Finding the balance in treatment for patients with rare facial clefts

Marijke E.P. van den Elzen

FINDING THE BALANCE IN TREATMENT FOR PATIENTS WITH RARE FACIAL CLEFTS

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OP ZOEK NAAR DE BALANS IN DE BEHANDELING
VAN PATIËNTEN MET EEN ZELDZAME AANGEZICHTSSPLEET

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Aan "ons pap en mam" en Maurits

Foto op kaft met dank aan:
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"Concerto"

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CHAPTER I

GENERAL INTRODUCTION

FIRST IMPRESSIONS

What was your first thought the second you saw this thesis? Have you secretly found yourself making a judgement about the content already? Purely based upon its first sight, reading the topic of this thesis or by reading my name? Don't judge a book by its cover they say, however, that is what we instinctively do on a daily basis, making judgments and comments on things, patients and people around us. Is it safe to cross the street? Is this patient critically ill? Can I trust this salesman? We learn to make these decisions in a split second, but can we always trust these first impressions?

The face is of major importance as we communicate and can usually not be ignored. A small infant learns using the face of his mother to read how he is doing, as it reflects its wellbeing. Later on, when the way of communicating improves, facial expressions and mimics lead to social reactions and interactions. Because of the strong relation between the face and its function in social encounters and communication, fascination has always existed on the appearance of the face and the presence of specific traits and even psychiatric or criminal constitutions. This field of study has been called physiognomy and was already practised in the first Babylonian Dynasty, and afterwards popularised by Aristotle and especially by Della Porta, Browne and Lavatar.(1) (As can be seen in Figure 1, (2))

Although physiognomy is based on 'normal and unaffected' faces, looking at a face with deformities also gives rise to a range of emotions. Besides the possible reflections of one's characteristics, feelings attached to physical appearance come from a rich variety of other sources, such as mythology, legends, fairy tales and other examples from history and contemporary society. As a result, in most cultures a child with a craniofacial deformity lead to either overprotection and adoration or in the majority of the cases to elimination, since it was often seen as an omen of mysterious warnings and prophesies.(3) The ethos of most of these sources is that especially beauty is all-important. In this, the face is seen as the mirror of the soul (Cicero); with that association that 'what is beautiful is good'.(4) Nevertheless, even very young infants, who have no notice of these confounding sources, have the ability to categorize on attractiveness. They seem to have the same aesthetic perception as adults and prefer to look at attractive faces.(5) Physical attractiveness is even stereotypically strongly associated with sociability, dominance, general mental health, intelligence and physical health.(6, 7) The rating of facial attractiveness decreases, with an increasing severity of the facial disfigurement.(8, 9) 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.(10) This is not only true for adults, even children at elementary school prefer to play with peers with either no deformity, a wheelchair, or a missing arm or leg, rather than a child with a facial deformity. The only peer that was even less preferred to play with, was the kid who suffered from obesity.(11)

Figure 1. Physiognomy according to Della Porta

FEATURES OF RARE FACIAL CLEFTS

Patients with rare facial clefts (other than just cleft lip and or palate), belong to a group of patients with craniofacial deformity. They can present with different appearances with a variable severity. Rare facial clefts can be uni- or bilateral, medially, para-median or oblique placed, including all layers of tissue though not always affected to the same extend. Also involvement of other body parts is possible. As a result, no specific overall phenotypical overview can be delineated.

Scientific writings on the appearance of these patients, often called "monsters" in history, are plentiful. Causes of these deformities were only sought in the developmental area since the concept of embryological formation gained more support, before that time divine and mystical causes were addressed. Therefore, most of the early 'observations' are fused with fantasy, although some good representations exist.(12) (See Figure 2, (12)) In addition, terminology on these craniofacial malformations has always been indecisive and classification has never reached consensus. One of the first who opted for a classification was Sömmering in 1791.(13) (See Figure 3, (13)) Later on, others also produced, however, the majority of these schemes are considered as insufficient since they were based only on soft tissue or data was left out.(14)

Figure 2. 'Observations' fused with fantasy

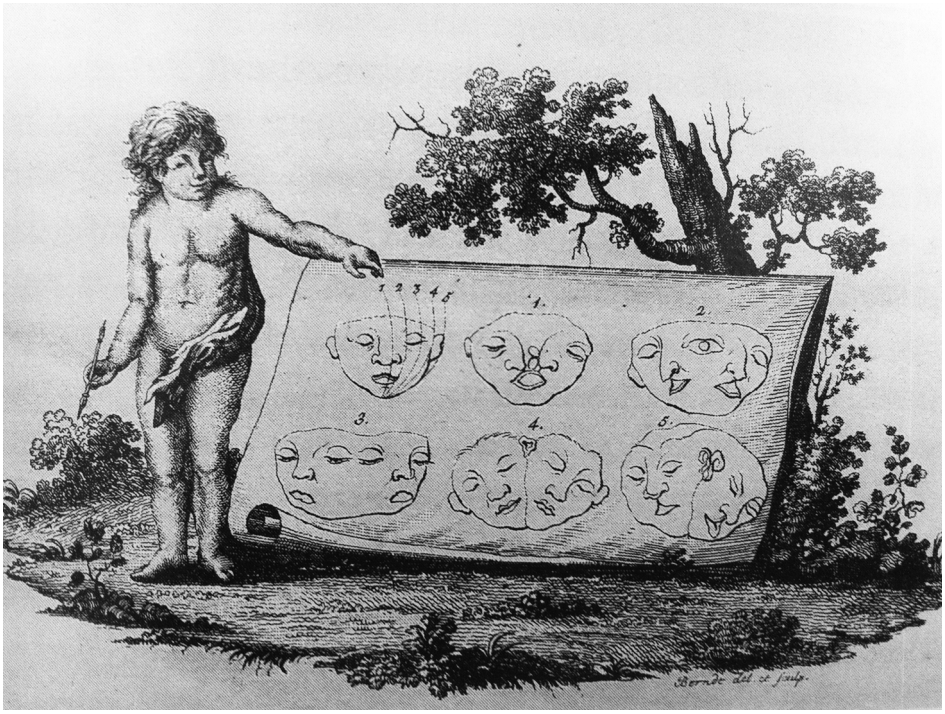

Figure 3. Classification according to Sömmering

Tessier provided one of the most important categorization systems in 1976, and still is one of the most commonly used. Although the classification is very practical, as it gives a topographic description of the site of the cleft, (See Figure 4 (15)) it does not address the morphogenesis that clarifies the mechanism of its formation. It must be stated nevertheless, that Tessier was the first that emphasized the relation between bony and soft tissue; "a fissure of the soft tissue corresponds, as a general rule, with a cleft of the bony structures".(15) Another important system of classification was made by Van der Meulen in 1983; the major advancement of this classification is that is based on pathomorphogenesis. To achieve a simple nomenclature, the term dysplasia was introduced since it covers all pathogenic and clinical aspects of a malformation.(16) (See Figure 5, (16)) A limitation of this classification however is that is in particular focussed on bony tissue and it is less convenient in its use. In both the Tessier as the Van der Meulen classification, multiple clefts in the same patient can occur.

The incidence of rare facial clefts is hard to estimate and varies in literature between 1.43 to 4.85 per 100.000 births.(17) Because the occurrence of a rare facial cleft is even higher in developmental countries, and most presented cohorts are derived from small communities, the accuracy of this incidence is doubtful. The estimation of the incidence in The Netherlands is around 1 in 400.000

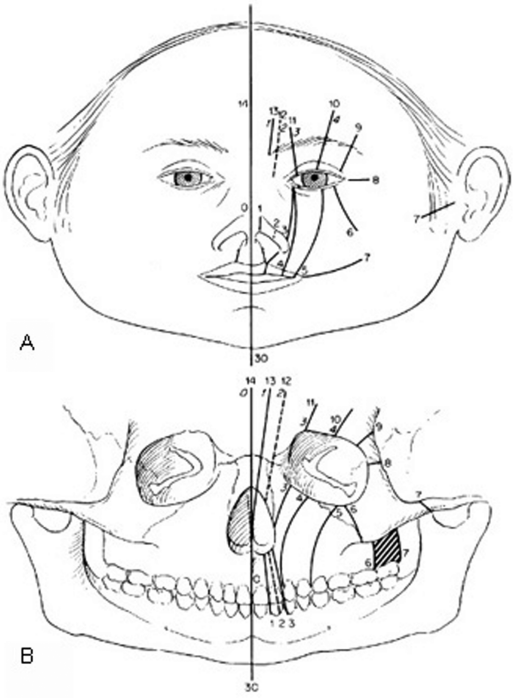

Figure 4. Classification according to Tessier

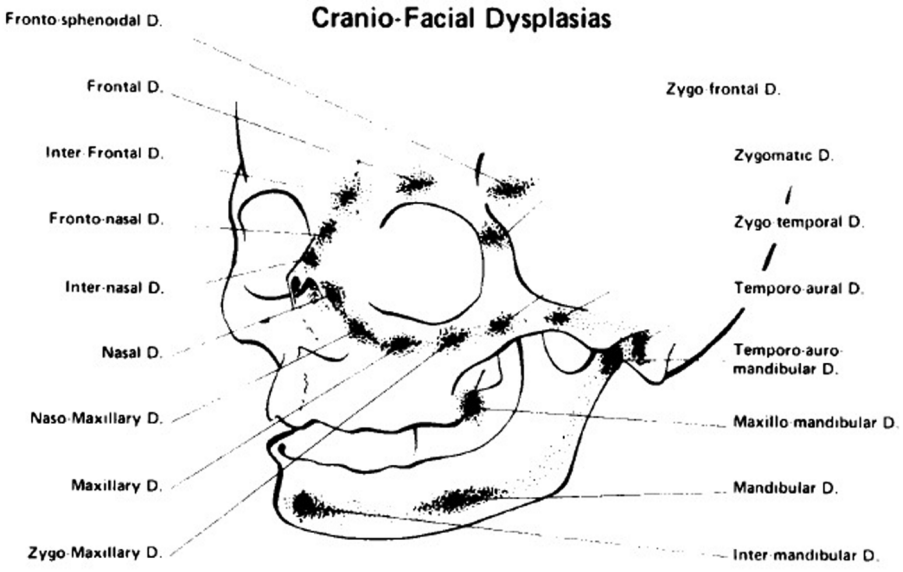

FIG. 2. Craniofacial helix symbolized by letter S.

Figure 5. Classification according to Van der Meulen

births for rare facial clefts alone, the incidence of hemifacial microsomia and Treacher Collins are both higher (respectively 1 in 4000 birhts and 1 in 50.000 births).(18)

Rare facial clefts develop during early pregnancy. The primitive growth and development of the face starts in the fourth week of embryonic life throughout the eighth week. The actual cause of a rare facial cleft often still remains unclear in most cases. Besides the possibility of disruptive processes, a genetic cause is found to be more likely in a part of this group of patients these days as well. In the past years a genetic origin has been found for Treacher-Collins (Tessier 6, 7, 8) in the TCOF1 and POLR1C gene,(19, 20) and the ALX 1 and ALX 3 gene have proven to be responsible for midline facial clefts (Tessier 0-14),(21, 22) also mutations in the *EFNB1* gene give rise to craniofrontonasal dysplasia.(23-30)

As a part of rare facial clefts, craniofrontonasal dysplasia (CFND) was first recognized as a specific syndrome by Cohen in 1979.(31) Subsequently, most common described phenotypical features in literature were coronal synostosis,(31-37) hypertelorism,(31, 33-37) bifid nasal tip,(31, 33, 35-37) fizzy and curly hair(35, 36) and longitudinal ridging and splitting of nails towards the end.(32, 34-37) As mentioned above, a loss-of-functioning mutations in the *EFNB1* gene has been found to be the cause of CFND.(23-30) Finding the genetic origin of this deformity was also made possible by the inclusion of a reasonable number of patients from the Craniofacial Team of the Sophia's Children's Hospital and Erasmus Medical Centre. Since the genetic cause of this deformity is know, screening for this mutation is possible. However, around 20% of the patients who undergo screening for CFND do not display a mutation in the *EFNB1* gene.(25, 29, 38)

SURGICAL TREATMENT

Surgical treatment has not always been possible, due to lack of refined anaesthetic techniques and possibilities to control blood loss for instance. The first report on closure of small defects such as a cleft lip dates from 20BC by Celsus.(39) Other examples of reports in literature on cutaneus closure of facial malformations date from 1828 by Delpech; repair of nasoschizis by a trilobed forehead flap,(40) in 1842 von Ammon; correction of epicanthal folds,(41) and in 1909 a rather extensive correction of the soft tissue by Jalaguier in a patient with bilateral oblique facial clefting.(42) More severe deformities could only be treated conservatively. Attempts to correct bony malformations were performed extracranial, so the optical illusion that the deformity was corrected was given. Only because of the extensive study on cadaver skulls and faces and the great vision and knowledge on anatomy of Tessier, it was made possible to operate intracranially and it opened a new door in surgery; craniofacial surgery. In 1964 he performed his first and famous transcranial orbital translocation in order to correct a patients hypertelorism.(43, 44) Inspired by Tessier, it was Van der Meulen who introduced craniofacial surgery for congenital anomalies in

Rotterdam. In 1979 he presented an different technique for correction of hypertelorism through a medial faciotomy.(45)

Because the congenital deformities such as CFND affect multiple facial units, including severe hypertelorism, nasal anomalies and facial asymmetry, most patients require several operations throughout life. In addition, also the other clefts such as oblique (Tessier 3,4,5), paramedian clefts (Tessier 1,2) and clefts of the midline (also known as Tessier 0-14) are major reconstructive challenges as well. Often serious asymmetry exists and multiple areas of the face are affected in patients with oblique and paramedian clefts. But also in the initially symmetrical medial facial clefts, asymmetry may arise as the patient matures. General treatment plans for amongst others, craniosynostosis or hypertelorism itself, are present in literature.(46-51) Strategies for the treatment of specifically patients with rare facial clefts are available as well.(14, 33, 36, 52-57) However, all previous conducted studies are limited by a small number of cases and/or a relatively short mean period of follow-up.(14, 33, 36, 47, 52, 54, 55, 57-66) This is of major importance, because 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.

THE EFFECT OF LOOKING DIFFERENT

Irrespective of whether or not patients underwent surgery; it is very likely that they still look 'different'. As mentioned before, living with a facial disfigurement often results in prejudices and concomitant disapproving reactions from others. People attribute emotions to others by deducting them from their facial expressions. Unfortunately, because of a facial deformity these expressions are often disturbed and conversations can be impeded. It should therefore be no surprise that previous conducted studies have shown that problems with social interactions are the main concern in this population.(67-70) The adopted different coping behaviours, to hide or compensate for their disfigurement, often make them unsociable, which gives rise to an interference with personal relationships, work life and leisure activities. (67, 70) The manner of reacting to these situations is different in every patient. The way a patient deals with these psychosocial difficulties can be called coping styles for the conscious approaches, and defense mechanisms for the unconscious approach.(71)

Surgical treatment is aimed at restoring an aesthetic and functional balance. Hopefully this will lead to a satisfied and self-accepting patient on the long term, so a 'normal life' can be lived. However, satisfaction and acceptance are not the same: a patient may be unsatisfied with the end result, but accepts his residual deformity. Reports specifically on acceptation of appearance are scarce.(72, 73) In studies concerning patients with chronic diseases or chronic pain, non-acceptance leads to

psychological distress and disability, reduced subjective health, depression, anxiety and emotional instability and avoidance.(72, 74-82) The model of avoidance behavior is based on a model of exaggerated pain perception in patients with chronic pain, who avoid movements and situations, so they will not experience pain. Since the reaction of avoidance in patients with chronic pain and facial disfigurement highly resembles,(83, 84) perhaps also the principals of acceptance might be alike as well. In view of the fact that amelioration of acceptance in patients with chronic diseases or pain, may induce an improved level of psychological well-being, less psychological distress and a higher level of emotional stability (72, 74-82), this can be true for patients with facial disfigurement as well.

AIMS AND OUTLINES OF THIS THESIS

As the name 'rare facial cleft' states, these deformities are uncommon. Ideally studies are set up like randomized controlled trials and big cohort studies. However, to set up such a study is basically impossible for this group of patients. Nevertheless, since nearly all patients with rare facial clefts in the Netherlands are treated in the Sophia's Children's Hospital and Erasmus Medical Centre a unique cohort has established in the past 40 years. Since the early seventies professor Van der Meulen started to treat these patients as one of the first in the world and was later joined by Vaandrager. This resulted not only in a very large cohort of this kind of patients, but also a follow-up from infancy throughout adulthood for nearly all of these patients. In conclusion we can state that based on the scarcity of this type of patients, this population is unique in its size, follow-up and accessibility. Therefore the studies combined in this thesis, were set up.

Since it is of major importance to adequately counsel parents of children with rare facial deformities, and to provide the best possible care and surgical treatment for every specific type of facial malformation, an early diagnosis is essential. At this moment, parents and patients are often confronted with physicians who are unaware of the diagnosis of their rare disorder. Nevertheless, as prenatal sonography has become the standard for all pregnant women, a guideline for facial clefts has been developed. But still, even for the consulted specialists it is hard to make the correct diagnosis at once. Since more and more genetic mutations are found to cause specific subgroups of facial malformations, individual diagnosis based on particular phenotypical features are important. Regarding patients with CFND, current literature contains detailed overviews of phenotypical features of large cohorts of possible CFND patients, but lack the genetic proof of a genuine CFND patient by having an *EFNB1* mutation. The reports in literature could therefore be contaminated with patients who are improperly pointed out as CFND patients. In **CHAPTER 2** a detailed overview of all phenotypical features of CFND patients, all with a confirmed *EFNB1* mutation, is provided. Providing these data will facilitate the diagnosis of patients who might have an *EFNB1* mutation in the future.

As mentioned before, either the small cohorts or the absence or short period of follow-up limited previous research is available on the ideal timing and type of surgery. Moreover, specific deformity related pitfalls, the influence of a restricted intrinsic growth potential or the possibilities of diminished growth due to surgical interventions was underexposed. A review on the long-term surgical results was set up for patients with CFND with proven *EFNB1* mutations in **CHAPTER 3**, for patients with oblique and paramedian facial clefts in **CHAPTER 4** and for symmetrical medial facial clefts in **CHAPTER 5**. The effect of diminished growth potential in the affected facial parts and consequent ideal timing and techniques for surgical treatment are presented in all of the above-mentioned chapters as well. Also a guideline deducted from these data is provided.

Living with a facial deformity surely affects one's psychological well being because of the reasons mentioned before. Scientific interest for this topic is not new, in fact, most research concerning psychological aspects of severe facial deformities dates from over ten years ago. Although surgeons are usually more interested in surgical innovations and novelties, psychological aspects of treatment must not be forgotten, as they are as important as surgical treatment.

Prior research focuses mainly on children and adolescents with facial deformities. Furthermore, overall results are often inconsistent, and difficult to compare due to methodological weaknesses, such as a small sample size, a lack of use of standardized questionnaires or suboptimal reference groups. In **CHAPTER 6** we investigate the impact of both congenital and acquired facial disfigurement on social functioning in adults and whether this differs from adults without facial disfigurement. In addition, the predictive value of a patient's objective and subjective appearance on social functioning will be evaluated. This is especially interesting, because surgery can influence both a patient's objective and subjective appearance; however, improvement of objective appearance does not always correlate with an increased patient's satisfaction with facial appearance.

The way a patient unconsciously deals with these psychosocial difficulties are defined as defense mechanisms. It is normal to develop different styles of defense over the lifespan, in which maturation is part of the process. In early developmental phases, defense styles are mainly immature; later on, these mechanisms develop into a mature defense style, although immature defenses remain available during life, even when mature styles have been developed. In prior studies it was shown that mature defenses are associated with better mental and physical health, and by contrast, immature defenses are associated with mental illness and greater. Therefore, in **CHAPTER 7** we objectify the levels of defense mechanisms in both patients with a congenital, acquired and without facial disfigurement. In addition we investigated the association of the defense mechanisms with objective and subjective appearance, self-esteem and fear of negative appearance evaluation.

Overall treatment is somehow aimed at achieving satisfaction and acceptance within the patients with these severe facial deformities. However, these definitions are not the same: a patient may be unsatisfied with the end result, but accept his residual deformity. Prior studies suggest that in patients with chronic diseases or chronic pain, non-acceptance leads to psychological distress and disability, reduced subjective health, depression, anxiety and emotional instability and avoidance.

For that reason we will investigate the prevalence of patients with non-acceptance, and look for risk factors to develop this non-acceptance in **CHAPTER 8**. Because most studies are on the level of the entire group of patients, it can be hard to identify an individual patient, hence, a short and specific screening tool tailored to test for non-acceptance in an individual patient is provided. Recognizing a patient at risk for non-acceptance is crucial for offering the best treatment to ameliorate acceptance and possibly thereby psychosocial functioning.

A summarizing discussion can be found in **CHAPTER 10**, followed by short summary in English and Dutch in **CHAPTER 11**.

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CHAPTER 2

PHENOTYPE OF EFNB1 MUTATIONS IN CRANIOFRONTONASAL DYSPLASIA

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ABSTRACT

Background: Craniofrontonasal dysplasia is an X-linked developmental malformation syndrome, caused by mutations in the *EFNB1* gene, which have only been described since 2004. A genotype-phenotype correlation seems not to be present. Since it is of major importance to adequately counsel parents of children with *EFNB1* mutations and the patients themselves and to improve diagnosis of new patients, more information about the phenotypical features is needed.

Methods: This study included 23 patients, (2 male, 21 female) with confirmed *EFNB1* mutations. All patients underwent a thorough physical examination and photographs were taken. If available, radiological images were also consulted.

Preliminary results: Hypertelorism, longitudinal ridging and/or spliting of nails, a (mild) webbed neck and a clinodactyly of one or more toes were the only consistent features observed in all patients. Phenotypical features that were observed frequently bifid tip of nose (91%) columellar indentation (91%) and were low implant of breasts (90%). Less common, but remarkable features were iris coloboma, cleft lip and palate, cryptorchism, hernia diaphragmatica, dextroposition of the heart, double vena cava superior and bidirectional shunt of the heart. In comparison with anthropometric data of facial proportions, patients with craniofrontonasal dysplasia had a significantly different face on multiple aspects. An overview of all phenotypical features is shown.

Conclusions: Patients with *EFNB1* mutations have a clear phenotype. Since the nomenclature "Craniofrontonasal Dysplasia" (CFND) can be confusing regarding the spectrum of phenotypical features, perhaps it should therefore be discarded, and be replaced by "*EFNB1*". A precise overview of all possible phenotypical features has not been reported. Therefore, this study will facilitate genetic counselling of parents and patients and contribute to the diagnostic and screening process of patients with an *EFNB1* mutation.

INTRODUCTION

Craniofrontonasal dysplasia (CFND) was identified as a specific subpopulation of frontonasal dysplasia, since it was delineated in a study by Cohen in 1979.[1] Afterwards, many other studies have focused on the manifestation of this syndrome. Most commonly depicted phenotypical features were coronal synostosis [1-11], hypertelorism [1, 4-14], bifid nasal tip [1, 4, 5, 8-10, 12, 13], fizzy and curly hair [8-11, 15] and longitudinal ridging and splitting of nails towards the end [3, 4, 6, 8, 9, 11-13]. It became clear that the majority of CFND patients were female. In addition, the female patients appeared to be affected more severely than male carriers, who showed only few mild symptoms or no clear features at all. A genetic basis was likely, because families with multiple affected members were reported.[2-4, 6-9, 12] However, there seemed to be a genetic paradox, since all daughters of affected males displayed severe symptoms of CFND, but no male to male transmission was seen and affected males portrayed only mild or no symptoms. Therefore, multiple modes for inheritance were proposed; germline mosaicism, autosomal dominant with sex-influenced expression, X-linked dominant, and metabolic interference.[2-4, 6-9]

The mystery was unraveled by a combination of results of multiple studies.[16-18] *EFNB1* was finally claimed to be located at Xq13.1 and loss of function mutations in *EFNB1* were proven to cause CFND.[10, 18-30] *EFNB1* encodes ephrin-B1, which is a transmembrane ligand for ephrin receptor tyrosine kinase. Because of random X-inactivation heterozygote females are uniquely mosaic for activated and inactivated cells, and by consequence a cell either does produce or does not produce a functional protein. These proteins are important for migration and pattern formation in the developmental process of the embryo.[31] The random pattern of expressing and non-expressing patches therefore leads to an abnormal sorting in cells, and in addition to ectopic tissue boundaries between these zones. The term for this process is called 'cellular interference'. [10] In hemizygous males all cells cannot produce a functional protein, and therefore this phenomenon cannot occur. Normal boundaries probably maintain through an alternative mechanism. [25] This could be via an ephrin redundancy [25] or promiscuity of the ephrin ligand/ receptor system.[10] An explanation for the few severely affected males reported in literature [6-8] could be a mosaicism in these patients, in which the wild-type to mutant ratio should be similar to that in heterozygous CFND females.[23, 26] Additional mechanisms were recently added to the phenotypic manifestation. Not only cellular interference, but also an impaired signalling capacity of ephrin-B1 and improper regulation of gap junctional communication should be responsible for the pathogenic process in CFND expression.[24, 28] A genotype-phenotype correlation has not been proven, and previous studies suggest that this is unlikely.[26]

Taken in all together, around 20% of the patients screened for CFND did not display a mutation in the *EFNB1* gene.[21, 23, 25] Multiple explanations have been proposed.[25] One of these explanations is misdiagnosis of some of the included patients. Studies following the discovery of the causal gene predominantly describe the location of new mutations, combined with a brief outline of phenotypic features of small families or cohorts.[18-20, 22, 27, 29, 30] Detailed overviews of

phenotypical features of large cohorts of possible CFND patients do exist,[3, 4, 6-10, 12, 30] but lack the genetic proof of a genuine CFND patient by having an *EFNB1* mutation. The reports in literature could therefore be contaminated with patients who are improperly pointed out as CFND patients.

