhaps more symptomatology as well. Consequently, this may

reduce their quality of life, lower their self-esteem and increase to all probability fear of negative appearance evaluation by others.

Of clinical interest is that no significant difference was seen on the three defense styles between acquired and congenital patients. It was considered that having an acquired facial deformity was tougher than living with a congenital facial deformity. [7, 8] As said before, since recent data showed that both the extent of the facial deformity as the time span living with the deformity did not affect the level of social and relational functioning, this assumption has to be abandoned. [9,10] (Unpublished data Versnel et. al 2010) The outcome of this study makes the inference plausible that patients with a congenital facial deformity bear the same burden as patients with an acquired facial deformity.

Previous studies showed that a change in defense style emerged after treatment and remission of the symptoms of various conditions, discarding the more immature defense styles, and using more of the mature defense styles over time. [17,19,31,35,38 45] However, a change in defense styles in the opposite direction is not reported yet. Additionally, it is expected that defense style may increase in utilisation and decrease in maturity in times of psychosocial conflict and emotional experiences (such as a facial disfigurement caused by trauma). All patients with an acquired facial deformity had their trauma that induced their facial disfigurement, more than two years before the study started. If the use of defense styles would stabilise, it should have occurred within this time.

In our study the objective severity of the facial deformity (OSFD) had no significant power to differentiate between the three defense styles. This is in accordance with previous conducted studies. They did not show a relationship between the severity of the disfigurement and the severity of psychosocial problems. [10,46] Since patients with an extensive deformity are aware that their deformity will be noticed during encounters, they are likely to anticipate. For patients with a milder deformity, it is often the uncertainty how others react, which on its turn induces more distress. Whatever the severity of the deformity is, confrontation might be avoided. [47] Irrespective from avoidance and anticipation, another wide variety of defense mechanisms are used to handle these potential problems emanated from the OSFD. In this study it could not be shown that a specific defense style is related to the OSFD.

There was a non-significant difference in the mean level of self-esteem (SE) between the patients with a congenital and an acquired facial deformity. Although this is not what we expected, a plausible explanation for this finding could be that patients with a facial deformation stress on other qualities than their physical appearance. [48] In contrast, SE

was associated with the mature and immature defense styles. This means that, the higher the level of SE is, the more likely to use mature defense styles; reversed, the lower the level of SE is the more likely to utilise immature defense styles.

The fear of negative appearance evaluation (FNAE) could not differentiate between the three defense styles. There was a non-significant difference in the level of the FNAE between the two patient groups. In an earlier study using the same population, the level of the FNAE was found to be high in the disfigured group compared to with the reference group. This implies that the FNAE is increased by facial disfigurement itself, and is unaffected by the severity of this disfigurement.(Unpublished data Versnel *et. al* 2010) This is supported by the expectation that those affected are aware of the reactions of others and may become excessively preoccupied with their appearance and the effect it has on others. [49] However, a direct effect of FNAE on defense styles used by patients on a daily basis could not be found in this study.

The mean satisfaction with their own facial appearance (SFA) had an insignificant difference between both patient groups. Also, the power of SFA to differentiate between the defense styles was found to be insignificant.

Methodological limitations

Since defense styles are unconscious, some researchers wonder if a person is capable of reflecting on their defense styles and prefer observations and interviews by an objective trained expert. Questionnaires differ from interviews concerning multiple aspects, regarding the estimation of the level of defense. First, a patient might present social wanted/ expected behaviour when he is interviewed face to face, instead of writing down his habits honestly. Second, in a questionnaire setting a patient has to write down how (and if) he remembers certain situations and his reaction, while in an interview setting the interviewer can interpret answers and can narrow down the question more tailored. Third, some defense styles are difficult to capture in a questionnaire, while an interviewer can be trained to identify such a defense mechanism. Fourth, a questionnaire can not accommodate the questions to the mood of the patient, while an interviewer can. In contrast, a questionnaire is a standardized method of measurement, while an interview is based on the interpretation of the interviewer. Additionally, administering a questionnaire is highly efficient in terms of time to be spent and it is less expensive.

The character of the design was cross-sectional. In order to get insight into stability and shifts of the utilisation of defense styles and mechanisms, it is highly recommended to design and conduct a longitudinal study about them. It might be that the immature

level of defense style decreases across time. Whether this expectation is plausible, should be evaluated longitudinally.

Finally, it is of great clinical interest not only to assess the defense styles but also the coping styles. Dealing with conflicts, manifesting unconsciously and consciously, it does make sense to measure coping behaviour as well. One would hypothesize that disfigured patients deal with internal and external conflicts both unconsciously and consciously.

Clinical implications

The fact that a low self-esteem goes hand in hand with utilisation of immature defense style suggests that professional help may be indicated for these patients. To all probability, professional help has to be focussed on enhancing the level of self-esteem of these patients. To our belief, it is less difficult to enhance self-esteem than to reduce immature defense style and mechanisms.

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CHAPTER 9

Long-term psychological functioning of adults with severe congenital facial disfigurement

Versnel SL, Plomp RG, Passchier J, Duivenvoorden HJ, Mathijssen IMJ

Submitted

Abstract

Background: Assessment of long-term psychological impact in adults with severe congenital facial disfigurement has remained limited. This study determined the impact of severe congenital facial disfigurement on long-term psychological functioning in these patients and evaluated differences with patients with acquired facial disfigurement and a non-facially disfigured reference group. Furthermore it was explored to what extent their psychological functioning is related to satisfaction with facial appearance (SFA), fear of negative appearance evaluation by others (FNAE), self-esteem (SE), and severity of the facial deformity (OS).

Methods: Fifty-nine adults born with a rare facial cleft, 59 adults with a traumatically acquired facial deformity in adulthood, and 120 non-facially-disfigured adults, completed standardized psychological, physical, and demographic questionnaires.

Results: Adults with severe congenital facial disfigurement had a rather normal psychological functioning, but appeared more prone to internalizing problems than the non-facially-disfigured adults. Several explanations for this relative good psychological functioning were given. In only one aspect they differed significantly from patients with an acquired facial deformity: the congenital group displayed fewer problems on the physical component of quality of life (PhysicalCS). SFA, FNAE and SE were good predictors of the different aspects of psychological functioning, except for the PhysicalCS.

Conclusion: Patients with severe congenital facial disfigurement have a better psychological functioning than expected. Improving SFA (by surgery), enhancing SE or lowering FNAE (by psychological support) could enhance psychological functioning on the long-term. Future research should be focussed on the individual patient and risk factors for maladjustment, rather than on group comparisons.

Introduction

'Who likes a monster?' was the reaction of an adult patient born with a rare facial cleft on an open question about her well-being. A further in-depth interview revealed severe psychological problems that affected her functioning in daily life tremendously. Although not all adult patients react the same way to their deformity, having to deal with a severe congenital craniofacial deformity is not always easy.

It is stated in literature that children with craniofacial disfigurement more often suffer from anxieties and depressive moods, have lower levels of self-esteem and quality of life and deal with learning disorders, family problems and both internalizing and externalizing behavioral problems; albeit results are inconsistent. [1-5]

However, what about psychological functioning of these patients in adulthood? Although our main goal of treatment for these patients is to establish 'normal' functioning in daily life, it is fairly unclear how successful we are in doing so since assessment of long-term psychological impact has remained limited.

Previous conducted studies in adults comprised mainly small sample sizes or mostly patients with a cleft-palate deformity, and administered non-standardized measures. [6, 7] Moreover, overall these studies show a lack of consensus concerning the issue of whether individuals with facial deformities do develop specific psychological problems on the long-term. [8] Furthermore, in literature comparison with other groups is limited. The question whether adults with craniofacial deformities suffer less from psychological sequelae than patients with a traumatically acquired facial deformity, as is suggested in literature, has little empirical support. [9]

Therefore, the objectives of this study were to 1) determine the impact of severe congenital facial disfigurement on long-term psychological functioning; 2) evaluate whether patients with severe congenital facial disfigurement differ from patients with acquired facial disfigurement regarding long-term psychological functioning; 3) explore to what extent their psychological functioning is related to satisfaction with facial appearance, severity of the facial deformity, fear of negative appearance evaluation by others, and to self-esteem.

Materials and methods

Study populations

Patients with a congenital deformity

For this group, adult patients with a rare facial cleft were included, since they represent a large spectrum of congenital facial deformities in all facial units in a different sequence and with a different degree of severity. [10,11] Of the 123 patients with an extensive rare facial cleft who had surgical treatment between 1969 and 2009 at the department of Plastic and Reconstructive Surgery of the Erasmus University Medical Center (ErasmusMC) Rotterdam, the Netherlands, 75 patients were approached to participate. The other 48 patients were excluded. Exclusion criteria were: deceased(4), incomplete data, [9] age under 18 years, [32] mentally retarded, [1] blind, [1] and insufficient knowledge of the Dutch language. [1]

Patients with an acquired facial deformity

This group consisted of patients who suffered from facial trauma at an adult age. Only patients with a minimum follow-up time of 2 years after initial reconstruction were selected, because it was more likely that physical and/or psychological consequences of the trauma had stabilized. The same exclusion criteria as for the congenital population were used. In addition, all patients with other visible congenital or traumatic disfigurements or who had suffered from personal assault were excluded. One-hundred-and-four patients were asked to participate.

Reference group without facial disfigurement

This group was composed of the patient population from five general practitioner practices in Rotterdam and of employees of the ErasmusMC without any congenital or acquired visible deformity. They were recruited by posters and exclusion was performed based on similar criteria as in the congenital group.

Design and procedure

A clinical-empirical cross-sectional design was conducted. Ethical approval was obtained from the Medical Ethical Committee of the ErasmusMC Rotterdam (MEC-2006-121).

A patient information form, questionnaires, an informed consent form were sent to the home addresses of the patients. Within one month they had to decide on their participation. Patients could withdraw at any time. If a patient refused to participate, his/her motive was asked. The reference group was handed the same package as the two patient groups and completed the questionnaires at home.

Assessments

Demographic information

This provided data on age, gender, and educational level.

