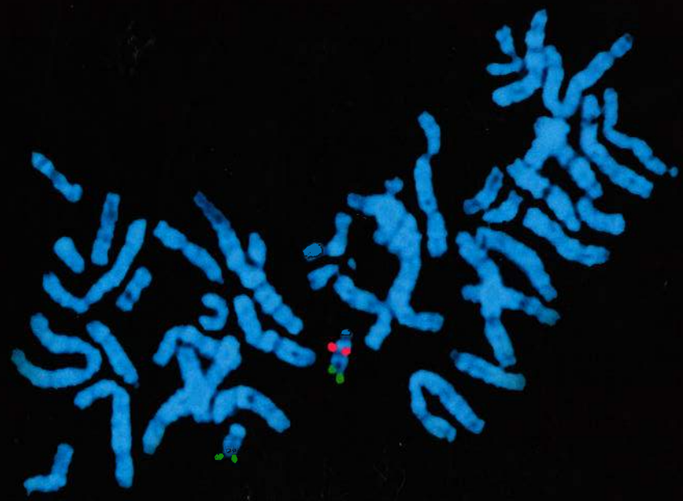
THE OTO-RHINO-LARYNGOLOGICAL MANIFESTATIONS OF THE VELO-CARDIO-FACIAL SYNDROME

Greet Vantrappen



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Greet Vantrappen

Thesis submitted in fulfillment of the requirements for the degree of
"Doctor in de Medische Wetenschappen"

Promotor: Professor K. Devriendt
Copromotor: Professor C.W.R.J. Cremers and Professor J.P. Fryns

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CHAPTER 1

INTRODUCTION

Adapted from :

* Vantrappen G, Rommel N, Cremers CWRJ, Devriendt K, Fryns JP. The velo-cardio-facial syndrome: the otorhinolaryngeal manifestations and implications. Int J Ped Otorhinolaryngol 1998;45:133-141

* Devriendt K, Vantrappen G, Vogels A, Rommel N, Swillen A, Gewillig M, Fryns JP. Het Velocardiofaciaal en Digeorge Syndroom als variabele expressie van een del22Q11. Tijdschr Belg Kinderarts 2000;2:230-233

1.1. THE DIGEORGE AND VELO-CARDIO-FACIAL SYNDROME : 35 YEARS EVOLUTION

Ontogenesis of the clinical syndrome

Approximately 10 years ago, it was discovered that a submicroscopic deletion in chromosome 22q11 causes a number of related syndromes including the DiGeorge and the Velo-Cardio-Facial syndromes (VCFS)(1, 2).
In 1968, A. DiGeorge, a pediatric endocrinologist, described a syndrome of congenital absence of the thymus with congenital hypoparathyroidism (3). In the following years, several additional symptoms were recognized such as the facial dysmorphism (minor ear defects, micrognathia) and, more importantly, congenital heart defects. Congenital heart defects, typically interrupted aortic arch or truncus arteriosus, were seen in most infants with this condition (4). The diagnosis of DiGeorge syndrome was therefore mainly made by pediatric cardiologists. The prognosis of these children was very poor, due to both the severity of the heart defect and the associated immune disturbance (4). However, the variability in clinical expression was already noted at an early stage (5) and this has led to the distinction of different categories including complete and partial DiGeorge syndromes (6).
In 1978, Shprintzen, working in an ENT-clinic, described " A new syndrome involving cleft palate, cardiac anomalies, typical facies, and learning disabilities: Velo-Cardio-Facial syndrome" (7). The cardiac defects in these children were less severe and thus compatible with survival into adulthood. Additional manifestations including the velopharyngeal insufficiency as well as learning disabilities became thus apparent. A wide variability in expression was also evident (8). The similarity with the DiGeorge syndrome was noted in some instances, resulting in nosological discussions (9)

Two years earlier, a Japanese author had reported on a condition comprising a dysmorphic facial appearance, outflow tract defects of the heart and developmental delays (10). Later, this entitity became known as the conotruncal anomaly face syndrome (CTAF). And still later it was noted that this syndrome had similarities to the Shprintzen and the DiGeorge syndromes (11).
As often is the case, these entities probably have been described before in the older literature, but did not gain general acceptance. For instance, in 1955, Sedlackova, a Czeck phoniatrician, described the velofacial hypoplasia. The main feature was congenital shortening of the soft palate, causing hypernasal speech, associated with facial dysmorphism (12). Likewise, the family reported by Strong et al. with familial right-sided aortic arch, mental deficiency, and facial dysmorphism probably is another example of the same entity (13).

Genetic basis of the syndrome

The unravelling of the etiology of these syndromes started in 1981, with a report of a family with four siblings with the DiGeorge syndrome carrying a partial monosomy of proximal chromosome 22q. This was the unbalanced result of a reciprocal translocation (20q11;22q11) in one of the parents (14). Subsequently, several additional patients with the DiGeorge syndrome and cytogenetically visible partial monosomies of chromosome 22q11 were noted. With the development of molecular biological tools, it was possible from the end of the 1980's to characterize the gene(s) involved in this syndrome. Soon, a minimal region of deletion overlap for DiGeorge syndrome was delineated on chromosome 22q11 through the study of several patients with visible chromosome 22q deletions (1). The major breakthrough was the observation that over 90% of DiGeorge syndrome patients have a submicroscopic deletion in this region (15, 16, 17, 18). Equally important was the discovery that the same deletion was also present in the majority of patients with the Velo-Cardio-Facial deletion syndrome (19). Later studies demonstrated that Sedlackova's velofacial syndrome and Takao syndrome were also caused by a submicroscopic deletion in chromosome 22q11 (11,20). More recently, it was shown that some cases of Cayler (21, 22) and Opitz BBBG syndrome (23, 24) can also be caused by a del22q11 (Table 1). It is now generally accepted that all these disorders represent the variable expression of the same genetic disorder. Of the several proposed names, we prefer "Velo-Cardio-Facial syndrome", since this refers to some of the major features of the del22q11(Fig 1).

Table 1
clinical entities associated with a del22q11

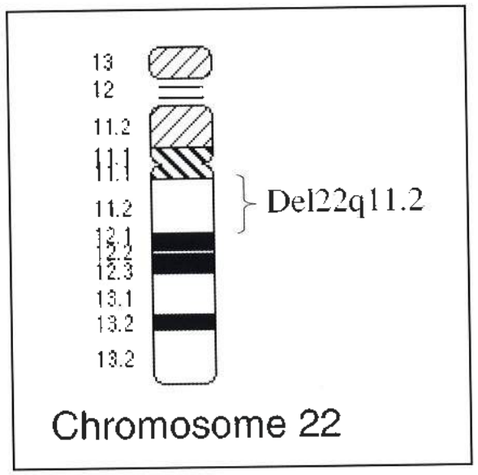
	Initial description	*del22q11 as a cause*
DiGeorge syndrome	DiGeorge, 1968	De La Chapelle, 1981
Velo-cardio-facial syndrome	Shprintzen, 1978	Scambler, 1992
Takao/CTAFS	Kinouchi, 1976	Burn, 1993
Sedlackova's velofacial syndrome	Sedlackova, 1955	Fokstuen, 2001
Cayler	Cayler, 1969	Giannnotti, 1994
Opitz BBBG	Opitz JM, 1969	McDonald-McGinn, 1995

The deletion on chromosome 22 is in most instances due to a *de novo* mutation occurring during gametogenesis, but in a smaller percentage, the deletion is inherited from one of the parents.

In search of the responsible gene(s)

Once the genetic cause of the Velo-Cardio-Facial syndrome was established, and a locus was identified, the major challenge was to identify the gene or genes responsible for the phenotype. In the majority of patients, the deletion is uniform in size (3 Mb in over 80%, 1.5Mb in the remainder) (25). Therefore, the size of the deletion cannot explain the variability in clinical expression. Based on exceptional patients with smaller and overlapping deletions but with a VCFS-phenotype, a smaller critical deletion region could be delineated. However, in this region, more than 24 genes have been identified. It is still not clear whether the disorder is a monogenic disorder or a contiguous gene deletion syndrome. Several candidate genes have been proposed, but despite extensive efforts, no mutations in any of these genes have been detected in patients with the DiGeorge syndrome or Velo-Cardio-Facial syndrome lacking a cytogenetic aberration. Efforts, therefore, focussed on mice models for DiGeorge syndrome, using engineered deletions in the orthologuous chromosomal region (26, 27). Recently, haploinsufficiency for the Tbx1-gene in mice was found to mimic the cardinal features of the DiGeorge/Velo-Cardio-Facial syndrome, including hypoplasia of the thymus and parathyroid glands, cardiac outflow tract abnormalities, abnormal facial structures and cleft palate (28, 29, 30).

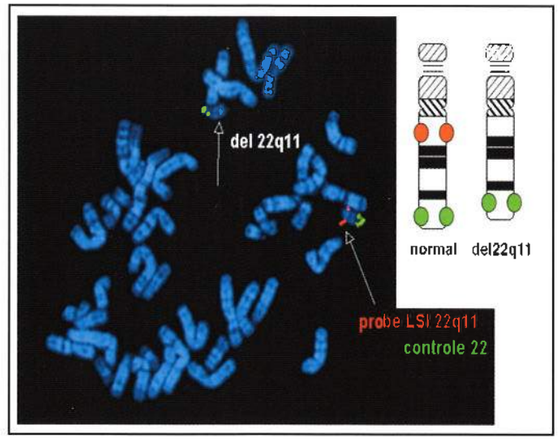
Figure 1
Schematic representation of chromosome 22



A genetic diagnostic test

After the introduction of the Fluorescence in Situ Hybridisation (FISH) technique in the early 1990's, the routine diagnosis of a del22q11 became possible (Fig 2) (31, 32)
This routine diagnostic test for a del22q11 has lead to the identification of a large number of patients with a wide spectrum of clinical manifestations. As a result, this has significantly altered our knowledge on this disorder. The most constant features seen in these individuals are congenital heart defects, learning difficulties, velopharyngeal insufficiency with or without cleft palate, and dysmorphic facial appearance. Many additional features, however, have been described. The diagnosis of more patients with atypical manifestations or with a partial syndrome led to the recognition that this syndrome is much more frequent than previously thought. It is now clear that the Velo-Cardio-Facial syndrome is one of the most frequent genetic disorders, with an estimated incidence at birth of 1/4000 (33). In Flanders, therefore, it can be expected that fifteen patients with this condition are born every year .
The delineation of this entity can be considered as one of the major advances in clinical genetics in the 1990's, with important practical consequences for other medical specialties including Ear-Nose-and Throat (ENT)-surgeons, pediatric cardiologists, psychiatrists and others (8,34,35,36,37,38).

Figure 2
Fluorescence in Situ Hybridisation (FISH)
for the detection of a del22q11.



1.2. THE OTO-RHINO-LARYNGOLOGICAL MANIFESTATIONS IN THE VELO-CARDIO-FACIAL SYNDROME

1.2.1. Clinical manifestations

The clinical spectrum associated with 22q11 micro-deletion is broad (8,37-43). Studies reporting large numbers of VCFS patients (Table 2) show that most patients have one or more major manifestation associated with the disorder, including a high incidence of cleft palate, velopharyngeal inadequacy or hearing loss. The incidence figures in the literature most likely overestimate the true incidence. In many centers, only those patients who present with the typical manifestations of the syndrome (e.g. major congenital malformations such as cleft palate or conotruncal heart defect) or with clinically significant anomalies (e.g. severe velopharyngeal insufficiency) will be diagnosed.
Moreover, patients with VCFS will be referred to the ENT clinic mainly when velopharyngeal insufficiency, a delay in speech and language development or hearing loss are present. This certainly introduces an ascertainment bias in studies reported from ENT departments. Therefore, incidence figures should be considered with caution.

ENT-manifestations including velopharyngeal inadequacy, feeding difficulties, speech and language delay or hearing loss are among the most frequent features of VCFS.
Velopharyngeal inadequacy may occur for a variety of reasons. In case of structural abnormalities of the palate, the term *velopharyngeal insufficiency (VPI)* is more appropriate. A cleft of the second palate is seen in 8 % to 85 % of VCFS patients (8,37,38,40,41). An open cleft is easily recognised whereas a submucous cleft can be only diagnosed after careful examination (40,44). The term *velopharyngeal incompetency* is the result of an underlying neurological disorder. In case of functional velopharyngeal inadequacy, the term *velopharyngeal dysfunction* is more appropriate. Poor mobility of the soft palate can result in the patients' inability to close the velopharyngeal aperture.
The velopharyngeal inadequacy and the general hypotonia seen in VCFS lead to an increased frequency of ***feeding problems*** in the first months of life, mainly as a result of frequent nasal regurgitation and a poor sucking reflex. Nipple compression (= positive pressure) and suction (= negative pressure) allow the infant to obtain nourishment by breast or bottle. In VCFS children these two components of sucking may not be present (45). In most neonates, these feeding problems settle after a few weeks. In VCFS children in whom safe oral feeding can not be established, alternative feeding such as tube feeding is mandatory.
In older children, the velopharyngeal inadequacy can result in ***hypernasality and nasal escape*** creating a poor speech intelligibility.

Table 2
VCFS features with their incidence in VCFS patients as reported in the literature

Feature	Thomas J.A. (review-1997) (38) (%)	Ryan A.K. (558 patients-1997) (37) (%)
Oto-rhino-laryngological		
cleft	85-98	9
VPI	?	32
hearing loss	75 (conductive)	33
Cardiovascular	80-85	75
Central nervous		
learning disabilities	100	18
mental retardation	40-50	
behavioral problems	10-20	9 (3-18 years) 18 (>18 years)
hypotonia	70-80	
renal		36
parathyroid		
hypocalcemia	10-20	60
immunological		
absent thymus	10	
skeletal		
scoliosis	15	3
growth		
growth retardation	35-40	83 (<P50) 36 (<P3)
microcephaly	40	

The receptive-expressive ***speech and language development*** is frequently delayed in VCFS (46). This can be part of a more general abnormal developmental progress or can be related to the behavioral and learning problems (47). Younger children with VCFS demonstrate greater speech impairment than older children with VCFS. Further studies are required to describe the course of speech and language impairments and to explore the relationship to learning disabilities (46, 48).

The ***hearing loss*** is usually of the conductive type as a result of chronic otitis media with effusion. The reported incidence of middle ear disease varies among different authors, probably as a result of an ascertainment bias. Shprintzen et al. reported an incidence of 77 % (43), Digilio et al. demonstrated an incidence of 45% (49) while Finkelstein et al. mentioned that only 22 % of his patients had middle ear problems (40). A minority of the patients with VCFS has a sensorineural hearing loss (43, 49). Audiological evaluation is recommended in patients with del22q11 in order to reduce the risk of speech deficit (49). However, specific and systematic knowledge regarding the ear disease in this syndrome is still scarce.

Besides these common manifestation in VCFS, rare anomalies such as ***laryngeal and glottic*** malformations have also been reported. Fokstuen et al. observed three patients with type III laryngeal atresia (glottic web) and 22q11.2 microdeletion (50). Stoler et al. report on two children with laryngeal webs and 22q11 deletions (51). The presence of familial laryngeal web in association with deletion 22q11.2 is for the first time mentioned in 1998 (52). Recently, McDonald-McGinn described the presence of a laryngeal web in one parent with a 22q11 deletion, identified following the diagnosis in a relative (53).

1.2.2. Diagnostic ENT procedures

The ***velopharyngeal function*** can be evaluated by the classic combination of indirect and direct techniques. These investigations, commonly used in every case of velopharyngeal dysfunction, are not specific for VCFS. When evaluating the velopharyngeal function, the patient has to repeat standard words and sentences, so cooperation of the patient is essential. Because of mental retardation and behavioral problems, known to be present in almost all VCFS children, these diagnostic procedures are often difficult to perform under the age of 5 years.

The *indirect techniques* attempt to describe quantitatively and qualitatively the perceptual sequellae of velopharyngeal inadequacy such as hypernasal resonance, nasal escape and compensatory speech related behavior (54, 55, 56). This evaluation can be performed from age three and must be done by experienced speech and language pathologists. Results are often difficult to interpret and difficult to compare because most methods rely on subjective measurements (57). To objectify and quantify the nasal escape, nasal airflow meters (nasal anemometers) have been introduced. These devices are expensive, need a large technical equipment and give no information on the quality of speech (58).

Direct assessment of the velopharyngeal function is viewing of the velopharyngeal isthmus and pharynx by combining nasopharyngoscopy and multiview videofluoroscopy (54-57,59-62).

Nasopharyngoscopy provides predominantly good qualitative information when assessing velopharyngeal function. Information on the size, shape and location of the velopharyngeal opening is obtained while the patient is repeating key phrases to stimulate velopharyngeal closure (54-56,61,63). It should be mentioned that nasopharyngoscopy underestimates the lateral pharyngeal wall movements (61, 62). Nowadays the flexible endoscope is likely to be of more interest than the rigid endoscope, particularly in young children, although the image resolution of the flexible scope is inferior (61, 62). Nasopharyngoscopy performed without sedation is difficult and almost impossible in children under age four.

The radiological image provides predominantly quantitative information when assessing velopharyngeal function synchronous with patients' speech (54-56,61,64). The videofluoroscopic session should include at least two radiographic views to obtain a three dimensional assessment. The lateral view provides useful information on velar displacement, on posterior pharyngeal wall movements and on tongue movements. A basal view can assess the relative movements of the palate, lateral and posterior pharyngeal wall. This basal view gives more reliable information on the degree of velopharyngeal inadequacy compared with the lateral view. Movements of the lateral pharyngeal wall during phonation are visualized on a frontal view. Because cooperation is needed, this radiological examination is best performed after the age of four to obtain useful and reliable information.

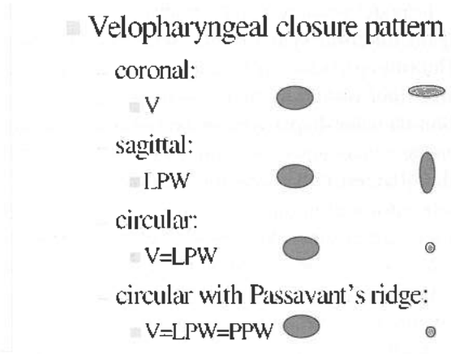
Golding-Kushner et al. (60) attempt to develop a protocol for standardizing the reporting of nasopharyngoscopy and multi-view videofluoroscopy, in order to provide an objective basis for diagnosis and treatment. This standardization is based on a ratio rather than absolute measurement (64, 60).

Nasopharyngoscopy in combination with multi-view videofluoroscopy identifies the type of velopharyngeal closure pattern based on variable contributions from the velum, lateral pharyngeal wall and posterior pharyngeal wall (57,59,65,66) (Fig 3). In the coronal pattern the velum is the most active component with relatively no or little lateral or posterior pharyngeal wall movements. This coronal pattern occurs in just over half of the patients, regardless

whether they have insufficiency or not (66). The sagittal valving pattern is the result of predominantly lateral pharyngeal movements with little contribution of the velum and no movements of the posterior wall. When equal contribution to closure occurs from the velum and the lateral pharyngeal wall, a circular pattern will be found. In the circular pattern with Passavant's ridge there is an additional movement of the posterior pharyngeal wall resulting in an sphincteric closure. Accurate assessment of these valving patterns in velopharyngeal inadequacy is essential prior to treatment.

The ***hearing loss*** can be evaluated by the different audiometric tests depending on the age of the child. In very young children, the hearing is tested in free field condition and by Oto-Acoustic-Emission (OAE). If hearing loss is suspected and otoscopy is normal, further assessment of hearing ability is performed by Auditory Brainstem Response (ABR). In older children, the hearing is assessed using classical headphones in a nois-isolated room.

Figure 3
The different valving patterns (Croft et al. 1981) (59)



V = velum - LPW = lateral pharyngeal wall - PPW = posterior pharyngeal wall

1.2.3. Treatment of ENT manifestations

The *objective* of treatment for ***velopharyngeal insufficiency*** is the elimination of nasal escape and hypernasality (67). There exists no one single therapy. The treatment is identical to that of any patient with velopharyngeal insufficiency. However, the mental retardation, the behavior problems and the

muscular weakness in VCFS patients may negatively influence the outcome. The *feeding problems* in the neonatal period usually settle after a few weeks. In VCFS children in whom safe oral feeding can not be established, alternative feeding such as tube feeding is mandatory (68).
In patients with mild hypernasality and mild articulatory problems, *speech therapy* is started as soon as possible. The therapeutic sessions in the very young children must rely on sound stimulation, on systematic articulation therapy for developping correct sound production and improvement of the velar function by using nasal versus oral air-stream exercises, and on palatal exercises like blowing if combined with sound production. This speech therapy will make the child more intelligible, enhancing the child's self-confidence and avoiding frustration. The speech therapist must be aware of the learning disabilities and concentration problems present in the majority of these VCFS children. Their cognitive ability tends to stay at a concrete level causing problems with abstract thinking and organization or planning (47,69). Their concentration problems and behavior problems will in some cases negatively influence the outcome of the speech therapy (47).
In VCFS patients not requiring a pharyngoplasty, an *adenoidectomy is an absolute contra-indication* because removing the adenoid will enlarge the velopharyngeal opening. This will result either in the sudden appearance of hypernasality in cases with no hypernasality before adenoidectomy, or in a more pronounced hypernasality in cases with already present hypernasality.
A *pharyngoplasty* is recommended in cases with moderate or severe velopharyngeal insufficiency where speech therapy did not result in obvious improvement of speech. This severe velopharyngeal insufficiency should be corrected as early as possible but may be delayed until after the cardiovascular surgery. Some centers prefer not to treat surgically before the age of 4 years because complications seem to occur less frequent after the age of four (70). Golding-Kushner stresses the importance of articulation therapy before pharyngeal flap surgery in order to correct compensatory speech disorders if present and to obtain correct articulatory placement and production (71).
Different surgical procedures are described depending on the diagnosed velopharyngeal closure pattern (67,70,72,73). Often a combination of surgical techniques is used to correct the velopharyngeal insufficiency. In patients with good velar elevation (coronal pattern), a sphincter pharyngoplasty is recommended (67,70,72-76). Lateral flaps are created and inserted transversally into the posterior pharyngeal wall so that during speech the velopharyngeal port can be closed. Where velar movement is poor and lateral pharyngeal wall movement is good (sagittal pattern), a superior or inferior based flap is appropriate (67, 73). This flap is elevated from the posterior pharyngeal wall and is inserted into the velum. During speech the lateral ports will be closed by mesial movements of the lateral pharyngeal walls (77). In cases where

velar and lateral pharyngeal wall movements are poor or absent, a palatal lengthening can be the first choice to obtain velopharyngeal closure (67, 73).
Pharyngeal flap surgery may produce immediate postoperative complications (16.4%) like hemorraghe, airway obstruction, wound dehiscence, fistula formation, pneumonia and cardiac arrest (67, 78). Late postoperative complications (12.3%), occurring more than three weeks after surgery, include hyponasality and snoring with obstructive apnoe's (67, 78). In some VCFS patients medial displacement or tortuosity of the internal carotid arteries is found which complicates pharyngeal flap surgery (79). Because there is not a strong correlation between the endoscopic observation of pulsations and the medial displacement of the internal carotids, some authors advocate to perform routinely magnetic resonance angiography (MRA) preoperatively (79,80).
Surgical treatment can not improve articulation and language as an immediate result. Postoperative intensive speech therapy remains necessary (67).

