Hands and Heads

Recording and classification of congenital anomalies of the upper limb and common oral clefts

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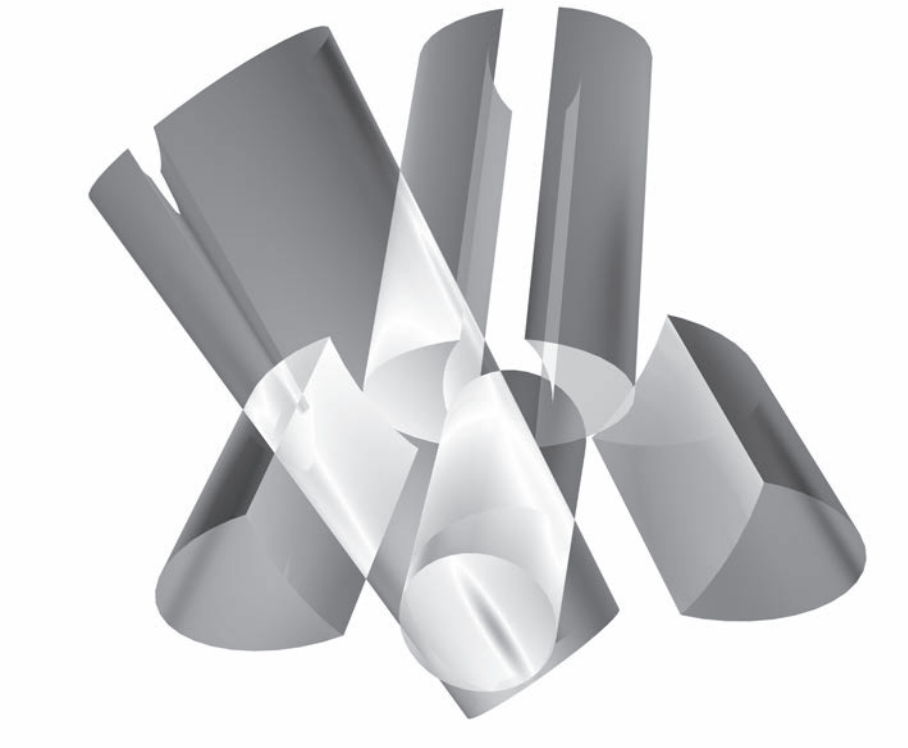
INTRODUCTION



The birth of a child is a tremendous event for the newborn, its parents, and surroundings. Usually, the pregnancy and labour are uneventful and the baby is healthy. The parents are utmost delighted. Shortly, the baby is laid on the chest of the mother for bonding between mother and child, and breastfeeding already starts, if desired. Family and friends come to see the most beautiful baby in the world. Soon, he opens his eyes, senses the environment, and he tries to grasp everything he can get his hands on and tries to put it in his mouth. Some time later he puts on a big smile, and begins talking in a totally unintelligible language. The grasping of things becomes more accurate, and he can pick up smaller objects. In time he raises himself, and begins to crawl, exploring the world, and before you know it he takes his first steps, unsteadily balancing his body on his legs, grasping any object around him for stability. In time language progresses in words and sentences the rest of the world can also understand.

Please try to imagine what a tremendous impact abnormal limbs and/or an abnormal face have on the aforementioned events. Initially, parents are often devastated. ‘Why did this happen to us?’ ‘Did we do something wrong?’ ‘Is it our fault?’ ‘What can be done about this?’ ‘What about future children?’ Family and friends are similarly shocked by the appearance of the newborn. Each year, parents of about 700 Dutch newborns will experience having a child with a congenital anomaly of the upper limb or with a common oral cleft[1,2]. Children with a congenital anomaly of the upper limb and/or face have a different childhood than children with normal limbs and faces. They become regular visitors of the hospital, often having multiple surgical procedures before school age, and they are extensively counseled by various physicians. In the Netherlands, children with these congenital anomalies are mostly referred to a specialised multidisciplinary team within a few months after birth. In case of congenital anomalies of the upper limb, such a team ideally consists of representatives of hand surgery, hand therapy, rehabilitation medicine, and clinical genetics. Patients with common oral clefts are regularly seen by cleft palate teams, ideally consisting of the following members; a plastic surgeon, a craniomaxillofacial surgeon, an orthodontist, a prosthodontist, an ENT specialist, clinical geneticist, and speech therapist. Both teams consult various specialists when needed, such as a psychologist, a social worker, or a paediatrician. Furthermore, other dilemmas should be solved, like ‘What is the etiology?’ ‘Is it an isolated anomaly?’ The questions raised by the parents should be adequately addressed by the treating physicians.

Only the results of developmental derailments can be observed in a child, and not the derailments themselves, because the morphological changes occurred during embryogenesis and foetal development. Therefore, the physician should be able to translate the observed abnormalities into the preceding developmental mechanisms. In order to allow this interpretation, normal development of the upper limbs and of the face, i.e., the primary and secondary palates, is briefly discussed.

Normal development

Development of any tissue or organ, including limbs and face shares basic principles. Forming a tissue or an organ requires cell proliferation thereby gaining volume. To provide a tissue with its future shape and function, cells differentiate and cells die as well. Differentiation means that a cell gets a more specialized function. An undifferentiated cell, i.e., a stem cell, which is able to become many cell types, loses this potential, and is bound to become a specific cell type. Specific genes are switched on and off, thereby determining cell fate. Which genes are activated or repressed largely depends on their environment. Besides mitosis, abundant cells die. When a cell receives a signal to die, a 'death' cascade is initiated. Several cascades exist in each cell, and the choice of the cascade appears to be dependent on the trigger of death and/or on the cell type[3]. Subsequently, the cell maintains its plasma membrane integrity, the cytoplasm shrinks, and the nucleus condensates and becomes pyknotic. These dead or apoptotic cells are removed by phagocytosis of neighbouring cells or specialized phagocytes[4,5]. One of the signals by which apoptotic cells are recognized and subsequently removed is exposure of a phospholipid at the outer leaflet of the plasma membrane[6-8]. The positional information of a cell at a certain time during development is considered to be the most important factor for proliferation, differentiation, and death. These cell biological processes are tightly regulated in time and space and orchestrate the enormous morphological changes in a developing limb and face. Basic limb and facial development occurs between 4 weeks and 12 weeks of development.

Upper limb

Forelimbs emerge from the lateral body wall at 4 weeks. The lower limbs develop slightly later than the upper limbs, and most factors controlling their morphogenesis are identical. This accounts for the often striking resemblance in phenotypes of the affected upper

and lower limbs, of which the lower limbs often exhibit a more severe phenotype. Limb development is usually described using three spatial axes, the proximo-distal axis, the antero-posterior axis, and the dorso-ventral axis. On the border between the dorsal and ventral surfaces of the limb, a ridge of specialized ectoderm is formed, i.e. the apical ectodermal ridge (AER). The AER is induced by factors secreted by the underlying mesoderm, which is called the progress zone. The AER is considered to be essential for outgrowth in the proximo-distal axis[9-11]. As the outgrowth continues, cells that are located proximally leave the progress zone. Cells in the future upper arm get their positional information earlier than cells in the forearm, and subsequently differentiation of proximal structures precedes distal structures. The forearm and hand plate are shaped by a balance in cell proliferation and apoptosis at the lateral borders of the developing limb, i.e. preaxial (thumb side) and postaxial (little finger side)[12,13]. Cells differentiate into preaxial or postaxial cells influenced by the zone of polarizing activity (ZPA), a specific group of cells, which resides at the postaxial border. Cell fate is determined by a decreasing gradient of morphogen from postaxial to preaxial[14]. The ZPA is considered to be one of the key players in the antero-posterior axis[14,15]. The last axis, the dorso-ventral axis, determines cell fate at the palmar and dorsal side[16]. If positional information is changed by absence of expression of protein that normally resides at the dorsal side, the dorsal side becomes ventral[17,18]. Though these three axes are often considered separately, these axes influence each other[15,18,19], and limbs develop in a true three-dimensional way.

Digital rays become visible at 7 weeks. The elbow joint is formed by apoptosis between upper arm and forearm. The mesodermal anlage of the forearm is divided into the future radius and ulna by apoptosis[12,13,20]. Fingers are formed by interdigital apoptosis, as are the joints in the wrist and fingers. Formation of skeletal elements involves three differentiation steps. Mesoderm differentiates into precartilaginous condensed mesoderm, which turns into cartilage, and finally into bone[23]. Precartilaginous mesoderm formation starts at 4.5 weeks, and chondrification at 5.5 weeks in a proximo-distal direction with a gradient from the preaxial to the postaxial side. Chondrification is completed by week 6. Ossification starts at 6 weeks and finishes postnatally. The direction of the definitive differentiation in bone centers is as follows: humerus, radius, ulna, scapula, metacarpals, distal phalanges, proximal phalanges, and middle phalanges. Finally the smaller carpals start to ossify[24]. Nails are formed during the first stages of the ossification of the distal phalanges. Differentiation of muscle starts with the formation of cartilage and ossification.

Face

The development of the face is mainly characterized by the embryogenesis of the primary and secondary palates. Normal embryonic development of the primary palate (lip and alveolus) can be divided into early and late embryonic development, i.e., 4-7 weeks of development and 7-12 weeks of development, respectively[25,26]. The secondary palate (hard and soft palate) develops in the late embryonic period (7-12 weeks of development). During early development, the primary palate is formed in an occipito-frontal direction by fusion of three outgrowing facial swellings around the left and right nasal placode, thereby transforming this placode via nasal groove into nasal tube. The maxillary process (occipitally) and subsequently the lateral nasal process (frontally) adhere and fuse with the medial nasal process[25,27]. Therefore, the nasal apertura is always surrounded by the lateral and medial nasal processes. During fusion, the ectoderm covering the mesenchymal cores of the swellings at the fusion side is enclosed, and an epithelial plate results (from occipital to frontal). This epithelial plate disappears by apoptosis, epitheliomesenchymal transformation (EMT), or cell migration[28-30], and vanishes last beneath the nostril. When late development starts, fusion of the mesenchymal cores of the facial swellings is complete. Subsequently, the primary palate differentiates by outgrowth of the lip and alveolus in a caudal direction. Furthermore, a left and right bone center of the maxilla develops, as well as two bone centers in each premaxilla[25,26]. These bone centers approach each other and fuse without forming sutures, except between the two premaxillae (the intermaxillary suture). Bony differentiation is accompanied by the development of facial musculature.

During the development of the secondary palate, the palatine processes grow out, elevate, adhere and fuse bilaterally with the primary palate, and then in the midline in a fronto-occipital direction[31,32]. They fuse with each other and with the nasal septum. Again ectoderm is enclosed during the fusion process, resulting in a Y shaped epithelial plate. Subsequently, this plate disappears by apoptosis, EMT, and migration of epithelial cells towards the nasal side of the plate[31,33-42]. The palatine bones develop bilaterally within the mesenchyme of the outgrowing palatine processes, from one bone center each. During the fusion process, they near each other and the bone centers of the maxilla and premaxillae, forming the median and transverse palatine sutures, and bilaterally the incisive sutures. Bony differentiation is accompanied by muscular differentiation. Briefly summarised: the primary palate fuses in an occipito-frontal direction, and the secondary palate fuses in a fronto-occipital direction.

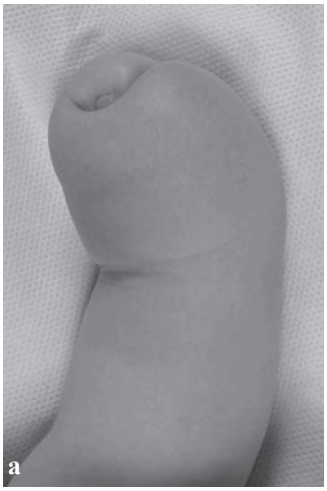
Interpretation of anomalies

Regardless whether anomalies originate from genetic and/or environmental factors, disturbances in the timing and amount of cell proliferation, cell differentiation, and cell death appear to be key players. The following examples show relatively clear consequences of derailments in cell proliferation, cell differentiation, and cell death. However, in more complex anomalies the relationships are often less clear.

Upper limb

Disruption of the AER results in transverse reduction defects (Figure 1a). The earlier the AER is disrupted, the more proximal structures fail to develop[43]. For example, a transverse reduction defect at the level of the wrist is considered to originate later than a reduction at the level of the humerus. Diminished cell death at preaxial and postaxial sites may lead to polydactyly (Figures 1c and d). Separation of the precartilaginous mesodermal condensations can be disturbed by a decrease in apoptosis. This would give rise to transverse synostosis[44]. Increased cell death may result in (partial) loss of the mesodermal models and thereby cause absent or malformed bones. Abnormal chondrification and/or ossification will also lead to absent or malformed bone(s). If the radius is hypoplastic or absent, i.e. radial longitudinal deficiency, it is reasonable to think that a combination of too much apoptosis and subsequent diminished differentiation has led to the phenotype (Figures 1e and f)[45]. If cell death is diminished in interdigital regions, (soft tissue) syndactyly results (Figure 1. Total absence of interdigital apoptosis leads to complete syndactyly (Figure 1b)[21,46]. Incomplete syndactyly located distally, proximally or in the middle, can be explained by focal lack of cell death. Decreased cell death during joint formation may result in longitudinal synostosis of phalanges of the same finger (symphalangism).

Considering formation of skeletal elements, derailments in all differentiation steps can occur. Lack of ossification of phalanges may result in finger buds. Hypoplastic middle phalanges and normal proximal and distal phalanges (brachydactyly) may be explained by defective ossification of the middle phalanges, whereas the other phalanges have already ossified. As ossification of the distal phalanx is accompanied by nail formation, the presence of a nail indicates that the distal phalanx has been formed.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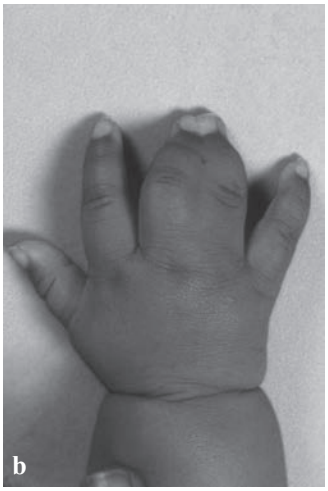
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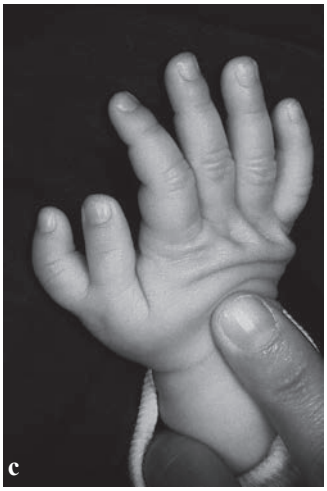
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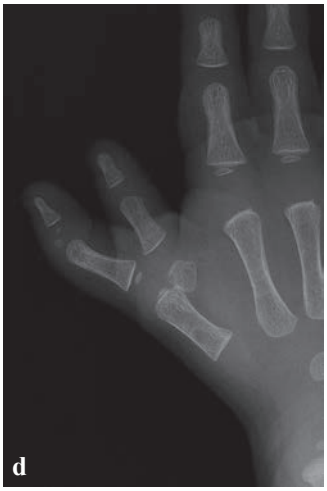
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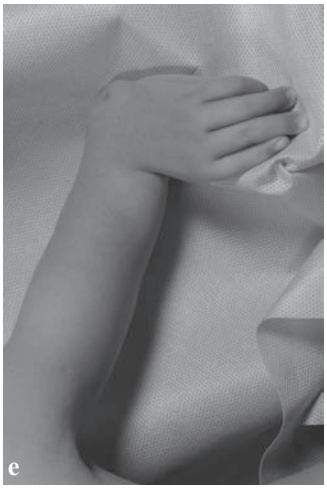
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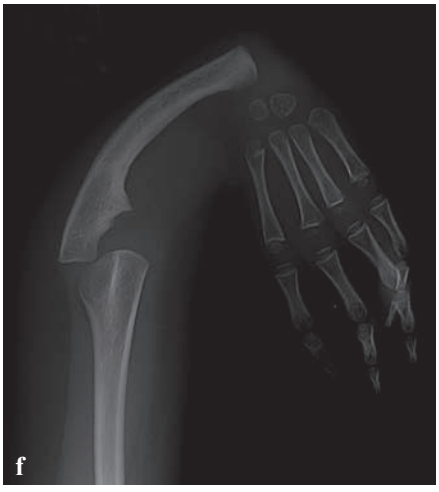
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Figure 1 (previous page)
a. Transverse reduction defect of the forearm.
b. Complete syndactyly. On X-ray no osseous involvement was seen (not shown).
c. Radial polydactyly.
d. The X-ray of c. with a clearly visible duplicated proximal and distal phalanx.
e. Radial longitudinal deficiency with absence of the thumb.
f. The radius is missing, as well as the whole first ray (same patient as e.).

Face

The various types of common oral clefts, i.e., clefts of the primary and secondary palate, can be explained as follows. If there is no fusion of the facial swellings at all, a complete cleft of lip and alveolar arch, and complete cleft of hard and soft palate emerges (Figure 2). If fusion stops at a certain place along the fusion lines, then the primary palate always gives rise to a complete cleft lip combined with an intact alveolar arch, or a partial (incomplete) cleft of the alveolar arch. The secondary palate shows either an intact hard palate and complete or incomplete cleft of the soft palate, or incomplete cleft of the hard palate and complete cleft of the soft palate (Figure 3).

An incomplete cleft lip always shows a tissue bridge beneath the nostril[26]. This implies that the facial swellings have been fused during early development. Therefore, an incomplete cleft lip results from incomplete caudal outgrowth of the lip during late development. This cleft can be accompanied by a normal alveolar arch, an incomplete cleft of the alveolar arch, a notch in the arch or a hypoplastic arch, or a submucous cleft of the alveolar arch (Figure 4). The abnormalities of the alveolar arch are the result from insufficient outgrowth of the premaxillary bone centers. Differentiation defects of the secondary palate concern a palatine bone that is absent, or has the wrong shape or is undersized, a submucous cleft, and/or aplastic or hypoplastic musculature.

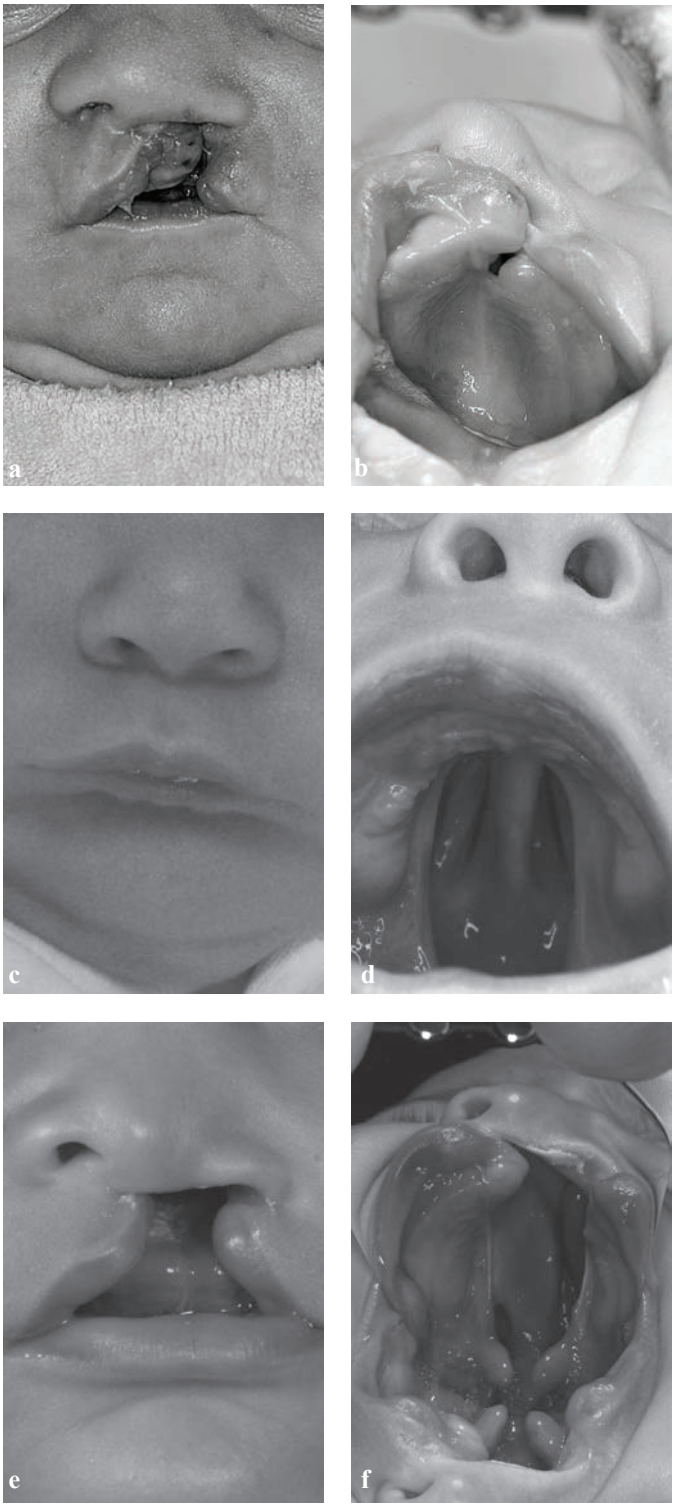

Figure 2
a. and b. Complete cleft of the lip and alveolus with an intact hard and soft palate.
c. and d. Complete cleft of the hard and soft palate with an intact lip and alveolus.
e. and f. Complete cleft of lip, alveolus, hard and soft palate on the left side.

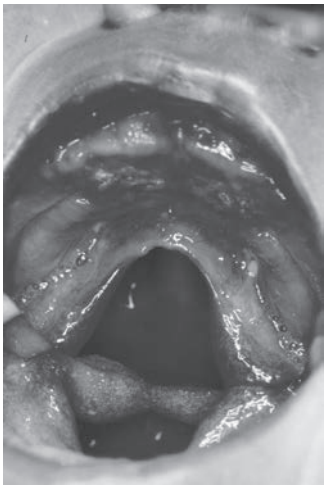

Figure 3
Incomplete cleft of the hard palate, and a complete cleft of the soft palate.

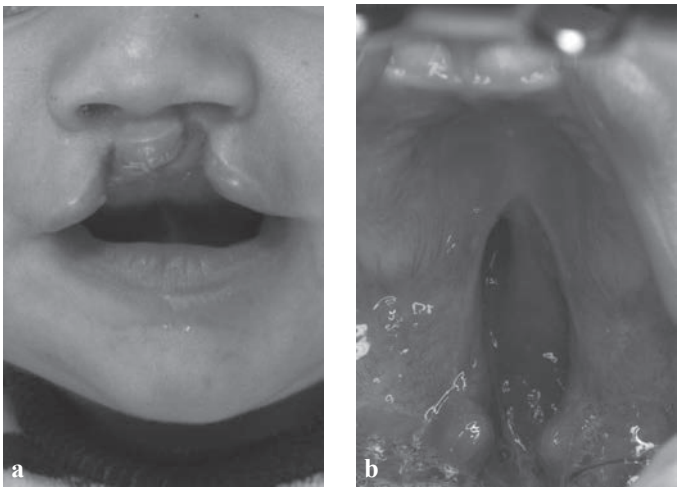

Figure 4
Bilateral incomplete cleft of the lip and alveolus (a), combined with an incomplete cleft of the hard and soft palate (b).

Outline

As said before, only the results of developmental derailments can be observed in a child, and not the derailments themselves. As a consequence, the explanation of the observed anomaly is an interpretation of what could have happened during embryogenesis or foetal development. Up till now, the enormous variability in appearance of the anomalies is categorized into classifications. Different types of anomalies that bear resemblance to each other are grouped. Most of the classifications are based on a presumed pathogenesis, and are thus interpretations of the anomalies. If, for any reason, a different explanation is proposed for the anomaly, the classification will not be sufficient anymore. This thesis will show that it is more appropriate to take one step before grouping anomalies into a classification. That step involves a proper description of the anomaly. The anatomical parts that form the anomaly should be thoroughly distinguished and recorded. Subsequently, these proper descriptions should serve as the basis of a classification. Therefore, this thesis will focus on recording and classification problems of congenital anomalies of the upper limb and of common oral clefts, and will introduce a new approach for both.

This thesis is divided into two parts. Chapters 2 and 3 embrace congenital anomalies of the upper limb, and chapters 4-7 report on recording and classification of common oral clefts. **Chapter 2** reports general problems with classifying congenital anomalies of the upper limb. **Chapter 3** presents a new recording system that describes each individual abnormality that make the congenital anomaly of the upper limb. **Chapter 4** presents a new recording system for common oral clefts in the same way as chapter 3 does for the upper limb. **Chapters 5** and **6** show the results of validating this new recording system. **Chapter 7** report a new classification system that reckons with the derailments of developmental mechanisms that ultimately lead to the different sub-phenotypes of common oral clefts. **Chapter 8** summarizes the results and will discuss directions for future clinical and fundamental research.

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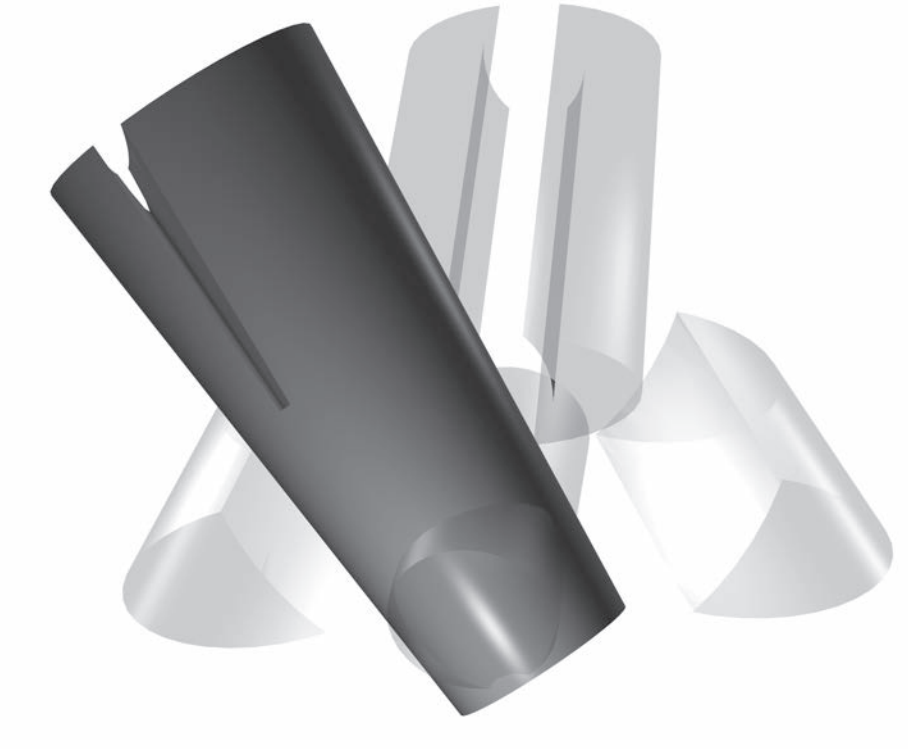
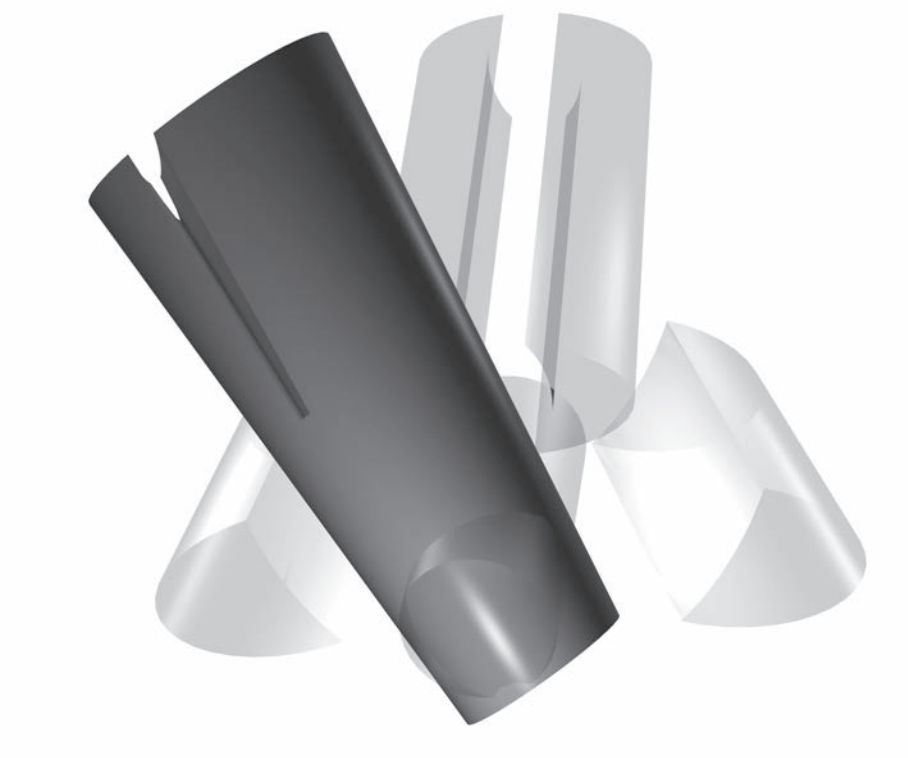
HANDS



CLASSIFICATION OF CONGENITAL ANOMALIES OF THE UPPER LIMB



AJM Luijsterburg, MA van Huizum, BE Impelmans, E Hoogeveen, C Vermeij-Keers, SER Hovius. Journal of Hand Surgery, British and European Volume. 2000, 25: 3-7. Updated.

SUMMARY

Six hundred and ninety-four patients with 993 anomalies of the upper limbs were classified according to the classification of Swanson et al[1]. The data from these patients were compared with previous studies, and similar discrepancies were found. One explanation for these discrepancies is a lack of uniformity in the classification of Swanson et al., which may be caused by out-dated knowledge of the pathogenesis of congenital limb anomalies. Therefore, it seems necessary to describe the anomalies instead of the diagnoses. A descriptive method is being validated in our outpatient department that records all anomalies of the upper limb.

INTRODUCTION

Congenital anomalies of the upper limb are relatively common. About 16 out of 10000 children are born with such an anomaly each year[2]. Because of the great variability in congenital anomalies of upper limb, accurate classification is of paramount importance to allow the pathogenesis to be studied. Several methods of classification have been developed[1-5]. The classification of Swanson et al[1] has been accepted by the American Society for Surgery of the Hand and the International Federation of Societies for Surgery of the Hand, and has been widely used. It was based on two parameters: embryonic failure during development and clinical diagnosis. It divides congenital anomalies of the upper limb into seven categories.

Several authors have previously studied the occurrence of congenital anomalies of the upper limb using the classification of Swanson et al[2, 6-9]. The present study describes the occurrence of these deficiencies in our department from 1972 to 1996 using the same classification and the problems of this classification are discussed.

PATIENTS AND METHODS

Between 1972 and 1996, 694 patients were referred to our department for assessment of a congenital upper limb deficiency. After a retrospective review of the medical records, all abnormal limbs were classified according to the classification of Swanson et al[1] (Table 1). Two hundred and ninety-nine patients had bilateral limb involvement, resulting in a total of 993 upper limb anomalies. Each limb was classified in one group with respect to the most important anomaly, as recommended by Swanson et al[1].

Table 1 Classification of the abnormal limbs in our series according to Swanson.

Main category		number of abnormal limbs	%
I	failure of formation of parts	225	22.7
II	failure of differentiation or separation of parts	431	43.4
III	duplication	209	21.0
IV	overgrowth	6	0.6
V	undergrowth	77	7.8
VI	congenital constriction band syndrome	37	3.7
VII	generalized skeletal abnormalities	9	0.8
Total		993	100.0

RESULTS

The frequencies of the most common diagnoses are listed in Table 2. A syndrome diagnosis was established in 104 cases (Table 3). Classification according to Swanson was often difficult when patients displayed more complex anomalies. This can be demonstrated by the following two cases.

Case 1

A female patient was first referred aged 9 years with bilateral type I radial deficiencies[10] and bilateral triphalangeal thumbs (Fig 1). These anomalies fitted into two different categories. Category I, subgroup B includes the radial deficiencies, and the triphalangeal

Table 2 Frequency of the most common diagnoses of the abnormal limbs.

Diagnosis	number of patients	%
radial polydactyly	139	14.0
syndactyly	126	12.7
synostosis	106	10.7
radial deficiency	85	8.6
cleft hand	72	7.3
brachydactyly/brachysyndactyly	68	6.8
ulnar polydactyly	66	6.6
camptodactyly	57	5.7

Table 3 Frequency of the most common syndromes.

Syndrome	number of patients
Apert	29
Poland	15
VACTERL*	12
FFU+	7

* vertebral abnormalities, anal atresia, cardiac abnormalities, tracheoesophagal fistula, oesophagal atresia, renal defects, radial dysplasia, lower limb abnormality; + femur fibula ulna complex.

thumbs fit into category III, subgroup 5. Since Swanson et al[1] allowed the choice of only one category, the triphalangeal thumbs were selected as the most important anomaly, and consequently the radial deficiencies were ignored.

Case 2

A 2-year-old boy was referred with a four-fingered left hand (Fig. 2a). The most radial digit was biphalangeal, and the second most radial digit was triphalangeal with a small malformed medial phalanx and a bifid distal phalanx. Both metacarpals were malformed and fused (Fig. 2b). Both ulnar metacarpals were stubby. This complex anomaly could be placed into category II, subgroup B because of the fused metacarpals, or into category I, subgroup B because of the absence of one ray, or into category III if the bifid distal phalanx were regarded as the most important anomaly. Arbitrarily, the fused metacarpals were selected, and therefore the malformation was classed in category II, subgroup B.