Since it is of major importance to adequately counsel patients with *EFNB1* mutations and/or their parents and to improve diagnosis of new patients, more information about the phenotypical features of genuine CFND patients with an *EFNB1* mutation is needed.

METHODS

Study population

This study was conducted at the Craniofacial Unit of the department of Plastic and Reconstructive Surgery of the Erasmus MC, University Medical Center in Rotterdam, The Netherlands. All patients with a diagnosis of craniofrontonasal dysplasia (CFND) based on a confirmed *EFNB1* mutation who were currently under treatment, or have been treated in the past, were included in this study. A total of 23 patients (21 female, two male) were selected. Five of these patients have been described in a prior study.[6]

Design and procedure

A cross-sectional observational study was designed and conducted. Ethical approval was received from the board of the Medical Ethical Committee of the Erasmus MC, University Medical Center Rotterdam (MEC-2006-121).

Complete series of standardised photographs of all patients were collected, combined with a review of the patient's medical file and physical examinations. If available, radiological images were also consulted. However, since this is a study with a retrospective character, not all images were still available and moreover could not always be used as a source of quantitative data. Patients were asked to participate for an extra physical examination and additional photographs to capture all bodily features. Some short questions on functioning and limitations of their body were asked as well. Patients or parents provided written consent for the use of patient images.

Measurement of facial proportions

For calculation of facial proportions, standardized (frontal and profile) photographs of all patients were printed. Selected photographs had to be taken prior to major surgical interventions, so genuine dimension could be evaluated. Since all evaluated facial proportions were ratios, no scaling or calibration problems existed. Calculated indexes were compared to values derived from anthropometric studies.[32] As can be seen in Figure 1, chosen indexes were; Intercanthal Index (Intercanthal width/ Biocular width); Upper Face Index (Upper face height/ Face width); Nasal Protrusion - Nose Height Index (Nasal tip protrusion/ Nose height); Nose - Craniofacial Height

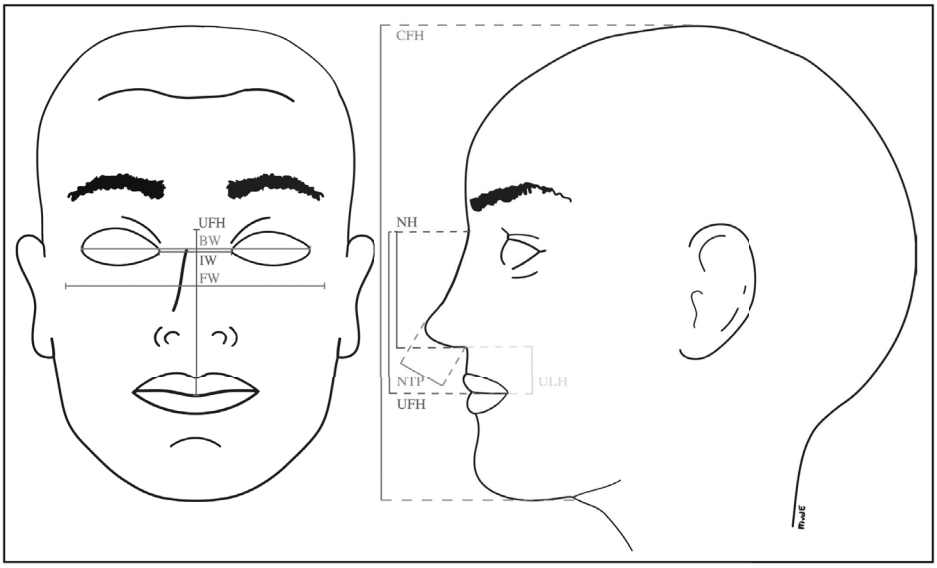

Figure 1. Anthropometric Facial Proportions (IW= Intercanthal width, BW= Biocular width, UFH= Upper face height, FW= Face width, NTP= Nasal tip protrusion, NH= Nose height, CFH= Craniofacial height, ULH= Upper lip height)

Index (Nose height/ Craniofacial height); Nose - Upper Face Height Index (Nose height/ Upper face height) and Upper Lip - Upper Face Height Index (Upper lip height/ Upper face height). Nomenclature of the mentioned indexes and measurements are directly derived from the referred anthropometric studies.[32]

Statistical analyses

As a measure of central tendency, percentages were calculated for categorical variables. For metric variables the mean was used as measure of central tendency, and the standard deviation was used as measure of dispersion. For statistical analysis we used the Statistical Package for the Social Sciences (SPSS) for Windows, version 18.0.

RESULTS

Twenty-three patients with proven *EFNB1* mutations (Table 1) were included in this study. A total of 20 females and three male CFND patients were identified. Five patients refused to participate for the additional physical examination and photographs. The main reason for not participating was an emotional or psychological problem with their bodily features, and seeing 'no use' in participating. One patient could not be contacted. Patients who did not want to participate however, had had standardised photographs taken during their treatment of at least their face, and sometimes hands, feet and chest. Medical files were available of all selected patients.

Table 1. Overview of mutations in the *EFNB1* gene

Gender	Nucleotide change	Protein change	Exon	Inheritance
Female	c.-95T>C (mosaic)	none	5'UTR	2
Male	*yet to be published (mosaic)*			
Female	c.1A>G (mosaic)	p.Met1	1	3
Female	c.30C>T	p.Gly10Gly	1	1
Female	c.109T>G	p.Trp37Gly	1	?
Female	c.161C>T	p.Pro54Leu	2	0
Female	c.196delC	p.Arg66fs	2	2 (daughter)
Female	c.228C>G	p.Tyr76X	2	1
Female	c.233T>C	p.Leu78Pro	2	2 (mother)
Female	c.233T>C	p.Leu78Pro	2	2 (daughter)
Female	c.266G>A	p.Cys89Tyr	2	1
Female	c.324dupA	p.Arg109fs	2	1
Female	c.339G>C	p.Lys113Asn	2	?
Female	c.360C>A	p.Asn120Lys	2	0
Female	c.368G>A	p.Gly123Asp	2	?
Female	c.407C>T	p.Ser136Leu	3	0
Female	c.451G>A	p.Gly151Ser	3	0
Female	c.492_499+2del10	p.Gly165fs	3	1
Male	c.496C>T (mosaic)	p.Gln166X	3	3
Female	c.496C>T	p.Gln166X	3	2 (sister)
Female	c.496C>T	p.Gln166X	3	2 (sister)
Female	c.543delC	p.Ser182fs	4	1
Female	c.564dupT	p.Val189fs	4	?

0= de novo, 1= sporadic, 2= familial, 3= mosaic, ?= parents not tested

Table 2. Difference of facial proportions of CFND patients compared to anthropometric means [32] (expressed in average standard deviations from mean)

	Intercanthal Index	Upper Face Index	Protrusion - Nose Height Index	Nose - Craniofacial Height Index	Nose - Upper Face Height Index	Upper Lip - Upper Face Height Index
Patients <6 years	+ 5.3 SD	- 2.1 SD	+ 1.7 SD[1]	- 3.4 SD[2]	- 4 SD[2]	+ 5.1 SD[2]
Patients >6 years	+ 4.7 SD	-1.5 SD	+ 1.6 SD	- 1.6 SD	- 2.0 SD	+ 2.8 SD
Total group	**+ 5.0 SD**	**- 1.8 SD**	**+ 1.7 SD**	**- 2.5 SD**	**- 3.0 SD**	**+ 4.0 SD**

[1]= *Youngest age of reference group is 6 years, difference probably slightly bigger if adequate reference would be available*
[2]= *Youngest age of reference group is 6 years, difference probably slightly smaller if adequate reference would be available*

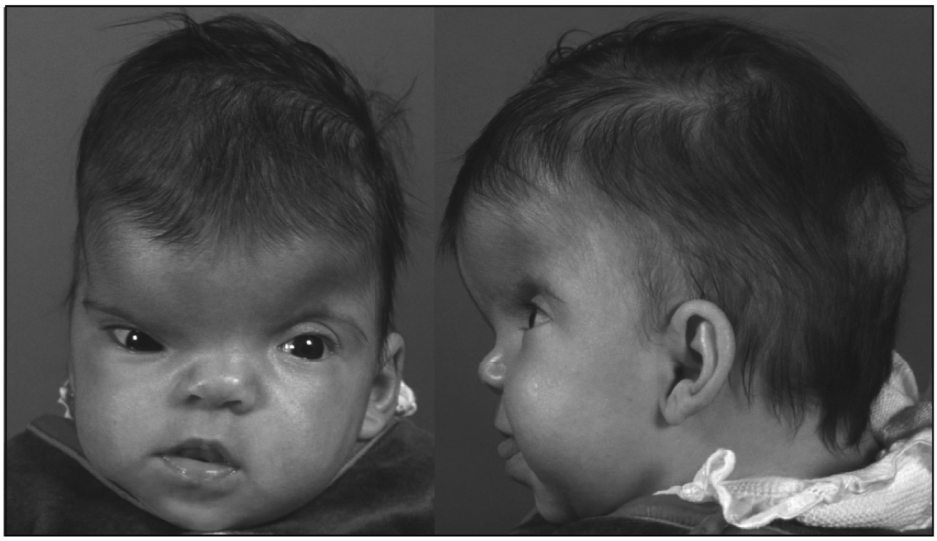

Figure 2. Patient displaying typical aberrant facial proportions

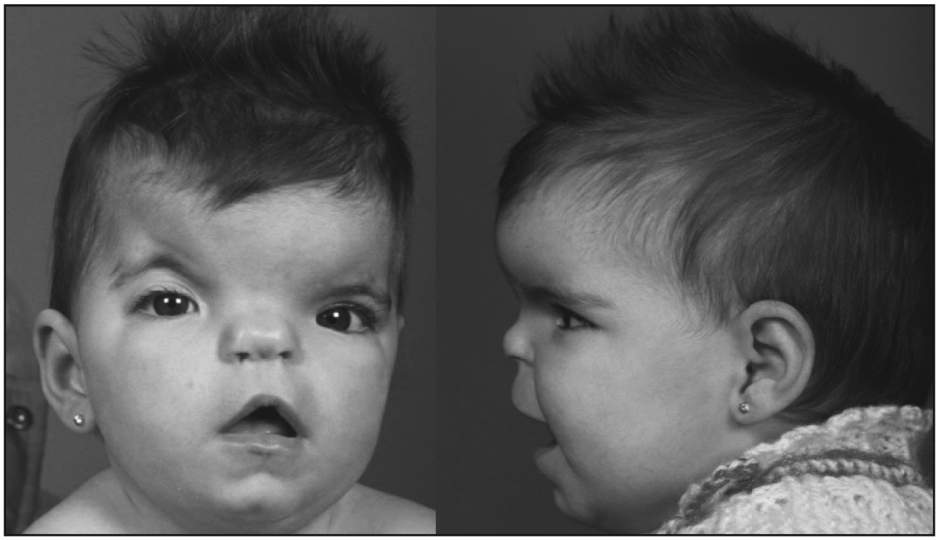

Figure 3. Patient displaying typical aberrant facial proportions

As can be seen in Table 2, Figure 2 and 3, the facial features of CFND patients significantly differs from the normal population (more than 2 SD's above the mean).[32] As expected, the intercanthal distance is much higher. The upper face (base of the nose to height of the commisure of the mouth) is relatively small compared to the width of the face (lateral points of zygoma). Compared to the height of the nose, the protrusion of the tip is relatively high. The height of the nose itself

however, is significantly too small, compared to both the total face as well as the upper face. In contrast to the upper lip, which is larger than normal.

General features

The average age of patients at evaluation was 18.0 years (range 0.5-44 years). Looking at the Body Mass Index of these patients revealed that 28% (n=5) were underweight, and 11% (n=2) were overweight. The span-length-ratio had a mean of 0.93 (range 0.77-0.99), indicating that in most patients their arm span was not equal to their total height, which is in contrast to the normal population.

Skull and face

Craniosynostosis was seen in 78% of all patients; 22% (n=5) had a left-sided coronal synostosis, 4% (n=1) had a right-sided coronal synostosis, 48% (n=11) had a bilateral sysnostosis of the coronal suture and 4% (n=1) had a bilateral coronal synostosis with synostosis of the sagittal suture. One patient had her craniosynostosis corrected abroad prior to her first presentation, and the exact type of synostosis was unclear. A very large anterior fontanel with delayed closure was seen in 33% (n=6). In two patients a corpus callosum agenesis was seen, and a partial agenesis of the corpus callosum in another three patients. Facial asymmetry was seen in 86% (n=19) of all patients, with a degree ranging from mild to severe; three of these patients had no history of craniosynostosis. A diminished development of the maxilla was sometimes observed (n=6) at different ages and variable degree. In addition, one patient had a groove in the middle of her alveolar ridge.

Hair

In our population 65% (n=15) of all patients had a widow's peak, and 26% (n=6) had a low anterior hairline. The hair itself was dry and with frizzy curls in 55% (n=12), dry and with watery curls in 36% (n=8) and 9% (n=2) showed normal hair. Parents reported that hair usually changed around 6-12 months, from soft baby hair into dry curly hair.

Zone of the orbits and eyes

All patients, 100% (n=23) displayed hypertelorism, with a variable degree from mild to severe. Orbital dystopia was seen in 32% (n=7) of them. A downslanting of the palpebral fissure was seen in 35% (n=8), with a variable severity, while an upslant of the palpebral fissure was seen in 48% (n=11), though usually only mild. Epicanthal folds were observed regularly, 39% (n=9) had a unilateral epicanthal fold, and 39% (n=9) had it bilateral. An aberrant form of the eyebrow was seen in 70% (n=16) of CFND patients. Rare observations were a coloboma of the iris (n=1) and heterochromia of the iris (n=1).

Functioning of the eye

Prior to a correction of the hypertelorism or orbital dystopia, a substantial number of ophthalmologic abnormalities were observed. The most commonly observed anomaly was strabismus 41%

(n=9), subdivided in strabismus divergens (n=3), strabismus sursoadductorius (n=4) and strabismus convergens (n=2), sometimes in combination with a Dissociated Vertical Deviation (DVD) (n=5). Nystagmus was also a common finding with 39% (n=9): four had a congenital nystagmus and four had a nystagmus latens. Hypermetropia was seen in three, of which two patients had a very high astigmatism, a solitary high stigmatism was described in one patient. Amblyopia was determined in two and an absent oblique superior muscle was pointed out in one patient.

Ears

Low set ears were a common finding 52% (n=12), while only two patients had an abnormal shape of the external ear.

Zone of the nose

Nearly all patients (91%, n=21) displayed a bifid tip of the nose. The same can be said for an indentation in the columella 91% (n=21), although not all patients with a bifid tip also had this indentation. A broad nasal base 70% (n=16) and flat nasal bridge 43% (n=10) were frequently observed as well. One patient had a fistula in the dorsum of her nose with an intracranial connection.

Zone of the mouth, maxilla and mandibulae

A usual observation was a tent-shaped mouth 39% (n=9), as well as a mild keel-shaped maxilla 35% (n=8). Crowding of the teeth was seen in 23% (n=5). Hypoplasia of the maxilla was reported in 18% (n=4), while 9% (n=2) had a mandibular prognatia. A cleft lip and palate was seen in only one patient, while one other patient had a mild notch in her upper lip.

Zone of the neck, shoulders, chest and back

A true short and webbed neck was seen in 67% (n=12) and in addition a mild webbing or pseudo webbing of the neck was seen in 33% (n=6). Rounded and sloping shoulders, often rather narrow, was observed in 89% (n=16). Sprengel's deformity (defined as one shoulder blade that sits higher on the back than the other) of the shoulders was quite common as well (69%, n=8). Three patients displayed an axillary pterygium (17%); unilateral in two patients, bilateral in one. A low implant of the breasts was seen in the majority of patients 90% (n=19), and in addition most of them had asymmetrical heights of their nipples 58% (n=11). Patients who were in their adolescence or adulthood also displayed an asymmetry of the breast volume 75% (n=6). Looking at the chest wall itself, revealed a pectus excavatum in 65% (n=11), although mild in most cases. A total of four patients were affected with both breast asymmetry and a pectus excavatum. All of the above is illustrated in Figure 4. Scoliosis was diagnosed in 46% (n=6).

Upper extremity

All patients (100%, n=23) had a longitudinal ridging and/ or splitting of nails towards the end, although the number of digits and severity differed. Only two patients were born with an extra

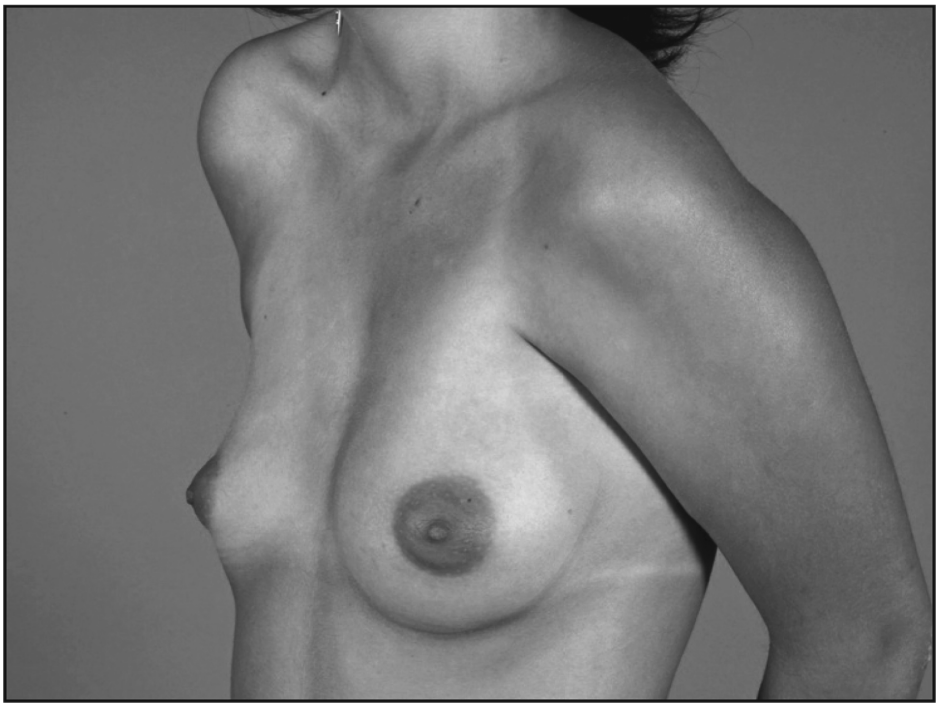

Figure 4. Patient displaying typical breast and chest deformities

digit (9%), and only three patients had a complete or incomplete syndactyly (13%). A clinodactyly of one ore more digits was a very frequently observed (74%, n=17) anomaly. A restricted range of motion of the arms, either abduction or elevation above the head was present in the majority of CFND patients (88%, n=15). This is probably due to the aberrant position of the clavicles, in combination with the earlier mentioned Sprengel's deformity. The available radiological images of the chest revealed that patients had either an aberrant curvature of their clavicles and/ or the angle of the clavicles with the sternum was bigger than normal. Either way, this resulted in a typical higher placement of the shoulders.

Lower extremity

As was seen in the hand, all patients (100%, n=23) had a longitudinal ridging and/ or splitting of nails of the toe towards the end, while both the severity as well as the number of toes differed. Duplication of toes was seen in 17% (n=4) and syndactyly in 30% (n=7). Clinodactyly of at least one toe, was again a consistent finding (100%, n=23), as illustrated in Figure 5. One patient suffered from asymmetrical lower-limb shortness (5%).

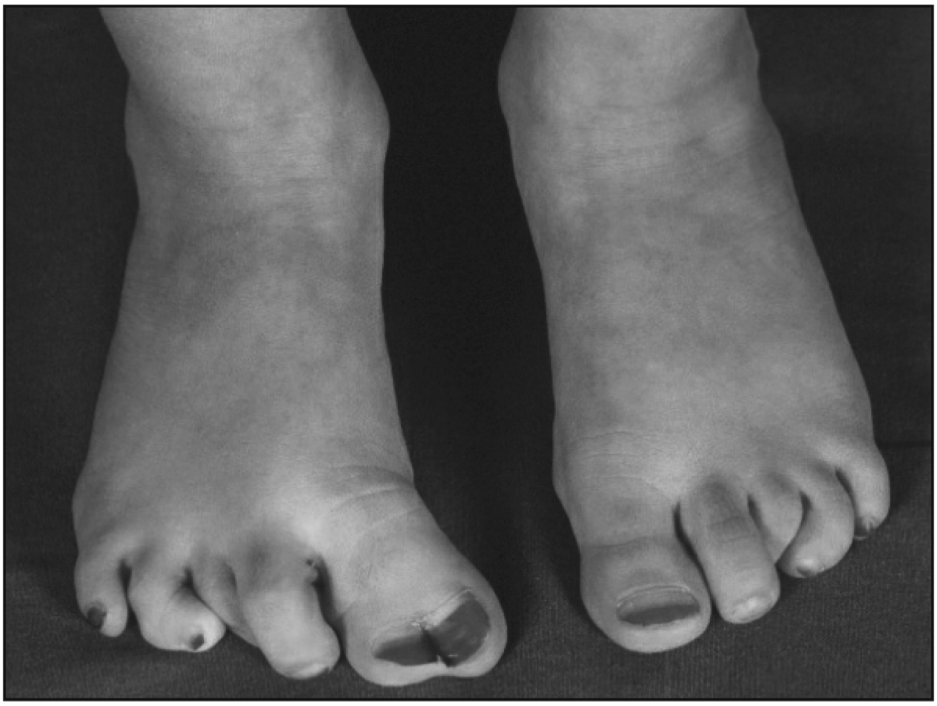

Figure 5. Patient displaying typical foot and toe deformities

Cardiac abnormalities

Three patients (13%) had problems concerning their heart. One patient had a patent ductus arteriosus, one had directly after she was born an atrial flutter of unknown origin, and one patient had multiple cardiac problems; dextroposition of the heart, two superior vena cavas, a bidirectional shunt and an atrium septum defect.

Other findings

An umbilical hernia was seen in one patient. Cryptorchidism was seen in one male, a café-au-lait spot was seen in one patient, while one other patient had a haemangioma. Two patients (9%) suffered from psoriasis and one patient had toddler's hypoglycaemia.

DISCUSSION

Genuine CFND patients, with proven *EFNB1* mutations, have a clear phenotype. However, a detailed overview of the phenotypical features of a large cohort had not been presented in literature before. As expected some of the reports in literature seem to be contaminated with patients who are improperly pointed out as CFND patients. The results from this study make the

diagnosis of some patients presented in literature therefore doubtful, based on their different facial proportions and dissimilar phenotype.[7, 14, 30] In other studies, some patients were classified as frontonasal dysplasia, while they actually match the typical phenotype of CFND.[13, 33, 34] Perhaps the nomenclature "Craniofrontonasal Dysplasia" (CFND) should therefore be discarded, and perhaps be replaced by "*EFNB1*-CFND".

This study leads us to the assumption, that in CFND patients with an *EFNB1* mutation, consistent features exist. These consistent features seem to be: hypertelorism; a certain degree of longitudinal ridging and/or spliting of nails of at least one digit or toe; a certain degree of a webbed neck; and a clinodactyly of one or more toes. In addition, different facial proportion, compared to normal individuals are observed in all patients.[32] These proportions are reflected in a relatively small upper face compared to the width of the face, a very short nose, with a relatively high protrusion compared to its length and a relatively long upper lip, compared to the upper face. It must be stressed that the projection of the nose itself in comparison to the whole face is very small, but since the length is about the same as the projection, this ratio is relatively high.

Features that were very common in the vast majority of patients, although not in all patients, can be entitled as 'very suggestive'. These are; bifid tip of the nose (91%); indentation of the columella (91%); low implant of breasts (90%); rounded, sloping and often rather narrow shoulders (89%) with reduced range of motion of the shoulders (88%); facial asymmetry (86%); craniosynostosis (78%); clinodactylia of at least one digit (74%); aberrant form of eyebrow (70%); broad nasal bridge (70%).

In the overviews in prior published studies, the frequency of phenotypical features (characterized by us as consistent or very suggestive) is either different or not presented, in all of the circumscribed patients. Nevertheless, they indeed seem to have a considerable overlap in presentation.[4, 6, 8, 9, 11, 12] Moreover, it is questionable if a bodily feature was not scored, whether it was not present, or just not reported or noticed. In addition, different definitions and opinions can exist for the scoring of some features as being abnormal.

Measurements of facial proportions are seldom reported, which is unfortunate. One study though, gave a description of the cranio-orbito-zygomatic region, based on CT-scans compared to a age-matched control value. Beside the obvious increased interorbital distance, they also found a degree of horizontal midface retrusion demonstrated by a shortened zygomatic arch length and an expanded interzygomatic buttress distance, suggestive for a bachycephalic morphology.[13] In addition, another study also described a short upper facial height [8] and compared it to anthropometric measurements. However, the short upper facial height seemed to be present in only 66% of their cases. A further study mentions midface hypoplasia [3], however, they do not support it with objective data or compare it to a normal reference group. These findings are in accordance to our data.