Specific and systematic knowledge regarding the treatment of ***ear*** pathology in VCFS is scarce. Treatment is similar to that of other conditions associated with hearing impairment. In childen with recurrent middle ear infections or with longstanding effusion otitis, the placement of ventilation tubes is indicated. If sensorineural hearing loss is present, the prescription of a hearing aid should be considered. As VCFS children are known to have delayed speech and language development and are at risk to present learning difficulties, a thorough audiological screening is strongly recommended so that appropriate treatment of the hearing loss can be started as soon as possible in order to reduce the risk of further speech deficit (46, 48).

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CHAPTER 2

AIMS AND METHODOLOGY OF THE STUDY

2.1. AIMS AND OUTLINE

After the introduction of a routine diagnostic test for the submicroscopic deletion in chromosome 22q11, a large number of VCFS patients were diagnosed. It soon became apparent that the ENT aspects of this disorder raised many questions regarding diagnosis, treatment and follow-up by the patients themselves, their parents and the physicians.
The overall aim of this study therefore is to gain better insight in the various ENT manifestations associated with the Velo-Cardio-Facial syndrome.

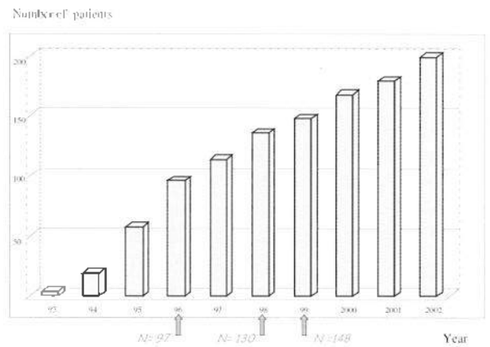
1. First, our aim is to increase awareness and knowledge of the VCFS, especially by the ENT specialists. This will lead to a more rapid recognition and diagnosis of children with this syndrome, which is essential for appropriate treatment and follow-up of the VCFS patient. To achieve this goal, we reviewed the entire group of patients diagnosed in our center, with regard to the different clinical manifestations and presenting symptoms. Moreover, such a comprehensive delineation of a study group is necessary for future studies.
2. Second, the aim is to create a better insight in the ENT problems associated with the VCFS. Therefore, we concentrated on the different ENT manifestations in patients with a proven deletion 22q11 (FISH). These studies included analysis of the velopharyngeal inadequacy, feeding difficulties, laryngeal manifestations and hearing loss.
3. Our final goal is to achieve a better diagnosis, treatment and follow-up of the different ENT manifestations associated with the VCFS, and thus try to formulate guidelines for the ENT specialists.

2.2. MATERIAL AND METHODS

At the Centre for Human Genetics in Leuven, there is a long standing tradition of multidisciplinary follow-up of patients with well-defined genetic syndromes. Since oto-rhino-laryngological manifestations are a major component of the Velo-Cardio-Facial syndrome, a multidisciplinary team for VCFS was formed in 1994, including an ENT-surgeon, a speech- and feeding therapist, an educational psychologist, a geneticist, a pediatric cardiologist and a psychiatrist.
All patients diagnosed with a del22q11 were seen by this multidisciplinary team and in many instances, a longitudinal follow-up was organized. Depending on the presence and severity of specific problems, this follow-up was personalized. Besides an up-to-date clinical care for these patients and their families, this follow-up project also provided a unique framework for clinical research on different aspects of this syndrome. The patients included in this

study were all recruited from this multidisciplinary research project for VCFS, and the characteristics of this study group will be described in chapter 3. In the literature, there are some patients with clinically diagnosed VCFS, but without del22q11. In our experience, these patients differ clinically from those with a del22q11 and, in our opinion, these individuals do not have the Velo-Cardio-Facial syndrome. Therefore, all patients included in this study have a proven deletion in chromosome 22q11, as demonstrated by means of Fluorescence In Situ Hybridisation (FISH - cfr introduction), using the probe DO832 (a gift from Prof. Dr. P. Scambler, ICH, London). This probe is within the critical deletion region for Velo-Cardio-Facial syndrome (Wadey).
Many patients with the Velo-Cardio-Facial syndrome present complex medical and developmental problems (Swillen). This is a major limiting factor in the systematic study of all aspects of this syndrome in all patients. Therefore, only those patients presenting clinically significant ENT manifestations could be evaluated and these results are included in this work.
A different number of patients are included in different stages of this study. This is a reflection of the increasing number of patients diagnosed with a deletion 22q11 over the six years of our study (Table1).

Table1
Cumulative number of diagnosed patients



Summary of the different number of patients throughout the study
→ 1996: 97 patients: 'Familial deletions of chromosome 22q11' (Chapter 3.2)hapter 3.2)
→ 1998: 130 patients: 'Presenting symptoms and clinical features' (Chapter 3.1)
→ 1998: 130 patients: 'Retrospective analysis of feeding and speech disorders' (Chapter 4.3)
→ 1999: 148 patients: 'The velopharyngeal and laryngeal manifestations' (Chapter 4.1)
→ 1999: 148 patients: 'Audiological en otoscopic results' (Chapter 4.5)

CHAPTER 3

THE VELO-CARDIO-FACIAL SYNDROME : DESCRIPTION OF THE LEUVEN STUDY GROUP

* Vantrappen G, Devriendt K, Swillen A, Rommel N, Vogels A, Eyskens B, Gewillig M, Feenstra L, Fryns JP. Presenting symptoms and clinical features in 130 patients with the velo-cardio-facial syndrome. The Leuven experience. Genet Counsel 1999;10: 3-9

* Swillen A, Devriendt K, Vantrappen G, Vogels A, Rommel N, Eyskens B, Gewillig M, Dumoulin M, Fryns JP. Familial deletions of chromosome 22q11: the Leuven experience. Am J Med Genet 1998;80:531-532

3.1. PRESENTING SYMPTOMS AND CLINICAL FEATURES IN 130 PATIENTS WITH THE VELO-CARDIO-FACIAL SYNDROME. THE LEUVEN EXPERIENCE

Vantrappen G, Devriendt K, Swillen A, Rommel N, Vogels A, Eyskens B, Gewillig M, Feenstra L, Fryns JP – Genet Counsel 1999;10:3-9

Summary

Between 1994 and 1998, we diagnosed in Leuven 130 patients with a 22q11 deletion. The deletion was familial in 14 out of 110 index patients (12%), which is significantly less compared to previous studies. In 10 patients, the deletion was maternal, in 4 patients paternal. A cardiac defect was the main presenting symptom in 49% of patients. The other patients were ascertained through developmental delay (16%), behavioral disturbances (7%), otorhinolaryngological manifestations (6%), psychiatric disorders (3%) and mental retardation (2%). In one patient hypocalcemia was the presenting feature, in another patient the severe immune deficiency lead to diagnosis.
Most patients presented a wide variety of the classical features of the Velo-Cardio-Facial syndrome. Velopharyngeal incompetence, learning difficulties or mostly mild mental retardation were almost always present, whereas clinical significant hypocalcemia or immune disturbances were rare. Previously un(der)recognised features include polyhydramnios, renal malformations and laryngotracheamalacia or laryngeal stenosis.

Introduction

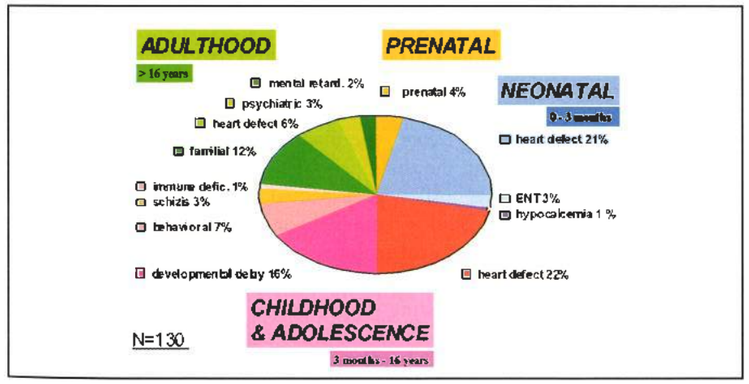
The recognition that the velo-cardio-facial syndrome (VCFS) and most cases with the DiGeorge syndrome (DGS) are caused by a microdeletion in chromosome 22q11 is one of the important discoveries in clinical dysmorphology in the last years. Previously, the clinical diagnosis of these syndromes could only be made with a reasonable degree of certainty in patients with a typical clinical presentation. However, with the advent of molecular cytogenetics, patients with mild features and atypical presentations can now be diagnosed. It is clear that the frequency of the syndrome is much higher than previously recognized and is now estimated at around 1/4000 live births (5). It became also clear that the DiGeorge syndrome and the Velo-Cardio-Facial syndrome are the variable expression of a single disorder.
As a consequence, the natural history and clinical spectrum of the DiGeorge syndrome and the Velo-Cardio-Facial syndrome, which were previously based on patients with the complete and therefore more severe manifestations, have also changed significantly. We here report the Leuven experience on the

clinical manifestations in a group of 130 consecutive patients with a deletion 22q11.

Study group

Patients were referred for various indications, including velopharyngeal incompetence or cleft palate, developmental delay, hypocalcemia, behavioral problems and mental retardation. No specific inclusion criteria were set. A second group of patients were identified through the paediatric cardiology unit, where all patients presenting with a conotruncal heart defect are systematically investigated for the presence of a deletion 22q11 (1).
In all patients, a high resolution G-banded karyotype was performed. Fluorescence in situ hybridization (FISH) using probe DO832 to detect a submicroscopic 22q11 deletion, was introduced in 1992 (16). All patients with a deletion 22q11 were examined clinically and both parents were tested for a deletion 22q11.
Since 1992, we have identified 130 individuals with a deletion 22q11. Of these, 18 had been diagnosed previously with the DiGeorge syndrome. Several other patients had been examined before, and tentative syndromic diagnoses included Mitochondrial Myopathy, Myotonic Dystrophy, Cohen syndrome, Kabuki syndrome, 3C syndrome and Stickler syndrome.
The age at diagnosis as well as the main presenting symptom varied widely (Fig 1). In a chronological order, the different presenting symptoms and most important clinical features at the different ages are discussed.

Fig. 1
The various presenting symptoms at the different ages in the Velo-Cardio-Facial syndrome



Results and discussion

Prenatal diagnosis

A prenatal diagnosis of a deletion 22q11 was made in 5 patients (Fig.1). In one foetus, the deletion was detected by amniocentesis performed because of the *familial* occurrence of the 22q11 deletion in the mother. The other patients presented anomalies initially detected by prenatal ultrasound. In two patients, a conotruncal *heart* defect was present. Until now, no systematic studies on the incidence of a deletion 22q11 in prenatally diagnosed cardiac defects are available. The two other patients were diagnosed because of the presence of an abnormal amount of amniotic fluid. *Oligohydramnios* i.e. a decreased amount of amniotic fluid, has been observed in one foetus presenting the Pottersequence (4). This foetus had bilateral non-functional kidneys i.e. unilateral renal agenesis with contralateral multicystic renal dysplasia, leading to absence of urine production and lack of amniotic fluid. This observation is not unexpected since urological malformations are seen in at least 10% of the VCFS patients (2).
In contrast, *polyhydramnios* was the presenting symptom in one patient. This foetus had also a conotruncal heart defect. Retrospectively, polyhydramnios was present in approximately 9% of all patients with a deletion 22q11, sometimes with onset in the beginning of the second trimester (6). The exact cause of the polyhydramnios is not known. However, one possible explanation is that the decreased swallowing contributes to this, since in many patients presenting with severe polyhydramnios, major feeding problems were observed in the first years of life. Therefore, testing for the presence of a deletion 22q11 could be considered in unexplained polyhydramnios, especially when other malformations associated with a deletion 22q11 are present.

Neonatal presentation

Nowadays, all patients with a 22q11 deletion and a *heart defect* should be diagnosed in the neonatal period. A congenital heart defect is present in approximately 85% of the VCFS patients (10,12). In the patients with a heart defect and born during the last 5 years, the diagnosis of a deletion 22q11 was made in the weeks following the diagnosis of the heart defect. In the vast majority of patients, this diagnosis was suspected on clinical grounds, since all patients had one or more additional clinical features of a deletion 22q11. In contrast, when no additional clinical features were present, a deletion 22q11 was never demonstrated. This is in agreement with other studies (11). In view of these results, it appears that testing for a deletion 22q11 in patients with a congenital heart defect can be restricted to those patients presenting additional features of the VCFS. However, this depends strongly on the experience

of the cardiologist with the clinical manifestations of 22q11deletion (10,12). In the neonatal period, the diagnosis of 22q11 deletion is usually also evident when other major VCFS malformations are present, such as hypoparathyroidism or cleft palate (Fig.1). *Hypoparathyroidism* is a frequent finding but in the majority of patients it was asymptomatic. In 3% of the neonates, the main presenting symptom was an *ENT problem*, including velopharyngeal incompetence, severe feeding problems and laryngotracheamalacia.
In contrast, the diagnosis can be delayed when only *atypical* or minor congenital malformations are present (Table I). One patient was first seen in the neonatal period with a large, unilateral multicystic kidney, which was surgically removed. During follow-up, a severe developmental delay was evident, but remained unexplained. CT-scan of the brain revealed a left cerebellar hemisphere hypoplasia (3). A deletion 22q11 in this boy was diagnosed at a later age when the VCFS was diagnosed in his sister. Also, *minor* signs can cause a delay in diagnosis. The velopharyngeal incompetence, present in almost all patients, leads to feeding problems. This is hardly ever recognized as a medical problem, especially when other features are absent. This is also true for failure to thrive, a typical feature for the Velo-Cardio-Facial syndrome, but aspecific. On the other hand, these minor signs may aid in the selection for testing for a deletion 22q11 in patients who have no or a major manifestation of a deletion 22q11.

Childhood

Between the age of 3 to 6 years, a second group of patients is diagnosed, namely those presenting with *developmental delay* (Fig.1). Development delay is one of the most common manifestations of a deletion 22q11 (9). Delayed gross motor development is frequently seen, but often attributed to the heart defect or frequent respiratory tract infections. Often, speech and language development is severely delayed (13) and almost all VCFS children need speech therapy. In addition, a number of children have *behavioral* disturbances (14). These problems of developmental delay and behavior do not always prompt a genetic evaluation. Since many of these children lack major congenital malformations, they probably are underdiagnosed, resulting in an overestimation of the incidence of major congenital malformations e.g. cardiac defects in larger series of patients with a deletion 22q11.
In one patient, the diagnosis of VCFS was made during childhood because of severe *immune deficiency*. Clinical evident immune deficiency with negative adverse reactions after a blood transfusion or routine childhood vaccination is very rare. Most children have clinical recurrent airway infections, however, without proven underlying disturbances in T-cell or B-cell immunity.

Table I
Atypical or minor congenital manifestations associated with the Velo-Cardio-Facial syndrome

Atypical malformations
- urological malformations
- anus: ectopy, imperforate anus
- club foot
- oesophageal atresia
- central nervous system malformations
- larynx: stenosis or web

Minor malformations
- feeding difficulties
- dysmorphic features
- failure to thrive
- hypotonia
- constipation

Adults

Adults presenting a deletion 22q11 can be attributed to 4 different categories (Fig 1.).
The largest group consist of adults who have a child with a deletion 22q11 and are found to be carrier of the deletion themselves. Of the 110 index patients diagnosed with a del22q11, a *familial* deletion was found in 14 (12%). The 14 families comprised a total of 34 persons with the deletion 22q11. Maternal inheritance was present in 10, paternal in 4 families. In two families, the index patient was a foetus. Swillen et al. (15) suggested that these parents have the mild manifestations of VCFS. This is true with regard to the major congenital malformations: none of the parents had the typical major malformations. However, all parents had the additional features including the ENT manifestations like feeding difficulties in infancy, recurrent otitis media and hypernasal speech. All parents had also learning difficulties and social functioning is poor without appropriate support. In none of these parents a genetic condition had been diagnosed previously or even suspected (15).
Mental retardation or psychiatric disturbances can also be a presenting symptom in adults. As in children, the *mental retardation* usually is mild to moderate (15). The most frequent observed *psychiatric* disorder is paranoid schizophrenia (8). The fourth group consists of adults that had a congenital *heart defect*. In these parents with 22q11 deletion, the risk for having a child with

the deletion is 50%. When no 22q11 deletion is found, the risk for a congenital heart defect in first degree relatives is much lower (3 %) (7).

Additional clinical features

Besides these more common presenting symptoms, additional clinical features associated with the VCFS may be recognized. In some patients *skeletal* malformations are seen including scoliosis (n=11), camptodactyly, syndactyly and clinodactyly (n=7). Another group of patients present with *gastrointestinal* problems like obstipation (n=11), ectopic anus (n=2) and achalasia of the oesophageal sfincter (n=1). *Hearing* problems are mostly related to dysfunction of the Eustachian tube resulting in otitis media with effusion. A smaller group has sensorineural hearing loss (n=4).

Prognosis

With regard to prognosis in this VCFS group, 8.5% died, mostly during the neonatal period. Seven patients died because of complex heart defects and one patient because of severe immune deficiency.
Prenatal death was noted in three patients.

Conclusion

It is clear that the clinical sprectrum of a deletion 22q11 is extremely wide. Besides the more common major malformations, many patients have only mild or atypical features. This stresses the importance of a multidisciplinary approach: patients with a deletion 22q11 deserve an individual approach by a multidisciplinary team experienced with the syndrome.

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3.2. FAMILIAL DELETIONS OF CHROMOSOME 22Q11. THE LEUVEN EXPERIENCE
LETTER TO THE EDITOR

Swillen A, Devriendt K, Vantrappen G, Vogels A, Rommel N, Eyskens B, Gewillig M, Dumoulin M, Fryns JP – Am J Med Genet 1998;80:531-532

To the Editor:

In this journal, Leana-Cox et al. (1) and Marino et al. (2) reported on familial deletions of chromosome 22q11. Both studies revealed a high percentage of familial 22q11 deletions, 25 and 21%, respectively, and a high percentage of maternal transmission. It should be noted that the frequency of familial cases attributed to the report by Leana-Cox et al. (25%) is a summary of five separate studies: the frequencies ranged from a low of 17% (3) to a high of 63% (1).

We would like to add our experience based on clinical and molecular evaluation of 97 families with a del22q11. All parents of the 97 index patients diagnosed with a del22q11 were examined for the presence of a del22q11, and a familial deletion was found in 12 (12.3%). The 12 families comprised a total of 32 persons with the del22q11 (Table I). Maternal inheritance was present in eight, paternal in four families. In two families the index patient was a fetus, presenting the Potter sequence (Family 10) (4), or stillbirth with Di George sequence present at autopsy (Family 3). In this Family 3, prenatal diagnosis in a subsequent pregnancy showed an affected fetus. Fetopathological examination showed absence of thymus and parathyoid glands. No heart defect was present.

This figure of 12.3% familial 22q11 deletions is significantly less than previously reported. One possible explanation could be that we have underdiagnosed familial cases. Patients with an inherited del22q11 differ from patients with a de novo del22q11 by a more pronounced developmental delay (5). However, in our series of 97 index patients a high proportion of patients (23%) was referred for evaluation of unexplained developmental delay. Alternatively, a preferential diagnosis of familial cases in the other studies could have occurred. This is supported by our experience: Amongst the first 25 index patients the deletion was familial in six of them (24%). Subsequently, the proportion of familial cases gradually decreased in time from 9/50 (18%), 10/75 (13.3%), reaching the current figure of 12/97 (12.3%).

We have also studied our data from a prospective study comprising all neonates with a conotruncal heart malformation referred to the pediatric cardiology

unit at the University Hospital Leuven. This is a referral center for Flanders, reducing possible biases regarding referral patterns of familial versus nonfamilial cases. All of these patients have been screened systematically for a del22q11 since 1994. So far, 19 patients were diagnosed with a del22q11, and only in one of them was the deletion found in one of the parents (5.2%). From the literature, there is no evidence for a correlation between the familial occurrence of del22q11 and the presence (or absence) of a heart defect. Also in our series, a congenital heart defect was present in 8/20 (40%) familial cases (excluding the parents), which does not differ from an estimated 50% incidence of heart defects in VCFS.

We therefore conclude that the familial occurrence of del22q11 may be less than reported so far, and the high proportion of familial cases reported could possibly be attributed to ascertainment bias.
A second point raised by Leana-Cox et al. (1) and Marino et al. (2) is that the parents ascertained through their children with a del22q11 represent the mild end of the clinical spectrum.
In our experience, this is true with regard to major medical manifestations of the deletion 22q11 as shown in table I. None of the parents had a congenital heart defect or other medical complication of the del22q11. Velo-pharyngeal insufficiency was the most constant medical finding in adults. On the other hand, psychosocial functioning was a major problem for the majority of parents. Most of them had learning difficulties in the past, and 6/12 adults (50%) were mildly to moderately mentally retarded. Poor social functioning and in some cases a psychiatric disorder was present. In this regard, adults did not differ from their children with del22q11.

TABLE I
Phenotypic and Developmental Findings in Familial Cases of del22q11

Family	Patient	Cardiac defect	Mental level (IQ)	Behavior/ Social functioning
1	Father	-	Borderline	depressive disorder
	Daughter(+)	TF+PA	NT	
	Son (+)	TF+PA	NT	
	Son	-	Mild MR	
2	Mother	-	Borderline	shy, timid
	Son	-	Mild MR (59)	shy, withdrawn
	Son	VSD	Moderate MR (<50)	ADHD
3	Mother	-	Moderate MR (50)	poor social functioning
	Daughter(+)	TF+PA		
4	Father	-	Mild MR	depressive disorder, anxious
	Son	TF	Moderate MR (55)	ADHD
	Daughter	-	Mild MR (60)	normal
5	Mother	-	Mild MR	poor social functioning
	Son(+)	TF		
	Daughter	-	Mild MR (59)	social problems, attention problems, aggressive behavior
	Son	-	Severe MR (24)	aggressive behavior
6	Mother	-	Mild MR	normal
	Daughter	ASD	Mild MR (68)	attention problems
7	Mother	-	Moderate MR	withdrawn, shy
	Daughter	-	Mild MR (61)	attention problems, withdrawn
8	Mother	-	Borderline	psychiatric illness
	Daughter	-	Borderline (85)	(schizophrenia)
	Daughter	TF	Borderline (77)	normal
				attention problems, withdrawn
9	Mother	-	Borderline	normal
	Daughter	-	Mild MR (62)	social problems
10	Father	-	Borderline	normal
	Fetus (+)			
11	Mother	-	Moderate MR (45)	poor social functioning
	Son	-	Mild MR (71)	pervasive developmental disorder
12	Father	-	Borderline	normal
	Son	-	Mild MR	social problems

MR: mental retardation: where indicated, the IQ-scores are given between (); when IQ-scores were not available, MR was based on the fact that the person followed special school for the mildly and moderately mentally retarded persons.
(+): died; -: anomaly absent; +: anomaly present; TF: tetralogy of Fallot; VSD: ventricular septum defect; ASD: atrial septum defect; PA: pulmonary valve atresia

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CHAPTER 4

VELOPHARYNGEAL - LARYNGEAL MANIFESTATIONS AND HEARING IN VELO-CARDIO-FACIAL SYNDROME

* Vantrappen G, Rommel N, Cremers CWRJ, Fryns JP, Devriendt K. Velopharyngeal and laryngeal manifestations in 47 patients with the Velo-Cardio-Facial Syndrome. Clin Otolaryngol, submitted

* Rommel N, Vantrappen G, Vander Poorten V, Hermans R, Fyns JP, Devriendt K. Methodology for pediatric videofluoroscopic assessment of the velopharyngeal function. Folia Phoniatr Logop, submitted

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4.1. THE VELOPHARYNGEAL AND LARYNGEAL MANIFESTATIONS IN 47 PATIENTS WITH THE VELO-CARDIO-FACIAL SYNDROME

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Abstract

The Velo-Cardio-Facial syndrome (VCFS) is a leading cause of velopharyngeal dysfunction and cleft palate. It is caused by a submicroscopic deletion in the long arm of chromosome 22 (band 22q11). During the last 6 years, 47 patients underwent an ENT-examination. We describe the different ENT manifestations in these 47 patients with VCFS and evaluate the need for surgical intervention. Most patients presented a wide variety of the classical features of the Velo-Cardio-Facial syndrome. Velopharyngeal dysfunction was almost always present whereas an isolated cleft lip/palate and laryngeal manifestations were observed in a minority of patients.