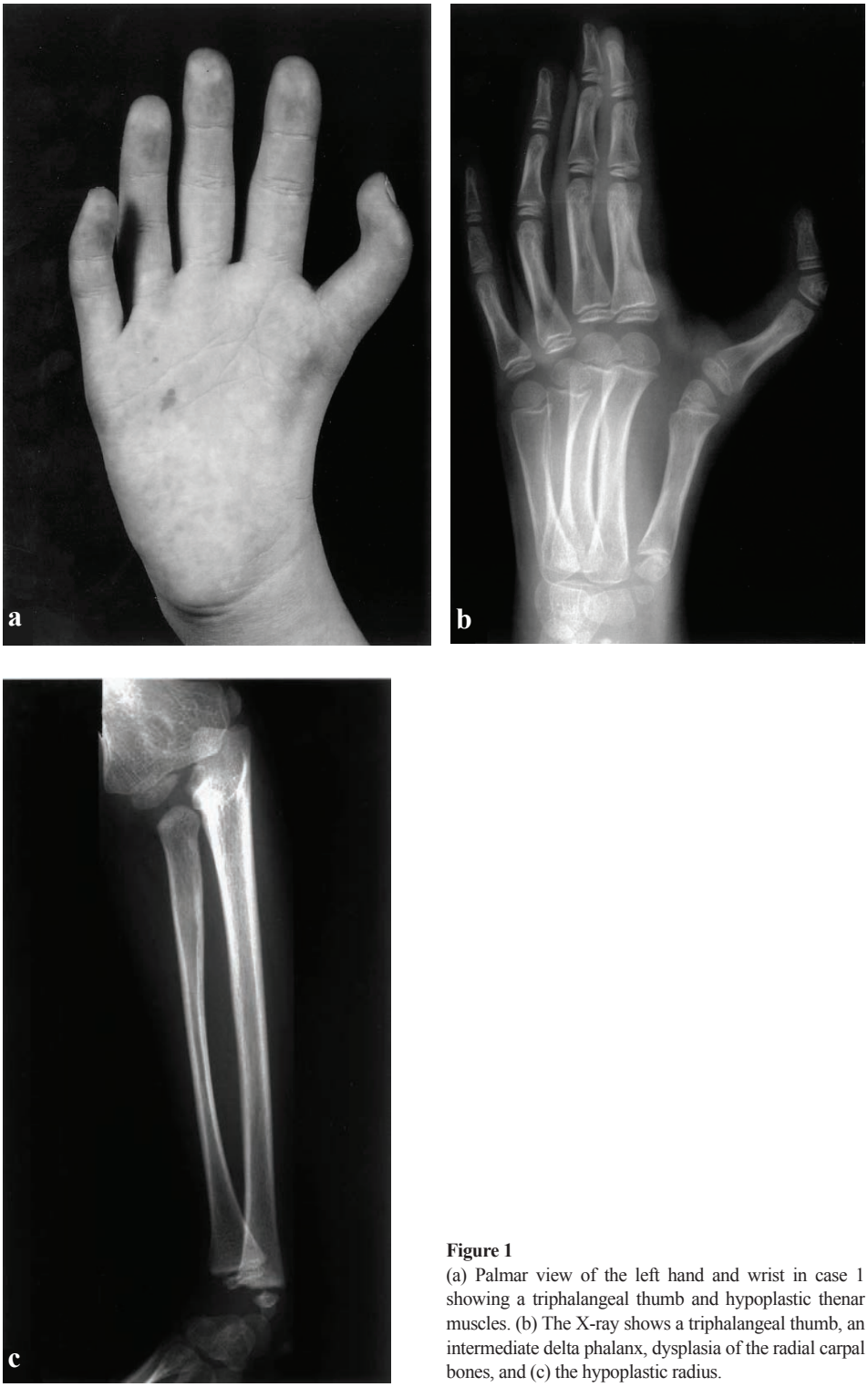


Figure 1
(a) Palmar view of the left hand and wrist in case 1 showing a triphalangeal thumb and hypoplastic thenar muscles. (b) The X-ray shows a triphalangeal thumb, an intermediate delta phalanx, dysplasia of the radial carpal bones, and (c) the hypoplastic radius.

DISCUSSION

This study reports the occurrence of congenital anomalies of the upper limb between 1972 and 1996 in our clinic. Interestingly, the number of patients each year has increased about 2 fold since the establishment of multidisciplinary consultations in 1989 (data not shown). This team consists of representatives from the departments of plastic surgery, clinical genetics, and rehabilitation medicine and hand therapy.

Previous studies have also used Swanson's classification[2, 6-9]. The most common diagnoses of these studies are listed in Table 4. The reports can be divided into European series (this report; by De Smet et al[7], and by Ekblom[11]), American series[2], Japanese series[9], and Chinese series[6, 8]. Our series is essentially similar to the Belgian series of De Smet et al[7]. The highest frequency of polydactyly is reported from China, and the European and Japanese series report a higher frequency than the American series. The high frequency of syndactyly and synostosis in our series is similar to other Western series. The European

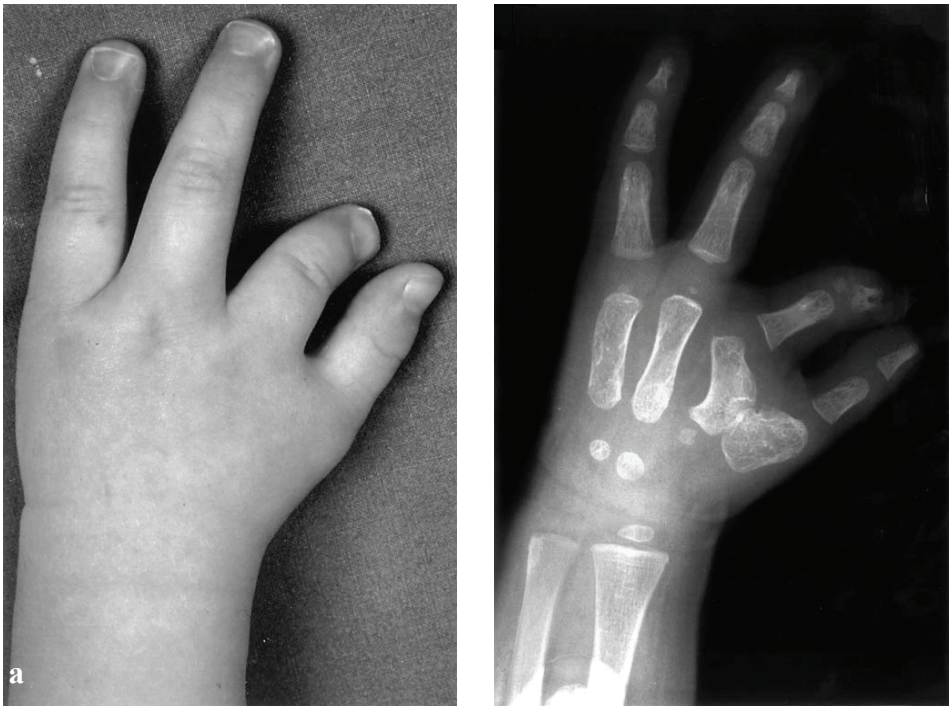


Figure 2
(a) Dorsal view of the left hand and distal forearm of case 2 showing a four-fingered hand. (b) X-ray shows malformed and fused metacarpals. The second most radial digit shows a malformed medial phalanx and a bifid distal phalanx. The ulnar metacarpals are stubby.

series report radial deficiency as a relatively common diagnosis. These discrepancies in frequencies may be due to variations among racial groups, different patient referral patterns, and lack of uniform classification[6].

The anomalies in a limb can often be placed into two or more different categories, as illustrated by the presented cases and by previous reports[2, 6, 7, 9]. Some authors have proposed modifications of the classification of Swanson et al[1] thereby claiming a more consistent approach. Leung et al[8] and De Smet et al[7] allowed the choice of more than one category for each abnormal limb, or added diagnoses that were not included in the original report of Swanson et al[1]. These modifications do not solve the problem that anomalies in a limb may fit into different categories. For example, a relationship has been demonstrated between polydactyly, syndactyly and typical cleft hand[12], and between brachysyndactyly, symbrachydactyly, and transverse deficiency[9, 13, 14]. These overlapping diagnoses are currently placed into different categories, and prevent consistency.

It is possible that the lack of a consistent classification is a result of out-dated knowledge of pathogenesis of congenital limb anomalies. In the last decade immense progress has been made concerning embryonic limb development, and several developmental mechanisms have been elucidated, such as the role of programmed cell death, and the roles of numerous genes. This progress will continue, and as a result our knowledge about the pathogenesis of congenital limb anomalies will improve. To overcome the difficulties inherent in other classifications, a descriptive method has been developed in our clinic. To prevent the record of each anomaly becoming out-dated by progress in knowledge about limb development, only individual aberrations are recorded and the anomalies are not categorized by diagnosis. After recording all anomalies, a new classification can be proposed, linked to the most recent insights in embryonic limb development. When these insights change, the classification can be adjusted without losing details about the anomalies. A prospective study is in progress to validate this descriptive method.

ACKNOWLEDGEMENTS

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Table 4 List of the most common diagnoses in previous studies

Leung et al. (1982): 326 patients, 396 limbs	**%**
polydactyly	39.9
syndactyly	14.9
syndromes	11.9
transverse arrest	6.8
trigger digits	6.3
Ogino et al. (1986): 943 patients, 955 hands	%
trigger finger	21.0
polydactyly	18.3
camptodactyly	6.5
clasped thumb	5.5
constriction band syndrome	4.8
Cheng et al. (1987): 578 patients, 728 limbs	%
radial polydactyly	32.8
syndactyly	11.1
generalized skeletal abnormalities	9.3
trigger finger	8.8
constriction band syndrome	6.6
Flatt (1994): ? patients, 2758 limbs	%
syndactyly	18.2
camptodactyly	6.9
transverse arrest	6.8
radial polydactyly	6.7
ulnar polydactyly	5.1
De Smet et al. (1997): 650 patients, 925 limbs	%
syndactyly	16.6
radial polydactyly	14.1
camptodactyly	7.9
synostosis	7.7
radial deficiency	6.8
Eklamp et al (2010): 562 patients, 815 limbs	
syndactyly	36.8
ulnar polydactyly	17.4
trigger digit	16.7
radial polydactyly	8.3
camptodactyly	7.1

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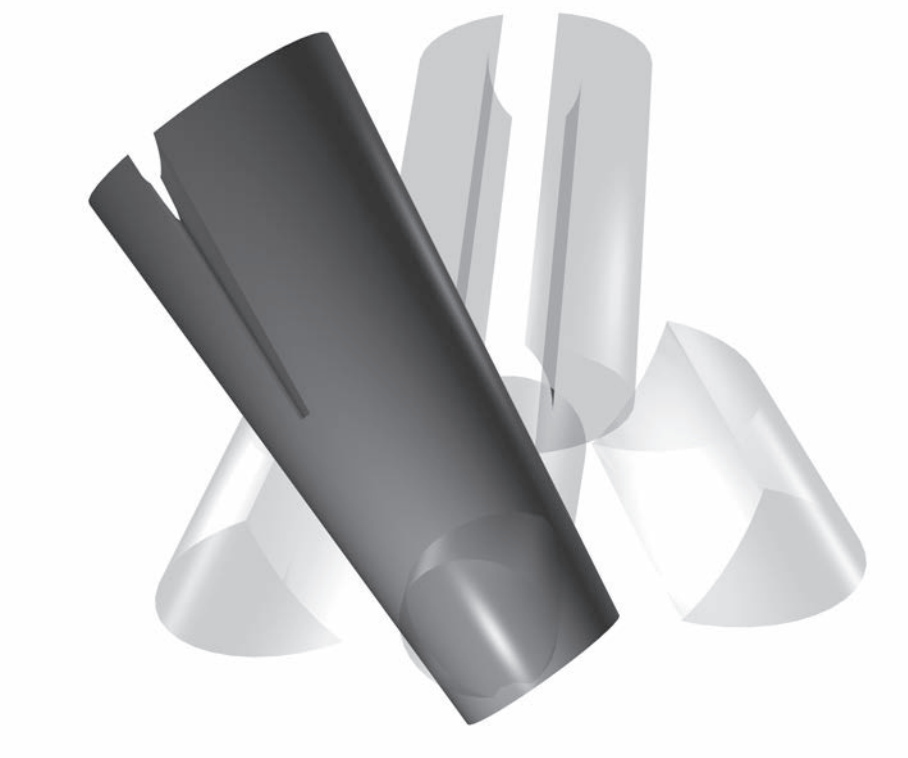
RECORDING CONGENITAL DIFFERENCES OF THE UPPER LIMB



AJM Luijsterburg, GJ Sonneveld, C Vermeij-Keers, SER Hovius. Journal of Hand Surgery, British and European Volume. 2003, 28: 205-214. Updated.

SUMMARY

Consistent classification of congenital differences of the upper limb is of paramount importance for the study of the pathogenesis. To overcome the inconsistencies of present classifications, a non-classifying recording method has been developed. This method records individual aberrations, including bone and soft-tissue defects. Between 1996 and 1998, a prospective study was performed to validate the method. Two hundred and thirty-one patients with upper limb differences were assessed, and all individual aberrations were recorded. These data can be transferred to any classification. It is concluded that the presented method will allow consistent grouping of patients without losing details about simple and complex differences.

INTRODUCTION

Congenital differences of the upper limb have been of interest for many years. Numerous papers and books describe their pathogenesis[1-19]. Consistent categorization of patients with regard to type of limb difference is of paramount importance to the study of pathogenesis. Therefore, several classifications have been developed[20-27]. The most frequently used classification, that of Swanson et al.[25], is based on embryonic failure during development and clinical diagnosis. Several authors have discussed the consistency of this classification[28-31]. In the last decade, immense progress has been made concerning embryonic limb development. Hence, the lack of consistency of the present classification schemes may be a result of out-dated knowledge of the pathogenesis of congenital limb differences[30, 32]. New insights into limb development will continue to improve our knowledge[33]. Thus, in order to prevent the difficulties inherent to the present classifications, we decided to describe the individual aberrations of the differences, using a descriptive method that has been developed in our clinic. This allows transfer of data to existing classifications.

PATIENTS AND METHODS

Between 1996 and 1998, 231 un-operated patients were referred to our clinic for assessment of a congenital upper limb difference. During their first visit, roentgenograms and photographs were taken, and after careful examination in a multidisciplinary setting, all patients were registered using the new recording form (Appendices 1 and 2). This form is based on morphology and topography. All aberrations of each bone are described. Bones can be absent, have the wrong shape (malformed), have the appropriate configuration but be too small (hypoplasia) or too large (hyperplasia), or be fused (synostosis). Non-separation of digits without bone involvement is called syndactyly. Bones may also be duplicated (polydactyly/duplication). Deviation of fingers in the radioulnar or dorsoventral plane is called clinodactyly or camptodactyly, respectively. Annular ring constrictions, as present in the congenital ring constriction syndrome, are described as well as tumours. Furthermore, trigger fingers are described as a separate category. Flexion and extension may be limited, without bony aetiology. Also, nails are described by their absence, abnormal shape, size (under-or oversized), their fusion, and their duplication.

Topography concerns all bone structures, in a proximodistal direction, from humerus to distal phalanx, and in a radioulnar way, from the thumb to the little finger. Combining these features in a two-dimensional table (Appendix 1), it should be possible to describe every combination of aberrations of the upper limb which contributes to the congenital difference. If an aberration does not fit in this table, a description can be given in the box ‘‘other aberrations of the upper limb, not appropriate above’’.

In order to provide information about the history of the patient and his or her family, a ‘‘general’’ section and a section concerning ‘‘other differences’’ are included.

All recorded differences were then transferred to the categories of the Swanson’s classification[25]. As recommended by Swanson et al.[25], the most important aberration of the difference was chosen to categorize. To demonstrate that this approach results in loss of valuable information, each difference was also transferred with respect to any detected aberration, other than the most ‘‘important’’ one, to Swanson’s classification[25].

RESULTS

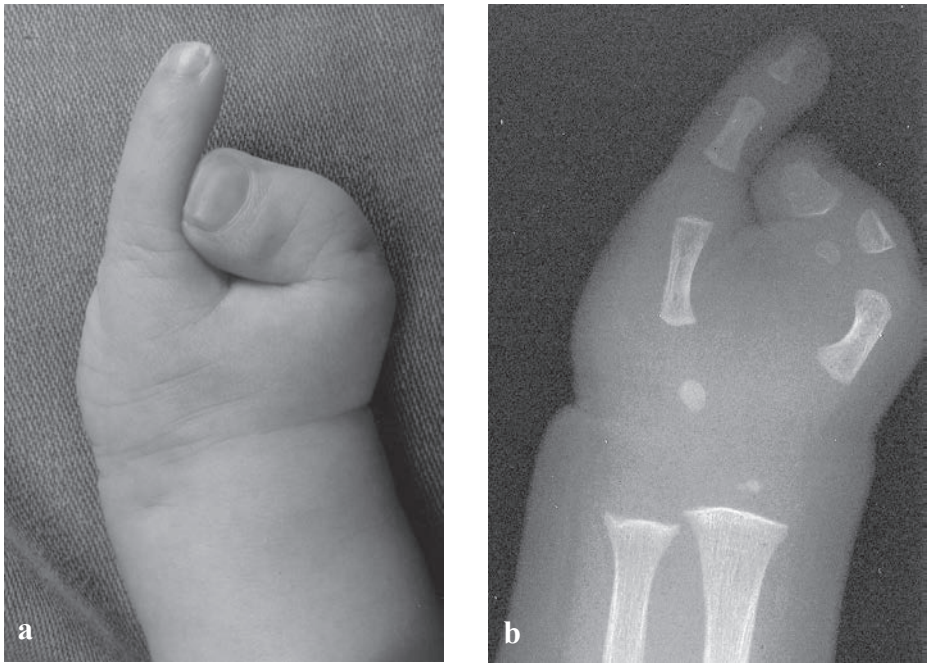
One hundred and forty patients were boys and 91 were girls. Ninety-nine patients displayed bilateral involvement, resulting in 330 abnormal limbs. The mean age at first visit was 4.6 years (range, 0.5 months–18.1 years) Occurrence among relatives was present in 15%. The mean gestational age was 39 (range, 28–42) weeks, and the mean birth weight was 3.2 (range, 0.8–4.6) kg. Congenital differences of other parts of the body were present in 22%, with differences in the lower limbs being the most frequent (12%). A syndrome diagnosis was established in 31 patients (13%). All individual aberrations could be recorded using the two-dimensional table. To demonstrate this, four patients are described.

Case 1

Case 1 was a 4-month-old boy with a congenital difference of the left arm (Figure 1). There was a duplication of P1, and a malformed P1 and P3 of the radial ray as well as a clinodactyly of the metacarpophalangeal joint. The distal phalanx in the thumb is recorded as P3 in order to allow registration of P1, P2 and P3 in a triphalangeal thumb. This ray also displayed a hyperplastic nail. Rays 2, 3 and 4 were totally absent as well as their nails. It was assumed that the central rays were absent, so the ulnar digit was designated as ray 5. The absent phalanx in digit 5 was designated as P2 because of the presence of the nail, which is related to P3.

Case 2

Case 2 was a 4-month-old boy referred with an affected left arm (Figure 2). Ray 1 displayed a hypoplastic P1 and malformed P3. Rays 2 and 3 showed a malformed P1, while P2 and P3 including the nail were absent. Ray 4 showed no P2, and a hypoplastic P1, P3 and nail. Ray 5 had a malformed P2, and a hypoplastic P1, P3 and nail. Furthermore, (soft-tissue) syndactyly was present between P1 of rays 2 and 3, between P1 of rays 3 and 4 and between P1 of rays 4 and 5, as well as clinodactyly of the fourth metacarpophalangeal and interphalangeal joints and of the fifth distal interphalangeal joint. The fifth distal interphalangeal joint also showed camptodactyly. Clinodactyly and camptodactyly are indicated between two adjacent bones, for example clinodactyly of the fourth ray in this case is recorded between the metacarpal and P1.



c

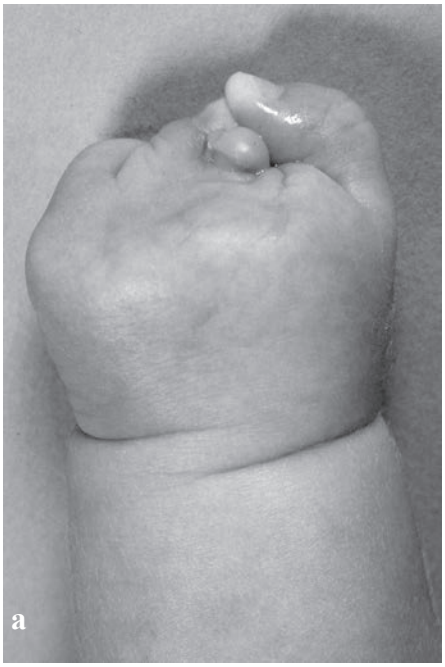
L = left R = right	H*	U*	R*	C*	Ray I MC*	Ray I P1	Ray I P2	Ray I P3	Ray I N*	Ray II MC*	Ray II P1	Ray II P2	Ray II P3	Ray II N*	Ray III MC*	Ray III P1	Ray III P2	Ray III P3	Ray III N*	Ray IV MC*	Ray IV P1	Ray IV P2	Ray IV P3	Ray IV N*	Ray V MC*	Ray V P1	Ray V P2	Ray V P3	Ray V N*	
Absence	L R	L R	L R	L R	L R	L R		L R	L R	X R	X R	X R	X R	X R	X R	X R	X R	X R	X R	X R	X R	X R	X R	X R	L R	L R	X R	L R	L R	Absence
Malformed [1]	L R	L R	L R	L R	L R	X R		X R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	Malformed [1]
Hypoplasia [2]	L R	L R	L R	L R	L R	L R		L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	Hypoplasia [2]
Hyperplasia [3]	L R	L R	L R	L R	L R	L R		L R	X R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	Hyperplasia [3]
Synostosis	L R	L R	L R	L R	L R	L R	L R	L R		L R	L R	L R	L R		L R	L R	L R	L R		L R	L R	L R	L R		L R	L R	L R	L R		Synostosis
Syndactyly / fusion						L R	L R	L R	L R		L R	L R	L R	L R		L R	L R	L R	L R		L R	L R	L R	L R		L R	L R	L R	L R	Syndactyly / fusion
Duplication / polydactyly	L R	L R	L R	L R	L R	X R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	Duplication / polydactyly
Clinodactyly					X R	X R		L R		L R	L R	L R	L R		L R	L R	L R	L R		L R	L R	L R	L R		L R	L R	L R	L R		Clinodactyly
Camptodactyly					L R	L R		L R		L R	L R	L R	L R		L R	L R	L R	L R		L R	L R	L R	L R		L R	L R	L R	L R		Camptodactyly
Ring constriction sec	L R	L R	L R	L R	L R	L R		L R		L R	L R	L R	L R		L R	L R	L R	L R		L R	L R	L R	L R		L R	L R	L R	L R		Ring constriction sec
Tumor	L R	L R	L R	L R	L R	L R		L R		L R	L R	L R	L R		L R	L R	L R	L R		L R	L R	L R	L R		L R	L R	L R	L R		Tumor
Trigger					L R					L R					L R					L R					L R					Trigger
Flexion impairment sec	L R	L R	L R	L R	L R					L R					L R					L R					L R					Flexion impairment sec
Extension impairment sec	L R	L R	L R	L R	L R					L R					L R					L R					L R					Extension impairment sec

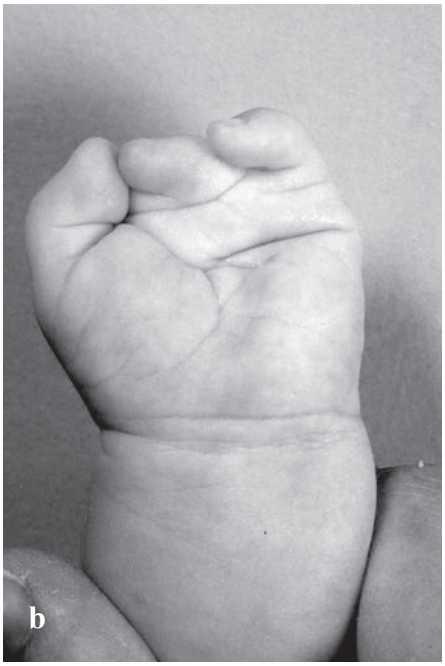
1 = present, wrong shape; appropriate configuration, undersized =2, oversized = 3

* H = humerus; U = ulna; R = radius; C = carpal bones; MC = metacarpal; N = nail

Figure 1

(a) Dorsal view of the left hand and wrist in case showing a hyperplastic radial ray and absence of the central rays. (b) The X-ray shows duplicated P1 of the radial ray with delta phalanx. The central rays are absent, as well as P2 of ray 5. (c) The record displays all aberrations.





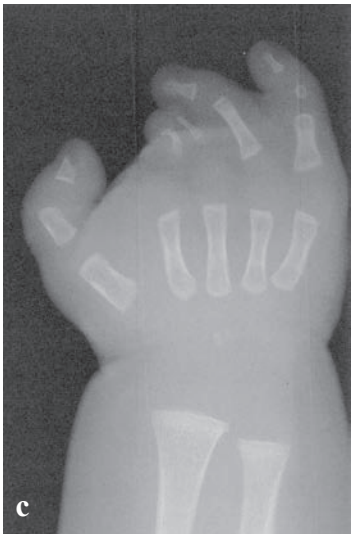


Figure 2
(a and b) Dorsal (a) and palmar (b) views of the left hand and distal forearm of case displaying clinodactyly of the joints of digits 4 and 5, camptodactyly of digit 5, and syndactylies of digits 2, and digits 3, 4. (c) The X-ray exhibits an hypoplastic P1 and malformed P3 of the thumb, absent, malformed, hypoplastic, and syndactylous phalanges of digits 2–5. (d) The record demonstrates that this more complex difference can be described in chart.

d

L = left R = right	H*	U*	R*	C*	Ray I MC * P1 P2 P3 N*	Ray II MC * P1 P2 P3 N*	Ray III MC * P1 P2 P3 N*	Ray IV MC * P1 P2 P3 N*	Ray V MC * P1 P2 P3 N *	
Absence	L R	L R	L R	L R	L R L R L R L R L R	L R L R X R X R L R	L R L R X R X R X R	L R L R X R L R L R	L R L R L R L R L R	Absence
Malformed [1]	L R	L R	L R	L R	L R L R X R L R	L R X R L R L R L R	L R X R L R L R L R	L R L R L R L R L R	L R L R X R L R L R	Malformed [1]
Hypoplasia [2]	L R	L R	L R	L R	L R X R L R L R	L R L R L R L R L R	L R L R L R L R L R	L R X R L R X R X R	L R X R L R X R X R	Hypoplasia [2]
Hyperplasia [3]	L R	L R	L R	L R	L R L R L R L R	L R L R L R L R L R	L R L R L R L R L R	L R L R L R L R L R	L R L R L R L R L R	Hyperplasia [3]
Synostosis	L R	L R	L R	L R	L R L R L R L R	L R L R L R L R	L R L R L R L R	L R L R L R L R	L R L R L R L R	Synostosis
Syndactyly / fusion					L R L R L R L R	X R L R L R L R	X R L R L R L R	X R L R L R L R	X R L R L R L R	Syndactyly / fusion
Duplication / polydactyly	L R	L R	L R	L R	L R L R L R L R L R	L R L R L R L R L R	L R L R L R L R L R	L R L R L R L R L R	L R L R L R L R L R	Duplication / polydactyly
Clinodactyly					L R L R L R	L R L R L R	L R L R L R	X R X R L R X R	L R L R X R X R	Clinodactyly
Camptodactyly					L R L R L R	L R L R L R L R	L R L R L R L R	L R L R L R L R	L R L R X R X R	Camptodactyly
Ring constriction sec	L R	L R	L R	L R	L R L R L R	L R L R L R L R	L R L R L R L R	L R L R L R L R	L R L R L R L R	Ring constriction sec
Tumor	L R	L R	L R	L R	L R L R L R	L R L R L R L R	L R L R L R L R	L R L R L R L R	L R L R L R L R	Tumor
Trigger					L R	L R	L R	L R	L R	Trigger
Flexion impairment sec	L R	L R	L R	L R	L R	L R	L R	L R	L R	Flexion impairment sec
Extension impairment sec	L R	L R	L R	L R	L R	L R	L R	L R	L R	Extension impairment sec

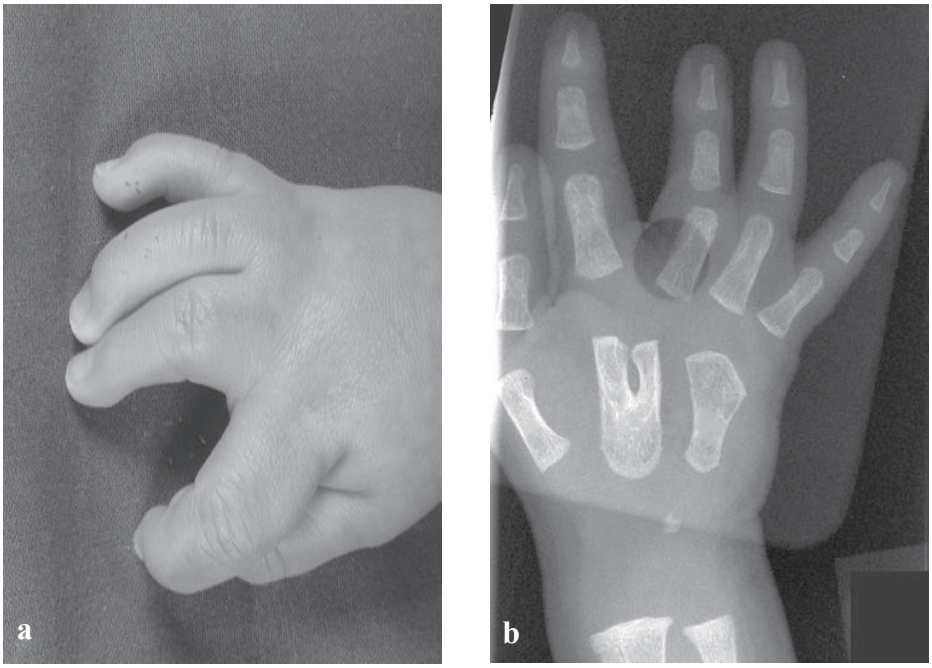
1 = present, wrong shape; appropriate configuration, undersized =2, oversized = 3
* H = humerus; U = ulna; R = radius; C = carpal bones; MC = metacarpal; N = nail

Case 3

A boy was referred at the age of 4 months with synostosis (complex syndactyly) of the second and third metacarpals, and of the fourth and fifth metacarpals of the right hand (Figure 3). The middle phalanx of ray 3 was hypoplastic. In the chart however, the specifics of synostosis between metacarpals 2 and 3 and separate synostosis between metacarpals 4 and 5 cannot be distinguished from synostosis between metacarpals 2 and 5. Furthermore, the metacarpophalangeal joints of rays 3–5 showed clinodactyly.

Case 4

A boy was referred at the age of 3 months with bilateral radial and ulnar synpolydactyly. Only the right arm is described (Figure 4). Firstly, the radial ray was duplicated and consisted of a radial biphalangeal ray and an ulnar triphalangeal ray with camptodactyly. Both rays had nails. In the chart, no distinction can be made between one triphalangeal and one biphalangeal thumb and polydactyly. Secondly, there was clinodactyly and camptodactyly of digits 3 and 4 in the proximal interphalangeal joints. Thirdly, there was

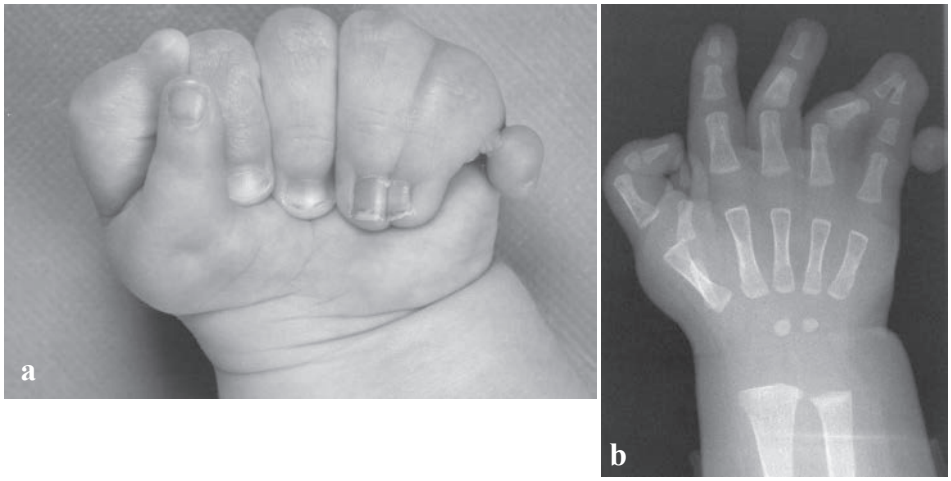


c

L = left R = right	H*	U*	R*	C*	Ray I MC* P1 P2 P3 N*	Ray II MC* P1 P2 P3 N*	Ray III MC* P1 P2 P3 N*	Ray IV MC* P1 P2 P3 N*	Ray V MC* P1 P2 P3 N*	
Absence	L R	L R	L R	L R	L R L R L R L R	L R L R L R L R L R	L R L R L R L R L R	L R L R L R L R L R	L R L R L R L R L R	Absence
Malformed [1]	L R	L R	L R	L R	L R L R L R L R	L R L R L R L R L R	L R L R L R L R L R	L R L R L R L R L R	L R L R L R L R L R	Malformed [1]
Hypoplasia [2]	L R	L R	L R	L R	L R L R L R L R	L R L R L R L R L R	L R L R L X L R	L R L R L R L R L R	L R L R L R L R L R	Hypoplasia [2]
Hyperplasia [3]	L R	L R	L R	L R	L R L R L R L R	L R L R L R L R L R	L R L R L R L R L R	L R L R L R L R L R	L R L R L R L R L R	Hyperplasia [3]
Synostosis	L R	L R	L R	L R	L R L R L R L R	X L R L R L R	X L R X L R	L R L R L R	X L R L R L R	Synostosis
Syndactyly / fusion					L R L R L R L R	L R L R L R L R	L R L R L R L R	L R L R L R L R	L R L R L R L R	Syndactyly / fusion
Duplication / polydactyly	L R	L R	L R	L R	L R L R L R L R	L R L R L R L R L R	L R L R L R L R L R	L R L R L R L R L R	L R L R L R L R L R	Duplication / polydactyly
Clinodactyly					L R L R L R	L R L R L R L R	X X L R L R	X X L R L R	X X L R L R	Clinodactyly
Camptodactyly					L R L R L R	L R L R L R L R	L R L R L R L R	L R L R L R L R	L R L R L R L R	Camptodactyly
Ring constriction sec	L R	L R	L R	L R	L R L R L R	L R L R L R L R	L R L R L R L R	L R L R L R L R	L R L R L R L R	Ring constriction sec
Tumor	L R	L R	L R	L R	L R L R L R	L R L R L R L R	L R L R L R L R	L R L R L R L R	L R L R L R L R	Tumor
Trigger					L R	L R	L R	L R	L R	Trigger
Flexion impairment sec	L R	L R	L R	L R	L R	L R	L R	L R	L R	Flexion impairment sec
Extension impairment sec	L R	L R	L R	L R	L R	L R	L R	L R	L R	Extension impairment sec

1 = present, wrong shape; appropriate configuration, undersized =2, oversized = 3
* H = humerus; U = ulna; R = radius; C = carpal bones; MC = metacarpal; N = nail

Figure 3
(a) Dorsal view of the right hand of case 3 exhibiting a hypoplastic middle finger and clinodactylies. (b) The X-ray shows a partial synostosis of the second and third metacarpals, complete synostosis of the fourth and fifth metacarpals, a hypoplastic P2 of ray 3, and clinodactyly of the metacarpophalangeal joints of rays 3–5. (c) The record of this patient.



c

L = left R = right	H*	U*	R*	C*	Ray I MC*	Ray I P1	Ray I P2	Ray I P3	Ray I N*	Ray II MC*	Ray II P1	Ray II P2	Ray II P3	Ray II N*	Ray III MC*	Ray III P1	Ray III P2	Ray III P3	Ray III N*	Ray IV MC*	Ray IV P1	Ray IV P2	Ray IV P3	Ray IV N*	Ray V MC*	Ray V P1	Ray V P2	Ray V P3	Ray V N*	
Absence	L R	L R	L R	L R	L R	L R		L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	Absence
Malformed [1]	L R	L R	L R	L R	L R	L R		L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	Malformed [1]
Hypoplasia [2]	L R	L R	L R	L R	L R	L R		L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	Hypoplasia [2]
Hyperplasia [3]	L R	L R	L R	L R	L R	L R		L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	Hyperplasia [3]
Synostosis	L R	L R	L R	L R	L R	L R	L R	L R		L R	L R	L R	L R		L R	L R	L R	L R		L R	L R	L R	L X		L R	L R	L X		Synostosis
Syndactyly / fusion						L R	L R	L R	L R		L R	L R	L R	L R		L R	L R	L R	L R		L X	L X	L R	L X		L X	L X	L R	L X	Syndactyly / fusion
Duplication / polydactyly	L R	L R	L R	L R	L X	L X	L X	L X	L X	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L X	L X		Duplication / polydactyly
Clinodactyly					L R	L R		L R		L R	L R	L R	L R		L R	L X	L X	L R		L R	L X	L X	L R		L R	L R	L R	L R		Clinodactyly
Camptodactyly					L R	L X		L X		L R	L R	L R	L R		L R	L X	L X	L R		L R	L X	L X	L R		L R	L R	L R	L R		Camptodactyly
Ring constriction sec	L R	L R	L R	L R	L R	L R		L R		L R	L R	L R	L R		L R	L R	L R	L R		L R	L R	L R	L R		L R	L R	L R	L R		Ring constriction sec
Tumor	L R	L R	L R	L R	L R	L R		L R		L R	L R	L R	L R		L R	L R	L R	L R		L R	L R	L R	L R		L R	L R	L R	L R		Tumor
Trigger					L R					L R					L R					L R					L R					Trigger
Flexion impairment sec	L R	L R	L R	L R	L R					L R					L R					L R					L R					Flexion impairment sec
Extension impairment sec	L R	L R	L R	L R	L R					L R					L R					L R					L R					Extension impairment sec

1 = present, wrong shape; appropriate configuration, undersized =2, oversized = 3

* H = humerus; U = ulna; R = radius; C = carpal bones; MC = metacarpal; N = nail

Figure 4

(a) Palmar view of the right hand and wrist of case 4 showing a duplicated radial ray, syndactyly of digits 4 and 5, and an ulnar polydactyly. (b) The X-ray exhibits a duplicated radial ray with a radial biphalangeal ray and an ulnar triphalangeal ray with camptodactyly, clinodactyly and camptodactyly of the proximal interphalangeal joints of digits 3 and 4, complete syndactyly of digits 4 and 5, and a duplicated P3 of digit 5. (c) The record of this complex hand.

a complete (soft-tissue) syndactyly of P1 and P2 of digits 4 and 5, as well as synostosis of both P3 and fusion of their nails. Finally, P3 of the fifth ray was duplicated as was its nail. To demonstrate that the data can be used to fit any classification, the data were transferred to the original classification of Swanson et al.[25] (Table 1). Each difference was transferred to one category with respect to the most important aberration, as recommended by Swanson et al.[25]. To demonstrate that valuable information was lost by this approach, each difference was transferred to the classification of Swanson et al.[25] with respect to any detected aberration (Table 2).