Fear of Negative Appearance Evaluation

The six-item Fear of Negative Appearance Evaluation Scale (FNAES) is a self-report assessment tool measuring apprehension about appearance evaluation on a five-point Likert-scale. The FNAES is reported to have good internal consistency and a similar convergent validity with measures of body image in the field of eating disorders. [12]

Satisfaction with facial appearance (SFA)

The Visual Analogue Scale (VAS), a self-report device, was used as a 100-mm continuous horizontal line anchored at the poles: 'very dissatisfied' at the left and 'very satisfied' at the right pole to measure the degree of satisfaction with their current facial appearance. The VAS has shown reliability and validity in studies on facial appearance. [13,14]

Self-esteem

The Rosenberg Self-Esteem Scale (RSES) is a 10-item self-report inventory measuring self-esteem on a four-point Likert-scale. [15] Good reliability and validity have been demonstrated. For assessment of self-esteem it is the most widely used tool. In this study the validated Dutch version was administered. [16]

Severity of facial disfigurement

Severity of facial disfigurement (OS) was scored independently by two experts in each patient of both patient groups by using the Versnel et al. scoring list with an objective scoring approach for facial disfigurement; [17] this was done based on recent post-operative standardised photographs.

Anxiety and depression

The Hospital Anxiety and Depression Scale (HADS) is a widely used 14-item self-report measure based on a four-point Likert-scale. It comprises two internal scales, 'Anxiety" and 'Depression', and has been found a robust an effective screening tool. [18] Severity is measured for both scales with a score of 11 and above indicating clinically significant levels of anxiety and depression. [19]

Adaptive functioning/Behavioral problems

The Adult Self-Report (ASR) of the Achenbach System of Empirically Based Assessments (ASEBA) assesses people's perception of their own functioning in the age from 18 to 59 years. It comprises 126 items on problem behaviors, using a 3-point Likert-scale, which are categorized into subscales. [20] The two broad band scales 'Internalizing' and 'Externalizing', as well as the Total Problem Score were used. Cut-off scores for the clinical range per age group and gender for these three total scores are available. Good reliability and validity has been demonstrated for the American version and the ASR has been used in Dutch population samples. [20,21]

Quality of life

The SF-36 Health Survey is a 36-item measure of quality of life, including physical and mental health. The physical domain subscales are physical functioning, role problems, bodily pain and general health. The mental domain subscales are vitality, social functioning, problems with work and daily activities due to emotional problems, and general mental health. High scores indicate greater satisfaction and healthy functioning. The Physical (PhysicalCS) and Mental (MentalCS) Component Summary measures were used; they take the correlation among the eight SF-36 subscales into account and are calculated with U.S. norm scores as a reference point. [22] Since these norm scores were used, the reference group did not complete the SF-36 Health Survey. The SF-36 is currently the most widely used measure of general health-related quality of life in medical settings and has good psychometric properties. [23]

Statistical analysis

The mean and standard deviation were used for metric variables, and percentages were given for categorical variables. With the Fisher-exact test differences on categorical variables between independent groups were analysed. Comparison of means between the three groups was performed with Analyses of Covariance (ANCOVAs) with adjustments for age, gender and education level. The percentage of patients within the clinical range

in each group was calculated with the raw scores according to the above mentioned cut-off points for the HADS and ASR. Differences on these percentages between groups were analysed with a logistic regression analysis with two groups as outcome variable, and adjustments for age, gender and education level (HADS) or only education level (ASR: since cut-off scores take age and gender into account). The predictive value of SFA, FNAE, SE, and OS for the different aspects of psychological functioning, were analysed using the method of multiple linear regression analysis (procedure ENTER). Statistical analysis was conducted with version 17.0 of the computer program SPSS.

Results

Fifty-nine (79%) of the 75 rare facial cleft patients participated. The other 16 patients refused for several reasons: eight did not respond to the letters (four lived abroad), three had traumatic experiences with treatment, two refused since they had already talked about it to the media in the past, and three patients found it psychologically too difficult. Fifty-nine (57%) of the 104 patients with a traumatically acquired facial disfigurement participated. The majority of the remaining patients in this group did not respond to the letters and could not be contacted.

Demographic characteristics

Table 1 shows the demographic characteristics of the three groups. The congenital patients differed statistically significant from the acquired patients on gender and age, and from the reference group on education level; therefore, all statistical analyses were adjusted for gender, age and education level.

Differences between the groups

No significant differences between the congenital and the reference group were seen in the mean scores of anxiety and depression, internalizing, externalizing and total behavioral problem scores, and the physical and mental component summary measures of quality of life (Table 2).

Mean scores of anxiety and depression fell within the 'normal/non-clinical' range in all three groups. The percentage of patients with a clinical level of anxiety was 11% in the congenital group, 11% in the acquired group and 3% in the reference group. After adjustments the difference between the congenital and the reference group was non-significant (p=0.29). Six percent in the congenital group, 9% in the acquired group

and 4% in the reference group demonstrated a clinical level of depression. Again after adjustments no significant statistical difference was found between the congenital and reference group (p=0.66).

Table 1: *Demographic characteristics*

				P-values[2)]	
	Congenital (*C*) N=59	**Acquired (*A*) N=59**	**Reference (*R*) N=120**	***C vs. A***	***C vs. R***
Gender (%)				0.01	0.73
Male	32.2	41.4	29.4		
Age (years)				0.01	0.21
Mean	34.05	43.07	36.65		
SD	12.92	14.59	16.43		
Min/Max	18/74	18/84	18/79		
Education level (%)				0.68	0.04
Primary school[1)]	35.1	27.6	17.2		
High school[1)]	47.4	55.2	59.5		
Postgraduation[1)]	17.5	17.2	17.2		
Severity facial deformity				0.001	-
Mean score	13.90	6.44	-		
SD	7.65	5.0	-		

[1)] % represent column percentages; [2)] p-values corrected for multiple testing, α= 0.025 (two-tailed)

Externalizing and Total problem scores showed no significant difference on the percentage of patients within the clinical range between the congenital and reference group (Externalizing: p=0.56, C:10%, A:7%, R:5%; Total: p=0.31, C:11%, A:9%, R:6%). However, the congenital group had more patients within the clinical range on Internalizing problem scores (25%) than the reference group (13%); albeit not statistically significant (p=0.08). In the acquired group 21% of the patients had internalizing problems.

The only statistically significant difference between the congenital and the acquired group was on the physical component summary(PhysicalCS); the acquired group had a lower mean score. This mean score was even lower than the U.S. norm population, whereas the congenital group scored better than the U.S. norm population. The percentages of patients within the clinical range were not statistically significantly

different between the congenital and acquired group regarding anxiety (p=0.70), depression (p=0.70), internalizing (p=0.73), externalizing (p=0.66) and total behavioral problems (p=0.66).

Table 2. *Differences between groups on psychological aspects*

	***C* (N=59)**		***A* (N=59)**		***R* (N=120)**		**P-values[2)]**	
	$\hat{\mu}$[1)]	$\hat{\sigma}$	$\hat{\mu}$[1)]	$\hat{\sigma}$	$\hat{\mu}$[1)]	$\hat{\sigma}$	***C vs. A***	***C vs. R***
Anxiety	4.26	3.94	5.01	4.01	3.78	3.92	.40	.54
Depression	4.10	3.66	5.38	3.64	4.40	3.57	.08	.76
Internalizing	15.28	10.81	14.34	10,89	12.20	10.73	.99	.10
Externalizing	9.29	6.33	8.54	6.38	7.20	6.28	.86	.08
Total problem	43.05	24.54	39.45	24.74	34.34	24.35	.86	.06
PhysicalCS	52.02	8.36	47.78	8.35	-	-	.02	-
MentalCS	51.59	10.27	50.62	10.26	-	-	.68	-
FNAE	18.02	6.38	15.87	6.48	14.09	6.29	.19	.001
SE	31.81	5.16	32.32	5.33	33.23	5.13	.64	.07
SFA	4.28	2.19	4.67	2.24	6.98	2.19	.54	.001

C*=Congenital group,* ***A****=Acquired group,* ***R****=Reference group,* $\hat{\mu}$*=mean,* $\hat{\sigma}$*=standard deviation,* ***Total problem****=Total behavioral problem score (ASR),* ***PhysicalCS****=Physical Component Summary measure of quality of life,* ***MentalCS****=Mental Component Summary measure of quality of life,* ***FNAE****=Fear of Negative Appearance Evaluation,* ***SE****=Self-esteem,* ***SFA****=Satisfaction with Facial Appearance,* **1)** *adjusted for mean values of age, gender and education level,* **2)** *corrected for multiple testing,* α*= 0.025 (two-tailed)*

Predictors of social and relational functioning

In Table 3 the predictive values of satisfaction with facial appearance(SFA) , fear of negative appearance evaluation(FNAE), self-esteem(SE), and objective severity(OS) are shown. They all appear to be significant predictors for the different aspects of psychological functioning, except for the physical component summary(PhysicalCS) of quality of life. Self-esteem is the strongest predictor for all the aspects of psychological functioning; the higher the self-esteem, the better the psychological functioning. SFA is not a significant predictor for externalizing problems.

Table 3. *Predictors of the different psychological aspects*

Population	Questionnaire	R^2	Candidate-Predictor	B	P
Congenital	**Anxiety**	.38	SFA	-.45	.01
		.31	FNAE	.35	.01
		.54	SE	-.64	.001
		.22	OS	-.08	.64
	Depression	.36	SFA	-.53	.001
		.34	FNAE	.50	.001
		.52	SE	-.71	.001
		.12	OS	-.01	.94
	Internalizing	.31	SFA	-.40	.02
		.36	FNAE	.42	.01
		.48	SE	-.61	.001
		.25	OS	.12	.50
	Externalizing	.24	SFA	-.31	.06
		.31	FNAE	.36	.02
		.37	SE	-.51	.01
		.20	OS	-.07	.69
	Total problem	.33	SFA	-.38	.02
		.39	FNAE	.38	.01
		.49	SE	-.57	.001
		.28	OS	.04	.82
	PhysicalCS	.31	SFA	.18	.17
		.29	FNAE	-.10	.44
		.31	SE	.19	.17
		.41	OS	-.09	.48
	MentalCS	.25	SFA	.48	.01
		.23	FNAE	-.42	.01
		.45	SE	.71	.001
		.06	OS	.18	.62

OS=Severity of the facial disfigurement

Discussion

Long-term psychological functioning

This study demonstrates that adults with severe congenital facial disfigurement appear to have a rather 'normal' psychological functioning. No differences were found on the mean scores of anxiety, depression, behavioral problems, and quality of life.