Introduction

The Velo-Cardio-Facial syndrome (VCFS) was delineated by Shprintzen in 1978 (1). Since then, the phenotypic spectrum has broadened to include velopharyngeal dysfunction with or without cleft palate, conotruncal heart malformations, characteristic facies, mental retardation, learning disabilities, cognitive and behavioral disorders, hearing loss, urogenital malformations, hypocalcaemia, immunological disorders and musculoskeletal abnormalities (2,3,4,5,6,7).
The Velo-Cardio-Facial syndrome (VCFS) is caused by a submicroscopic deletion in the long arm of chromosome 22 (band 22q11). Previously, the clinical diagnosis of this syndrome could only be made with a reasonable degree of certainty in patients with a typical clinical presentation. Nowadays, the diagnosis of this syndrome can be confirmed by a routine genetic test, detecting this submicroscopic deletion in chromosome 22q11, commonly based on fluorescent in situ hybridization (FISH) (8,9). This diagnostic procedure has greatly enlarged the clinical spectrum of the VCFS so that very mild cases with only a few clinical characteristics and cases with new features -such as malformations of the kidneys, cerebellum, limbs, or oesophagus- can be included. It is now evident that the incidence of VCFS is much higher than previously thought and is estimated at 1:4000 live births (10,11).
We here report our experience on the velopharyngeal and laryngeal manifestations in 47 patients with a proven deletion 22q11 (FISH).

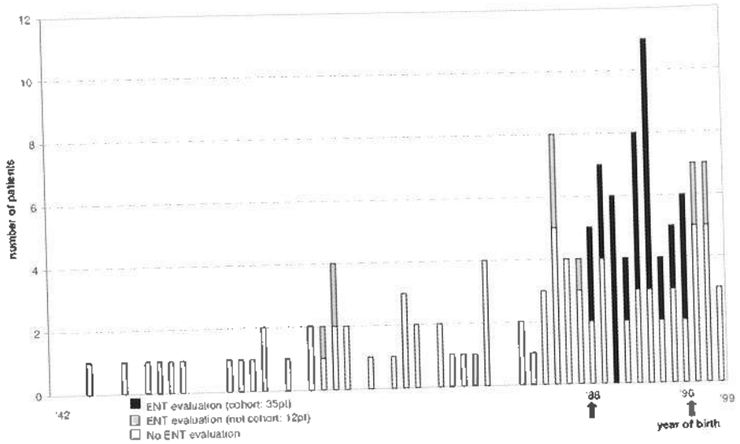
Study group and Methods

Patients
Between 1994 and 1999, a deletion 22q11 has been diagnosed in 148 patients referred for molecular diagnosis of the Velo-Cardio-Facial syndrome to the Center for Human Genetics. Most patients (56%) were referred because of the presence of a conotruncal heart defect. A smaller group of patients presented with features such as developmental delay, velopharyngeal dysfunction, behavioral problems, hypocalcemia, immune disturbances and laryngeotracheamalacia.
In all patients the submicroscopic 22q11 deletion was demonstrated by Fluorescence In Situ Hybridization (FISH) using probe DO832 (8). Because of the possible autosomal dominant inheritance, both parents were also tested for a deletion 22q11.

We have selected a cohort of 56 patients with age between 4 to 12 years (figure 1). This age group was chosen because in our experience, the ENT problems needing a more thorough work-up in children with VCFS, usually present after the age of four years. Moreover, at younger age, ENT examination is difficult, especially in children with VCFS who can be very anxious (12). Of this cohort-group, 35 patients could be clinically assessed. The other 21 VCFS patients could not be examined for various reasons: 9 patients were lost to follow-up; 5 patients were being followed in an institute or school for children with mental retardation; 7 patients presented no clinically significant ENT-problems and therefore, there was no opportunity for a more extensive work-up.
In addition, 12 VCFS-patients who did not belong to this cohort-group were examined at the ENT-department because of significant ENT manifestations. This group includes 4 patients younger than 4 years of age and 8 individuals older than 12 years (figure 1).

Methods
In each of these 47 patients, a thorough clinical ENT examination of the nose and throat was performed. An experienced speech-language therapist evaluated the velopharyngeal function by listening to spontaneous speech and by using standard speech samples (13). Due to the (albeit minor) radiation hasard, investigation of the velopharyngeal dysfunction by videofluoroscopic assessment of the velopharyngeal isthmus was only performed on indication. The main indication consisted of children with obvious clinical velopharyngeal dysfunction who did not respond to speech therapy over a period of at least 6 months. They were referred for further radiological examination to obtain objective quantitative information concerning the velopharyngeal dysfunc-

Fig 1
Study group of VCFS patients according to age



tion. To visualize the velopharyngeal isthmus, a small amount of radio-opaque contrast fluid (barium) is dripped into the nose. A frontal, lateral and base view is taken during phonation [p,m,s,a]. Because cooperation is needed and because children with VCFS are anxious (12), these children are well prepared by their own speech language pathologist during at least 3 weeks before this radiological investigation (14,15).

Results

From 1995 till 2000, we have identified 148 individuals with the Velo-Cardio-Facial syndrome having a deletion 22q11. Forty-seven patients underwent a detailed ENT examination. The age of these 47 patients varied from age 2 to age 35 (mean age: of 10 years). The largest group is situated between the age of 4 years and 12 years (= cohort-group: 35 patients). There was an equal distribution between males (n=23) and females (n=24).

Structural anomalies of the palate, pharynx and larynx were seen in 9 patients (Table 1): 5 children presented a cleft of the soft palate. Two of them had a submucous cleft while the other 3 patients presented an overt cleft palate. None of the other patients with a del22q11 in the total group of 148 patients had a cleft palate, and therefore, the incidence of cleft palate in our group is

5/148 or 2%. One patient had tracheamalacia that resolved spontaneously. Two children presented glottic stenosis. In one of them the stenosis was so severe that a tracheotomy had to be performed in the neonatal period because. After repeated laser surgery of this glottic stenosis without definitive success, a laryngofissure with placement of a temporary laryngeal stent was performed at the age of 7 years. A few years later, at the age of 11 years, the tracheotomy was closed. Laryngoscopy demonstrated a smaller anterior-posterior diameter but with good mobility of both arythenoids. Now, at the age of 17 years, his voice remains hoarse and weak but there are no problems with breathing. The other child with glottic stenosis presented in the neonatal period with high pitched voice and stridor evoked by excitation. Recently, at the age of 5 years, this glottic web was dissected and Mitomycine C was locally administered. Currently, 6 months postoperative, her voice and breathing are normal.
One child presented with persistent swallowing problems, recurrent lung infections during infancy, and massive nasal reflux of solid food. A videofluoroscopic investigation of the swallowing act revealed achalasia of the upper esophageal sphincter, which was surgically treated by myotomy of the upper esophageal sphincter.

Table 1
Structural anomalies in 47 patients with the VCFS

Clinical manifestation	number	
Cleft soft palate	5	(1)
Tracheamalacia	1	(1)
Glottic stenosis	2	(1)
Achalasia UES	1	(1)

UES = Upper Esophageal Sphincter
(.) indicates number of patients with this manifestation assessed outside the cohort (cohort n=35 and outside n=12)

The most common manifestation necessitating further ENT assessment was velopharyngeal dysfunction. The clinical presentation of velopharyngeal dysfunction varies with age, and common symptoms include feeding difficulties in the neonatal period, middle ear problems during childhood and hypernasal speech later in life (16,17). We examined speech problems i.e. hypernasal speech and articulatory disturbances related to velopharyngeal insufficiency. Most patients (88%) presented with velopharyngeal insufficiency but the severity varied widely. Compensatory articulation was present in 37%. All of them received speech therapy and were reassessed after 6 months. In those

patients where no progression could be detected by clinical speech-language evaluation, further videofluoroscopic assessment was performed as a means to objectively evaluate the velopharyngeal function. We established a standardized protocol for the assessment of velopharyngeal function using videofluoroscopy. Twenty-one patients underwent this radiographic investigation (Table 2). In 2 of them, there was no cooperation of the child so that further results could not be obtained. Because of clinically significant velopharyngeal dysfunction, a pharyngoplasty was performed in both of them. In another 2 children, a good functioning of the velopharyngeal istmus was seen and further speech therapy was recommended. In the remaining 17 patients velopharyngeal dysfunction was demonstrated by videofluoroscopy: in most of them (n=12), the velopharyngeal dysfunction was caused by an inappropriate elevation of the soft palate. In a minority (n=4) the videofluoroscopic assessment of the velopharyngeal isthmus demonstrated an insufficient elevation of the soft palate in combination with an insufficient approximation of the lateral pharyngeal walls. Only in one patient the velopharyngeal dysfunction was the result of insufficient approximation of the lateral pharyngeal walls while there was a good elevation of the soft palate. In all of these 17 patients, surgery was proposed, which was declined by the parents in 4 of them. So, thirteen children out of this group of 17 underwent a pharyngoplasty: 2 patients had a submucous cleft of the soft palate while the other 11 patients had no cleft. All patients needed speech therapy postoperatively.

Table 2
Videofluoroscopic assessment in 21 VCFS patients

VP function		Number	Therapy		
No cooperation	2	(0)	→ Pharyngoplasty	2	
Good VP function	2	(0)	→ Speech therapy		
VP dysfunction	17	(3)			
= SP	12	(1)	→ Pharyngoplasty	10	
			= no cleft	8	(1)
			= submucous cleft	2	
			→ Pharyngoplasty declined	2	
= SP& LPW	4	(2)	→ Pharyngoplasty	2	
			→ Pharyngoplasty declined	2	(2)
= LPW	1	(0)	→ Pharyngoplasty	1	

VP = velopharyngeal
SP = soft palate
LPW = lateral pharyngeal wall
(.) indicates number of patients with this manifestation assessed outside the cohort (cohort n=35 and outside cohort n=12)

Different types of surgery were performed in 22 patients for various indications (Table 3). These include the patient with achalasia of the upper esophageal sphincter, 2 patients with laryngeal stenosis and 5 patients with a cleft palate. A pharyngoplasty was performed in 14 patients without a cleft palate. Only in one patient, there was no radiographic assessment of the velopharyngeal dysfunction prior to surgery. All the other 13 patients underwent this videofluoroscopic investigation.

Table 3
Different types of surgery performed in 22 VCFS patients

Surgery	Number	
Cleft palate with lenghtening	5	(1)
Pharyngoplasty without cleft	14	(2)
Glottic stenosis	2	(1)
Achalasia UES : myotomy UES	1	(1)

(.) indicates number of patients with this manifestation assessed outside the cohort (cohort n=35 and outside cohort n=12)

Discussion

One of the classical features of the Velo-Cardio-Facial syndrome is cleft palate (1,17). However, in our series, only 5 patients had a cleft palate with two having a submucous cleft. In the total group of 148 patients no additional individuals had a cleft palate, resulting in an incidence of 2%. This is somewhat lower compared to other series, but this may be explained by a different ascertainement. For instance, the series of Shprintzen report an incidence of overt cleft palate of 100% (1,17), but there probably is an ascertainement biased towards patients with ENT problems. In the series of 558 patients presented by Ryan et al. (5), 9% of the patients had cleft palate, but there might be an overrepresentation of patients with the typical clinical spectrum which includes overt cleft palate. Alternatively, in our series, a relative large proportion of patients is referred for congenital heart disease resulting in a relative lower percentage of patients referred for ENT manifestations.

A more frequent manifestation is velopharyngeal insufficiency (VPI). In our series, velopharyngeal insufficiency was present in 88% but the severity varied widely. Compensatory articulation as a result of VPI could be found in 37% of the patients. Ryan et al (5) reported an incidence of velopharyngeal

insufficiency of 32%. Taken together, this suggests that VPI is a more frequent manifestation of VCFS than overt cleft palate, and deletion testing should, therefore, especially be considered in patients with velopharyngeal dysfunction. In concordance with this conclusion is the observation that a higher incidence of a del22q11 is found in persons with VPI than with in persons with cleft palate. Zori et al. (18) documented a high frequency of 22q11 deletions (FISH) in patients presenting with velopharyngeal insufficiency (VPI) of unknown cause (6/16 patients) while the frequency in patients with remaining VPI following primary cleft palate surgery was rather low (1/7 patients). Mingarelli et al. (19) demonstrated that among the 38 patients with isolated cleft (33 posterior cleft + 5 complete cleft) no single case of 22q11 deletion was found using FISH.
The clinical presentation of this velopharyngeal dysfunction can vary widely. At the age when the majority of our patients were investigated, hypernasality and articulation disturbances were the most common manifestations.
Twenty-one patients underwent a radiological investigation i.e. a videofluoroscopic session of the velopharyngeal isthmus to objectively evaluate the velopharyngeal function. This radiographic examination was only performed when indicated on clinical grounds. In most patients the velopharyngeal dysfunction was related to an inappropriate elevation of the soft palate. In a minority the videofluoroscopic assessment of the velopharyngeal isthmus demonstrated an insufficient elevation of the soft palate in combination with an insufficient approximation of the lateral pharyngeal walls. In one patient the velopharyngeal dysfunction was related to an insufficient approximation of the lateral pharyngeal walls with good elevation of the soft palate. When reviewing the literature, no recent data concerning the type of velopharyngeal closure pattern according to Croft (20) in VCFS could be found. The differences in results among studies are due to a number of different methodological variables and the absence of strict standardization of diagnostic procedures. However, a standardization for the reporting of velopharyngeal valve function using nasopharyngoscopy and multiview videofluoroscopy was published in 1990 in order to further develop a common methodology (21).

Since the discovery of a del22q11 as the cause of VCFS, an objective diagnosis of this syndrome has become possible. This resulted in a marked expansion of the clinical spectrum of this syndrome and allowed to include in this entity some rare ENT anomalies.
Laryngeal manifestations of the Velo-Cardio-Facial syndrome were present in 3 patients: two children presented with glottic stenosis and one child had laryngeotracheamalacia that resolved spontaneously. Laryngeal manifestations have been occasionally reported in VCFS. Fokstuen et al. observed three patients with type III laryngeal atresia (glottic web) and 22q11.2 microdeletion

(22). Stoler et al. reported on two children with laryngeal webs and 22q11 deletions. (23). The presence of familial laryngeal web in association with deletion 22q11.2 was for the first time mentioned in 1998 (24). Given the rarity of this type of laryngeal malformation, and its apparent association with the VCFS, it has been recommended to investigate for 22q11 deletion in patients presenting with laryngeal manifestations, especially in combination with congenital heart defects.

One child in our group of patients with VCFS presented with achalasia of the upper esophageal sphincter and underwent a mytomy of this sphincter. To the best of our knowledge, this has never been reported in VCFS to date.

Conclusion

This study reports on the ENT defects and disorders observed in 47 patients with VCFS and evaluates the need for surgical intervention. The present report further illustrates that VCFS must be suspected in each patient with velopharyngeal dysfunction, which is much more common than an overt cleft palate. In addition, rare anomalies such as tracheamalacia, glottic stenosis, or achalasia of the upper esophageal sphincter may occur as part of this syndrome.

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4.2. METHODOLOGY FOR PEDIATRIC VIDEOFLUOROSCOPIC ASSESSMENT OF THE VELOPHARYNGEAL FUNCTION

Rommel N, Vantrappen G, Vander Poorten V, Hermans R, Fryns JP, Devriendt K – Folia Phoniatr et Logop, submitted

Background

The velopharyngeal valve consists of two major components : the nasopharyngeal and the velar component. The nasopharyngeal component has the superior pharyngeal constrictor as anatomical substrate and is shaped as an incomplete muscular cylinder with an anterior opening where the velum is inserted. The velar component, also a muscular structure, is attached to the posterior side of the hard palate and interdigitates with the nasopharyngeal component. There is a direct correlation between the harmonic cooperation of these components, called "velopharyngeal valving", and articulation. Hence, multiview videofluoroscopy of this valve reveals clinically important information. The aim of pediatric videofluoroscopy is imaging the velopharyngeal valve in motion during speech.

Indications

The indication for radiological assessment of the velopharyngeal function is the patient with velopharyngeal dysfunction, when an initial course of speech therapy during 6 months has not resulted in further improvement of speech. This videofluoroscopic evaluation quantifies and reveals the mechanism of velopharyngeal failure and helps in clarifying whether further speech therapy or rather surgery is the most optimal subsequent treatment strategy.
One single patient should not have more than one fluoroscopic examination, unless absolutely critical to treatment planning [1]. Parameters to be considered in the decision whether or not to proceed to videofluoroscopy include age, mental status, consistency of velopharyngeal dysfunction, status of the articulation and treatment options.
A common disorder associated with velopharyngeal dysfunction is the Velo-Cardio-Facial syndrome (VCFS). This syndrome is caused by a deletion on the long arm of chromosome 22 (del22q11) [2,3]. Feeding difficulties and speech- and language problems, commonly described symptoms in these VCFS patients [4], can be related to velopharyngeal dysfunction.
The aim of the current paper is to describe an useful clinical protocol for videofluoroscopy designed for children with the Velo-Cardio-Facial syndrome.

Methodology

Child preparation
As children with VCFS are limited in coping with new situations [5], it is of major importance to prepare the child for this radiological examination. After a thorough clinical examination of the velopharyngeal function during speech, instructions are given to the parents or the speech therapist involved. All methodological steps are summarized on a protocol, written specifically for parents (suppl 1). An adequate amount of time is provided to go through the procedure with the often mentally restricted children, using drawings specifically designed for them (suppl 2).
The preparation of the child begins already four weeks before the videofluoroscopy. The first step is to instillate physiological solution in both nostrils using a syringe. The child is in supine position when 2-3 ml of solution is injected. This handling should be repeated by preference on a daily basis. This enables the child to handle the liquids without distress during the study.
Secondly, the parents or the speech-pathologist are requested to rehearse a speech sample. The following sound are studied : [a, m, p, s] and when possible diadochokinesis is assessed. The proposed speech sample is covering the most distinctive phonemic contexts in as few as possible sounds, as the attention span of this VCFS patient group is limited.
The parents repeatedly explain the course of the procedure to the child in order to familiarize the child with the course of the examination.

Radiological examination
The child is in supine position on the horizontal fluoroscopic table and, although videofluoroscopy requires only a low dose of radiation, proper shielding is applied [6]. As videofluoroscopy is established to assess the physiology of the soft tissues of the pharynx which are not clearly visible under radiographic assessment, it is necessary to coat the nasopharynx and oropharynx with barium, which is opaque to ionising radiation. Approximately 2 ml of barium is squirted into each nostril. The radiologist instillates barium in the nose, comparable to the saline injection training situation at home. After instillation, the fluoroscopic table is turned into a vertical position, the child is seated between the image intensifier and the fluoroscopic table. Depending on the child's motor skills, the child is placed in a MAMA® chair (&#61650), a specially designed chair considered to be the optimal seat for videofluoroscopic studies in infants and children. A lead ruler with known dimensions is placed laterally on the skin covering the mandibular body in a horizontal position, to enable later assessment of the magnification factor for the image. The studies are performed using continuous digital fluoroscopy pictures are obtained successively in lateral, frontal and base view, the latter being extremely

important. On the lateral view, the external acoustic meatus is bilaterally superimposed, and in this way rotation or tilting of the head is avoided. The head is in a neutral position, avoiding flexion or extension of the neck. The base view is obtained with the child in prone position and the neck in hyperextension; the X-ray tube is angled to obtain an as good as possible axial view of the velopharyngeal sphincter region.
All studied sounds, visually supported by symbols, are pronounced twice during fluoroscopy in each radiological view. When possible, the child is requested to swallow about 3 ml of barium to assess velopharyngeal function during swallowing. Deglutition of a liquid bolus enables visualisation of bolus propulsion by the anterior-posterior movement of the tongue and its influence on the velopharyngeal closure.

Clinical relevance

Understanding the anatomy and physiology of the velopharyngeal valve in a patient with velopharyngeal dysfunction, helps us to predict the possible outcome of further speech therapy on one hand, or to decide upon the need for and the possibility of success of surgical therapy. Therefore, the velopharyngeal closure type i.e., coronal–sagittal–circular–circular with Passavant's ridge [7], and the presence and location of a gap is of major importance in the decision making on the type of surgical intervention. In this respect, the major point of interest is the degree of lateral pharyngeal wall movement prior to surgery. This is because the success of the most frequently performed operation for restoration of velopharyngeal competence, the superiorly based pharyngeal flap procedure, depends on the degree of medial movement of the lateral pharyngeal walls against the edges of an adequately tailored flap [8].

Conclusion

Pediatric videofluoroscopy plays a major role in the identification of the degree and the mechanism of a velopharyngeal disorder and its effect on speech. Apart from the low dose of radiation and the limited discomfort of the instillation of barium in the nose, it is a non-invasive methodology applicable in young children. The obtained information elegantly complements clinical evaluation of nasality. When used in association with a thorough preparation of the child, this technique reveals clinically relevant and essential information for the treatment of the child with velopharyngeal dysfunction, especially in the subgroup of children with the Velo-Cardio-Facial syndrome (del22q11).

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Suppl 1: Course of the videofluoroscopic assessment of the velopharyngeal function

1. Radiological examination

The child with maximum two persons i.e., one parent and/or speech therapist, enters the radiological investigation room. The child is laying down on the table.

A small amount of white radio-opaque barium is with a syringe instilled into the nose. After this, the child may sit up. A small lead ruler is attached laterally to the skin of the cheek.

To obtain reliable information, the radiological images are taken successively in a lateral, frontal and basal view. All studied sounds, visually supported by symbols, are pronounced twice during fluoroscopy in each radiological view. Following sounds are tried to be pronounced:

* lateral view:	[m]	(also holding on the sound)
	[a]	(also holding on the sound)
	[p]	
	[s]	(also holding on the sound)
* frontal view:	[m]	(also holding on the sound)
	[a]	(also holding on the sound)
	[p]	
	[s]	(also holding on the sound)
*basal view:	[m]	(also holding on the sound)
	[a]	(also holding on the sound)
	[p]	
	[s]	(also holding on the sound)

Depending on the aim of the radiological investigation, the child is requested to swallow about 3ml of barium.