Table 1 Frequencies of the most important aberration of each limb difference after transfer to one category of the classification of Swanson et al.[25].

Main category		**number of abnormal limbs**	**%**
I	failure of formation of parts	135	40.9
II	failure of differentiation/separation of parts	119	36.1
III	duplication	61	18.5
IV	overgrowth	3	0.9
V	undergrowth	8	2.4
VI	congenital constriction band syndrome	4	1.2
VII	generalized skeletal abnormalities	0	0
Total		330	100

Table 2 Frequencies of all aberrations of each limb difference after transfer to as many categories as necessary to describe the difference according to the classification of Swanson et al.[25].

Main category		**number of abnormal limbs**	**%**
I	failure of formation of parts	159	32.8
II	failure of differentiation/separation of parts	239	49.3
III	duplication	65	13.4
IV	overgrowth	3	0.6
V	undergrowth	15	3.1
VI	congenital constriction band syndrome	4	0.8
VII	generalized skeletal abnormalities	0	0
Total		485	100

DISCUSSION

Consistent grouping of congenital differences of the upper limb is very important for the study of their pathogenesis. Furthermore, intracentre and national and international intercentre studies concerning frequency, treatment and surveillance of these differences require sound descriptions of the differences. Such a system must be straightforward and must give a full description of the differences, including more complex differences. These conditions are conflicting, and concessions have to be made. Previously, the consistency of the most frequently used classification of Swanson et al.[25] has been discussed, and modifications have been suggested[6, 28, 29, 31, 32]. From these reports, it is clear that the proposed modifications improve the Swanson's classification, but they do not provide consistency[30].

Therefore, a recording form was developed in our clinic which allows description of all aberrations forming the differences. In this way, the differences are neither categorized nor classified. In addition, no division is made on diagnosis, because establishing diagnoses interprets the observed aberrations and consequently results in loss of information about the aberrations. Cases 1 and 2 can serve as an example because of their identical diagnosis symbrachydactyly. Our results show that the aberrations of simple and more complex differences could be consistently recorded. After recording, diagnoses could be established, and all differences could be transferred to the classification of Swanson et al.[25] (Table 1). Table 2 clearly shows the gain of information if any detected aberration was transferred instead of the most important aberration. Often these differences had aberrations that were transferred to separate categories and subcategories. This emphasizes the importance of describing the aberrations instead of categorizing the differences.

Every system has its limitations, and the reproducibility of each depends on mutual agreement concerning the rules and regulations for form completion. Our choice was to record all aberrations. However, some specific details cannot be recorded, such as the distinction between synostosis of metacarpals 2, 3 and 4, 5, and metacarpal synostosis 2–5 (case 3), and the distinction between syndactyly of rays 2–5, and syndactyly of rays 2,3 and 4,5 (case 2). In such cases, further descriptions should be written down on the form (item ''other aberrations''). This system also does not record cross bones, the number of epiphyses in delta phalanges, and nerve, vessel and individual tendon aberrations. Therefore, these specific details still have to be written down on the form (item ''other aberrations''). However, descriptions of such specific details may differ between observers.

In most countries, children with congenital differences of the upper limb are treated in a multidisciplinary setting and/or in centres where extensive knowledge about the differences has been accumulated. This recording system has been specifically developed for these settings, and is not intended for use in less specialized hand surgery practices.
In general, this recording system allows consistent description of differences. However, its inter- and intra-observer variability is not known. After recording, each difference can be transferred to any classification. When diagnoses are modified because of new data about the pathogenesis, the same records can be used to implement these modifications. The system also does not lose details about simple and complex differences. It can improve consistency in intra-and intercenter studies concerning the pathogenesis, frequencies, treatment, and surveillance of congenital differences of the upper limb.

Appendix 1 | **Hospital** | Institute of Plastic Surgery | **Please fill in white boxes**

1. GENERAL INFORMATION

Date of this registration _____
Patient identification number _____
Date of birth _____
Gender ◯ Male ◯ Female ◯ Unknown
Name of physician _____
Clinical genetics consulted ◯ Yes ◯ No ◯ Unknown
If affirmative, please specify location _____
Adoption or foster child ◯ Yes ◯ No ◯ Unknown

Caucasian father ◯ Yes ◯ No ◯ Unknown
Caucasian mother ◯ Yes ◯ No ◯ Unknown
Consanguinity ◯ Yes ◯ No ◯ Unknown
If affirmative, please specify _____
Occurrence among relatives ◯ Yes ◯ No ◯ Unknown
If affirmative, please specify _____
Birth weight (grams) _____
Gestational age (weeks) _____
Remarks about pregnancy ◯ Yes ◯ No ◯ Unknown
If affirmative, please specify _____

2. ABERRATIONS OF THE UPPER LIMB

L = left R = right	H*	U*	R*	C*	Ray I MC*	Ray I P1	Ray I P2	Ray I P3	Ray I N*	Ray II MC*	Ray II P1	Ray II P2	Ray II P3	Ray II N*	Ray III MC*	Ray III P1	Ray III P2	Ray III P3	Ray III N*	Ray IV MC*	Ray IV P1	Ray IV P2	Ray IV P3	Ray IV N*	Ray V MC*	Ray V P1	Ray V P2	Ray V P3	Ray V N*	
Absence	L R	L R	L R	L R	L R			L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	Absence
Malformed [1]	L R	L R	L R	L R	L R	L R		L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	Malformed [1]
Hypoplasia [2]	L R	L R	L R	L R	L R	L R		L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	Hypoplasia [2]
Hyperplasia [3]	L R	L R	L R	L R	L R	L R		L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	Hyperplasia [3]
Synostosis	L R	L R	L R	L R	L R	L R	L R	L R		L R	L R	L R	L R		L R	L R	L R	L R		L R	L R	L R	L R		L R	L R	L R	L R		Synostosis
Syndactyly / fusion						L R	L R	L R	L R		L R	L R	L R	L R		L R	L R	L R	L R		L R	L R	L R	L R		L R	L R	L R	L R	Syndactyly / fusion
Duplication / polydactyly	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	Duplication / polydactyly
Clinodactyly					L R	L R		L R		L R	L R	L R	L R		L R	L R	L R	L R		L R	L R	L R	L R		L R	L R	L R	L R		Clinodactyly
Camptodactyly					L R	L R		L R		L R	L R	L R	L R		L R	L R	L R	L R		L R	L R	L R	L R		L R	L R	L R	L R		Camptodactyly
Ring constriction sec	L R	L R	L R	L R	L R	L R		L R		L R	L R	L R	L R		L R	L R	L R	L R		L R	L R	L R	L R		L R	L R	L R	L R		Ring constriction sec
Tumor	L R	L R	L R	L R	L R	L R		L R		L R	L R	L R	L R		L R	L R	L R	L R		L R	L R	L R	L R		L R	L R	L R	L R		Tumor
Trigger					L R					L R					L R					L R					L R					Trigger
Flexion impairment sec	L R	L R	L R	L R	L R					L R					L R					L R					L R					Flexion impairment sec
Extension impairment sec	L R	L R	L R	L R	L R					L R					L R					L R					L R					Extension impairment sec

Abnormal shoulder Left ◯ Yes ◯ No ◯ Unknown Right ◯ Yes ◯ No ◯ Unknown
Other aberrations of the upper limb, not appropriate above Left ◯ Yes ◯ No ◯ Unknown _____
Right ◯ Yes ◯ No ◯ Unknown _____

(Preliminary) diagnosis of the left arm ◯ **Yes** ◯ **No** ◯ **Unknown** _____
(Preliminary) diagnosis of the right arm ◯ **Yes** ◯ **No** ◯ **Unknown** _____

3. OTHER ABERRATIONS

Circulatory system ◯ Yes ◯ No ◯ Unknown _____
Respiratory system ◯ Yes ◯ No ◯ Unknown _____
Digestive system ◯ Yes ◯ No ◯ Unknown _____
Urogenital system ◯ Yes ◯ No ◯ Unknown _____
Central nervous system ◯ Yes ◯ No ◯ Unknown _____
Vertebral column ◯ Yes ◯ No ◯ Unknown _____
Body wall ◯ Yes ◯ No ◯ Unknown _____
Head and neck area ◯ Yes ◯ No ◯ Unknown _____
Skin ◯ Yes ◯ No ◯ Unknown _____
Lower limbs ◯ Yes ◯ No ◯ Unknown _____
(Preliminary) common diagnosis ◯ Yes ◯ No ◯ Unknown _____

1 = absent; 2 = present, wrong shape; 3 = right shape, too small; 4 = right shape, too large
* H = humerus; U = ulna; R = radius; C = carpal bones; MC = metacarpal; N = nail

Please send form to Mrs Dr Chr. Vermeij-Keers; Institute of Plastic Surgery; EE 1251A; Erasmus University Rotterdam; Postbus 1738; 3000 DR Rotterdam; The Netherlands

Appendix 2

- One recording form for each un-operated patient.

- Please only use ball point to mark the white boxes and to write text.

- The bold terms in this manual concern terms in the recording form.

Ad **2. ABERRATIONS OF THE UPPER LIMB**

- Recording is based on a morphological description of the congenital differences. Roughly, these can be divided into bony and soft tissue defects.

- More than one abnormality can be marked. If abnormalities can not be recorded, please mark the box **other aberrations of the upper limb, not appropriate above**, and specify the abnormalities.

- Bony defects
  - The concerning bones are **absent** or present (normal, **malformed**, **hypoplastic** or **hyperplastic**). Furthermore, please note any nail abnormalities. The terms **malformed**, **hypoplasia**, and **hyperplasia** are explained in the footnotes of the recording form, as well as the abbreviations.
  - Fusion of bones can exist in transverse and longitudinal direction. Both cases are described as **synostosis**, and the concerning bones should be marked.
  - Triphalangeal thumbs are noted as **polydactyly** of **P2** of **ray I**.

- Soft tissue defects
  - In soft tissue **syndactyly** the height is indicated by recording concerning bones, for example a complete syndactyly of ray 3 and 4 is marked as **syndactyly** of **P1, P2** and **P3** of **ray III** and **IV**.
  - In **clino-** and **camptodactyly** the corresponding bones are noted. If for example a clinodactyly of the proximal interphalangeal joint of ray 5 exists because of a P1, please mark **aplasia** of **P1** of **ray V** *and* **clinodactyly** of **P1** and **P2** of **ray V**.
  - If constriction bands are present, **ring constriction sec** is *also* noted at the level of the corresponding bones. For example, a constriction band is present at the level of right fourth P2, and P3 and the nail are absent, **ring constriction sec** of **P2** of **ray IV** *and* **agenesis** of **P3** and **N** of **ray IV** are marked.
  - **Tumors** also include lymphatic and/or vascular tumors, and are marked at the level of the corresponding bones.
  - Trigger fingers and thumbs are only indicated by the involved ray.
  - **Flexion- and/or extension impairment sec** concerns flexion and/or extension impairments without primary bone defects. Flexion impairment resulting from for example synostotic phalanges are *not* marked under this heading.

- If a diagnosis of the aberrations of the *upper limb* has been established, specify it in the box **(preliminary) diagnosis of the left and/or right arm**, after checking the **Yes** box.
  Example: i) Poland's syndrome with a hypoplastic hand: please fill in hypoplastic hand (**not** Poland, see also *Ad 3*), ii) **absence** of **P1** and **P3** of **ray I**, please fill in absent thumb.

Ad **3. OTHER DIFFERENCES**

- **Body wall** concerns the thoracic and abdominal wall.

- Pelvic aberrations are marked in the box **lower limbs**.

- If for example the aberrations are part of Poland's syndrome, please check the box (**preliminary) common diagnosis**, **Yes**, and fill in Poland. If the aberrations are not part of any syndrome, association, sequention, please mark this box **No**.

Remarks about the recording form and this manual may be adressed to: Mrs Dr Vermeij-Keers, Institute of Plastic Surgery, Room EE-1251A, Erasmus University Rotterdam, P.O. Box 1738, 3000 DR Rotterdam, the Netherlands. Phone: +31-10-4087242, Fax: +31-10-4089410, Email: Vermeij@plch.fgg.eur.nl
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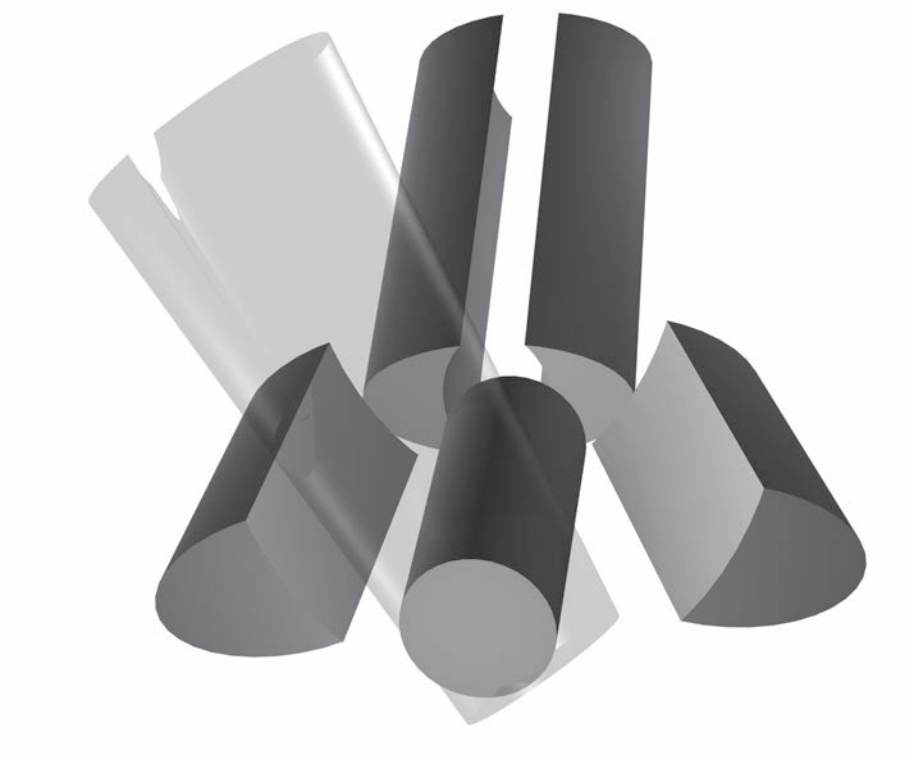
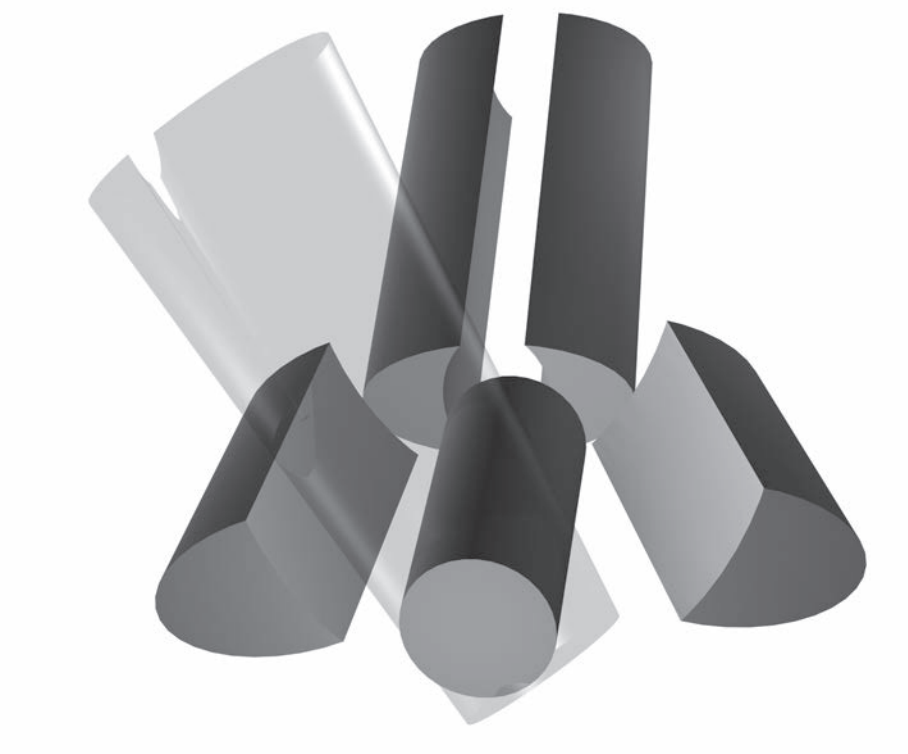
HEADS

COMMON ORAL CLEFTS



4

TEN YEARS RECORDING COMMON ORAL CLEFTS WITH A NEW DESCRIPTIVE SYSTEM



AJM Luijsterburg, C Vermeij-Keers. Cleft Palate - Craniofacial Journal. 2011, 48: 173-182.

SUMMARY

Objective After introducing a new descriptive recording system for congenital craniofacial abnormalities in The Netherlands, common oral clefts are highlighted.

Design Prospective observational study

Setting Fifteen cleft palate teams, united in the Dutch Association for Cleft Palate and Craniofacial Anomalies, registered patients from 1997 to 2006.

Patients All unoperated patients with a common oral cleft were included.

Main outcome measures Detailed information and birth prevalence rates of cleft lip/alveolus, cleft lip/alveolus and palate, and cleft palate were provided, relating referral age, gender, family history, additional congenital abnormalities, and syndrome diagnoses to these three categories.

Results 3512 patients were included, resulting in an overall prevalence of 16.6 per 10,000 live births. Patients showed a cleft lip/alveolus (28%), a cleft lip/alveolus and palate (39%), or a cleft palate (33%). The three categories exhibited very heterogeneous cleft types. Mean referral age was 5.8 months (median 3 weeks). Birth weight was the lowest in cleft palate patients (3238 grams; $p<0.001$-0.009). Cleft palate patients showed less positive family history concerning congenital anomalies (23%, $p<0.001$-0.013), but more syndrome diagnoses were established in this category (24%, $p<0.001$). 10% of all cleft patients showed additional abnormalities of the head and neck area, and 13% displayed congenital anomalies of other systems.

Conclusions This new recording method allows adequate description of common oral clefts. Many cleft types exist within these three categories and should be differentiated, because they originate from different time frames and/or cell biological mechanisms during embryogenesis.

Key words descriptive recording system, common oral clefts, prevalence.

INTRODUCTION

Registration and classification of congenital anomalies in general, and common oral clefts in particular, is of paramount importance to provide a solid basis for epidemiological, clinical and/or fundamental research. Several registration and classification systems have been developed in order to consistently categorise the observed types of common oral clefts[1-12]. These systems provide details about the cleft types according to anatomic appearance, and adequately describe the more frequent variations. However, infrequent types of clefting often can not be classified, except for the classification of Kriens[10], adjusted by Koch[3], which is very time-consuming to fill in. Therefore, we have developed a new recording system on behalf of the Dutch Association for Cleft Palate and Craniofacial Anomalies (NVSCA) and the system is embedded in the working group "Registration". This system, the NVSCA registration, records the individual abnormalities of the primary (lip and alveolus) and secondary palate (hard and soft palate including the uvula) that form the common oral cleft. To anticipate all conceivable abnormalities, the system is based on embryology, morphology and topography. Furthermore, all other individual craniofacial abnormalities can be described, including all types of craniosynostosis, congenital ear anomalies etcetera. The cleft types are not categorised or coded in any way, as this would lead to loss of information. Additional congenital abnormalities of other systems of the body can be indicated as well.

After importing the data in a specific developed computer program, categorisation may follow depending on proposed queries; specific categorisation may be necessary for specific queries.

Since 1997 all unoperated patients that were referred for assessment of an oral cleft, have been recorded nation-wide. In The Netherlands, almost every child with an oral cleft is referred to a cleft palate team.

It should be noted that this system is an anonymous recording system. For studies using anonymous data approval of NVSCA board is needed, for patient identification also approval of all teams concerned is required. The patient identification number of the cleft palate team, the birth date and gender can be used to find the patient's hospital records.

This paper introduces the new recording system and reports the results of ten years of recording common oral clefts in The Netherlands. Gender, race, referral age, adoption/ foster child, birth weight, gestational age, family history, other congenital anomalies, and syndrome diagnoses / sequences / associations were related to the three common

categories, cleft lip/alveolus, cleft lip/alveolus and palate, and cleft palate. Detailed information and birth prevalence rates were presented of the three categories of common oral clefts.

MATERIALS AND METHODS

Patients and NVSCA recording form

In ten years (1997-2006), 3512 unoperated patients were referred for the first time to a multidisciplinary consultation for assessment of a cleft lip and/or alveolus and/or palate. After careful examination these patients were recorded using the NVSCA recording form. The form is well organised (one page only), and is fast and easy to fill in. It is composed of three parts: 1) a general section (e.g. ethnic origin), 2) a section for craniofacial abnormalities including common oral clefts, and 3) a section for any congenital abnormality of other parts of the body (Figure 1); a manual is available (Figure 2). The section for craniofacial abnormalities includes common oral clefts. In a two dimensional table, the X-axis shows topography (e.g. lip, pre/max, i.e. alveolus, and hard palate), and on de Y-axis morphology is depicted (e.g. complete, incomplete, and submucous clefts). In addition, absent (agenesis), malformed (aplasia), and undersized (hypoplasia) or oversized (hyperplasia) parts of the lip, alveolus and palate can be noted in section 2, as well as all other craniofacial malformations.

The authors assessed all forms, and members of the cleft palate teams provided additional information if necessary. In this study only common oral clefts with or without associated abnormalities were included. Median cleft lip and atypical clefts were excluded for their different pathogenesis.

Gender, race, referral age, adoption/foster child, birth weight, gestational age, family history, other congenital anomalies, and syndrome diagnoses / sequences / associations were related to the three common categories. We assume that the cleft palate teams assess nearly all patients with a common oral cleft, and therefore we were able to produce birth prevalence rates (live births). These birth prevalence rates were computed using general data from the Dutch Central Bureau of Statistics (CBS) and the birth dates of the patients.

Registration of clefts and craniofacial malformations | **Hospital** | Dutch Association for Cleft Palate and Craniofacial Anomalies | **Please fill in white boxes**

1. GENERAL

Date of this registration _____
Patient identification number _____
Date of birth _____
Gender ◯ Male ◯ Female ◯ Unknown
Name of physician _____
Clinical genetics consulted ◯ Yes ◯ No ◯ Unknown
If affirmative, please specify center _____
Adoption or foster child ◯ Yes ◯ No ◯ Unknown

Caucasian father ◯ Yes ◯ No ◯ Unknown
Caucasian mother ◯ Yes ◯ No ◯ Unknown
Consanguinity ◯ Yes ◯ No ◯ Unknown
If affirmative, please specify _____
Congenital abnormalities among relatives ◯ Yes ◯ No ◯ Unknown
If affirmative, please specify _____
Birth weight (grams) _____
Gestational age (weeks) _____
Remarks about pregnancy ◯ Yes ◯ No ◯ Unknown
If affirmative, please specify _____

2. ABNORMALITIES OF THE HEAD AND NECK AREA

L = left R = right M = median	Mouth							Ala nasi	Septum nasi	Calvaria / facial skull										Orbita	Eyes	Eye-lids	Ears	Soft tissue*
	Lip	Pre./ max.*	Pre.*	Pal. dur.*	Pal. mol.*	Uvula	Ton.*			Par.*	Occ.*	Tem.*	Fro.*	Nas.*	Zyg.*	Max.*	Man.*	l.o.d.*						
Cleft									M												L R			
Complete	L R	L R		L R																				
	M		M	M	M	M	M										M							
Incomplete	L R	L R		L R																				
	M		M	M	M	M	M										M							
Submucous	L R	L R		L R																				
	M		M	M	M	M	M										M							
Agenesis[1]	L R		L R	L R	L R	L R		L R		L R		L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R
	M						M		M		M													M
Aplasia[2]	L R		L R	L R	L R	L R	L R	L R		L R		L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R
	M						M		M		M													M
Protruding																						L R	L R	
Adherent							L R															L R	L R	
Appendages																						L R	L R	L R
																								M
Hypoplasia[3]	L R		L R	L R	L R	L R	L R	L R		L R		L R	L R	L R	L R	L R	L R		L R	L R	L R	L R	L R	L R
	M								M		M							M						M
Hyperplasia[4]	L R		L R	L R	L R	L R	L R	L R		L R		L R	L R	L R	L R	L R	L R		L R	L R	L R	L R	L R	L R
	M								M		M							M						M
Synostosis										L R	L R	L R	L R	L R	L R	L R	L R							
										M			M				M							
Non synostosis										L R	L R	L R	L R	L R	L R	L R	L R							
										M			M				M							

Other abnormalities of the head and neck area, not appropriate above ◯ Yes ◯ No ◯ Unknown _____

■ **(Preliminary) diagnosis** ◯ **Yes** ◯ **No** ◯ **Unknown** _____

3. OTHER ABNORMALITIES

Circulatory system ◯ Yes ◯ No ◯ Unknown _____
Respiratory system ◯ Yes ◯ No ◯ Unknown _____
Digestive system ◯ Yes ◯ No ◯ Unknown _____
Urogenital system ◯ Yes ◯ No ◯ Unknown _____
Central nervous system ◯ Yes ◯ No ◯ Unknown _____
Vertebral column ◯ Yes ◯ No ◯ Unknown _____
Body wall ◯ Yes ◯ No ◯ Unknown _____
Skin ◯ Yes ◯ No ◯ Unknown _____
Upper limbs ◯ Yes ◯ No ◯ Unknown _____
Lower limbs ◯ Yes ◯ No ◯ Unknown _____
(Preliminary) common diagnosis ◯ Yes ◯ No ◯ Unknown _____

1 = absent; 2 = present, wrong shape; 3 = right shape, too small; 4 = right shape, too large
* Pre./max. = premaxilla - maxilla; Pre. = premaxilla; Pal.dur. = palatum durum; Pal.mol. = palatum molle; Ton. = tongue; Par. = os parietale; Occ. = os occipitale; Temp. = os temporale; Fro. = os frontale; Nas. = os nasale; Zyg. = zygoma; Max. = maxilla; Man. = mandible; l.o.d. = interorbital distance; Soft tissue = soft tissue of the head and neck area

Please send form to Mw Dr Chr. Vermeij-Keers; Research Unit Department of Plastic and Reconstructive Surgery; Room EE 1591; Erasmus MC - University Medical Center Rotterdam; P.O. Box 2040; 3000 CA Rotterdam; The Netherlands

ISBN 90-76580-03-0

Figure 1
Recording form of the NVSCA registration. Reproduced by kind permission of the Department of Plastic and Reconstructive Surgery, Erasmus MC - University Medical Center Rotterdam, The Netherlands.

Manual for the NVSCA registration form

- One registration form for each un-operated patient.
- Please only use ballpoint to mark the white boxes and to fill in the text boxes
- The bold terms in this manual refer to the items in the registration form.

Ad **2. ABNORMALITIES IN HEAD AND NECK AREA**

- The registration is based on aberrant embryonic development of the face and skull. Roughly, embryonic development can be distinguished in fusion of the facial/palatine swellings and differentiation of the calvarian and facial bones, and soft tissue. Only fusion and differentiation defects of the primary palate (right and/or left) and of the secondary palate (left or right or median) are registered as cleft. All other defects of bones and soft tissue, including clefts, are registered on the basis of their absence or presence and shape (**agenesis** or **aplasia**, **hypoplasia**, and **hyperplasia**), except for colobomas of the eyeball (see below). The definition of **agenesis**, **aplasia**, **hypoplasia**, and **hyperplasia** and the explanation of the abbreviations are decribed in the footnotes of the registration form.
- More abnormalities can be filled in for the same patient. If an abnormality can not be registered, this abnormality should be scored in the box **other abnormalities of the head and neck area, not appropriate above, yes**, and it should be specified.
- Cysts and fistulas of the tongue in the median are scored as **aplasia** of the **tongue** in the **median** plane.
- Hypotelorism and hypertelorism may be accompanied with an aberrant septum nasi in the median plane. For example, hypotelorism could be accompanied with **agenesis**, **aplasia** or **hypoplasia** of the **septum nasi**, and hypertelorism could be accompanied with **cleft** (= bifid), **aplasia**, or **hypoplasia** of the **septum nasi**. Furthermore, the aberrant interorbital distances (**i.o.d.**) is registered.
- **Non synostosis** concerns a skull shape comparable with synostosis, but the sutures are open. Synostosis of sutures are registered as **synostosis** of the involved bones. **Synostosis** of both frontal bones, or both parietal bones are registered in the **median**.
- Colobomas of the eyeball concern fusion defects of the fissure, and these are scored as **cleft** of the **eyes**.
- Entropion and ectropion should be registered as **protruding eyelids**. Ptosis and phimosis of the eyelids, and epicanthal folds are scored as **aplasia** of the **eyelids**. Microblepharon is registered as **hypoplasia** of the **eyelids**.
- Colobomas of the eyelids, ears and ala nasi, are scored as **aplasia** of the **eyelids**, **ears**, and **ala nasi**.
- Aberrant position of the ears, such as low set or tilted ears, is filled as **miscellaneous ears**.
- If a diagnosis of the *head and neck area* has been established, **(preliminary) diagnosis** should be filled in (**yes**) and should be specified. Moreover, all abnormalities should be registered in this box.

Ad **3. OTHER ABNORMALITIES**

- **Body wall** concerns thoracic and abdominal wall
- Abnormalities of the shoulder and pelvis are filled in as abnormalities of **upper** and **lower limbs**, respectively.
- If the abnormalities are part of a syndrome, **(preliminary) common diagnosis** should be filled in (**yes**), and it should be specified

Figure 2
Manual for the NVSCA registration form.

Statistical analysis

Statistical analysis was performed using chi-square test for dichotomous variables (gender, race, adoption/foster child, family history, other congenital anomalies, syndrome diagnoses). Independent samples t-test was used for continuous variables (gestational age and birth weight). P values below 5% were considered to be statistically significant. Statistics were performed using a software package (SPSS v 14.0®).

RESULTS

General information

2050 male and 1462 female patients were recorded (ratio male/female = 1.40). The common oral clefts were subdivided into three categories being cleft lip/alveolus (CL/A), cleft lip/alveolus and palate (CL/AP), and cleft palate (CP).

The parents were Caucasian in 2943 cases, and not Caucasian in 352. The remainder 217 patients had parents with a mixed race (147), or with an unknown race (70). In 75 cases the parents were related to each other (any degree of relationship). 41 couples were cousins (second degree relatives) of which 21 were Caucasian (0.7% of all Caucasian parents), and 20 were non-Caucasian (6% of all non-Caucasian parents). 18 couples had a third degree relationship, and in 16 couples the degree of relationship was unknown.

Mean age at referral was 5.8 months, and the median referral age was 21 days (range 0 days - 43 years). 9% of all cleft patients was referred older than one year (n=299). Late referral age was evaluated using following parameters: adopted/foster child and cleft category. 143 patients were adopted/foster children (mean referral age = 18 months). 78 of the 143 adopted/foster children with a common oral cleft were referred after one year of age (55%). This is significantly more than the 221 of the 3327 non-adopted patients ($p<0.001$, mean referral age of all non-adopted patients = 5 months). Significantly more non-adopted CP patients visited a cleft palate team later than 12 months of age compared with CL/A and CL/AP patients (both $p<0.001$), and CL/A and CL/AP patients did also differ in referral age ($p=0.011$; Table 1).

Mean birth weight was 3294 grams (range 780-5612 grams). CL/A and CL/AP patients had a significantly higher birth weight than CP patients ($p <0.001$ and $p= 0.009$, respectively; means CL/A 3364 grams, CL/AP 3291 grams; CP 3238 grams). However, if patients with

Table 1 Referral age (age in months) of non-adopted patients related to category of cleft. The non-adopted patients are divided into a referral age less than one year (<1), or more than one year (>1), and their category of common oral clefts.

		Category			
	Age	**CL/A**	**CL/AP**	**CP**	**Total**
Non-adopted	< 1	896	1251	959	3106
	> 1	28	18	175	221
	?	8	18	12	38
Adopted	< 1	24	29	12	65
	> 1	20	46	12	78
	?	1	1	2	4

additional congenital anomalies of the head and neck area and/or other parts of the body were excluded, no significant differences in birth weight were observed (means CL/A 3393 grams, CL/AP 3331 grams, and CP 3326 grams; p=0.200-0.700).

Mean gestational age was 39 weeks (range 26–43 weeks). No significant differences were observed between patients with CL/A, CL/AP or CP (p=0.190–0.959).