Several studies support positive adjustment and quite efficient coping in patients with congenital craniofacial deformities. [24] A systematic review on psychosocial effects of having a cleft lip/palate concluded that the majority of patients do not appear to experience major psychological problems; but lack of uniformity and consistency of the studies made it impossible to draw definite conclusions. [8]

How do we interpret the rather 'normal' psychological functioning found in this study? In most studies little attention is given to 'normal' results and it seems difficult to accept that people manage to live rather normal with a severe disfigurement. [25,26]

The lack of problematic psychological functioning in adults with severe facial disfigurement could be explained in several ways. Firstly, change in internal standards (recalibration), change in values (reprioritization), and change in meaning of quality of life (reconceptualization) can cause a response-shift, resulting in a good self-perceived quality of life and psychological functioning. Mechanisms to achieve recalibration, reprioritization and reconceptualization are coping, social comparisons (e.g. contrast-effect/downward comparison: judge your physical condition as more positive than that of another person with a more severe physical condition), and adjustment of goals and expectations. [27] Downward comparison is used by many patients with various physical/medical conditions and leads to self enhancement. [28] Adults might be more capable of recalibration, reprioritization and reconceptualization than children and adolescents, which could lead to better psychological functioning at adulthood.

Secondly, there is the concept of ego constriction that can be applied by these patients. This is a process to avoid psychological pain triggered from an external stimulus by restricting activity in that specific area. [29] It can result in 'normal' psychological functioning, but be detrimental to for example social functioning in that it is restricted.

Furthermore, the facial deformity is one of many naturally occurring stressors in life that must be adapted to. [25] People without a facial deformity also have to deal with all kinds of occurring/immanent stressors which can have an impact on psychological functioning comparable to a facial deformity.

Fourthly, there are some methodological issues that could explain the lack of differences in psychological functioning. Disease specific questionnaires reveal more

differences than generic questionnaires (e.g. FNAES); therefore more questions related to facial appearance should be used. In addition, since the mean group scores do not differ, problems in psychological functioning are not of that kind that they account for the whole group of congenital facially disfigured people. An individual approach seems important and should not be conducted by psychometric tests only, but also by personal interview/ assessment. [30,31]

The latter is supported by the results of the analysis of the percentage of patients within the clinical range. In contrast with the comparison of the means, this approach revealed a tendency of more patients with internalizing problems in the congenital group compared to the reference group. Therefore, although this was not significant, adults with congenital facial deformities seem to be prone for internalizing problems. Internalizing problems comprise problems that are mainly within the self, such as withdrawal from social contacts.

It is suggested the incidence of psychological problems increases with age in childhood. [3] Young children probably cope better because they are less aware of their disfigurement or the consequences, or better at denying problems; [3,26] moreover, adolescence is a difficult and challenging period. [32] However, others noted more depression and behavioral problems in children than in adolescents. [33]

Psychological developmental stages seem to play a role in one's psychological status. The fact that psychological problems might increase with age in childhood, does not imply this necessarily continues in adulthood. A longitudinal study in a random population cohort concluded that the great majority of children with emotional and behavioral problems was not at risk for problem behavior in middle adulthood. [21]

Differences between congenital and acquired

Only a difference on the PhysicalCS was found between patients with congenital and acquired facial deformities; the acquired group suffered from more physical problems. These physical problems are composed of limitations in social/role activities due to physical problems, bodily pain, and tiredness. This implies adaptation to physical problems might take a long time or that traumatically acquired facial disfigurement could be related with more physical impairment. Furthermore congenital deformities occur pre-memory and a patient has therefore no knowledge of how life would be without the disfigurement and concomitant physical problems. [34]

The scores on the MentalCS imply that both groups have no psychological distress. So despite people with a congenital facial deformity have had more time to get used to their deformity, it does not result in better long-term psychological functioning.

In contrast to the results of this study, previous studies on facial trauma patients document more anxiety, depression and psychological stress compared to the normal population. [35,36] However, these studies had methodological weaknesses and were conducted in acute settings (up to 12 months post-trauma), and assessed patients with concomitant injury and assault. Therefore, only patients two years or more after the traumatic event and without personal assault or brain injury were included; this might explain the better outcome in this study.

Predicting factors

Self-esteem is the strongest predictor for all the aspects of psychological functioning. Other studies also state that people with low self-esteem may be at risk for the development of psychological problems, anxiety, depression, or satisfaction with life. [37] Therefore self-esteem should be assessed and ameliorated by psychological support when low. Furthermore, also surgery can increase self-esteem and satisfaction with facial appearance and improve psychological functioning. [38]

Objective severity has no predictive value for psychological distress, but self-perceived satisfaction with facial appearance does. In treatment patients' (including children's) wishes and expectations regarding their facial appearance should therefore be taken into account; but they also have to be realistic. [39] FNAE appeared a good predictor of psychological functioning. Therefore, psychological support should also be focussed on training patients to rely less on the opinion of others. Physical problems appear not to be influenced by the examined predictors.

Methodological limitations

Selection bias of patients may be present, although the participation rate(79%) in the congenital group and in the traumatically acquired group(57%), can be considered relatively high compared with other studies. Furthermore not all aspects of psychological functioning and predicting factors were evaluated.

Conclusion

Adults with congenital facial disfigurement have a rather 'normal' psychological functioning, but they are more prone to internalizing problems. They only differ from patients with an acquired facial deformity on physical problems. Improving patient's satisfaction with his/her facial appearance by surgery, and improving self-esteem or

lowering FNAE by psychological treatment, could enhance psychological functioning on the long-term. Future research should be focussed on the individual patient and risk factors for maladjustment, rather than on group comparisons; also because of inconsistency of results in literature.

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DISCUSSION, SUMMARY AND APPENDICES

CHAPTER 10

General discussion/ Algemene discussie

Introduction

Let's Face it!

Treatment of rare and complex conditions like rare facial clefts is difficult and the search for the most 'ideal' treatment has preoccupied many and is still going on. As plastic surgeons we are responsible for the surgical treatment, but there is more to treatment than that. Knowledge on the causes of the pathology, as well as knowledge on the consequences of the pathology and treatment, are important and essential for optimal treatment. Regarding all three parts, causes, treatment and consequences, a lot of controversy still exists in literature after centuries.

The aim of this thesis was to evaluate the long-term results of treatment of patients with a rare facial cleft and improve knowledge about causes, treatment and consequences of this pathology. To address these goals several studies were conducted in a population of 123 patients with a rare facial cleft who have been treated in the Sophia Children's Hospital and the Erasmus Medical Centre in Rotterdam since 1969. A genetic study was performed in collaboration with the Weatherall Institute of Molecular Medicine of Oxford University. Also a scoring list was developed for assessment of severity of facial deformity, prior to, during, and after completion of surgical correction. Furthermore two studies on long-term surgical results, one in patients with oblique facial clefts and one in patient with a midline cleft, were done. Several psychosocial studies were conducted to evaluate the long-term psychosocial functioning and the influence of certain factors on that outcome. In the last studies a group of adults with facial disfigurement traumatically acquired at adulthood, and a group of adults without any facial disfigurement were included. In this chapter the findings and conclusions from this thesis are summarized and discussed in relation to the questions put forward in **CHAPTER 1**.

Causes

Close observation of the pre-operative baby photo's of all patients who got diagnosed with having a rare facial cleft, revealed one specific resembling phenotype of a midline cleft in six individuals, belonging to 4 different families. A. recessive inheritance was assumed in these families. The genetic study conducted in these families identified mutations in ALX3, situated on chromosome 1, responsible for encoding the *aristaless*-related ALX homeobox 3 transcription factor, and essential for normal facial development in humans. This recessively inherited frontonasal malformation, which we term frontorhiny, is characterized by a distinctive facies, with hypertelorism, wide nasal bridge, short nasal ridge, bifid nasal tip, broad columella, widely separated slit-like nares, long philtrum with prominent bilateral swellings, and midline notch in the upper lip and alveolus. Additional recurrent features present in a minority of individuals have been ptosis and midline dermoid cysts of craniofacial structures.

The clinical significance is that with identification of this phenotype, a specific treatment plan for surgical reconstruction can be developed. One of the possible features which should be taken into account is the presence of multiple defects in the cribriform plate of the ethmoid bone, which can be associated with rhinorrhea of cerebrospinal fluid and meningitis. With the identification of this new mutation we can also provide genetic counselling for patients with this phenotype and their families. The others however, like the patient presented in **CHAPTER 1**, can not be given a definite answer about the cause of their rare facial cleft. It might for a few patients still be a reason not to have children of their own, as has been the case until now, just because they remain afraid to pass their deformity on.

The fact that 4 of the 7 families with genetically confirmed frontorhiny came from our population of rare facial clefts, points out the uniqueness of this population and its database. Close observation of the pre-operative baby photo's furthermore made clear that the whole group of patients who have been diagnosed with a rare facial cleft, is a reservoir in which more and more specific phenotypes are being recognised; including a sporadic craniofrontonasal dysplasia which wrongly has been classified as rare facial cleft. The low incidence of rare facial clefts requires an international approach to make good identification of specific phenotypes possible. If their might be more genetic causes in this patient group, than they should be sought in the patients with symmetrical or midline pathology. The asymmetrical rare facial clefts rather appear to be caused by disruptive processes; we think the amnion band can be discarded as a cause.

Treatment

Long-term assessment of surgical results showed that there is still room for improvement of surgical treatment of patients with a rare facial cleft; we can do better! A surgeon has to face many challenges in the surgical corrections of rare facial clefts, and despite all the efforts it remains a fact that the grand majority will never have a 'normal' facial appearance or complete normal facial function.

For the assessment of treatment results we developed an objective scoring list which specifically included craniofacial deformities of the different facial parts; other previously developed scoring lists did not take craniofacial malformations into account. It showed good reliability and internal consistency and can give an indication of the improvement of the facial deformities by treatment. Since this scoring list depends on the observations of a person, it might not be 100% objective. For complete objectivity, quantitative measurements are necessary. However, quantitative assessment requires standardized imaging, which is difficult to realize in long-term retrospective studies. Regardless of the previous argument, the deformities in these patients are so diverse and complex that we think there is no good additional value for quantitative measurements as assessment tool of long-term surgical results in this population. They are only valuable in this population for assessing the hypertelorism correction and the midface advancements.