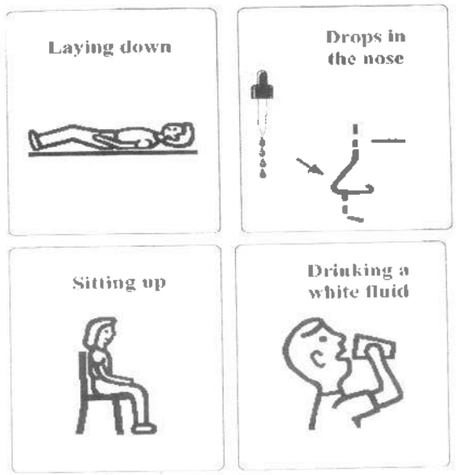
These studies of speech and swallowing are recorded on continuous digital videoscopy so that afterwards appropriate interpretation and analysis can be performed.

2. *Preparation of the VCFS child during the speech therapy four weeks before the radiological examination*

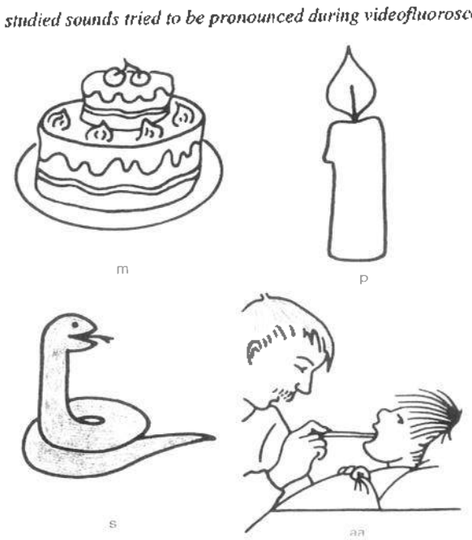
- Explain to the child that a little amount of white fluid will be squirted into each nostril. This can be trained daily by instilling physiological solution in the nose using a syringe.
- The following sounds are studied: [a,m,p,s] and whenever possible the sounds [a] and [s] should be holding on for some time.
- Explain the child that he/she will have to drink a small amount of white fluid.

Suppl 2: Drawings to support the child when pronouncing the studied sounds during videofluoroscopy

Preparation of the child during the speech therapy



The studied sounds tried to be pronounced during videofluoroscopy



Suppl 3: Speech sample (Dutch) covering the most distinctive phonemic contexts

Aap

Paard

Papa

Kat

Rood

Pot

Zwarte piet

Lang

4.3. RETROSPECTIVE ANALYSIS OF FEEDING AND SPEECH DISORDERS IN 50 PATIENTS WITH VELO-CARDIO-FACIAL SYNDROME

Rommel N, Vantrappen G, Swillen A, Devriendt K, Feenstra L, Fryns JP
Genet Counsel 1999;10:71-78

Summary

This paper summarizes and analyses our observations on feeding and speech disorders in 50 patients with the Velo-Cardio-Facial syndrome. In order to contribute to a better delineation of type and etiology of these feeding and speech problems, our clinical findings in these patients are compared with those reported in the literature.

Introduction

The chromosome 22q11deletion syndrome is associated with a wide variety of phenotypic abnormalities previously recognized as DiGeorge syndrome and Velo-Cardio-Facial syndrome (13, 21). Feeding, speech and language problems are commonly described symptoms in these patients. In the literature prolonged feedings and nasal regurgitation are reported as the most frequent feeding problems. Speech problems include hypernasality and compensatory speech patterns. Typically, children with VCFS also have a significant delay in onset of their language development. All these manifestations can be directly or indirectly related to velopharyngeal dysfunction. Until now only few quantitative data on feeding and speech in VCFS have been reported. The purpose of this study was to better specify feeding, swallowing, speech and language disorders in patients with a deletion 22q11.

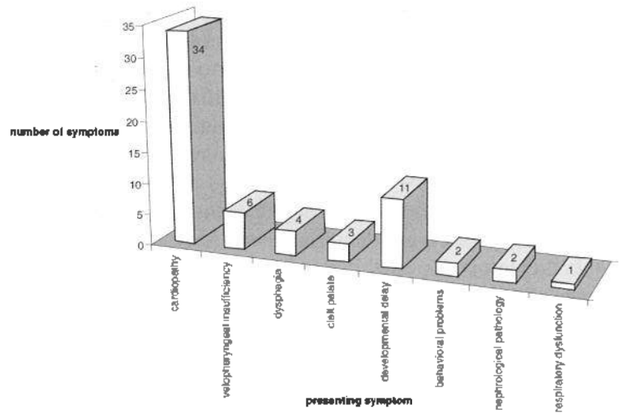
Materials and methods

Data were obtained retrospectively by reviewing hospital charts and parents questionnaires from 50 patients (24M, 26F) out of a total of 130 patients diagnosed with a deletion 22q11. In all patients a G-banding karyotype was performed on a peripheral blood lymphocyte culture and FISH analysis using probe Do832 confirmed the presence of a 22q11deletion. Their age ranged from 1 month to 29 years of age. All patients presenting feeding and speech disorders have been examined by a multidisciplinary team consisting of a clinical geneticist, a pediatric otolaryngologist, an educational therapist and a speech pathologist.

Results

Presenting symptoms
To assess whether the presenting symptoms of feeding, speech or language problems can lead to the diagnosis of VCFS, the referral pattern of these 50 children was analyzed. Since 13/50 patients presented multiple pathologies, relative frequencies are given. Results are shown in figure 1. The patient was referred for cardiopathy in more than half of the patients (34/63), velopharyngeal insufficiency in 6/63, developmental delay in 11/63, dysphagia in 4/63, cleft palate in 3/63, behavioral problems in 2/63, uronephrological pathology in 2/63 and respiratory dysfunction in 1/63.

Figure 1
Symptoms in this series of 50 patients



The medical history revealed palatal or pharyngeal flap surgery in 13/50 patients. Of these, 8 had a cleft palate. Detailed information on the pregnancy was available in 22 patients and polyhydramnios was noted in 12. Three of these patients needed palatal surgery.
Hospitalization was related to the primary medical pathology i.e. mostly because of the congenital heart defect, in 41 of the 50 patients. 47% of the children were hospitalized because of respiratory problems, 32% because of feeding problems such as insufficient intake and sucking problems.

Feeding & swallowing

Babies born with a cleft palate or velopharyngeal insufficiency present major feeding problems for normal feeding, especially nursing. This is explained by the fact that the oral cavity can not be separated from the nasal cavity and, as a result the baby is unable to suck (16).

Ninety-six percent of the patients with VCFS had feeding disorders starting from birth on. Nasal regurgitation due to velopharyngeal insufficiency occurred in 73%. Also suck-swallow-breath coordination was disorganized in 40% of the children with VCFS. This incoordination makes the baby at the risk for aspiration of food. Disorganized feeders have no abnormal oral motor patterns, but have a lack of rhythm and coordination during sucking (12). Fifty eight percent of this group of patients had a poor suck. For optimal therapeutic advice, one has to evaluate two components of sucking (20) i.e. *compression* (positive pressure) and *suction* (negative pressure) ; 25% of the VCFS patients in this series experienced difficulties to create intraoral positive pressure which means insufficient compression component of sucking when the baby is closing the lips and the mandible is moving upward 33% had a insufficient suction component of sucking, meaning that no adequate intraoral negative pressure can be created or maintained, either due to the veluminsufficiency or through inadequate downward movement of the mandible.

It is important for the infant to be able to maintain normal respiration during feeding. As already mentioned above, the respiratory problems seen in children with VCFS should not be underestimated. As the respiratory function is closely related to feeding and swallowing, it seems logical that poor respiration can result in decreased endurance and insufficient intake. In 31% of the patients, this problem manifested itself by habituation to the nipple and fatigue resulting in long feeding periods. Habituation has been defined (12) as the inability of the infant to continue sucking when the intraoral sensory cue of the nipple is no longer novel. Although the suck is initially intact and appears to be within normal limits, rapid deterioration occurs with subsequent discontinuation of the suck. If the nipple is wiggled or removed from the mouth and reinserted, the infant will begin to suck again.

Children with VCFS experience problems not only in the oral phase of swallowing, Also the pharyngeal phase of swallowing needs to be evaluated. One patient, a 10 month old boy with major nasal regurgitation on semisolid and mixed consistencies, but not on fluids, was found to have achalasia of the m. cricopharyngeus of the upper esophageal sphincter.

The third important phase of swallowing, is the esophageal phase. In 38% of the children, parents reported vomiting. No further esophageal specifications were found.

In those children in whom safe oral feeding cannot be established, alternative feeding needs to be started. In this group, 17% needed tubefeeding. However,

this population includes many older patients, dating from a time when specific feeding assessment and treatment were not yet generally known.

Only few data on constipation in VCFS are published (19). In the present population, 11% presented with severe constipation which needed specific medical treatment. In clinical practice, constipation often contributes to the feeding problems because of the gastrointestinal dysmotility.

Speech and resonance

All children born with cleft palate or veluminsufficiency are at risk for communication impairment. In general, children with a cleft lip and/or palate as part of a syndrome are at greater risk to develop complex communication impairment than those with cleft lip and/or palate only (22).

The general judgment of speech, i.e. how well a listener can understand speech, is called intelligibility (22). Intelligibility is influenced by many variables including articulation, resonance, nasal air emission, laryngeal phonation, rate and fluency of speech stress, accent and intonation. Intelligibility is decreased by both articulation and hypernasality. Of these two factors, articulation seems to have a more direct influence than hypernasality (9, 18, 22). In children with VCFS, intelligibility represents a significant problem. In the present study-group, only 34% of the patients could be well understood during early childhood by parents and environment.

ARTICULATION

Articulation errors can be classified as *phonetic* or *phonologic*.

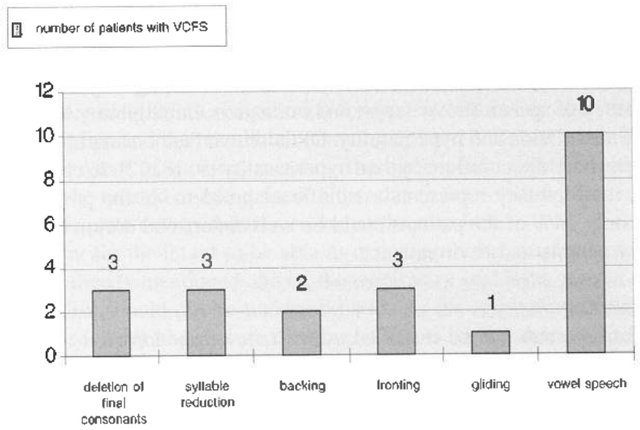
Phonetic errors are errors in the formation of the speech sounds and are related to abnormalities in anatomy, function and/or oral motor control. A distinctive category of errors of place of articulation is described as compensatory speech (22). This is a secondary disorder and may occur in patients who have inadequate closure of the velopharyngeal valve or a cleft or a fistula in the hard palate. (10, 20, 22). Compared with normal oral consonants, the sounds are then produced more posterior and inferior in the vocal tract, by posterior positioning of the tongue associated with true and false vocal fold adduction (glottal stop), or abnormal positioning of the arythenoid cartilage and epiglottis (laryngeal stop, fricative, or affricate)(6).

Typical primary phonetic disorders could not be recognized in the present VCFS patient population, whereas the use of compensatory speech patterns was seen in 13/50 patients. 7/13 patients used pharyngeal stop sounds, glottal stops were used in 5/13 patients and middorsum palatal fricatives in 1 patient.

Phonologic errors indicate a difficulty in the child's organization, learning and representing of the sound units and sound system of its language (22). A descriptive study of phonologic processes in preschool children with cleft palate, with or without cleft lip, indicated early delays in phonologic develop-

ment, particularly for the processes of deletion of final consonants, syllable reduction and backing (1). These delays were less apparent by the age of 4 to 5 years, when the phonologic skills of the children with cleft palate were similar to noncleft counterparts. The data of children with VCFS showed similar results : 22/50 patients had a phonological disorder. Figure 2 shows the different types of phonological disorders recognized and their occurrence.

Figure 2
Phonological disorders in 22/50 patients with VCFS



PHONATION

Patients with borderline velopharyngeal closure or cleft palate are thought to be at risk for hoarseness, secondary to hyperfunctional use of the vocal cords thereby resulting in vocal cord edema, nodules or other pathology (22). It is hypothesized that this occurs as the patient uses laryngeal hyperfunction to compensate for borderline valving (8). Abnormal pitch in patients with VCFS has already been documented by Shprintzen et al.(14). Also in this study population, phonation was found to be high pitched (6/14), hoarse (5/14) or was used at low intensity (4/14). The use of a soft voice can be related to the patients' inability to create sufficient oral pressure during speech, or may be an attempt to reduce the perception of hypernasality or nasal air emission (22).

RESONANCE

Persistent airway impairment can affect later speech quality in a variety of ways. Resonance disorders refer to hypernasality and other disturbances that occur supraglottally. Most commonly, hypertrophied adenoids and tonsils or nasal obstruction create hyponasal resonance or cause the child to become a habitual mouth breather (3).

In the present study, 43/50 patients had abnormal resonance. Of these 11 presented with hyponasal speech i.e. a reduction in normal nasal resonance. In only 2 of them, this resulted from partial blockage of the airway. 32/43 patients had hypernasal speech which is the perception of inordinate nasal resonance during the production of vowels. This results from inappropriate coupling of the oral and nasal cavities (3).

Habitual mouth breathing was described in 9/50 patients. As only 2/43 of the patients presented with partial blockage of the nasal airway which resulting in hyponasality, this cannot be the sole explanation for habitual mouth breathing in the child with VCFS. The general hypotonia seen in patients with VCFS may also contribute. Only 5 of the 50 patients presented oral motor hypotonicity.

Language

Delayed onset of language in children with cleft lip or palate has been reported in many studies over the past years. Although many of these studies have revealed a high incidence of language-related deficits in this population compared with normal developing peers (11, 17), some of these children developed communication and language skills at a rate comparable to their peers (4). Nevertheless, there exists a subgroup of children with cleft lip or palate presenting a risk of a transitory or permanent impairment in receptive and expressive language functioning (2, 4, 7). Ninety percent of the patients in this series presented with a delayed onset of language development. First words were developed at a mean age of 18 months and the age when the first two word sentences developed ranged from 13 months to 7 years of age. No data on standardized testing were available.

In patients with clefting or conditions associated with clefting, information on the features of language i.e. semantics, syntax, morphology and pragmatics, is almost nonexistent (22). In the area of syntax it has been reported that mean sentence length is shorter in those with clefts compared to noncleft peers (7). The present study also revealed a preferential use of short sentences, one or two word sentences, without the use of function words. Regarding morphology, most problems are reported in conjugations.

Children with gross articulation errors who rely on spoken language experience less problems with expressive language compared to children who rely on an alternative language system (15). In this population, 12/27 patients were

using signs, 11 of them were using non-universal signs. Parents were advised to combine the self-made signs with spoken language in order to stimulate the expressive language and reduce frustration. Universal sign-language was not recommended.

Conclusion

In conclusion, in the present group of 50 patients, feeding and swallowing disorders less commonly lead to the diagnosis of the velo-cardio-facial syndrome compared to other major presenting symptoms, although they are present in 90% of the children. We found that 47% of the patients were hospitalized for respiratory problem. Whether this is related to an undefined dysphagia remains to be demonstrated.
Furthermore, it can be concluded that the phonological disorders need more specification. A more detailed report of the phonological abilities may offer the clinician an additional framework for planning and conducting treatment of speech problems in VCFS children.
This study noted a high prevalence of compensatory speech.The finding of a low prevalence of oral hypotonia supports the rational of Golding-Kushner (5) that nonspeech and labial exercises or activities intended to increase the strength or range of motion, are not recommended for patients with compensatory speech. Compensatory speech is usually due to an error in learning rather than to muscle paralysis or weakness (5).
The results from this retrospective study will form the basis for a prospective study, which should allow us to better clarify the type and etiology of severe feeding and speech disorders in children with VCFS.

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4.4. POLYHYDRAMNIOS AS A PRENATAL SYMPTOM OF THE DI-GEORGE/VELO-CARDIO-FACIAL SYNDROME

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Summary

Prenatal diagnosis of the DiGeorge/Velo-Cardio-Facial syndrome has become possible since it was recognized that this syndrome is caused by a submicroscopic deletion in chromosome 22q11. In a sporadic patient presenting a conotruncal heart defect and polyhydramnios, the del22q11 was made prenatally by fluorescence *in situ* hybridization (FISH) after amniocentesis. Seven additional patients with a del22q11 were identified, who presented during pregnancy with polyhydramnios. In one of them, unilateral hydronephrosis was present. These findings further add to a growing list of clinical presentations of a del22q11 and suggest that in patients with polyhydramnios and a conotruncal heart defect or uropathy, fetal karyotyping should be complemented by FISH for a del22q11.

Introduction

The DiGeorge syndrome (DGS) is characterized by the association of a conotruncal heart defect, thymus hypoplasia, hypoparathyroidism and a specific facial dysmorphism (1). Many patients present a partial DGS, often with features overlapping with the Velo-Cardio-Facial or Shprintzen syndrome (VCFS). VCFS is characterized by a conotruncal heart defect, cleft palate, facial dysmorphism and learning difficulties (2). Recently, it was found that a submicroscopic deletion in chromosome 22q11 is present in the vast majority of patients with the DGS or VCFS (3,4). Accordingly, DGS and VCFS became regarded as a variable expression of the same genetic defect, and these conditions became collectively known as the DG/VCF syndrome (5). Fluoresence *in situ* hybridisation (FISH) for the detection of a del22q11 became available, identifying the region commonly deleted in chromosome 22q11 (6). The phenotypic spectrum of DG/VCFS and often mild symptoms and new clinical features became recognized (7, 8). Del22q11 is therefore much more frequent than initially realized, with an incidence of approximately 1 in 4000 to 1 in 5000 (9). We report here the prenatal diagnosis of a del22q11 in a patient presenting a heart defect and polyhydramnios, and report on seven additional patients with a del22q11 who retrospectively were found to present polyhydramnios.

Case report

Patient 1 is the first child of healthy, unrelated parents. The pregnancy was complicated by polyhydramnios, clinically detected at 30 weeks and by ultrasound at 33 weeks. At that time, a conotruncal heart defect was found, most likely tetralogy of Fallot (TOF), with 50 per cent overriding of the aorta and hypoplastic pulmonary arteries. There was a single umbilical artery. Karyotyping in cultured amniotic fluid cells established a normal female karyotype, 46,XX (T-banding). FISH using probe DO832 (6) showed a del22q11 in all metaphases, in two different flasks. Infectious serology (cytomegalovirus, toxoplasmosis and Parvo B19) in the mother remained negative. Karyotype and FISH for a del22q11 in the parents were normal.
Delivery was at term, with birth weight 2.8 kg (p3-25), length 51.5 cm (p75-97), and head circumference 34.6 cm (p25-50). In the neonatal period, there were respiratory and circulatory problems. Truncus arteriosus type I, with a right aortic arch was found by ultrasound and catheterization. No thymus could be visualized by ultrasound or on chest X-ray.
Clinically, dysmorphic features typical of DG/VCFS were present, with mildly dysplastic ears, a small mouth, retrognathia and slender fingers. In addition, an ectopic anus was present. Renal ultrasound was normal. No hypocalcaemia was recorded under continuous intravenous calcium supplementation. On day 7, acute heart failure with irreversible cardiocirculatory collapse occurred, probably related to an insufficiency of the truncal valve. Autopsy confirmed the congenital heart defect. Additional findings include an absence of the isthmus of the thyroid gland, severe hypoplasia of the thymus, bilobar right lung, and absent right umbilical artery. A karyotype on peripheral white blood cells showed a normal female karyotype, but no del22q11 could be detected in white blood cells by FISH, indicating mosaicism for a del22q11. No cells were left to check their identity through DNA analysis, and comparison with parental chromosome polymorphisms was not informative. A fibroblast culture failed.

These observations prompted a review of the available medical records of patients with a del22q11 identified at our centre. Records containing information with regard to pregnancy were available from 51 additional patients. The presence of polyhydramnios during pregnancy was recorded in seven additional patients. The clinical findings are summarized in table I.

Table I
Clinical features in eight DG/VCFS patients with polyhydramnios

ID	ONSET	DELIVERY (weeks of gestation)	BW (kg)	VELO-PHARYNGEAL	HEART
1	30	40	2.800	-	TA+PA
2	33	38	2.850	Tube f.(15)	TOF
3	28-32	38	2.370	cleft pal./FD	TOF, hemitruncus
4	20	38	2.850	severe FD	normal
5	n.rec	33	2.250	Tube f.	TA
6	<35	36	1.870	severe FD	small ASD/PS
7	<20	38	3.480	severe FD	TOF, PA , MAPCA's
8	n.rec	40	3.050	Tube f.	normal

n.rec = not recorded; tube f. = Nasogastric tube feeding (number of months); FD = feeding difficulties; TA = truncus arteriosus; PA = pulmonary atresia; ASD = atrial septal defect; PS = pulmonary stenosis; TOF = tetralogy of Fallot; MAPCA's = major aorto-pulmonary collateral arteries

The severity of the polyhydramnios ranged from mild and transient in patient 3 to severe in patients 2, 4 and 7. One patient (patient 2) was referred for expert ultrasound investigation, whereas routine ultrasound examination did not detect any associated anomalies in the others. Patient 2 is the second child of young, healthy parents. Massive polyhydramnios was detected at a gestational age of 33 weeks. Ultrasound showed the presence of unilateral hydronephrosis. A heart malformation was suspected, but could not be demonstrated with certainty. Amniocentesis showed a normal female karyotype. The polyhydramnios remained unexplained. The girl was born at a gestational age of 38 weeks, with birth weight 2.850 kg. A heart malformation, tetralogy of Fallot was diagnosed. Hydronephrosis, caused by a pelvi-ureteral junction obstruction, was present but regressed spontaneously. The child had severe feeding difficulties, with pronounced nasal reflux of milk and poor sucking. Nasogastric tube feeding was required until the age of 15 months. Now, at the age of 4 years, the diagnosis of DG/DG/VCFS has been made, based on the presence of the conotruncal heart defect, hypernasal speech and typical facial features. A *de novo* del22q11 was demonstrated.

Intrauterine growth retardation, defined as birth weight below the tenth centile for gestational age, was found in eight of the 51 patients (15.6 per cent). Five patients were born prematurely (gestational age below 37 weeks, range 29-36weeks), including two of the patients with polyhydramnios. A low birth weight, defined as birth weight below 2500 g, irrespective of gestational age, was found in 12 of the patients (per cent).