There is a fair chance that not all possible phenotypical features of CFND are present within our population. A few other features that were not evaluated in this study, are presented in literature:

myoclonus with poor hearing; pelvic kidney; bilateral vesico-ureteral reflux; hip girdle anomalies;[11] median cleft lip/ palate [8]; asymmetric mandible [9]. Furthermore, some studies state that CFND patients have a normal intelligence,[8, 10, 12, 15] while others claim that some may have learning difficulties to a variable degree.[3, 4, 10, 23, 33] In this study intelligence was not measured.

Additional features that are reported in other studies of patients with *EFNB1* mutations, include; diaphragmatic hernia [18, 19, 21, 22, 27] dysplastic clavicles and clavicle pseudoarthrosis;[8-12, 18, 20, 23] accessory nipples;[10] high arched palate;[4, 9-12, 33] uterus arcuatus;[10] duplication of uterus, kidneys and ureters;[10] and low posterior hairline [8, 12, 22].

One of the limitations of this study is the low number of males. Although CFND manifests particularly in females, and affected males express significantly less features, this overview would have been more complete if more males had been available. In addition, one of the evaluated males has a mosaic mutation, and as a consequence he is affected as severely as the females. A clear phenotype of affected males could not be given, since only one male was evaluated, he displayed clear features of CFND, though in a mild degree.

Another limitation is that not all included patients agreed to participate in this study. However good standardized photographs were available. This is the reason though, that the denominator changes between different features. If all patients participated, the percentages would have been even more reliable.

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CHAPTER 3

LONG-TERM SURGICAL OUTCOME FOR CRANIOFACIAL DEFORMITIES OF PATIENTS WITH CRANIOFRONTONASAL DYSPLASIA WITH PROVEN EFNB1 MUTATIONS

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ABSTRACT

Background: Craniofrontonasal dysplasia (*EFNB1* gene mutations) has a variable phenotype. Most patients require multiple operations throughout life. Different treatment strategies are suggested in literature, but lack the support of long-term results. Based on our results, a guideline for surgical treatment is given.

Methods: Twenty-three patients with a genetically proven craniofrontonasal dysplasia were evaluated on long-term surgical results. Medical charts and standardized photographs of all patients were retrieved for details and results of performed operations. The final result was scored based on severity of the initial and remaining facial deformities and need for revisional surgery.

Results: Two patients had a mild phenotype and requested no surgery. The average number of operations was 5.0 for the adult patients. The observered abnormalities of the facial skeleton (hypertelorism, orbital dystopia and midface hypoplasia) appear to be primarily induced by the genetic defect and not secondary to either craniosynostosis or surgical procedures.

Conclusions: Correction of hypertelorism and orbital dystopia, if present, is preferably done with a median faciotomy. A first costochondral graft for the correction of the dorsum of the nose can be performed simultaneously, as well as a correction of the medial canthi. A definite correction of the nose can best be performed at skeletal maturity, together with other secondary corrections.

INTRODUCTION

Craniofrontonasal dysplasia (CFND) was first recognized as a syndrome by Cohen in 1979.(1) Subsequently, most common described phenotypical features were coronal synostosis,(1-7) hypertelorism,(1, 3-7) bifid nasal tip,(1, 3, 5-7) fizzy and curly hair(5, 6) and longitudinal ridging and splitting of nails towards the end.(2, 4-7) A combination of studies proved (8-10) a loss-of-functioning mutations in the *EFNB1* gene to be the cause of CFND.(10-17)

Because the congenital deformities affect multiple facial units, including severe hypertelorism, nasal anomalies and facial asymmetry, most patients require several operations throughout life. Treatment plans for craniosynostosis or hypertelorism itself are plentiful.(18-23) Tailored strategies for the treatment of patients with CFND however, are poorly detailed,(3, 6) with the exception of one study.(24) Moreover, since the genetic cause of this disorder was unclear for so long, these overviews lack the proof of presenting genuine CFND patients. Diagnosis of some patients presented in literature is doubtful, based on their different facial proportions and dissimilar phenotype in comparison to presented patients with *EFNB1* mutations.(25-27) This is also reflected in the possibilities and recommendations for treatment, because every syndrome has its specific difficulties and possible pitfalls, due to a different growth-pattern or growth restrictions. In addition, all of the prior studies lack true long-term results to substantiate their proposed treatments.(3, 6, 19, 24) Therefore we present our long-term results of the surgical treatment of patients with CFND-*EFNB1* mutations. Based on our results, a guideline for surgical treatment is given.

PATIENTS AND METHODS

All patients who have been treated from 1978 to 2011 at our Craniofacial Unit, with a diagnosis of craniofrontonasal dysplasia (CFND) and a confirmed *EFNB1* mutation (Table 1) were included in this study. *Patients under the age of 16 were included only for evaluation of their facial growth (if possible), but excluded for the assessment of long-term surgical results.*

The complete series of photographs of each patient at various ages, taken by a professional photographer, were collected. The patient's medical chart was retrieved for details on performed operations. Since this was a retrospective study, radiological images were not available as quantitative parameters for all patients. Objective final surgical results were assessed, based on severity of the initial and the remaining facial deformities, using the scoring list according to Versnel (28), and based on the need for revisional surgery, using the Whitaker classification.(29, 30)

Table 1. Overview of mutations in the *EFNB1* gene

Gender	Nucleotide change	Protein change	Exon	Inheritance
Female	c.-95T>C (mosaic)	none	5'UTR	2
Male	*yet to be published (mosaic)*			
Female	c.1A>G (mosaic)	p.Met1	1	3
Female	c.30C>T	p.Gly10Gly	1	1
Female	c.109T>G	p.Trp37Gly	1	?
Female	c.161C>T	p.Pro54Leu	2	0
Female	c.196delC	p.Arg66fs	2	2 (daughter)
Female	c.228C>G	p.Tyr76X	2	1
Female	c.233T>C	p.Leu78Pro	2	2 (mother)
Female	c.233T>C	p.Leu78Pro	2	2 (daughter)
Female	c.266G>A	p.Cys89Tyr	2	1
Female	c.324dupA	p.Arg109fs	2	1
Female	c.339G>C	p.Lys113Asn	2	?
Female	c.360C>A	p.Asn120Lys	2	0
Female	c.368G>A	p.Gly123Asp	2	?
Female	c.407C>T	p.Ser136Leu	3	0
Female	c.451G>A	p.Gly151Ser	3	0
Female	c.492_499+2del10	p.Gly165fs	3	1
Male	c.496C>T (mosaic)	p.Gln166X	3	3
Female	c.496C>T	p.Gln166X	3	2 (sister)
Female	c.496C>T	p.Gln166X	3	2 (sister)
Female	c.543delC	p.Ser182fs	4	1
Female	c.564dupT	p.Val189fs	4	?

0= de novo, 1= sporadic, 2= familial, 3= mosaic, ?= parents not tested

RESULTS

Twenty-three patients in 21 families with proven *EFNB1* mutations met our inclusion criteria (Table 1); 21 patients were female and two were males. Five of these patients have been described in a prior study.(4) At time of evaluation 14 patients were still under treatment. Eleven patients were under the age of 16 years.

Average age at time of inclusion was 18.0 years (range 0.5-44 years). The mean number of years of follow-up of the adult patients was 25.3 years (range 16-39). Two of the 23 patients had no surgical interventions; one female because she was only mildly affected (Figure 1.), another female patient had no craniosynostosis and was still too young for a hypertelorism correction. As can be seen in Table 2, adult patients had had an average of 4.9 (range 2-10) operations during their total treatment. Prior to referral to our Craniofacial Unit, one patient was treated in another hospital in the Netherlands, and two in hospitals abroad (Colombia and Belgium). Exact data on the operations performed abroad could not be obtained.

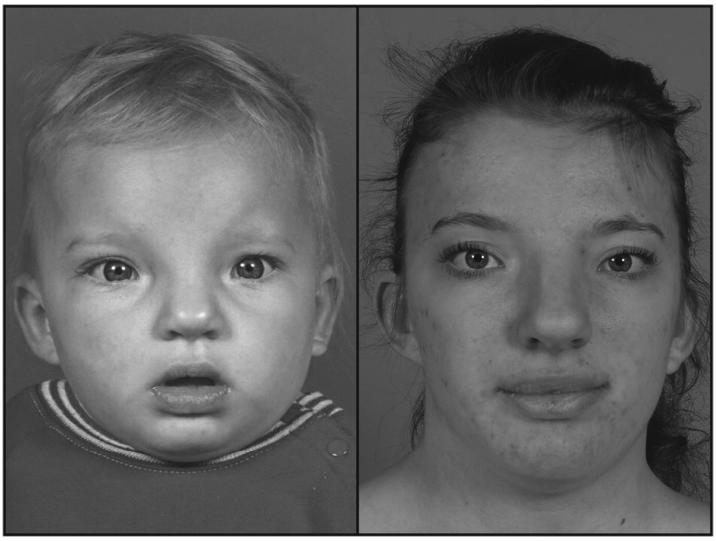

Figure 1: A CFND patient with an initially mild presentation who underwent no surgical procedures; the hypertelorism and orbital dystopia at mature age appear to be primarily induced by the genetic defect and not secondary to either craniosynostosis or surgical procedures

Table 2. Overview of surgical procedures

	Patients (n)		Performed operations (n)		Age first operation (years)	
	Affected	Operated[1]	mean	range	median	range
Total number of operations	23	21	4.9*	2-10*	1.0	0,25-20
Craniosynostosis	16					
Frontosupraorbital advancement		13	1,1	1-2	0,7	0,25-1,33
Occipital expansion		3	1,7	1-2	0,5	0,5-0.6
Eyes and orbits	23					
Orbital box osteotomy		8	1.4*	1-2*	7.0	0.6-20
Medial faciotomy		7	1*	1*	4.0	4-15
Soft tissue (canthal corrections)		13	1.9*	1-4*	6,5	1-22
Bone (corrections on orbits)		13	1,6*	1-3*	7	1-22
Nose	22					
Soft tissue		4	2,7*	1-6*	4	4-15
Bone/cartilage		11	2,6*	1-7*	5,5	1-20
Maxilla, oral cavity and lips	13					
Le Fort I		3	1,3*	1-2*	15	14-17
Soft tissue		1	2*	2*	1	1
Bone		3	1.3*	1-2*	15	15-22

[1]= Operated at time of evaluation, patients of all ages

*= adult patients only, because infants/ adolescents have not completed treatment

Mean total follow-up of adult patients 25.3 years (range 16-39 years)

Craniosynostosis

Craniosynostosis was seen in 78% of all patients; 22% (n=5) had a left-sided coronal synostosis, 4% (n=1) had a right-sided coronal synostosis, 48% (n=11) had a bilateral sysnostosis of the coronal suture and 4% (n=1) had a bilateral coronal synostosis with synostosis of the sagittal suture. One patient had her craniosynostosis corrected abroad prior to her first presentation, and the exact type of synostosis was unclear.

Frontosupraorbital advancement

The majority of patients underwent a frontosupraorbital remodelling (n=13). The patient with bilateral coronal synostosis in combination with the sagittal suture presented himself for the first time at the age of 13 months, over 30 years ago. At that time, it was decided to correct the hypertelorism together with the hypertelorism at the age of 3 years. One patient had a bilateral orbital box osteotomy together with her frontosupraorbital advancement. Only one of the patients underwent a redo of the frontosupraorbital advancement because of an asymmetry at the age of ten years. Two other patients had an augmentation of the forehead with bone cement. Looking at the adult patient (n=13), nine of them developed bitemporal hollowing, though three of them only in a mild degree. Simultaneous with the frontosupraorbital advancement four patients underwent a reduction of the bone of the glabellar area by medialisation of the lateral and supraorbital rim.

Occipital expansion

Three patients with bilateral coronal synostosis underwent an occipital expansion at the age of six months, to leave the frontosupraorbital area untouched and facilitate a future medial faciotomy. In two cases springs were used, which were removed after two months. The patient with the regular occipital expansion developed persistent papil edema two years after this procedure and required a redo occipital expansion with springs.

Eyes and orbits

All patients had hypertelorism, though one adult had a relative mild form that did not require surgical intervention, with no progression over time. At the time of evaluation, six patients were still too young to undergo a correction of their hypertelorism, but will probably be operated for their hypertelorism in the future. A generally mild orbital dystopia was seen in 10 patients of the total group and no specific procedure was performed or indicated to correct this deformity, however, in one patient this was corrected during a redo orbital box osteotomy for her relapse of a hypertelorism. Moreover, the severity of orbital dystopia didn't increase as the face matured. Five of the patients with orbital dystopia had no history of craniosynostosis, three other patients had a bilateral coronal synostosis and two a left sided unilateral coronal synostosis. In seven of them the orbital dystopia was evident prior to any surgical intervention, and in three of them (2 without synostosis and 1 with bilateral synostosis) only a few years afterwards. Orbital dystopia therefore appears to reflect a primary intrinsic growth disorder rather than a secondary deformity resulting from the coronal suture synostosis. (Figure 1)

Orbital box osteotomy

An orbital box osteotomy for the correction of hypertelorism was performed in eight patients. (Figure 2) The average intraorbital distance, as measured during surgery, went from 33.2 mm (range 28-39 mm) to 19.8 mm (range 16-25 mm). As many as 63% (n=5) needed a redo for correction of the residual hypertelorism by a medial faciotomy (n=3) or orbital box osteotomy (n=2). This was due to an undercorrection in all of the patients. Average age of the first orbital box osteotomy of patients who underwent a redo was 5.3 years, while the average age of patients who had only one procedure was 12.7 years.

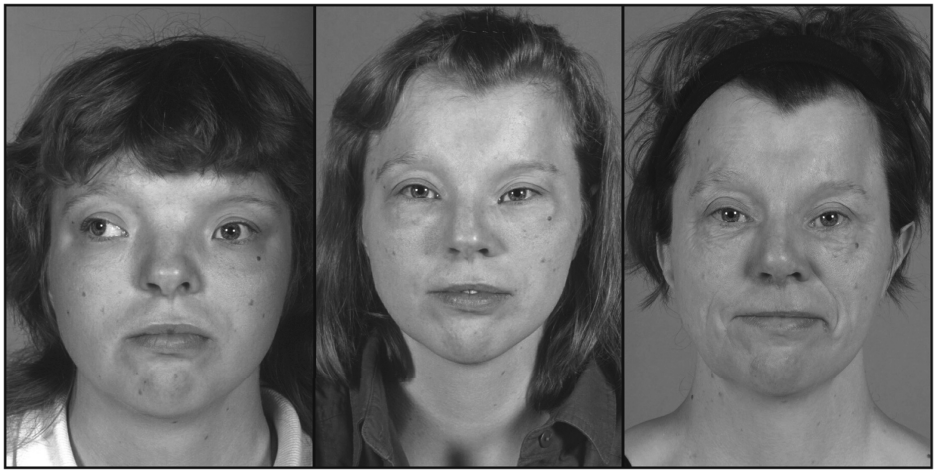

Figure 2: A CFND patient pre- and post surgery; she underwent an orbital box osteotomy at the age of 20 years, and the result 26 years afterwards.

Medial faciotomy

Hypertelorism was corrected via a medial faciotomy in seven patients. (Figure 3) The average intraorbital distance, as measured during surgery, went from 35.3mm (range 33-37 mm) to 23mm (range 20-24mm). No redo's of the medial faciotomy were indicated.

Soft tissue

The majority of patients had epicanthal folds either unilaterally or bilateral. Medial canthopexies were performed in the majority of patients (n=12), with an average of 1.2 (range 1-2) corrections in all adult patients. Lateral canthopexies were performed in 7 patients, with mean of 1.2 (range 1-2) corrections. Cathopexies were performed simultaneously with either a correction of hypertelorism or correction of the nose. One patient had a correction of his medial canthus and lower eyelid via a musculocutaneous flap derived from the upper eyelid. Permanent correction of the medial canthus and it's surrounding zone proved difficult, since six of the twelve adults still displayed an asymmetry, although asymmetry was often seen before canthopexies as well.

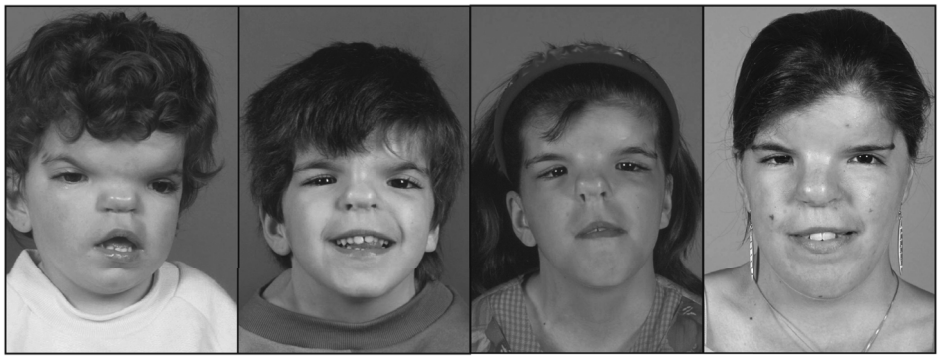

Figure 3: A CFND patient pre- and post surgery; she underwent a medial faciotomy at the age of 4, and the result 16 years afterwards.

Bone

In addition to the correction of hypertelorism, eight patients had a graft placed to augment their orbits; most grafts were placed on the lateral orbital wall (n=5). Grafts harvested in the same procedure originated from the skull (n=5), the costochondral area (n=2) or from the iliac crest (n=1). In another four patients the supralateral part of the orbital rim became too protruding once the face matured and had to be milled.

Nose

Anomalies of the nose were seen in all patients, common findings are a bifid tip (n=20) and an indentation in the columella (n=20). Generally speaking all noses were significantly too short, and too flat and broad at its base, and these deformities became more obvious as the face matured. (Figure 4.)

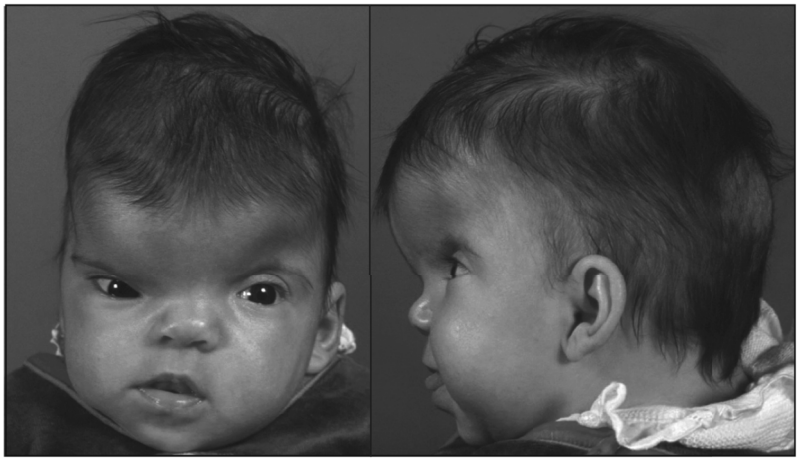

Figure 4: The proportions the nose of CFND patients are generally too short in total length and too broad and flat at its base from the first instance

Soft tissue

Procedures were performed in four patients; correction of ala (n=1); correction of columella (n=1); excision of fistula (n=1); correction of surplus of skin in the midline of the glabella and nose after correction of hypertelorism (n=2); correction of the nasal ostium (n=1); and insertion of a tissue expander at tip of nose (n=1). The overall average of soft tissue corrections in adult patients was quite high (mean 2.5, range 1-6), due to re-operations once the face matured. Average age at time of first correction was 7.3 years (range 4-15). Overall, one of the most difficult parts of the soft tissue of the nose to correct is the inset of the nostrils; at least five of the adults had a persisting asymmetry at this level.

Bone and cartilage

Because the nose is too short from the start, a lot of corrections to lengthen the nose were made on the level of the bone and cartilage. Though at an adult age the length of the nose still remained too short, despite multiple corrections. Most often performed procedure was placement of a graft to augment the dorsum (n=9). Types of used grafts were costochondral (n=6), skull (n=4) or iliac crest (n=2), average number of corrections with a graft for the dorsum was 1.5 (range 1-4). Four patients had a narrowing of their nasal dorsum by osteotomies. Other refinements on the dorsum were done in another four patients; reducing the base of the nasal bone (n=4); correction of nasal septum deviation (n=1); graft in columella (n=1); corrections of the nasal tip (n=6); removing of the osteosynthesis material (n=3) and 5 patients had minor correction of the tip, upper and lower laterals. On the whole, the mean number of operations in adults on bone and cartilage level of the nose was relatively high with 2.3 (range 1-7).

Maxilla, oral cavity and lips

A V-shaped maxilla including anterior open bite was frequently observed (n=7). This deformity was correction together with the hypertelorism via a medial faciotomy. Intrinsic dental abnormalities such as crowding of the teeth (n=5) and missing teeth, were corrected by simultaneous orthodontic treatment.

Le Fort I

Although a usually mild maxillary hypoplasia was observed in radiological images in 7 patients, most of these patients were still under the age of 16 years. None of them had had a surgical intervention at the orbital or maxillary level. Three adult patients underwent a conventional Le Fort I osteotomy (n=3) or a Le Fort I with distraction (n=1). One of these patients previously had an orbital box osteotomy, one patient underwent the Le Fort I osteotomy simultaneously with the orbital box osteotomy and one patient had a prior medial faciotomy. All three patients had a clear maxillary hypoplasia prior to their correction of the hypertelorism, of which one had an additional cleft lip and palate. Due to insufficient effect and malocclusion in one patient, a second Le Fort I osteotomy in combination with a bilateral sagittal split osteotomy of the mandible was performed 5 years later.

Soft tissue

A cleft lip and palate was seen in only one patient, she underwent the usual protocol for closure of the cleft lip and soft palate.

Bone

A bone graft in the alveolar ridge was placed for correction of the cleft in this same patient. Other corrections performed in other patients were; advancement of chin (n=1); milling of zygoma (n=1) and onlay bone graft of zygoma (n=1).

No major complications such as death or blindness were observed. Minor complications due to the surgical interventions were; leakage of cerebrospinal fluid which required a lumbal drainage (n=1) and a simultaneous aspiration pneumonia (n=1) after an orbital box osteotomy together with a Le Fort 1 procedure in the same patient; skin perforation of metal wire (n=1) after frontosupraorbital remodelling, threatening of skin perforation of a columellar bone graft whereby the graft had to be shortened (n=1) and an entrapment of the lateral rectus muscle of the left eye (n=1) after a medial faciotomy.

Nineteen out of 23 patients had an asymmetry of their face at time of evaluation, this includes the two patients who had no surgical treatment. Looking at the adult patients only, most common features that caused the asymmetry were; position and shape of eyebrows (n=8); shape and position of medial canthi and its surrounding zone (n=6); orbital dystopia (n=6); the height of the inset of nostril (n=5); asymmetrical tip of nose (n=1); unilateral ptosis (n=2); asymmetrical shape of forehead (n=2); upshoot of one eye (n=1); and lower eyelid deformity (n=1). Also the presence of a widow's peak became more obvious over time. As can be seen in Table 3, none of the zones showed a significant change in the objective severity after treatment. The need of revisional surgery of the adult patients, expressed by the Whitaker score, revealed four CFND patients with a category I, seven with a category II and one patient with a category III.

Table 3. Objective severity of facial deformity (Versnel score).

	Pre Treatment (m, range)	Post Treatment[1] (m, range)	Improved (n=15)	Difference[2]
Total score	9.3 (4-12)	9.4 (4-16)	6 (55%)	n.s.
Zone of the forehead	2.8 (1-4)	2.2 (1-4)	5 (45%)	n.s.
Zone of the nose	2.9 (0-4)	2.5 (0-5)	2 (18%)	n.s.
Zone of the orbits	3.2 (2-5)	3.5 (2-5)	2 (18%)	n.s.
Zone of the maxilla	0.2 (0-2)	0.7 (0-2)	0 (same or worse)	n.s.
Zone of the mouth	0.2 (0-2)	0.3 (0-2)	0 (same or worse)	n.s.
Zone of the mandible	0	0.2 (0-2)	0 (same or worse)	n.s.

m= mean, p= p-value, n.s.= non significant

[1]= After treatment and/ or at time of maturation of the face

[2]= paired T-test, α= 0.05

DISCUSSION

As is described in this study, the *EFNB1* mutation has a variable phenotype and expression which needs a specific treatment plan for restoring the aesthetic and functional balance. The focus in this overview is particular on the patients with severe and evident deformities. We must state, however, that in patients with a mild expression the risk of a reconstruction in contrast to the benefit and potential improvement must be considered.

The objective analyses of the severity of the deformity revealed that the facial appearance improved in the majority of the patients after surgical treatment. However, most of the mean scores of the evaluated zones differed very little in before and after treatment scores. An explanation for this minor difference is that some features disappeared, while other appeared or became more obvious particularly due to an asymmetry; for instance, the asymmetry of the forehead due to the craniosynostosis improved, but the widow's peak or asymmetrical malposition of the eyebrows became more obvious.

Despite extensive literature on risks on elevated intracranial pressure (ICP) in the various types of syndromic craniosynostosis, these data lack for CFND. Annual fundoscopy up to the age of six should be part of the clinical protocol in the presence of craniosynostosis, perhaps also for the patients without craniosynostosis. In general, correction before the age of 1 year is recommended. (21, 22) The frontosupraorbital advancement gives a stable result, but causes scar tissue, which may hamper the medial faciotomy later. Occipital expansion has the advantage of leaving the anterior skull and forehead untouched and adding more intracranial volume compared to a fronto-orbital advancement, but leaves the forehead and orbital dysmorphology uncorrected. Therefore, in case of craniosynostosis the occipital expansion is preferred, however in case of an unilateral synostosis of the coronal suture a simultaneous stripcraniectomy of the affected suture with insertion of springs should be considered to correct the asymmetry in a young patient (before 6 months of age). Nevertheless, if the patient is older a regular frontosupraorbital advancement is probably better to correct the asymmetry. Development of orbital dystopia cannot be prevented.