The distinction between oblique and paramedian clefts on one hand, and the midline clefts on the other, was based on the presence of specific deformities, and the asymmetrical and symmetrical nature of the deformities, which both have different implications for treatment. For both groups a useful guideline for surgical treatment was provided in which the influence of growth, the timing and the techniques were incorporated. Especially knowledge on vertical dystopia was limited. Long-term follow-up revealed that vertical dystopia appears not to be caused by previous surgery, but by unilateral growth deficiencies of the maxilla. In all patients with vertical dystopia, it was present at the age of four, and it should ideally be treated shortly after that age. In contrast to frequent relapse of vertical dystopia after correction, relapse of hypertelorism after correction appeared to be very rare. Another striking observation was that deterioration of nasal reconstruction performed at a young age seemed inevitable. After evaluation of the long-term results we think nose reconstruction is best postponed until adolescence for several reasons. The influence of growth was also seen in the shortage of soft tissues on the long term, and some techniques provided better long-term results than others. For correction of orbital dystopia in mild cases grafting seems sufficient, but in more severe

cases orbital translocation is necessary. Costochondral grafts showed the best long-term results in both orbital and nasal reconstructions. For an optimal final result in selected cases, correction of midface hypoplasia at adolescence is necessary.

Besides an aberrant appearance, these patients frequently suffer from functional problems of the different facial parts. In this population the main problems comprise tearing of the eyes and deficient nasal functions. In **CHAPTER 6** we have seen that function of the face is important for satisfaction with facial appearance. It is therefore important to address functional problems as good as possible in treatment to ameliorate patient's satisfaction with the end result. Tearing of the eyes can in certain cases be solved by reconstruction of the canalicular system. Restoring functions of the nose, however, can be difficult in many cases, since some of the basic elements essential for nasal function are missing due to the congenital pathology.

In general the mean number of performed operations per patient was considered too high by the surgeons; early surgical treatment in non-specialised centres also contributed to this. The provided guidelines based on new knowledge regarding influence of growth, best timing and techniques, should help to minimize the number of operations and ameliorate long-term surgical results. Important in this is to be patient and postpone certain corrections in most cases to give them a chance on a more optimal result at adulthood. Although it is difficult to convince the patient and its parents, it prevents that all good options will already have been used when further reconstruction at an adult age is required; several more reasons support this tendency to postpone surgical treatment. Firstly we have demonstrated in **CHAPTERS 7-9** of this thesis that the intensity of the psychological burden for patients caused by the deformity is not directly related to the severity of the deformity. In addition, the intermediate results in these patients often still show severe deformities and patients may still be teased or looked at. Furthermore there is a major influence of intrinsic growth deficiencies on early reconstructions in this patient group; they are not comparable to children with a traumatically acquired facial deformity. Therefore surgeons need to have the guts to wait!

Consequences

Long-term assessment of psychosocial functioning demonstrated that also in this aspect of treatment of patients with a rare facial cleft, there is still room for amelioration; once again we can do better! Although the majority of these patients can achieve a good level of psychosocial functioning, completely 'normal' psychosocial functioning will require

a lot of effort from patient and professionals, and will be very difficult to accomplish for many of them.

In **CHAPTER 6** we demonstrated that there is a big individual difference in the level of satisfaction with facial appearance in adults with a rare facial cleft, but the overall level of satisfaction in these patients is significantly lower than in patients without a facial disfigurement. Despite all the surgical corrections, patients still don't have the same general level of satisfaction with facial appearance as the people without facial disfigurement. This also implies that the surgeon can be very happy with the surgical results, but that it is even more important how the patient experiences it. In this context it is therefore also essential that a surgeon gives his patient realistic expectations; the wish for a completely 'normal' facial appearance cannot be fulfilled in most cases.

The **CHAPTERS 7-9** revealed that this group of patients in general has a higher fear of negative appearance evaluation, displays a decrease in frequency of interpersonal functioning, is more prone to internalizing behavioural problems, and uses the immature defense styles (subconscious coping) more frequently in comparison with the people without facial disfigurement. However, there is no difference between these groups regarding the level of self-esteem, social avoidance and distress, and externalizing behaviour, depression and anxiety, and overall quality of life.

Moreover, patients with a rare facial cleft do not differ from patients with a traumatically acquired facial deformity on level of satisfaction, psychosocial functioning and the way of coping, except in having a partner and children, and experiencing physical problems. Patients with a congenital facial deformity have been confronted with the consequences of their deformity their whole lives and, therefore, have had more time to get used to the situation and find ways to cope; however this does not seem to give them an advantage regarding long-term outcome. Patients with an acquired deformity on the contrary have had less time to deal with the sudden change in reactions from others and within themselves, but they can rely more on their pre-traumatic psychosocial functioning. This results in the difference between the two groups in having a partner and partly in having children; appearance remains an important characteristic in partner choice. The fact that the congenital group displayed less physical-related problems implies adaptation to physical problems might take a long time, or that traumatically acquired facial disfigurement could be related with more physical impairment. Furthermore congenital deformities occur pre-memory and a patient has therefore no knowledge of how life would be without the disfigurement and concomitant physical problems

Fear of negative appearance evaluation by others (FNAE) and self-esteem (SE) were strong psychological determinants of satisfaction with facial appearance and of psychosocial functioning. Only self-esteem seemed to have the power to differentiate the mature and the immature defense-styles within the disfigured groups. A high level of education, a small number of affected facial parts and good facial function were additional determinants of a high level of satisfaction with facial appearance. Satisfaction with facial appearance itself appeared to improve social and relational functioning. In contrast to self-perceived satisfaction with facial appearance, objective severity of the deformity has no influence on psychosocial wellbeing. Patient's perception of the surgical treatment is therefore a critical component of eventual outcome and should not be overlooked.

Patients with facial disfigurement should be screened for low SE and high FNAE, which can be considered as risk factors for the development of a lower level of satisfaction with facial appearance and psychosocial problems. A combination of surgical correction (with attention paid to restoring facial functions) and psychological help to increase SE and lower FNAE may improve patient satisfaction, reduce immature defense styles and ameliorate psychosocial functioning on the long-term. Psychological treatment should concentrate on social skills and dysfunctional cognitive-affective processing.

Overall, adults with a rare facial cleft are coping rather well, and suffer from limited psychosocial sequelae. Despite a better psychosocial outcome in general than expected, there is still room for amelioration. The burden caused by the facial deformity should not be underestimated; some have severe problems and a few would not even have children because they don't want them to have to put up with the same. In general they will always have to work harder to accomplish the same as a non-disfigured person and sometimes will have to settle with less; this is for example the case with finding a partner or a job.

These studies also demonstrate that psychosocial outcome is not simply dependent on factors related with the craniofacial deformity, but that it is a complex interaction between patient, environment and treatment. One way of reducing the problems is to make society more aware and improve the reactions of people. It is a noble effort, but it is difficult to accomplish a reduction of the prejudices in people who are not familiar with the pathology; like one of the patients with a rare facial cleft said during one of the interviews: 'I also turn around when someone has an 'abnormal' appearance. It seems a natural reaction to look at everything that is different from 'normal standards'. Looks are important in our society, but it doesn't reveal what is 'inside'; as has been said before: 'There's no art to find the mind's construction in the face'. If society cannot be completely

changed, it is important to educate the patients and help them in developing a good way how to deal with the problems related to their facial appearance. The knowledge of the results of these studies already led to more frequent referral of patients to a psychologist; this includes patients with a traumatically acquired facial deformity.

Limitations of the study

Rare and complex pathology as rare facial clefts are a challenge to study. The comment could be raised that it is only a limited population; however, it is one of the largest series in the world with the longest follow-up. The treatment guideline for surgical reconstruction was developed based on a retrospective case-study. Profound statistical evidence is missing, but it is unlikely that it ever will be available due the rarity of the cases. With modernisation of registration and imaging in hospitals future research might be more complete.

Regarding the assessment of psychosocial functioning, the number of questionnaires was limited due to the total number of participating patients. Outcome is dependent on many factors that enhance or impede the chances of positive adjustment, but it was not possible to study them all.

No matched-case-control study groups were used; it was impossible to collect a group of patients with a traumatically acquired facial disfigurement with similar demographic characteristics as the congenital group. Besides that, our reference group consisted of both patients from several general practitioners and employees of the Erasmus University Medical Centre. Among the last mentioned group the number of students was relatively large, which might bias the findings. The significant differences in baseline characteristics (age, gender and education level) between the groups were statistically adjusted in all analyses. When indicated, the severity of facial deformity was included as covariate in analyses between the congenital and acquired group.

Another methodological limitation of this clinical-empirical study was that it is questionable whether the patients in this study adequately represent the target population. It is plausible to assume that the most assertive and motivated patients entered the study. Therefore, selection bias may be there. The participation rate (79%) in the congenital group can be considered high. As at least six of the 16 non-participants were dissatisfied with treatment or had psychological problems, outcomes of the congenital group may be worse than presented here. The participation rate of the traumatically acquired group is low (57%), but relatively high when compared with other studies in literature.

Furthermore, this study is cross-sectional of character. It is of utmost clinical interest to design and conduct an observation study of longitudinal nature; this in order to evaluate the impact of upbringing, surgical treatment and/or psychological treatment on the different aspects of psychosocial functioning. Outcome assessment of patients who had no treatment whatsoever, will never be possible due to a lack of untreated patients.

The importance of it all…

Dealing with a severe facial deformity as a rare facial cleft is a difficult and challenging task, for both patient and doctor. This thesis demonstrates that we really have been helping these patients with our treatment on the long-term with surgical improvement of facial appearance in almost all patients, and better psychosocial functioning than expected in the majority of patients. However, these studies also show how we can do better! With improved knowledge of causes, treatment and consequences, we can offer a more complete treatment plan to these patients with better long-term outcome. In addition it enables us to give a patient a more detailed insight into long-term outcome of treatment, resulting in more realistic expectations and a more satisfied patient. Furthermore, although it is not the surgeon's profession, it is also his/her task to identify patients at risk of developing psychosocial problems and who are in need of psychosocial treatment; this allows appropriate preventative measures. The results of the studies provide some important risk factors for which patients can be screened and indicate where psychological treatment should focus on.

Since rare facial clefts are a congenital deformity encompassing a variety of deformities from mild to very severe of all facial parts, results can be extrapolated to other patients with congenital craniofacial deformities who face similar problems. As well the gained knowledge on surgical techniques and timing, as the psychosocial problems, could be useful in the treatment of patients with other congenital craniofacial deformities. Moreover, the studies also gave more insight into psychosocial problems of patients with a traumatically acquired facial deformity and demonstrated that they are at risk of developing psychosocial problems and should be screened and offered help.