Discussion

The prenatal diagnosis of DG/VCFS has become possible since the recognition that most patients with this syndrome have a deletion in chromosome 22q11 (3,4). In pregnancies at high risk for a del22q11, i.e., when one of the parents carries the deletion, prenatal diagnosis has already been reported (4,10). However, early prenatal diagnosis of a del22q11 in sporadic cases is important, since it could improve management of the pregnancy, including counselling of the parents with regard to prognosis as well as avoiding other investigations. A second benefit lies in the possible prevention of severe complications that may occur during the neonatal period, such as hypocalcaemia or graft-versus host reactions (11). Neonates requiring intensive care or invasive diagnostic or therapeutic procedures are particularly at risk for those complications, and this applies to many patients with a del22q11. A high degree of suspicion of DG/VCFS is therefore mandatory in the neonatal period. However, many features of DG/VCFS are lacking in neonates and the facial dysmorphism can be minimal. Neonates with a conotruncal heart defect are therefore routinely screened for the presence of a del22q11 in our centre. A logical extension of this would therefore be to screen those patients presenting prenatally with features of DG/VCFS for the presence of a del22q11.

Heart and urological malformations and cleft palate are the major structural anomalies in DG/VCFS, with retrognathia and hypertelorism as the main dysmorphic features (2). In one of the patients presented here, the prenatal finding of a conotruncal heart defect led to the diagnosis a del22q11. In another patient, unilateral hydronephrosis was detected prenatally, at a time when FISH for del22q11 was not routinely available. Other malformations are rare, but many different structural abnormalities have been occasionally detected in patients, such as central nervous system anomalies, e.g., cerebellar hypoplasia and spina bifida (12,13); upper limb malformations (11,14); club feet (15); oesophageal atresia (16); and cleft lip (17).

A previously unreported symptom of DG/VCFS is polyhydramnios, as found in eight out of 52 patients (16 per cent) in the present study. The severity and time of onset of the polyhydramnios was variable, but in one patient it was

already present before 20 weeks. The most likely explanation for the polyhydramnios is a decreased swallowing of amniotic fluid. In DG/VCFS, feeding difficulties, with poor sucking, long-lasting feeds, and nasal reflux, are frequently observed during infancy and are related to the velopharyngeal insufficiency or cleft palate and hypotonia (2,17). All eight patients presenting with polyhydramnios had major feeding difficulties. The feeding problems were extreme in three of them, requiring gastric tube feeding during several months. Pronounced hypernasal speech was found in all six patients above the age of 3 years. Patient 1 never received oral feedings, and feeding behaviour could therefore not be evaluated.

Since polyhydramnios can be the presenting symptom of DG/VCFS, the question arises in which instances of polyhydramnios is prenatal diagnosis with FISH for a del22q11 indicated. Polyhydramnios with associated fetal malformations is considered an indication for fetal karyotyping, given the significant risk of a chromosomal anomaly (18,19). In the present series of eight patients with polyhydramnios and a del22q11, five had a significant structural anomaly. However, only two of the eight patients were referred for a level II ultrasound investigation, and in these two, associated malformations were detected prenatally (heart defect with single umbilical artery, and hydronephrosis with the suspicion of a heart defect). Three other patients had a conotruncal heart malformation missed on routine ultrasound investigation. This underscores the need for expert ultrasound examination in cases of unexplained polyhydramnios (20). We therefore propose that a standard chromosome analysis should be complemented by FISH for a del22q11 in otherwise unexplained polyhydramnios associated with malformations frequently found in DG/VCFS. In contrast to this, unexplained polyhydramnios in an echographically normal foetus is not an indication for fetal karyotyping (21,20), and probably also not for the detection of a del22q11. Even though the diagnosis of DG/VCFS in these fetuses could improve obstetrical and neonatal management, the condition is probably not sufficiently frequent to advocate FISH for a del22q11 as a routine investigation in all cases of unexplained polyhydramnios. Moreover, prenatal diagnosis of a del22q11 is less critical in patients without structural anomalies, who have a lower risk for neonatal complications. Additional studies are necessary to confirm our findings and evaluate the incidence of a del22q11 in polyhydramnios.

In one patient in this study, with typical features of DG/VCFS/DiGeorge sequence, a del22q11 was detected prenatally in amniocytes but not in white blood cells postnatally. This indicates somatic mosaicism, which has been reported before in DG/VCFS (22). Germline mosaicism, the presence of a mutation in a proportion of germ cells but not in other somatic tissues, has

been described for several genetic disorders and can explain the recurrence of a dominant disorder in siblings of unaffected parents without a detectable mutation. For del22q11, this has been reported in two instances, suggesting that even when the parents have no del22q11 there is a recurrence risk higher than the population risk (23,24).

In conclusion, the recent recognition that DG/VCFS is a frequent disorder with variable clinical expression and the fact that it can now be routinely diagnosed prenatally prompt an increased awareness of DG/VCFS. Further studies are needed to address the precise incidence of a del22q11 in polyhydramnios and in specific malformations detected prenatally. The available evidence suggests that prenatal diagnosis with FISH for a del22q11 is indicated in addition to routine karyotyping in a fetus with a conotruncal heart defect and in unexplained polyhydramnios associated with a urological malformation and/or other malformations frequently found in VCFS.

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4.5. AUDIOLOGICAL AND OTOSCOPIC RESULTS IN THE VELO-CARDIO-FACIAL SYNDROME

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Otol & Neurotol, submitted

Abstract

Objective: The Velo-Cardio-Facial syndrome (VCFS) is a leading cause of velopharyngeal dysfunction, often leading to otitis media and hearing loss. Hearing was evaluated in a cohort of 32 VCFS patients younger than 12 years. The results of otoscopy and tone-audiometry in these patients are presented in combination with other manifestations of the VCFS. ***Study Design:*** A retrospective analysis of the audiometric data and otoscopic findings in 32 patients. ***Setting:*** A multidisciplinary 22q11 deletion clinic at the University Hospitals Leuven. ***Patients:*** A cohort of 32 VCFS patients with age between 4 to 12 years was selected (Mean age 83 months, SD=26.31). The submicroscopic 22q11 deletion was demonstrated in all patients by FISH using probe DO832. ***Main outcome measure:*** Otoscopic and audiometric data were recorded and analyzed in combination with other manifestations of the VCFS including cleft palate, performed pharyngoplasty, congenital heart defect and intelligence profile. ***Results:*** Hearing impairments at young age of more than 25 dB are documented in one third of the tested ears and are mostly conductive. Pure sensorineural hearing impairments are rare. Cleft palate is associated with a higher prevalence of effusion otitis compared to the non-cleft VCFS patients of our study group. In the pharyngoplasty group, normal hearing was significantly more observed in comparison to children without palatal surgery. Two facts may account for this observation. First, all the children without palatal surgery and with effusion otitis had a serious congenital heart defect which may have contribute to a decision to postpone the placement of tympanic ventilation tubes. Secondly, tympanostomy tubes were routinely placed during velopharyngeal surgery. A hearing loss over 25 dB was more frequently observed in the group of VCFS children with a congenital heart defect compared to children without congenital heart defect. There was a significant difference in otoscopic findings between these two groups: effusion otitis and tympanic drains were more frequently noted in children with congenital heart defect, while in children without congenital heart defect a normal otoscopy was more often observed. This finding might be related to a less efficient ventilatory function of the Eustachian tube in patients with congenital heart defect. No differences were found between developmentally delayed and normal children. ***Conclusions:*** As most VCFS children have delayed speech and language development and are known to be at risk for learning difficulties, a

thorough audiological screening is recommended in these patients in order to reduce the risk of speech problems and to prevent worsening of the learning difficulties.

Introduction

The Velo-Cardio-Facial syndrome (VCFS) was delineated by Shprintzen in 1978 as a syndrome with cleft palate, conotruncal heart defects, characteristic facial features and learning difficulties (1). About 10 years ago, it was shown that this syndrome is caused by a submicroscopic deletion in the long arm of chromosome 22 (band 22q11). Using Fluorescence In Situ Hybridization (FISH), this submicroscopic deletion can now routinely be demonstrated so that even patients with mild and/or atypical presentations can be diagnosed. Since the introduction of this diagnostic test, the phenotypic spectrum of VCFS has broadened to include velopharyngeal dysfunction with or without cleft palate, cognitive and behavioral disorders, hearing loss, urogenital malformations, hypocalcaemia, immunological disorders, growth retardation, musculoskeletal abnormalities and various other malformations. (2-8).
ENT-manifestations including velopharyngeal dysfunction and speech- and language delay are the most constant features of VCFS (9-12). In the treatment and follow-up of these two manifestations, assessment of the hearing is of primordial importance. For this reason, we have evaluated hearing in a cohort of 32 patients with a del22q11.

Study group and Methods

In total, 148 patients have been diagnosed with a deletion 22q11 after referral to the Center for Human Genetics for molecular diagnosis of the Velo-Cardio-Facial syndrome. Most patients (56%) were referred because of the presence of a conotruncal heart defect. A smaller group of patients presented with features such as developmental delay, velopharyngeal dysfunction, behavioral problems, hypocalcaemia or immune disturbances and laryngotracheamalacia.
In all patients the submicroscopic 22q11 deletion was demonstrated by Fluorescence In Situ Hybridization (FISH) using probe DO832 (13). Because of the possible autosomal dominant inheritance, both parents were always tested for a deletion 22q11.

We have selected a cohort of 56 patients aged between 4 to 12 years. This age group was chosen because in our experience, the ENT problems needing a more thorough work-up in children with VCFS, usually present after the age of four years. Moreover at younger age, reliable ENT examination is often

difficult to obtain in children with VCFS who can be very anxious (14). In 32 patients (Mean age 83 months; SD = 26.31) of this cohort-group the hearing could be assessed. The other 24 VCFS patients could not be examined for various reasons: 8 patients were lost to follow-up; 5 patients were being followed in an institute or school for children with mental retardation; 11 patients presented no clinically significant otological problems and therefore, there was no opportunity for a more extensive work-up.

In each of these 32 VCFS patients, the hearing was assessed using the classic hearing tests. All hearing tests were performed with headphones in a noise-isolated room. To obtain reliable and comparable audiometric data, the mean air-conduction value for 0.5, 1.0, 2.0 kHz (= Fletcher-index) for both ears separately was determined. This resulted in 64 average hearing levels. Prior to this audiological investigation, both ears were inspected by microscope to evaluate the external meatus, the tympanic membrane and the aeration status of the middle ear. Children were classified into 5 categories according to the otoscopic result (normal otoscopy, Eustachian tube dysfunction, tympanic drain, otitis media with effusion, tympanic perforation). Hearing loss was classified in seven groups according to Forton (15)(ANSI 1969) (Table 1)

Table 1
the degree of hearing loss (ANSI 1969 – Forton G.)

Average AC HL (dB)	*Hearing loss*
-10 to 15	normal
16 to 25	discrete
26 to 40	mild
41 to 55	moderate
56 to 70	moderately serious
71 to 90	serious
≥91	profoundly deaf

We also evaluated the relationship between hearing loss and the presence of a cleft palate, soft palate surgery, congenital heart defect and intelligence profile .
Intelligence was evaluated using appropriate intelligence tests such as the WPPSI (Wechsler Primary Preschool Scale of Intelligence) and WISC-R (Wechsler Intelligence Scale for Children-Revised) according to the age of the individual (14). A Full Scale IQ (FSIQ) was calculated (M = 100; SD = 15) and mental retardation was defined as FSIQ < 71.

Data analysis

Statistical analysis was performed using the SAS system (Release, 6.12, the SAS Institute, Cary, NC, USA). For the comparison of hearing levels between right and left ear, we used non-parametric procedures (Wilcoxon Rank Sum Test) because of non normal sample distribution. In order to evaluate the relationship between the audiological and otoscopic findings, and presence of a cleft palate, soft palate surgery, congenital heart defect (CHD) or FISQ, we used Chi-square tests and Fisher's Exact tests. Statistical significance was defined as a p-value < 0.05.

Results

The audiological results of *both ears separately* are presented. In our group of 32 VCFS children, the difference in average hearing tresholds at low frequencies and the difference in Fletcher-index (0.5-1-2 kHz) was not significantly different between the left and right ear (Wilcoxon Rank Sum test; $p = 1.000$ resp $p = 0.925$).
Only in three patients the difference in average hearing loss between the left and the right ear exceeded 15 dB. In two of these children the more pronounced hearing loss in one ear was due to sensorineural hearing loss. In one patient the difference in average hearing threshold between left and right ear, with the worst ear presenting a conductive hearing loss, could not be explained. In all the other VCFS children (n= 29 patients) the difference in average hearing threshold between both ears was less than 15 dB.
Hearing was assessed in 32 VCFS patients resulting in 64 otoscopic and audiometric findings. The results of this hearing assessment in our *cohort* are presented in fig 1. In more than two thirds of the examined ears (45/64), hearing ability was better than 26 dB. In one third (19/64), a hearing loss over 25 dB was found mainly related to otitis media with effusion (12/19). A moderate sensorineural hearing loss was present in one ear of two different patients (2/19). Two ears with a tympanic drain and one ear with normal otoscopy presented a conductive hearing loss (3/19). Besides the recurrent middle ear infections in the past and the possible lack of attention during the hearing tests, no other plausible explanation could be found for this conductive hearing loss. In the remaining two ears (2/19), the tympanic membrane was perforated due to recurrent middle ear infections. None of the studied patients presented a hearing loss over 56 dB.

Because cleft palate and velopharyngeal dysfunction are common findings in VCFS, we evaluated the audiological results in VCFS patients with cleft palate, with pharyngoplasty and those without palatal surgery. These results are presented in fig2, fig3, fig4.

Fig1
Otoscopic and audiometric findings in VCFS cohort

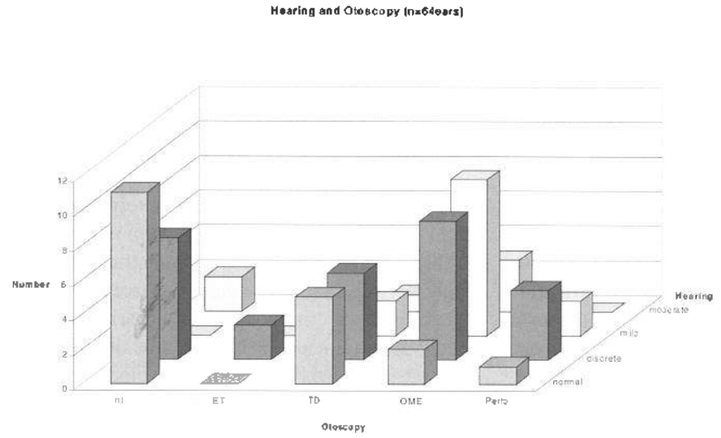
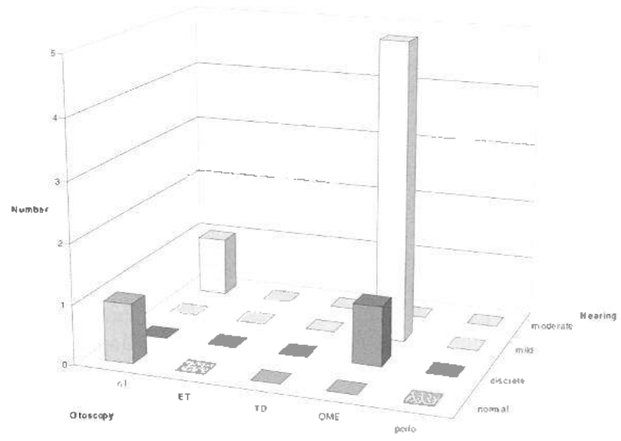


Fig.2
Otoscopic and audiometric findings in VCFS patients with cleft palate



nl = normal otoscopy *TD = tympanic drain* *Perfo = perforation of tympanic membrane*
ET = Eustachian tube dysfunction *OME = otitis media with effusion*

Clinical ENT examination revealed a *cleft palate* in four patients: two patients with an overt cleft and two with a submucous cleft. In most ears (5/8 ears) a mild conductive hearing loss was present as a result of otitis media with effusion. In one ear (1/8) with effusion otitis, the hearing was discretely decreased. A moderate unexplained conductive hearing impairment was present in one ear (1/8) with normal otoscopy. In one ear (1/8) hearing and otoscopy were normal (Fig2).

A *pharyngoplasty* for velopharyngeal dysfunction was performed in thirteen patients. In most ears (23/26) the hearing was normal or discretely diminished with a normal otoscopy in eight ears (8/23) and tympanic drain in seven ears (7/23). Otoscopy in the remaining eight ears (8/23) demonstrated effusion otitis in three ears and tympanic perforation in five ears. In three ears (3/26), the audiological assessment demonstrated a mild conductive hearing loss: two ears with otitis media with effusion and one ear with tympanic drain but without explanation for the associated conductive hearing loss (Fig3).

In sixteen VCFS children *without cleft palate and without pharyngoplasty*, nearly two thirds of the tested ears (20/32) had a hearing better than 26 dB. In one third (12/32) the hearing loss exceeded 25 dB and was in most ears (7/12) due to otitis media with effusion (Fig4).

Audiological and otoscopic findings of the group of VCFS patients with pharyngoplasty (n=26 ears) were *compared* to the group of VCFS patients without palatal surgery (n=32 ears). The pharyngoplasty was performed because of severe velopharyngeal insufficiency not responding to speech therapy.
A hearing loss over 25 dB was significantly less frequently observed in children with pharyngoplasty than children without palatal surgery ($\chi 2 = 5.043$, df = 1, p = 0.025). Otoscopy proved to be normal in nearly one third in both groups. On otoscopy, effusion otitis was found to be relatively more frequent in the patients without palatal surgery (13/32 or 41% versus 5/26 or 19%) while tympanostomy tubes for treating middle ear diseases were more frequently placed in the group of children with pharyngoplasty (8/26 or 31% versus 5/32 or 16%). A perforation of the tympanic membrane as a result of recurrent middle ear infections, was a more frequent finding in the group of pharyngoplasty (5/26 or 19% versus 2/32 or 6%). However, these differences in otoscopic findings are not statistically significant (Fisher's Exact Test, p = 0.129). There is a tendency towards more tympanic drains and perforations in the group of children with pharyngoplasty, explaining the less frequent effusion otitis and the better hearing levels in this group of children with pharyngoplasty.

Fig 3
Otoscopic and audiometric findings in VCFS patients with pharyngoplasty

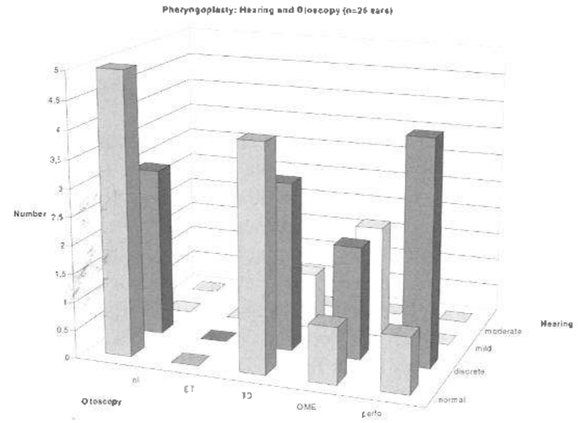
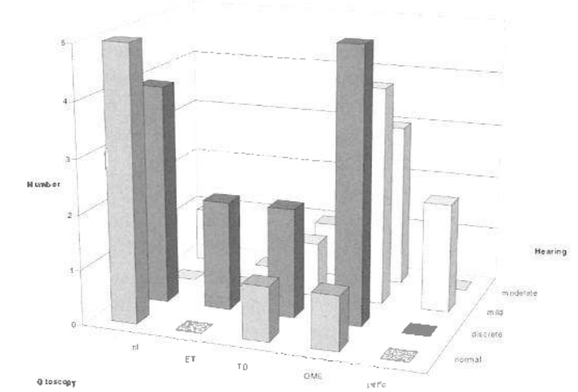


Fig4
Otoscopic and audiometric findings in VCFS patients without cleft palate and without pharyngoplasty



nl = normal otoscopy *TD = tympanic drain* *Perfo = perforation of tympanic membrane*
ET = Eustachian tube dysfunction *OME = otitis media with effusion*

We also compared children with a cleft palate to children without a cleft palate or pharyngoplasty. However, the sample size of the cleft palate group was very small (n = 8 ears), so conclusions should be interpreted with caution. Although there was a high incidence of hearing loss and effusion otitis in the cleft group, compared to the non-cleft group, we did not find any statistical differences in the presence of hearing loss (Fisher's Exact Test, p = 0.110) nor in otoscopy (Fisher's Exact Test, p = 0.416) between those two groups.

As a *conotruncal congenital heart defect* (CHD) is a common finding in VCFS, we compared the audiological and otoscopic results in VCFS patients without CHD (n=34 ears) to those with CHD (n= 30 ears). These results are presented in fig 5 and fig 6. Children with a CHD present more frequently with a hearing loss of more than 25 dB (12/30 ears) compared to children without a CHD (7/34 ears) although the difference does not reach statistical significance ($\chi 2$ = 2.877, df = 1, p = 0.090). With regard to the otoscopic findings, we found a statistically significant difference between children with a CHD compared to those without CHD (Fisher's Exact Test, p<0.001). We observed more tympanostomy drains (11/30 versus 2/34) and more effusion otitis (13/30 versus 9/34) in children with CHD, while perforations of the tympanic membrane (0/30 versus 7/34) and normal otoscopy (6/30 versus 14/34) were more present in children without CHD.

Mental retardation is a frequent finding in VCFS. Therefore, we assessed the intelligence profile in all VCFS children included in the cohort. More than 60% of the patients (n=20 patients) had a normal or borderline intelligence (FSIQ>70) while nearly 40% (n=12 patients) presented with mild mental retardation (FSIQ 55-70). Their hearing results are presented in fig 7 and fig 8.
In the group of children with normal or borderline IQ (n=40 ears), hearing was normal or discretely diminished in 29 of the 40 ears examined. The hearing loss was more pronounced in the remaining 11 ears (11/40) mainly as the result of otitis media with effusion (9/11) (Fig7).
In the group of children with mild mental retardation (n=24 ears), 16 ears (16/24) showed a normal or discretely diminished hearing loss. The hearing loss was mild in six of them (6/24) due to otitis media with effusion (3/6), a perforation of the tympanic membrane (2/6), and unclear underlying pathology (1/6). Two ears (2/24) presented moderate sensorineural hearing loss (Fig8).
The hearing results in the VCFS group of children with FSIQ>70 were comparable to those with FSIQ<71 ($\chi 2$ = 0.245, df = 1, p = 0.621). There were no differences in otoscopic findings between the FISQ<71 group and the FISQ>70 group (Fisher's Exact Test, p = 0.352).