Occurrence of any congenital anomaly among relatives was present in 26% of the cases. More patients with a CL/A or CL/AP (27% and 29%, respectively) showed a positive family history, than the CP patients (23%; p=0.013, and p<0.001, respectively). 21% of the patients showed a positive family history for common oral clefts (22% of the CL/A patients, 24% of the CL/AP patients, and 16% of the CP patients). In the CP group, significantly less patients with positive family history for common oral clefts were observed when compared to CL/A or CL/AP (both p<0.001), whereas no significant difference was observed between CL/A and CL/AP patients (p=0.329).

Types of common oral clefts within the three categories

All frequent cleft types could be easily recorded. For instance the recording of a right-sided complete cleft lip and alveolus (Figure 3a), a right-sided complete cleft lip, alveolus and hard palate, and a complete cleft of the soft palate (Figure 3b), and an incomplete cleft of the palatum molle and a complete uvular cleft are shown in Figure 3c. Infrequent or unique clefts could also be described such as a left-sided incomplete cleft of the lip with a submucous component, combined with an ipsilateral incomplete alveolar cleft (Figure 4a), a complete cleft lip on the left side, a complete cleft lip and alveolus on the right side, a left sided incomplete cleft of the hard palate with a anterior submucous part, a

a

L = left R = right M = median	Mouth						
	Lip	Pre./ max.*	Pre.*	Pal. dur.*	Pal. mol.*	Uvula	Ton.*
Cleft							
Complete	L X R M	L X R	M	L R M	M	M	M
Incomplete	L R M	L R	M	L R M	M	M	M
Submucous	L R M	L R	M	L R M	M	M	M
Agenesis[1]	L R M		L R	L R	L R	L R	M
Aplasia[2]	L R M		L R	L R	L R	L R	L R M
Protruding							
Adherent							L R
Appendages							
Hypoplasia[3]	L R M		L R	L R	L R	L R	L R
Hyperplasia[4]	L R M		L R	L R	L R	L R	L R

b

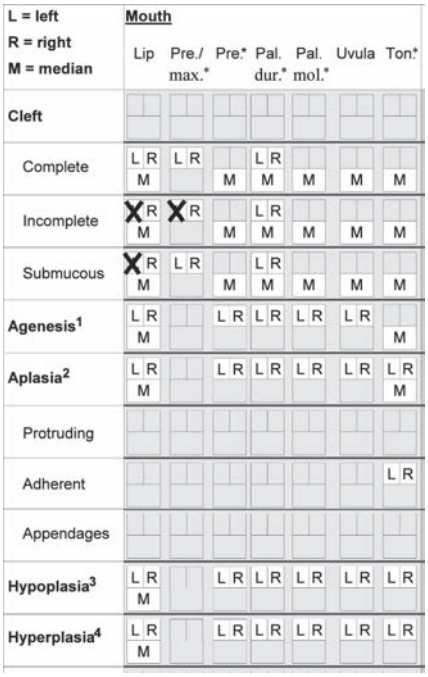
L = left R = right M = median	Mouth						
	Lip	Pre./ max.*	Pre.*	Pal. dur.*	Pal. mol.*	Uvula	Ton.*
Cleft							
Complete	L X R M	L X R	M	L X R M	X	X	M
Incomplete	L R M	L R	M	L R M	M	M	M
Submucous	L R M	L R	M	L R M	M	M	M
Agenesis[1]	L R M		L R	L R	L R	L R	M
Aplasia[2]	L R M		L R	L R	L R	L R	L R M
Protruding							
Adherent							L R
Appendages							
Hypoplasia[3]	L R M		L R	L R	L R	L R	L R
Hyperplasia[4]	L R M		L R	L R	L R	L R	L R

c

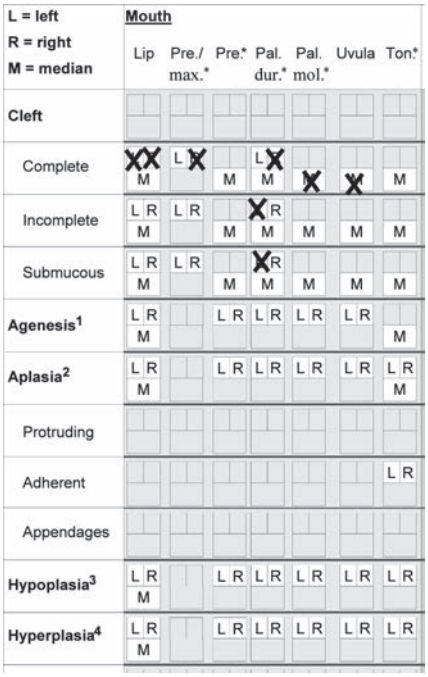
L = left R = right M = median	Mouth						
	Lip	Pre./ max.*	Pre.*	Pal. dur.*	Pal. mol.*	Uvula	Ton.*
Cleft							
Complete	L R M	L R	M	L R M	M	X	M
Incomplete	L R M	L R	M	L R M	X	M	M
Submucous	L R M	L R	M	L R M	M	M	M
Agenesis[1]	L R M		L R	L R	L R	L R	M
Aplasia[2]	L R M		L R	L R	L R	L R	L R M
Protruding							
Adherent							L R
Appendages							
Hypoplasia[3]	L R M		L R	L R	L R	L R	L R
Hyperplasia[4]	L R M		L R	L R	L R	L R	L R

Figure 3
A fast and easy recording of a right-sided complete cleft lip and alveolus (a), a right-sided complete cleft lip, alveolus and hard palate, and a complete cleft of the soft palate (b), and an incomplete cleft of the palatum molle and a complete uvular cleft (c).

a



b



c

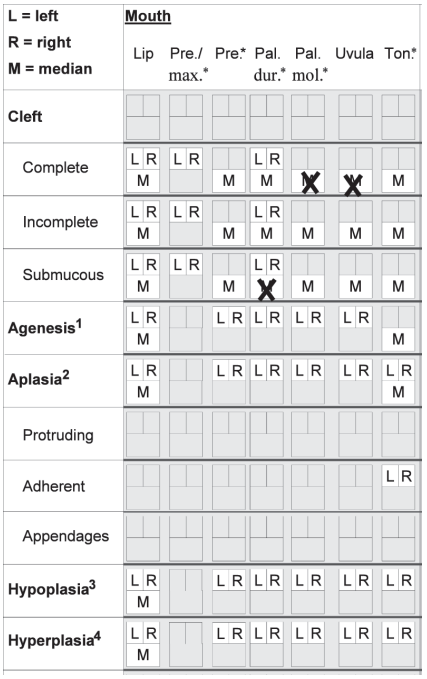


Figure 4
Examples of recording infrequent or unique clefts. (a) A left-sided incomplete cleft of the lip with a submucous component, combined with an ipsilateral incomplete alveolar cleft. (b) A complete cleft lip on the left side, a complete cleft lip and alveolus on the right side, a left sided incomplete cleft of the hard palate with a anterior submucous part, a right sided complete cleft of the hard palate, and a complete cleft of the soft palate. (c) A median submucous cleft of the hard palate and a complete cleft of the soft palate.

right sided complete cleft of the hard palate, and a complete cleft of the soft palate (Figure 4b), or a median submucous cleft of the hard palate and a complete cleft of the soft palate (Figure 4c).

977 patients had CL/A (28%). The ratio male/female was 1.72. The most common types of CL/A were incomplete cleft lip (374 patients), incomplete cleft lip and alveolus (267 patients), and complete cleft lip and alveolus (133 patients) (Table 2). Incomplete cleft lip with or without an incomplete alveolar cleft was on the left side in 64%, on the right side in 29%, and bilateral in 7%. A complete cleft lip and alveolus showed left, right, and bilateral involvement in 56%, 31%, and 13%, respectively. Furthermore, 39 and 38 cases exhibited complete cleft lip and incomplete cleft alveolus, and complete cleft lip, respectively, and another 126 patients showed 20 infrequent cleft types (data not shown).

1363 patients showed a CL/AP (39%) with a ratio male/female of 2.04. Most frequently a complete cleft of the lip, alveolus, and palate was observed (863 patients, 63%) (Table 2). Of these cases, 384 clefts of the lip and alveolus were located at the left side (44%), 222 patients showed a cleft lip/alveolus on the right side (26%), and bilateral involvement of the lip and alveolus was present in 257 patients (30%). In addition to the less frequent CL/AP types indicated in Table 2, 251 patients showed 86 infrequent cleft types (data not shown).

1172 patients showed a CP (33%). The ratio male/female was 0.79. Most frequently a complete cleft of the soft palate was observed (394 patients, 34%), followed by a complete cleft of the hard and soft palate (274 patients, 23%) and an incomplete cleft of the hard palate combined with a complete cleft of the soft palate (237 patients, 20%). In addition, 54 and 52 cases (Table 2) exhibited a submucous and incomplete cleft of the soft palate, respectively, and another 161 patients showed 30 infrequent types of CP (data not shown).

Additional abnormalities

355 patients showed one or more additional congenital craniofacial abnormalities (10%, Table 3). Most frequently mandible abnormalities were observed (239 patients, 68%), which is consistent the high frequency of Pierre Robin sequence. 442 patients displayed any congenital anomaly of other parts of the body (13%, Table 4), of which congenital anomalies of the circulatory system were the most frequent (32%). Patients with or without syndrome diagnosis were included in the abovementioned additional anomalies. Syndromic cases, cases with additional anomalies, and isolated cases were distinguished. 21% of the common oral cleft patients was not isolated (10% CL/A, 13% CL/AP, 40%

Table 2 The most common types of CL/A, CL/AP, and CP. Left- and/or right-sided clefts are not distinguished here (C = complete cleft, I = incomplete cleft, S = submucous cleft, n = number of patients).

Lip		Alveolus		Hard palate		Soft palate			n
C	I	C	I	C	I	C	I	S	
	x								374
	x		x						267
x		x							133
x			x						39
x									38
x		x		x		x			863
	x	x		x		x			73
x		x		x	x	x			50
x	x	x		x		x			50
	x		x	x		x			38
	x		x		x	x			38
						x			394
				x		x			274
					x	x			237
								x	54
							x		52

CP) (Table 5).

1109 patients (32%) were referred to a clinical geneticist, and a syndrome / sequence / association was observed in 212 patients (19% of the referred patients). 2403 patients were not referred to a clinical geneticist, and a syndrome / sequence / association was observed in 121 cases (5% of the non referred patients). In 1% of the CL/A patients a syndrome diagnosis was established, and in 3% and 24% of the CL/AP and CP patients, respectively (all $p<0.001$). The patients with a syndrome diagnosis were referred to a clinical geneticist in 20% of the CL/A patients, and in 39% and 37%, of the CL/AP and CP patients, respectively. Pierre Robin sequence was the most frequent diagnosis (Table 6), occurring only in CP patients, and CL/AP patients mostly showed trisomie 21 or trisomy 13.

Table 3 The most frequent additional congenital abnormalities of the head and neck area besides common oral clefts. Note that one patient may exhibit more than one abnormality (n= number of patients).

Abnormality	n	Specification
Mandible	239	239 hypoplasia (232 bilateral, 7 unilateral)
Ears	62	35 hypoplasia or aplasia; 23 appendages; 4 miscellaneous
Maxilla	19	16 hypoplasia (10 bilateral, 6 unilateral); 3 miscellaneous
Soft tissue	18	9 hypoplasia; 5 aplasia; 4 miscellaneous
Interorbital distance	17	10 hypertelorism, 7 hypotelorism
Eyelids	17	13 aplasia; 4 miscellaneous

Table 4 Number of patients with congenital anomalies of other parts of the body. Note that one patient may have more than one affected body part (n= number of patients).

Abnormality	n	Specification
Circulatory system	142	42 ventricle septum defects, 22 atrium septum defects, 9 tetralogy of Fallot, 69 miscellaneous
Lower limbs	124	35 clubfeet, 15 syndactyly, 13 hip dysplasias, 8 clinodactylies, 7 polydactylies, 46 miscellaneous
Upper limbs	97	15 hypoplastic parts, 12 polydactylies, 11 clinodactylies, 8 camptodactylies, 8 syndactylies, 43 miscellaneous
Respiratory system	80	25 apnoes, 13 tracheomalacies, 7 respiratory insufficiencies, 35 miscellaneous
Urogenital system	76	15 hypospadias, 7 micropenises, 7 hydronefrosis, 6 kidney cysts, 4 unilateral absent kidneys, 37 miscellaneous
Central nervous system	76	15 retarded cases, 7 epilepsias, 7 hydrocephalus, 6 hypotonia, 6 absent corpus callosum, 35 miscellaneous
Digestive system	71	18 feeding problems, 10 esophagal atresias, 9 anal atresias, 8 gastro-esophagal refluxes, 26 miscellaneous

Table 5 Isolated cases, syndromic cases, and cases with additional anomalies related to category of cleft. Isolated were those patients without other abnormalities observed, nor a syndrome diagnosis. Syndromic cases were patients with a syndrome / sequence / association (including Pierre Robin) with or without additional anomalies, and cases with additional anomalies had additional congenital craniofacial abnormalities or anomalies of other parts of the body without a syndrome / sequence / association..

	Category						n	
	CL/A		CL/AP		CP			
Isolated	884	90%	1178	87%	703	60%	2765	79%
Syndromes	10	1%	44	3%	279	24%	333	9%
Additional anomalies	83	9%	141	10%	190	16%	414	12%

Table 6 The most frequent syndromes / sequences / associations observed in the three categories of common oral clefts (n= number of patients).

Syndrome	n	CL/A	CL/AP	CP
Pierre Robin	191			191
Deletion 22q11	22		2	20
Trisomy 21	14		6	8
Van der Woude	9		4	5
Trisomy 13	7		5	2
Stickler	7			7
Goldenhar	7	2	3	2
EEC	5		3	2
Charge	4	2	1	1
Opitz	3	1	1	1

Birth prevalence

Birth prevalence rates were computed using the birth registry of the CBS, and the birth dates of the patients. Between 1/1/1997 and 31/12/2006 1970872 children were born in The Netherlands. As adopted/foster children most commonly are born outside The Netherlands we decided to exclude adopted/foster children when calculating birth prevalence rates. Not every child with a common oral cleft who is born in 2006 had already been recorded in 2006. For instance, when a child is born in December 2006, it is readily possible that it has not yet visited a cleft palate team in 2006. 3261 patients with common oral clefts remained, resulting in a prevalence of 16.6 per 10000 live births (1 per 604 live births). The birth prevalence rates between 1997 and 2006 are depicted in Figure 5.

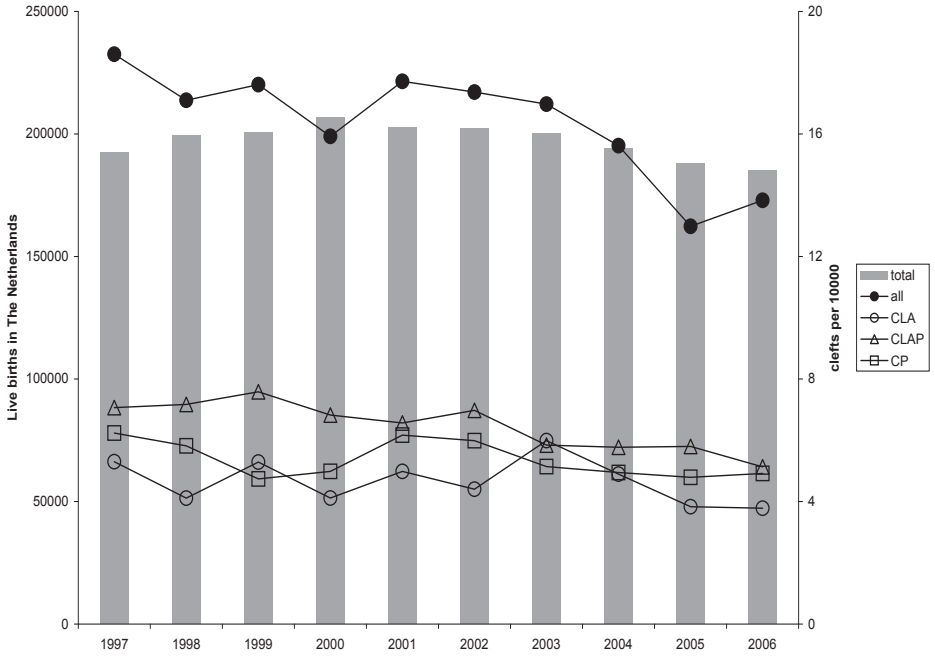


Figure 5
Birth prevalence rates of common oral clefts 1997-2006. The columns represent the number of live births in The Netherlands, and the quantity is shown on the left side. The dots and squares are the number of patients with a common oral cleft per 10,000 live births, and the right side shows the quantity.

DISCUSSION

Recording and classification of common oral clefts should enable clinical and/or fundamental research. Among the objectives are surveillance for changes in frequencies of specific cleft types. Furthermore, clinical outcome largely depends on the phenotype of the cleft patient. Therefore, consistent description is required to evaluate any treatment strategy, to compare the results with other studies, and to improve interdisciplinary communication. This also applies for fundamental researchers who are searching for genetic factors responsible for different cleft types, gene functions and gene-environmental interactions.

The NVSCA registration, as is shown in the results, can consistently describe all individual craniofacial abnormalities. All common oral clefts were divided into the three well-known categories: CL/A (28%), CL/AP (39%), and CP (33%). Other studies also have shown an excess of CL/AP[13-15]. As is shown in several tables many cleft types could be described within these categories. The first two examples of infrequent clefts can not adequately be described by previous classifications without losing details about the individual abnormalities[6,7,10-12]. To assess the reliability of the acquired data, we have conducted a validation study[16]. Besides consistent description of all individual craniofacial abnormalities, the fast and easy recording is another strength of the NVSCA registration. This highly improves compliance by the physicians who actually assess cleft patients during their busy outpatient clinics. Any registration system has its flaws. Specific details about the cleft are not noted, such as the width of the cleft, or the cleft proportion in incomplete cleft lip. Furthermore, the NVSCA registration is not an ongoing registration, and underestimation of for instance congenital anomalies of other parts of the body or other (discrete) craniofacial anomalies will result. It may be useful to record all cleft patients again after 6 years[17], thereby completing the additional abnormalities, enabling study of true isolated cleft cases. Additional anomalies of other body parts are also recorded. However, this part of the registration is based on verbatim descriptions of diagnosis, and incompleteness and inaccuracies result. Therefore, it could be beneficial to construct a recording form for each body part. We have introduced such a recording system for congenital anomalies of the upper limb[18], which is based on the same principles as the NVSCA registration. In this way linkage between the different forms could allow more complete analysis of for instance common oral clefts and upper limb anomalies. At last, this registry concerns live births, who live long enough to visit a cleft palate team.

All still births as well as all live births who die before the first visit to a cleft palate team, are not recorded, leading to an underestimation of birth prevalence rates.

In our study the cleft palate teams assessed 91% of the patients with a common oral cleft within 12 months of age (85% within 5 months of age). This high percentage for early referral may be due to the adequate infrastructure and the sound embedding of the cleft palate teams in the Dutch welfare system.

Late referral (>12 months of age, n=299) may be partly due to the fact whether or not the child is adopted. 55% of the adopted children are seen for the first time in a cleft palate team later than one year of age. Most likely, these children are presented so late because they arrive later in life at the new parents / guest family. Of the non-adopted children 6% visit the cleft palate team older than one year (221 patients). Another factor contributing to late referral may be children with cleft palate: 175 children are referred late (15% of all cleft palate patients). In 77 patients an (in)complete cleft of the hard and/or soft palate was observed (data not shown). The remaining 98 children showed submucous clefts, aplastic or hypoplastic hard and/or soft palates. Thus, the proportion of late referrals of CP children could be diminished by more thorough postnatal assessment by e.g. general physicians, midwives, gynaecologists, and pediatricians.

Mean birth weight was the highest in the CL/A category. After exclusion of additional anomalies no significant differences were observed. However, birth weight in all cleft patients were lower than in the general population (3453 grams [3421-3485]), but the clinical explanation is obscure.

The ratio male / female was high in the CL/A group and the CL/AP group, but was reversed in the CP group, as is in accordance with literature[13,15,19].

One in four patients showed a positive family history for any congenital abnormality, and one in five for common oral clefts. Common oral clefts occurred less frequent among relatives in the CP group, 22% versus 26% CL/A and 29% CL/AP, respectively. Furthermore, in 9% a syndrome diagnosis / sequence / association was observed (one in four patients with a CP). In one in three patients a clinical geneticist was consulted for further assessment. Only half of the patients with additional congenital abnormalities of the head and neck area and/or congenital anomalies of other parts of the body were referred to the clinical geneticist.

90% of the CL/A patients was isolated and 86% and 60% of the CL/AP and CP patients, respectively. Other studies have shown lower percentages of isolated cases[13,20-25]. Methodological factors that may cause variation in frequency of isolated cased have been discussed previously[26]: case definition and inclusion/exclusion criteria, timing of medical

examination, variable clinical expression of associated anomalies, ability to establish syndrome diagnosis, patient selection, sample size, sources of ascertainment, and true population differences. As the NVSCA registration is not an ongoing registration it is likely to underreport additional anomalies. Furthermore, it is known that mild additional congenital abnormalities of the head and neck area are difficult to observe (personal communication, A.J.M. Luijsterburg, Chr. Vermeij-Keers), and that congenital anomalies of other parts of the body may reveal themselves later in life. As a consequence, relevant data are not recorded leading to an underestimation of these additional abnormalities. This may account for the lower proportion of additional abnormalities and syndrome diagnoses. In our opinion a clinical geneticist/pediatrician for an extensive assessment of the congenital anomalies should therefore see all cleft patients.

Common oral clefts are among the most frequent congenital anomalies. Our study revealed a prevalence of 16.6 per 10,000 live births over a 10-year period in The Netherlands. This is in accordance with prevalence rates in Western Europe[27,28]. Our birth prevalence rates are slightly underestimated because each year about 20 patients die in the first weeks of life, which is mostly before attending a cleft palate team[29]. All our recorded cases represent about 93% of the estimated live born cleft patients.

As the normal development of the primary and secondary palate evolves from 6-14 weeks of gestation, common oral clefts develop during the same period. As the different types develop at a specific time during this two month period, and additionally the underlying cell biological mechanisms are specific for different cleft types[30], a valid description of the cleft types is a conditio sine qua non. Such a consistent description of common oral clefts is provided by the NVSCA registration. In this way, it may be possible to relate the observed cleft types to specific time periods, and subsequently specific known and unknown genes which are expressed during these periods, may be identified.

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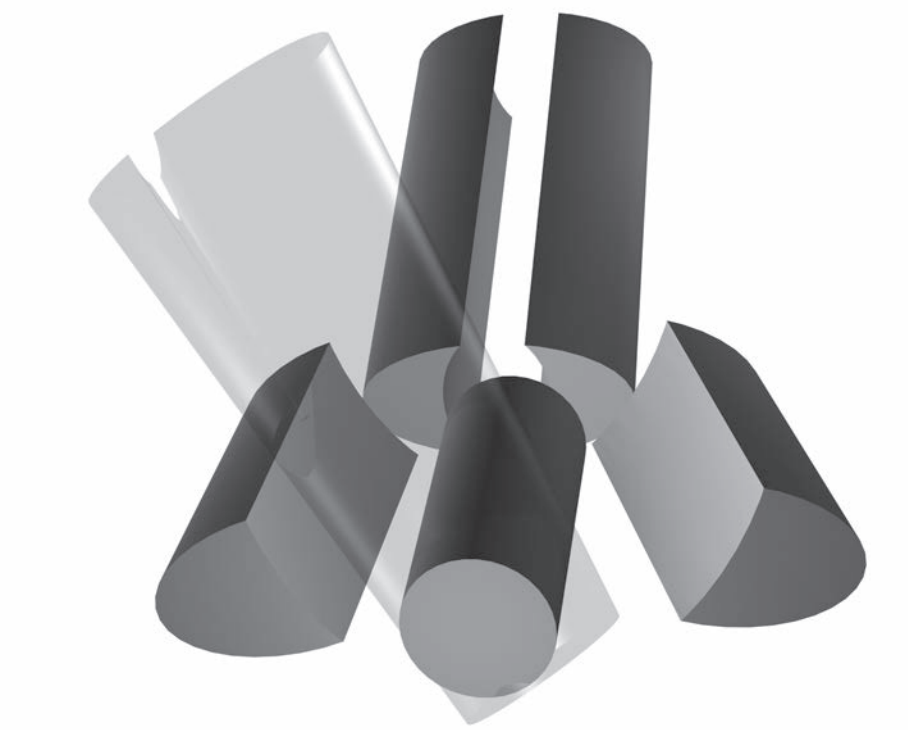
5

VALIDATION OF THE NVSCA REGISTRY FOR COMMON ORAL CLEFTS: STUDY DESIGN AND FIRST RESULTS



AM Roozendaal, AJM Luijsterburg, AD Mohangoo, ED Ongkosuwito, S Anthony, C Vermeij-Keers. Cleft Palate – Craniofacial Journal. 2010, 47: 534-543.

SUMMARY

Objective: Since 1997 the Dutch Association for Cleft Palate and Craniofacial Anomalies (NVSCA) maintains a national registry of congenital craniofacial anomalies; data on three common oral cleft categories (cleft lip/alveolus = CL/A, cleft lip/alveolus and palate = CL/AP, and cleft palate = CP) and general items are validated.

Design: Retrospective observational study.

Setting: All fifteen Dutch cleft palate teams registered presurgery patients with common oral clefts (n=2553) from 1997-2003.

Patients: A random sample of 250 cases was used, 13 cases were excluded.

Main outcome measures: The corresponding medical data were reviewed; these medical data served to validate the NVSCA registry data. Prevalence comparisons, 2x2 tables and validity measures were performed.

Results: The cleft categories most accurately recorded were CL/A and CP. Both categories had an observed agreement of 98%, kappa of 0.94 and a sensitivity and specificity of 97%. CLA/P had an observed agreement of 95%, kappa of 0.89, a sensitivity of 90% and specificity of 99%. Regarding the general items, observed agreement and kappa were highest for adoption/foster child (99%; 0.76) and lowest for remarks about pregnancy (63%; 0.20). Sensitivity ranged from 25% (consanguinity) to 97% (Caucasian mother) and specificity was high for all items (>93%) except for Caucasian father and mother (approximately 35%).

Conclusions: The NVSCA registry is a valuable tool for quality improvement and research because validity on all three common oral cleft categories is very good. Validity on the general items is reasonable to satisfying and appears to be related to the type of information.

Keywords: cleft lip, cleft palate, registry, validation

INTRODUCTION

International registries

Oral clefts are one of the most common congenital anomalies in humans. Worldwide, the prevalence of oral clefts varies between 4.8 and 28.6 per 10,000 live births and stillbirths (with or without termination of pregnancy)[1] with a considerable variation between gender, ethnic groups, socioeconomic conditions and geographic regions[2-6].

In many studies concerning oral clefts, median cleft lip and atypical facial clefts are included. However, these clefts should be considered as different craniofacial anomalies because of their different pathogenesis[7,8]. Therefore, the term "common oral clefts" (OCs), which comprises cleft lip/alveolus and/or cleft palate, is introduced in this paper.

OCs are very complex and heterogeneous birth defects. During embryonic development of the head and neck area, many different cell biological mechanisms and genes are involved, related to different time frames[8,9]. Disturbance of this complex developmental process can result in many different types of OCs with variable degree of severity on clinical presentation[7]. Classically, OCs are divided into two categories: cleft lip with or without cleft palate (CL±P) and cleft palate only (CP), because of their embryologic and epidemiologic differences[3]. However, recently some studies have emphasized grouping cleft lip only (CL) and cleft lip with cleft palate (CLP) into different conditions, because of differences concerning their prevalence, relation to gender, relation to consanguinity and laterality, and different associations with other congenital anomalies[10,11]. Although the aetiopathogenesis has been widely studied, it is still poorly understood for all three categories of clefts. When considered as single defects, many genetic and environmental factors, such as nutrition and smoking, have been suggested[3,9,12,13]. To facilitate further genetic and aetiopathological studies and to improve prevention, diagnostics and treatment, detailed descriptions of OCs and other anomalies of the head and neck area are needed.

The importance of registering the type and number of congenital anomalies is long recognised. Worldwide, several congenital anomaly registries were established after the thalidomide 'epidemic' in the 1960s[5,14-19]. Most registries use a coding system based on the International Statistical Classification of Diseases and Related Health Problems (ICD) published by the World Health Organization. Because the ICD is not sufficiently detailed for more specialized purposes some registries use extensions of its codes, for

example the British Pediatric Association Classification of Diseases (BPA)[4,5,18,20]. The ICD (tenth revision) has a section entitled "Cleft lip and cleft palate" (Q35-37) to record oral clefts (median cleft lip included)[21]. These codes can give some information regarding the morphology and topography of the oral cleft, but not in great detail. Therefore, many registries do not supply the detailed information required for OCs as well as for other craniofacial congenital anomalies.

National registries

In the Netherlands, theoretically all surviving children with OCs who stay in the country are treated by one of the fifteen cleft palate teams[22]. These teams offer multidisciplinary treatment to patients with OCs according to the team protocols. Members of the teams belong to the Dutch Association for Cleft Palate and Craniofacial Anomalies (NVSCA). Important goals of this association are: a) description of the frequency and distribution of all categories and subgroups of OCs and other craniofacial anomalies, b) promotion of clinically-related research on aetiology, prevention, diagnostics and treatment of oral clefts and other craniofacial anomalies, and c) planning and quality surveillance[23,24]. In order to fulfil these goals a new descriptive recording form was developed based on the embryology of the head and neck area, expressing the morphology and topography of the anomalies[8,25,26]. Since 1997 the NVSCA maintains a national registry of congenital craniofacial anomalies, including OCs. Reporting is done for all new presurgery patients with OCs by the cleft palate teams through the standard NVSCA recording form (Appendix 1[22]).

Before 1997, precise national prevalence of OCs was not known in the Netherlands. Felix-Schollaert et al.[27] described an oral cleft prevalence of 13.8-17.7 per 10,000 live and stillbirths among children born in Dutch hospitals during 1982 and 1983. Hoeksma et al.[28] reported an estimated oral cleft prevalence of 17.3-18.9 per 10,000 live births for a one-year-period, based on questionnaires and medical records. Since 1981, Eurocat Northern Netherlands (NNL) maintains a congenital anomaly registry for the region Northern Netherlands. Recording is based on ICD/BPA codes and regional prevalence rates of CL±P and CP among live and stillbirths (including termination of pregnancy) are provided[2,20]. In addition, the National Obstetric and Neonatal Registries (LVR/LNR) record diagnoses of several congenital anomalies among live births and stillbirths from 16 weeks of gestation, and provide data regarding CL±P and CP from 1996 that were first published in an annual report in 2001[29]. In 2005, the prevalence of OCs in the Netherlands

was estimated based on the NVSCA registry and LVR/LNR. The estimated national prevalence was 19.2 per 10,000 live births and the ascertainment – the proportion of cases recorded in at least one of the two registries – of OCs in live births appeared to be high (96%)[30].

Validation of registries

Worldwide, medical information is routinely collected and ICD coded in a variety of medical registries. In the past two decades, these registry data have been widely used for health research[31]. Because in practice registry data can only be used for research purposes when registries provide reasonably valid information, many registries have been validated[17,31-34]. Therefore, a validation project of the NVSCA registry that evaluates data quality is essential to avoid invalid conclusions.

The NVSCA registry has a unique recording method, which is not based on a coding system but on the detailed description of the morphology and topography of each anatomic structure of the anomalies of the head and neck area e.g. lip, alveolus, hard and soft palate including uvula[22,26]. These detailed recording data are collapsible to more general diagnoses/codes and allow classifying oral clefts in many different ways. For instance, NVSCA data can be compared with those of other Dutch registries which include ICD/BPA codes (Eurocat NNL) or the categories: CL±P and CP (LVR/LNR). Vice versa, data of these registries cannot be converted into the detailed information of the NVSCA registry. Even when the quality is good, data of these registries do not reflect the severity and specific characteristics of OCs; for example, no distinction is made between cleft lip and cleft alveolus[20,29]. Therefore medical records were used as our gold standard to validate the detailed NVSCA data.

The aim of this study was to provide a comprehensive profile on the validity of the NVSCA registry data for common oral clefts in the Netherlands. In view of the huge amount of data available, the present study describes the study design and results after evaluation of the first part of the NVSCA recording form: i.e. the general items and the three common oral cleft categories. The validity of more specific features (side, topography and morphology) of the oral clefts and the associated additional congenital anomalies will be reported in future papers.

METHODS

NVSCA recording form and registry

The NVSCA registry is an anonymous prospective case registry that is formally fixed in accordance with the Dutch privacy law. All Dutch cleft palate teams record their live-born presurgery patients on the standard NVSCA form, after careful examination by one of their consulting physicians. The form is subdivided into a general section (including infant/parental characteristics e.g. gender, consanguinity and birth weight), a section for craniofacial anomalies including OCs, and a section for congenital anomalies of other parts of the body (Appendix 1). All individual anomalies of the head and neck area can be fully described by checking options regarding side, topography and morphology. In addition the form gives space for verbatim descriptions of a) craniofacial anomalies not appropriate by checking options, b) (preliminary) diagnosis of craniofacial anomalies and c) congenital anomalies of other organ systems[22,25,26]. Furthermore, a manual is included (Appendix 2). The form is usually completed in the postnatal period. When patients are adopted or the oral cleft is detected later in infancy, the form is completed (before surgery) at a later age[22]. The completed forms are sent to the NVSCA registry, the working group "Registration" checks the forms and subsequently the recorded information is transferred to the NVSCA registry database. At the end of each year the cleft palate teams perform case-ascertainment activities. Note that the NVSCA is not an ongoing registry and that no data from other sources are included.

Subjects

The validation project of registry data reported over a seven-year period was initiated and carried out in all fifteen cleft palate teams. Each team gave written permission for the review of patients' medical data. Principles outlined in the Declaration of Helsinki were followed. Between 1 January 1997 and 31 December 2003, 2553 patients with OCs (median cleft lip and atypical facial clefts excluded) with or without associated congenital anomalies were recorded in the NVSCA registry and transferred to the NVSCA database. From this database a random sample of 250 cases was taken.

Data collection and verification

The cleft palate teams supplied medical information on all responsible disciplines (Plastic Surgery, Orthodontics, Pediatrics, Clinical Genetics, Maxillofacial Surgery and Otorhinolaryngology). A single investigator (AMR) obtained relevant data of 250 cases by making a de-identified copy by digital camera of medical records (including information about clinic visits, consultations, diagnostic tests and hospitalizations), colour photographs, panoramic radiographs and dental casts. To be considered adequate, the information had to include at least one medical record. For 241 cases (96.4%) medical information was available for inspection and this criterion was met. Preoperative and/or postoperative colour photographs were obtained for 193 cases (77.2%). Panoramic radiographs and dental casts were retrieved for 26 cases (10.4%) and 91 cases (36.4%), respectively. Apart from the nine untraceable cases, one case with insufficient medical data and three cases which were operated on the oral cleft before registration were also excluded. Subsequently, this resulted in a total of 237 cases that remained in the study.
The same investigator, trained in recording principles and practice, performed data verification. The medical data were examined blindly and each of the 237 cases was reregistered with use of the standard NVSCA recording form (Appendix 1). The criteria used to define the type of OCs were established in collaboration with a second investigator (CVK) and in accordance with existing literature[7,8]. Guidance statements from the registry manual (Appendix 2) were used to record present congenital anomalies. All cases with unclear clinical information were discussed with the second investigator. Subsequently, the recorded data were transferred to an independent reregister database. This database was checked for nonexistent, inappropriate and invalid data, and corrected when necessary.