The observed abnormalities of the facial skeleton (hypertelorism, orbital dystopia and midface hypoplasia) appear to be primarily induced by the genetic defect and not secondary to either craniosynostosis or surgical procedures. As for the correction of the hypertelorism, this study showed that medial faciotomy gives a stable result, and needs less corrections and no redo's afterwards in comparison with the orbital box osteotomy. In addition, no direct disturbance of the growth potential of the maxillary area or teeth is observed, even in patients treated at a young age. Nevertheless, the position of the tooth germs should be respected.(31, 32) This is in accordance with previous studies,(31, 33, 34) though others still advocate to postpone correction of hypertelorism correction until after 8 years.(23) In non syndromic coronal suture synostosis, a decrease of the orbital dystopia towards normal usually occurs after correction of the skull.(35) In these CFND patients however, the orbital dystopia persisted. Nevertheless, since it was usually mild and did not increase over the

years, it did not necessarily need a separate operation for correction or could be corrected during medial faciotomy. In addition, a medial faciotomy gives a stable correction of the alveolair arch. The hypoplasia of the midface is also usually mild, a conventional Le Fort I is sufficient to correct this, and distraction is only needed by exception. Although modifications for correction of facial asymmetry are available,(24) it is hard to completely erase the asymmetry. This study supports the idea that this is not due to inferior techniques, but rather at the combined level of skull base and facial skeleton.

The zone of the nose needed most operations. This is mainly due to the proportions the nose has from the first instance. It is both too short in total length and too broad and flat at its base. From a prior study we know that the stability of a costochondral graft is better, than a graft that originates from the skull or iliac crest.(33, 34, 36, 37) The problem is that a graft does not grow along with the growth of the total face, so an initially good result of a nasal reconstruction deteriorates over time.

Based on the long-term results of this study, together with the evaluated growth of the face in patients with an *EFNB1* mutation, this plan for treatment is developed as can be seen in Figure 5. It must be mentioned that this overview focuses only on craniofacial deformities. For the treatment of upper or lower extremities, thoracic or other (skeletal) disfigurements, additional procedures are to be considered.

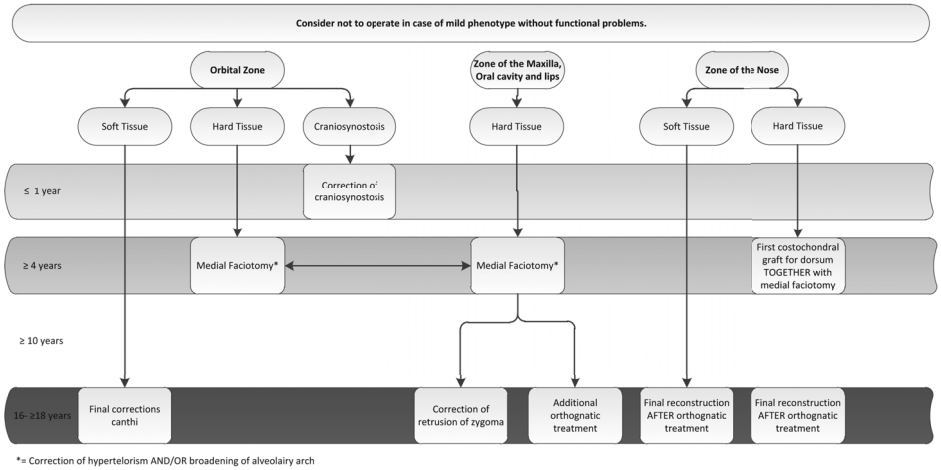

Figure 5: Guideline for surgical treatment

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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.

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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 Centre of the Erasmus Medical Centre 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. Since this was a retrospective study, including patients who started treatment as far as 40 years ago, only few radiological images were obtainable as quantitative parameters. Final surgical results were objectively assessed and agreed upon by three specialists, 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), the mean follow-up was 26.4 years (SD 7.8, range 15-40). Eighteen patients had a unilateral cleft.

In general

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 seemed to deteriorate 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.

The objective severity of the total facial deformity significantly improved after treatment, as can be seen in Table 1. Looking at the specific units, also the zone of the nose and the mouth significantly improved. As for the need for additional surgery, 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.

Table 1. Objective severity of facial deformity (Versnel score)

	Pre Treatment (m, range)	Post Treatment[1] (m, range)	Improved (n=29)	Difference[2]
Total score	19.24 (4-51)	14.52 (1-28)	27 (93%)	p< 0.001*
Zone of the forehead	2.14 (0-5)	1.93 (0-4)	14 (48%)	n.s.
Zone of the nose	5.86 (1-10)	3.41 (0-9)	22 (76%)	p< 0.001*
Zone of the orbits	5.86 (0-18)	5.48 (0-14)	15 (52%)	n.s.
Zone of the maxilla	1.69 (0-4)	1.79 (0-4)	8 (28%)	n.s.
Zone of the mouth	3.52 (0-20)	1.83 (0-8)	14 (48%)	p= 0.005*
Zone of the mandible	0.07 (0-2)	0.07 (0-2)	0 (same)	n.s.

*m= mean, SD= standard deviation, p= p-value, n.s.= non significant, *= improvement*

[1]= After treatment and/ or at time of maturation of the face

[2]= paired T-test

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 (Fig. 1). For correction

of the lower eyelid the cheek flap was superior (Fig.1, 2, 3, 4, 5), while the forehead flap showed tissue mismatch especially regarding thickness (Fig.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 whom 16 had one or more redo's (mean: 3.2, range: 1-8). Microphtalmia was never corrected completely (Fig.3). In six patients a dacrocystorhinostomia was performed; multiple adults complained of tearing eyes.

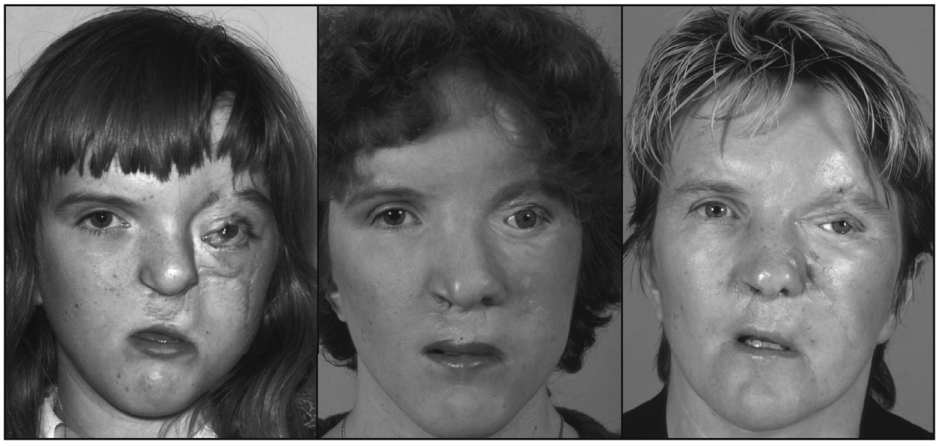

Figure 1.a.-1.c.: Monolateral medial maxillary dysplasia.

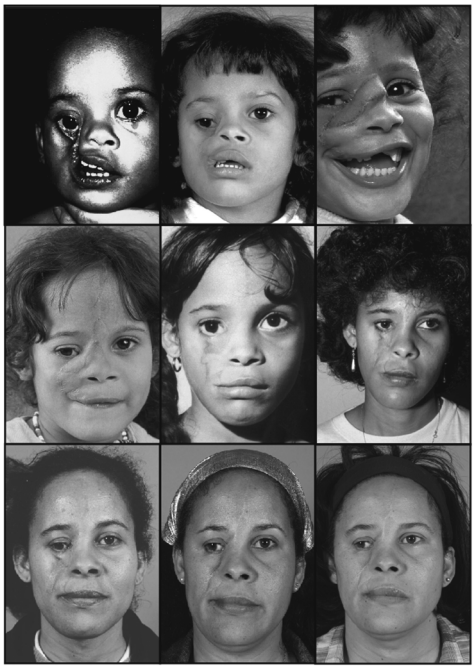

Figure 2.a.-2.i: Female patient at different ages during treatment for monolateral maxillary dysplasia. On the age of six grafts were placed in the orbital floor to correct her mild dystopia, in addition a forehead flap was performed to correct the soft tissue of the nose (figure 2.c.). No progression of the vertical dystopia occurred, however at the age of 29 corrections of the graft were made and the forehead flap was replaced by a cheek flap (figure 2.g.).

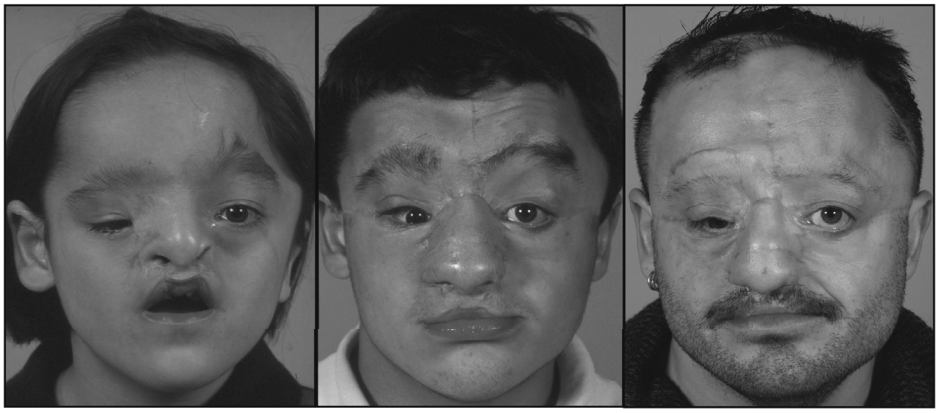

Figure 3.a.-3.c: Bilateral complete nasomaxillary dysplasia.

Correction of hypertelorism.

Seventeen patients had hypertelorism at birth, and in 14 patients a 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. 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. 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 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 hindsight 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 had 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 (Fig.1, 2); it only reduced the dystopia from severe to mild. Only in mild dystopia grafts gave stable and sufficient results on the long-term (Fig.4). Patients who had an orbital elevation at an age older than four years, had no relapse of the vertical dystopia. 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.

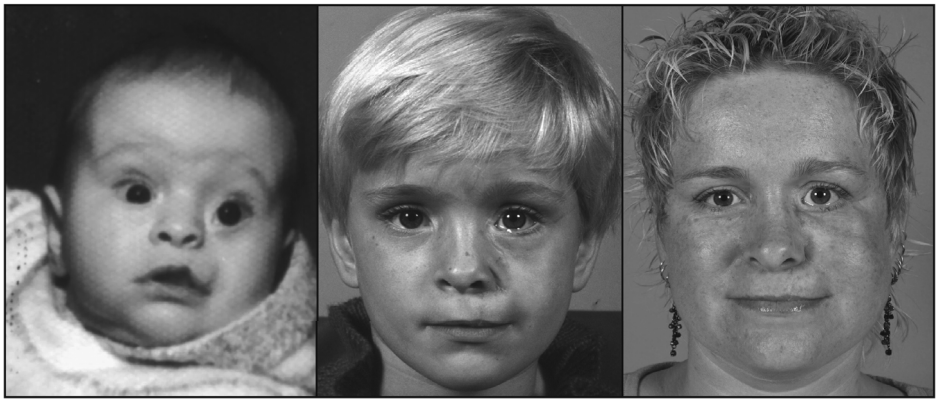

Figure 4.a.-4.c.: Medial maxillary dysplasia. A cheek flap and grafting of the orbital floor (2 times) gave stable results over time. In adulthood lipofilling was performed.

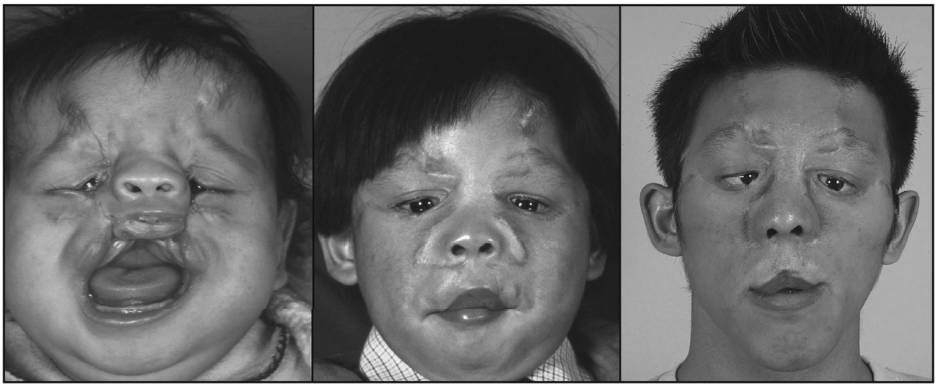

Figure 5.a.-5.c.: Bilateral medial maxillary dysplasia

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 (osteotomy/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 (Fig.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 were performed. Numerous patients had been operated previously in non-specialized centres, 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, and 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 (figure 7).

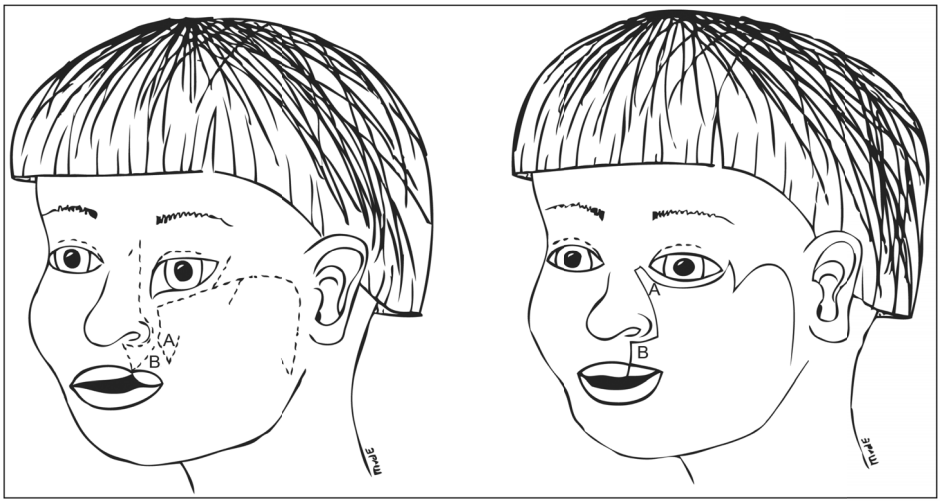

Figure 6: With this technique optimal use of the cheek flap is possible. Lowering/ partial failure of the cheek flap can be caused by gaining suboptimal length initially, by performing an insufficient medial canthopexy, or by growth deficiency of the maxilla.

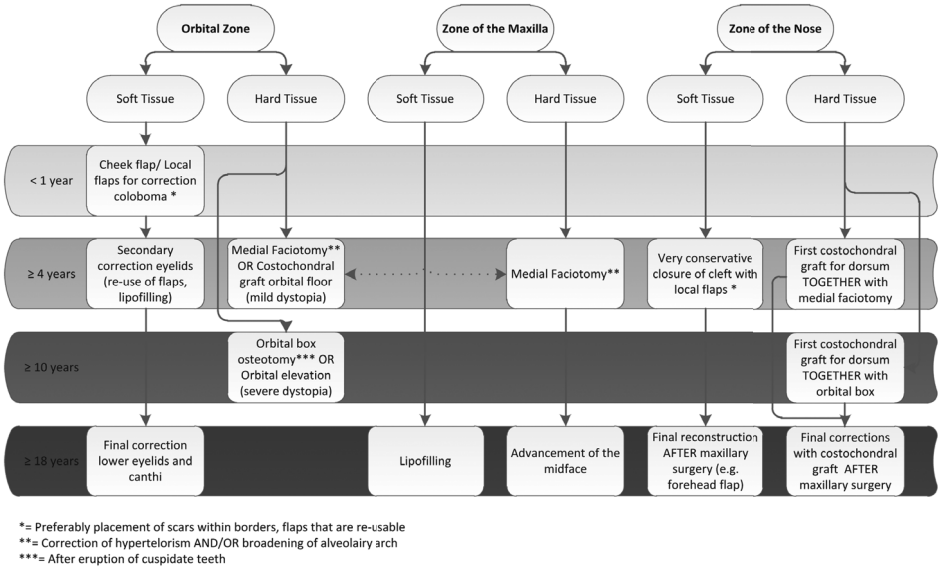

Figure 7: Treatment Algorithm

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 (Fig.6: see A); at an older age further transposition of the flap is possible. For colobomas 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 the cleft, which can be brought into the nose. Later reconstruction might be indicated if both the upper and lower canalicular systems are hypoplastic.

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] This information might be extrapolated to other indications for early correction of orbital dystopia, such as other congenital pathologies of the orbits, traumas or after removal of malignancies. In mild cases grafting might be sufficient, but in more severe cases orbital translocation, preferably after 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 after eruption of the cuspidate teeth. 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 4- >10 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 medialisation 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 > 18 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 clefts, 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. Diminished intrinsic growth potential is probably the inducement for facial growth disturbances, instead of early surgical intervention. Early soft tissue corrections are best performed with placement of the scars within the borders of the facial units and with flaps that are reusable. The provided guidelines for treatment should help to ameliorate final results.

CONFLICT OF INTEREST

None.

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CHAPTER 5

LONG-TERM RESULTS AFTER 40 YEARS EXPERIENCE WITH TREATMENT OF RARE FACIAL CLEFTS: PART 2- SYMMETRICAL MEDIAN CLEFTS

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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 centre 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 Centre 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. Since this was a retrospective study, including patients who started treatment as far as 40 years ago, only few radiological images were obtainable as quantitative parameters. Final surgical results were objectively assessed and agreed upon by three specialists, 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 (thirteen women, seven men) were included, out of a total of 123 patients with a rare facial cleft. At time of follow-up, 5 patients were under the age of sixteen and still under treatment; these patients were excluded for analysis of surgical results. The average age at inclusion was 27 (range 2-52). The mean years of follow-up of the adult patients were 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]

Four patients underwent one or more surgical procedure 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 centre, 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.

The objective severity of the total facial deformity improved after treatment, as can be seen in Table 1, although not significantly. Looking at the specific units, the zone of the nose significantly improved at the end of their surgical treatment. However, the forehead and maxilla significantly

Table 1. Objective severity of facial deformity (Versnel score)

	Pre Treatment (m, range)	Post Treatment[1] (m, range)	Improved (n=15)	Difference[2]
Total score	7.13 (4-12)	6.27 (1-14)	9 (60%)	n.s.**
Zone of the forehead	0.29 (0-1)	1.07 (0-3)	0 (same or worse)	p= 0.003
Zone of the nose	4.07 (1-5)	2.36 (0-5)	11 (73%)	p= 0.004*
Zone of the orbits	1.43 (0-3)	1.14 (0-3)	5 (33%)	n.s.
Zone of the maxilla	0 (0)	0.50 (0-2)	0 (same or worse)	p= 0.05
Zone of the mouth	0.93 (0-2)	0.57 (0-2)	3 (20%)	n.s.**
Zone of the mandible	0 (0)	0 (0)	0 (same)	n.s.

*m= mean, p= p-value, n.s.= non significant, *=improvement, **= trend for improvement*

[1]= After treatment and/ or at time of maturation of the face

[2]= paired T-test

worsened. As for the need for additional surgery, the Whitaker score revealed nine patients with a category I, seven with a category II and three patients with a category III.

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. Widow's peaks or eyebrow deformities became more obvious once the patient matured, however these deformities were seldom corrected (Table1).

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 1 to 19 years, the medial faciotomy at age ranging from 1 to 7 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.

Skull base

Three patients, all under the age of 16, were born with a basal encephalocele. Before the age of one year they underwent a cranialisation 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]

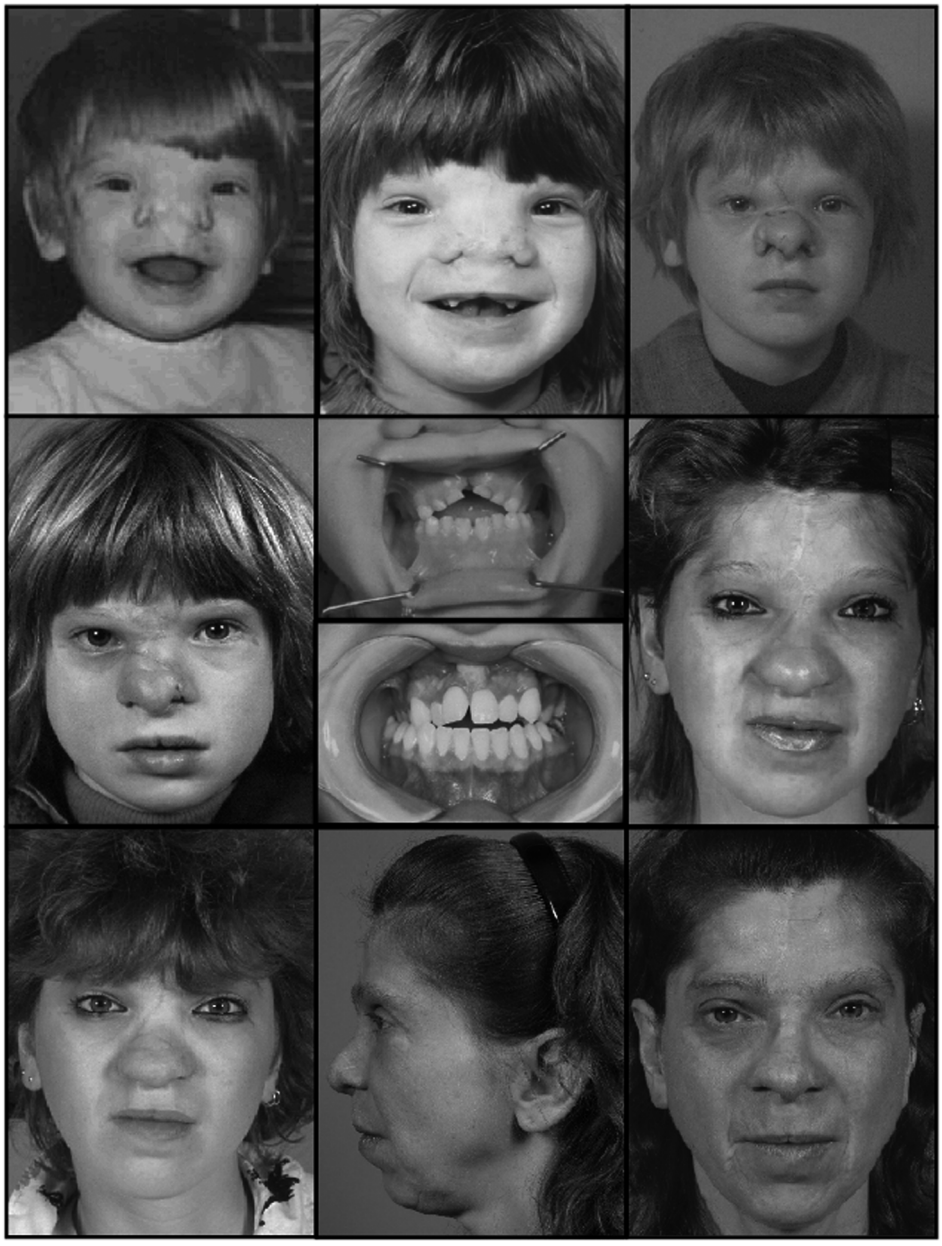


Figure 1.a.-1.j.: Female patient at different ages during treatment. Hypertelorism was corrected with a medial faciotomy according to Van der Meulen at the age of seven (figure 1.c.). A stable long-term result is shown. A clear keel-shaped maxilla is shown prior to a medial faciotomy (figure 1.e.). Post-surgery only a mild maxillary hypoplasia is present (figure 1.f.). The first nose reconstruction was done at the age of seven years (figure 1.c.), with a patchwork-like soft tissue at a young age (figure 1.d.). At the age of seventeen final corrections of the nose (bone and soft tissue) were made (figure 1.g.-1.i.).

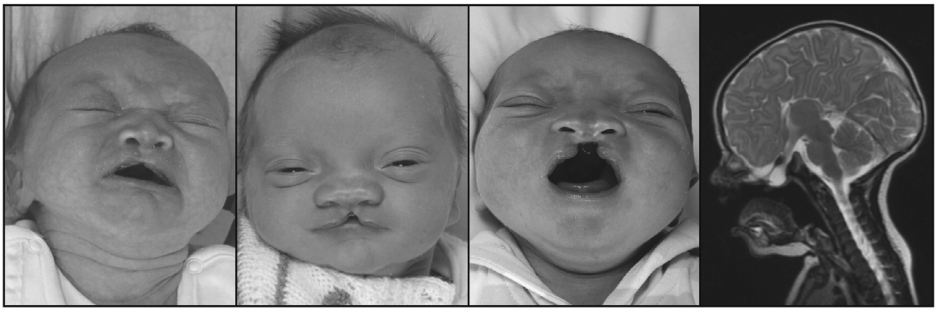


Figure 2.a.-2.c.: Three male patients with basal encephalocele, all aged less than a month. Patients had a typical notch or true cleft at the centre of their upper lip.
Figure 2.d.: MRI illustrating the skull base defect and brain herniation.