Fig.5
Otoscopic and audiometric findings in VCFS patients without congenital heart defect

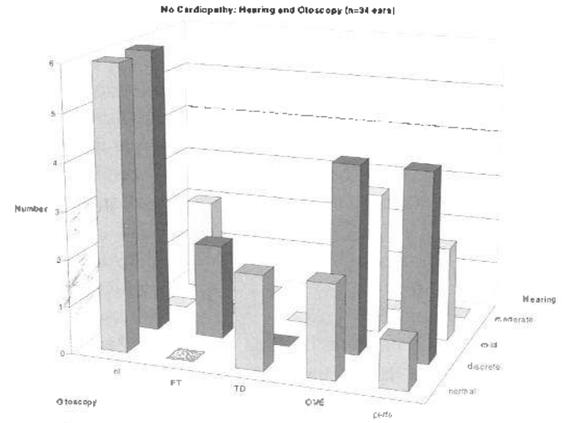
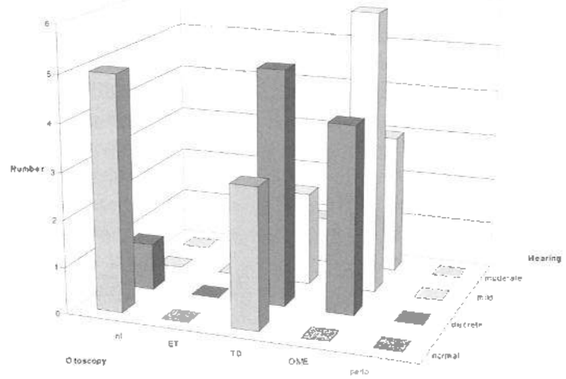


Fig 6
Otoscopic and audiometric findings in VCFS patients with congenital heart defect



nl = normal otoscopy *TD = tympanic drain* *Perfo = perforation of tympanic membrane*
ET = Eustachian tube dysfunction *OME = otitis media with effusion*

Fig. 7
Otoscopic and audiometric findings in VCFS patients with FISQ > 70

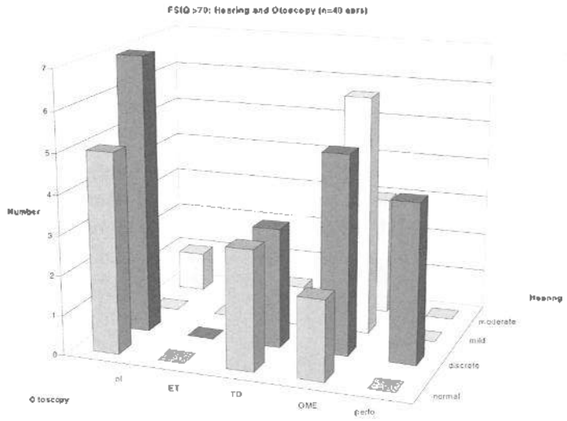
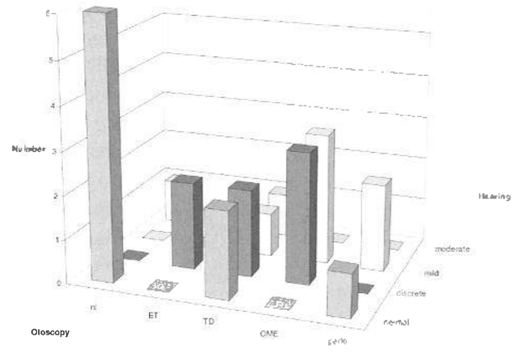


Fig. 8
Otoscopic and audiometric findings in VCFS patients with FISQ < 71



ni = normal otoscopy *TD = tympanic drain* *Perfo = perforation of tympanic membrane*
ET = Eustachian tube dysfunction *OME = otitis media with effusion*

Discussion

Hearing ability and otoscopy in a cohort of 32 VCFS children were assessed. We selected a cohort of patients aged between 4 to 12 years because in our experience, the ENT problems needing a more thorough work-up usually present in this age category. Only those patients of the VCFS cohort who were in follow-up at the Leuven Department and who were otological at risk could be examined. This creates a certain bias in the current research.
The results of both ears separately are presented resulting in 64 audiometric and otoscopic findings. Pirila et al. analyzed in 1992 the average asymmetry between the hearing thresholds levels in the left and right ears in a normal random population. They noted a slight statistically significant average superiority of the left ear at low frequencies in all age groups (16). Statistical analysis of the audiological data in our cohort could not demonstrate a significant difference in average hearing thresholds at low frequencies nor in Fletcher-index (0.5-1-2 kHz) between the left and right ear. Only in three patients the difference in average hearing loss between the left and the right ear exceeded 15 dB. In two of these children the more pronounced hearing loss in one ear was due to sensorineural hearing loss. In one patient the difference in average hearing threshold between left and right ear could not be explained. In all the other VCFS children (n= 29 patients) the difference in average hearing threshold between both ears was less than 15 dB.

This current study assessing hearing ability in VCFS children indicates that nearly one third of the patients (19/64 or 30%) present with hearing impairment of more than 25 dB, mainly (17/19) of a conductive nature and due to otitis media with effusion (12/17). A sensorineural hearing loss was found in a minority of the patients (2/64 or 3%). These findings differ compared to the ***VCFS literature.*** Shprintzen et al. (2,17) reported a 77% incidence of *conductive hearing loss* in their 39 patients with VCFS without further delineation of the degree of this conductive hearing impairment. Reyes et al. (18) documented conductive hearing impairment in 51% of the VCFS patients, the majority of which was situated between 20 an 40 dBHL. The lower prevalence of conductive hearing loss in our cohort might be explained by the lower presence of cleft palate in our study group. Shprintzen et al. (2) and Reyes et al. (18) reported a prevalence of cleft palate in respectively 100% and 82% of their VCFS patients. It is generally known that Eustachian tube function in cleft palate patients is poor, resulting in a higher incidence of middle ear diseases (19,20). Digilio et al. (21) documented conductive hearing impairment in 45% of their 27 VCFS patients of which two thirds was situated between 21 and 40 dBHL. Interestingly, a cleft palate was found occasionally in 15%, a finding similar to the prevalence of cleft palate in our cohort (12%). The lower preva-

lence of conductive hearing loss in our cohort might be explained by the presence of tympanostomy drains in more than 20%, which is an otoscopic finding not presented in the group of Digilio et al. (21).
Sensorineural hearing loss in VCFS was documented in 15% of the patients reported by Digilio et al.(21). They mentioned cerebral ischaemia and cerebral malformations in three patients with bilateral and serious (> 80 dBHL) sensorineural hearing impairment. Reyes et al. (18) documented sensorineural hearing loss in 4% of their patients with a del22q11. None of their patients underwent advanced radiographic imaging to determine possible inner ear or cerebral malformations. No brain malformations were documented in the two patients with unilateral moderate sensorineural hearing loss included in our cohort.

The prevalence of hearing loss (19/64 or 30%) and otitis media with effusion (22/64 or 34%) in VCFS children is higher when compared to the ***'normal' population.*** However, it is difficult to draw conclusions because relatively few epidemiologic studies of otitis media have been reported and because a lot of factors such as age, sex, socioeconomic status and season of the year are affecting the occurrence of otitis media.
An extensive study of 7.5-8-year-old Dutch children documented a 7% prevalence of unilateral otitis media with effusion and a 4% prevalence of conductive hearing loss of at least 15 dB in the better-hearing ear (22). The high frequency of *middle ear problems* in our cohort (34%) can be attributed to velopharyngeal insufficiency, which is almost always present to some degree in children with a del22q11. Middle ear disease i.e., recurrent otitis media and chronic otitis media with conductive hearing loss, frequently occurs with velopharyngeal dysfunction as a result of eustachian tube dysfunction (23).
The prevalence of unilateral *sensorineural hearing loss* of more than 26 dB in 'normal' children is reported in the literature to be 13 per 1000 (1.3%) (24), which is less compared to our study (3%). This means that, although the relatively low prevalence of sensorineural hearing impairment in our study compared to other VCFS studies, sensorineural hearing loss must be considered in the evaluation of children with a del22q11.

The high incidence of middle ear effusion i.e., six ears (6/8), in the four ***cleft palate*** patients is in accordance with the literature. Eustachian tube dysfunction resulting in chronic ear disease and conductive hearing loss, is now generally accepted as a virtually universal complication in infants with cleft palate (25-27). Also, Reyes et al. demonstrated that the prevalence of conductive hearing loss secondary to middle ear disease in VCFS is comparable to the prevalence found in isolated cases of cleft palate (18).

A ***pharyngoplasty*** for velopharyngeal insufficiency was performed in thirteen children. Although it is known that middle ear disease frequently occurs with velopharyngeal insufficiency as a result of Eustachian tube dysfunction (23), hearing ability was normal or discretely diminished in most ears (23/26). Therefore, we compared the otoscopic findings of the group of VCFS children with pharyngoplasty (n=26 ears) to the group of VCFS children ***without palatal surgery*** (n= 32 ears).
A *perforation* of the tympanic membrane was more frequently observed in the group of VCFS children with pharyngoplasty compared to those without: 19% (5/26) versus 6% (2/32). Tympanic perforations are mainly the result of recurrent middle ear infections. The higher prevalence of recurrent middle ear infections in the 'pharyngoplasty' group might be associated with the more pronounced velar dysfunction and thus less efficient ventilatory function of the Eustachian tube. *Effusion otitis* is surprisingly a more frequent otoscopic finding in our group of children without palatal surgery compared to the 'pharyngoplasty' group (13/32 or 41% versus 5/26 or 19%). This might be explained by two facts. On one hand, nearly all the children without palatal surgery and with effusion otitis had a serious congenital heart defect. In this particular patient group, placement of tympanic ventilation tubes requiring a general anesthesia, might have been postponed because of the underlying extensive risk which results in a higher prevalence of effusion otitis. On the other hand, tympanostomy tubes were routinely placed during velopharyngeal surgery resulting in a lower prevalence of effusion otitis in the 'pharyngoplasty' group.

Another common associated pathology in VCFS is a ***conotruncal congenital heart defect*** (CHD). We compared the audiological and otoscopic results of VCFS patients with a CHD (n=30 ears) to those without CHD (n= 34 ears).
A hearing loss over 25 dB was more frequently observed in the group of VCFS children with a CHD compared to children without a CHD. There was a significant difference in otoscopic findings between these two groups. In children with a CHD, effusion otitis and tympanic drains for the treatment of effusion otitis or recurrent middle ear infections, were more noted. Otitis media with effusion was mainly present in these children with a serious CHD without palatal surgery while tympanic drains were mainly present in children with a CHD who needed a pharyngoplasty. In children without a CHD, normal otoscopy was more observed. The higher prevalence of effusion otitis and tympanic drains in the group of children with CHD might be related to a less efficient ventilatory function of the Eustachian tube in these patients. This relationship between conotruncal heart anomalies and Eustachian tube anomalies is also mentioned in the literature. Todd JL et al. reported a twofold increased occurrence of otitis media proneness in children with isolated conotruncal cardiac anomalies, in contrast to children with nonconotruncal ano-

malies (28). The supports the concept that a neural crest determined branchial field defect influences the development of the cardiac outflow tract and the Eustachian tubes.

No differences in hearing levels nor in otoscopy were found between children with mental retardation and children with normal ***intelligence*** profile.

Conclusion

Hearing loss and middle ear problems in VCFS are frequent in VCFS and are related to velopharyngeal insufficiency. Hearing loss of at least 25 dB was found in nearly one third of the ears, the majority of which was conductive and due to otitis media with effusion. A sensorineural hearing loss was present in a small minority of the patients.
Cleft palate is associated with a higher prevalence of effusion otitis compared to the non-cleft patients. Children who needed a pharyngoplasty for velopharyngeal insufficiency presented significantly more with normal hearing compared to children without palatal surgery. This might be explained by two facts. First, nearly all the children without palatal surgery and with effusion otitis had a serious congenital heart defect which might have been postponed the placement of tympanic ventilation tubes. Secondly, tympanostomy tubes were routinely placed during velopharyngeal surgery.
Hearing loss over 25 dB was more frequently observed in the group of VCFS children with a congenital heart defect compared to children without congenital heart defect. There was a significant difference in otoscopy between these two groups: effusion otitis and tympanic drains were more frequently noted in children with congenital heart defect, while in children without congenital heart defect a normal otoscopy was more observed. This finding might be related to a less efficient ventilatory function of the Eusatchian tube in patients with congenital heart defect.
No differences were found between developmentally delayed and normal children.

As VCFS children are known to have delayed speech and language development and are known to be at risk for learning difficulties, a thorough audiological evaluation is recommended in order to reduce the risk of speech problems and to prevent worsening of the learning difficulties. Early and appropriate otologic management to prevent long-term sequelae is advised.

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CHAPTER 5

NEW GENETIC ASPECTS OF VELOPHARYNGEAL INSUFFICIENCY

* Vantrappen G, Rommel N, Cremers CWRJ, Fryns JP, Devriendt K. Mosaic trisomy 8 as cause of velopharyngeal insufficiency. Am J Med Genet 2002; 108:337-338

* Vantrappen G, Rommel N, Wellens W, Cremers CWRJ, Fryns JP, Devriendt K. Autosomal dominant isolated velopharyngeal insufficiency. Clin Genet 2002;61:74-76

5.1. MOSAIC TRISOMY 8 AS A CAUSE OF VELOPHARYNGEAL INSUFFICIENCY

Vantrappen G, Rommel N, Cremers CWRJ, Fryns JP, Devriendt K
Am J Med Genet 2002;108:337-338

Letter to the Editor:

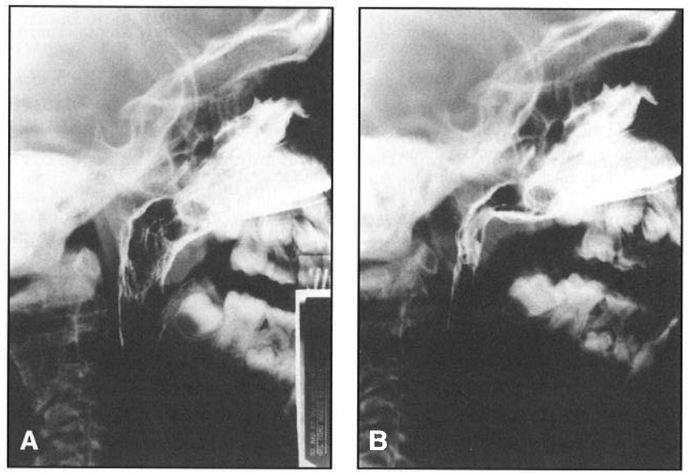
Congenital velopharyngeal insufficiency (VPI) is the result of a structural malformation of the nasopharyngeal structures. Common symptoms are feeding difficulties, nasal regurgitation of milk, recurrent middle ear infections and, at an older age, hypernasal speech (1,2). During the last years VPI has received much interest of clinical geneticists, since it is a major symptom of the Velo-Cardio-Facial syndrome (VCFS) (3). VPI resistant to speech therapy is an indication for a surgical correction i.e. a pharyngoplasty. During the last 10 years, 41 persons underwent this procedure at the Department Otorhinolaryngology - Head and Neck Surgery of the University Hospital, Leuven, Belgium. Of these, seven were diagnosed with a del22q11 (17 %). Interestingly, two patients were diagnosed with mosaic trisomy 8.
Patient 1 was referred for delayed speech and language development. Clinical examination demonstrated a hypernasal speech due to an anatomical disproportion of the nasopharyngeal structures, confirmed by pharyngography (Fig. 1). There was no overt or submucous cleft of the soft palate. She showed several additional physical anomalies, such as camptodactyly of several toes, deep plantar and palmar grooves, congenital dyslocation of the elbows, frontal bossing. Weight at the age of 6 years was 16.9kg (<3rd centile), length 112.7cm (3rd-25th centile) and head circumference 51.8cm (50-75th centile). Mental development was normal, and she was in a normal school setting. Karyotype analysis on white blood cells revealed mosaic trisomy 8, with 47,XX+8 in eight cells and normal 46,XX in three cells. Since speech therapy did not lead to a satisfactory improvement, a pharyngoplasty (i.e. pharyngeal flap surgery combined with pushback – incision according to Wardill) was done at age 8 years. This resulted in a marked reduction of hypernasal speech and thus better intelligibility.

Patient 2, now 6 years old, was seen at age 2 weeks for facial dysmorphism. He was born at 41 weeks of gestation, with weight 3.4kg, length 52cm, and head circumference 34cm. There was a facial dysmorphism, with ptosis of the left eye and low set ears, a short neck, camptodactyly of fingers and toes, prominent palmar grooves, and limited movements of the hips and knees. The trunk was long and narrow. Karyotype analysis showed mosaic trisomy 8,

with 47,XY+8 in 11 cells and 46,XY in 7 cells. Mild developmental delay was evident during follow-up, but motor and speech development was specifically delayed, with the first words at age 3 years. The speech was hypernasal and consisted mainly of vowels reducing the intelligibility. Clinical examination revealed an anatomical disproportion of the nasopharyngeal structures, with poor mobility of the soft palate and lateral pharyngeal walls. There was no submucous cleft of the soft palate. Videofluoroscopic examination of the nasopharyngeal area confirmed these anomalies. A pharyngoplasty was performed at age 5 years. Clinical evaluation after 12 months revealed a significant improvement in intelligibility with reduced hypernasality.

Thus far, VPI has not been reported in the mosaic trisomy 8 syndrome. However, the prevalence of cleft palate or high-arched palate in patients with trisomy 8 is reported in the literature to vary from 43% to 66% (4). It may be that VPI without structural defect and cleft palate represent the spectrum of the same malformative process. Similarly, in the VCFS, both overt or submucous cleft palate as well as VPI without anatomical defects can be observed (5).
The suspected duplication region of chromosome 8 responsible for the cleft palate has been located to 8q21 (6).

Fig 1
Pharyngography (lateral view) in patient 1



A: Velopharyngeal isthmus in rest position.
B: Velopharyngeal insufficiency when pronouncing the vowel 'ie'

The two children with mosaic trisomy 8 reported here have a nearly normal mental development, but presented with severe expressive language and speech delay. An early diagnosis of VPI is essential, since it may lead to a more rational treatment of the speech problems. Also, most children with VPI are prone to recurrent middle ear infections and common colds. Adenotomy is one of the most frequently performed interventions in children with recurrent upper airway infections. However, in children with VPI, an adenotomy will result in a more pronounced hypernasality and therefore in reduction of intelligibility (7).
Treatment of the VPI starts in all patients with speech therapy. In those patients with no or little improvement, surgical intervention is indicated, leading to significant improvement of the VPI symptoms in most cases, as was seen in our two patients.

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5.2. AUTOSOMAL DOMINANT ISOLATED VELOPHARYNGEAL INSUFFICIENCY

Vantrappen G, Rommel N, Wellens W, Cremers CWRJ, Fryns JP, Devriendt K Clin Genet 2002:61: 74-76

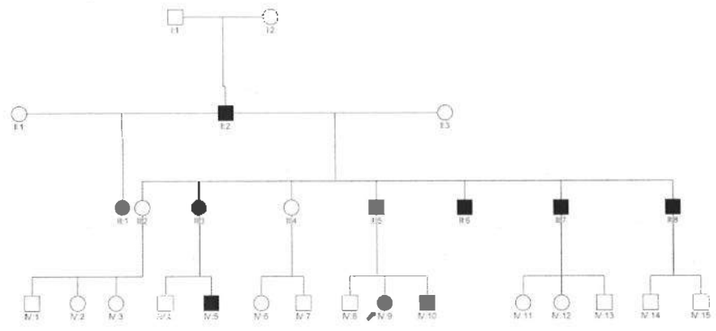
To the Editor:

In 1981, in this journal, Andres et al. (1) described a three generation family with autosomal dominant isolated velopharyngeal incompetence. This disorder was assigned an entry in Mendelian Inheritance in Men, MIM 167500. Velopharyngeal insufficiency is a major feature of the velo-cardio-facial syndrome (2), and this anomaly has therefore gained more interest in the clinical genetics specialty. It is surprising that despite this renewed interest, no additional families with autosomal dominant isolated velopharyngeal insufficiency have been reported since its original description. We here describe another family with this velopharyngeal disorder.
The index patient, (Fig.1: IV:9) was referred for severe velopharyngeal insufficiency without overt or submucous cleft of the soft palate. She presented delayed speech development, with hypernasal speech. She received speech therapy from the age of 3 years until 10 years, without clinical improvement. Clinical examination revealed a short and totally immobile soft palate with anatomical disproportion of the velopharyngeal structures. These findings were confirmed on a pharyngographic investigation (Fig.2). A pharyngoplasty (i.e. pharyngeal flap surgery combined with pushback – incision according to Wardill) was performed at the age of 10 years, without significant clinical improvement.
Her younger brother (Fig.1: IV:10) had the same anomaly. He also presented delayed speech development and hypernasal speech, due to the same radiologically confirmed short and immobile soft palate. Speech therapy between the ages of 5-8 years did not result in major improvement. Subsequently, at the age of 9 years, a pharyngoplasty was performed, with moderate improvement. Their father, a healthy individual of 50 years (Fig.1: III:5) has also suffered from marked hypernasal speech since childhood. Besides speech therapy, no other investigations or therapies were done. The father and his two affected children have had normal mental and physical development, and clinical examination did not reveal any additional anomalies. Cardiac ultrasound was normal in all three of them. Karyotype was normal, and a deletion in chromosome 22q11 was excluded.

Family history revealed that several other individuals had marked hypernasal speech (Fig.1). In some of them (III:7, III:8 and IV:5) this was precipitated by

adenotonsillectomy (Fig.1). Individual III-3 has a small ventrikal septal defect (VSD) and III:6 has an unexplained mild developmental delay. But otherwise, all these individuals are reported to be healthy. In individuals III:3 and IV:5, a deletion in chromosome 22q11 was also excluded.

Fig 1
Genealogy of the family



In this family velopharyngeal insufficiency is present, caused by an immobile, short soft palate. None of the individuals had manifestations of the velo-cardio-facial syndrome, and a deletion in chromosome 22q11 was excluded. The inheritance, with affected males and females in multiple generations, as well as male to male transmission is compatible with autosomal dominant inheritance. Velopharyngeal insufficiency was not associated with a submucous cleft palate, suggesting that this may represent a distinct condition, with a different pathogenesis compared to clefting. However, it is not certain whether this holds for all cases of velopharyngeal insufficiency, since in the Velo-cardio-Facial syndrome, individuals with a deletion in chromosome 22q11 may present an overt cleft of the soft palate or may present velopharyngeal insufficiency with submucous cleft of the soft palate, as well as velopharyngeal insufficiency without cleft (3).

In retrospect, it is not precluded that in the family reported by Andres et al. (1), affected individuals have the velo-cardio-facial syndrome since some persons in this family presented mental retardation. However, no individual of that family exhibited a congenital cardiopathy, a common clinical feature in the Velo-cardio-Facial syndrome (4). It could be interesting to check the affected family members for a deletion 22q11.