Data analysis

In the present study the following variables were validated: the general information (Clinical Genetics consulted, adoption/foster child, Caucasian father and mother, consanguinity, congenital abnormalities among relatives, common oral clefts among relatives, birth weight, gestational age and remarks about pregnancy) and the three common oral cleft categories (cleft lip/alveolus = CL/A, cleft lip/alveolus and palate = CL/AP, cleft palate = CP). These variables concern at birth information and obvious external defects, for which recording should be virtually complete[4]. To validate these items as accurate as possible, all available medical information, i.e. the reregister, was

used for comparison, since this reregister was the most complete available reflection of the cases' characteristics. Consequently, the NVSCA database was compared with the reregister database for concordance of information. Note that one case could contribute to more than one difference between the databases. In case of disagreement between the NVSCA and reregister database on the common oral cleft category (n=12), the second investigator reviewed the medical data blindly and recorded the oral cleft independently. Regarding all twelve cases, the findings of the second investigator agreed with those of the first investigator.

Statistical analysis

Characteristics of the study population are presented as percentages or means ± 1SD for the NVSCA database and reregister database. Comparisons were performed using the Chi-square test and Student's paired t-test.

To assess whether the NVSCA database accurately reproduced what was recorded in the reregister database, the observed agreement was assessed for dichotomous variables using two by two tables. In addition, the kappa statistic (κ) was used to describe agreement beyond chance. Kappa avoids the assertion that the reregister database has to be considered as a reference standard and it determines the extent to which the two databases identified the same cases, i.e. inter-database agreement[33,35]. According to the criteria reported by Landis and Koch and described by Quan et al.[31], a κ-value ranging from 0-0.20 indicates poor agreement; 0.21-0.40 fair agreement; 0.41-0.60 moderate agreement; 0.61-0.80 substantial agreement; 0.81-1 near perfect agreement. Because the reregister database could be considered as the best reflection of the cases' conditions, this database was designated as the gold standard to calculate sensitivity (the number of positive cases in the NVSCA database confirmed in the reregister database divided by the total number of positive cases in the reregister database), specificity (the number of NVSCA negatives confirmed by the reregister divided by the total number of negatives in the reregister), positive predictive value (the number of NVSCA positives that are confirmed by the reregister, divided by the total number of NVSCA positives) and negative predictive value (the number of NVSCA negatives confirmed by the reregister divided by the total number of NVSCA negatives). For continuous variables the differences between the databases were presented as medians and ranges and Pearson correlation coefficients were calculated.

For all outcome measures 95% confidence intervals [95% CIs] were calculated by assuming a normal distribution around the point estimate.

RESULTS

Characteristics of the study population are shown in Table 1. Distribution of gender, adoption/foster child, consanguinity, birth weight and common oral cleft categories were comparable between the databases. Although gestational age was similar on average between the databases, there appeared to be a significant difference on case level ($p=0.043$). Clinical Genetics consulted, congenital abnormalities among relatives, common oral clefts among relatives, and remarks about pregnancy were more often recorded in the reregister database ($p<0.05$), whereas Caucasian father and mother were more often recorded in the NVSCA database ($p<0.001$).

Agreement between the NVSCA and reregister database on the dichotomous general variables is shown in Table 2. The highest observed agreement was found for adoption/foster child and consanguinity (over 97%) and the lowest observed agreement was found for remarks about pregnancy (62.6%). For the remaining variables the observed agreement ranged from 73.4% (Clinical Genetics consulted) to 84.8% (common oral clefts among relatives). The κ-value ranged from 0.20 (remarks about pregnancy) to 0.76 (adoption/foster child); one item was at the level of poor agreement, three at the level of fair agreement, three at the level of moderate agreement and one at the level of substantial agreement. Sensitivity ranged from 25.0% for consanguinity to 96.5% for Caucasian mother. Meanwhile, specificity was high for all items (over 92%) except for Caucasian father and mother (36.4% and 31.3%, respectively). Positive predictive value was low for consanguinity (25.0%), but ranged for the other variables from 71.4% (adoption/foster child) to 96.8% (Clinical Genetics consulted). Negative predictive value ranged from 60.3% for remarks about pregnancy to 99.6% for adoption/foster child.

Validation of birth weight and gestational age was based on 196 and 186 cases, respectively, because of missing values in the NVSCA and reregister database. Agreement on birth weight was observed for 151 cases. For the remaining 45 cases a median difference of 50 gram was found with a range of 1 to 3010 grams. The Pearson correlation coefficient was 0.93 (95% CI: 0.91-0.95). Gestational age corresponded for 143 cases between the databases and disagreed for 43 with a median difference of 1 week and a range of 1 to 10 weeks. A Pearson correlation coefficient of 0.89 (95% CI: 0.86-0.92) was found.

Table 3 shows the agreement on the common oral cleft categories between the databases. The observed agreement was high for all three categories: 97.5% for both CL/A and CP and 94.9% for CL/AP. The κ-value was 0.94 for both CL/A and CP and 0.89 for CL/AP; all were at the level of near perfect agreement. The sensitivity was 98.6% for both

CL/A and CP, 89.7% for CL/AP and the specificity was over 97% for all categories. The positive and negative predictive values were over 93% for all three categories.

Table 1 Characteristics of the study population in the NVSCA database and reregister database.

Characteristic	**NVSCA**		**Reregister**		**Comparison***
General information	**Valid cases (n)**		**Valid cases (n)**		**p value**
Gender, % boys†	57.4	237	57.4	237	
Clinical Genetics consulted, % yes	26.2	237	51.1	237	<.001
Adoption/foster child, % yes	3.0	237	2.5	237	.779
Caucasian father, % yes	86.5	237	72.2	237	<.001
Caucasian mother, % yes	88.6	237	71.7	237	<.001
Consanguinity, % yes	1.7	237	1.7	237	1.0
Congenital abnormalities among relatives, % yes	23.2	237	40.5	237	<.001
Common oral cleft among relatives, % yes	13.9	237	23.2	237	.009
Birth weight in grams (mean ± SD)	3290 ± 718	218	3234 ± 699	208	.600
Gestational age in weeks (mean ± SD)	39 ± 2.4	216	39 ± 2.3	197	.043
Remarks about pregnancy, % yes‡	16.1	174	43.9	174	<.001
Common oral cleft					
Cleft lip/alveolus, % yes	31.6	237	30.0	237	.691
Cleft lip/alveolus and palate, % yes	37.6	237	40.9	237	.452
Cleft palate, % yes	30.8	237	29.1	237	.688

*Chi Square test for proportions; paired Student's t-test for continuous variables; † Gender information was given for medical data retrieval and therefore not compared between the databases; ‡ Introduced in 1999 on the NVSCA recording form and gradually filled in by the cleft palate teams.).

Table 2 Agreement between the NVSCA database and reregister database (gold standard) on general items (n = 237) * CI = confidence interval; † number of valid cases = 174.

General information	Agreement	κ value		Sensitivity	
	%		(95% CI)	%	(95% CI)
Clinical Genetics consulted	73.4	0.47	(0.38-0.57)	49.6	(40.4-58.8)
Adoption/foster child	98.7	0.76	(0.50-1.00)	83.3	(35.9-99.6)
Caucasian father	78.9	0.38	(0.25-0.51)	95.3	(91.0-98.0)
Caucasian mother	78.1	0.34	(0.21-0.47)	96.5	(92.5-98.7)
Consanguinity	97.5	0.24	(-0.16-0.64)	25.0	(0.6-80.6)
Congenital abnormalities relatives	76.8	0.48	(0.37-0.59)	50.0	(39.6-60.4)
Common oral cleft relatives	84.8	0.50	(0.37-0.64)	47.3	(33.7-61.2)
Remarks about pregnancy†	62.6	0.20	(0.09-0.32)	26.6	(17.3-37.7)

General information	Specificity		(+) predictive value		(-) predictive value	
	%	(95% CI)	%	(95% CI)	%	(95% CI)
Clinical Genetics consulted	98.3	(93.9-99.8)	96.8	(88.8-99.6)	65.1	(57.6-72.2)
Adoption/ foster child	99.1	(96.9-99.9)	71.4	(29.0-96.3)	99.6	(97.6-100.0)
Caucasian father	36.4	(24.9-49.1)	79.5	(73.3-84.8)	75.0	(56.6-88.5)
Caucasian mother	31.3	(20.6-43.8)	78.1	(71.9-83.5)	77.8	(57.7-91.4)
Consanguinity	98.7	(96.3-99.7)	25.0	(0.6-80.6)	98.7	(96.3-99.7)
Congenital abnormalities relatives	95.0	(90.0-98.0)	87.3	(75.5-94.7)	73.6	(66.6-79.9)
Common oral cleft relatives	96.2	(92.2-98.4)	78.8	(61.1-91.0)	85.8	(80.2-90.3)
Remarks about pregnancy†	92.6	(85.4-97.0)	75.0	(55.1-89.3)	60.3	(51.9-68.3)

Table 3 Agreement between the NVSCA database and reregister database (gold standard) on common oral cleft category (n = 237). CI = confidence interval; CL/A = cleft lip/alveolus; CL/AP = cleft lip/alveolus and palate; CP = cleft palate.

Common cleft category	Agreement %	κ value		Sensitivity %	(95% CI)
CL/A	97.5	0.94	(0.89-0.99)	98.6	(92.4-100.0)
CL/AP	94.9	0.89	(0.84-0.95)	89.7	(81.9-94.9)
CP	97.5	0.94	(0.89-0.99)	98.6	(92.2-100.0)

Common cleft category	Specificity %	(95% CI)	(+) predictive value %	(95% CI)	(-) predictive value %	(95% CI)
CL/A	97.0	(93.1-99.0)	93.3	(85.1-97.8)	99.4	(96.6-100.0)
CL/AP	98.6	(94.9-99.8)	97.8	(92.1-99.7)	93.2	(87.9-96.7)
CP	97.0	(93.2-99.0)	93.2	(84.7-97.7)	99.4	(96.6-100.0)

DISCUSSION

Validity NVSCA registry

This study assessed the accuracy and completeness of a part of the recording data of the NVSCA registry on OCs. The general information and oral cleft categories were validated using a reregister database based on all available medical data for comparison. The oral cleft categories (CL/A, CL/AP and CP) were recorded most accurately and completely in the NVSCA registry. All categories were identified perfectly with validity measures of more than 89% and near perfect agreement (Table 3).

In contrast, regarding the general information data quality varied by item (Table 2). Information on consultation of Clinical Genetics was missing for about 50% of the cases. This is related to the fact that generally the patient is recorded in the postnatal period before the clinical geneticists are consulted. Regarding data on adoption/foster child and consanguinity, the quality was good. For these two items a "high agreement but low kappa" was found, which can be explained by the low prevalence of these items. This phenomenon was described by Feinstein and Cicchettis[35]. They identified the following paradox: when the vertical and horizontal marginal totals of the 2x2 tables are symmetrically unbalanced, high observed agreement values can be associated with low κ-values. The items Caucasian father and mother were considerably overestimated in the

NVSCA database with more than 60% false positives. This may not be surprising because the distinction between the Caucasian race and other races may sometimes be too subtle for recorders. Regarding the occurrence of congenital abnormalities among relatives and common oral clefts among relatives there may be insufficient inquiry by the specialists, because approximately 50% of the information recorded in the reregister database was found in the NVSCA database. For the item remarks about pregnancy, 27% of the reregister information was recorded in the NVSCA registry. This could be explained by the fact that "remarks about pregnancy" is a not well-defined item. As a result, it is not clear for the recorder what has to be recorded at this item. Birth weight and gestational age were underreported on the NVSCA recording form as well as in the medical records. Since both are at birth information, the only explanation for the degree of underreporting and disagreement is insufficient and inaccurate reporting and documentation. Overall, validity on the general items was expected to be higher because most of this information could be directly transcribed at admission. However, incompleteness of data on certain registry key items (for example, gestational age) is also reported elsewhere[36].

Publications on the evaluation of data quality of congenital anomaly registries are scarce[19,36] and few data are available on the validity of registration of oral clefts[14,17]. However, numerous articles have described the operations and strategies for case ascertainment of congenital anomaly registries. These show that case ascertainment is often still a problem and varies by defect, region and hospital[15,16,19]. For example, according to Boyd et al.[15], in the UK the surveillance of congenital anomalies by the national register is currently inadequate. Nevertheless, the ascertainment for oral clefts appeared to be among the highest in this register, 83% for CL±P and 71% for CP. A Norwegian study reported an ascertainment of 94% for CLP cases in a national birth registry and a lower ascertainment of 83% and 57% for CL and CP cases, respectively[17]. In another Scandinavian study, the ascertainment of oral clefts was 78% (CL: 74%, CLP: 84% and CP: 75%) for the Swedisch Birth Defects Registry[14]. As mentioned before, Anthony et al.[30] estimated the total number of live birth cases with OCs during 2002 in The Netherlands based on two Dutch registries: the NVSCA and LVR/LNR. 87% of the total number of cases found in this study appeared to be reported to the NVSCA registry, which is rather comparable to the ascertainment of the studies mentioned above. Because cases with severe additional anomalies resulting in neonatal deaths may not reach the cleft palate teams, these are most often not included in the NVSCA registry. This might explain why the ascertainment was not 100%.

Problems with registry data

In general, problems with quality of registry data can be caused by incorrect data entry, lack of entry of available information, or the original information may be correctly entered into the database but may not reflect the true condition or characteristics of the case[34]. The latter can arise as a result of physicians' misdiagnoses, incomplete documentation, or incomplete/incorrect recording of a condition[31].

As many congenital anomaly registries are based on (ICD) codes, they are affected by specific problems inherent in coding systems. Certainly, coding is essential for data management and retrieval in birth defects surveillance programs, because they process large numbers of cases[4,5,18]. Furthermore, coding allows aggregation of similar cases. Thus, when collecting data on a large scale the use of standard coding systems is necessary; however, it is also known that it brings structural limitations. Codes reduce the amount of clinical detail and coders will differ with respect to definitions and their application[4,16,18,32,33]. Moreover, coding is generally based on written medical data and thus correct recording of a condition also depends on the quality of this information[32].

The NVSCA recording form is designed to prevent recording errors as much as possible. However, accurate and complete recording still depends on the knowledge and the willingness of physicians to record accurately. To prevent problems with interpretation of the recording form as much as possible, the NVSCA provides a registry manual (Appendix 2).

Recently a digital NVSCA recording form was developed to make recording easier and to promote accurate and complete recording[23]. This has many advantages: no paperwork has to be sent by mail and can be lost, data do not need to be transferred from a paper form to a digital database, and obligatory fields are used for e.g. birth weight and gestational age.

Strengths and limitations

One of the strengths of this study is the national distribution of the sampling frame, including cleft palate teams of large urban teaching/specialist hospitals as well as of small regional ones. During the last decade the diagnostic strategy and management of patients with OCs have undergone important changes. For example, most cleft palate teams now use imaging procedures and digitalization, which is needed for multidisciplinary treatment and favours this retrospective study. The retrieval of medical records was successful; for almost all cases at least one medical record (96.4%) was obtained with in addition pre-/postoperative colour photographs and/or panoramic radiographs and/or

dental casts (82.8%).

Based on the strengths described above, the medical data were considered as the best available reflection of the cases' conditions, and therefore information extracted from these data was accepted as the gold standard. However, the use of medical data to validate registry data also has limitations. Medical data can never be equal to the presentation of patients in the outpatient clinical setting. In the present study, the amount and quality of medical information varied between the teams. For example, for some teams dental casts were lacking and in some cases less extensive medical information was caused by death of the patient, or change of the treating cleft palate team. Nevertheless, no systematic pattern regarding the quality of medical data was found when analyzing case characteristics and the oral cleft categories could be recorded successfully for all 237 cases. Another limitation is that although review of medical data was particularly thorough, errors that occur when clinical information is documented in the medical records cannot be captured[31,32]. On the other hand, an advantage of our method is that practice activity was examined retrospectively, so staff was not alerted to the study beforehand and had no opportunity to change recording behaviour.

Conclusions

Despite the limitations and challenges described, this study provides useful information on the quality of the NVSCA registry data that varies by type of information. Validity appears to be very good for the three common oral cleft categories and reasonable to satisfying for the general items. As a result of this study and other data quality measures[30], the quality level of the NVSCA registry appears to be high. To attain the goals of the NVSCA optimally, it is important to get more insight in the detailed data. Therefore, further analysis will be carried out of the specific common oral cleft features (side, topography and morphology) and associated additional congenital anomalies.

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Registration of clefts and craniofacial malformations | **Hospital** | Dutch Association for Cleft Palate and Craniofacial Anomalies | **Please fill in white boxes**

1. GENERAL

Date of this registration _____
Patient identification number _____
Date of birth _____
Gender ◯ Male ◯ Female ◯ Unknown
Name of physician _____
Clinical genetics consulted ◯ Yes ◯ No ◯ Unknown
If affirmative, please specify center _____
Adoption or foster child ◯ Yes ◯ No ◯ Unknown

Caucasian father ◯ Yes ◯ No ◯ Unknown
Caucasian mother ◯ Yes ◯ No ◯ Unknown
Consanguinity ◯ Yes ◯ No ◯ Unknown
If affirmative, please specify _____
Congenital abnormalities among relatives ◯ Yes ◯ No ◯ Unknown
If affirmative, please specify _____
Birth weight (grams) _____
Gestational age (weeks) _____
Remarks about pregnancy ◯ Yes ◯ No ◯ Unknown
If affirmative, please specify _____

2. ABNORMALITIES OF THE HEAD AND NECK AREA

L = left R = right M = median	Mouth							Ala nasi	Septum nasi	Calvaria / facial skull										Orbita	Eyes	Eye-lids	Ears	Soft tissue*
	Lip	Pre./ max.*	Pre.*	Pal. dur.*	Pal. mol.*	Uvula	Ton.*			Par.*	Occ.*	Tem.*	Fro.*	Nas.*	Zyg.*	Max.*	Man.*	l.o.d.*						
Cleft									M												L R			
Complete	L R	L R		L R																				
	M		M	M	M	M	M										M							
Incomplete	L R	L R		L R																				
	M		M	M	M	M	M										M							
Submucous	L R	L R		L R																				
	M		M	M	M	M	M										M							
Agenesis[1]	L R		L R	L R	L R	L R		L R		L R		L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R
	M						M		M		M													M
Aplasia[2]	L R		L R	L R	L R	L R	L R	L R		L R		L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R
	M						M		M		M													M
Protruding																						L R	L R	
Adherent							L R															L R	L R	
Appendages																						L R	L R	L R
																								M
Hypoplasia[3]	L R		L R	L R	L R	L R	L R	L R		L R		L R	L R	L R	L R	L R	L R		L R	L R	L R	L R	L R	L R
	M								M		M							M						M
Hyperplasia[4]	L R		L R	L R	L R	L R	L R	L R		L R		L R	L R	L R	L R	L R	L R		L R	L R	L R	L R	L R	L R
	M								M		M							M						M
Synostosis										L R	L R	L R	L R	L R	L R	L R	L R							
										M			M				M							
Non synostosis										L R	L R	L R	L R	L R	L R	L R	L R							
										M			M				M							

Other abnormalities of the head and neck area, not appropriate above ◯ Yes ◯ No ◯ Unknown _____

■ **(Preliminary) diagnosis** ◯ **Yes** ◯ **No** ◯ **Unknown** _____

3. OTHER ABNORMALITIES

Circulatory system ◯ Yes ◯ No ◯ Unknown _____
Respiratory system ◯ Yes ◯ No ◯ Unknown _____
Digestive system ◯ Yes ◯ No ◯ Unknown _____
Urogenital system ◯ Yes ◯ No ◯ Unknown _____
Central nervous system ◯ Yes ◯ No ◯ Unknown _____
Vertebral column ◯ Yes ◯ No ◯ Unknown _____
Body wall ◯ Yes ◯ No ◯ Unknown _____
Skin ◯ Yes ◯ No ◯ Unknown _____
Upper limbs ◯ Yes ◯ No ◯ Unknown _____
Lower limbs ◯ Yes ◯ No ◯ Unknown _____
(Preliminary) common diagnosis ◯ Yes ◯ No ◯ Unknown _____

1 = absent; 2 = present, wrong shape; 3 = right shape, too small; 4 = right shape, too large
* Pre./max. = premaxilla - maxilla; Pre. = premaxilla; Pal.dur. = palatum durum; Pal.mol. = palatum molle; Ton. = tongue; Par. = os parietale; Occ. = os occipitale; Temp. = os temporale; Fro. = os frontale; Nas. = os nasale; Zyg. = zygoma; Max. = maxilla; Man. = mandible; l.o.d. = interorbital distance; Soft tissue = soft tissue of the head and neck area

Please send form to Mw Dr Chr. Vermeij-Keers; Research Unit Department of Plastic and Reconstructive Surgery; Room EE 1591; Erasmus MC - University Medical Center Rotterdam; P.O. Box 2040; 3000 CA Rotterdam; The Netherlands

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Appendix 1

Recording form of the NVSCA registry. Reproduced by kind permission of the Department of Plastic and Reconstructive Surgery, Erasmus MC - University Medical Center Rotterdam, The Netherlands.

Manual for the NVSCA registration form

- One registration form for each un-operated patient.
- Please only use ballpoint to mark the white boxes and to fill in the text boxes
- The bold terms in this manual refer to the items in the registration form.

Ad **2. ABNORMALITIES IN HEAD AND NECK AREA**

- The registration is based on aberrant embryonic development of the face and skull. Roughly, embryonic development can be distinguished in fusion of the facial/palatine swellings and differentiation of the calvarian and facial bones, and soft tissue. Only fusion and differentiation defects of the primary palate (right and/or left) and of the secondary palate (left or right or median) are registered as cleft. All other defects of bones and soft tissue, including clefts, are registered on the basis of their absence or presence and shape (**agenesis** or **aplasia**, **hypoplasia**, and **hyperplasia**), except for colobomas of the eyeball (see below). The definition of **agenesis**, **aplasia**, **hypoplasia**, and **hyperplasia** and the explanation of the abbreviations are decribed in the footnotes of the registration form.
- More abnormalities can be filled in for the same patient. If an abnormality can not be registered, this abnormality should be scored in the box **other abnormalities of the head and neck area, not appropriate above, yes**, and it should be specified.
- Cysts and fistulas of the tongue in the median are scored as **aplasia** of the **tongue** in the **median** plane.
- Hypotelorism and hypertelorism may be accompanied with an aberrant septum nasi in the median plane. For example, hypotelorism could be accompanied with **agenesis**, **aplasia** or **hypoplasia** of the **septum nasi**, and hypertelorism could be accompanied with **cleft** (= bifid), **aplasia**, or **hypoplasia** of the **septum nasi**. Furthermore, the aberrant interorbital distances (**i.o.d.**) is registered.
- **Non synostosis** concerns a skull shape comparable with synostosis, but the sutures are open. Synostosis of sutures are registered as **synostosis** of the involved bones. **Synostosis** of both frontal bones, or both parietal bones are registered in the **median**.
- Colobomas of the eyeball concern fusion defects of the fissure, and these are scored as **cleft** of the **eyes**.
- Entropion and ectropion should be registered as **protruding eyelids**. Ptosis and phimosis of the eyelids, and epicanthal folds are scored as **aplasia** of the **eyelids**. Microblepharon is registered as **hypoplasia** of the **eyelids**.
- Colobomas of the eyelids, ears and ala nasi, are scored as **aplasia** of the **eyelids**, **ears**, and **ala nasi**.
- Aberrant position of the ears, such as low set or tilted ears, is filled as **miscellaneous ears**.
- If a diagnosis of the *head and neck area* has been established, **(preliminary) diagnosis** should be filled in (**yes**) and should be specified. Moreover, all abnormalities should be registered in this box.

Ad **3. OTHER ABNORMALITIES**

- **Body wall** concerns thoracic and abdominal wall
- Abnormalities of the shoulder and pelvis are filled in as abnormalities of **upper** and **lower limbs**, respectively.
- If the abnormalities are part of a syndrome, **(preliminary) common diagnosis** should be filled in (**yes**), and it should be specified

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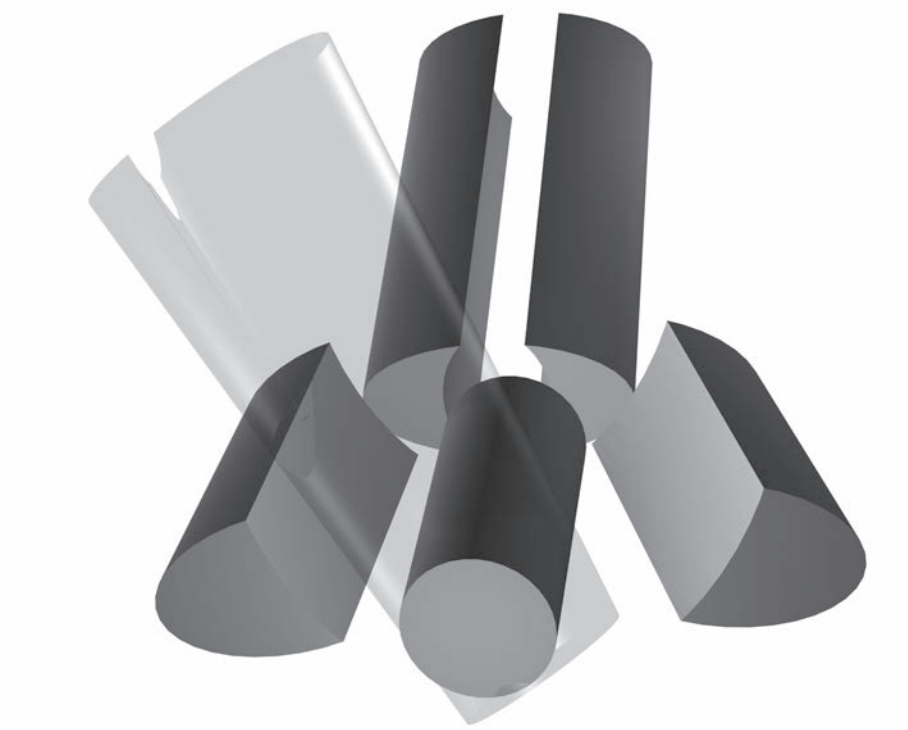
6

VALIDATION OF THE DUTCH REGISTRY COMMON ORAL CLEFTS: QUALITY OF RECORDING SPECIFIC ORAL CLEFT FEATURES



AM Roozendaal, AJM Luijsterburg, AD Mohangoo, ED Ongkosuwito, S Anthony, C Vermeij-Keers. Cleft Palate – Craniofacial Journal. 2012, 49: 609-617.

SUMMARY

Objective: Since 1997, common oral clefts (OCs) in the Netherlands have been recorded in the national OC registry using a unique descriptive recording system. This study validates data on the topographic-anatomical structure, morphology, and side of individual anomalies of the primary palate and secondary palate that form the OC.

Design: Validation study.

Setting: All 15 Dutch cleft palate teams reporting presurgery OC patients to the national registry.

Patients: A random sample of 250 cases registered in the national database with OCs during 1997-2003; 13 cases were excluded.

Main outcome measures: By linking registry data with clinical data, we identified differential recording rates by comparing the prevalence, and we measured the degree of agreement by computing validity and reliability statistics.

Results: The topographic-anatomical structures (lip, alveolus, hard and soft palate) of the anomalies had near perfect inter-database agreement with a sensitivity of 88%-99%. However, when analyzing the individual anomalies in detail (morphology and side), validity decreased and depended on morphological severity. This association was most evident for anomalies of the secondary palate. For example, sensitivity was higher for "complete cleft hard palate" (92%) than for "submucous cleft hard/soft palate" (69%).

Conclusions: Overall, validity of Dutch registry data on OCs is good, supporting the feasibility of this unique recording system. However, when analyzing OC data in detail, the quality appears to be related to anatomical location and morphological severity. This might have implications for etiologic research based on registry data, and guidelines on neonatal examination.

Keywords: cleft lip, cleft palate, registry, validation.

INTRODUCTION

Common oral clefts (OCs) are very complex and heterogeneous birth defects affecting the lip, alveolus, hard palate, soft palate, and uvula. In the embryonic development of the primary palate (the presumptive lip and alveolus) and secondary palate (the presumptive hard palate, soft palate, and uvula), many different cell-biological mechanisms and genes are involved, related to different time frames. During the formation of the primary palate and secondary palate, complex embryological processes - including outgrowth, fusion, and differentiation (into bone and musculature) of the facial swellings and of the palatine processes - take place[1-3]. Disturbance of these developmental processes can result in many different cleft types with variable degree of severity on clinical presentation[3-5].

Although the aetiopathogenesis of OCs has been widely studied, it is still poorly understood[6]. To facilitate further genetic and aetiopathological studies and to improve prevention, diagnostics, and treatment, it is of paramount importance that details of all OC types are described and recorded. Worldwide, many registration systems have been developed in order to record congenital anomalies, including OCs[7-12]. These registries classify OCs according to the International Classification of Diseases (ICD) or its extensions, thereby providing some information about topography, but not always complete information about morphological severity (e.g. completeness or incompleteness of the cleft)[7,10,13]. Since different oral cleft types, which have specific topographic and morphologic features, originate from different time frames and are related to specific genes and cell-biological mechanisms, detailed information on the topography and morphology is essential for fundamental research on OCs. Therefore, a unique detailed recording system for OCs and other craniofacial anomalies has been developed on behalf of the Dutch Association for Cleft Palate and Craniofacial Anomalies (NVSCA). This unique NVSCA system is based on the embryology of the head and neck area and records all the individual anomalies of the primary and/or secondary palate that form the OC. Besides the topographic-anatomical structure and side, the morphology of each anomaly can be described to anticipate all conceivable anomalies. Since its establishment in 1997, virtually all new live-born presurgery patients with OCs in the Netherlands - an average of 351 patients per year - have been reported to the national NVSCA registry[5].

The main purpose of the NVSCA registry is to provide a solid basis for epidemiological, clinical, and fundamental research. To serve this purpose, it is crucial to ensure that the data provided by the registry are of high quality. Sound description and complete

reporting of OCs and their specific features are necessary to maintain high standards of data quality. Previously, it was shown that the case-ascertainment of OCs in the NVSCA registry is high[14]. In addition, we found recently that the NVSCA registry has high quality data on the three OC categories: cleft lip/alveolus; cleft lip/alveolus and palate; and cleft palate[15]. As described by Luijsterburg and Vermeij-Keers[5], these three categories manifest very heterogeneous cleft types, composed of individual anomalies of the primary and/or secondary palate having specific features regarding topographic-anatomical structure, morphology, and side. However, it is unknown how complete and accurate the individual anomalies in OCs have been recorded in the NVSCA registry.

The aim of this study was to investigate the quality of the NVSCA data on the individual anomalies of the primary palate and secondary palate in OCs, by validating the registry data on the specific features of the anomalies: topographic-anatomical structure, morphology, and side. By linking the NVSCA database with a new independent reregister database derived from medical data review, we were able to identify differential recording rates by comparing the prevalence and to measure the degree of agreement by computing validity and reliability statistics.

METHODS

NVSCA registry

The methodology of the NVSCA registry is described in detail elsewhere[5,15] and is summarized here. The NVSCA registry is an anonymous registry that was formally established in accordance with Dutch privacy law. All Dutch cleft palate teams report their new live born patients with OCs - before these patients have an oral cleft operation - using the NVSCA recording form. This form is composed of three parts: a general section (infant/parental characteristics), a section for craniofacial anomalies including OCs, and a section for congenital anomalies of other organ systems; a manual is available[5,15]. The section for OCs consists of a two-dimensional table, in which the specific features of the individual anomalies that form the OC can be described. As shown in Figure 1, the X-axis shows the topographic-anatomical structures: lip, alveolus (embryologically developed from the premaxillae and maxillae), hard palate (palatum durum), soft palate (palatum molle), and uvula. The Y-axis depicts the morphology (complete, incomplete, and submucous), and the checking boxes represent the side (left, right, and median).

The recording form is completed by the consulting physician during the first visit of the patient to the cleft palate team, and subsequently the form is sent to the NVSCA registry. The "Registration" working group checks the recorded data before these are transferred to the NVSCA database. In addition, the cleft palate teams perform case-ascertainment activities annually. Note that the NVSCA does not have active follow-up of patients, and that no data from other sources are included.

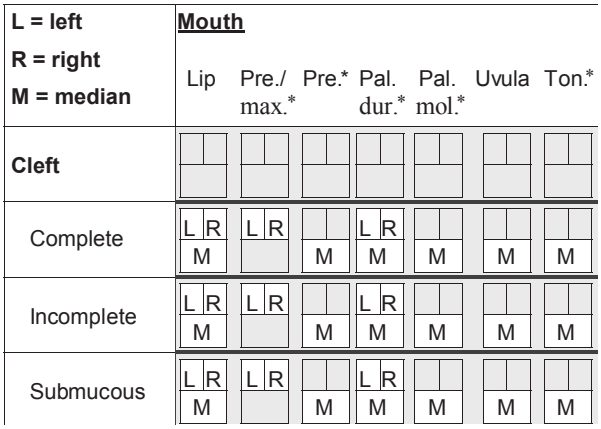


Figure 1
Section of the NVSCA recording form for common oral clefts in which the specific features of the individual anomalies that form the oral cleft can be described. The X-axis shows the topographic-anatomical structures: lip, alveolus (embryologically developed from the premaxillae and maxillae), hard palate (palatum durum), soft palate (palatum molle), and uvula; the Y-axis depicts the morphology: complete, incomplete, and submucous; and the checking boxes represent the side: left, right, and median. Pre./Max. = premaxilla – maxilla; Pre. = premaxilla; Pal.dur. = palatum durum; Pal.mol. = palatum molle, Ton = tongue..

Subjects

This validation study was initiated and carried out in the 15 Dutch cleft palate teams; all gave written permission for review of patients' medical data. Principles outlined in the Declaration of Helsinki were followed. During a seven-year-period (1997-2003), 2553 patients were registered in the national NVSCA database with an OC. Patients with median cleft lip/alveolus or atypical facial clefts were excluded because of their different pathogenesis[1,4]. From this database, a study population of 250 cases was selected using a standard random-sampling technique in SPSS version 17.0®.

Data collection and verification

We used medical data to validate the NVSCA data on the specific features of the individual anomalies in OCs. The methods of medical data collection and verification were described in a previous paper by Rozendaal et al.[15] and are summarized here.

The relevant medical information, including medical records, color photographs, panoramic radiographs, and dental casts, was supplied by the cleft palate teams. For 241 of the 250 cases (96.4%), the minimum criterion for inclusion - the availability of at least one medical record - was met. Apart from the nine untraceable cases, we excluded one case that had insufficient medical information to record the cleft, and three cases that had undergone oral cleft surgery before registration. This resulted in a total of 237 cases that remained in the study.

Using the medical information that was created before as well as after completion of the original NVSCA recording forms, a single investigator (AMR) recorded each case blindly on the standard NVSCA form[15]. The criteria used to define the type of OC were established in accordance with existing literature[1]. If the medical information was insufficient to record a specific feature, for example the morphology or side of the hard palate, the investigator noted this on the form. This was done to allow exclusion of the case at a later stage from the specific feature's analysis. All the recorded data were then transferred to an independent reregister database, and finally, this database was checked for nonexistent, inappropriate, and invalid data.