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.

Fourteen patients had one or more operations for reconstruction of their nose (mean age first surgery: 4.4 years, range 0-19). All 14 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 Maxillary 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 at the start of adolescence, this was

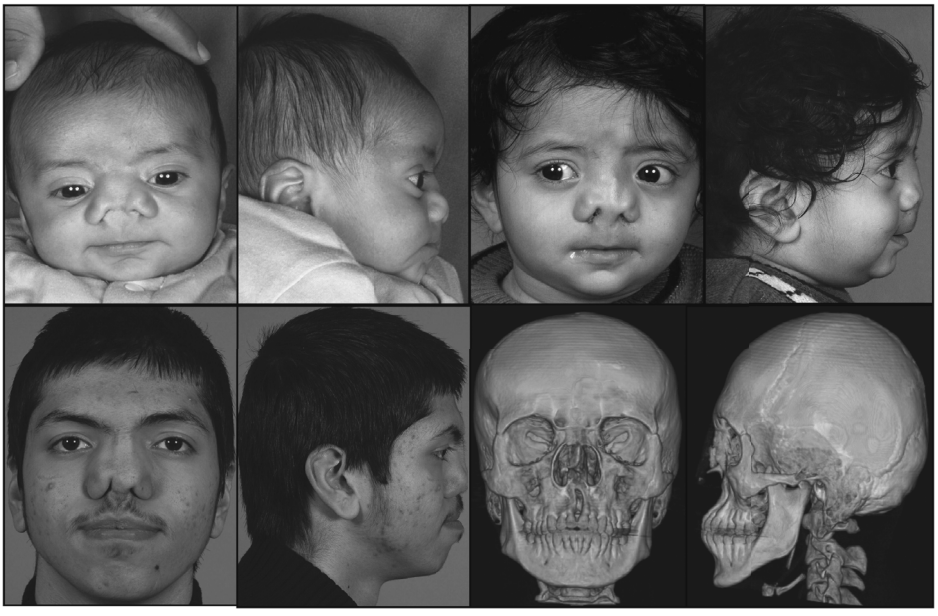


Figure 3.a.-3.h.: Male patient with Frontorhiny (ALX3 mutation), aged 2 months, 1 year and 17 years. The single surgical intervention was reconstruction of nasal dorsum at the age of 1. A clear underdevelopment of the maxillary region and restricted growth in the nasal area is shown. Patient is scheduled for a Le Fort II advancement and consecutive reconstruction of his nasal septum, dorsum, tip, and alar rims.

unusual thereafter and seen only in two cases (Figure 3). Overall, growth potential was evidently absent or diminished at the site of the cleft, resulting in an hourglass alike deformity; a 3-dimensional underdevelopment in the midface (Table 1).

Complications

A total of 8 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.

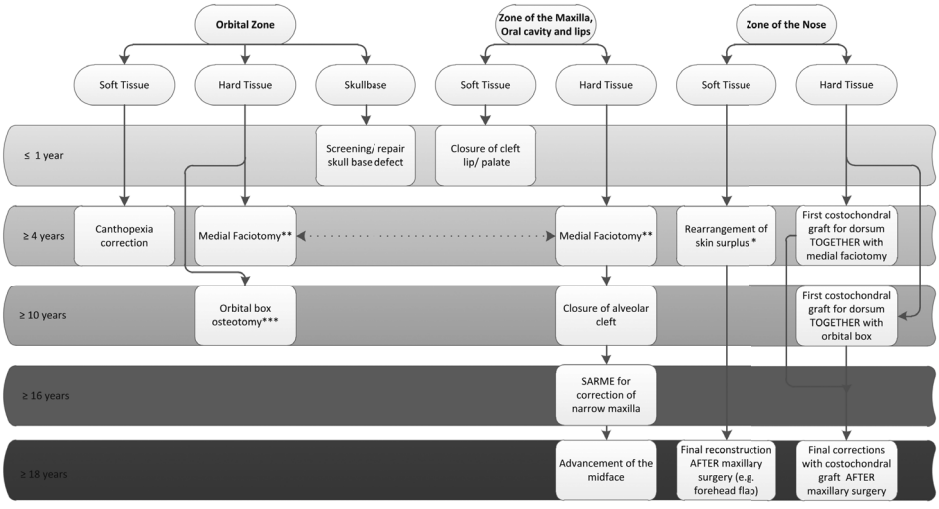
Patients who were primarily treated at our centre had better aesthetic results, with a lower number of operations, demonstrating the impact of gaining experience. Overall, the mean number of operation sessions was relatively high (mean 7.6, range 1-15). This was due to learning curve and exploration 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 buds into 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]



*= Preferably placement of scars within borders, flaps that are re-usable
**= Correction of hypertelorism AND/OR broadening of alveolairy arch
***= After eruption of cuspidate teeth

Figure 4: Treatment Algorithm

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 hourglass 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 (Figure 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 (Figure 4). 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.

Age <1-1 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 paediatrician 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 3 months and a cleft palate at the age of 9 months.

Age 4->10 year: 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 after the age of 10, after eruption of the cuspidate teeth.

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

Age 16->18 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 or older, prior to this procedure a SARME (Surgically Assisted Rapid Maxillary Expansion) can be performed. Early corrections may result in an undercorrection at a later age due to the growth restriction that 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 centre 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.

CONFLICT OF INTEREST

None.

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CHAPTER 6

ADULTS WITH CONGENITAL OR ACQUIRED FACIAL DISFIGUREMENT: IMPACT OF APPEARANCE ON SOCIAL FUNCTIONING.

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ABSTRACT

This study evaluates the impact of congenital and acquired facial disfigurement on social functioning in adults and whether this differs from adults without facial disfigurement. Moreover, the predictive value of objective and subjective appearance on social functioning is explored.

Fifty-nine adults with severe congenital facial disfigurement, 59 adults with traumatically acquired facial deformities in adulthood, and 120 adults without facial disfigurement, completed the Scale for Interpersonal Behaviour, Social Avoidance and Distress Scale, and Visual Analogue Scale for facial appearance satisfaction.

The impact of congenital and acquired facial disfigurement on social functioning in adults is similar and significantly differed from the reference group. The level of stress evoked by interpersonal behaviour, and social anxiety and distress were not significantly different between the groups. Only the patient's subjective appearance was a predictor of social functioning.

Avoiding stress caused by stigmatization and uncertainty about reactions of others, leads to less frequent interpersonal behaviour in adults with facial disfigurement. The fact whether the deformity is congenital or acquired in adulthood has no influence on social functioning. Patient's satisfaction with facial appearance is more important than the objective severity of the deformity; in this context realistic expectations of the patient considering additional surgery are important.

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. In this, the face is seen as the mirror of the soul *(Cicero)*; with that association that 'what is beautiful is good'.*(Dion et al., 1972)* Nevertheless, even very young infants have the ability to categorize on attractiveness, have the same aesthetic perception as adults and prefer to look at attractive faces.*(Ramsey et al., 2004)* Physical attractiveness is stereotypically strongly associated with sociability, dominance, general mental health, intelligence and physical health.*(Eagly et al., 1991; Feingold, 1992)* The rating of facial attractiveness decreases, with an increasing severity of the facial disfigurement.*(Tobiasen et al., 1991; Okkerse et al., 2001)* 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.*(Rankin and Borah, 2003)* Facial disfigurement has even been called the last bastion of discrimination.*(McGrouther, 1997)*

It is difficult for people with a facial disfigurement 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.*(Kapp-Simon, 1986; Pillemer and Cook, 1989; Pope and Ward, 1997; Rumsey et al., 2004)* Therefore, it is not surprising that, in comparison with non-disfigured, physically impaired patients display more inhibition on social behaviour. Moreover, they tend to withdraw from peers and are more probable of being disliked by peers. The adopted different coping behaviours, to hide or compensate for their disfigurement, often make them unsociable, which gives rise to an interference with personal relationships, work life and leisure activities.*(Pillemer and Cook, 1989; Pope and Ward, 1997)*

However, most of these studies were performed in children and adolescents.*(Kapp-Simon, 1986; Pillemer and Cook, 1989; Pope and Ward, 1997; Okkerse et al., 2001)* Therefore research on social functioning of adults with congenital facial disfigurement is limited. Furthermore, overall results were inconsistent, and difficult to compare due to methodological weaknesses, such as a small sample size, a lack of use of standardized questionnaires or suboptimal reference groups. Moreover, only two studies have distinguished congenital from acquired facial deformities.*(Robinson et al., 1996; Bradbury et al., 2006)* 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.*(Robinson et al., 1996; Sarwer et al., 1999; Thompson and Kent, 2001)*

Multiple factors might be involved regarding the extent to which a facial disfigurement affects social functioning. These factors can be extra-personal components such as cultural, general awareness and tolerance in society or family (especially during upbringing).*(Partridge, 1997)* Even more important are the intra-personal components since they are more susceptible to change or treatment; in this context severity of the disfigurement (objective appearance), and dissatisfaction with

facial appearance (subjective appearance) are important. Surgery can influence both a patient's objective and subjective appearance; however, improvement of objective appearance does not always overlap with increasing patient's satisfaction with facial appearance. In literature it seems that a patient's satisfaction with facial appearance has more influence on psychological distress than the objective severity of the facial deformity,*(Love et al., 1987; Malt and Ugland, 1989; Ramstad et al., 1995; Sarwer et al., 1999; Rumsey et al., 2004)* but the predictive value for social functioning in adults with congenital facial disfigurement has never been investigated as far as we could find.

The objectives of this study therefore were to evaluate the impact of both congenital and acquired facial disfigurement on social functioning in adults and whether this differs from adults without facial disfigurement. Moreover, we wanted to explore the predictive value of a patient's objective and subjective appearance on social functioning.

MATERIAL 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.*(Tessier, 1976; van der Meulen et al., 1983)* 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 Centre or Sophia Children's Hospital, Rotterdam, the Netherlands, were invited to participate in this study. Patients with hemifacial microsomia and other mild facial clefts were excluded. The other 48 patients were excluded because they met one or more of the following removal 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).*(Versnel et al., 2009)*

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 congenital group were used and also all patients with an additional visible congenital disfigurement were excluded. A total of 104 patients were invited to participate in this study.

Reference group without facial disfigurement.

Adults 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, to form a reference group. 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. 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 Centre. 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 and educational level.

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.*(Watson and Friend, 1969)* The SADS has proved to have a good reliability, validity and adequate test-retest reliability.*(Watson and Friend, 1969; Pinto and Phillips, 2005)* The English version was translated into Dutch fully according to recommendations for good translation methods.*(Peters and Passchier, 2006)*

Interpersonal Behaviour

The Scale for Interpersonal Behaviour (SIB) was designed for clinical assessment concerning the state of assertiveness: the probability of the response or performance ('F': symbolizing frequency of interpersonal behaviour), and the degree of discomfort or distress ('S': representing stress evoked by interpersonal behaviour). The SIB comprises 50 items scored twice (once in terms of frequency and once in terms of degree of stress). The 50-item version of SIB appears to be four dimensional for

both frequency (F) and stress (S); (1) praising others and the ability to deal with compliments (FPOS/ SPOS), (2) display of negative feelings (FNEG/ SNEG), (3) initiating assertiveness (FASS/ SASS) and (4) expression of and dealing with personal limitations (FLIM/ SLIM). The SIB has demonstrated good reliability and good validity, and has proven to be a sensitive measure of change.*(Arrindell and van den Ende, 1985)* 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.*(Versnel et al., 2009)* The VAS is a frequently used measure and it has shown reliability and validity in studies on facial appearance.*(Oosterkamp et al., 2007)*

Severity of facial disfigurement

Two experts independently scored the objective severity of facial disfigurement (OS) 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.*(Versnel et al., 2007)* Recent post-operative standardized photographs of all patients were used. 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 differences between groups. A Fisher-exact test was used or analysis of differences on categorical variables between groups. Analyses of covariance (ANCOVA) 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 differences 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 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 (β) was calculated. As outcome variable the scores of the social functioning questionnaires were used. The variances explained by the predictor variables were calculated by multiple correlation squared (R^2). 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: non-responding (n=8), treatment had been traumatic (n=3), had interviews with the media and did not want to talk anymore (n=2), emotionally too difficult to discuss their disfigurement (n=3).

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

Demographic characteristics

Characteristics are shown in Table 1. The congenital group differed statistically significant from the acquired group 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 group 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)	*Acquired (A)*	*Reference (R)*	*P-values[2] for differences between groups*	
	N=59	*N=59*	*N=120*	***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		
Post-graduation [1]	17.5	17.2	23.3		
Severity facial deformity				0.001	-
Mean score	13.90	6.44	-		
SD	7.65	5.0	-		

[1] represents column percentages

[2] p-values corrected for multiple testing, α= 0.025 (two-tailed)

Differences between the groups

Congenital versus acquired.

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

Congenital versus normal reference.

Comparing the congenital group with the reference group demonstrates that they did not differ significantly on scores of the SADS, as can be seen in Table 2. A significant difference was observed between the congenital group and the reference group regarding frequency of interpersonal behaviour (SIB) including less frequently reporting their negative feelings (FNEG), less frequently initiating assertiveness (FASS) and a clear trend towards less frequently expressing their personal limitations (FLIM); all groups scored analogously on frequency of displaying positive feelings (FPOS). Remarkably, there was no significant difference between the groups in the level of stress they experienced on the four dimensions of the SIB. Patients with a congenital or acquired facial deformity were significantly less satisfied with their facial appearance compared to persons without a facial deformity.

Table 2. Differences between groups on social functioning questionnaires

	Congenital (N=59)		Acquired (N=59)		Reference (N=120)		P-value2)		
							C vs. A		*C vs. R*
	mean [1]	*SD*	*mean* [1]	*SD*	*mean* [1]	*SD*	[1]	[3]	
SADS	17.59	4.29	19.36	4.37	18.40	4.25	.06	.22	.21
FPOS	3.14	.76	2.98	.77	3.09	.77	.36	.10	.71
FNEG	2.71	.64	2,71	.66	2.99	.63	.99	.84	.01
FASS	3.00	.66	3.14	.66	3.21	.64	.29	.88	.048
FLIM	3.32	.63	3.40	.63	3.53	.61	.62	.78	.04
SPOS	1.95	.80	1.93	.80	1.88	.78	.85	.44	.57
SNEG	2.14	.83	2.13	.85	2.13	.81	.92	.58	.99
SASS	2.11	.80	1.97	.82	1.96	.79	.43	.80	.20
SLIM	1.82	.68	1.74	.70	1.68	.67	.75	.70	.19
SFA	4.28	2.19	4.67	2.24	6.98	2.19	.54	.43	.001

***SADS**=Social Avoidance and Distress Scale, **FPOS/SPOS**=behavioral/cognitive-affective aspects of praising others / dealing with compliments, **FNEG/SNEG=**behavioral/cognitive-affective aspects of display of negative feelings, **FASS/SASS**=behavioral/cognitive-affective aspects of initiating assertiveness, **FLIM/SLIM**=behavioral/cognitive-affective aspects of expression of/dealing with personal limitations, **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

Predictors of social functioning

As can be seen in Table 3, satisfaction with facial appearance (SFA) (subjective appearance) appears to be a significant predictor for the dimensions of social functioning. The more satisfied patients are with their facial appearance, the better their social functioning is. On the contrary, the severity of facial disfigurement (objective appearance) had no significant predictive value.

Table 3. Predictors of different social functioning aspects in facial disfigured patients (Cleft and Acquired)

Questionnaire	R^2	Candidate-Predictor	β	p-value
SADS	.31	SFA	.33	.001
	.24	OS	-.17	.10
FPOS	.07	SFA	.26	.02
	.05	OS	-.15	.20
FNEG	.04	SFA	.19	.09
	.03	OS	-.15	.20
FASS	.07	SFA	.23	.04
	.06	OS	-.15	.18
FLIM	.12	SFA	.23	.03
	.12	OS	-.18	.10
SPOS	.14	SFA	-.35	.01
	.05	OS	.09	.43
SNEG	.09	SFA	-.24	.02
	.05	OS	.02	.90
SASS	.13	SFA	-.29	.01
	.06	OS	.05	.70
SLIM	.16	SFA	-.25	.02
	.11	OS	.03	.81

***SFA**= Satisfaction with Facial Appearance, **OS**=Objective Severity of the facial disfigurement*

DISCUSSION

Differences between groups

Congenital versus acquired.

No differences could be demonstrated in social functioning between people with congenital and people with acquired facial disfigurement. Therefore, the assumption that having a congenital or an early acquired facial disfigurement beneficially influences adjustment regarding social functioning can be discarded.*(Robinson et al., 1996)* So, the fact that the congenital group had more time to get used to the situation and adjust to it, does not mean they cope better with social situations. On the other hand the acquired group does not seem to benefit significantly from the fact that they often already had a good social network before their appearance was changed.

Having a different appearance influences a patients' behaviour and the reaction by others. It is possible that people with facial disfigurement, regardless of the fact whether it is congenital or acquired at adulthood, become preoccupied with their appearance and the effect it may have on others. This may result in a self-fulfilling prophecy where the person anticipates negative reactions and behaves in such a way (defensively, aggressive, shy) that others are invited to react negatively. *(Partridge, 1997; Robinson, 1997)*

Congenital versus normal reference.

No significant difference was found in the level of social avoidance and distress between the congenital and normal reference group. This is in line with a prior study,*(Cheung et al., 2007)* and in contrast with another.*(Berk et al., 2001)* The fact that there was a significant difference in frequency of interpersonal behaviour between the congenital and reference group, but no significant difference on the SADS, can have several explanations. 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 focused 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.

A clear difference on frequency of interpersonal behaviour was seen between the congenital group and the group without disfigurement. More specifically, patients in the congenital group less frequently reported their negative feelings (FNEG), less often initiated assertiveness (FASS) and expressed their personal limitations less frequently (FLIM). Remarkably, the groups behaved analogously regarding the frequency of expressing positive feelings. This could be explained by the fact that expressing positive feelings is less threatening compared to the other aspects of behavioural 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. No significant differences in the stress aspects of interpersonal functioning were observed between the congenital group and the normal reference group. 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.*(Lethem et al., 1983; Newell, 1999)* 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.*(Brakel. 2004)* Above all, adults without facial disfigurement might avoid social situations and feel distressed in social situations too.

Predictors of social functioning

The predictive value of satisfaction with facial appearance (the patients' subjective appearance) was significant for the dimensions of social functioning, except for the frequency of displaying negative feelings.

As expected, patients with facial disfigurement were significantly less satisfied with their facial appearance.*(Pope and Ward, 1997; Sarwer et al., 1999; Lawrence et al., 2004; Versnel et al., 2009)* The severity of the facial deformity (objective appearance) was not a significant predictor for the dimensions of social functioning. This is in accordance with previous conducted studies. They show no relationship between the severity of the disfigurement and the level of distress.*(Robinson et al., 1996; Mannan et al., 2006)* 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),*(Macgregor, 1990)* 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.

CONCLUSION

In conclusion we can state that avoiding stress caused by stigmatization, and uncertainty about the reactions of others, forms the base of avoidance behaviour. Although the avoidance leads to a reduced stress level, it also leads to restricted social behaviour with less frequent interpersonal behaviour. While the stress dimensions of 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 behaviour can be expected. We therefore suggest, in addition to surgical treatment, to provide psychological treatment, which should focus on stress coping in daily social functioning.

Surgical corrections of the deformities can also help to improve social 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.*(Versnel et al., 2009)* However, objective improvement of the deformity is insufficient for improvement of social 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.

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 was lower (57%). 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.

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CONFLICT OF INTEREST:

None.

ETHICAL APPROVAL:

Ethical approval was received from the board of the Medical Ethical Committee of the Erasmus University Medical Centre Rotterdam (MEC-2006-121).

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CHAPTER 7

DEFENSE MECHANISMS IN CONGENITAL AND ACQUIRED FACIAL DISFIGUREMENT: A CLINICAL-EMPIRICAL STUDY

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ABSTRACT

It is of clinical interest to investigate the degree to which patients with a facial disfigurement utilize defense styles. Therefore, fifty-nine adults born with rare facial clefts, 59 patients with facial deformities acquired at an adult age, and a reference group of 141 adults without facial disfigurements completed standardized questionnaires. There was a significant difference between groups with and without disfigurements on immature defense styles, with the disfigured group using the immature style more frequently. There was a trend for the non-disfigured group to use more mature defense styles. No difference between congenital and acquired groups was seen on individual types of defense style. Self-esteem had the strength to differentiate mature and immature defense styles within our disfigured groups. The association of low self-esteem and the utilization of immature defense styles suggests that professional help may tailor treatment on discussing immature defense style and problems triggering or maintaining this style.

INTRODUCTION

Since a person's face cannot be ignored during encounters, conversations, or other usual daily activities, therefore patients with a facial deformity are confronted with disapprovals and prejudices on a regularly basis. They have to live with the stigma of being seen as less sociable, intelligent, honest, trustworthy, effective, and above all, less attractive (Eagly, 1991; Feingold, 1992; Rankin and Borah, 2003). In previous studies, it was shown that ratings of facial attractiveness decrease as the severity of the disfigurement increases (Tobiasen et al, 1991). Despite this, facial disfigurement patients' self-esteem is not seriously lowered, yet their social avoidance behavior and fear of negative appearance evaluation are substantial (Rankin and Borah, 2003; Versnel et al, 2011). In addition, self-perceived (satisfaction with) facial appearance is negatively associated with level of participation in social events (Pope et al, 1997; Versnel et al, 2011). An earlier study showed that patients with a congenital or acquired facial disfigurement avoided social interactions and the concomitant psychological pain, thereby avoiding cognitive-affective stress situations (Versnel et al, 2011). This phenomenon is also known as *ego restriction* (Brakel, 2004). Having an acquired facial deformity is considered more difficult than living with a congenital facial deformity (Bradbury et al, 2006; Sarwer et al, 1999). However, this assumption can no longer be justified, since recent data showed that neither the extent of the facial deformity nor the time span living with the deformity influenced levels of social and relational functioning (Lawrence et al, 2004; Wallis et al, 2006). Therefore, it is of great clinical interest to gain insight into the way these patients deal with their disfigurement.

The conscious approach deals with *coping styles*, while the unconscious approach concerns *defense mechanisms* (Vaillant and Drake, 1985). In this study we focused on the unconscious approach; in casu, the defense mechanisms. Sometimes we ask ourselves in retrospect why we acted in a certain way, and we may conclude that our behavior was a result of an unconscious process, a defense mechanism. *Defense mechanisms* may be defined as automatic psychological responses that individuals use in response to external and internal stress and conflict (DSM-IV, 1994). The definition originated from the field of psychoanalysis. Defense mechanisms are considered to be of fundamental value for adequately managing internal and external conflicts (American Psychiatric Association, 1994). In psychodynamics, Sigmund Freud was the first to conceptualize defense mechanisms, which were considered to protect the ego against anxiety, while Vaillant operationalized defense mechanisms in concrete terms (Freud, 1966; Vaillant, 1971) Anna Freud states that the use of rigid defense mechanisms disturbs adaptive functioning (Freud, 1966). She also postulated that personal growth and maturation implies maturation of defense mechanisms. The psychoanalytic personality-theory of normal development states that different styles of defense develop naturally over the lifespan, in which maturation is part of the process. In early developmental phases, defense styles are mainly immature; later on, these mechanisms develop into a mature defense style. Immature defenses remain available during life, even when mature styles have been developed. *Mature defense mechanisms* (e.g., sublimation, humor, anticipation, and suppression) are best summarized as the recognition of a threat, where concomitant pain is controlled until the

threat can be dealt with. In *immature defense mechanisms* (e.g., projection, passive aggression, and acting out), the occurrence of a threat is denied, or the responsibility is externalized. In *neurotic defense mechanisms* (e.g., undoing, idealization and reaction formation), localized in between the mature and immature defense mechanisms, the event is recognized, the responsibility is accepted, but the meaning is transformed in some way that may improve adaptation (Andrews et al, 1989).

Predominantly, mature defenses are associated with better mental and physical health; by contrast, immature defenses are associated with mental illness and greater psychopathology (Bond et al, 1983; Bond and Perry, 2004). It is plausible that patients with facial disfigurement utilize certain defenses more than do individuals without facial disfigurement, but this question has yet to be empirically studied.

Therefore, objectives of this study were, 1) Do the levels of defense mechanisms in patients with a facial disfigurement differ from those in 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 whose clefts were operated on between 1972 and 2007 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 facial clefts 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, so as to focus our analysis on a more severely deformed patient group. 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). The 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 two 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 were 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 gain insight into the psychological sequelae of having a facial disfigurement, we introduced a reference group without a facial disfigurement (n = 141), which consisted 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 time. 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

The original Defense Style Questionnaire (DSQ-66) was constructed as an instrument for evaluating oneself on defense style (Bond et al, 1983). The assumption was that conscious representations of unconscious defense processes can be identified by self-observation (Bond et al, 1983). The questionnaire administered in the present study was a translated Dutch version by W. Trijsburg, A. van 't Spijker, and R. Van, of the revised DSQ consisting of 42 items (Andrews et al, 1993). An extra type of defense mechanism, "repression," was included, which did not appear in 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 includes all 21 defense mechanisms, each represented by two items; the mechanisms are acting out, altruism, anticipation, autistic fantasy, denial, devaluation, displacement, dissociation, humor, idealization, isolation, passive aggression, projection, rationalization, reaction formation, somatization, splitting, sublimation, suppression, undoing, and repression.