It is to be continued…

Treatment of these patients starts at a very young age and the success is then dependent on an interaction of several factors: the patient, the parents and the treatment. It is often practically impossible to provide all the children with an extensive psychosocial assessment. Therefore development and selection of a good and practical screening instrument, also based on available questionnaires in this field, can be of help for better and more complete assessment of the children needing psychological help. A psychosocial profile of the adult patient in need for professional support could contribute to the development of this screening instrument. With this screening instrument a prospective, longitudinal study should be conducted for evaluation of the effect of surgical and psychological treatment. Furthermore the search for scientific evidence of the causes of rare facial clefts continues.

Recommendations

Overall, this thesis demonstrates it is important that patients should be treated in specialised centres, for both surgical reconstruction and psychological help; this in order to give them the most optimal chances on a good long-term outcome. Additional experience is gained by concentrating treatment in these specialised centres. Since a surgeon will only be able to adjust treatment based on a limited period of follow-up during his/her career, and seldom sees the long-term results of a patient he/she has treated, it is very important to pass experiences onto the next generation of surgeons. Furthermore international multicentre studies are necessary to increase the sample size of the population and improve scientific statistical evidence.

Research on psychosocial functioning should be focussed on the individual patient rather than on group comparisons. Moreover it is important to identify more factors that impede or enhance final psychosocial adjustment, like coping, teasing, and social support. This should preferably be done in a longitudinal study design with screening at certain ages.

CHAPTER 11

Summary/ Samenvatting

Summary

Details on history and background of rare facial clefts, their causes, treatment, and consequences were described in **CHAPTER 1**. Congenital 'rare facial clefts' are a very rare condition and encompass a wide variety of craniofacial dysmorphologies. All facial parts and all tissue-layers of the face can be involved in various degrees of severity. They can occur unilaterally or bilaterally, in the midline of the face or more paramedian or oblique. The affected soft tissue and/or skeletal elements show a disturbed growth-pattern, resulting in more obvious or more severe deformities over the years. The cause of rare facial clefts has been subject of discussion for more than a century, and there is still a lack of consensus and scientific evidence. Although the majority of rare facial cleft types seem to be the result of a disruptive process, there are several reports in literature that suggests a genetic cause; however, in none of these reports the genetic cause was proven. Treatment of rare facial clefts started in the 19th century, and had a major breakthrough in 1967 with the introduction of revolutionary craniofacial techniques by Tessier. Since then many additional techniques have been developed. Despite all the experience, there still exists controversy in treatment of rare facial clefts regarding techniques and timing. This is due to several factors: the complexity of the pathology, the rarity of the cases and the lack of good long-term follow-up. Facially disfigured people have to cope with all the prejudices and concomitant disapproving reactions from others in their daily life. Therefore development of psychosocial problems in this population of patients with facial deformities seems self-evident. Although there is now a considerable amount of literature on this topic, it is patchy and limited in adults. Overall, results are often inconsistent, and difficult to compare due to methodological weaknesses. The objective of this thesis was to improve knowledge on causes, treatment and consequences of rare facial clefts. The necessity for more knowledge regarding this pathology was demonstrated with a case report of a patient with a rare facial cleft. The final goal was to ameliorate a patient's treatment and psychological support in order to achieve a better surgical and psychological outcome on the long-term.

CHAPTER 2 reported the identification of recessive mutations in the *ALX3* homeobox gene, as cause for a distinctive presentation of frontonasal dysplasia, which was termed frontorhiny. This frontonasal malformation was characterized by a distinctive facial appearance, with hypertelorism, wide nasal bridge, short nasal ridge, bifid nasal tip, broad columella, widely separated slit-like nares, long philtrum with prominent bilateral swellings, and midline notch in the upper lip and alveolus. Additional recurrent features present in a minority of individuals were ptosis and midline dermoid cysts

of craniofacial structures. Assuming recessive inheritance, we mapped the locus in three families to chromosome 1 and identified mutations in *ALX3*. *ALX3* locates at band 1p13.3 and encodes the *aristaless*-related ALX homeobox 3 transcription factor. In total 7 different homozygous pathogenic mutations in 7 families were identified, all predicting severe or complete loss of function. In conclusion, *ALX3* is essential for normal facial development in humans and deficiency causes a recessively inherited clinically recognisable phenotype, which we term frontorhiny. After publication of this study, an article was published on three siblings with a striking resemblance of facial appearance to the patients with frontorhiny. We suggested molecular genetic testing of *ALX3* in this family.

In **CHAPTER 3** the development of a standardized scoring list with an objective approach for the outcome assessment of congenital craniofacial surgery was described. For each facial unit, deformities of shape or contour, malposition and soft tissue involvement were evaluated, with additional scoring for specific congenital deformities of that area. This new developed measurement was tested on pre-and postoperative photographs of patients with rare facial clefts and reliability and validity were demonstrated. Due to the ability to provide quantification of outcome, it can also be used as a measurement for the severity of congenital facial disfigurement. Because of its properties it can serve as an instrument to compare outcome between techniques, surgeons and centers in a more objective and standardized way.

CHAPTER 4 revealed the results of long-term evaluation of treatment of oblique and paramedian rare facial clefts. Treatment of twenty-nine adults with an oblique or paramedian facial cleft was evaluated based on series of photographs, 3D-CT's, X-rays, operation data, and experts' opinion. This study provided new details regarding surgical techniques and timing, influence of growth, and difficulties of this pathology on the long-term. The mean number of performed operations per patient was 10.6 (range:1-26). Vertical dystopia was not caused by previous surgery, but by growth deficiencies of the maxilla. In all patients with vertical dystopia, it was present at the age of four, and it should ideally be treated shortly after that age. In mild cases grafting seems sufficient, but in more severe cases orbital translocation is necessary. Cheek advancement flaps are preferred for the correction of cheek and lower eyelid deficiencies. Costochondral grafts showed the best long-term results in both orbital and nasal reconstructions. Major nose reconstruction is best delayed until adolescence for several reasons. For an optimal final result in selected cases, correction of midface hypoplasia at adolescence is necessary. Overall the three-dimensional underdevelopment of the midface region plays a central role in the deformities of most patients, but is complex and difficult to correct. The

provided treatment guideline in this chapter should help to minimize the number of operations and ameliorate long-term results; it is of the utmost importance that surgical treatment is performed in specialized recognized craniofacial centers.

In **CHAPTER 5** long-term surgical results of surgical treatment of twenty patients with a pure symmetrical median cleft, were analysed in a similar way as in chapter 4. The mean number of performed operations per patient was 7.6 (range:1-15). The long-term surgical outcome was overall initially good, but worsened over time, especially in the zone of the nose. Scarring outside the borders of the facial units of the nose (in the midline) was a frequent problem. When initially sufficient soft tissue of the nose is present, an L-incision can give good results until later major reconstruction. Once the face has matured, a midface advancement and a major secondary nose correction should be considered for satisfactory projection. An adequate and stable result of hypertelorism correction was observed for both the orbital box osteotomy and medial faciotomy. Special attention should be given to patients diagnosed with a midline cleft and especially with frontorhiny, since they can have skull base defects. Overall, the intrinsic growth restriction of the central midface is often unpredictable. This makes it hard to achieve perfect reconstructions. Early referral to a specialised centre is essential. The provided guidelines help to improve the final results and minimize the total number of operations.

CHAPTER 6 displayed the evaluation of the level of satisfaction with facial appearance of congenital and of acquired facially disfigured adults, and the exploration of demographic, physical and psychological determinants of this satisfaction. The congenital (N=59) and acquired (N=59) group did not differ significantly in the level of satisfaction with facial appearance. However, they both were significantly less satisfied than the reference group (N=201) without facial disfigurement. In facially disfigured adults, level of education, number of affected facial parts and facial function were determinants of the level of satisfaction. High fear of negative appearance evaluation by others (FNAE) and low self-esteem (SE) were strong psychological determinants. Although FNAE was higher in both patient groups, SE was similar in all three groups. Patients with a facial disfigurement appear to compensate for the deficits they recognize in themselves by placing greater emphasis on other qualities, or perhaps they adapt their goals and values in order to keep their self-esteem at a good level. Patients with facial disfigurement should be screened for low SE and high FNAE. A combination of surgical correction (with attention for facial profile and restoring facial functions) and psychological help (to increase SE and lower FNAE) may improve patient satisfaction.

In **CHAPTER 7** a study on social and relational functioning of adults with a congenital facial disfigurement (N=59) or a traumatically acquired facial disfigurement at adulthood (N=59) was described. In addition the relation of social and relational functioning with satisfaction with facial appearance (SFA), fear of negative appearance evaluation by others (FNAE), self-esteem (SE), and the severity of the facial deformity (OS), was evaluated. Social and relational functioning did not differ between congenital and acquired facially disfigured people; except for the fact that patients with a congenital deformity less frequently had a partner or children. The congenital and acquired group differed significantly from the normal reference group (N=120) on the behavioural dimensions by displaying a decrease in frequency of interpersonal functioning. Avoiding stress caused by stigmatisation, fear of negative evaluation and uncertainty about the reactions of others, forms the base of avoidance behaviour in facially disfigured people. Although the avoidance leads to a reduced stress level, it also leads to ego-constriction. SE was a strong predictor for all dimensions of social and relational functioning. SFA and FNAE were good predictors for the cognitive-affective dimensions, but not for the behavioural dimensions. OS was no predictor of social and relational functioning. Improving a patient's SE or SFA, and reducing FNAE can contribute to an amelioration of social and relational functioning. Psychological treatment should concentrate on social skills and dysfunctional cognitive-affective processing.

CHAPTER 8 investigated the degree to which patients with a facial disfigurement utilise defense styles. Moreover it was analysed whether satisfaction with facial appearance (SFA), fear of negative appearance evaluation by others (FNAE), self-esteem (SE), and severity of the facial deformity (OS), had a predictive value for the used defense styles. There was a significant difference between the group with (N=118) and the group without (N=108) a disfigurement on immature defense styles, meaning that the disfigured group used the immature style more frequently. There was a trend, albeit statistically insignificant, for the non-disfigured group to use more of the mature defense styles compared to the disfigured group. No difference was seen on any individual defense mechanism. Looking at the predictor variables, only self-esteem seemed to have the power to differentiate the mature and the immature defense styles within our disfigured groups. The fact that a low self-esteem comes with utilisation of immature defense styles suggests that professional support may be indicated for these patients. To our belief, it is less difficult to enhance self-esteem than to reduce immature defense styles and mechanisms.