Statistical analysis

To get complete insight into the quality of the detailed registry data on the individual anomalies of the primary palate and secondary palate, their specific features were validated step-by-step. First, we analyzed the topographic-anatomic structures (lip, alveolus, hard palate, and soft palate including the uvula), then the morphology of the topographic-anatomic structures (e.g. complete cleft lip), then the side of the topographic-anatomical structures (e.g. left cleft lip), and finally the morphology and side of the topographic anatomical structures (e.g. left complete cleft lip), i.e. the complete reflection of the individual anomaly. Note that the side of the soft palate including the uvula was not analyzed, since clefts of the soft palate and uvula always develop in the median.

The prevalence of the specific features in the individual OC anomalies was calculated for both the NVSCA and the reregister. In addition, the NVSCA database was compared with the reregister database for concordance of individual patient data. Note that one case may

contribute to more than one difference between the databases. In case of disagreement between the databases on a specific feature (n=99), a second investigator (CVK) reviewed the medical data blindly and recorded the OC independently on a new NVSCA recording form. If the two investigators disagreed, there was discussion until consensus was reached (n=21).

It is known that the "disease prevalence" can affect reliability and validity statistics[16-18], and that the confidence intervals in reliability and validity statistics reflect the precision of the outcome measures. We validated therefore only those anomalies individually that had: a) a prevalence of n>10 in the NVSCA database; and b) a sufficiently small 95% confidence interval (CI) for all reliability and validity measures (distance between the upper and lower limit of 95% CI <0.50 for kappa and <50% for sensitivity, specificity, positive predictive value, and negative predictive value). The anomalies not meeting these two criteria were grouped together with their embryologically related anomalies according to the classification of fusion and differentiation defects. The concept of this classification was described in detail previously[3] and is briefly explained here. This classification is based on the normal and abnormal development of the primary and secondary palate. During the formation of these structures, fusion and differentiation processes are regulated in time and place. Disturbances of these complex processes can give rise to fusion and/or differentiation defects of the lip, alveolus, hard palate, and soft palate including the uvula. Theoretically, all individual anomalies of the primary palate and secondary palate that form the OC can be classified as a fusion or differentiation defect. The template for deciding which anomaly is a fusion or differentiation defect is listed in Table 1[3].

When analyzing the morphology and/or side of the topographic-anatomical structures, the following anomalies were grouped together. We grouped "submucous cleft lip" together with "incomplete cleft lip", since both are differentiation defects of the lip. The differentiation defect "submucous cleft alveolus" was grouped together with "incomplete cleft alveolus", which is - in combination with an "incomplete/submucous cleft lip" - also a differentiation defect of the alveolus. We grouped "submucous cleft hard palate" together with "submucous cleft soft palate", as both anomalies are late differentiation defects of the secondary palate. The new group "submucous cleft hard/soft palate", which still had a 95% CI that was too wide, was not grouped further, because other differentiation defects of the secondary palate do not exist. "Incomplete cleft soft palate" and "complete cleft soft palate" were grouped together, because both are fusion defects of the soft palate. The anomaly "right cleft hard palate" was grouped together with "left

Table 1 Classification of the individual cleft anomalies of the primary palate and secondary palate according to fusion and differentiation defects. Any combination of anomalies of the lip, alveolus, hard palate, and soft palate is allowed.

fusion defects	primary palate	complete cleft lip
		complete cleft alveolus
		incomplete cleft alveolus **(only if the lip is normal or has a complete cleft)**
	secondary palate	complete cleft hard palate
		incomplete cleft hard palate
		complete cleft soft palate including uvula
		incomplete cleft soft palate including uvula
differentiation defects	primary palate	incomplete cleft lip
		submucous cleft lip
		incomplete cleft alveolus **(only if the lip has an incomplete or submucous cleft)**
		submucous cleft alveolus
		hypoplastic lip/alveolus
	secondary palate	submucous cleft hard palate
		submucous cleft soft palate including uvula

cleft hard palate", since both are unilateral fusion defects of the hard palate. Because the anomaly "right submucous cleft alveolus" had not been recorded in the NVSCA database, it was not validated. Finally, because practically all incomplete and submucous clefts of the hard palate present in the NVSCA database were median clefts, the side was not validated for these anomalies.

The prevalence data were presented as numbers and percentages. Prevalence comparisons between the databases were performed using the Chi-square test. P values of <0.05 were considered statistical significant.

While the comparison of prevalence rates indicates the extent to which the two databases detected the specific features of the individual anomalies, it does not indicate whether they have identified the same patients, and whether the NVSCA database accurately reproduced what was recorded in the reregister. We therefore determined the extent to which the two databases identified the same cases, i.e. the inter-database agreement, by calculating the kappa (κ). Kappa describes the agreement beyond chance and avoids the assertion that the reregister database has to be considered as a reference standard[16,19]. According to criteria reported by Landis and Koch[20] and described by Quan et al.[21], a κ value ranging from 0-0.20 indicates poor agreement; 0.21-0.40 fair agreement; 0.41-0.60

moderate agreement; 0.61-0.80 substantial agreement; and 0.81-1 near perfect agreement. To assess whether the NVSCA database accurately reproduced what was recorded in the reregister, we used the reregister - the best available reflection of the cases' conditions - as the gold standard to calculate the sensitivity (number of NVSCA positives confirmed by the reregister, divided by the total number of reregister positives), specificity (number of NVSCA negatives confirmed by the reregister, divided by the total number of reregister negatives), positive predictive value (number of NVSCA positives confirmed by the reregister, divided by the total number of NVSCA positives), and negative predictive value (number of NVSCA negatives confirmed by the reregister, divided by the total number of NVSCA negatives). For all outcome measures, 95% CIs were calculated, assuming a normal distribution around the point estimate. Statistics were performed using two software packages (SPSS version 17.0® and Stata version 10.0®).

RESULTS

Prevalence of specific features of individual anomalies in common oral clefts

Table 2 presents the prevalence of the specific features of the individual anomalies of the primary and secondary palate by database. The prevalence of the 4 topographic-anatomical structures (lip, alveolus, hard palate, and soft palate including the uvula) in the NVSCA database was similar to that in the reregister database. For the 2 structures of the primary palate (lip and alveolus), the distribution of the morphology, of the side, and of the morphology and side in the NVSCA was similar to that in the reregister. For 1 structure of the secondary palate (hard palate), however, 3 anomalies were underreported significantly in the NVSCA (incomplete cleft hard palate: p=0.007; median cleft hard palate: p=0.009; and median incomplete cleft hard palate: p=0.006). Only 1 anomaly (left complete cleft hard palate) was significantly less frequent in the reregister than in the NVSCA (4.8% vs. 11.0%, p=0.015).

Agreement on specific features of individual anomalies in common oral clefts

Table 3 shows the degree of agreement between the databases for the specific features of the individual anomalies of the primary and secondary palate. When analyzing the morphology and/or side of the topographic-anatomical structures, several anomalies did

not meet the criteria for validation (i.e. they had a prevalence of n<10 in the NVSCA database and/or 95% CIs for reliability and validity measures that were too wide). These anomalies were therefore grouped together with their embryologically related anomalies as described in the methods section.

Topographic-anatomical structure

All 4 topographic-anatomical structures had near perfect inter-database agreement (κ value: 0.82-0.98) with a sensitivity of 87.8% or over, a specificity and positive predictive value of more than 95%, and a negative predictive of 84.5% and over.

Morphology of topographic-anatomical structure

After regrouping the anomalies, 4 anomalies of the primary palate remained. Table 3 shows that the κ value ranged from 0.67 to 0.84; 1 anomaly (incomplete/submucous cleft alveolus) was at the level of substantial agreement, and 3 were at near perfect agreement. Sensitivity ranged from 68.4% for "incomplete/submucous cleft alveolus" to 97.0% for "complete cleft lip". Positive predictive value ranged from 78.3% for "complete cleft lip" to 97.7% for "incomplete/submucous cleft lip". The specificity and negative predictive value were over 87% for all 4 anomalies.

For the remaining 4 anomalies of the secondary palate, the κ value ranged from 0.43 to 0.91; 1 anomaly (incomplete cleft hard palate) was at the level of moderate agreement, 2 were at substantial agreement, and 1 (complete/incomplete cleft soft palate) was at near perfect agreement. Sensitivity was 35.3% for "incomplete cleft hard palate", 69.2% for "submucous cleft hard/soft palate", and over 91% for the other 2 anomalies. Positive predictive value ranged from 75.0% for "incomplete cleft hard palate" to 98.7% for "complete/incomplete cleft soft palate". The specificity and negative predictive value were over 87% for all 4 anomalies.

Side of topographic-anatomical structure

Table 3 shows that all 4 anomalies of the primary palate had near perfect inter-database agreement (κ value: 0.84-0.95), with a sensitivity of 81.4% or over and a specificity, positive predictive value, and negative predictive value of more than 91%.

For the secondary palate, there were 2 remaining anomalies after regrouping. 1 anomaly (left/right cleft hard palate) had a κ value of 0.42 (moderate agreement), sensitivity of 73.7%, positive predictive value of 35.9%, and specificity and negative predictive value of 88.0% and over. The other anomaly (median cleft hard palate) had a κ value of 0.62

Table 2 Prevalence of specific features of individual anomalies of the primary palate and secondary palate in common oral clefts (total sample size: n = 237).

Specific feature of individual abnormality	NVSCA		Reregister		cases with info*	
	n	%	n	%	n	p value†
Topographic-anatomical structure						
primary palate						
cleft lip	164	69.2	164	69.2	237	1.000
cleft alveolus	126	53.4	139	58.9	236	0.228
secondary palate						
cleft hard palate	117	50.0	128	54.7	234	0.309
cleft soft palate	160	67.5	166	70.0	237	0.552
Morphology of topographic-anatomical structure						
Primary palate						
complete cleft lip	83	35.2	67	28.4	236	0.114
incomplete cleft lip	85	36.0	102	43.2	236	0.110
submucous cleft lip	5	2.1	13	5.5	236	0.055
complete cleft alveolus	80	34.2	83	35.5	234	0.771
incomplete cleft alveolus	46	19.7	57	24.4	234	0.220
submucous cleft alveolus	2	0.9	0	0.0	234	0.156
Secondary palate						
complete cleft hard palate	94	40.9	83	36.1	230	0.292
incomplete cleft hard palate	16	7.0	34	14.8	230	**0.007**
submucous cleft hard palate	6	2.6	6	2.6	230	1.000
complete cleft soft palate	151	64.8	154	66.1	233	0.770
incomplete cleft soft palate	7	3.0	6	2.6	233	0.778
submucous cleft soft palate	7	3.0	12	5.2	233	0.242
Side of topographic-anatomical structure						
Primary palate						
left cleft lip	120	50.6	122	51.5	237	0.854
right cleft lip	79	33.3	77	32.5	237	0.845
left cleft alveolus	96	40.9	102	43.4	235	0.575
right cleft alveolus	58	24.7	70	29.8	235	0.214
Secondary palate‡						
left cleft hard palate	24	10.6	13	5.7	227	0.059
right cleft hard palate	15	6.6	7	3.1	227	0.080
median cleft hard palate	73	32.2	100	44.1	227	**0.009**

Specific feature of individual abnormality	NVSCA		Reregister		cases with info*	
	n	%	n	%	n	p value†
Morphology and side of topographic-anatomical structure						
Primary palate						
left complete cleft lip	57	24.2	47	19.9	236	0.267
right complete cleft lip	45	19.1	37	15.7	236	0.331
left incomplete cleft lip	60	25.4	70	29.7	236	0.303
right incomplete cleft lip	32	13.6	38	16.1	236	0.437
left submucous cleft lip	3	1.3	8	3.4	236	0.127
right submucous cleft lip	2	0.8	5	2.1	236	0.253
left complete cleft alveolus	60	25.6	56	23.9	234	0.668
right complete cleft alveolus	43	18.4	46	19.7	234	0.724
left incomplete cleft alveolus	34	14.5	42	17.9	234	0.316
right incomplete cleft alveolus	14	6.0	19	8.1	234	0.367
left submucous cleft alveolus	2	0.9	0	0.0	234	0.156
right submucous cleft alveolus	0	0.0	0	0.0	234	1.000
Secondary palate‡						
left complete cleft hard palate	25	11.0	11	4.8	228	**0.015**
right complete cleft hard palate	15	6.6	9	3.9	228	0.134
median complete cleft hard palate	54	23.7	61	26.8	228	0.387
left incomplete cleft hard palate	0	0.0	1	0.4	228	0.317
right incomplete cleft hard palate	1	0.4	0	0.0	228	0.317
median incomplete cleft hard palate	15	6.6	33	14.5	228	0.006
left submucous cleft hard palate	0	0.0	0	0.0	228	1.000
right submucous cleft hard palate	0	0.0	0	0.0	228	1.000
median submucous cleft hard palate	6	2.6	6	2.6	228	1.000

* Number of cases that had sufficient information to record the topographic-anatomical structure, morphology and/or side of the individual anomalies.
† p value presents statistical significance level between the NVSCA and reregister database in prevalence of feature/anomaly; $p<0.05$ is used to determine statistical significance and is presented in bold format.
‡ Side of the soft palate was not analyzed, since clefts of the soft palate always develop in the median.

Table 3

Agreement between the NVSCA database and reregister database (gold standard) on specific features of individual anomalies of the primary palate and secondary palate in common oral clefts (total sample size: n = 237)*

Specific feature of individual abnormality	κ value (95% CI)	Sensitivity % (95%CI)	Specificity % (95%CI)	(+) Predictive value % (95%CI)	(-) Predictive value % (95%CI)	Cases †
Topographic-anatomical structure						
primary palate						
cleft lip	0.98 (0.95-1.00)	99.4 (96.6-100.0)	98.6 (92.6-100.0)	99.4 (96.6-100.0)	98.6 (92.6-100.0)	237
cleft alveolus	0.82 (0.75-0.89)	87.8 (81.1-92.7)	95.9 (89.8-98.9)	96.8 (92.1-99.1)	84.5 (76.4-90.7)	236
Secondary palate						
cleft hard palate	0.84 (0.77-0.91)	88.3 (81.4-93.3)	96.2 (90.6-99.0)	96.6 (91.5-99.1)	87.2 (79.7-92.6)	234
cleft soft palate	0.92 (0.87-0.98)	95.8 (91.5-98.3)	98.6 (92.4-100.0)	99.4 (96.6-100.0)	90.9 (82.2-96.3)	237
Morphology of topographic-anatomical structure						
Primary palate						
complete cleft lip	0.81 (0.73-0.89)	97.0 (89.6-99.6)	89.3 (83.7-93.6)	78.3 (67.9-86.6)	98.7 (95.4-99.8)	236
incomplete/submucous cleft lip	0.82 (0.74-0.89)	81.9 (73.2-88.7)	98.5 (94.6-99.8)	97.7 (92.0-99.7)	87.2 (80.7-92.1)	236
complete cleft alveolus	0.84 (0.77-0.91)	88.0 (79.0-94.1)	95.4 (90.7-98.1)	91.3 (82.8-96.4)	93.5 (88.4-96.8)	234
incomplete/submucous cleft alveolus	0.67 (0.56-0.78)	68.4 (54.8-80.1)	94.9 (90.6-97.6)	81.3 (67.4-91.1)	90.3 (85.1-94.2)	234
Secondary palate						
complete cleft hard palate	0.77 (0.69-0.86)	91.6 (83.4-96.5)	87.8 (81.3-92.6)	80.9 (71.4-88.2)	94.9 (89.7-97.9)	230
incomplete cleft hard palate	0.43 (0.25-0.60)	35.3 (19.7-53.5)	98.0 (94.9-99.4)	75.0 (47.6-92.7)	89.7 (84.8-93.4)	230
submucous cleft hard/soft palate‡	0.77 (0.58-0.97)	69.2 (38.6-90.9)	99.5 (97.5-100.0)	90.0 (55.5-99.7)	98.2 (95.4-99.5)	230
complete/incomplete cleft soft palate	0.91 (0.86-0.97)	95.5 (91.0-98.2)	97.4 (90.8-99.7)	98.7 (95.3-99.8)	91.4 (83.0-96.5)	233

* 95% CI = 95% confidence interval

† Number of cases that had sufficient information to record the topographic-anatomical structure, morphology and/or side of the individual anomalies.

‡ This group had a distance of >50% between the upper and lower limit of the 95% CI for the sensitivity but was not grouped further, because other embryologically related anomalies do not exist.

§ The side of the soft palate was not analyzed, since clefts of the soft palate always develop in the median.

Specific feature of individual abnormality	**κ value**	**Sensitivity**	**Specificity**	**(+) Predictive value**	**(-) Predictive value**	**Cases †**
	(95% CI)	**% (95%CI)**	**% (95%CI)**	**% (95%CI)**	**% (95%CI)**	
Side of topographic-anatomical structure						
Primary palate						
left cleft lip	0.95 (0.91-0.99)	96.7 (91.8-99.1)	98.3 (93.9-99.8)	98.3 (94.1-99.8)	96.6 (91.5-99.1)	237
right cleft lip	0.94 (0.90-0.99)	97.4 (90.9-99.7)	97.5 (93.7-99.3)	94.9 (87.5-98.6)	98.7 (95.5-99.8)	237
left cleft alveolus	0.84 (0.73-0.91)	88.2 (80.4-93.8)	95.5 (90.4-98.3)	93.8 (86.9-97.7)	91.4 (85.4-95.5)	235
right cleft alveolus	0.85 (0.78-0.93)	81.4 (70.3-89.7)	99.4 (96.7-100.0)	98.3 (90.8-100.0)	92.7 (87.8-96.0)	235
Secondary palate§						
left/right cleft hard palate	0.42 (0.25-0.58)	73.7 (48.8-90.9)	88.0 (82.8-92.1)	35.9 (21.2-52.8)	97.3 (93.9-99.1)	227
median cleft hard palate	0.62 (0.52-0.72)	66.0 (55.8-75.2)	94.5 (89.0-97.8)	90.4 (81.2-96.1)	77.9 (70.5-84.2)	227
Morphology and side of topographic-anatomical structure						
Primary palate						
left complete cleft lip	0.80 (0.71-0.90)	93.6 (82.5-98.7)	93.1 (88.5-96.3)	77.2 (64.2-87.3)	98.3 (95.2-99.7)	236
right complete cleft lip	0.79 (0.69-0.90)	91.9 (78.1-98.3)	94.5 (90.3-97.2)	75.6 (60.5-87.1)	98.4 (95.5-99.7)	236
left incomplete/submucous cleft lip	0.81 (0.73-0.90)	79.7 (68.8-88.2)	98.1 (94.7-99.6)	95.2 (86.5-99.0)	91.4 (86.2-95.1)	236
right incomplete/submucous cleft lip	0.79 (0.68-0.90)	76.9 (60.7-88.9)	98.0 (94.9-99.4)	88.2 (72.5-96.7)	95.5 (91.7-97.9)	236
left complete cleft alveolus	0.82 (0.73-0.90)	89.3 (78.1-96.0)	94.4 (89.9-97.3)	83.3 (71.5-91.7)	96.6 (92.6-98.7)	234
right complete cleft alveolus	0.88 (0.80-0.96)	87.0 (73.7-95.1)	98.4 (95.4-99.7)	93.0 (80.9-98.5)	96.9 (93.3-98.8)	234
left incomplete cleft alveolus	0.72 (0.60-0.84)	69.0 (52.9-82.4)	97.4 (94.0-99.1)	85.3 (68.9-95.0)	93.5 (89.1-96.5)	234
right incomplete cleft alveolus	0.64 (0.45-0.84)	57.9 (33.5-79.7)	98.6 (96.0-99.7)	78.6 (49.2-95.3)	96.4 (93.0-98.4)	234
Secondary palate§						
left/right complete cleft hard palate	0.45 (0.28-0.61)	78.9 (54.4-93.9)	88.0 (82.8-92.1)	37.5 (22.7-54.2)	97.9 (94.6-99.4)	228
median complete cleft hard palate	0.49 (0.36-0.62)	57.4 (44.1-70.0)	89.2 (83.4-93.4)	66.0 (51.7-78.5)	85.1 (78.9-90.0)	228

(substantial agreement), sensitivity of 66.0%, specificity and positive predictive value of over 90%, and negative predictive value of 77.9%.

Morphology and side of topographic-anatomical structure

For the 8 anomalies of the primary palate that remained after regrouping, the κ value ranged from 0.64 for "right incomplete cleft alveolus" to 0.88 for "right complete cleft alveolus"; 5 anomalies were at the level of substantial agreement, and 3 at near perfect agreement. Sensitivity ranged from 57.9% for "right incomplete cleft alveolus" to 93.6% for "left complete cleft lip". Positive predictive value ranged from 75.6% for "rightt complete cleft lip" to 95.2% for "left incomplete/submucous cleft lip". Meanwhile, specificity and negative predictive value were high for all 8 anomalies (over 91%).

For the secondary palate, 2 anomalies remained for validation. "Left/right complete cleft hard palate" had a κ value of 0.45 (moderate agreement), sensitivity of 78.9%, positive predictive value of 37.5%, and specificity and negative predictive value of 88.0% and over. The anomaly "median complete cleft hard palate" had a κ value of 0.49 (moderate agreement), sensitivity of 57.4%, positive predictive value of 66.0%, and specificity and negative predictive value of over 85%.

DISCUSSION

This continuation of the NVSCA validation study shows that the quality of the NVSCA data on the specific features of the individual anomalies in OCs varies by type of anomaly. By linking the NVSCA database with a new independent reregister database derived from medical data review, we found that validity of the registry data is related to anatomical location and morphological severity of the individual anomalies.

The following results illustrate the pattern of recording in the NVSCA. The topographic-anatomical structures of the individual anomalies of the primary palate (lip and alveolus) and of the secondary palate (hard and soft palate) were identified perfectly in the NVSCA and had high validity measures (85%-99%) with near perfect inter-database agreement. However, when analyzing the anomalies more in detail, i.e. analyzing the morphology and/or side, the validity decreased and appeared to be related to the type of anomaly. Firstly, anomalies of the primary palate were recorded better than anomalies of the secondary palate; the inter-database agreement was near perfect for most primary palate

anomalies, while it was moderate to substantial for most secondary palate anomalies. This suggests better registration of externally visible anomalies (such as cleft lip/alveolus) than anomalies that require a diagnostic procedure (such as opening the mouth for inspection and palpating the palate). In addition, validity was related to morphological severity, since "severe" anomalies were generally recorded better than "mild" anomalies. This association applied to both the primary and secondary palate, but was most evident for the secondary palate. For example, 35% of the "incomplete cleft hard palates" and 69% of the "submucous cleft hard/soft palates" present in the reregister was also present in the NVSCA, compared with more than 91% of the "complete cleft hard palates" and "complete/incomplete cleft soft palates".

Although many registries record OCs, studies on the validity of OC data are scarce. There are some studies, however, that describe the case-ascertainment of OCs in medical registries[9,11,12,22]. In one study, that of Kubon et al.[9], this was done in relation to the various cleft types within the three main OC categories. Similar to our study, they found that registration in the Norwegian medical birth registry was more complete for clefts of the primary palate than for clefts of the secondary palate. They suggested that this could be explained by the delayed diagnoses of clefts of the hard/soft palate and thus incomplete routine examination of newborns, which was also reported in other studies[22-24]. Different from registries that receive information from birth admissions or hospital discharge records, the NVSCA receives the OC data directly from the cleft palate teams, which are expected to be focused on oral clefts and to examine patients carefully[15]. Still, part of our findings may be explained by incomplete examination, since the number of patients - and probably the experience and routine of diagnostics - varies strongly among the 15 Dutch cleft palate teams.

Delayed diagnosis of cleft palate might have several clinical implications. For example, the presence of a cleft palate is often associated with additional congenital anomalies and syndromes[6], and the diagnosis of a cleft palate should therefore generate an even more extensive examination of the newborn.

Additionally, our findings that the quality of recording increased with the morphological severity of the anomalies, and that this association was most evident for the secondary palate, are also consistent with the findings of Kubon et al.[9]. Perhaps more unexpectedly, both studies showed that besides morphologically mild clefts of the secondary palate, those of the primary palate, which are clearly visible and require surgery, also tended to be underreported. A possible explanation for these findings is that greater morphological severity of an anomaly might be a factor which encourages doctors to report better.

The under-representation of morphologically mild anomalies may have consequences for research on registry data. These anomalies develop during other stages in embryological development and can be related to other cell-biological mechanisms and genes than morphologically severe anomalies[1-3]. Consequently, studies based on registry data examining environmental factors or genes that are associated with morphologically mild clefts might underestimate the importance of such factors and genes.

The strength of this study is that all cleft palate teams gave permission to collect the medical data. The sampling frame thus had a national distribution, including cleft palate teams of large urban teaching and specialist hospitals as well as of small regional ones. Most of these treatment centers have carried out high quality documentation needed for modern multidisciplinary treatment, which favors our retrospective detailed evaluation. However, the use of medical data to validate registry data also has its limitation. It can never be equal to the presentation of the patient in the outpatient clinical setting, and therefore it is never 100% accurate[17,21]. As we showed previously[15], the amount and quality of the medical data varied by cleft palate team. For some cases, the collected medical information was insufficient to evaluate certain specific features of the individual anomalies, and these cases had therefore to be excluded from the features' analysis in this study.

Another limitation is that, although we grouped anomalies having a sample prevalence of $n<10$ together with their embryologically related anomalies, there were still considerable differences in the prevalence rates of the evaluated anomalies; morphologically mild anomalies were for example less prevalent in the study sample than morphologically severe anomalies. Since it is known that "disease prevalence" can affect the reliability (kappa) or validity statistics (sensitivity, specificity, positive and negative predictive value)[16-18] we used to measure the degree of agreement between the NVSCA and reregister, the differences in validity of registry data on morphologically severe and mild anomalies might partially be explained by the differences in prevalence.

Finally, the study sample was not large enough to examine all anomalies of the primary palate and secondary palate individually. Nevertheless, we were able to analyze most of the individual anomalies in OCs recorded over a 7-year-period, thereby evaluating the feasibility of the unique descriptive NVSCA recording system for OCs.

Our study is the first that validates descriptive registry data on OCs. The unique NVSCA system records the individual anomalies of the primary palate and secondary palate that form the OC by describing the specific features (topographic-anatomical structure, morphology, and side) of each anomaly. This study shows that the quality of the NVSCA

data on the specific features of the individual anomalies in OCs varies by type of anomaly and is related to anatomical location and morphological severity. Greater morphological severity of an anomaly might be a factor which encourages doctors to report better, but underreporting might also partly be explained by incomplete examination of the oral cleft. These factors might have implications for e.g. genetic and etiologic research based on registry data, and for guidelines on neonatal examination by the cleft palate teams.

Conclusions

Despite the limitations and challenges described, this study shows together with other quality studies[14,15] that, overall, the data quality of the NVSCA registry on OCs is high, supporting the feasibility of the unique NVSCA recording system. However, data on morphologically severe clefts can be interpreted with higher confidence than those on morphologically mild clefts. In contrast to ICD-based registries, the NVSCA registry has valid detailed OC data that are collapsible to more general diagnoses or codes, which allows classifying OCs in many different ways. This makes the NVSCA registry a very valuable tool for epidemiological, clinical, and fundamental research and for the improvement of OC care.

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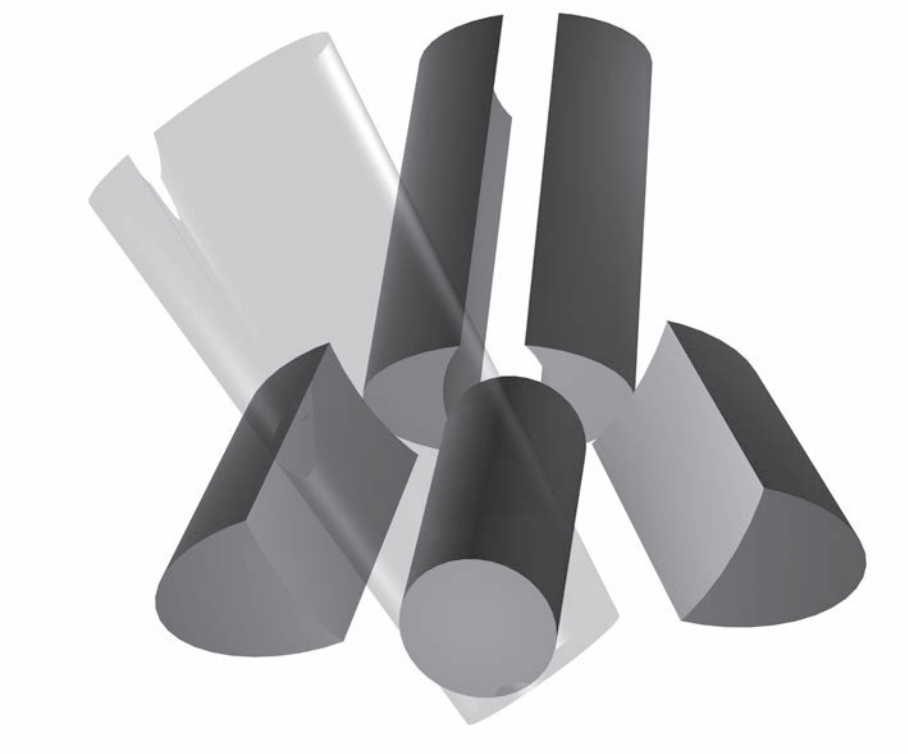
CLASSIFYING COMMON ORAL CLEFT: A NEW APPROACH AFTER DESCRIPTIVE REGISTRATION



AJM Luijsterburg, AM Rozendaal, C Vermeij-Keers. Cleft Palate - Craniofacial Journal. 2013, Epub.

SUMMARY

Objective Using the Dutch Oral Cleft Registration, which records the morphology and topography of common oral clefts, a new classification based on the (patho)embryology of the primary and secondary palates was tested.

Design Prospective observational study.

Setting The fifteen cleft palate teams in the Netherlands register patients to the national registry.

Patients All unoperated patients with common oral clefts reported between 1997 and 2006 inclusive were included.

Main outcome measures The classification is based on the pathoembryological events that ultimately result in various sub-phenotypes of common oral clefts. Patients within the three categories cleft lip/alveolus (CL/A), cleft lip/alveolus and palate (CL/AP) and cleft palate (CP) were divided into three subgroups: fusion defects, differentiation defects, and fusion and differentiation defects. A timetable was constructed to relate the type of clefting to the time of derailment during embryonic development.

Results 3512 patients were included. Patients with CL/A showed 22% fusion defects, 75% differentiation defects, and 3% fusion and differentiation defects. CL/AP patients and CP patients mostly showed fusion defects (70% and 89%, respectively). We were able to relate almost all (over 90%) cleft sub-phenotypes to specific weeks in embryonic development.

Conclusions This classification provides new cleft subgroups that may be used for clinical and fundamental research. The sub-phenotypes of these subgroups originate from different time frames during embryonic development and different cell biological mechanisms, thereby enabling more accurate data for, e.g., gene identification and/or environmental factors.

Keywords common oral cleft, classification, congenital abnormality, cleft lip, cleft palate, registry

INTRODUCTION

Common oral clefts are one of the most frequent congenital anomalies worldwide[1]. Ethnic, socioeconomic, and geographic variations may partly account for the large multifactorial group of nonsyndromic common oral clefts[2-4]. A quest for identifying genes and environmental factors responsible for these anomalies has been done for years. However, only a small part of the nonsyndromic common oral clefts have been related to specific genes and/or environmental factors, such as MSX1 or smoking[4-8]. Within this multifactorial group, huge variations in cleft sub-phenotypes exist. These various cleft types originate from different developmental time periods (Vermeij-Keers, unpublished data)[9], and therefore have different exposures to genes and environmental factors[10]. If patients with different cleft sub-phenotypes are treated as a single group, linkage studies with genes and/or environmental factors may not be as fruitful as hoped[8]. Therefore, a new classification based on the human embryology of the primary and secondary palates was previously introduced (Vermeij-Keers, unpublished data)[11, 12]. In this classification, different sub-phenotypes of common oral clefts are distinguished based on different cell biological mechanisms and related to different time periods in embryonic development.

Such a classification can be applied only if detailed phenotype descriptions of the common oral clefts are available. In 1997, a new descriptive recording system was developed on behalf of the Dutch Association for Cleft Palate and Craniofacial Anomalies (NVSCA)[13]. This system, the NVSCA registry, consistently records all abnormalities of each anatomic structure that form the common oral cleft.

Recently, the feasibility of our new classification was shown for clefts of the primary palate using adult unoperated patients from Indonesia (Vermeij-Keers, unpublished data). In addition, we used this embryological approach to validate NVSCA registry data on the specific oral cleft features[11]. Previously, we divided broad categories into fusion and/or differentiation defects[12], but it is unknown whether this classification is complete and feasible for all cleft sub-phenotypes of the primary and secondary palates among newborns. In this study, we applied the classification to unoperated infants with common oral clefts using detailed data of the cleft subphenotypes from the NVSCA registry. After considering the normal and abnormal development of the primary and secondary palates, their clefts were first traditionally classified into three categories: cleft lip/alveolus (CL/A), cleft lip/alveolus and palate (CL/AP), and cleft palate (CP). Subsequently, we classified the various cleft sub-phenotypes within these categories into fusion and/or differentiation defects.

Finally, we constructed a timetable, relating the various fusion and/or differentiation defects to weeks in embryonic development.

MATERIALS AND METHODS

Patients

In this study, we included all unoperated patients with a common oral cleft that had been reported by the 15 multidisciplinary cleft palate teams to the NVSCA registry between 1997 and 2006 inclusive. After careful examination, the consulting physicians (plastic surgeon, orthodontist or pediatrician) recorded these patients using the NVSCA recording form[13]. All forms were examined for incorrect, inconsistent, or insufficient data by the authors. If additional information was needed, it was provided by the cleft palate teams. In addition, the registry data were systematically validated[11, 14, 15].
In this study, only common oral clefts were included. Median cleft lip and atypical facial clefts were excluded for their different pathogenesis[9, 16].

Embryological basis of the classification

To place the different subphenotypes of oral clefts into the correct time periods and cell biological mechanisms during human embryonic development, the normal and abnormal development of the primary and secondary palates should be understood and is therefore briefly reviewed here.

Normal development of primary and secondary palates: fusion and differentiation

Normal embryonic development of the primary palate (the presumptive lip and alveolus) can be divided into early and late embryonic development (i.e., 4 to 7 weeks of development and 7 to 12 weeks of development [postconception], respectively)[9, 10, 17]. In contrast, the development of the secondary palate (the presumptive hard and soft palates, including the uvula) takes place in the late embryonic period (7 to 12 weeks of development). During early development, the primary palate is formed in an occipito-frontal direction by fusion of three outgrowing facial swellings around each nasal placode (left and right). First, the maxillary

process (occipitally) and subsequently the lateral nasal process (frontally) adhere and fuse with the medial nasal process[9, 17, 18]. As a consequence, the lateral and medial nasal processes always surround the nasal apertura. During the fusion process, the ectoderm covering the mesenchymal cores of the swellings on the fusion side is enclosed and an epithelial plate (the nasal fin) is formed. From the occipital part of this plate, the oronasal membrane (i.e., bucconasal membrane) develops and subsequently ruptures by cell death (6 to 7 weeks of development). During the same weeks, the epithelial plate gradually disappears by programmed cell death followed by epitheliomesenchymal transformation (EMT) and/or migration (Vermeij-Keers, unpublished data)[17, 19-23]. The last location for the epithelial plate to disappear is at the fusion of the presumptive lip, beneath the nostril.