The DSQ-42 was translated into Dutch, then back-translated by a native speaker who was not familiar with the original English version of the DSQ. Defense mechanisms were hierarchically classified into three defense levels, in accordance with psychodynamic theory and according to maturity level: mature, neurotic, and immature (Vaillant, 1971; Vaillant, 1976). Individual defense

scores are calculated by the average of the two items for each given defense mechanism, and style scores are calculated by the average of the scores of the defenses under each style. Each item was evaluated on a Likert 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, called defense styles (namely mature, neurotic, or immature), but not for measuring individual defense mechanisms. The DSQ-42 has been validated for three levels of defense styles, covering 20 individual defense mechanisms. Internal consistency and criterion validity of the questionnaire have been well established (Bond et al, 1983; Bond and Perry 2004).

Objective Severity of facial disfigurement

Two experts independently scored the objective severity of facial disfigurement (OS) in each patient for both the congenital and traumatic acquired groups using the (Versnel et al, 2007) quantified scoring list for facial disfigurement. The higher the score, the more units of hard and/or soft tissue are deformed. Recent post-operative standardized 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 (Versnel et al, 2007).

Self-esteem

The Rosenberg Self-Esteem Scale (RSES) is a 10-item self-report inventory measuring self-esteem on a four-point Likert-scale (Rosenberg, 1989). It is the most widely used measure for assessing self-esteem. Good reliability and validity have been reported. A validated Dutch version is available (Schmitt and Allik, 2005).

Fear of Negative Appearance Evaluation Scale

The six-item Fear of Negative Appearance Evaluation Scale (FNAES) is a self-report measure assessing cognitive aspects of social anxiety and fear about appearance evaluation (Lundgren et al, 2004; Peters and Passchier, 2006). The FNAES is sensitive to emotional distress and helps to determine the magnitude of the distress over one's negative appearance, avoidance of evaluative situations, and the expectation that others would evaluate one negatively (Lundgren et al, 2004; van der Meulen et al, 1983). The FNAES has been found to have good validity and internal consistency as a measure of reliability (Lundgren et al, 2004; Peters and Passchier, 2006; van der Meulen et al, 1983). This scale was translated fully into Dutch according to recommendations for good translation (Peters and Passchier, 2006).

Satisfaction with facial appearance

Patients' satisfaction with their own facial appearance (SFA) was measured using the Visual Analogue Scale (VAS), a 100-mm horizontal line anchored by word descriptors at the extremes: "very dissatisfied" at the left and "very satisfied" at the right. Patients were asked to mark the location on

the line that they felt represented their perception of their current appearance. This measure has been shown to be highly associated with the Body Cathexis Scale (Versnel et al, 2009). The VAS is a frequently used measure that has shown good reliability and validity in studies on facial appearance (Marcusson et al, 2002; Oosterkamp et al, 2007).

STATISTICAL ANALYSES

As a measure of central tendency for continuous data, we used the mean, including the standard deviation, as a measure of dispersion. In the cases of categorical data, 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 applied analysis of variance (ANOVA) for independent observations. When we adjusted for gender and age, we used analysis of covariance (ANCOVA) for independent observations. We also used the method of linear regression analysis; as a measure of individual performance of the predictor variable, the standardized regression coefficient (β) was estimated, including the corresponding 95% confidence intervals (95% CI). All analyses were adjusted for gender and age. As a measure of model performance, we present the determination coefficient (R^2), symbolizing 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 used the Statistical Package for the Social Sciences (SPSS) for Windows, version 15.

RESULTS

General characteristics

The study population in the congenital facial disfigurement group (n = 59) was 32.2% male (n = 19) and in the acquired group (n = 59), 57.6% male (n = 34). The reference group (n = 141)

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
OS[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

was 58.6% male (n = 63). As can be seen in Table 1, the mean age of the acquired group was significantly higher than those of the congenital and the non-disfigured groups (resp. 43 years vs. 34 and 34 years, $p< 0.001$). The means of the objectively assessed severities of facial deformities (OS) of the patients in the congenital and acquired groups were significantly different, with the congenital disfigured group being the most severely affected (resp. 11.71 vs. 3.99, $p < 0.001$). Self-esteem (SE) was about equally distributed between the two groups, as were fear of negative appearance evaluation (FNAE) and satisfaction with their own facial appearance (SFA).

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, with the disfigured group utilizing the immature style more often. In addition, there was a trend (non-significant) for the non-disfigured group to use more of the mature defense styles in comparison with the disfigured group, as can be seen in Table 2.

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

	Disfigured		Non-disfigured						Testing values			
	Mean	*SD*	*Mean*	*SD*	*p-value*	β	*95% CI of* β		*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	0.01	0.26	4.16	1	232	0.04

[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 significant difference was seen on any individual defense mechanism, as shown in Table 3. Looking at specific defense mechanisms of the group of patients with a facial disfigurement in comparison with those of the non-disfigured group, some significant differences were found on scores on individual defense mechanisms: the non-disfigured group had higher scores on sublimation ($p < 0.05$), anticipation ($p < 0.003$), and displacement ($p < 0.02$), while the group of patients with a facial disfigurement scored higher on rationalization ($p < 0.005$), projection ($p < 0.001$), denial ($p < 0.02$), and passive aggression ($p < 0.01$).

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

	Congenital		Acquired						Testing values			
	Mean	*SD*	*Mean*	*SD*	*p-value*	β	*95% CI of* β		*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

Evaluating the strength of our predictor variables to differentiate between the three defense styles, the objectively assessed severity of the facial disfigurement (OS) did not show a significant differential effect, which is shown in Table 4. Within our disfigured groups, self-esteem (SE) had the ability to differentiate the mature and immature defense styles. Neither fear of negative appearance evaluation (FNAE) nor satisfaction with their own facial appearance (SFA) had a significant differential effect.

Table 4. Differential quality of joint selected variables on defense styles[1]

Outcome variable:						
OS	β	*t-value*	*p-value*	*95% CI of* β		R^2=*0.01*
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	
Immature defense style	-0.04	-0.35	0.73	-0.25	0.17	
SE	β	*t-value*	*p-value*	*95% CI of* β		R^2=*0.26*
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	
Immature defense style	-0.34	-2.95	<0.01	-0.56	-0.11	
FNAE	β	*t-value*	*p-value*	*95% CI of* β		R^2=*0.09*
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	
Immature defense style	0.20	1.68	0.73	-0.03	0.43	
SFA	β	*t-value*	*p-value*	*95% CI of* β		R^2=*0.07*
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	
Immature defense style	-0.23	-1.80	0.08	-0.47	0.02	

[1]= Corrected for age and gender

DISCUSSION

The disfigured patients differed 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. Within the category of immature defense mechanism, projection and denial are considered healthier (Perry, 1993). Although the disfigured patients did not differ from the reference group on mature and neurotic defense styles, they did differ on the following specific defense mechanisms: sublimation, rationalization, anticipation, and displacement. On all these defense mechanisms the disfigured patients used it in particularly more in an immature manner. This is consistent with what we expected on a clinical basis.

In our previous studies we concluded that in general, patients with a facial disfigurement tend to display avoidant behavior of a phobic nature (Versnel et al, 2011). Fear of psychosocial difficulties is worse than the psychosocial difficulties themselves (Newell, 1999). Therefore, patients with a

facial disfigurement may show similar defense styles as patients with a social phobia. Earlier studies have investigated whether patients with various psychopathologies could be differentiated by their defense styles (Bond et al, 1983; Bond and Vaillant, 1986). The literature shows that particular immature defenses styles are related to depressive state (Kipper et al, 2005), panic disorders (Kipper et al, 2004; Kipper et al, 2005), social anxiety disorders (Blaya et al, 2006), and personality psychopathology (Mulder et al, 1999). Whereas neurotic and immature defenses are associated with social phobia, anxiety disorders (Kipper et al, 2005), panic disorders and obsessive compulsive disorders (Andrews et al, 1993; Blaya et al, 2006; Bond et al, 1983; Bronnec et al, 2005; Heldt et al, 2007; Heldt et al, 2003; Hovanesian et al, 2009; Hyphantis et al, 2009; Hyphantis et al, 2005; Kipper et al, 2004; Kipper et al, 2005; Mulder et al, 1999; Muris et al, 2003; Pollock and Andrews, 1989). According to the above presented literature, the expected predominant defense style of 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 (Hyphantis et al, 2009; Hyphantis et al, 2005). However, since data were not compared to a reference group, and provided data were not comparable, this study could not be used. Previous research has demonstrated that more mature defenses are significantly associated with better adjustment and, consequently, better mental and physical health (Bond et al, 1983; Bond and Perry, 2004).

On the whole, immature defense styles are associated with mental and physical illnesses and greater symptomatology, as expected (Bond et al, 1983; Bond and Perry, 2004; MacGregor et al, 2003; Muris et al, 1996). If we apply these conclusions to the patients in our population with a facial deformity, it may be justified to suggest that these patients are at risk for having or developing symptomatic disorders and/or problems in functioning, consequently reducing their quality of life, lowering their self-esteem, and increasing 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 initially supposed that having an acquired facial deformity was more difficult than living with a congenital facial deformity (Bradbury et al, 2006; Sarwer et al, 1999). However, as stated earlier, since neither extent of facial deformity nor time span living with the deformity was shown to affect levels of social and relational functioning (Lawrence et al, 2004), this assumption has to be abandoned. 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 have shown that a change in defense style emerged after treatment and remission of the symptoms of various conditions, discarding the more immature defense mechanisms, and using more of the mature defense mechanisms over time (Andrews et al, 1993; Bond and Perry, 2004; Bronnec et al, 2005; Heldt et al, 2007; Kipper et al, 2005; Schauenburg et al, 2007). However, a change in defense style in the opposite direction has not yet been reported. Additionally, it is expected that defense style would increase in immaturity 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 experienced the trauma that induced their facial disfigurement more than two years before the study started.

In our study the objective severity of the facial deformity (OS) had no significant power to differentiate among the three defense styles. This finding is in accordance with previous studies that showed no relationship between the severity of the disfigurement and the severity of psychosocial problems (Mannan et al, 2006; Wallis et al, 2006). Since patients with an extensive deformity are aware that their deformity will be noticed during encounters, they are likely to use anticipation. For patients with a milder deformity, it is often the uncertainty of how others will react that in turn induces more distress. In addition to anticipation, a wide variety of defense mechanisms may be used to handle potential problems resulting from OS. However, in this study, it could not be shown that a specific defense style is related to OS.

There was a non-significant difference in the mean level of self-esteem (SE) between patients with a congenital and those with an acquired facial deformity. Although unexpected, a plausible explanation for this finding could be that patients with a facial deformity base their self-esteem on qualities other than their physical appearance (Levine et al, 2005). In contrast, SE was associated with the mature and immature defense styles: the higher the level of SE, the more likely the use of mature defense styles, and conversely, the lower the level of SE, is the more likely the use of immature defense styles.

Fear of negative appearance evaluation (FNAE) could not differentiate among the three defense styles, and there was no statistically 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 with the reference group. This implies that the FNAE is increased by facial disfigurement itself, rather than by the severity of this disfigurement (Versnel et al, 2011). This notion is supported by the expectation that those affected are aware of the reactions of others and may become excessively preoccupied with their appearance and its effect on others (Macgregor, 1989). However, a direct effect of FNAE on defense styles used by patients on a daily basis could not be found in this study.

Mean satisfaction with patients' own facial appearance (SFA) did not significantly differ between the two 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 question the extent to which people are capable of reflecting on their defense styles and thus prefer observational methods involving interviews rated by an objective, trained expert (Perry and Ianni, 1998). Questionnaires differ from interviews in several important respects regarding the estimation of the level of defense. First, a patient might present socially expected behavior 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, whereas in an interview setting

the interviewer can interpret answers and tailor questions accordingly. Third, some defense styles are difficult to capture in a questionnaire, whereas an interviewer can be trained to identify such defenses. Fourth, a questionnaire cannot accommodate the questions to the mood of the patient, whereas an interviewer can. Finally, administering a questionnaire is highly efficient in terms of time and is less expensive. Weighing these multiple concerns, we chose the questionnaire method because, a large sample of patients was tested and the researchers were familiar with this method.

The character of the design was cross-sectional. In order to gain insight into stability and shifts in the utilization of defense styles and mechanisms, a longitudinal study format is highly recommended. It might be that the level of immaturity in defense style decreases over time, and this question is best evaluated longitudinally (Bond and Perry, 2004).

A last comment regards difference in patient characteristics between the congenital and acquired group on the objective severity of the deformity (OS). A difference in age and gender was seen as well, however, all analyses were corrected for age and gender. In addition, since OS had no significant power to differentiate among the three defense styles and previous studies also concluded that OS is insignificant concerning psychosocial struggles (Lawrence et al, 2004) no correction was made.

CONCLUSIONS

This study made clear that the only significant difference between the group with and the group without a facial disfigurement was found on the immature defense styles. As expected, patients with facial disfigurements used the immature styles more frequently. Furthermore a trend for the non-disfigured group was encountered on the use of the mature defense styles, which was greater compared to the disfigured group. No difference between the congenital group and the acquired group was seen on any of the individual types of defense styles. Within our constituted predictor variables, only self-esteem had the strength to differentiate the mature and the immature defense styles within our disfigured groups. The fact that low self-esteem goes hand-in-hand with the utilization of immature defense styles, suggests that professional help may tailor treatment on discussing immature defense style and problems triggering or maintaining this style.

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CONFLICT OF INTEREST

We certify that there was no conflict of interest by any of the authors.

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CHAPTER 8

ASSESSING NON-ACCEPTANCE OF FACIAL APPEARANCE IN ADULT PATIENTS AFTER COMPLETE TREATMENT OF THEIR RARE FACIAL CLEFT

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ABSTRACT

Background Treatment of patients with congenital severe facial disfigurements is aimed at restoring an aesthetic and functional balance. Besides an adequate level of satisfaction, acceptance of facial appearance is important to achieve, since non-acceptance is thought to lead to daily psychological struggles. In this study we objectified the prevalence of non-acceptance of adult patients who were treated for their severe facial clefts, evaluated risk factors and developed a screening tool.

Methods Fifty-nine adults with completed treatment for their severe facial cleft were included. All patients underwent a semi-structured in-depth interview and filled out the Body Cathexis Scale.

Results Non-acceptance with facial appearance was present in 44%; of the non-accepters 72% experienced troubles in everyday activities related to their appearance, versus 35% in accepting patients. Acceptance did not correlate with objective severity or bullying in the past. Risk factors for non-acceptance were high self-perceived visibility, troublesome puberty period and emotion focused coping strategy. Also presence of functional problems showed to be highly associated.

Conclusions The objective severity of the residual deformity does not correlate with the acceptance of patients' facial appearance, but the self-perceived visibility does. The process of non-acceptance resembles the process seen in patients with Body Dysmorphic Disorders. Surgical treatment is no guarantee for an improvement of acceptance and is therefore discouraged in patients who match the risk factors for non-acceptance, unless it solves a functional problem. We therefore recommend screening patients for non-acceptance and to consider psychological treatment before surgery is performed.

INTRODUCTION

Patients with severe facial clefts experience multiple operations from a very young age until adulthood. Treatment is aimed at restoring an aesthetic and functional balance. Hopefully this will lead to a satisfied and self-accepting patient on the long term, so a 'normal life' can be lived. It must be stated that satisfaction and acceptance are not the same: a patient may be unsatisfied with the end result, but accepts his residual deformity.

The abundant number of studies on acceptance, cover cohorts of patients with a specific chronic disease or chronic pain.(4-6, 9, 12, 13, 15, 16, 18, 20, 21, 26, 27) Reports specifically on acceptation of appearance are scarce though.(8, 20) Within the published studies, acceptance is defined as a willingness to have unwanted experiences on some occasions, with reorientation towards positive everyday activities and functioning.(16) In studies concerning patients with chronic diseases or chronic pain, non-acceptance leads to psychological distress and disability, reduced subjective health, depression, anxiety and emotional instability and avoidance.(5, 6, 9, 14, 16, 18, 20, 21, 26, 27) Earlier studies on patients with congenital severe facial disfigurement reported that the main problems are on the social functioning level, due to prejudices and reactions of disapprovals by others.(17, 25) This results in a fear-avoidance behavior, where patients avoid confrontations so they will not experience stress.(11, 17) The model of avoidance behavior is based on a model of exaggerated pain perception in patients with chronic pain, who avoid movements and situations, so they will not experience pain. Since the reaction of avoidance in patients with chronic pain and facial disfigurement is similar, perhaps also the principals of acceptance might be alike as well. In view of the fact that amelioration of acceptance in patients with chronical diseases or pain, may induce an improved level of psychological well-being, less psychological distress and a higher level of emotional stability (5, 6, 9, 14, 16, 18, 20, 21, 26, 27) this might be applicable for patient with congenital severe facial disfigurements too.

In our opinion, the evaluation of satisfaction with the appearance of patients with severe congenital disfigurement is not enough: a patient's acceptance of their facial appearance is of similar clinical importance. Recognizing a patient at risk for non-acceptance is crucial for offering the best treatment to ameliorate acceptance and possibly thereby psychosocial functioning.

Our first objective was to investigate the prevalence of patients with non-acceptance, and to look for risk factors to develop this non-acceptance. Because most studies are on the level of the entire group of patients, it can be hard to identify an individual patient. Therefore, the second objective was to construct a short and specific screening tool tailored to test for non-acceptance in an individual patient.

MATERIAL AND METHODS

Study population

Only adult patients with a congenital severe facial deformity were recruited. Seventy-five out of the 123 selected patients with a rare facial clefts (e.g. midline and oblique facial cleft, Treacher Collins syndrome) who were operated between 1969 to 2009 at the department of Plastic and Reconstructive Surgery 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. This patient cohort was chosen, because they encompass deformities in all facial units in a different sequence.(24, 29) We choose to leave out hemifacial microsomia as this is a relatively large subpopulation, which would be overrepresenting a specific type of deformity.

A total of 48 patients were excluded because they met one or more of the following removal 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).

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).

Patients were sent a cover letter, a patient information form, questionnaire, and an informed consent form to sign by mail. After receiving the completed questionnaire, an appointment was made for the interview, which was held at patients' home address.

QUESTIONNAIRE

Body Cathexis Scale

A prior study introduced the modified version of BCS; the Facial-BCS. Both the original version,(23) as the Facial-BCS, were used. The original BCS contains 46 items with a 5-point response scale, to measure the satisfaction and function of the body parts. The original BCS comprises the whole body and the face as well, however, it does not comprise all important facial parts and functions. Therefore, in the Facial-BCS extra facial parts and functions were added. A total of five scores were calculated; the original BCS, the Facial-BCS and the three sub-scores the BCS-appearance-of-face, the BCS-function-of-face and the BCS-whole-body-without-face. All scores showed to have good internal consistency reliability.(30) A validated Dutch version of the original BCS is available.(3)

Interview

The semi-structured in-depth interview covered the potential predictive factors as chosen and divided into the external factors; upbringing, religion and bullying; and internal factors; coping

styles, the value of the opinion of others, troublesome puberty and troubles in everyday activities, self-perceived visibility and whether they had the wish to undergo psychological treatment. This methodology was chosen in order to collect data in a qualitative manner, since standardized scales might be insensitive to the particular issues of these patients.(25) All the interviews were conducted by a single researcher SLV. The majority of the questions were open-ended, and responses were followed by a question elaborating on the motives behind their answer. The interview data were assessed using a thematic analysis, on the basis of which themes in qualitative material could be identified by a coding scheme.

Potential predictive factors

Objective severity of facial disfigurement

Besides the patients' answers in the interview to cover the external and internal potential predictive factors, the severity of the residual facial disfigurement in each patient was independently scored by two experts by using the scoring list according to Versnel et al. for facial disfigurement. (31) Recent post-operative standardized photographs of all patients were used. The average score was calculated in case of different scores.

Measurement of non-acceptance of facial appearance

The presence of non-acceptance was not queried as a direct question towards the patient, however, this was calculated by the answer on multiple questions derived from the interview. Questions concerning non-acceptance were composed by two of the authors (HJD and SLV). In this study a patient was scored as non-accepting, if they encountered true difficulties by looking in a mirror, or if they reported not to be used to their facial appearance, or frequently had psychological struggles due to their appearance with a seriously severe character. The questions in this measurement were chosen because they represent general everyday pursuits, unthreatening to answer, but very relevant for acceptance; the questions are not about whether or not the patients liked their appearance, but how much negative impact these unwanted experiences gave them, and thus indirectly the willingness to experience them.

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. Furthermore the method of logistic regression analysis was used, non-acceptance was coded 1, and acceptance was coded 0. As a measure of individual performance of the predictor variable, the odds ratio (OR) was estimated, including the corresponding 95% confidence intervals (95% CI). All the analyses were adjusted for gender and age. 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

Fifty-nine (79%) of the 75 rare facial cleft patients who met our inclusion criteria participated. The other 16 patients refused for several reasons: non-responding (n=8, 4 lived abroad), treatment had been too traumatic (n=3), had interviews with the media about their disfigurement and did not want to talk anymore (n=2), and emotional difficulties (n=3). Patient characteristics can be seen in Table 1 and 2.

Table 1. Patient characteristics

		n=59
Gender (%)	Male	32.2
	Female	67.8
Age (years)	Mean	34.05
	SD	12.92
	Min-Max	18-74
Education level (%)	Primary school [1)]	35.1
	High school [1)]	47.4
	Postgraduation[1)]	17.5
Severity facial deformity	Mean score	13.90
	SD	7.65

[1)] Represents column percentages
SD= standard deviation

Table 2. Details on patient characteristics

Patient number	Type of clefts*	Uni- or biliateral	Number of surgeries	OSRFD	Gender
1	2, 3, 4, 5, 10	bi	16	19	female
2	pure midline (0-14)		14	4	female
3	Treacher-Collins (6,7& 8)		1	26	male
4	Treacher-Collins (6,7& 8)		1	5	female
5	2, 3, 11	uni	18	18	male
6	CFND (0-14 + craniosynostose)		4	4	female
7	pure midline (0-14)		4	7	female
8	Treacher-Collins (6,7& 8)		3	8	female
9	Treacher-Collins (6,7& 8)		7	19	male
10	pure midline (0-14)		6	10	female
11	0, 2, 3, 4, 5, 9, 11	bi	9	26	female
12	ALX3 (0-14)		5	10	female
13	4	bi	10	20	male
14	Treacher-Collins (6,7& 8)		1	1	female
15	1, 2, 3	uni	26	23	male
16	CFND (0-14 + craniosynostose)		8	20	female
17	Treacher-Collins (6,7& 8)		2	14	male

Table 2. Details on patient characteristics (continued)

Patient number	Type of clefts*	Uni- or biliateral	Number of surgeries	OSRFD	Gender
18	2, 3, 7, 8, 11	bi	7	14	female
19	0, 1, 2, 3, 10	bi	14	23	female
20	Treacher-Collins (6,7& 8)		6	4	male
21	0, 2, 3	uni	3	23	female
22	Treacher-Collins (6,7& 8)		1	13	male
23	CFND (0-14 + craniosynostose)		7	11	female
24	Treacher-Collins (6,7& 8)		4	5	female
25	3	bi	10	14	male
26	pure midline (0-14)		9	7	female
27	0, 2, 3	bi	2	6	female
28	3	uni	4	12	female
29	Treacher-Collins (6,7& 8)		3	10	female
30	2, 3	uni	12	9	male
31	Treacher-Collins (6,7& 8)		3	11	female
32	Treacher-Collins (6,7& 8)		5	6	female
33	2, 3	uni	11	6	female
34	1, 2, 3	uni	15	7	female
35	3, 4	uni	10	16	female
36	CFND (0-14 + craniosynostose)		10	19	male
37	3, 4	uni	5	12	female
38	Treacher-Collins (6,7& 8)		5	10	female
39	CFND (0-14 + craniosynostose)		2	11	female
40	CFND (0-14 + craniosynostose)		2	10	female
41	ALX3 (0-14)		15	6	female
42	Treacher-Collins (6,7& 8)		3	4	female
43	2, 3	uni	18	20	male
44	Treacher-Collins (6,7& 8)		1	16	female
45	0, 3	bi	3	4	male
46	0, 2, 3, 4, 11	bi	12	10	male
47	3	uni	15	22	female
48	ALX3 (0-14)		15	21	male
49	Treacher-Collins (6,7& 8)		6	17	female
50	CFND (0-14 + craniosynostose)		2	9	female
51	2, 3	uni	16	8	female
52	Treacher-Collins (6,7& 8)		7	20	male
53	Treacher-Collins (6,7& 8)		2	14	male
54	0, 2	uni	5	2	female
55	Treacher-Collins (6,7& 8)		5	11	female
56	1, 2, 3, 4	uni	11	13	female
57	0, 1, 2	uni	9	15	female
58	Treacher-Collins (6,7& 8)		3	15	male
59	1, 2, 3, 11	uni	14	22	male

**= some patients have multiple clefts simultaneously*

OSRFD= Objective Severity of Residual Facial Deformity according to the Versnel scoring list (31)

Prevalence of non-acceptance

The first objective of this study was to objectify the amount of patients with non-acceptance with facial appearance; this was present in 44% of all patients. A total of 72% patients with non-acceptance reported troubles in everyday activities due to their appearance, versus 35% in accepting patients, which is a significant difference (p= 0.01). Also the patients' wish to undergo psychological treatment was significantly different (p= 0.002) between non-accepting and accepting patients (respectively 48% and 11%).