The aim of the study in **CHAPTER 9** was to determine the impact of severe congenital facial disfigurement on long-term psychological functioning and evaluate possible

differences with patients with acquired facial disfigurement (N=59) and a non-facially disfigured reference group (N=120). Furthermore it was explored to what extent their psychological functioning is related to satisfaction with facial appearance (SFA), fear of negative appearance evaluation by others (FNAE), self-esteem (SE), and severity of the facial deformity (OS). Results revealed that patients with congenital facial disfigurement (N=59) had a rather 'normal' psychological functioning on the long-term, but they appeared more prone to internalizing behavioural problems than the people in the non-disfigured reference group. Several explanations for this rather good psychological functioning were given. There was only one aspect in which they differed significantly from patients with an acquired facial deformity: the congenital group displayed fewer problems on the physical component of quality of life; however, the mental component of quality of life was similar. SFA, FNAE and SE were good predictors of the different aspects of psychological functioning, except for the physical component of quality of life. Improving SFA (by surgery), enhancing SE or lowering FNAE (by psychological support) could enhance psychological functioning on the long-term. Future research should be focussed on the individual patient and risk factors for maladjustment, rather than on group comparisons.

In **CHAPTER 10** the major findings of the present thesis regarding causes, treatment and consequences of rare facial clefts were discussed and recommendations for the future research were given. The identification of the mutations in the *ALX3* gene as cause of frontorhiny enables us to provide genetic counselling for patients with this phenotype and their families. The long-term assessment of surgical results showed that there is still room for improvement of surgical treatment of patients with a rare facial cleft. The guidelines on techniques and timing that are given should help to reduce the number of operations and ameliorate the final results; surgeons should best postpone some major reconstructions to avoid the often detrimental influence of growth. Overall, adults with a rare facial cleft are coping rather well, and suffer from limited psychosocial sequelae. Compared with the normal population, they are less satisfied with their facial appearance, have a higher FNAE, display a decrease in frequency of interpersonal functioning, have less frequently a partner or children, use immature defense styles more often, and are more prone to internalising behavioural problems. Differences between patients with congenital and acquired facial disfigurement are limited to more physical problems, and more partners and children in the acquired population. Despite a better psychosocial outcome in general than expected, there is still room for amelioration. A combination of surgical correction (with attention paid to restoring facial functions) and psychological support to increase SE and lower FNAE may improve patient satisfaction,

reduce immature defense styles and ameliorate psychosocial functioning on the long-term. Psychological treatment should concentrate on social skills and dysfunctional cognitive-affective processing. Future studies on causes and treatment should be conducted in multiple centres, over several generations and preferably internationally, because of the low incidence of this pathology. Research on the psychological effects of having congenital facial disfigurement in the future should be focussed on the individual patient and risk factors for maladjustment, rather than on group comparisons. This should preferably be done in a longitudinal study design with screening at certain ages.

Samenvatting

Details over geschiedenis en achtergrond van zeldzame aangezichtsspleten, hun oorzaken, behandeling en gevolgen werden beschreven in **HOOFDSTUK 1.** Aangeboren zeldzame aangezichtsspleten zijn een zeer zeldzame aandoening en omvatten een uitgebreide variatie aan craniofaciale afwijkingen. Alle delen en weefsellagen van het gezicht kunnen aangedaan zijn in verschillende mate van ernst. De aangezichtsspleten kunnen enkelzijdig of dubbelzijdig voorkomen, mediaan in het gezicht, meer paramediaan of schuin. De aangedane weke en/of skeletale delen vertonen een afwijkend groeipatroon, hetgeen resulteert in duidelijkere en ernstigere afwijkingen in de loop van de jaren. De oorzaak van zeldzame aangezichtsspleten is al meer dan een eeuw onderwerp van discussie en het ontbreekt nog steeds aan consensus en wetenschappelijk bewijs. Alhoewel de meerderheid van de verschillende types zeldzame aangezichtsspleten het resultaat lijken te zijn van disruptieve processen, zijn er toch verschillende rapportages in de literatuur die een genetische oorzaak suggereren. Echter in geen van deze artikelen is een genetische oorzaak bewezen. De behandeling van zeldzame aangezichtsspleten begon in de 19^{e} eeuw en beleefde een enorme doorbraak in 1967 met de introductie van revolutionaire craniofaciale technieken door Tessier. Sindsdien zijn er veel nieuwe technieken ontwikkeld. Ondanks alle ervaring, bestaat er nog steeds controverse over de behandeling van zeldzame aangezichtsspleten ten aanzien van technieken en timing. Dit is te wijten aan verschillende factoren: de complexiteit van de pathologie, de zeldzaamheid van de gevallen en het gebrek aan goede lange termijn follow-up. Mensen met een misvorming in het aangezicht moeten in hun dagelijks leven omgaan met alle vooroordelen en de daarmee gepaard gaande afkeurende reacties van anderen. Daarom lijkt de ontwikkeling van psychosociale problemen in deze groep vanzelfsprekend. Alhoewel er nu een aanzienlijke hoeveelheid literatuur over dit onderwerp beschikbaar is, is het erg divers en gelimiteerd voor volwassenen. Daarnaast zijn de resultaten over het algemeen vaak niet consistent en moeilijk vergelijkbaar door methodologische zwakheden. Het doel van dit proefschrift was dan ook om de kennis over oorzaken, behandeling en gevolgen van zeldzame aangezichtsspleten te verbeteren. De noodzaak naar meer kennis over deze aandoening werd gedemonstreerd aan de hand van casuïstiek beschrijving van een patiënt met een zeldzame aangezichtsspleet. De uiteindelijke doelstelling was het verbeteren van de chirurgische behandeling en psychologische ondersteuning van een patiënt om zo een beter chirurgisch en psychosociaal eindresultaat te verkrijgen op de lange termijn.

HOOFDSTUK 2 rapporteerde over de identificatie van recessieve mutaties in het *ALX3* homeobox gen als oorzaak voor een specifieke presentatie van frontonasale dysplasie, genaamd frontorhinie. Deze frontonasale malformatie werd gekarakteriseerd door een kenmerkend gezicht met hypertelorisme, een brede neusbrug, een korte neusrug, een bifiede neustip, een brede columella, wijde gescheiden spleetvormige neusgaten, een lang philtrum met prominente bilaterale zwellingen en een inkeping in the mediaanlijn van de bovenlip en alveolus. Aanvullende terugkerende kenmerken aanwezig in een minderheid van de personen, waren ptosis van de oogleden en dermoidcystes van craniofaciale structuren in de mediaanlijn. Met recessieve overerving als veronderstelling, werd de locus in drie families gelinkt aan chromosoom 1 en werden er mutaties in *ALX3* geïdentificeerd. *ALX3* is gelokaliseerd op band 1p13.3 en codeert de *aristaless*-gerelateerde ALX 3 homeobox 3 transcriptor factor. In totaal werden er zeven verschillende homozygote pathogene mutaties in 7 families geïdentificeerd, die allen ernstig of volledig verlies van functie voorspellen. Concluderend is *ALX3* essentieel voor een normale ontwikkeling van het aangezicht in mensen en een defect veroorzaakt een recessief overerfbaar klinisch herkenbaar fenotype, genaamd frontorhinie. Na publicatie van deze studie werd een ander artikel gepubliceerd over 3 familieleden met een uitgesproken gelijkenis van het aangezicht met dat van de patiënten met frontorhinie. We hebben vervolgens gesuggereerd deze familie moleculair genetisch te testen op *ALX3*.

In **HOOFDSTUK 3** werd de ontwikkeling van een gestandaardiseerde scoringslijst, met een objectieve benadering voor de beoordeling van de resultaten van craniofaciale chirurgie, beschreven. Voor alle delen ('facial units') van het gezicht werden afwijkingen van vorm of contour, afwijkende positie en weke delen betrokkenheid geëvolueerd, met aanvullend scoren van de specifieke congenitale afwijkingen van dat deel. Dit nieuw ontwikkelde meetinstrument werd getest op pre- en postoperatieve foto's van patiënten met een zeldzame aangezichtsspleet en betrouwbaarheid en validiteit werden aangetoond. Door de mogelijkheid om de uitkomst te kwantificeren, kan het ook dienen als meetinstrument voor de mate van ernst van de congenitale aangezichtsafwijking. Omwille van zijn eigenschappen kan de scoringslijst gebruikt worden om uitkomsten van verschillende technieken, chirurgen en centra te vergelijken op een meer objectieve en gestandaardiseerde wijze.

HOOFDSTUK 4 onthulde de resultaten van de lange termijn evaluatie van schuine en paramediane zeldzame aangezichtsspleten. De behandeling van 29 volwassenen met een schuine of paramediane zeldzame aangezichtsspleet werd geanalyseerd met behulp van fotoseries, 3D-CT's, röntgenfoto's, operatieverslagen en de opinie

van experts. Deze studie verschafte nieuwe details ten aanzien van chirurgische technieken en timing, invloed van groei, en moeilijkheden van deze aandoening op lange termijn. Het gemiddeld aantal uitgevoerde operaties per patiënt was 10.6 (range 1-26). Verticale dystopie werd niet veroorzaakt door voorafgaande chirurgie, maar door groeistoornissen van de maxilla. Bij alle patiënten met verticale dystopie, was de verticale dystopie aanwezig op de leeftijd van 4 jaar en zou idealiter net na deze leeftijd behandeld moeten worden. In milde gevallen lijkt het plaatsen van een graft voldoende, maar in ernstige gevallen is verplaasting van de orbita nodig. Wanglappen hebben de voorkeur voor correctie van afwijkingen van wang en onderooglid. Ribkraakbeen grafts gaven de beste lange termijn resultaten in zowel orbita- als neusreconstructies. Uitgebreide neusreconstructies worden het best uitgesteld tot de adolescentie omwille van verschillende redenen. Voor een optimaal eindresultaat is in bepaalde gevallen een correctie van de hypoplasie van de midface regio noodzakelijk. Over het algemeen speelt de driedimensionele onderontwikkeling van de midface regio een centrale rol in de afwijkingen van de meeste patiënten, maar is het complex en moeilijk om te corrigeren. Het aangereikte behandelvoorstel in dit hoofdstuk zou moeten helpen om het aantal operaties te minimaliseren en de lange termijn resultaten te verbeteren; het is hierbij van groot belang dat patiënten in gespecialiseerde erkende craniofaciale centra worden behandeld.