When late development starts, the mesenchymal cores of the facial swellings have fused completely. Subsequently, the primary palate differentiates by (1) outgrowth of the lip and alveolar process in a caudal direction, thereby causing the labial groove, and (2) the development of a left and right bone center of the maxilla and two bone centers in each premaxilla[9, 17]. These bone centers approach each other and fuse without forming sutures, except between the two premaxillae (the intermaxillary suture). Bony differentiation is accompanied by the development of facial musculature.

During the development of the secondary palate, the palatine processes grow out, elevate, adhere, and fuse bilaterally with the primary palate and then in the median plane in a fronto-occipital direction[23-28]. They fuse with each other and with the nasal septum. Again, ectoderm of the various processes is enclosed during the fusion process, and a Y-shaped epithelial plate forms. Subsequently, this plate disappears gradually by programmed cell death followed by EMT and/or migration of epithelial cells towards the nasal side of the plate[9, 23, 24, 29-40]. Although the cell fate underlying the disappearance of the epithelial plate has been controversial for many years, two recent review papers[41, 42] showed that none of the three possible cell biological mechanisms (programmed cell death, EMT, and migration) can be excluded.

While the palatine processes grow out, the bone centers of the palatine bones develop bilaterally. During the fusion process, they approach each other and the bone centers of the maxilla. The same holds for the maxilla and premaxillae. In this way, the median and transverse palatine sutures develop, as well as the bilateral incisive sutures. In addition, bony differentiation is accompanied by muscular differentiation. In conclusion, the primary and secondary palates develop in opposite directions: the facial swellings fuse in an occipito-frontal direction, while the palatine processes fuse in a fronto-occipital direction.

In view of the above, disturbances during the development of the primary and/or secondary palates give rise to fusion and/or differentiation defects. Examples of different cleft subphenotypes in relation to the various developmental periods and cell biological mechanisms are discussed below.

Abnormal development of primary and secondary palates: fusion and differentiation defects

Complete cleft lip and alveolus, early embryonic development

This type of clefting represents no fusion at all and is therefore considered a fusion defect, because of insufficient outgrowth of the facial swellings, lack of adherence of these swellings, or failure of programmed cell death/EMT/migration, that is, the epithelial plate does not develop or it remains intact. During the latter situation, further differentiation causes the ectoderm to separate again at the fusion site, resulting in a complete cleft lip and alveolus extending to the incisive foramen (Figures 1 and 2). As this process is completed before the secondary palate starts to fuse, these primary palatal defects are independent of the secondary palatal defects[9]. As a result, complete cleft lip and alveolus can be observed with a normal secondary palate (Figure 1b), or with an abnormal secondary palate, such as a complete cleft palate (Figure 2b). In the last case, it is readily possible that the palatal shelves could not have reached each other because of the width of defect of the primary palate.

If fusion of the primary palate stops at a certain place along the fusion line, this always gives

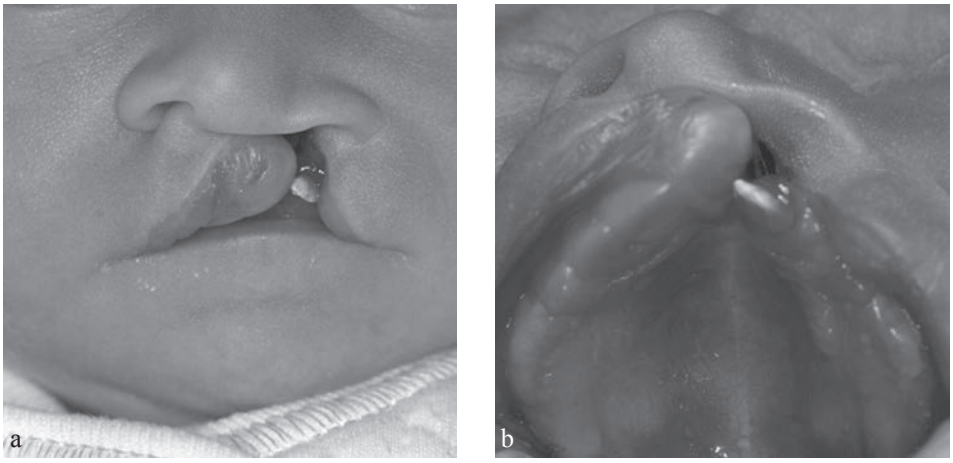


Figure 1
a) A complete left cleft of the lip and alveolus. b) The secondary palate is intact.

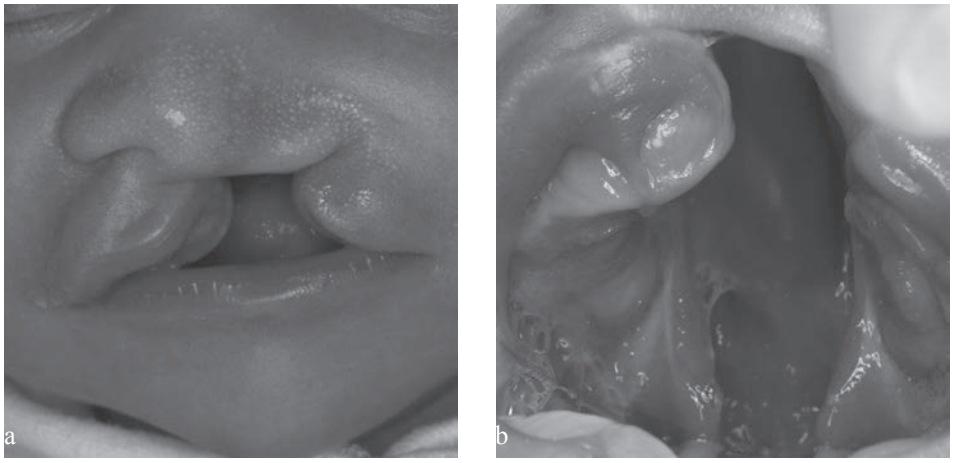


Figure 2
A complete left cleft of the lip/alveolus (a), hard and soft palate (b).

rise to a complete cleft lip combined with an intact alveolar process, or an incomplete cleft of the alveolar process.

Incomplete cleft lip with or without an incomplete cleft alveolus, late embryonic development
After fusion of the maxillary and lateral nasal processes with the medial nasal process, the primary palate differentiates by outgrowth of the lip and alveolus into a caudal direction. Since the fusion process has been completed at that stage, an incomplete cleft lip always displays a tissue bridge below the nostril (Vermeij-Keers, unpublished data)[10, 12]. Consequently, the left incomplete cleft lip and cleft alveolus of the patient in Figure 3a have their origin in incomplete caudal outgrowth and/or differentiation of the primary palate during late embryonic development (i.e., a differentiation defect). The right side of the same patient shows an incomplete cleft lip and a normal alveolus, demonstrating the about same starting point of disruption (incomplete outgrowth of the lip during late embryonic development). The presence of incomplete outgrowth of the alveolus at one side with normal outgrowth of the contralateral alveolus in the same individual might be explained by left/right asymmetry in the timing of the bony differentiation. The tissue bridge under de right nostril is larger than at the left side, suggesting that the outgrowth of the right lip started earlier than that of the left lip. Likewise, we presume that differentiation of the right alveolus preceded the differentiation of the left alveolus. When the event of disruption occurred, it is readily possible that differentiation of the right alveolus had already been completed, while that of the left alveolus was still differentiating, resulting in a normal right alveolus and an incomplete cleft of the left alveolus. A notch in the arch, hypoplasia, or a

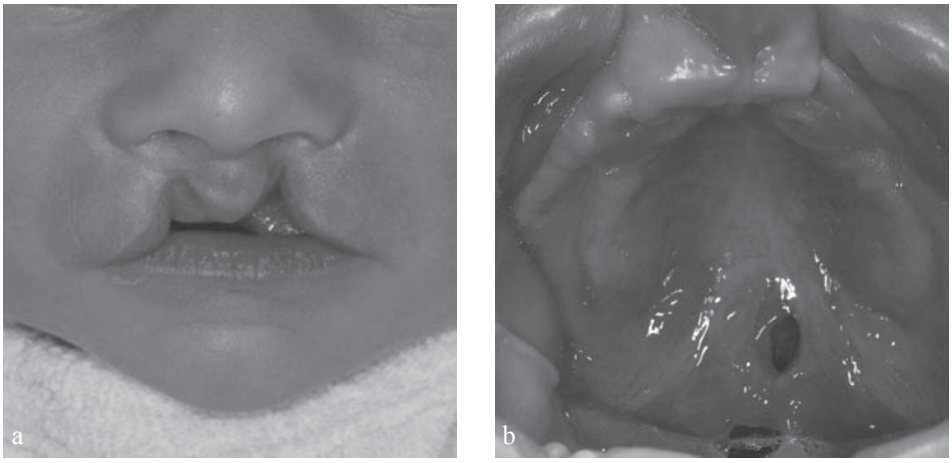


Figure 3
a) A bilateral asymmetric incomplete cleft lip with a normal right alveolus, and an incomplete cleft of the left alveolus combined with, (b) a complete cleft of the soft palate.

submucous cleft of the alveolar arch can also accompany the incomplete cleft lip. It is most likely that the abnormalities of the alveolar arch are the result from insufficient outgrowth of the premaxillary bone centers rather than the maxillary centers (Vermeij-Keers, unpublished data).

Incomplete cleft lip and ipsilateral complete cleft alveolus, early and late embryonic development

In an incomplete cleft lip with an ipsilateral complete cleft alveolus (Figures 4a,b and 5a), the fusion process of the lip has been completed because a tissue bridge beneath the nostril has been formed. It is therefore a differentiation defect of the lip, which arises during late embryonic development. In the case of a small tissue bridge combined with an ipsilateral complete cleft alveolus (Figure 4b), the term Simonart's band is used. The alveolar defect is a fusion defect that can be explained by a too wide oronasal membrane or a local persistence of the epithelial plate in front of the oronasal membrane. This part of the epithelial plate does not disappear by programmed cell death / EMT / migration during the early embryonic development (Vermeij-Keers, unpublished data). As is shown by these two patients, the appearance of the primary palate does not predict the appearance of the secondary palate (Figures 4b and 5b).

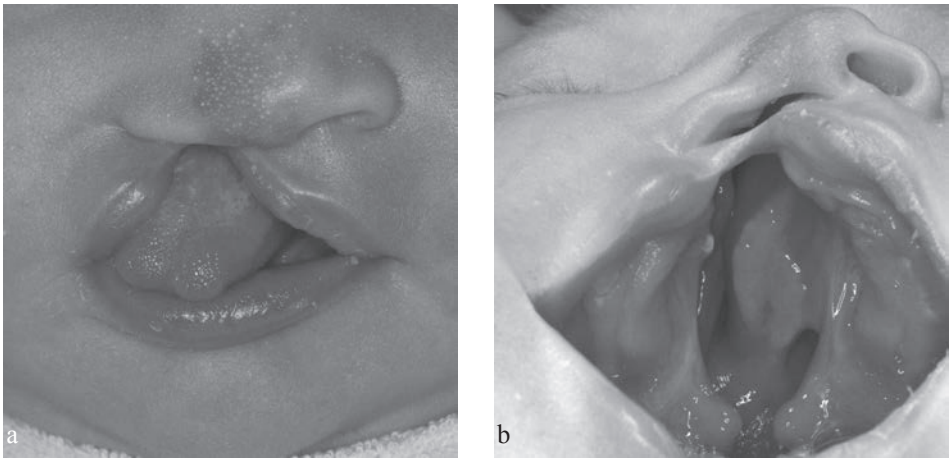


Figure 4
a) An incomplete right cleft of the lip, a complete alveolar cleft combined with, b) a complete cleft of the hard and soft palate.

Complete cleft hard and soft palate, late embryonic development

If the palatine processes do not grow out or elevate insufficiently, a complete cleft of the hard and soft palate will result. This type of cleft can also occur when the palatine processes elevate, but do not adhere or fuse with the primary palate, with each other, and with the nasal septum (Figures 2b and 4b). These fusion defects develop early in secondary palatogenesis during the late embryonic period.

Incomplete cleft hard palate and complete cleft soft palate, late embryonic development

After elevation of the palatine processes, adhesion/fusion occurs in a fronto-occipital direction. If along this fusion line the fusion process is disrupted, various types of cleft palate can be observed (i.e., fusion defects). Relative early disruption of this fusion process may result in an incomplete cleft of the hard palate and complete cleft of the soft palate (including the uvula; Figure 5b). Somewhat later in development the hard palate is fused. If the fusion process stops after fusion of the hard palate, an intact hard palate will result, combined with a complete or incomplete cleft of the soft palate. Whether there will be a complete or incomplete cleft of the soft palate depends on the time of disruption. If disruption occurs later during the fusion process, more of the soft palate will be intact (Figure 3b). Therefore, an incomplete cleft of the hard palate combined with a complete cleft of the soft palate precedes complete and incomplete clefts of the soft palate.

Subclinical features of clefting regarding the primary and/or secondary palates

Milder expression of clefting can also be observed, such as a submucous cleft lip (also known as forme fruste, congenital scar, and microform, subsurface or subcutaneous cleft), submucous cleft palate, and bifid uvula. Except for the latter cleft type, which results from a fusion defect at the end of the fusion process of the secondary palate, these subclinical phenotypes can be considered as differentiation defects. Submucous clefts result from defective differentiation into bone and/or musculature, after completion of the fusion process. Other differentiation defects of the secondary palate include: (1) absence (agenesis) of the palatine bone, (2) a palatine bone and/or maxilla (palatine part) that is undersized (hypoplasia), or a submucous cleft, and/or (3) hypoplastic musculature.

Furthermore, with our concept of fusion/differentiation defects, special types of human cleft sub-phenotypes can be explained, such as an (in)complete cleft of the hard palate combined with an intact soft palate and uvula[43, 44]. This type may be the result of local insufficient programmed cell death / EMT / migration within the enclosed epithelial plates. Recently, it was reported that differential expression of proteins in the developing anterior and posterior secondary murine palate may cause too short anterior palatal shelves because of diminished cell proliferation and increased programmed cell death. The anterior palatal shelves do not reach each other, and a cleft of the hard palate remains. At that spot, the epithelium of the palatine processes persists, which causes a local fusion defect[45]. Another explanation of non-fusion of the anterior palatal shelves was described based on thickened palatal epithelium in $Tbx1^{-/-}$ mice[46].

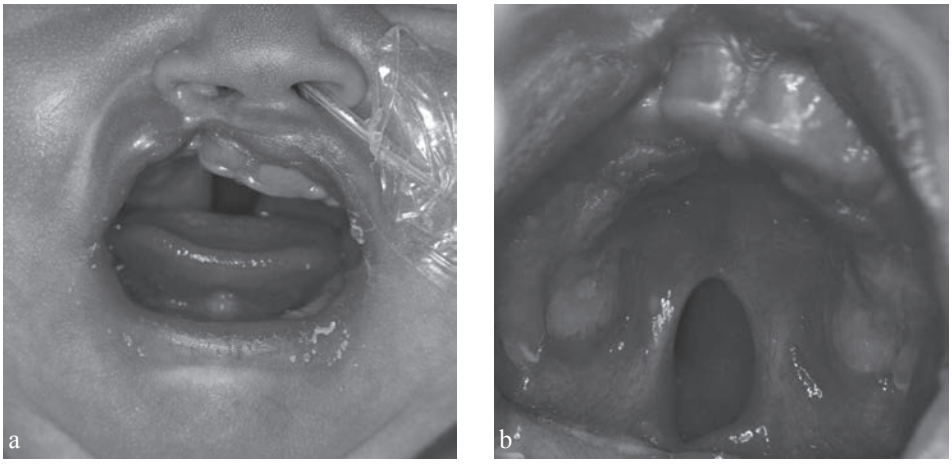


Figure 5

a) An incomplete cleft of the right lip and a complete alveolar cleft combined with, b) an incomplete cleft of the hard palate and a complete cleft of the soft palate.

Classification

In line with recent studies[11, 13, 47, 48], we divided our study population into the three categories, (CL/A, CL/AP, and CP). As we have shown previously, these categories manifest very heterogeneous cleft sub-phenotypes[11, 13]. To classify these types, the common oral clefts were divided into fusion and/or differentiation defects of the primary palate (lip and alveolus), the secondary palate (hard and soft palate, including the uvula), or both. The template for deciding which abnormality of the lip, alveolus, and hard and soft palates is a fusion defect or a differentiation defect is listed in Table 1. Theoretically, any combination of clefts of the lip, alveolus, hard and/or soft palates is possible, so each category was subdivided into three subgroups: fusion (F) defects, differentiation (D) defects, and fusion and differentiation (FD) defects.

Table 1 Classification of cleft subphenotypes of the primary and secondary palates: division into fusion and/or differentiation defects.

fusion defects	primary palate	complete cleft lip
		complete cleft alveolus (extending to the incisive foramen)
		incomplete cleft alveolus **(only if the lip is normal or has a complete cleft)**
	secondary palate	complete cleft hard palate
		incomplete cleft hard palate
		complete cleft soft palate
		incomplete cleft soft palate
		complete uvular cleft
		incomplete uvular cleft
differentiation defects	primary palate	incomplete cleft lip
		submucous cleft lip+
		hypoplastic lip
		incomplete cleft alveolus **(only if the lip has an incomplete or submucous cleft)**
		submucous cleft alveolus
		hypoplastic lip/alveolus
	secondary palate	submucous cleft hard palate
		hypoplastic hard palate
		submucous cleft soft palate (including uvula)
		hypoplastic cleft soft palate (including uvula)

Any combination of abnormalities of the lip, alveolus, and hard and soft palates is allowed (adapted from Rozendaal et al.[12] and Vermeij-Keers et al.[9])
+ synonyms: congenital scar, forme fruste, subsurface cleft lip, subcutaneous cleft lip, and microform cleft lip

RESULTS

The national registry recorded 3512 patients with a common oral cleft from 1997 to 2006. Twenty-eight percent of all patients showed a CL/A, 39% showed a CL/AP, and 33% exhibited a CP. The subdivision of the cleft sub-phenotypes - within these categories - into F defects, D defects, and FD defects is presented in Table 2. CL/A patients showed in 22% an F defect, in 75% a D defect, and in 3% an FD defect. CL/AP patients showed most frequently F defects (70%) and FD defects (29%). The vast majority of the CP patients displayed an F defect (85%).

As FD defects in CL/AP patients (n = 389) may involve F defects and D defects of the primary palate as well as of the secondary palate, we divided the study group into F, D, and FD defects concerning the primary and secondary palates (Table 3). The FD defects in CL/AP patients were mostly D defects (n = 159, 41%) or FD defects (n = 205, 52%) of the primary palate combined with F defects of the secondary palate. Of the 2340 patients with a defect of the primary palate, 1182 (51%) patients showed an F defect, 914 (39%) patients exhibited a D defect, and 244 (10%) patients showed an FD defect. A total of 2535 patients had a defect of the secondary palate and an intact primary palate. In 92% of the patients (n=2321), an F defect was observed, and in the remaining 8%, a D defect (n = 123) or FD defect (n = 91) was identified.

Table 2 Classification of the sub-phenotypes within the three cleft categories: division into fusion and/or differentiation defects (n=3512, Dutch Oral Cleft Registry 1997-2006).

Type	Subgroups			Total
	F	D	FD	
CL/A	213	729	35	977
CL/AP	960	14	389	1363
CP	997	101	74	1172
Total	2170	844	498	3512

F = fusion defects, D = differentiation defects, FD = fusion and differentiation defects.

Table 3 Classification of all patients with common oral clefts (n=3512) into fusion and/or differentiation defects of the primary and/or secondary palates, based on data from the Dutch Oral Cleft Registry 1997-2006.

Primary palate	Secondary palate				Total
	No defect	F	D	FD	
F	213	960	6	3	1182
D	729	159	14	12	914
FD	35	205	2	2	244
No defect		997	101	74	1172
Total	977	2321	123	91	3512

F = fusion defects, D = differentiation defects, FD = fusion and differentiation defects.

Fusion and/or differentiation defects of the primary palate

As shown in Table 4, F defects of the primary palate (n = 1183) mostly were complete clefts of the lip/alveolus (62% in CL/A and 96% in CL/AP patients). Complete cleft lip combined with an incomplete cleft alveolus, as well as complete cleft lip, were less frequently observed. Together, these three types of clefting accounted for 99% of all F defects of the primary palate.

Ninety-two percent (n = 914) of D defects of the primary palate were incomplete clefts of the lip/alveolus (37% CL/A; 69% CL/AP), or incomplete clefts of the lip (51% CL/A; 20% CL/AP), or submucous clefts of the lip (5% CL/A; 4% CL/AP).

FD defects (n = 244) were mainly incomplete clefts of the lip combined with ipsilateral complete clefts of the alveolus (51% CL/A, 42% CL/AP). In 23% of the CL/A patients and in 40% of the CL/AP patients, a complete cleft lip/alveolus was observed with a contralateral incomplete cleft lip, an incomplete cleft lip/alveolus, or an incomplete cleft lip and complete cleft alveolus.

Table 4 Distribution of sub-phenotypes of the primary palate: division of the cleft lip/alveolus patients (n=977) and the cleft lip/alveolus and palate patients (n=1363) into fusion and/or differentiation defects.

		CL/A	CL/AP
Fusion defect	CCLA	134	932
	CCL+ICA	39	9
	CCL	37	18
	Miscellaneous	3	10
Differentiation defect	ICLA	267	128
	ICL	374	37
	SCL	36	7
	Miscellaneous	52	13
Fusion and differentiation defects	ICL+CCA	18	88
	CCLA; ICL	3	33
	CCLA; ICLA	5	27
	CCLA; ICL+CCA	0	24
	Miscellaneous	9	37

CCLA = complete cleft lip + complete cleft alveolus
CCL+ICA = complete cleft lip + incomplete cleft alveolus
CCL = complete cleft lip
ICLA = incomplete cleft lip + incomplete cleft alveolus
ICL = incomplete cleft lip
SCL = submucous cleft lip
ICL+CCA = incomplete cleft lip + complete cleft alveolus (differentiation defect + fusion defect)
CCLA; ICL = complete cleft lip + complete cleft alveolus combined with a contralateral incomplete cleft lip
CCLA; ICLA = complete cleft lip + complete cleft alveolus combined with a contralateral incomplete cleft lip + incomplete cleft alveolus
CCLA; ICL+CCA = complete cleft lip + complete cleft alveolus combined with a contralateral incomplete cleft lip + complete cleft alveolus (differentiation defect + fusion defect).

Fusion and/or differentiation defects of the secondary palate

Table 5 presents that F defects of the secondary palate (n = 2321) were mostly complete cleft palates in CL/AP patients (86%). Complete cleft palate, incomplete cleft of the hard palate combined with a complete cleft of the soft palate, and complete cleft of the soft palate were observed in 91% of the CP patients.

D defects (n = 123) were mostly submucous clefts of the hard and/or soft palate (80% CL/AP, 68% CP). FD defects (n = 91) were predominantly submucous clefts of the hard and/or soft palate combined with an (in)complete uvular cleft (71% CL/AP, 69% CP), or submucous cleft of the hard palate combined with a complete cleft of the soft palate (12% CL/AP, 26% CP).

Table 5 Distribution of sub-phenotypes of the secondary palate: division of the cleft lip/alveolus and palate patients (n=1363) and cleft palate patients (n=1172) into fusion and/or differentiation defects.

		CL/AP	CP
Fusion defect	CCP	1142	274
	ICHP; CCSP	93	237
	CCSP	51	394
	ICSP	19	52
	I/CCU	17	37
	Miscellaneous	2	3
Differentiation defect	SCSP	12	55
	SCHP+SCSP	6	14
	HH/SP	1	29
	Miscellaneous	3	3
Fusion and differentiation defects	SCH/SP+I/CCU	12	51
	SCHP+CCSP	2	19
	Miscellaneous	3	4

CCP = complete cleft palate
CCSP = complete cleft of the soft palate
ICHP = incomplete cleft of the hard palate
ICSP = incomplete cleft of the soft palate
I/CCU = (in)complete cleft of the uvula
SCSP = submucous cleft of the soft palate
SCHP = submucous cleft of the hard palate
HH/SP = hypoplastic hard and/or soft palate
SCH/SP = submucous cleft of the hard and/or soft palate.

Timetable common oral clefts

As fusion and differentiation defects of the primary and secondary palates originate at different time periods, a timetable was constructed, relating the observed defects to weeks of development (Figure 6). For FD defects consisting of a fusion defect and a contralateral differentiation defect of the primary palate, both defects were considered to originate at different time points (independently). For example, a patient with a complete cleft lip/alveolus combined with a contralateral incomplete cleft lip was considered to have sustained two disruptions during development. The first disruption was a fusion defect of the primary palate at one side (early embryonic development), and the second disruption concerned insufficient outgrowth/differentiation of the lip after fusion of the primary palate (late embryonic development). Both disruptions were counted in the timetable, once in the F group, and once in the D group (e.g., 3 CL/A patients and 33 CL/AP patients; Table 4).

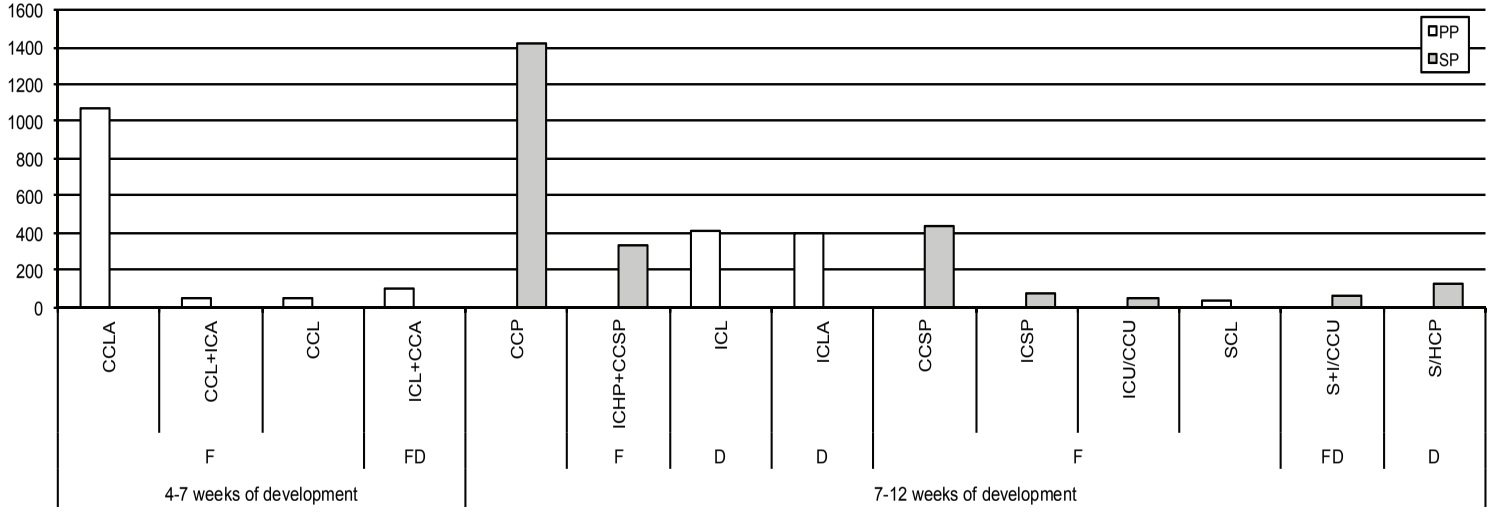


Figure 6
Timetable for the most frequent sub-phenotypes of the primary and secondary palate (n=3512, Dutch Oral Cleft Registry 1997-2006)
PP= primary palate, SP = secondary palate, F = fusion defect, D = differentiation defect, FD = fusion and differentiation defect
CCLA = complete cleft lip alveolus, CCL+ICA = complete cleft lip and incomplete cleft alveolus, CCL = complete cleft lip, CCP = complete cleft palate, ICL+CCA = incomplete cleft lip and complete cleft alveolus, ICHP+CCSP = incomplete cleft of the hard palate and complete cleft of the soft palate, ICL = incomplete cleft lip, CCSP = complete cleft of the soft palate, ICSP = incomplete cleft of the soft palate, ICU/CCU = (in)complete uvular cleft, SCL = submucous cleft lip, S+I/CCU=submucous cleft palate and (in)complete uvular cleft, S/HCP=submucous cleft palate or hypoplastic palate

DISCUSSION

This study demonstrates that our unique classification system can be applied successfully to unoperated newborns/infants having various sub-phenotypes of common oral clefts. Using detailed cleft data from the NVSCA registry, we were able to classify all clefts into fusion and/or differentiation defects. This was possible because we previously introduced the NVSCA registry, which describes the individual abnormalities of the common oral cleft[11, 13]. Furthermore, we were able to construct a timetable expressing fusion and/or differentiation defects in weeks of development, based on early and late embryonic development of the primary palate and on late embryonic development of the secondary palate.

The main strength of our study was the use of the national validated NVSCA database, which allowed us to analyze detailed data on a relatively large sample of patients affected with many different cleft sub-phenotypes. The NVSCA registry records all individual abnormalities that form the oral cleft, that is, the morphology and side of each anatomic structure (lip, alveolus, hard palate, and soft palate including the uvula). These data can be translated to any classification, new or old[49]. In contrast to this system, most available classification systems interpret the observed abnormalities that form the common oral cleft[1]. As a consequence, morphological details such as whether the cleft is complete, incomplete or submucous are lost. As interpretations of these abnormalities will change by increasing knowledge about normal and abnormal development, adjustment of previously classified patients to new insights - such as a new classification - is often impossible.

Another strength of our study is that we used morphological sequelae that are more or less independent of progress in developmental biology. All parts of the primary and secondary palates grow out, adhere and fuse in a given time period, and somewhat later (primary palate) or during the same time period (secondary palate) they differentiate into bone and/or musculature. Therefore, it seems logical to divide the common oral clefts into fusion defects, differentiation defects, or a combination of fusion and differentiation defects (Tables 1 and 2). During the last decades, immense progress has been made concerning identification of candidate genes and environmental factors with respect to non-syndromic common oral clefts[7, 10, 20, 50-55]. However, elucidating pathways in their development is extremely difficult because of the multigenetic influences and their interaction with environmental factors[8, 22, 56, 57]. Furthermore, the classification systems that have been used for these studies are interpretations of the observed abnormalities. In other words, one does not reckon with the time periods at which various common oral clefts are originated. If one could relate groups

of cleft types to specific time periods, identification of specific known and unknown genes that are expressed during these periods may follow. Also, submucous and microform clefts (including orbicularis oris muscle defects) are often not registered in other classifications. However, these subclinical forms may be just as important for further delineating the pathogenesis, clinical genetics, and understanding of the epidemiology[7, 8].

As shown by our findings, the pathoembryological sequelae can be described in any individual case. Transfer of our data to this classification caused no problems, all patients fitted in a subgroup (Table 3). In addition, we constructed a timetable that can be used as a guideline for relating the type of clefting to the time period expressed in weeks of development. For instance, complete cleft lip/alveolus arises significantly earlier in development than incomplete cleft lip (Figure 6). In identifying genes and/or environmental factors, one should therefore distinguish these types and restrict the possible/candidate genes and environmental factors to the time period involved.

At the same time, this timetable also had some limitations. First, over 90% of the common oral clefts, but not all clefts, fitted in the timetable. Also, some fusion defects of the secondary palate were difficult to fit in the table. Theoretically, a complete cleft palate can originate from different mechanisms during two different time periods in late embryonic development. Complete cleft palate can originate relatively early during late development (7 to 9 weeks of development) because of insufficient outgrowth and elevation of the palatal shelves. However, lack of adhesion / programmed cell death and/or EMT and/or migration later during late embryonic development (9 to 11 weeks of development) may cause the same defect. Arbitrarily, all complete cleft palate cases were accumulated and placed in the early period of late embryonic development (Figure 6). Because of the possible different cell biological mechanisms and the different originating time frames, investigating complete cleft palate patients for common pathways may be hazardous. If one selects defects of the secondary palate in which a part of the hard palate or the whole hard palate has been fused, one can rule out insufficient outgrowth and elevation of the shelves, thereby limiting the number of mechanisms, and relating only to one time period.

In conclusion, our unique classification of common oral clefts provides subgroups reckoning with morphology and underlying cell biological mechanisms, and with the time period during which a given common oral cleft evolves. In this way, more accurate data may become available for further clinical and fundamental research. For international use of this new classification adjustment of the ICD-10 cleft coding system (Q35-Q37) is required with regard to sub-phenotypes, such as incomplete cleft lip/alveolus and submucous cleft palate.

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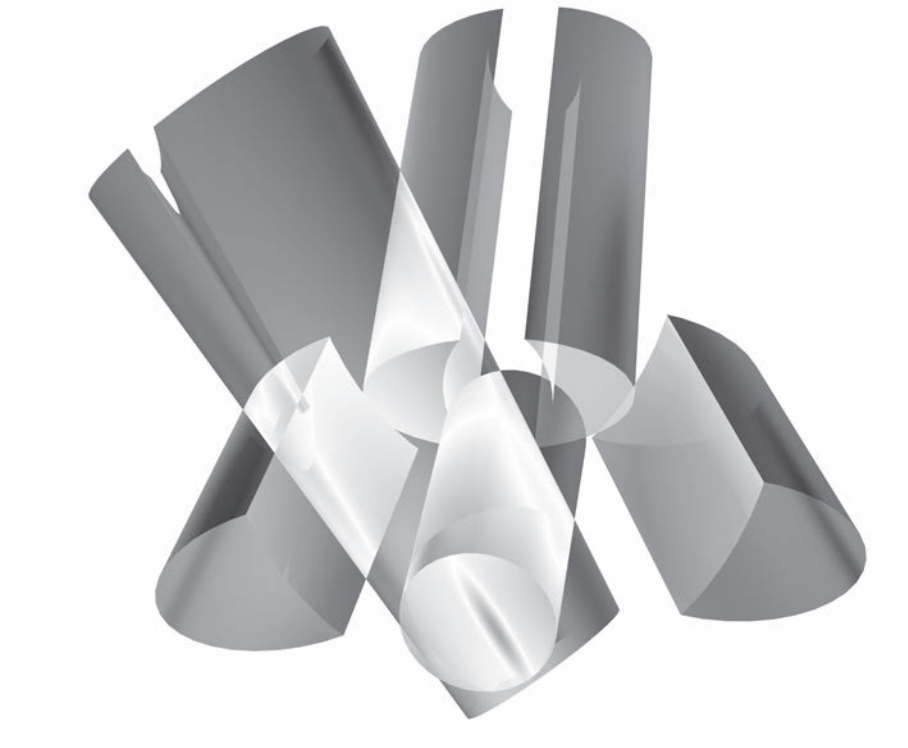
DISCUSSION



Many questions arise when parents are confronted with a congenital malformation of their newborn child. 'Why did this happen to us?' 'Did we do something wrong?' 'Is it our fault?' 'What can be done about this?' 'What about future children?' 'What is the etiology?' 'Is it an isolated anomaly?' In order to address these questions, one should first establish the nature of the anomaly. Querying the medical history and careful physical examination are important cornerstones of establishing the diagnosis. Which part or parts of the body is or are involved? Are other organs involved? What are the exact abnormalities that form the anomaly? The observed abnormalities that make an anomaly are often discrete or not distinct. Furthermore, the combination of abnormalities often does not represent a clear-cut example of an anomaly, such as the bifid distal phalanx of a radial ray in a four digit hand, combined with a hypoplastic medial phalanx of the adjacent finger and synostosis of both radial metacarpals (Chapter 3). Additional anomalies of other parts of the body will often not be visible yet, but will expose themselves after several years[1]. Furthermore, the physician should know when to search for further anomalies, for instance in case of thumb anomalies or cleft palate because of increased frequency of systemic anomalies[2,3]. Clinical geneticists are trained to delineate a combination of congenital anomalies into a known or unknown syndrome / sequence. Most often they can participate in discussions about the pathogenesis of the anomalies. Therefore, referral to a clinical geneticist is indicated if other congenital anomalies are observed and/or in case of a positive family history.