Predictive factors

The risk factors associated with non-acceptance are presented in Table 3. Since gender was disproportionally represented in this population, and age had a significant correlation with non-acceptance (p= 0.04) all outcomes were corrected for both age and gender, educational level was not associated with acceptance and therefore left out.

Acceptance was not associated with the external factors objective severity of the residual deformity, being religious, protective upbringing and bullying in the past. However, the associated risk factors for non-acceptance were the internal factors emotional coping strategy, troublesome puberty due to facial appearance and high self-perceived visibility of the residual deformity. It must be stressed, that the external factor protective upbringing, as well as the internal factor valuing the opinion of others as well as an avoiding coping style, all had a high odds-ratio, but an insufficient effect to be significantly different between acceptors and non-acceptors.

Table 3. Association of non-acceptance with potential predictive factors

Risk factors	OR	95% CI		p-value
*External factors**				
Objective severity	1.12	0.99	1.27	0.09
Religious	1.09	0.34	3.48	0.89
Protective upbringing	0.34	0.10	1.15	0.08
Bullying in past	0.91	0.19	4.29	0.91
*Internal factors**				
Avoiding coping style	0.67	0.38	1.19	0.17
Emotional coping style	3.45	1.39	8.54	**0.01**
Valuing opinion of others	1.92	0.98	3.77	0.06
Troublesome puberty	2.40	1.43	4.03	**0.00**
Self-perceived visibility	1.97	1.06	3.69	**0.03**

*All corrected for gender and age
Non-acceptance coded 1, acceptance coded 0
OR= Odds Ratio, CI= confidence interval

Association of non-acceptance with satisfaction of facial appearance

Since the BCS is seen as a measurement of satisfaction, the association of the BCS and its subscales with non-acceptance was calculated, as can be seen in Table 4. Non-acceptance was highly associated (p= < 0.01) with all scores of BCS, except for the score of the BCS-body-without-face. In addition, the BCS-function-of-face showed to have a remarkably high odds-ratio as well (OR= 0.11).

Table 4. Association of Body Cathexis Scale BCS with non-acceptance*

Scale or subscale	OR	95% CI		p-value
Original BCS	0.91	0.85	0.96	**0.002**
Facial-BCS	0.88	0.82	0.95	**0.001**
BCS-appearance-of-face	0.80	0.69	0.91	**0.001**
BCS-function-of-face	0.11	0.02	0.55	**0.007**
BCS-whole-body-without-face	0.90	0.77	1.06	0.20

*All corrected for gender and age
Non-acceptance coded 1, acceptance coded 0
OR= Odds Ratio, CI= confidence interval

DISCUSSION

It must be stated that in most cases, even after optimal surgical treatment was given, total normalization of the facial features is seldom achieved and a patient has to face a degree of residue. (28, 32) An earlier study conducted within the same patient population learned that the vast majority of these patients (83.1%) are not satisfied with this end-result, even when an optimal reconstruction is achieved.(30) At that point, surgical options for improvement are limited. Therefore, acceptance of their own face is important to achieve, especially for the patient unsatisfied with the appearance of their face. The different numbers of patients being unsatisfied with facial appearance (83%) and unable to accept it (44%) clearly illustrates that these are two separate entities to measure outcome. All of the patients that could not accept the appearance of their face were also unsatisfied, while only 53% of the unsatisfied patients could not accept their appearance. The patients with non-acceptance suffer from this on a daily base and indicate themselves a higher wish for psychological support.

In this study, the internal predictive factors high self-perceived visibility of the residual deformity, psychological troubles during puberty and an emotional coping style, are associated with non-acceptance. However, not all potential predictive factors showed a significant difference between groups of accepting and non-accepting patients, perhaps because of the relatively small group of patients in which this study was performed. But looking at the high odds-ratio and the clear significant tendency, it is most likely that if our study population would have been larger, also the protective upbringing, valuing the opinion of others as well as an avoiding coping style would be

differentiating factors between acceptors and non-acceptors. Moreover, the relatively small group also limits the number of risk factors that can be investigated. In addition, the retrospective nature of some of the questions in the interview might induce a bias; on the other hand, this is how the patient experienced the event in hindsight.

Ideally, a patient at risk for non-acceptance should be identified within a few minutes at the outpatient clinic. Most of the published studies concerning acceptance with appearance are not appropriate for an outpatient clinic setting, particularly due to their length. Finding an individual patient at risk can therefore be hard. To tackle this problem, we constructed a screening tool for non-acceptance (Figure 1) according to questions and predictive factors derived from the interview used in this study. For the reason that this study is just descriptive and explorative towards the screening tool for non-acceptance, further research is necessary to validate and support our screening tool. At this moment, the tool is tested at the Outpatient Clinic of the Craniofacial Team. In addition, this screening tool and the prevalence of non-acceptance must be tested in different types of patients, e.g. reconstructive and aesthetic patients, before conclusions made in this study can be extrapolated to other patient groups.

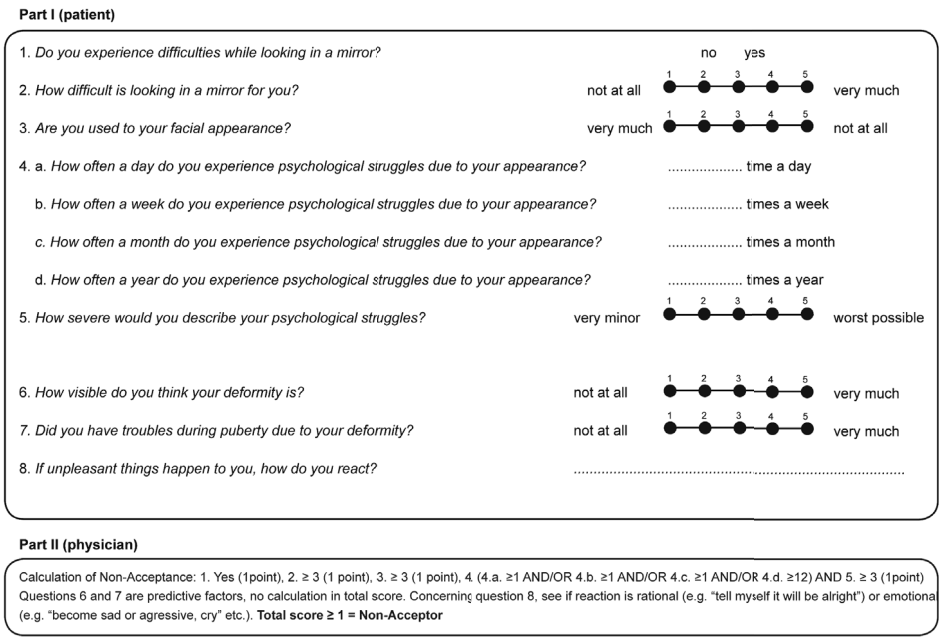

Figure 1. Questionnaire for Non-Acceptance

Our results on non-acceptance and its predictive factors imply that amelioration of acceptance with the deformed facial appearance in these patients can be achieved by adjusting to these internal processes and thus most likely by professional psychological help. The high ratio of patients

with a wish for psychological treatment (48%) also reflects this. Studies on acceptance of chronic pain showed promising results with Cognitive Behavioral Therapy.(10, 33) Since both the group of patients with chronic pain as well as our facially disfigured patients have comparable patterns of fear-avoidance and areas of psychological struggles due to their ailment,(11, 17) the results of psychological treatment might be extrapolated to patients with congenital severe facial disfigurement. In addition, the importance of the upbringing and the troubles suffered during puberty illustrate that acceptance may be founded at a young age. Therefore, parents should know about the effect of a protective upbringing and the standards and values they teach their children. A combined therapy of patients and their parents could therefore be helpful.

Our observation that the objective severity has no association with acceptance, suggests that surgery alone might not be the answer to the problems encountered by these patients. However, surgical options to correct residual abnormalities in their face are often available. So the question is when to operate in a non-accepting patient? The answer to this may be found in a different group of patients. There are some similarities between the non-accepting patients in this study and patients with Body Dysmorphic Disorder (BDD). The definition of BDD in short is a pre-occupation with an imagined or slight physical abnormality, which causes significant distress or impairment in social, occupational or other areas of functioning.(2, 22) Non-accepting patients with a residual deformity after completed surgical treatment of their facial cleft have a pre-occupation with their deformity, which also leads to social impairment, and is irrespective of its severity of objective visibility. In studies concerning patients with BDD, surgery rarely improves the situation. (1, 7, 19) In contrast, psychological treatment has proven to be more effective in most cases.(1) Surgical treatment in non-accepting patients with a residual deformity after complete treatment of their facial disfigurement should therefore be carefully reconsidered, as their expectations may be unrealistic. Exception on this recommendation is a surgical procedure to solve functional problems. This study showed that a low score on the BCS-function-of-face has a high association with non-acceptance. This implies that the better the function of the face, the more likely the acceptance of the face is. Therefore a distinction should be made on the character of the patients' wish for additional surgery. The final recommendation therefore is to be reserved to surgical interventions in non-accepting patients with a residual deformity after completed surgical treatment, unless the treatment aims at restoring a functional problem.

We conclude that acceptance of one's facial appearance is a different outcome measurement than satisfaction with facial appearance, and has high relevance to surgical decision making for the surgeon and serious impact on social functioning for the patient. Almost half of the adult patients with a rare facial cleft did not accept their facial appearance after completion of surgical treatment. The short questionnaire provided in this study facilitates recognition of these non-acceptors. The objective severity showed not to correlate with the acceptance of patient's facial appearance, nevertheless the self-perceived visibility does. Therefore, it is very unlikely that an additional surgical

correction will change the way patients see themselves. Moreover, residual deformities will be visible even after excellent surgical results are achieved. We therefore would like to shine a light on the option not to operate these patients who completed surgical treatment, but who face a residual deformity, unless it solves a functional problem.

Extrapolation to other groups of patients

As mentioned earlier, since this study covers a very specific and rare group of patients with severe facial deformities, an extrapolation of these conclusions to other groups of patients cannot immediately be made. The number of patients (44%) with non-acceptance is rather large in this group. In order to rule out other reasons than the fact that the non-acceptance of this group of patients just is relatively high, we would like to emphasize that we can not subscribe this result to a selection bias, since all patients who met our inclusion participated in this study. The 16 patients who did not respond to our invitation to participate in this study even were the less courageous and emotionally struggling patients. If they would have participated, it is very likely that the number of non-acceptors was even higher. Nevertheless, the total number of patients participating in this study is relatively small. Due to the rareness of these facial deformities, a larger number was not possible. However, this may distort the outcome of this study both by the relative small number of patients as well as the very specific group of patients, Also, this observation is made from a single measurement. In order to find out of the process of non-acceptance might be dynamic, a longitudinal study would be illustrative.

In conclusion, to validate this screening tool and to estimate the prevalence of non-acceptance amongst other types of patient groups, this study must be executed in other different types surgical subgroups, such as reconstructive and aesthetic patients, and in a larger number of patients, before conclusions made in this study can be extrapolated to other patient groups.

CONFLICT OF INTEREST

None.

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CHAPTER 9

SUMMARIZING DISCUSSION

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The aim of this thesis basically comes down to tailoring the treatment for patients with rare facial clefts. Treatment usually starts with making a diagnosis. In view of the fact that it is of major importance to adequately counsel parents of children with rare facial deformities, and to provide the best possible care and surgical treatment for every specific type of facial malformation, an early diagnosis is essential.

MAKING A DIAGNOSIS

CHAPTER 2 discusses a detailed overview of all phenotypical features of CFND patients, all with a confirmed *EFNB1* mutation. Since prior studies revealed that around 20% of the patients screened for CFND did not display a mutation in the *EFNB1* gene, more information about the phenotypical features of patients with a confirmed *EFNB1* mutation was needed. Our study showed that CFND patients, confirmed by an *EFNB1* mutations, undeniably have a clear phenotype; Hypertelorism, longitudinal ridging and/ or splitting of nails, a (mild) webbed neck and a clinodactyly of one or more toes were shown to be consistent features observed in all patients. Phenotypical features that were observed frequently bifid tip of nose (91%) columellar indentation (91%) and were low implant of breasts (90%). Less common, but remarkable features were iris coloboma, cleft lip and palate, cryptorchism, hernia diafragmatica, dextroposition of the heart, double vena cava superior and bidirectional shunt of the heart. In addition a comparison was made with anthropometic data of general facial proportions. Patients with CFND appeared to have a significantly different face on multiple aspects. As the nomenclature "Craniofrontonasal Dysplasia" (CFND) can be confusing regarding the spectrum of phenotypical features, perhaps it should therefore be discarded and be replaced. Because until now it is unkown if mutations in the *EFNB1* gene can cause deformities other than CFND, the abbrevation "*EFNB1*-CFND" is probably most applicable.

PLANNING FOR SURGICAL TREATMENT

After a specific diagnosis in a patient with a rare facial cleft is made, surgical treatment is often considered. However, since the incidence of these facial clefts is extremely low, previous studies on tailoring timing and type of surgery to these specific conditions were limited.

CHAPTER 3 covers a review on the long-term surgical results of CFND patients with proven *EFNB1* mutations, treated for their facial deformities. The focus in this overview is particular on the patients with severe and evident deformities. In patients with a mild expression however, the risk of a reconstruction in contrast to the benefit and potential improvement must be considered. All zones of the face and accompanying long-term surgical results of specific procedures and

pitfalls in these zones come to the attention. The observed abnormalities of the facial skeleton (hypertelorism, orbital dystopia and midface hypoplasia) appear to be primarily induced by the genetic defect and not secondary to either craniosynostosis or surgical procedures. Correction of hypertelorism and orbital dystopia, if present, is preferably done with a median faciotomy. A first costochondral graft for the correction of the dorsum of the nose can be performed simultaneously, as well as a correction of the medial canthi. A definite correction of the nose can best be performed at skeletal maturity, together with other secondary corrections. Based on the results in this study, an algorithm was formed as a treatment guideline. In addition, a specialized centre is preferred for the execution of all steps of the surgical sequence.

CHAPTER 4 concerns the review on the long-term surgical results for patients with oblique and paramedian facial clefts, and **CHAPTER 5** does the same for symmetrical medial facial clefts. Similar to Chapter 5, all zones of the face as well as details regarding surgical techniques and timing, influence of growth, and difficulties of this pathology on the long-term are covered.

CHAPTER 4 specifically revealed that 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. Concerning orbital and nasal reconstructions, costochondral grafts showed the best long-term results in both. Based on our results, major nose reconstruction is best delayed until adolescence. For an optimal final result in selected cases, correction of midface hypoplasia at adolescence is necessary. The most important lesson learned in this study is that the three-dimensional underdevelopment of the midface region plays a central role in the deformities of most patients, however, it is complex and difficult to correct. The provided guideline at the end of this chapter should help to minimize the number of operations and ameliorate long-term results.

Long-term surgical outcome as presented in **CHAPTER 5** showed to be 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. Reconstructing the nose is the most challenging aspect of patients with a median facial cleft, especially the nasal dorsum and projection of the nose. 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. Regarding the correction of hypertelorism, an adequate and stable result was observed for both the orbital box osteotomy and medial faciotomy, even when performed at a young age. Direct referral to a specialized centre benefits the number of operations. 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. 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.

PROVIDING PSYCHOLOGICAL HELP

Living with a facial deformity surely affects one's psychological well-being. Although surgeons are usually more interested in surgical innovations and novelties, psychological aspects of treatment must not be forgotten, as they are as important as surgery in the overall treatment of patients with rare facial clefts.

CHAPTER 6 covers the impact of both congenital and acquired facial disfigurement on social functioning in adults and whether this differs from adults without facial disfigurement. It seemed that the impact of congenital and acquired facial disfigurement on social functioning in adults is similar and significantly differs from a reference group without facial disfigurement. The level of stress evoked by either interpersonal behaviour or social anxiety and distress were not significantly different between both the congenital and acquired group.. The assessment of possible predictors for social functioning revealed that only the patient's subjective appearance was strong enough to be pointed out as a predictor. Most important conclusion of this study was that stigmatization and uncertainty about reactions of others caused avoidence of stress.. The fact whether the deformity is congenital or acquired in adulthood had no influence on this social functioning. Patient's satisfaction with the facial appearance is more important than the objective severity of the deformity; in this context realistic expectations of the patient considering additional surgery are important.

CHAPTER 7 discusses the levels of defense mechanisms (unconscious counterpart of coping mechanisms) in both patients with a congenital and, acquired facial disfigurement and without facial disfigurement. A significant difference was found between groups with and without disfigurements on immature defense styles, with the disfigured group using the immature style more frequently. In addition, there was a trend for the non-disfigured group to use more of the mature defense styles. No difference between congenital and acquired groups was seen on any of the individual types of defense style. Self-esteem was the only predictor variable that had the strength to differentiate mature and immature defense styles within our disfigured groups. The association of low self-esteem and the utilization of immature defense styles suggests that professional help may tailor treatment on discussing immature defense style and problems triggering or maintaining this style.

CHAPTER 8 covers the prevalence of patients with non-acceptance of their residual facial deformity. Besides an adequate level of satisfaction, acceptance of facial appearance is important to achieve, since non-acceptance is thought to lead to daily psychological struggles. In this study, non-acceptance with facial appearance was present in 44%; of the non-accepters 72% experienced troubles in everyday activities related to their appearance, versus 35% in accepting patients. Acceptance did not correlate with external factors as objective severity of their residual facial deformity or bullying in the past. Risk factors for non-acceptance in this group were all internal factors; high self-perceived visibility, troublesome puberty period and emotion focused coping strategy. Also presence of functional problems showed to be highly associated. Most importantly, the objective severity of the residual deformity does not correlate with the acceptance of patients' facial appearance, but the self-perceived visibility does. Surgical treatment is therefore no guarantee for an

improvement of acceptance and is therefore discouraged in patients who match the risk factors for non-acceptance, unless it solves a functional problem.

EVALUATION OF THESIS AND FUTURE PERSPECTIVES

The quest for new genetic mutations has been a very expensive and time-consuming type of research. Nevertheless numerous new mutations have been found within the last couple of years. The search for the mutation in patients with CFND specifically took very long, because of its extraordinary type of expression and the possibility of a mosaic mutation pattern. Within the coming years "whole genome sequencing" probably will win popularity. This type of testing results in an extensive amount of data (there are roughly six billion base pairs in each human diploid genome). Storage and evaluation of these genomic data requires a considerable amount of computing power and storage capacity. And as computers and processors become smarter, faster and cheaper, also "whole genome sequencing" will become more affordable and thereby therefore more available. The clarification of the genetic background of the more commonly encountered craniofacial malformations leaves us with a mixed group of patients with unknown cause. In this population the number of patients with a specific phenotype is very low; this may be partially explained by one or more genetic changes that cause a wide phenotypic spectrum and partially by several genetic alterations that all have a very low incidence. As some patients display such an aspecific phenotype, searching for a mutation is rather aspecific too. The costs for a quest for all the associated mutations are relatively high, as all genes are tested separately in contrast to whole genome sequencing. Particularly with the growing number of more rare causative genetic alterations, whole genome sequencing could be time- and cost-effective as tool for counselling and for research purposes. The interpretation of the data obtained with whole genome sequencing requires a large reference group of 'normal people' to filter the non-significant noise out of the enormous amount of data. At present, a reference databank of over 1000 controls is available at the department of Bioinformatics at the Erasmus MC.

In the perspective of the CFND patients as presented in chapter 2, 3 and 4, it would be interesting to thoroughly look at the patients who are pointed out in literature as CFND patients, but who lacked the proof of having an *EFNB1* mutation. Do they even fit the label "CFND based on *EFNB1* mutation" if we compare them to the phenotypical features found in our study? And if they do, is a mosaic mutation pattern ruled out? Or can we perhaps look for another mutation in the same pathway or proximity of this pathway?

An interesting finding in the study on the phenotype of CFND patients, and the assessment of long-term results of surgical treatment of the patients with either CFND, oblique, paramedian and symmetrical medial facial clefts is the finding that there is of a variable restriction in growth. This restriction in growth which is irrespective of the performed operations, but also seems independent on the type of mutation or initial phenotype. A phenotype-genotype correlation in patients

with CFND has never been found and both left and right side of the face and vault can be affected which will for instance result in a synostosis of one or more sutures.

Surprisingly craniosynostosis was tended to be overrepresented on the left side in patients with CFND; 19% (n=4) left-sided, 5% (n=1) had a right-sided, 43% (n=19) had a bilateral sysnostosis of the coronal suture and 5% (n=1) had a bilateral coronal synostosis with synostosis of the sagittal suture. Looking closer to the patients with oblique end paramedian clefts, this overrepresentation of the left sided oblique facial cleft is seen as well; 38% (n=10) left sided, 22% (n=10) right sided oblique facial cleft; 9% (n=4) left and midline sided and 0% right and midline sides clefts, and 20% bilateral oblique facial clefts.,In The exact way of developing this fundamental restriction in growth (with an overrepresentation of deformities occurring on the left side of the face) can probably not be based on the type of mutation, nor on the initial phenotype, nor on the type and timing of surgery. However, in the ordinary cleft lip and palate malformations, an overrepresentation on the left side is seen as well.

Regarding the assessment of long-term results of surgical treatment of the patients with either CFND, oblique, paramedian and symmetrical medial facial clefts, the evaluation would be scientifically ideal when performed in a randomised control trial (RCT) type of study. However, as in many surgical fields a RCT set-up is almost impossible due to multiple reasons; the types of patients in for surgery, the complexity of surgical interventions, and the disposition of surgeons. Furthermore, the assessment is complicated by the constant innovation and adjustment of the surgical procedures themselves. Because this is a known issue in surgical research, a series of papers was published about surgical innovation and its evaluation.(1-3)

Table 1. Stages of surgical innovation (1-3)

	Stages 0–1 (Innovation)	Stage 2a (Development)	Stage 2b (Exploration)	Stage 3 (Assessment)	Stage 4 (Long term)
Number and types of patients	Single digit, highly selected (or pre-human)	Few, selected	Many, mixed but not all	Many, variable	Almost all
Number of surgeons	Very few	Few, innovators	Many	Many, early majority	Most, late majority
Ethics	Sometimes	Yes	Yes	Yes	No
Learning curve in human beings	No	Yes	Yes	Maybe	No

A five-stage concept was suggested to scientifically describe the development of innovative surgical procedures (see Table 1). Although it is practically impossible in this field of surgery to set up a RCT (golden standard type of research), it is also difficult to decide to start a formal research in a developing field. If done too early in the process of innovation, the definitive technique might not be fully refined and the constraints of an RCT could obstruct innovation, and if too late, the balance could be lost. In addition, surgeons seem to desire to make their own decisions about the selection

of the intervention rather than a computer or other randomization system. These preferences of both surgeon and/or the patients (and his/her parents) are rarely based on evidence. In addition, to be more specific in this field of surgical innovations for patients with rare facial clefts, the group of patients receiving treatment is very small. Setting up an RCT will take ages to complete. Furthermore the RCT evaluation has to be very large to achieve adequate statistical power to rule out serious but rare outcome (eg, mortality) and to differentiate between subtle differences in outcome,. This does not mean that non-RCT studies have no value; An alternative set-up of research should however be performed in a systematic manner, be well-planned and conducted, and precise evidence should be reported. In earlier studies surgeons mainly focused on short-term clinical measures of technical success and harm. As can be seen in the table of stages of innovation, long-term evaluation is the most evolved stage from which the most reliable data can be obtained. In this study, focus is especially made on the long-term character of the outcome. Since all the procedures are performed in the same hospital, with overall the same surgical teams performing these procedures, and the evidence is reported as precise as possible, with no data being lost to follow-up, these evaluations can be considered as the highest achievable. The performed evaluations however are not conducted only on one type of surgical procedure. In stead a complete overview of a complete treatment with adjunct innovations and refinement of surgical procedures for patients with rare facial clefts is presented.

Interestingly, the ideal study on a specific treatment should contain assessment of both clinical and patient-reported outcomes. This means in the majority of cases that this information is captured in a questionnaire assessing health- related quality of life. However, despite the recent interest in this area, there seems to be a gap between measuring health-related quality of life outcomes and using the information to change surgical practice.(1-3)

Concerning the outcomes of this study, the concluding algoritms will hopefully improve the overall outcome and reduce the number of procedures. However, the effect of these algorithms can only be evaluated after a considerable amount of patients underwent a full diagram of surgical treatment, and this will take at least over 20 years. Respecting the ongoing innovations and adjustments, these algoritms will most likely need some adjustments themselves too. However, it seems unlikely that the amount of changes and new possibilities in treatment options for patients with rare facial clefts will occur, as they have over the past 40 years.

In the upcoming years attention ideally should be drawn to all healthcare workers who may be confronted with facial deformities in general. Especially healthcare workers who perform (standard) prenatal ultrasounds, gynaecologists and paediatricians, and midwives should have easy access to information on facial deformities and on how to refer these patients to a dedicated craniofacial centre. Deformities in the face are regularly detected, but not interpreted as a possible facial cleft. As the child is born it comes clear afterwards that the deformity was visible at prior imaging. The importance of an early (or even prenatal) referral to a specialized centre for a multi-disciplinary treatment must be stressed. A national guideline for the treatment of these patients will hopefully

facilitate to centre this care to specific referral hospitals, with specialised multi-disciplinary teams. As a result of this study, this guideline is now recently developed.