In **HOOFDSTUK 5** werden de lange termijn resultaten van de chirurgische behandeling van 20 patiënten met een puur symmetrische mediane aangezichtsspleet geanalyseerd op een vergelijkbare manier als in hoofdstuk 4. Het gemiddeld aantal uitgevoerde operaties per patiënt was 7.6 (range 1-15). De chirurgische lange termijn resultaten waren over het algemeen initieel goed, maar verslechterden gedurende de jaren; vooral in de zone van de neus. Littekenvorming buiten de grenzen van de esthetische units van de neus (in de mediaanlijn) was een frequent probleem. Als initieel voldoende weke delen van de neus aanwezig zijn, dan kan reconstructie met een L-incisie goede resultaten geven in afwachting op een latere uitgebreide reconstructie. Als het gezicht uitgegroeid is, zouden een midface advancement met een uitgebreide secundaire neusreconstructie overwogen moeten worden om voldoende projectie te verkrijgen. ‘Orbital box’ osteotomie en mediale faciotomie gaven beiden een adekwaat en stabiel resultaat voor hypertelorisme correctie. Speciale aandacht moet worden gegeven aan patiënten met frontorhinie, aangezien ze schedelbasis afwijkingen kunnen hebben. Algemeen genomen is de intrinsieke groeibeperking van het centrale deel van het gezicht, de midface, vaak onvoorspelbaar. Dit maakt het moeilijk om perfecte reconstructies te verkrijgen. Vroege verwijzing naar een gespecialiseerd centrum

is essentieel. De gegeven handleiding voor behandeling zou moeten helpen om de uiteindelijke resultaten te verbeteren en het totaal aantal operaties te verminderen.

HOOFDSTUK 6 beschreef de evaluatie van de mate van tevredenheid met het uiterlijk van het gezicht van volwassenen met een aangeboren of verworven afwijking van het gezicht. Daarnaast werden ook de demografische, fysieke en psychologische determinanten van deze tevredenheid geëxploreerd. De aangeboren (N=59) en verworven groep (N=59) verschilden statistisch niet significant in de mate van tevredenheid met het uiterlijk van het gezicht. Deze beide groepen waren wel signifcant minder tevreden dan de referentiegroep zonder afwijkingen in het aangezicht (N=201). In volwassenen met een afwijking in het aangezicht waren het opleidingsniveau, het aantal aangedane delen van het gezicht en de functie van het gezicht determinanten van de mate van tevredenheid. Veel angst om negatief beoordeeld te worden door anderen (FNAE) en lage zelfwaardering (SE), waren sterke psychologische determinanten. Alhoewel de FNAE hoger was in beide patiëntengroepen, was de mate van SE vergelijkbaar in alle drie de groepen. Patiënten met een afwijking in het gezicht blijken te compenseren voor de gebreken die ze in zichzelf herkennen door grotere nadruk te leggen op andere kwaliteiten, of misschien passen ze hun doelen en waarden aan, om zo hun SE op een goed niveau te houden. Patiënten met een afwijking in het gezicht zouden gescreend moeten worden op een lage SE en hoge FNAE. Een combinatie van chirurgische correctie (met aandacht voor het profiel van het aangezicht en het herstel van functies van het gezicht) en psychologische ondersteuning (om het SE te verhogen en de FNAE te verlagen), kan de tevredenheid van patiënten met hun uiterlijk verbeteren.

HOOFDSTUK 7 was een studie over sociaal en relationeel functioneren van volwassenen met een aangeboren aandoening in het gezicht (N=59) en volwassenen met een traumatisch verworven afwijking van het gezicht op volwassen leeftijd (N=59). In deze studie werd ook de relatie onderzocht van sociaal en relationeel functioneren met tevredenheid met het uiterlijk van het gezicht (SFA), angst om negatief beoordeeld te worden door anderen (FNAE), zelfwaardering (SE) en ernst van de afwijking (OS). Sociaal en relationeel functioneren waren niet significant verschillend tussen de aangeboren en verworven groep; met uitzondering van het feit dat patiënten met een aangeboren aandoening minder frequent een partner of kinderen hadden. De aangeboren en verworven groep verschilden significant van de normale referentiegroep (N=120) ten aanzien van de gedrags dimensies doordat ze een lagere frequentie van interpersoonlijk functioneren lieten zien. Het vermijden van stress door stigmatisering, angst om negatief beoordeeld te worden en onzekerheid over de reacties van anderen, vormt de basis voor vermijdingsgedrag in personen met een aangezichtsafwijking.

Alhoewel het vermijdingsgedrag leidt tot een gereduceerd stessniveau, leidt het ook tot ego-constrictie. SE was een sterke voorspeller voor alle dimensies van sociaal en relationeel functioneren. SFS en FNAE waren goede voorspellers voor de cognitief-affectieve dimensies, maar niet voor de gedrags dimensies. OS was geen voorspeller van sociaal en relationeel functioneren. Verbetering van SE en SFA en het verminderen van FNAE, kunnen bijdragen tot een verbetering van het sociaal en relationeel functioneren. Psychologische ondersteuning zou zich moeten concentreren op sociale vaardigheden en op dysfunctionele cognitief-affectieve processen.

HOOFDSTUK 8 onderzocht de mate waarin patiënten met een afwijking in het aangezicht gebruik maken van defensie-stijlen. Daarnaast werd er geanalyseerd of tevredenheid met het uiterlijk van het gezicht (SFA), angst om negatief beoordeeld te worden door anderen (FNAE), zelfwaardering (SE) en ernst van de afwijking (OS), een voorspellende waarde voor het gebruik van defensie stijlen hebben. Er was een significant verschil tussen de groep met (N=118) en de groep zonder (N=108) een afwijking in het gezicht op het gebied van immature defensie-stijlen; de groep met aangezichtsafwijkingen gebruikte de immature stijlen vaker. Er was een trend, alhoewel statistisch niet significant, dat de groep zonder afwijkingen in het gezicht meer mature defensie-stijlen gebruiken in vergelijking met de groep met afwijkingen in het gezicht. Er werd geen verschil gezien ten aanzien van individuele defensie-mechanismen. Kijkend naar de voorspellende variabelen, bleek alleen SE de power te hebben om de mature en immature stijlen te kunnen differentiëren binnen de patiëntengroepen. Het feit dat een laag SE gepaard gaat met het gebruik van immature defensie-stijlen, suggereert dat professionele ondersteuning geïndiceerd is voor deze patiënten. Naar onze mening, is het minder moeilijk om SE te verhogen, dan om immature defensie-stijlen en -mechanismen te verminderen.

Het doel van de studie in **HOOFDSTUK 9** was om te bepalen wat de impact is van ernstige aangeboren aangezichtsafwijkingen op het psychologisch functioneren op lange termijn. Bovendien wilden we de mogelijke verschillen evalueren met patiënten met een verworven aandoening in het gezicht (N=59) en een referentie groep zonder afwijkingen in het gezicht (N=120). Daarnaast werd onderzocht tot op welke hoogte hun psychosociaal functioneren gerelateerd was aan tevredenheid met het uiterlijk van het gezicht (SFA), angst om negatief beoordeeld te worden door anderen (FNAE), zelfwaardering (SE) en ernst van de afwijking (OS). De resultaten onthulden dat patiënten met aangeboren aangezichtsafwijkingen (N=59) een nogal 'normaal' psychologisch functioneren op de lange termijn hadden. Ze leken wel meer vatbaar te zijn voor internaliserende gedragsproblemen dan de niet aangedane mensen in

de referentie groep. Verschillende verklaringen voor dit nogal goed psychologisch functioneren werden gegeven. Er was maar 1 aspect waarin ze significant verschilden van patiënten met een verworven aangezichtsafwijking: de groep met aangeboren afwijkingen vertoonde minder problemen op de fysieke component van de kwaliteit van leven; de mentale component van kwaliteit van leven daarentegen was vergelijkbaar. SFA, FNAE en SE waren goede voorspellers van de verschillende aspecten van psychologisch functioneren, behalve van de fysieke component van kwaliteit van leven. Het verbeteren van SFA (door chirurgie), het verhogen van SE of het verlagen van FNAE (door psychologische ondersteuning), zou het psychologisch functioneren op de lange termijn kunnen verbeteren. Toekomstig onderzoek zou zich moeten richten op de individuele patiënt en op risicofactoren voor een slechte aanpassing, eerder dan op groepsvergelijkingen.

In **HOOFDSTUK 10** werden de belangrijkste bevindingen van dit proefschrift aangaande oorzaken, behandeling en gevolgen van zeldzame aangezichtsspleten besproken en werden er aanbevelingen voor de toekomst gedaan. De identificatie van mutaties in het *ALX3* gen als oorzaak voor frontorhinie, maakt het mogelijk genetische 'counselling' te geven aan patiënten met dit fenotype en hun familie. De lange termijn evaluatie van chirurgische resultaten laat zien dat er nog ruimte is voor verbetering van chirurgische behandeling van patiënten met een zeldzame aangezichtsspleet. De behandelrichtlijnen aangaande technieken en timing die zijn gegeven, zouden moeten helpen om het aantal operaties te verminderen en de eindresultaten te verbeteren; chirurgen kunnen het best enkele uitgebreide reconstructies uitstellen om de vaak nadelige invloed van de groei te vermijden. Algemeen genomen functioneren volwassenen met een zeldzame aangezichtsspleet nogal goed en lijden zij aan beperkte psychosociale gevolgen. In vergelijking met de normale populatie, zijn ze minder tevreden met het uiterlijk van hun gezicht, hebben ze een hogere FNAE, tonen ze een vermindering in de frekwentie van interpersoonlijk functioneren, hebben ze minder vaak een partner of kinderen, gebruiken ze meer immature defensie-tijlen en zijn ze meer vatbaar voor internaliserende gedragsproblemen. Verschillen tussen patiënten met aangeboren en patiënten met verworven aangezichtsafwijkingen zijn beperkt tot meer fysieke problemen en meer partners en kinderen in de verworven populatie. Ondanks een betere psychosociale uitkomst over het algemeen dan verwacht, is er nog steeds ruimte voor verbetering. Een combinatie van chirurgische correctie (met aandacht voor het herstel van functies van het gezicht) en psychologische ondersteuning om het SE te verhogen en de FNAE te verlagen, kan de tevredenheid van patiënten met hun uiterlijk verhogen, de immature defensie-stijlen verminderen en het psychosociaal

functioneren op de lange termijn verbeteren. Psychologische ondersteuning zou zich moeten concentreren op sociale vaardigheden en op dysfunctionele cognitief-affectieve processen. Toekomstig onderzoek naar oorzaken en behandeling zou verricht moeten worden in meerdere centra, over meerdere generaties en bij voorkeur internationaal, gezien de lage incidentie van deze aandoening. Onderzoek naar de psychosociale effecten van het hebben van een zeldzame aangezichtsspleet zou zich moeten richten op de individuele patiënt en op risicofactoren voor een slechte aanpassing, eerder dan op groepsvergelijkingen. Dit zou bij voorkeur moeten worden gedaan in een longitudinale studie opzet met screening op gezette leeftijden.