Fig. 2
Pharyngography (lateral view) in the index patient

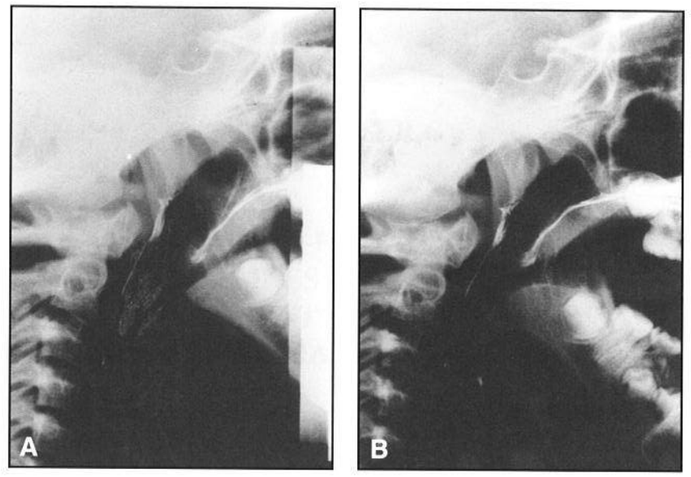


Fig.2.a: velopharyngeal structures in rest position
Fig.2.b: velopharyngeal insufficiency when pronouncing the vowel 'ie'

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CHAPTER 6

VELO-CARDIO-FACIAL SYNDROME: GUIDELINES FOR DIAGNOSIS, TREATMENT AND FOLLOW-UP OF ENT MANIFESTATIONS

* Vantrappen G, Rommel N, Swillen A, Cremers CWRJ, Fryns JP, Devriendt K. Velo -Cardio-Facial Syndrome: guidelines for diagnosis, treatment and follow-up of ENT-manifestations
Acta ORL Belgica, in press

6.1. VELO-CARDIO-FACIAL SYNDROME: GUIDELINES FOR DIAGNOSIS, TREATMENT AND FOLLOW-UP OF ENT-MANIFESTATIONS

Vantrappen G, Rommel N, Swillen A, Cremers CWRJ, Fryns JP, Devriendt K
Acta ORL Belgica, in press

Abstract

The Velo-Cardio-Facial Syndrome (VCFS), caused by a submicroscopic deletion in the long arm of chromosome 22, has a broad clinical spectrum of ENT manifestations including velopharyngeal dysfunction, hearing problems and laryngotracheal anomalies and several other defects and disorders. In the current report we present guidelines for diagnosis, treatment and follow-up of the ENT manifestations in patients with a deletion 22q11, based on our experience and on data from the literature.

Introduction

During the past decade, it has become clear that the Velo-Cardio-Facial Syndrome (VCFS) is one of the most frequent genetic syndromes associated with ENT manifestations. The syndrome, with an estimated annual incidence of 1/4000 to 1/5000 (1), is caused by a microdeletion in chromosome 22 (del22q11). A putative clinical diagnosis can be confirmed using a specific cytogenetic test demonstrating this deletion (2,3). This has lead to the recognition of a wide variety of symptoms in VCFS (4,5,6,7,8). Congenital conotruncal heart defects, velopharyngeal dysfunction, learning disabilities and facial dysmorphism are the most frequent features. With regard to the ENT manifestations in the VCFS, velopharyngeal dysfunction in varying degrees of severity is almost always present. In our study-group, 88% of the VCFS presented with velopharyngeal dysfunction. Many children with a del22q11 have also hearing problems, mainly as a result of otitis media with effusion or tympanic membrane perforations while a minority of the VCFS patients have laryngotracheal problems (9).
In this study we propose guidelines towards the ENT specialist for diagnosis, treatment and follow-up of VCFS children (table 1).

Guidelines for diagnosis, treatment and follow-up according to age of the patient

In the neonatal period, *feeding difficulties* are frequently observed in infants with a del22q11. As the children with the Velo-Cardio-Facial Syndrome (VCFS)

often present with multiple medical problems, the feeding difficulties may be secondary to the associated medical pathology such as congenital heart disease or nephro-urological malformation.

When feeding difficulties are observed, an accurate clinical assessment of the oral cavity should exclude the presence of a congenital anomaly such as (submucous) cleft palate. The oral feeding and swallowing evaluation should be performed by a speech-language pathologist familiar with VCFS or with pediatric feeding difficulties. This involves assessment of tongue and jaw movements during nutritive and non-nutritive sucking, using the Neonatal Oral Motor Assessment Scale (NOMAS)(10). This scale classifies the oral motor skills of babies from birth to 3 months of age into normal, disorganized and dysfunctional sucking. During observation, respiratory functions and clinical symptoms of oropharyngeal dysmotility such as aspiration or nasal regurgitation are assessed. Additional radiological assessment of the oropharyngeal phase of swallowing is performed when indicated (11). In infants presenting with feeding and/or swallowing problems after the age of three months oral motor skills and oral sensory functions are evaluated using the milestones for normal oral motor development (11).
Most infants with the Velo-Cardio-Facial Syndrome have transient feeding difficulties, which can be overcome by adequate advice to the parents (12). In those neonates with persistent feeding difficulties, nasogastric tube feeding may be necessary. Gastrostomy feeding is advised in case the nasogastric tube feeding exceeds a period of six months. In the mean time oral stimulation is provided (12).
Congenital *hearing loss* in VCFS appears to be rare (13). At the present time, there is insufficient evidence that this group of children should be treated differently from other children during early infancy. However, in Flanders, neonates with VCFS, as well as all other neonates, may benefit from a systematic evaluation of the hearing by the ALGO-screening-test, performed by the Health Department. This is an automatic version of the Auditory Brainstem Response (ABR). This so-called AABR (Automatic ABR) is based on the classic clinical ABR (14,15). When the hearing is normal, no further investigations are necessary. When repeated ALGO-screening indicates a hearing loss, further evaluation of the hearing is performed i.e. hearing tests in free field condition, oto-acoustic-emission (OAE) and Auditory Brainstem Response (ABR) under general anesthesia. Appropriate treatment and follow-up is recommended conform to other children with hearing loss.

Between 1 and 3 years of age, recurrent respiratory infections and speech & language development are the main interest of the ENT-field.
Similar to the children presenting with an overt cleft palate, *recurrent ear-*

and nose infections are also common in VCFS. In the children with a congenital heart defect, treatment with antibiotics is recommended. The placement of tympanic drains is indicated in children with frequent ear infections. An adenoidectomy, however, is contra-indicated in the Velo-Cardio-Facial Syndrome because most children with a del22q11 have inadequate velopharyngeal closure (16). Only in those children with planned pharyngoplasty, an adenoidectomy 2 months prior to the surgical correction can be performed (17).
Since young children with VCFS frequently have delayed language and speech development, and since they are at risk for conductive hearing loss, regular assessment of the *hearing* is recommended in all children. Hearing in this age group can be tested in free field condition. The placement of tympanic drains is indicated in children with a longstanding serious hearing impairment as a result of an otitis media with effusion.

Under the age of 2 years, *speech and language development* can be assessed by the N-CDI (Nederlands-Communicative Development Inventories). This test for Dutch speaking children from 8 to 30 months of age, evaluates speech comprehension and production as well as the understanding of signs (18,19)
Another option is the 'Nederlandstalige Nonspeech Test' (NNST). This test can be used in children from 12 to 21 months of age and evaluates prelingual and early lingual aspects as well as verbal and non-verbal communication (18,20).
At the ages of 2 and 3 years, the speech and language development is evaluated by an experienced speech-language pathologist using the RTOS-test for Dutch speaking children (Reynell Taalontwikkelingsschalen) (21,22). In children with obvious delay in speech and language development, speech therapy is initiated. We recommend, as suggested in the literature, individual speech therapy during short time periods (e.g. 20 – 30 minutes a day) at frequency rate of 3 to 5 times a week (23). In children with the Velo-Cardio-Facial Syndrome, speech production (active language skills) is delayed while speech comprehension (passive language skills) usually is in accordance with general mental development. For this reason, signing with verbal stimulation (SMOG) may be encouraged to avoid frustration in young children with obvious delay in speech production (24).

When evaluating speech and language development, the general medical condition, mental development and behavioral problems must be considered since these factors may influence the outcome of the speech therapy (25). Therefore, we recommend an annual evaluation of the general cognitive development and behavior, as well as a medical check-up. These evaluations will gain in efficiency when performed simultaneously by the speech pathologist and the educational psychologist, and discussed with the physicians.

Between the age of 3 to 6 years, the *speech and language problems* can be specified more precisely into problems with language development, velopharyngeal function and articulation. A speech-language evaluation is performed annually in all children with VCFS in order to allow the appropriate therapeutic measures to be initiated.

1. Language

The language skills are determined by the RTOS (21) and the articulation adequacy is evaluated by UAO-(Utrechts Articulatie Onderzoek)(26) or AAO-(Antwerps Articulatie Onderzoek) (27) tests.

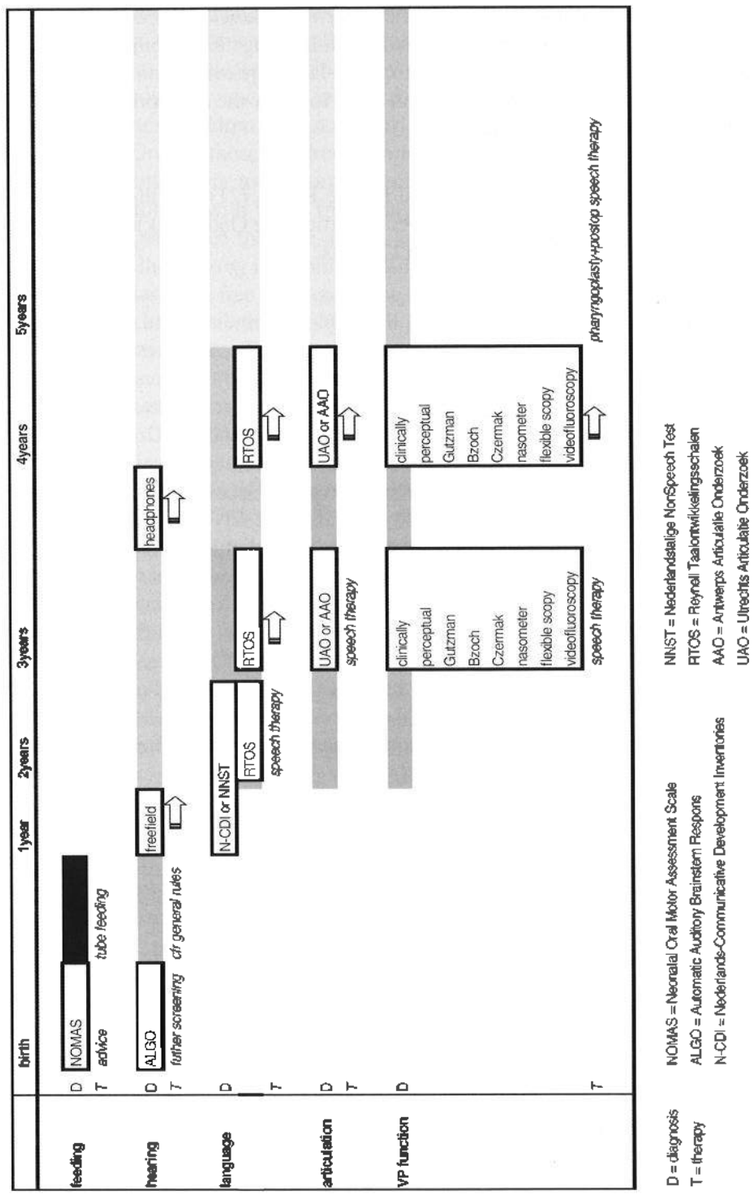
2. Resonance

The velopharyngeal function can be assessed using indirect and direct techniques (28,29,30,31). The perceptual assessment of the nasal resonance using spontaneous and standardized speech material is preferably done by an experienced speech-language pathologist. Additional standardized tests are performed, e.g. the Gutzmann [a]–[i] test, the Bzoch test and the Czermak mirror test [a], [s], [m] (32,33). The nasometer is an instrument that registers changes in resonance during standardized speech samples. The appeal of nasometry is its computerization and its objectivity (34,35). The ENT-specialist evaluates the velopharyngeal anatomy and function by inspection of the oral cavity and by assessment of the velopharyngeal port using the flexible nasopharyngolaryngoscope (36). A videofluoroscopic investigation (frontal, lateral and base view) for assessing the velopharyngeal function in rest and during standardized speech samples is performed by the radiologist and speech pathologist (37). Videofluoroscopic evaluation of the velopharyngeal valve is indicated for the child presenting with abnormal nasal resonance not responding to speech therapy or for preoperative evaluation of the velopharyngeal function .

3. Articulation

In most children with VCFS a compensatory speech is present such as glottal or pharyngeal stops and pharyngeal fricatives. Treatment should emphasize correct place and manner of articulation, but compensatory errors may require techniques such as overaspiration, use of sustained [h] to establish strong articulation contacts (23). Nonspeech lingual and labial exercises, NDT (Neuro Developmental Treatment) techniques, exercises to increase the range of motion or to strengthen tongue or lips are therapic modalities which are to be avoided (23).

In children with delayed speech-language development, speech *therapy* is initiated, and evaluated every 6 months. Speech therapy can be continued in children showing good progress. In children without obvious improvement after speech therapy, objective evaluation of the velopharyngeal function by videofluoroscopic investigations will be indicated. A pharyngoplasty is pro-



posed in those children with anatomical disproportion of the velopharyngeal isthmus or with velopharyngeal dysfunction. Speech therapy remains necessary postoperatively. To our knowledge and experience, the outcome of the speech therapy and/or pharyngoplasty will be negatively influenced by the presence of mental retardation, a significant congenital heart defect or the recurrent airway infections frequently seen in VCFS.
Speech and language problems often persist during further life (38). Older children may benefit from continued speech and language therapy in order to maintain the obtained level of speech and language. For children following special education in Flanders, the speech therapy can usually be provided at school. To our knowledge, no standardized studies on the efficacy of speech therapy or surgery for velopharyngeal dysfunction have been published (39).

At the age of 4-5 years and at any time before the initiation of speech therapy, the *hearing* can be tested using the classical headphones. If hearing loss is documented, a regular 6 monthly check-up of the hearing is recommended.

Conclusion

An appropriate diagnosis, therapy and regular follow-up are essential in VCFS children. Because of the broad clinical spectrum, a multidisciplinary approach is strongly recommended. It is only on this regular and multidisciplinary base that a child with a del22q11 can profit best from the individual adapted therapy.

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CHAPTER 7

GENERAL DISCUSSION AND PERSPECTIVES

7.1. CLINICAL IMPORTANCE OF THE VELO-CARDIO-FACIAL SYNDROME

7.1.1. The Velo-Cardio-Facial Syndrome: an important syndrome for the ENT-specialist to recognize

7.1.1.1. The Velo-Cardio-Facial syndrome is a frequent disorder

Since the start in the early 1990's, it became obvious that the VCFS has an unprecedented ***variability*** not only in the presence of the different clinical manifestations but also in the severity of the clinical expression. The most constant features of this syndrome are congenital heart defects, velopharyngeal insufficiency with or without cleft palate, facial dysmorphic features and learning difficulties. Many patients have only partial syndromes, often with very mild manifestations, or may even present with atypical anomalies such as esophageal or urological malformations (see chapter 3). It is now clear that the VCFS is one of the most frequent genetic disorders (Table 1), with an estimated ***incidence*** at birth of 1/4000. It can be therefore expected that in Flanders, with an annual birth rate between 60.000 and 70.000, at least fifteen patients with this condition are born every year. In our experience, over the past 10 years, between 1 and 4 of these children did not survive infancy due to a severe congenital heart defect.

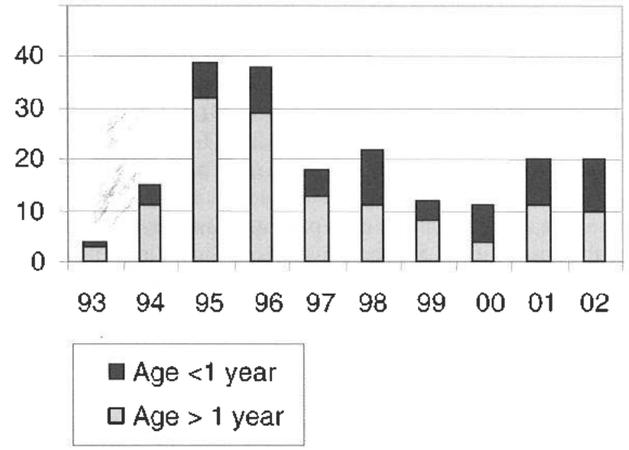
Table1
Incidence at birth of other well known genetic disorders

Genetic disorder	Incidence at birth
Trisomie 21	1/1000 (1)
Velo-Cardio-Faciaal	1/4000 (2)
Branchio-Oto-Renaal	1/40.000 (3)
Treacher Collins	1/50.000 (4)
Isolated cleft lip/palate	11.13/10.000 (5)

Table 2 shows the ***number of patients*** diagnosed every year at the Leuven Center for Human Genetics. Since the advent of a routine diagnostic test in the 1990's, at the beginning of the current study, a lot of new patients were diagnosed every year. This can be explained by two facts. On the one hand, all patients with clinical suspicion of the VCFS/DiGeorge syndrome were tested for a del22q11 by FISH. On the other hand, all patients with a conotruncal heart defect were systematically screened for a del22q11. However, even in

more recent years, the number of patients diagnosed is more than 15 per year, because of the diagnosis of older patients, not recognized before.

Table 2
Number of patients diagnosed during the last 10 years at the Leuven Center for Human Genetics



7.1.1.2. Major Malformations

The variability in clinical expression can be appreciated by looking at the diverse presenting symptoms and different ages at which the diagnosis is made (chapter 3). When major malformations such as a congenital heart defect and cleft palate are present, the diagnosis is usually made ***neonatally*** or during the first years of life.

At the Leuven Center, with a large congenital cardiology clinic, *congenital heart defects* as presenting symptom represent a large part of the group of VCFS patients. This is not unexpected, since over 50% of patients with a del22q11 have a congenital heart defect, and for this reason, all infants with a conotruncal heart defect are screened for the presence of a del22q11 at the time of diagnosis of their heart defect. Since 15% of the patients with a conotruncal heart defect have a del 22q11 (6) and since the clinical appreciation of the minor dysmorphism can often be very difficult (7), one could advocate routine testing of these children by means of FISH for a del22q11.

The number of infants diagnosed with a *cleft palate* as presenting symptom is lower compared to those patients with a congenital heart defect. Karen Brondum-Nielsen reported a 27% incidence of del22q11 in patients with cleft pa-

late and congenital heart defect or/and mental disabilities (8). Mingarelli et al. demonstrated that among the 38 patients with isolated celft (33 posterior cleft + 5 complete cleft) no single case of 22q11 deletion was found using FISH (9). Routine testing for del22q11 in patients with an isolated cleft palate is not done in most Centers, unless the children present with additional manifestations of the Velo-Cardio-Facial syndrome. A high prevalence of 22q11 deletions should be expected among cases with a combination of cleft palate and congenital heart defect or/and mental disabilty. In our experience, ENT manifestations rarely lead to the diagnosis during infancy. For instance, by 1999, only 3% of neonates were primarily diagnosed through an ENT-problem, including severe velopharyngeal insufficiency (VPI) and laryngotracheamalacia. This is not unexpected, since the classical ENT-manifestations which are usually milder, mainly become evident at an older age.

Hypoparathyroidism and *thymic hypoplasia* are relatively frequent malformations but remain asymptomatic in most patients. However, it is important to be aware of the possibility of hypoparathyroidism. Since (latent) hypocalcemia entails a risk during surgical interventions, calcium levels should be monitored in every child with VCFS undergoing a surgery or during major illness. The immune disturbances theoretically may result in severe immune deficiency and in adverse reactions during child routine vaccinations with live vaccins, but in our experience, this is exceptional.

Early diagnosis of VCFS is important so that appropriate management of associated malformations or manifestations can be started as soon as possible.

7.1.1.3. Minor manifestations

Table 2 and chapter 3 clearly show that many VCFS patients are only diagnosed at an ***older age***.These individuals usually do not present with major malformations, but were diagnosed because of a combination of other minor manifestations. From these studies, it was also apparent that it will remain a challenge to diagnose those patients presenting only minor features of the del22q11.

Besides *psychomotor delay* and *behavioral difficulties*, ENT problems such as velopharyngeal insufficiency, laryngeal anomalies or sensorineural deafness are important features to be recognized. The clinical presentation of *velopharyngeal insufficiency* varies with age and includes feeding difficulties in the neonatal period, middle ear problems during childhood or speech problems such as hypernasal speech during adolescence. *Laryngeal* anomalies such as laryngotracheamalacia or glottic stenosis are rare. *Sensorineural hearing loss* is found in a minority of the patients. It is essential that each ENT specialist is familiar with the VCF- syndrome, since these children will often present to the ENT department. Through a number of lectures in Flanders, this syndrome has gained more interest amongst ENT specialists, which in turn

resulted in a change of referral pattern. During the past years, the importance of VPI in relation to this syndrome also has become better recognized by ENT surgeons and a larger proportion of patients were diagnosed with an ENT problem as a presenting symptom of the VCFS: of the last 50 patients diagnosed since 1998, 15% were referred because of ENT manifestations compared to 6% of the first 130 diagnosed patients in our series.

Table 3
Major and atypical or minor congenital malformations associated with the Velo-Cardio-Facial syndrome

Major malformations presenting at birth
Congenital conotruncal heart defect
cleft palate
thymus aplasia or hypoplasia
Atypical malformations presenting at birth
urological malformations (multicystic renal dysplasia, renal agenesis …)
anus: ectopy, imperforate anus
club foot
oesophageal atresia
central nervous system malformations
larynx: stenosis or web
Minor manifestations
feeding difficulties
dysmorphic features : long and slender fingers, retrognathia, small ears, …
failure to thrive
hypotonia
constipation

7.1.1.4. Velopharyngeal insufficiency: an important sign to recognize

Therefore, over the last years, VPI has become an important sign to recognize in the clinical practice. During the evaluation of children with syndromic or familial forms of VPI, we recognized that VPI can also occur as an isolated, ***autosomal dominant disorder*** (chapter 5). The VPI in the described family was not associated with a submucous cleft palate but was caused by an immobile, short soft palate. None of the individuals had manifestations of the VCFS, and a deletion in chromosome 22q11 was excluded. It is surprising that despite the renewed interest for VPI in the clinical genetics specialty, no additional families with autosomal dominant isolated VPI have been reported since its original description.

In addition, we described VPI as a clinically important sign in two children with ***mosaic trisomy 8*** (chapter 5). These two children had nearly normal mental development, but presented with severe expressive language and speech delay. Videofluoroscopic examination revealed an anatomical disproportion of the nasopharyngeal isthmus, with poor mobility of the soft palate. There was no (submucous) cleft of the soft palate. Since speech therapy for severe hypernasality did not lead to a satisfactory improvement, a pharyngoplasty was performed. This resulted in a marked reduction of hypernasal speech and thus better speech intelligibility. Thus far VPI had not been reported in the mosaic trisomy 8 syndrome. However, the prevalence of high-arched palate in patients with trisomy 8 is reported in the literature to vary from 43% to 66% (10). To the best of our knowledge, the presence of a cleft palate in trisomy 8 mosaicism has been mentioned in the literature in only one boy (10).

7.1.1.5. Multidisciplinary approach of the VCFS patient: a must

Given the associated findings in VCFS, these children have to be followed in specialized multidisciplinary teams consisting of a pediatric cardiologist, an ENT-specialist, a speech and language pathologist, a clinical geneticist, a child and adolescent psychiatrist and an educational psychologist (Table 4). Each of them has expertise in his field allowing correct diagnosis, appropriate treatment and individual follow-up. Since children with a del 22q11 are at risk of having behavior problems, learning difficulties, mental retardation and speech –and language delay, it is extremely important to support the child in all these different aspects.