Although surgeons in general are usually not primarily interested in studies and novelties concerning the psychological treatment of patients with facial deformities, the effect of a tailored psychological treatment can alter considerably the well-being of a patients a lot. One of the problems with most of the current research concerning the psychological evaluation of patients in general and patients with facial deformities in particular is that they evaluate groups of patients. To implement assessments of patients at an outpatient clinic basis, to identify the patients at risk so treatment can be offered, more validated and compact questionnaires are needed.

Patients with severe congenital facial disfigurement (irrespective of its objective severity) overall did not differ from patients with an acquired facial deformity in these studies. It would be very interesting to test patients with a different type of request for help at a plastic surgical outpatient clinic (such as post-bariatric, consultations and requests for aesthetic surgery) on the same psychological assessments. Data derived from this study stresses the importance of the expectancy and overall psychological well-being of these patients, regarding the satisfaction and acceptance after surgery. Perhaps motivation for surgery, satisfaction and acceptance afterwards have identical patterns in these patients. Insights on the psychological aspects of different kinds of patients will improve the opinion on the approach and appraisal of patients in general. Furthermore it will hopefully improve the outcome of treatment by being restraint in performing surgery or opting for a psychological treatment in some.

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CHAPTER 10

ENGLISH SUMMARY

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CHAPTER 11

NEDERLANDSE SAMENVATTING

DIAGNOSEVORMING

Het doel van dit proefschrift was om de behandeling voor patiënten met zeldzame aangezichtsspleten (rare facial clefts) te verbeteren. Gebruikelijk begint de behandeling bij het stellen van een diagnose. Het is erg belangrijk om ouders van kinderen met een zeldzame aangeboren afwijking in het gelaat gericht te adviseren en begeleiden, en de meest optimale zorg en chirurgische behandeling gericht de specifieke afwijking in het gelaat te geven. Daarbij is een diagnose in een vroeg stadium van deze behandeling essentieel.

HOOFDSTUK 2 geeft een gedetailleerd overzicht van alle fenotypische kenmerken van patiënten met Craniofrontonasale Dysplasie (CFND), waarbij de afwijking is bevestigd met een mutatie in het *EFNB1* gen. Eerdere studies aantoonde dat ronde de 20% van alle patiënten die klinisch mogelijk in aanmerking zouden kunnen komen voor de diagnose CFND, geen mutatie in het *EFNB1* gen hadden. Daarom is er meer informatie nodig over het fenotype van patiënten die zowel klinisch de diagnose CFND hebben als ook de genetische mutatie. Onze studie toonde aan dat CFND patiënten met een bewezen *EFNB1* mutatie, een ononkenbaar duidelijk fenotype hebben; in ieder geval hypertelorisme, longitudinale ribbels en/ of splijting van de nagels, (milde) webvorming van de nek en een clinodactylie van een of meerdere vingers en/ of tenen waren kenmerken die alle patiënten vertoonden. Andere kenmerken die vaak werden waargenomen waren; gespleten neuspunt (91%), gespleten columella (91%) en lage implant van de borsten (90%). Minder frequent, maar wel opmerkelijk was een iris coloboma, cheilognatopalatoschisis, cryptorchisme, hernia diafragmatica, dextropositie van het hart, dubbele vena cava superior en een bidirectionele shunt van het hart. Aanvullend werd er ook een vergelijking gemaakt met de antropometrische data van het gemiddelde gelaat. Patiënten met CFND bleken een significant ander gezicht te hebben dan dit gemiddelde gezicht, op verschillende aspecten. Omdat de naamgeving "Craniofrontonasale Dysplasie" (CFND) verwarrend kan zijn ten aanzien van het spectrum van de fenotypische kenmerken, is het wellicht raadzaam om deze te vervangen. Aangezien het vooralsnog onduidelijk is of mutaties in het *EFNB1* geen ook andere afwijkingen dan CFND kunnen voortbrengen, is de naam "*EFNB1*-CFND" voor deze afwijking wellicht het meest toepasselijk.

PLANNING VOOR CHIRURGISCHE BEHANDELING

Nadat een specifieke diagnose bij een patiënt met een zeldzame aangezichtsspleet is gemaakt, wordt een chirurgische behandeling vaak overwogen. Echter, aangezien de incidentie van deze aandoening extreem laag is, is het aantal onderzoeken over het aanpassen van de soort operatie en de beste periode voor deze procedure erg beperkt.

HOOFDSTUK 3 beschrijft een overzicht van de chirurgische lange termijn resultaten van CFND patiënten met een bewezen *EFNB1* mutatie. Het zwaartepunt lag met name op de patiënten met ernstige en duidelijk zichtbare afwijkingen. In patiënten met een milde expressie, moet het risico

van een reconstructie echter worden afgewogen tegen het voordeel en de mogelijke verbetering die de reconstructie met zich mee brengt. Alle regio's van het gelaat en de bijbehorende de daarbij behorende procedures worden beoordeeld op hun chirurgische lange termijn resultaten en specifieke valkuilen. De waargenomen afwijkingen in het skelet van het gelaat (zoals hypertelorisme, orbitale dystopie en midface hypoplasie) lijkien primair geïnduceerd door het onderliggende genetische defect en niet secundair aan of de craniosynostose ofwel de chirurgische interventies. Correctie van het hypertelorsime en de orbitale dystopie, indien daar sprake van was, wordt bij voorkeur gedaan door een mediane factiotomie. Een eerste rib graft voor de correctie van het neusdorsum kan gelijktijdig worden verricht, alsook een correctie van de mediale canthi. Een definitieve correctie van de neus kan het beste worden verricht als het skelet is uit gegroeid, samen met andere secundaire correcties. Aan de hand van de resultaten van deze studie is er een algoritme opgesteld die kan dienen als richtlijn voor de behandeling. Een laatste toevoeging is dat alle stappen van deze chirurgische opeenvolging bij voorkeur worden uitgevoerd in een gespecialiseerd centrum.

In **HOOFDSTUK 4** wordt zo'n zelfde overzicht gegeven over de lange termijn resultaten van de chirurgische behandeling van patiënten met een schuine en paramediane aangezichtsspleet, **HOOFDSTUK 5** doet dat voor de symmetrische mediane aangezichtsspleten. Ook in deze hoofdstukken worden alle regio's in het gelaat behandelt met het oog op het type en timing van chirurgische technieken, de invloed van groei en moeilijkheden specifiek bij deze pathologie.

HOOFDSTUK 4 onthult daarbij specifiek dat verticale dystopie niet wordt veroorzaakt door voorafgaande operaties, maar door een gebrek aan groei van de maxilla. Bij alle patiënten met verticale dystopie was de aanwezigheid en de ernst van de dystopie reeds duidelijk op de leeftijd van vijf jaar, en zou idealiter niet lang daarna moeten worden behandelt. In milde gevallen lijkt het plaatsen van grafts voldoende, maar in de meer uitgesproken gevallen is een translocatie van de orbitae noodzakelijk. Wat betreft de orbitale en nasale reconstructies lieten ribgrafts de beste resultaten zien op de lange termijn. Gebaseerd op onze resultaten, wordt het advies gegeven om uitgebreide reconstructies van de neus uit te stellen tot in de adolescentie. Voor een optimaal eindresultaat is bij een geselecteerde groep patiënten een correctie van de midface hypoplasie op een jong volwassen leeftijd noodzakelijk. Belangrijkste conclusie uit deze studie is dat de driedimensionale onderontwikkeling in de regio van het midface een centrale rol speelt in de afwijkingen die de patiënten vertonen, het is echter complex en moeilijk om volledig te corrigeren. De richtlijn op het einde van dit hoofdstuk zou het aantal operaties per patiënt moeten kunnen verkleinen en de lange termijn resultaten moeten kunnen verbeteren.

De lange termijn resultaten zoals deze worden gepresenteerd in **HOOFDSTUK 5** laat zien dat aanvankelijk goede resultaten vaak verslechteren over de tijd, met name in de regio van de neus. Het reconstrueren van de neus is het meest uitdagende aspect van patiënten met een mediale aangezichtsspleet, in het bijzonder het dorsum en de projectie van de neus. Vanwege een afwezigheid van een adequate groeipotentie in de regio van de neus, verslechterd het resultaat

als de regio's rondom de neus wel groeien. Wat betreft de correctie van het hypertelorisme werd er een goed en stabiel resultaat geobserveerd bij patiënten die een orbitale boxosteotomie ondergingen, alsook een mediale faciotomie, zelfs als dit op een jonge leeftijd gebeurde. Patiënten die van het begin af aan werden behandeld in een gespecialiseerd centrum ondergingen in totaal minder operaties. De intrinsieke groei beperking ter plaatste van de spleet en de direct omliggende structuren is onvoorspelbaar, wat de reconstructie bemoeilijkt en waarop lastig te anticiperen is. Operaties die (te) vroeg zijn uitgevoerd vereisen als gevolg daarvan vaak een re-operatie om de esthetische en functionele onbalans te herstellen op het moment dat het gelaat is uitgegroeid. Incisies die worden gemaakt op jonge leeftijd zouden weloverwogen moeten zijn, zodat ze tijdens toekomstige chirurgische procedures opnieuw te gebruiken zijn. Bij het plannen van operaties voor deze patiënten zou de richtlijn, zoals gegeven in het betreffende hoofdstuk, in acht moeten worden genomen.

BIEDEN VAN PSYCHOLOGISCHE HULP

Het leven met een afwijking in het gelaat heeft zeker een effect op iemands psychologisch welbevinden. Alhoewel chirurgen over het algemeen meer zijn geïnteresseerd in chirurgische innovaties en ontwikkelingen, is ook het psychologische aspect van het leven met een dergelijke aandoening interessant. Bij de algehele behandeling van patiënten met een ernstige afwijking in het gelaat is de psychologische begeleiding evenzo belangrijk.

HOOFDSTUK 6 behandelt de impact van zowel een congenitale als ook een op latere leeftijd verworven afwijking in het gelaat op het sociaal functioneren van volwassenen en kijkt of dit verschilt met volwassenen zonder afwijking in het gelaat. Het blijkt dat de impact van een aangeboren of verworven afwijking in het gelaat op het sociaal functioneren hetzelfde is, maar beide significant verschillend van de referentiegroep zonder afwijking in het gelaat. De hoeveelheid stress die wordt ontlokt bij zowel interpersoonlijk gedrag als ook de sociale angst en spanning zijn niet significant verschillend tussen de congenitale en verworven groep. De zoektocht naar mogelijke voorspellers van het sociaal functioneren leverde slechts een voorspeller op; de patiënt zijn subjectieve beoordeling van zijn uiterlijk. De belangrijkste conclusie van dit onderzoek was dat stigmatisering en onzekerheid over de mogelijke reactie van anderen ontwijkend gedrag en stress veroorzaakt. Hierbij maakt het niet uit of deze afwijking aangeboren of verworven is. De tevredenheid van de patiënt met zijn eigen uiterlijk is maakt wel verschil, in tegenstelling tot de objectieve ernst van de afwijking. In deze context zijn realistische verwachtingen van een aanvullende operatie erg belangrijk.

HOOFDSTUK 7 bespreekt de niveaus van afweermechanismen (de onbewuste tegenhanger van copings-mechanismen) in zowel patiënten met een congenitale als ook een verworven afwijking in het gelaat, en patiënten zonder afwijkend gelaat. Er wordt een significant verschil beschreven tussen de groepen met een afwijking in het gelaat en patiënten zonder afwijking in het gelaat op

het gebied van de zogenaamde onvolwassen afweermechanismen. De patiënten met een afwijking in het gelaat gebruikte deze onvolwassen afweermechanismen vaker, en de patiënten zonder afwijkend gelaat lieten een trend zien om de volwassen afweermechanismen meer te gebruiken. Er werd geen verschil gevonden tussen eenieder van de groepen en elk van de individuele types van afweermechanismen. Alleen zelfvertrouwen had de kracht als enige voorspeller om te differentiëren tussen volwassen en onvolwassen afweermechanismen. De associatie tussen een laag zelfvertrouwen en het gebruik van onvolwassen afweermechanismen suggereert dat professionele hulp de problemen die deze vorm van afweer ontlokken of vasthouden kan aanpakken.

HOOFDSTUK 8 laat de prevalentie van patiënten die het restant van hun afwijking in het gelaat aan het einde van de behandeling niet kunnen accepteren zien. Naast een goed niveau van tevredenheid, is het ook belangrijk om het uiterlijk van het gelaat te accepteren, aangezien het niet accepteren hiervan tot dagelijkse psychologische strijd leidt. In dit onderzoek lieten maar liefst 44% van de patiënten zien hun uiterlijk niet te kunnen accepteren, hiervan ondervond maarliefst 72% problemen op een dagelijkse basis, als direct gevolg van hun uiterlijk. In de groep die hun gelaat wel accepteerde was dit 35%. Acceptatie correleerde niet met externe factoren als de objectieve ernst van de resterende afwijking in het gelaat of pesterijen in het verleden. Alle risicofactoren voor het niet accepteren van het uiteindelijke resultaat bleken interne factoren te zijn; hoge zelf ondervonden zichtbaarheid van de afwijking, een moeizame puberteit en een emotie gerichte copings-strategie. Ook de aanwezigheid van functionele problemen waren hiermee hoog geassocieerd. De belangrijkste conclusie was dat de objectieve ernst van de resterende afwijking in het gelaat niet correleerde met de acceptatie, maar dat de zelf ondervonden zichtbaarheid wel. Een chirurgische behandeling is daarom geen garantie voor een verbetering van de acceptatie, en wordt afgeraden bij patiënten waarbij de risicofactoren overeenkomen, tenzij het een functioneel probleem oplost.

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Beste paranimfen, lieve **Sarah Versnel** en **Joyce Florisson**, wat een eer dat jullie vandaag aan mijn zijde willen staan. De twee zusjes zoals velen denken, of een en dezelfde persoon. Jullie donkere haren en "licht zuidelijk accent" zorgden nogal eens voor verwarring en nog veel vaker voor verwondering of bewondering. Saar, je ging me voor op meerdere vlakken... De lijn van het onderzoek dat je hebt opgestart en jouw boekje zijn moeilijk te evenaren voor mij als opvolger. En Joyce, met jou heb ik van iedereen de meeste tijd doorgebracht op dat kleine hokje op de 15de. En wat waren we productief, en onze gemeenschappelijke interesses zorgden altijd voor goede afleiding... De combinatie tussen goede collega's en goede vrienden, daar zijn jullie een voorbeeld van! Lieve paranimfen, jullie waren er altijd bij als we op congres gingen in het buitenland, en iedere keer was het een feest. Elkaars presentaties kenden we zo ongeveer van buiten, omdat we die wel 100 keer voor elkaar oefenden. Wie had ik dan ook beter kunnen vragen voor deze taak? Als ik mijn presentatie niet meer kan geven of de tekst niet meer weet, kunnen jullie hem vast voor me invullen, en een feest wordt het met jullie erbij altijd! Bedankt dat jullie zo'n fijne collega's zijn, en bedankt dat jullie zulke lieve vriendinnen zijn...

Lieve schoonfamilie; **Ben** en **Mia Van 't Land**, **Karine** en **Robbert van Wesenbeeck**, **Sonja** en **Bas Meeuws**, **Johan** en **Evelien Van 't Land- de Cuyper** en natuurlijk de kids, jullie zijn altijd geïnteresseerd geweest naar de inhoud en voortgang van mijn onderzoek en mijn verdere werk, bedankt daarvoor! De afgelopen periode ben ik helaas niet bij alle "Van 't Land familie events" geweest omdat ik de avonduren, weekenden, en andere vrije momenten nogal eens moest vullen met de totstandkoming van dit proefschrift en/of diensten. Nu deze gereed is zal ik hier meer bij kunnen zijn.

Lieve **opa en oma Van den Elzen** en **opa en oma Christiaans**, jullie zijn het voorbeeld van hard werkende mensen. Of het nou een veter-strik-diploma was, een autorijbewijs of artsexamen, jullie zijn op iedereen trots. En ik ben trots op jullie, op jullie levenslust en op jullie liefde voor de familie. Jullie vraag hoe lang het nog duurt voordat ik nu eindelijk eens klaar ben met studeren en de opleiding, wordt nog altijd gevolgd door verbazing als ik het aantal jaren noem. Maar we komen dichterbij het einde, en van in ieder geval deze promotie is bereikt. En dat betekent ook dat ik weer meer tijd zal hebben, tijd die ik graag invul door een bezoekje aan jullie te brengen. Ik weet dat jullie het eeuwige leven niet hebben, maar hoop dat ik jullie nog heel lang bij me in de buurt heb.

Lieve **Paul** en **Anke** lief broertje en lief zusje, bedankt dat jullie mijn siblings zijn! Ik weet dat je familie niet kan kiezen, maar dat je die krijgt. Maar als ik zou kunnen kiezen, dan had ik weer voor jullie gekozen. Paul, ik ken geen andere broertjes die verse groetensoep komen maken als hun grote zus ziek en alleen thuis is. Jouw nuchtere kijk op de wereld is goed voor mij, jouw verhalen en avonturen maken me altijd aan het lachen. Jij wijst me erop om gewoon gewoon te blijven, en normale woorden te gebruiken. En Anke, jij bent altijd de lachebek geweest, maar ook nu kletsen we steeds vaker over dingen die er toe doen en waar we mee zitten. Samen met jou dansen

is fantastisch, en nu in hetzelfde ziekenhuis werken is helemaal gezellig. **Max**, jou als aanstaande schoonbroer kan ik natuurlijk niet vergeten. Jij bent altijd geïnteresseerd in de medische wetenschap (in bepaalde aspecten daarvan net iets meer dan de andere...). Fijn dat jij als immer vrolijke noot bij de familie hoort. Broertje en zusje, ik ben trots op wat jullie bereikt hebben. Naar mate we ouder worden, word onze band alleen maar sterker. Ik ben blij dat we lekker met z'n drieën uit eten gaan, een concert van Alicia Keys bezoeken en met z'n allen op stap kunnen. Ik weet dat ik altijd op jullie kan rekenen, voor alles, bedankt daarvoor.

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Lieve, lieve **Maurits**! Hoe kan ik jou bedanken voor alles wat je voor me hebt gedaan? Alles wat ik hier aan dank schrijf, daar doe ik je tekort mee. Het was een traject met een aantal onverwachte wendingen. En op ieder punt was jij er voor me. Bedankt dat je me de ruimte geeft om me te ontplooien, bedankt voor de positieve kijk die jij op het leven hebt, bedankt voor alle honderden kopjes thee die je voor met hebt gemaakt terwijl ik aan het boekje werkte, bedankt dat we nu echt weer samen in Eindhoven wonen, bedankt voor je onvoorwaardelijke liefde. Nu dit boekje klaar is, wordt er een hoofdstuk voor ons afgesloten en wordt het tijd voor vrije tijd. Het maakt niet uit wat we gaan doen, samen met jou is het leven altijd fijn! Ik ben heel blij en trots dat ik met je getrouwd ben, ik hou ontzettend veel van je. Het volgende hoofdstuk gaat over ons...

PUBLICATIONS

Sarah L.Versnel, Marijke E.P. van den Elzen, Jacques C. van der Meulen, Eppo B, Wolvius, Charlotte S. Biesmeijer, Michiel J.M.Vaandrager, Irene M.J. Mathijssen, *Long-term results after 40 years experience with treatment of rare facial clefts: Part 1-oblique and paramedian clefts*, J Plast Reconstr Aesthet Surg, 2011 Oct; 64(10): 1334-43, Epub 2011 Jun 1

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Michels AC, van den Elzen ME, Vles JS, van der Hulst RR., *Positional plagiocephaly and excessive folic Acid intake during pregnancy*., Cleft Palate Craniofac J. 2012 Jan;49(1):1-4. Epub 2011 Jul 8

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CURRICULUM VITAE

On the 4th of April 1983 Marijke Elisabeth Petronella van den Elzen was born in Gemert, the Netherlands, as the eldest child of three. After attending the Jenaplanschool "De Pandelaar" (elementary school), she went to the "Gymnasium" of the Commanderij College in Gemert, where she graduated in 2001. Despite of the fact she had no doctors in her family, she knew from the time she was a little girl that she wanted to become a doctor herself. In 2001 she was allowed to start medical school at the University of Maastricht. Although congenital deformities always had her special interest, it wasn't until her general clinical internships that she discovered that surgery in general and plastic surgery in particular fitted her best. Having become totally enthusiastic about plastic surgery, she dedicated her whole last year of her medical school to this subject (WESP and GEZP internships), and even holidays were spent at the department of Plastic and Reconstructive surgery. Even before she graduated in 2007 she was contracted as a resident (AGNIO) in Plastic Surgery for a few months at the University Hospital of Maastricht, and smoothly thereafter at the Erasmus Medical Centre in Rotterdam. During the following year she started doing research in collaboration with dr. S.L. Versnel and prof.dr. I.M.J. Mathijssen. After a full year of working as a resident, a job as a PhD student was offered. The research covered most of the aspects of the treatment for patients with rare facial clefts, as can be read in this thesis. In December 2010 she was accepted for the plastic surgery training program, and as a result she moved to Eindhoven in June 2011 to start working as a resident (AGNIO) in Plastic Surgery again. Until that time, she had worked for 2,5 years as a full-time PhD student. More recently, in January 2012 she started as a resident in training (AIOS) at the department of General Surgery in the Catharina Hospital in Eindhoven, where she is working untill to now. In august 2010 she married Maurits van 't Land.

PhD PORTFOLIO

Name PhD student:
Marijke van den Elzen
Erasmus MC Department:
Plastic and Reconstructive Surgery

PhD period: **1-11-2008 t/m 01-09-2012**
Promotor: **Prof.dr. S.E.R. Hovius**
Supervisor: **Prof.dr. I.M.J. Matijssen**

1. PhD training

	Year	Workload (Hours/ECTS)
General academic skills		
- Biomedical English Writing and Communication *Scientific writing in English for publications, NIHES*	2010	56/ 2
Research skills		
- Statistics: *Biostatistics for Clinicians, NIHES*	2009	28/ 1
- Methodology: *Introduction to Clinical Research, NIHES*	2009	28/ 1
In-depth courses (e.g. Research school, Medical Training)		
- Microsurgery training (+/- twice a month)	2008-2011	310/ 11
Presentations (national and international conferences)		
- RBSPS/ NVPC, *Transethmoidale encephalocele: an overview of 3 patients*, Den Bosch (the Netherlands)	2008	28/ 1
- ISCFS, *Social and relational functioning with facial disfigurement*, Oxford (United Kingdom)	2009	28/ 1
- NVSCA, *Sociaal and relationeel functioneren van patiënten met een afwijkend uiterlijk*, Tilburg (the Netherlands)	2009	28/ 1
- NVPC, *Sociaal and relationeel functioneren van patiënten met een afwijkend uiterlijk*, Maastricht (the Netherlands)	2010	28/ 1
- NVPC, *Long-term results treatment of median facial clefts*, Rotterdam (the Netherlands)	2010	28/1
- NVSCA, *Lange termijn resultaten na chirurgische behandeling van patiënten met een zeldzame aangezichtsspleet*, Den Haag (the Netherlands)	2010	28/ 1
- ISCFS, *Phenotype of patients with Craniofrontonasal Dysplasia with proven EFNB1 mutations*, Livingstone (Zambia)	2011	28/ 1
- ISCFS, *Surgical treatment of patients with Craniofrontonasal Dysplasia with proven EFNB1 mutations; long-term results*, Livingstone (Zambia)	2011	28/ 1
- ISCFS, *Assessing non-acceptance of facial appearance in adult patients after complete treatment of their rare facial cleft*, posterpresentatie, Livingstone (Zambia)	2011	28/ 1

	Year	Workload (Hours/ECTS)
Attendance national and international conferences		
- NVPC, Utrecht (the Netherlands)	2008	28/ 1
- RBSPS/ NVPC, Den Bosch (the Netherlands)	2008	28/ 1
- NVPC, Utrecht (the Netherlands)	2009	28/ 1
- ISCFS, Oxford (United Kingdom)	2009	28/ 1
- NVPC, Maastricht (the Netherlands)	2009	28/ 1
- NVSCA, Tilburg (the Netherlands)	2009	28/ 1
- NVPC, Rotterdam (the Netherlands)	2010	28/ 1
- ESCFS, Rotterdam (the Netherlands)	2010	28/ 1
- NVPC, Amsterdam (the Netherlands)	2010	28/ 1
- NVSCA, Den Haag (the Netherlands)	2010	28/ 1
- ISCFS, Livingstone (Zambia)	2011	28/ 1
Grants		
- CZ Fonds	2009	
- Stichting Achmea Gezondheidszorg	2009	

2. Teaching activities

Lecturing		
- Introductie in de Plastische Chirurgie (keuzeonderwijs 2e, 3e en 4e jaars)	2008- 2011	14/ 0.5
Supervising practicals and excursions		
- Coach national and international microsurgery courses	2008- 2011	96/ 3.5
- Practicum Gezwollen gewrichten/ Anatomie bovenste extremiteiten (keuzeonderwijs 2e, 3e en 4e jaars)	2008- 2010	28/ 1
- Practicum macroscopisch hechten (keuzeonderwijs 2e, 3e en 4e jaars)	2008- 2011	28/ 1
Other		
- Keuzeonderwijs Craniofaciale Chirurgie (keuzeonderwijs 3e jaars); planning, begeleiding, beoordeling	2008- 2010	84/ 3
- Writing and lay-out Scientific Activities Report 2003-2008 Department of Plastic and Reconstructive Surgery (ISBN 978-90-9024626-0)	2009	120/ 4
- Writing and lay-out Informatiefolders afdeling Plastische Chirurgie/ Esser Stichting	2010	60/ 2