APPENDICES

Acknowledgements

Publications

Curriculum vitae

PhD Portfolio

Dankwoord

Publicaties

Curriculum vitae

PhD Portfolio

Acknowledgements/ Dankwoord

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Publications/ Publicaties

Hovius SER, **Versnel SL**, Zuidam JM. *Tendon Transfer in the Congenital Hand. Tendon Transfers in Reconstructive Hand Surgery.* Parthenon Publishing 2005; Book: Chapter 9.

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Moolenburgh SE, Mureau MA, **Versnel SL**, Duivenvoorden HJ, Hofer SO. *The impact of nasal reconstruction following tumour resection on psychosocial functioning, a clinical-empirical exploration*. Psychooncology. 2009 Jul;18(7):747-52.

Twigg SR, **Versnel SL**, Nürnberg G, Lees MM, Bhat M, Hammond P, Hennekam RC, Hoogeboom AJ, Hurst JA, Johnson D, Robinson AA, Scambler PJ, Gerrelli D, Nürnberg P, Mathijssen IM, Wilkie AO. *Frontorhiny, a distinctive presentation of frontonasal dysplasia caused by recessive mutations in the ALX3 homeobox gene*. Am J Hum Genet. 2009 May;84(5):698-705.

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Versnel SL, van den Elzen MEP, Wolvius EB, Biesmeijer CS, Vaandrager JM, van der Meulen JC, Mathijssen IMJ. *Long-term results after 40 years experience with treatment of rare facial clefts: Part 1- Oblique and paramedian clefts.* Submitted.

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Versnel SL, van den Elzen MEP, Hovius SER, Passchier J, Duivenvoorden HJ, Mathijssen IMJ. *Social and relational functioning of adults with congenital or acquired facial disfigurement.* Submitted.

Van den Elzen MEP, **Versnel S**L, Mathijssen IMJ,Duivenvoorden HJ. *Defense mechanisms in congenital and acquired facial disfigurement; a clinical-empirical study.* Submitted.

Versnel SL, Plomp RG, Passchier J, Duivenvoorden HJ, Mathijssen IMJ. *Long-term psychological functioning of adults with severe congenital facial disfigurement.* Submitted.

Curriculum Vitae

Sarah Lisa Versnel was born on September 13th 1978 in Heerlen, the Netherlands. When she graduated from the gymnasium at the Heilig-Hart College Maasmechelen in 1996, she started medical school at the University of Leuven (Belgium). After 5 theoretical years, she returned to the Netherlands to continue her studies with two years of internships at the ErasmusMC in Rotterdam. During these internships she performed research at the department of Plastic and Reconstructive Surgery of the ErasmusMC (Prof. dr. S.E.R. Hovius, dr. I.M.J. Mathijssen). To seek adventure and experience, she worked as a junior house officer at the Townsville General Hospital in Townsville (Australia) after obtaining her medical degree in 2003. At the end of 2004 she returned to Rotterdam to work as resident at the department of Plastic and Reconstructive Surgery of the ErasmusMC. One year later she was accepted for the plastic surgery training program. A three year period as a PhD student, which commenced in 2005, preceded the start of her surgical training. The research was focused on causes, treatment and consequences of rare facial clefts as presented in this thesis (Prof. dr. S.E.R. Hovius, Prof. J. Passchier, dr. I.M.J. Mathijssen). In October 2010 she finished her two years of Basic General Surgery Training at the department of General Surgery, Onze Lieve Vrouwe Gasthuis Amsterdam (Dr. M.F. Gerhards). Currently she is continuing her training at the department of Plastic and Reconstructive Surgery, ErasmusMC Rotterdam (Prof. dr. S.E.R. Hovius).

PhD Portfolio

Name PhD student: **Sarah Versnel**	PhD period: **1-11-2005 t/m 1-11-2010**
Erasmus MC Department:	Promotor(s): **Prof. S.E.R. Hovius,**
Plastic and Reconstructive Surgery	**Prof. J. Passchier**
	Supervisor: **Dr. I.M.J Mathijssen**

1. PhD training	**Year**	**Workload (Hours/ECTS)**
General academic skills		
– Biomedical English Writing and Communication	*2007*	*50 hrs*
Research skills		
– Statistics		
– *Biostatistics for clinicians*	*2008*	*20 hrs*
– Methodology		
– PHD day ErasmusMC		
– *Introduction to clinical research*	*2008*	*8 hrs*
– *CPO minicursus: Methodolgie van patientgebonden*	*2006*	*20 hrs*
onderzoek en voorbereiding van subsidieaanvragen	*2006*	*5 hrs*
In-depth courses (e.g. Research school, Medical Training)		
– *Evidence Based Medicine*	*2010*	*20 hrs*
– *Paediatric Clinical Epidemiology*	*2006*	*20 hrs*
Presentations		
– *NVPC (Amsterdam)*	*2010*	*20 hrs*
– *EURAPS (Barcelona, Spanje)*	*2009*	*40 hrs*
– *NVSCA (Nijmegen)*	*2008*	*10 hrs*
– *NVPC / RBSPS (Den Bosch)*	*2008*	*20 hrs*
– *EURAPS (Funchal, Madeira)*	*2008*	*40 hrs*
– *NVPC (Utrecht)*	*2007*	*10 hrs*
– *12th International Congress of the ICFS (Salvador da Bahia, Brazilië)*	*2007*	*40 hrs*
– *ECSAPS, (Londen, Engeland)*	*2006*	*40 hrs*
– *NVVH (Amsterdam)*	*2005*	*10 hrs*
– *NVSCA (Rotterdam)*	*2005*	*40 hrs*
– *NVPC (Noordwijk)*	*2005*	*40 hrs*
– *11th International Congress of the ISCFS, (Brisbane, Australië)*	*2005*	*40 hrs*

1. PhD training	Year	Workload (Hours/ECTS)
International conferences		
– *13th Esser course (Rotterdam)*	*2009*	*8 hrs*
– *13th International Congress of the ICFS (Oxford, Engeland)*	*2009*	*30 hrs*
– *EURAPS (Barcelona, Spanje)*	*2008*	*30 hrs*
– *European society of Craniofacial Surgery ESCFS (Lille, France)*	*2008*	*20 hrs*
– *NVPC / RBSPS (Den Bosch)*	*2008*	*8 hrs*
– *12th Esser course (Rotterdam)*	*2008*	*8 hrs*
– *EURAPS (Funchal, Madeira)*	*2008*	*30 hrs*
– *12th International Congress of the ICFS (Salvador da Bahia, Brazilië)*	*2007*	*30 hrs*
– *ECSAPS, (Londen, Engeland)*	*2006*	*20 hrs*
– *European society of Craniofacial Surgery ESCFS (Oxford, Engeland)*	*2006*	*20 hrs*
– *FESSH (Göteborg, Zweden)*	*2006*	*30 hrs*
– *11th International Congress of the ISCFS, (Brisbane, Australië)*	*2005*	*30 hrs*
Seminars and workshops		
– *NVPC (Amsterdam)*	*2010*	*8 hrs*
– *NVPC (Maastricht)*	*2009*	*8 hrs*
– *NVPC (Utrecht)*	*2009*	*8 hrs*
– *Esser lectures (Rotterdam)*	*2008*	*8 hrs*
– *NVPC (Zeist)*	*2008*	*4 hrs*
– *NVSCA (Nijmegen)*	*2007*	*8 hrs*
– *Esser lectures (Rotterdam)*	*2007*	*8 hrs*
– *Wondcongres (Rotterdam)*	*2007*	*8 hrs*
– *NVPC (Utrecht)*	*2007*	*4 hrs*
– *NVSCA (Zwolle)*	*2006*	*8 hrs*
– *NVPC (Utrecht)*	*2006*	*8 hrs*
– *Wondcongres (Rotterdam)*	*2006*	*8 hrs*
– *NVPC (Utrecht)*	*2005*	*8 hrs*
Other *Grants*		
– *Nuts-Ohra grant*	*2007*	
– *METC (Rotterdam)*	*2007*	

2. Teaching activities	**Year**	**Workload (Hours/ECTS)**
– *Teacher Microsurgery Course Skillslab*	*2006-2007-2008*	*50 hrs*
– *Teaching plastic surgery within training of Emergency department nurses, OR-assistant nurses, anaesthetics assistant and physiotherapist at the Erasmus Medical Centre Rotterdam and the Albeda College Rotterdam*	*2007-2008*	*80 hrs*
– *Elective craniofacial education for third year medical students*	*2006-2007*	*120 hrs*
– *Regular and elective education for medical students on pathology and anatomy of upper extremities*	*2006-2007-2008*	*100 hrs*
Lecturing		
– *LAPOSA (Rotterdam)*	*2009*	*40 hrs*
Supervising Master's theses		
– *Facial clefts*	*2009-2010*	
– *Treacher-Collins*	*2008-2010*	
– *Supervising students*	*2008*	
Other		
– *Contribution to organisation: "Esser Master Class: New Frontiers in Arthroscopic Wrist Surgery"*		
– *Contribution to organisation: Hand Flap Surgery and Wrist Surgery – 2nd International Dissection Course, Utrecht*		
– *Contribution to organisation: 12th Esser Course: Aesthetics in Facial Reconstruction: New Perspectives 2nd Course, Rotterdam*		
– *Contribution to organisation: 11th Esser Course, Aesthetics in Facial Reconstruction, Rotterdam*		


Je moet gewoon
doen wat je wilt,
kletsen doen ze toch.


Wijze spreuk aan de muur bij een patiënt…