The ideal classification system should be simple, and a full description should be provided of the anomaly[4]. These conditions are conflicting, and concessions have to be made. Several classification systems have been developed with details about the limb anomalies or the cleft types according to anatomic appearance and embryology, and frequent occurring variations are adequately described (Chapters 2, 4 and 7). For groups of hand anomalies several clinical sub-classifications have been developed to aid the physician in the choice of treatment strategy[5]. However, infrequent anomalies can often not be classified. Furthermore, classifications result from various interpretations of the observed abnormalities[6] (Chapters 2-4, and 7). Our knowledge about normal and abnormal embryonic development has clearly expanded during the last years, thereby changing interpretations[6-8] (Chapters 2 and 7). Obviously, this does not improve consistency of classification.

One of my first experiences with this inconsistency concerned a male foetus[9]. His parents requested termination of pregnancy because of ultrasound confirmation of severe upper and lower limb anomalies and intestinal atresia. Post mortem examination showed transverse reduction anomalies and jejunal atresia. Obviously, the parents wanted to know why this had happened. After careful examination of the foetus, it was demonstrated that the chorionic villus sampling may have caused these congenital anomalies due to disruption of end-arteries in the limbs and jejunum. Classifying the observed limb anomalies of this foetus using well-known classifications was not possible. To resolve this issue, a search was started to classify limb anomalies. As no system seemed to be able to describe sufficient details of the anomalies, we decided to analyse and describe each individual abnormality (anatomical as well as morphological) forming the anomalies of this foetus. To investigate whether inconsistencies existed among other congenital upper limb anomalies, all patients with a congenital upper limb anomaly who had visited the Plastic Surgery Department at the Erasmus Medical Center Rotterdam in 25 years (1972-1996) were evaluated using one of the most common classifications, the Swanson classification[10] (Chapter 2). Indeed, the Swanson classification was not consistent in a considerable number of patients. Out-dated knowledge of pathogenesis of congenital limb anomalies may cause this lack of uniformity. In the last decades great progress has been made concerning embryonic limb development, and several developmental mechanisms have been elucidated, such as the role of programmed cell death, and the role of numerous genes. This progress will continue, and consequently the ideas about the pathogenesis of congenital limb malformations will differentiate further. Swanson's classification is predominantly based on diagnosis, and the diagnosis is largely based on knowledge of the pathogenesis of congenital limb malformations. In order to overcome these difficulties, we extended the philosophy of describing each individual abnormality to all congenital upper limb anomalies (Chapter 3). We developed a new recording system that describes the anomalies by its abnormalities. After recording all abnormalities forming the anomaly, we could easily reproduce the Swanson classification, and showed that about 1/3 of the available information was lost if the anomaly was directly classified. This clearly shows the benefit of proper description before classification.

During the same time, another area of recording congenital anomalies was investigated at our department. This area concerned congenital craniofacial anomalies under auspices of the Dutch Association for Cleft palate and Craniofacial Anomalies. Quite the same problems existed in classifying these anomalies. Existing classifications could not

consistently group observed abnormalities, without compromising them. Therefore, we again returned to the basics of describing all abnormalities forming the anomaly. We developed a new recording system for all craniofacial anomalies that describes the abnormalities forming the anomaly. We started with common oral clefts (Chapter 4), and all observed abnormalities constituting the cleft sub-phenotypes could be recorded. This system has been validated, and possesses sufficient validity for the three cleft categories, cleft lip/alveolus, cleft lip/alveolus and palate, and cleft palate (Chapters 5 and 6).

These two recording systems combined with knowledge of basic normal and abnormal processes during embryogenesis and fetal development, should allow an explanation in most cases of how the anomaly may have emerged. In the future, additional information will obviously be provided by the rapidly expanding knowledge regarding genetic aspects of development. New classifications can be proposed, adapted to the most recent insights in embryonic development. When these insights change, this classification can be adjusted without losing details about the recorded anomalies. Chapter 7 can serve as an example of such a new classification. This classification reckons with the topography and morphology of the cleft sub-phenotypes and corresponding developmental time period; fusion defect, differentiation defects of a combination of both are distinguished. In contrast to other classifications submucous and microform clefts (including orbicularis oris muscle defects) can be recorded and classified as differentiation defects. These subclinical forms may be useful for further dissecting the components of the pathogenesis, clinical genetics, and the epidemiology[11,12]. In conclusion, this classification will enable more accurate data for further clinical and fundamental research.

Besides informing patient and parents about the anomaly, consistent recording and classification is also very important to allow the pathogenesis to be studied. Furthermore, intra centre and national and international intercentre studies concerning frequency, treatment, and surveillance of the anomalies require consistent description of the anomalies. Most birth defect registries to date use a coding system based on the International Statistical Classification of Diseases and Related Health Problems (ICD), which has now reached its tenth revision[13]. One of the strengths of most birth defect registries is that they are well structured organisations with huge networks, with regional, national and international collaborations. Massive amounts of data are collected, checked for duplicate values, updated and are included in ever expanding databases. After a selected time period, different codes can be withdrawn from that database, and several correlations between general characteristics or other congenital anomalies can

be established. Furthermore, relating specific congenital anomalies to gene profiles may elucidate common pathways concerning (patho)embryology. Over different time periods birth prevalence rates can be computed, as well as changes between them. One of the goals of these registries is surveillance of congenital anomalies. For instance, changes in frequency of a certain anomaly may be indicative for a causative environmental agent, and subsequently appropriate preventive measures could be taken. All of these investigations assume consistent recording of the anomaly to be studied. If anomalies are not consistently recorded by these codes, and if these codes do not follow basic principles of (patho)embryogenesis, conclusions may be drawn with difficulties. Tables 1 and 2 show most ICD codes for congenital anomalies of the upper limb and of common oral clefts, respectively. These codes prevent a comprehensive approach. Describing congenital anomalies of the upper limb using ICD10 will result in suboptimal grouping. Each patient with a common oral cleft will fit into ICD10, however, no relationship with the developmental derailments is expected for cleft lip with or without palate (Chapter 7). Furthermore, subclinical forms can not be classified as a separate entity. Again gross grouping of pathoetiological different cases is to be expected. If these pathoethiological different anomalies are studied as one group, one compares apples with oranges. Therefore, studies using ICD10 may not be as promising as hoped for. Interestingly, physicians who are dealing with congenital upper limbs or with common oral clefts in daily practice, often use other registries than ICD10. The recording systems introduced in this thesis avoid lumping of the anomalies and prevent to some extent splitting of the anomalies. Lumping means grouping anomalies together and being less specific without too many subdivisions, and splitting means description of the anomalies and division of every variety into different categories[14-16]. If requested one can lump and split as pleased, by combining individual abnormalities that form the anomaly. Furthermore, translation to ICD10 or to a more specialised classification can be done without problems.

All tissues and organs in the human body are formed by the three cell biological processes, cell proliferation, cell differentiation, and cell death, and all different tissues and organ systems display specific congenital malformations. It should be possible to develop similar recording systems for other areas than limb and face, such as the vascular, digestive, urogenital, and respiratory systems. In this way, by linking all future recording systems, combined with the present and future knowledge about (patho-)embryology, progress can be expected in for example determining gene and gene functions, or surveillance of congenital anomalies. This approach will ultimately lead to better counseling of parents who are expecting or have a child with a congenital anomaly.

Table 1 ICD 10 codes concerning congenital upper limb anomalies

Q68	Other congenital musculoskeletal deformities	
	Excludes: reduction defects of limb(s) (Q71-Q73)	
	Q68.1	Congenital deformity of hand
		Congenital clubfinger
		Spade-like hand (congenital)
	Q68.8	Other specified congenital musculoskeletal deformities
		Congenital:
		• deformity of clavicle, elbow, forearm
		• dislocation of elbow; elbow; scapula
Q69	Polydactyly	
	Q69.0	Accessory finger(s)
	Q69.1	Accessory thumb(s)
	Q69.9	Polydactyly, unspecified: Supernumerary digit(s) NOS
Q70	Syndactyly	
	Q70.0	Fused fingers: Complex syndactyly of fingers with synostosis
	Q70.1	Webbed fingers: Simple syndactyly of fingers without synostosis
	Q70.4	Polysyndactyly
	Q70.9	Syndactyly, unspecified: Symphalangy NOS
Q71	Reduction defects of upper limb	
	Q71.0	Congenital complete absence of upper limb(s)
	Q71.1	Congenital absence of upper arm and forearm with hand present
	Q71.2	Congenital absence of both forearm and hand
	Q71.3	Congenital absence of hand and finger(s)
	Q71.4	Longitudinal reduction defect of radius: Clubhand (congenital), radial clubhand
	Q71.5	Longitudinal reduction defect of ulna
	Q71.6	Lobster-claw hand
	Q71.8	Other reduction defects of upper limb(s): Congenital shortening of upper limb(s)
	Q71.9	Reduction defect of upper limb, unspecified
Q73	Reduction defects of unspecified limb	
	Q73.0	Congenital absence of unspecified limb(s): Amelia NOS
	Q73.1	Phocomelia, unspecified limb(s): Phocomelia NOS
	Q73.8	Other reduction defects of unspecified limb(s)
		Longitudinal reduction deformity of unspecified limb(s)
		Ectromelia NOS }
		Hemimelia NOS } of limb(s) NOS
		Reduction defect }
Q74	Other congenital malformations of limb(s)	
	Excludes: polydactyly (Q69.-); reduction defect of limb (Q71-Q73); syndactyly (Q70.-)	
Q74.0	Other congenital malformations of upper limb(s), including shoulder girdle	
	Accessory carpal bones	
	Cleidocranial dysostosis	
	Congenital pseudarthrosis of clavicle	
	Macrodactylia (fingers)	
	Madelung's deformity	
	Radioulnar synostosis	
	Sprengel's deformity	
	Triphalangeal thumb	
Q79	Congenital malformations of the musculoskeletal system, not elsewhere classified	
	Excludes: congenital (sternomastoid) torticollis (Q68.0)	
	Q79.8	Other congenital malformations of musculoskeletal system
		Absence of muscle, tendon
		Accessory muscle
		Amyotrophia congenita

		Congenital constricting bands; shortening of tendon
		Poland's syndrome
Q87	Other specified congenital malformation syndromes affecting multiple systems	
	Q87.2	Congenital malformation syndromes predominantly involving limbs
		Syndrome:
		• Holt-Oram
		• Klippel-Trénaunay-Weber
		• nail patella
		• Rubinstein-Taybi
		• sirenomelia
		• thrombocytopenia with absent radius [TAR]
		• VATER

Table 2 ICD 10 codes concerning common oral clefts

Use additional code (Q30.2), if desired, to identify associated malformations of the nose.		
Excludes:	Robin's syndrome (Q87.0)	
Q35	Cleft palate	
	Includes:	fissure of palate; palatoschisis
	Excludes:	cleft palate with cleft lip (Q37.-)
	Q35.1	Cleft hard palate
	Q35.3	Cleft soft palate
	Q35.5	Cleft hard palate with cleft soft palate
	Q35.7	Cleft uvula
	Q35.9	Cleft palate, unspecified
Q36	Cleft lip	
	Includes:	cheiloschisis; congenital fissure of lip; harelip; labium leporinum
	Excludes:	cleft lip with cleft palate (Q37.-)
	Q36.0	Cleft lip, bilateral
	Q36.1	Cleft lip, median
	Q36.9	Cleft lip, unilateral
		Cleft lip NOS
Q37	Cleft palate with cleft lip	
	Q37.0	Cleft hard palate with bilateral cleft lip
	Q37.1	Cleft hard palate with unilateral cleft lip
		Cleft hard palate with cleft lip NOS
	Q37.2	Cleft soft palate with bilateral cleft lip
	Q37.3	Cleft soft palate with unilateral cleft lip
		Cleft soft palate with cleft lip NOS
Q37.4	Cleft hard and soft palate with bilateral cleft lip	
Q37.5	Cleft hard and soft palate with unilateral cleft lip	
	Cleft hard and soft palate with cleft lip NOS	
Q37.8	Unspecified cleft palate with bilateral cleft lip	
Q37.9	Unspecified cleft palate with unilateral cleft lip	
	Cleft palate with cleft lip NOS	

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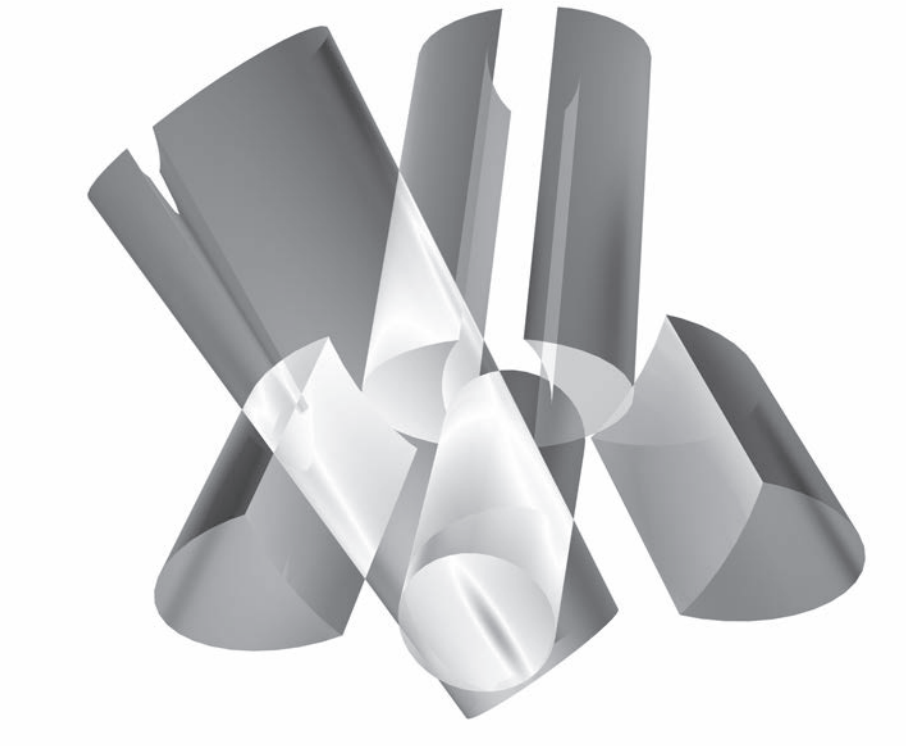
SUMMARY



Congenital anomalies display a great variability, even within the same diagnosis. This thesis focuses on problems of classification of congenital anomalies of the upper limb and of common oral clefts. It provides a new approach for initial assessment of children with these anomalies.

Chapter 2 Classification of congenital anomalies of the upper limb

The data from 694 patients with a congenital anomaly of the upper limb treated from 1972 until 1996 in Erasmus Medical Center Rotterdam were classified according to the classification of Swanson et al. (J Hand Surg [Am], 1983), and compared with previous studies. The Swanson classification - based on embryonic failure during development and clinical diagnosis - has been accepted by the American Society for Surgery of the Hand and the International Federation of Societies for Surgery of the Hand and is used worldwide. Our study revealed similar discrepancies as in literature (an anomaly fitted in different categories, arbitrary choice of the most important abnormality). A lack of uniformity in the classification can account for these discrepancies, which may be caused by out-dated knowledge of the pathogenesis of congenital limb anomalies. Therefore, it seems necessary to describe the anomalies instead of the diagnoses, and classify afterwards.

Chapter 3 Recording congenital differences of the upper limb

To overcome the inconsistencies of present classifications, a non-classifying recording method was developed. This method records individual aberrations, including bone and soft tissue defects. In a prospective study, 231 patients of the Erasmus Medical Center Rotterdam were successfully recorded. It has been shown that these data can be transferred to any existing classification. Consistent grouping of patients is now possible without losing details about simple and complex anomalies.

Chapter 4 Ten years recording common oral clefts with a new descriptive system

A new descriptive recording system for congenital craniofacial abnormalities - including common oral clefts - was introduced nationally by the Dutch Association for Cleft Palate and Craniofacial Anomalies (NVSCA) in 1997. All 3512 unoperated common oral cleft patients that were referred to a Dutch cleft team from 1996 until 2006 were included in this study (prevalence of 16.6 per 10,000 live births). Patients showed a cleft lip/alveolus (CL/A, 28%), a cleft lip/alveolus and palate (CLA/P, 39%), or a cleft palate (CP, 33%). The three categories exhibited very heterogeneous cleft types. This new recording method allows adequate description of common oral clefts. Many cleft types exist within these three categories and should be differentiated, because they originate from different time frames and/or cell biological mechanisms during embryogenesis.

Chapter 5 Validation of the NVSCA registry common oral clefts: study design and first results

This chapter concerns part one of the validation of the NVSCA registry. The study group consisted of a random sample of 250 patients with common oral clefts; 13 cases were excluded. The NVSCA registry is a valuable tool for quality improvement and research because validity on all three common oral cleft categories is very good. Validity on the general items is reasonable to satisfying and appears to be related to the type of information.

Chapter 6 Validation of the Dutch registry common oral clefts: quality of recording specific oral cleft features

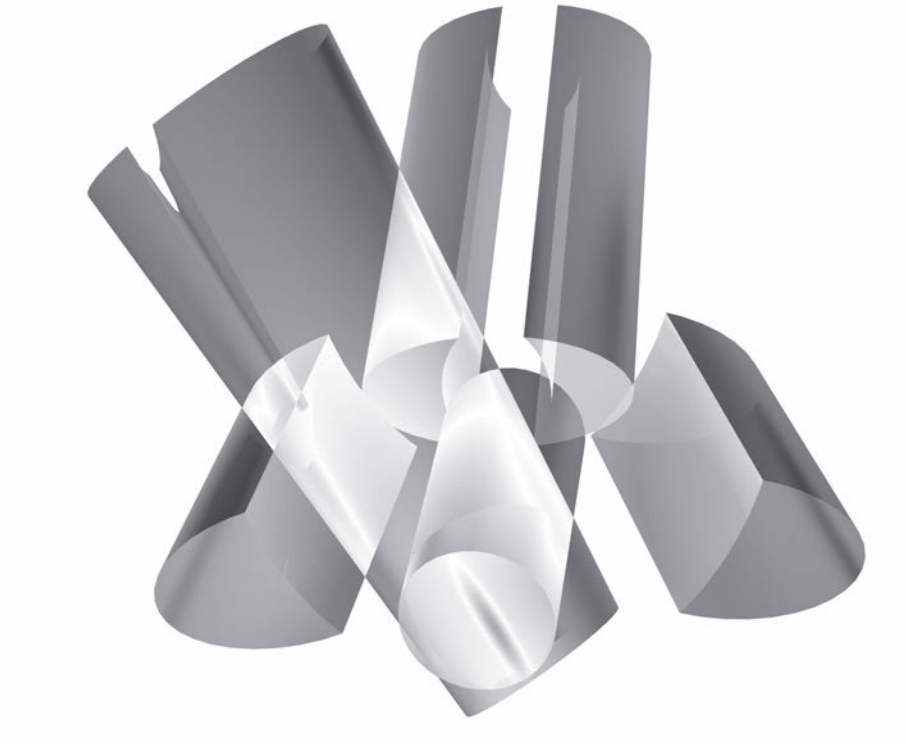
In part two of the validation of the NVSCA registry the cleft types within the categories are further analysed. Overall, validity of Dutch registry data on oral clefts is good, supporting the feasibility of this unique recording system. However, when analyzing cleft data in detail, the quality appears to be related to anatomical location and morphological severity. This finding might have implications for etiologic research based on registry data, and guidelines on neonatal examination.

Chapter 7 Classifying common oral clefts: a new approach after descriptive registration

Using the Dutch Oral Cleft Registration, which records the topography and the morphology of common oral clefts, a new classification based on the (patho)embryology of the primary and secondary palate was tested. The primary and secondary palates arise by fusion of distinct facial swellings, and they grow out and differentiate. These processes occur earlier in the primary palate than in the secondary palate. Disturbances of the fusion and/or differentiation processes may give rise to the cleft types. In our study, cleft types were subdivided into fusion defects, differentiation defects, or a combination of both. From 1997 until 2006 3512 oral cleft patients were included. Patients with CL/A showed in 22% fusion defects, in 75% differentiation defects, and in 3% a combination of both. CL/AP patients and CP patients mostly showed fusion defects (70% and 89%, respectively). A timetable was constructed to relate the type of clefting to the time of derailment during embryonic development. This new classification provides new subgroups that may be used for fundamental and clinical research. These subgroups originates from different time frames during embryonic development and different cell biological mechanisms, thereby enabling more accurate data for gene identification and/or environmental factors.

All tissues and organs in the human body are formed by the three cell biological processes, cell proliferation, cell differentiation, and cell death. All different organs display specific congenital anomalies caused by the same basic processes. It should be possible to develop similar recording systems for other areas than the upper limb and head, such as the circulatory, digestive, urogenital, or respiratory system. In this way, by linking all future recording systems, combined with the present and future knowledge about (patho-)embryology, progress can be expected in for example determining genes and gene functions, or surveillance of congenital anomalies.

DUTCH SUMMARY



Aangeboren afwijkingen vertonen een grote variëteit, zelfs binnen dezelfde diagnosegroep. Dit proefschrift concentreert zich op classificatieproblemen van aangeboren afwijkingen van de bovenste extremiteit en van schisis. Het geeft een nieuwe benadering voor de eerste beoordeling van kinderen met deze afwijkingen.

Hoofdstuk 2 Classificatie van aangeboren afwijkingen van de bovenste extremiteit
De gegevens van 694 patiënten met een congenitale afwijking van de bovenste extremiteit uit de jaren 1972 tot 1996 van het Erasmus Medisch Centrum Rotterdam werden geclassificeerd volgens de classificatie van Swanson et al. (J Hand Surg [Am], 1983) en vervolgens vergeleken met de literatuur. De Swanson classificatie - gebaseerd op embryonale stoornis en klinische diagnose - is geaccepteerd door de American Society for Surgery of the Hand en de International Federation of Societies for Surgery of the Hand en wordt wereldwijd gebruikt. In onze studie werden dezelfde discrepanties gevonden als in de literatuur (een afwijking past in verschillende categorieën, arbitraire keuze maken wat de belangrijkste afwijking is). Een gebrek aan uniformiteit in het classificeren kan dit verklaren, welke veroorzaakt kan zijn door gedateerde kennis van de pathogenese van congenitale extremiteitsafwijkingen. Daarom lijkt het aangewezen om de afwijkingen te beschrijven in plaats van de diagnose vast te leggen, en vervolgens te classificeren.

Hoofdstuk 3 Registratie van aangeboren afwijkingen van de bovenste extremiteit
Om de inconsistenties van de bestaande classificaties te verhelpen, is een niet classificerende registratiemethode ontwikkeld voor congenitale afwijkingen van de bovenste extremiteit. Deze methode registreert individuele afwijkingen, inclusief bot- en weke delen defecten. In een prospectieve studie werden vervolgens 231 patiënten van het Erasmus Medisch Centrum Rotterdam geregistreerd. Het is gebleken dat de zo verkregen gegevens eenvoudig vertaald kunnen worden naar reeds bestaande classificaties. Consistente groepering van de patiënten is nu mogelijk zonder dat details van simpele en complexe afwijkingen verloren gaan.

Hoofdstuk 4 Tien jaar registratie van schisis middels een nieuw beschrijvend systeem
Een nieuwe beschrijvende registratiemethode voor congenitale craniofaciale afwijkingen - inclusief schisis - werd landelijk geïntroduceerd door de Nederlandse Vereniging voor Schisis en Craniofaciale Afwijkingen (NVSCA) in 1997. Alle 3512 patiënten met een schisis die zijn aangemeld bij een Nederlands schisisteam van 1997 tot en met 2006 werden geïncludeerd in deze studie (prevalentie 16.6 per 10.000 levend geborenen). In 28% betrof het een cheilo(gnatho)schisis, 39% had een cheilo(gnatho)palatoschisis en 33% had een palatoschisis. De drie categorieën laten zeer heterogene schisistypen zien, die met behulp van deze nieuwe registratiemethode adequaat beschreven kunnen worden. Niet alleen tussen de categorieën maar ook binnen elke categorie moeten de schisistypen onderscheiden worden, omdat zij ontstaan tijdens verschillende tijdsperiodes en/of via verschillende celbiologische mechanismen tijdens de embryogenese.

Hoofdstuk 5 Validatie van de NVSCA registratie betreffende schisis: studieontwerp en eerste resultaten
Dit hoofdstuk betreft deel één van de validatie van de NVSCA registratie. De studiegroep omvatte een random sample van 250 patiënten met schisis; 13 casus werden geëxcludeerd. De NVSCA registratie blijkt een waardevol handvat te zijn voor kwaliteitsverbetering en onderzoek omdat de validiteit van de drie schisiscategorieën zeer goed is. De validiteit betreffende de algemene items is redelijk tot bevredigend en lijkt gerelateerd te zijn aan het type informatie.

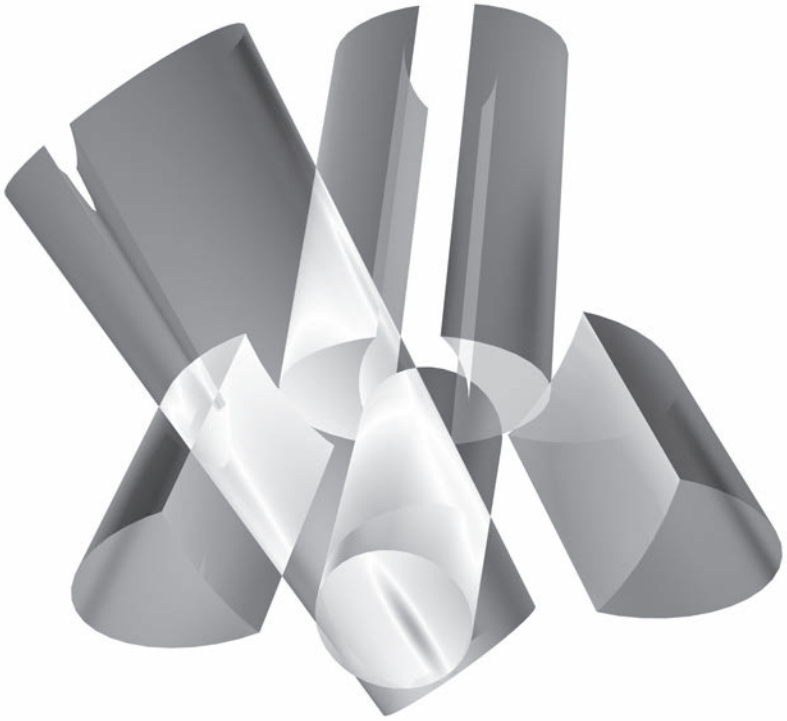
Hoofdstuk 6 Validatie van de Nederlandse registratie betreffende schisis: de kwaliteit van de registratie van specifieke schisiskenmerken
In deel twee van de validatie van de NVSCA registratie worden de schisistypen binnen de categorieën verder geanalyseerd. In het algemeen is de validiteit goed, wat de betrouwbaarheid van dit unieke registratiesysteem ten goede komt. Wanneer de schisis egevens in detail geanalyseerd worden, blijkt de kwaliteit gerelateerd te zijn aan de anatomische locatie en morphologische ernst. Deze uitkomst zou gevolgen kunnen hebben voor etiologisch onderzoek gebaseerd op deze registratiedata, en richtlijnen voor neonataal onderzoek.

Hoofdstuk 7 Classificatie van schisis: een nieuwe benadering na beschrijvende registratie

Door gebruik te maken van de NVSCA schisisregistratie, die de topografie en de morfologie van schisis registreert, werd een nieuwe classificatie getest die gebaseerd is op de (patho-)embryologie van het primaire en secundaire palatum. Het primaire en secundaire palatum ontstaat door fusie van verschillende aangezichtsstructuren en vervolgens door uitgroei en differentiatie hiervan, waarbij de ontwikkeling van het primaire palatum in tijd iets voorloopt op het secundaire palatum. Stoornissen in deze fusie- en/of differentiatieprocessen kunnen aanleiding geven tot de verschillende schisistypen. Onze studie verdeelde dan ook de schisistypen van het primaire en/of secundaire palatum in fusiedefecten, differentiatiedefecten of een combinatie van beide. Van 1997 tot 2006 werden 3512 patiënten met schisis geïncludeerd. Patiënten met een cheilo(gnatho) palatoschisis of een palatoschisis hadden meestal een fusiedefect (70%, respectievelijk 89%). Cheilo(gnatho)schisis patiënten hadden in 22% van de gevallen een fusiedefect, 75% had een differentiatiedefect en 3% een combinatie van beide. Een tijdstabel werd gepresenteerd waarbij het schisistype gerelateerd werd aan de tijdsperiode waarin dit is ontstaan tijdens de embryonale ontwikkeling. Deze nieuwe classificatie geeft nieuwe subgroepen die gebruikt kunnen worden voor fundamenteel en klinisch onderzoek. Deze subgroepen stammen uit verschillende tijdsperiodes tijdens de embryonale ontwikkeling, en ontstaan door verschillende celbiologische mechanismen. Hierdoor zijn meer accurate data beschikbaar voor de identificatie van genen en/of omgevingsfactoren, die een rol zouden kunnen spelen bij het ontstaan van schisis.

Alle weefsels en organen in het menselijk lichaam worden gevormd door de drie celbiologische mechanismen: celproliferatie, celdifferentiatie en celdood. Alle verschillende weefsels/organen hebben specifieke congenitale afwijkingen die op verstoring van dezelfde basisprocessen berusten. Het moet dan ook mogelijk zijn om gelijkende registratiesystemen te ontwikkelen voor andere gebieden dan hand en hoofd, zoals voor de tractus circulatorius, digestivus, urogenitalis of respiratorius. Op deze manier, als alle toekomstige systemen verbonden worden, kan voortuitgang verwacht worden op het terrein van bijvoorbeeld de determinatie en functies van genen, of de kwaliteitsbewaking van congenitale afwijkingen, wanneer deze gecombineerd worden met de huidige en toekomstige kennis over de (patho-)embryologie.

ACKNOWLEDGEMENTS



MANY HAVE BEEN INDISPENSABLE FOR THE REALISATION OF THIS THESIS.

I HIGHLY APPRECIATE ALL YOUR SUPPORT.

CURRICULUM VITAE

BORN 11 SEPTEMBER 1973, HALSTEREN

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1998-1999	RESEARCH FELLOW PLASTIC SURGERY, ERASMUS MC, ROTTERDAM
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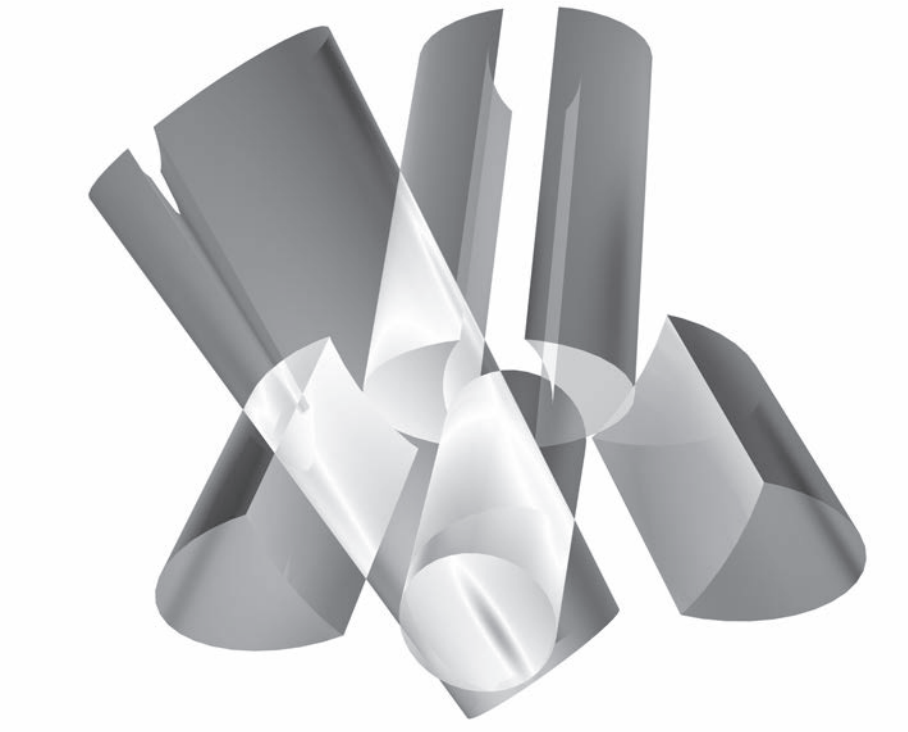

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PhD Portfolio

Summary of PhD training and teaching

A.J.M. Luijsterburg Department of Plastic, Reconstructive and Hand Surgery, Erasmus MC, Rotterdam	PhD period: 2000-2012 Promotor(s): Prof. Dr S.E.R. Hovius Supervisor: Dr. C. Vermeij-Keers	
1. PhD training		
	Year	Workload (Hours/ECTS)
General courses - Biomedical English Writing and Communication - Laboratory animal science	 Self taught 1999	 Full time 120
Specific courses (e.g. Research school, Medical Training) - Microsurgery - MD Residency Plastic, Reconstructive and Hand Surgery	 2000 2004-2010	 24 Full time
Presentations - Kyoto, Japan. Fifth international symposium on congenital differences of the upper limb. Presentation. - Barcelona, Spain. Seventh Congress of the Federation of European Societies for Surgery of the Hand. Poster. - Cardiff, UK. First International Symposium on Prevention and Epidemiology of Congenital Malformations. 2 Posters. - Sheffield, UK. Spring Meeting of the British Society for Surgery of the Hand. Presentation. - Amsterdam. Eigth Congress of the Federation of European Societies for Surgery of the Hand. Invited Speaker. - Rotterdam. "Meer aan de hand". Nederlandse Vereniging voor Kindergeneeskunde. Invited Speaker. - Leuven, Belgie. Nederlandse Vereniging voor Schisis en Craniofaciale Afwijkingen. Presentation. - Bologna, Italie. Seventh European Craniofacial Congress. Presentation. - Bilbao, Spain. Eigth European Craniofacial Congress. 2 Presentations.	 2000 2000 2000 2001 2002 2003 2003 2003 2007	 60 20 40 60 180 20 20 60 60
2. Teaching		
	Year	Workload (Hours/ ECTS)
Supervising practicals and excursions, Tutoring - Supervisor microsurgery courses - LISA Hand	 2000-2009 2006	 80 each year 20
Supervising Master's theses - Several medical students	 2000-2004	 120