7.1.2. Genetic background of the Velo-Cardio-Facial Syndrome

The deletion on chromosome 22 is in most cases due to a ***de novo*** mutation occurring at gametogenesis. In a smaller percentage, the deletion is inherited from one of the parents. In our experience, a ***familial*** deletion was found in 12.3%. Other studies (11,12) reporting on familial deletions of chromosome 22q11, found a percentage of 25% and 21% respectively. The figure of 12.3% familial 22q11 deletions in our series is significantly less than previously reported. A possible explanation could be that we have underdiagnosed familial cases; on the other hand, it is also possible that the higher proportion in the other reports is to be attributed to ascertainment bias. Recently, McDonnald-McGinn reported a 10% familial incidence of the deletion22q11 which is close to our figure of 12.3% (13). Because parents ascertained through their children with a del22q11 represent the mild end of the clinical spectrum, it has been advised to systematically investigate the parents of a child with the VCFS for a del22q11. However, in our experience, all adults with a del22q11 have typical (minor) manifestations of VCFS which are easily recognized by anyo-

Table 4
specialized multidisciplinary team

pediatric cardiologist:	congenital heart defect
ENT-specialist:	velopharyngeal dysfunction cleft palate ear en hearing problems laryngotracheal malformations
speech and language pathologist:	feeding difficulties speech –and language development
clinical geneticist:	dysmorphic features anthropometric data genetic counseling minor/atypical malformations
child and adolescent psychiatrist:	anxiety behavior problems psychiatric disturbances
educational psychologist:	behavior problems mental retardation

ne having experience with the syndrome (chapter 3). For instance, velopharyngeal insufficiency was the most constant medical finding in these adults. Also in these adults, history was typical for VCFS: this VPI presented as feeding difficulties in the neonatal period, recurrent airway infections during childhood and hypernasal speech later in life. Also, psychosocial functioning was a major problem for the majority of parents. Most of them had experienced learning difficulties in the past and also in this group of indivuduals, 50% had a mild to moderate mental retardation. In some of them, a psychiatric disorder was present. These data are confirmed by a recent study by McDonald-McGinn (13).

In case of an ***inherited*** deletion, the risk for the parents to have a child with VCFS is 50% (*autosomal dominant* inheritance). One of the major difficulties is that the *severity* of the disorder cannot be predicted. There exists not only a wide interfamilial but also a wide intrafamilial variability. For instance, a parent with a del22q11 but without major malformations can have a VCFS child

with serious congenital malformations such as a serious, even lethal conotruncal heart defect. Another remarkable observation in our VCFS series, but also made by others (13), is the finding of a *discordant* clinical picture in a monozygote twin. One of them presented a cardiac malformation which was absent in the other. This indicates that the clinical picture of VCFS can not be explained by genetic or environmental factors only, but that stochastic factors during develompent may play a role as well. When the parents do not have a del22q11, there is a recurrence risk higher than the population risk due to *germline mosaicism*. This risk is estimated at about 1/200 and is explained by the presence of a mutation in a proportion of germ cells but not in other somatic tissues (14).

7.2. THE MULTIDCISPLINARY VCFS TEAM IN LEUVEN.

7.2.1. The rationale and progress of the current study

The very broad clinical spectrum and the relatively high incidence of this syndrome were the motivation to start a multidisciplinary team in 1994. In the beginning, the syndrome with all his different aspects, was not well delineated in the literature and new manifestations were continuously reported on. So, we started to study and evaluate the different clinical manifestations of the disease in the Leuven VCFS group in order to gain more insight in the clinical picture. Later we concentrated our efforts on the main ENT-features of the syndrome i.e. velopharyngeal inadequacy and hearing impairment and analyzed the different diagnostic and therapeutic procedures decribed in the literature. As we got more expertise with the ENT manifestations related to a del22q11, we evaluated the velopharyngeal function, hearing, feeding problems and laryngeal malformations in a cohort of VCFS patients. The evalution was done according to existing diagnostic procedures, but adapted to VCFS based on our initial experience. Moreover, the diagnostic protocols and the treatment modalities had to be adjusted to the many other medical, psychosocial or educational problems these individuals are confronted with. These studies performed over the last several years allowed us to formulate practical guidelines for the diagnosis, treatment and follow-up of ENT manifestations in individuals with the VCFS. These guidelines are intended to aid the ENT-specialist and speech-language pathologist. Nowadays, the VCF-syndrome is well delineated and is more rapidly recognized and diagnosed so that appropriate and personalized treatment can be initiated as soon as possible. Further research will be directed at refining existing protocols, mainly for the diagnosis and treatment of the most common anomaly velopharyngeal insufficiency.

7.2.2. The limitations and bias in the current study

The patients included in this study were all recruited from this multidisciplinary research project for VCFS. In the literature, there are a number of reports in which the diagnosis of VCFS is based on clinical grounds, without confirmation by del22q11. All patients included in this study have a proven deletion in chromosome 22q11, as demonstrated by means of Fluorescence In Situ Hybridisation (FISH - cfr introduction), using the probe DO832 (a gift from Prof. Dr. P. Scambler, ICH, London). This probe is within the critical deletion region for Velo-Cardio-Facial syndrome and is deleted in the vast majority of cases with a del22q11(15,16,17).
Many patients with the Velo-Cardio-Facial syndrome present with complex medical and developmental problems (18). This is a major limiting factor in

the systematic study of all aspects of this syndrome in all patients. Therefore, only those patients presenting with clinically significant ENT manifestations could be evaluated and were included in this study. Another bias of this study is the referral pattern: a large part of the patients were referred by the department of pediatric cardiology.
A different number of patients were included in different stages of this study. This is related to the length of the study and the ever increasing number of patients diagnosed with a deletion 22q11 over the years.

7.3. THE VARIOUS AND VARIABLE ENT MANIFESTATIONS IN THE VELO-CARDIO-FACIAL SYNDROME

7.3.1. Structural ENT anomalies in the VCFS

In our series, five patients had a ***cleft palate***, two having a submucous cleft. In the total group of 148 patients no additional individuals had a cleft palate. Therefore, in our series, cleft palate has an incidence of 2%. This is lower compared to other series, but this may be explained by a different ascertainment. For instance, the initial series of Shprintzen reported an incidence of overt cleft palate of 100% (19). This almost certainly can be explained by the fact that all these patients were assessed at an ENT-clinic, and that initially, only those cases with the full clinical spectrum were recognized. In the series of 558 patients presented by Ryan et al. and in a recent review of 102 VCFS patients by Dyce et al., respectively 9% and 11% of the patients had cleft palate, but again, there might be an overrepresentation of patients with the typical clinical spectrum which includes overt cleft palate (20,21). Alternatively, in our series, a relatively large part of the patients was referred on the basis of congenital heart disease, resulting in a relatively lower percentage of patients referred for ENT manifestations.
Children with cleft palate have significantly higher frequency of speech symptoms related to velopharyngeal function than children without cleft palate. However, children with a cleft in the soft palate only, with no additional malformations, have satisfactory speech, while children with a cleft palate accompanied by additional malformations or as part of a syndrome should be considered to be at risk for speech problems (22). The cleft repair in VCFS children is identical to the cleft repair in children without del22q11. At the Leuven department, closure of the cleft palate is planned at age one and performed according to Wardill-Kilner incision with in the same procedure also a palatal lengthening (push-back). Residual velopharyngeal insufficiency after palatal repair is found in children with and without del22q11 and varies from 10 to 20 percent in most centers (23). At the Leuven department, one child out of the group of five VCFS children with palate repair needed secondary velopharyngeal surgery to correct residual velopharyngeal insufficiency. The presence of mental retardation and behavioral problems as frequently found in children with del22q11 will negatively influence the outcome of either speech or reconstructive therapy.

In rare cases, laryngeal anomalies were found such as ***glottic stenosis*** and ***laryngotracheomalacia*** (chapter 4). This suggests that children with congenital laryngeal malformations should undergo an evaluation for the presence of VCFS, certainly when other malformations of the syndrome are present.

Achalasia of the upper esophageal sphincter was present in one neonatus with del22q11. Because of serious feeding problems and recurrent aspiration pneumonia's, a myotomy of the upper esophageal sphincter was performed. To the best of our knowledge, this rare anomaly has never been reported in the VCFS literature so far. Only esophageal malformations such as esophageal atresia or tracheoesophageal fistula have been mentioned in the literature to be present in sporadic cases with a del 22q11 (24,25). However, in the other reported cases of infantile achalasia of the upper esophageal sphincter, no mention was made about testing for a del22q11.

7.3.2. Velopharyngeal insufficiency as the most frequent ENT manifestation of the VCFS

Velopharyngeal insufficiency without cleft palate is a frequent manifestation of VCFS. This velopharyngeal insufficiency may be due to various abnormalities that cause a disproportion of the velopharyngeal isthmus and result in the patients' inability to adequately close the velopharyngeal aperture.
Testing for a del22q11 should be considered in all individuals with velopharyngeal insufficiency. In concordane with this conclusion is the observation that a higher incidence of a del22q11 is found in persons with VPI than in persons with cleft palate. Zori et al. documented a high frequency of 22q11 deletions (FISH) in patients presenting with VPI of unknown cause (6/16 patients) while the frequency in patients with remaining VPI following primary cleft palate surgery was very low (1/7 patients) (26).

The clinical presentation of this velopharyngeal insufficiency varies with age, and common symptoms include feeding difficulties in the neonatal period, middle ear problems during childhood and hypernasal speech later in life.

7.3.2.1. The neonatus with feeding difficulties

In our experience, in the neonatal period, ninety-six percent of the neonates with a del 22q11 have major ***feeding difficulties*** starting from birth on. Because of VPI, the oral cavity can not be adequately separated from the nasal cavity and, as a result, the baby is unable to suck. *Nasal regurgitation* due to velopharyngeal insufficiency occurred in 73% of our patients. Besides, *suck-swallow-breath coordination* was disorganized in 40% of the children with VCFS. This incoordination puts the baby at the risk of food aspiration. Disorganized feeders do not have abnormal oral motor patterns, but have a lack of rhythm and coordination during sucking. In 31% of the patients, *habituation* to the nipple and fatigue, resulting in long feeding periods was noted. Habituation has been defined as the inability of the infant to continue sucking when the intraoral sensory cue of the nipple is no longer novel. Although the

suck is initially intact and appears to be within normal limits, rapid deterioration occurs with subsequent discontinuation of the suck. If the nipple is wiggled or removed from the mouth and reinserted, the infant will begin to suck once again.
In most neonates, these feeding problems settled after a few weeks. In 17% of the VCFS children in whom safe oral feeding could not be established, alternative feeding such as tube feeding was mandatory.
Most likely, the feeding difficulties are ***multifactorial*** in origin and, besides the *VPI*, the *hypotonia* in combination with a *congenital heart* defect may also play a role.
As described in chapter 4, a significant proportion of children presented with ***polyhydramnios***. This probably is a manifestation of reduced swallowing in utero, as suggested by the observation that those children presenting with severe polyhydramnios had more severe feeding difficulties during neonatal period compared to the others.
Based upon our experience, we formulated ***guidelines*** for diagnosis and treatment of these feeding difficulties (chapter 6). An accurate *clinical assessment* of the oral cavity must exclude the presence of a congenital anomaly such as (submucous) cleft palate. The oral feeding and swallowing evaluation should be performed by a speech-language pathologist familiar with VCFS and pediatric feeding difficulties. This involves assessment of tongue and jaw movements during nutritive and non-nutritive sucking, using the *Neonatal Oral Motor Assessment Scale (NOMAS)*. Additional *radiological assessment* of the oropharyngeal phase of swallowing is performed when indicated. Most VCFS infants have transient feeding difficulties, which can be overcome by adequate *advice* to the parents. In those neonates with persistent feeding difficulties, *nasogastric tube* feeding may be necessary. *Gastrostomy* feeding is advised in case the nasogastric tube feeding exceeds a period of six months. In the mean time oral stimulation is provided.

7.3.2.2. The child with recurrent middle ear infections and hearing loss

During childhood middle ear problems such as ***recurrent middle ear infections*** and otitis media with effusion are a frequent finding. We analysed the otoscopic and audiological findings in a cohort of 32 children with a proven del22q11. ***Hearing loss*** and middle ear problems are frequently found in VCFS and are related to the velopharyngeal dysfunction. A hearing loss of at least 25 dB was found in nearly one third of the ears, the majority of which was conductive and due to otitis media with effusion. These figures are lower compared to the VCFS literature. Shprintzen et al. (2000) and Reyes et al. (1999) reported on an incidence of conductive hearing loss of 77% and 51% respectively of their VCFS patients (27,28). Recently, Dyce at al. (2002) mentioned that 52% of their VCFS patients had chronic or recurrent otitis media (21).

The lower prevalence of *conductive hearing loss* in our cohort may be related to the lower prevalence (2%) of cleft palate in our study group. Shprintzen et al. and Reyes et al. mentioned a prevalence of cleft palate in respectively 100% and 82% of their VCFS patients (27,28). It is well known that Eustachian tube function in cleft palate patients is poor and results in a higher incidence of middle ear diseases.
A *sensorineural hearing loss* occurred in a small minority (3%) of our cohort. Digilio et al. (1999) documented sensorineural hearing loss in 15%, in most of them as a result of cerebral ischemia and cerebral malformations (29). In our children with unilateral moderate sensorineural hearing loss, no brain malformations were documented.
Because a cleft palate, conotruncal congenital heart defect (CHD) and mental retardation are common findings in VCFS, the ***influence of these factors*** was analysed.
We found that patients with *cleft palate* have a tendency to develop a higher prevalence of effusion otitis compared to the non-cleft patients. In the *pharyngoplasty* group, normal hearing was significantly more frequent in comparison to children without palatal surgery. This result is surprising because a pharyngoplasty, performed for severe velopharyngeal insufficiency, is accompanied with a more pronounced Eustachian tube dysfunction and should thus result in a higher prevalence of hearing impairment due to effusion otitis. Therefore, we compared the otoscopic findings of the group of VCFS children with pharyngoplasty to the group of VCFS children without palatal surgery. Effusion otitis, resulting in hearing loss, was a more frequent otoscopic finding in the group of children without palatal surgery. This can be explained by two facts. First, nearly all the children without palatal surgery and with effusion otitis had a serious congenital heart defect. In this particular patient group, the placement of tympanic ventilation tubes, requiring a general anesthesia, might have been postponed because of the underlying anesthesia risk, thereby resulting in a higher prevalence of effusion otitis. Second, tympanostomy tubes were routinely placed during velopharyngeal surgery resulting in a lower prevalence of effusion otitis in the pharyngoplasty group.
A relationship between *conotruncal heart anomalies* (CHD) and Eustachian tube anomalies is mentioned in the literature (30). Therefore, we compared the audiological and otoscopic results in VCFS patients with a CHD to those without CHD. A hearing loss over 25 dB was more frequently observed in the group of children with a CHD. There was a significant difference in otoscopic results between these two groups. In children with a CHD, effusion otitis and tympanic drains for the treatment of effusion otitis or recurrent middle ear infections, were noted more often. Otitis media with effusion was mainly present in these children with a serious CHD without palatal surgery, while tympanic drains were mainly present in children with a CHD who needed a pha-

ryngoplasty. In children without a CHD, normal otoscopy was more frequently observed. The higher prevalence of effusion otitis and tympanic drains in the group of children with CHD might be related to a less efficient ventilatory function of the Eustachian tube. Todd JL et al. reported a twofold increased occurrence of otitis media proneness in children with so-called isolated conotruncal cardiac anomalies, in contrast to children with non-conotruncal anomalies (30). A major criticism of this study is the fact that del22q11 was not excluded in this cohort of patients.
Mental retardation is a frequent finding in VCFS. We found no differences in hearing between developmentally delayed and normal children.

Based on our experience, we formulated ***guidelines*** for the diagnosis and treatment of these middle ear problems in VCFS (chapter 6). Hearing assessment is recommended in all VCFS children not only because they are at risk for conductive hearing loss due to Eustachian tube dysfunction but also because they frequently have delayed language and speech development. Hearing in Belgian neonates is systematically evaluated by the Health Department by the *ALGO-screening* test. In those neonates with hearing loss, further investigations such as hearing tests in free field condition, oto-acoustic-emission (OAE), Auditory Brainstem Response (ABR) are performed. In older children, aged 4 to 5 years, hearing can be assessed using the classical hearing tests with *headphones* in a noise-isolated room and should be preferentially done at any time before the initiation of speech therapy. As VCFS children are known to have delayed speech and language development and are known to be at risk for learning difficulties, a thorough audiological evaluation is recommended in order to reduce the risk of speech problems and to prevent worsening of the learning difficulties. Early and appropriate otologic management to prevent long-term sequelae is advised. In children with recurrent middle ear infections or with longstanding otitis media with effusion, the placement of *tympanic drains* is indicated. General anesthesia in patients with a del22q11 is not without risk because of the often associated congenital heart defect, hypoparathyroidism, immune disturbances and airway malformations. So might hyperventilation reduce serum ionized calcium to values where seizures are possible. An inhaled anesthetic in patients with Tetralogy of Fallot or truncus arteriosus might reduce cardiac output. The presence of micrognathia or laryngeal malformation might create problems during intubation and the immuun disturbances make the VCFS patient more susceptable to infections. Therefore, it is important to continually evaluate the patient for possible hyopcalcemia, possible airway difficulties and sepsis and to prevent problems by taking special interventions such as the use of irradiated blood or strict aseptic precautions (31,32). Besides, endocarditis prophylaxis during surgical interventions is recommended in children with a CHD. Similar to children with a cleft palate,

recurrent nose infections are also common in VCFS. An *adenoidectomy is contra-indicated* in VCFS because most children with a del22q11 have inadequate velopharyngeal closure. An adenoidectomy can only be performed in those VCFS children 2 months prior a planned pharyngoplasty. The treatment and follow-up of a child with VCFS may be very difficult because of the associated anxiety and behavioral problems these children often present.

7.3.2.3. The adolescent with speech and language problems

Later in life, the velopharyngeal insufficiency may result in ***speech problems*** such as *hypernasal speech* and *articulatory disturbances*. The severity of VPI can varies widely: some patients have pronounced VPI compromising the speech intelligibility while in others it is minimal and without clinical consequences.

To ***evaluate the velopharyngeal function*** during speech, different techniques can be performed which are commonly used in every case of VPI and which are therefore not specific for VCFS. Because of mental retardation and behavioral problems, known to be present in almost all VCFS children, these diagnostic procedures are often difficult to perform under the age of 4 to 5 years since cooperation of the VCFS child is essential to obtain valid and reliable results.

An experienced *speech-language pathologist* evaluates the language development, the articulation and the nasal resonance. *Nasal anemometers* objectively quantifies the nasal escape. These devices are expensive, need a large technical equipment and give no information on the quality of speech. *Nasopharyngoscopy* provides predominantly good qualitative information when assessing velopharyngeal inadequacy. Information on the size, shape and location of the velopharyngeal opening is obtained while the patient is repeating key phrases to stimulate velopharyngeal closure. The *radiological* assessment, in at least two radiographic views, provides predominantly quantitative and objective information when assessing velopharyngeal inadequacy synchronous with patients' speech. This videofluoroscopic investigation identifies the type of velopharyngeal closure pattern based on variable contributions from the velum, lateral pharyngeal wall and posterior pharyngeal wall. It plays a major role in the identification of the degree and the mechanism of a velopharyngeal disorder and its effect on speech.

When reviewing the literature, no recent data concerning the type of *velopharyngeal closure pattern* according to Croft in VCFS could be found (33). Also the differences in results among studies are due to a number of different methodological variables and the absence of strict standardization of diagnostic procedures. However, understanding the anatomy and physiology of the velopharyngeal valve in a patient with velopharyngeal inadequacy, is very use-

ful to predict the possible outcome of further speech and to decide on the need for and the possibility of success of surgical therapy. Therefore, the velopharyngeal closure type i.e., coronal–sagittal–circular–circular with Passavant's ridge, and the presence and location of a gap is of major importance in the decision making on the type of surgical intervention.

We examined ***speech problems*** in a cohort of 47 children with a proven del22q11. Most patients presented velopharyngeal insufficiency with *hypernasal speech* (88%) but the severity varied widely. *Compensatory articulation* was present in 37%. All children initially received speech therapy and were reassessed after 6 months. In those patients where no progression could be detected by clinical speech-language evaluation, further *videofluoroscopic* assessment was performed as a means to objectively evaluate the velopharyngeal function. Twenty-one patients underwent this radiographic investigation. In two of them, there was no cooperation of the child so that further results could not be drawn. Because of clinically significant velopharyngeal insufficiency, a pharyngoplasty was performed in both of them. In another two children, a good functioning of the velopharyngeal isthmus was seen and further speech therapy was recommended. In the other seventeen patients velopharyngeal insufficiency was demonstrated by videofluoroscopy: in most of them (n=12), the velopharyngeal insufficiency was caused by an inappropriate elevation of the soft palate. In a minority (n=4) the videofluoroscopic assessment of the velopharyngeal isthmus demonstrated an insufficient elevation of the soft palate in combination with an insufficient approximation of the lateral pharyngeal walls. Only in one patient the velopharyngeal insufficiency was the result of insufficient approximation of the lateral pharyngeal walls while there was a good elevation of the soft palate. In all of these seventeen patients, surgery was proposed which was declined by the parents in four of them. Finally, thirteen children out of this group of seventeen children underwent a pharyngoplasty: two patients had a submucous cleft of the soft palate while the other eleven patients had no cleft. All patients needed speech therapy postoperatively.

We established a ***standardized protocol*** for the assessment of velopharyngeal function in children using *videofluoroscopy*. As children with VCFS are limited in coping with new situations, it is of major importance to prepare the child for this radiological examination. The preparation of the child begins already four weeks before the videofluoroscopy. After a thorough clinical examination of the velopharyngeal function during speech, instructions are given to the parents or the speech therapist involved. All methodological steps are summarized on a protocol, written specifically for parents. The parents repeatedly explain the course of the procedure to the child in order to familiarise

the child with the course of the examination. An adequate amount of time is provided to go through the procedure with the often mentally restricted children, using drawings specifically designed for them. Only in this way, we can obtain an optimal and reliable radiological assessment of the velopharyngeal function during speech in children with a del22q11.

Based on our experience, we formulated ***guidelines*** for diagnosis and treatment of these speech problems (chapter 6). The speech and language development can be assessed by different standardized tests depending on the age of the child. The *RTOS-test* for Dutch speaking children (Reynell Taalontwikkelingsschalen) is a test frequently used by our experienced speech-language pathologist to evaluate the speech and language development from the age of 2 years. In children aged between 3 to 6 years, the speech and language development can be evaluated more precisely. The speech and language problems can be specified into language development, velopharyngeal function (resonance) and articulation. The *language skills* are determined by standardized test such as the frequently used RTOS. The *velopharyngeal function* can be assessed using different techniques: perceptual assessment of the nasal resonance by an experienced speech-language pathologist, nasometry to objectively register changes in resonance during standardized speech samples, nasopharyngoscopy and videofluoroscopy to evaluate the velopharyngeal closure pattern during speech. The *articulation* is assessed by the speech therapist using standardized testmaterial. In most children with VCFS a compensatory speech is present such as glottal or pharyngeal stops and pharyngeal fricatives. In VCFS children mainly the speech production is delayed while the speech comprehension is in accordance with general mental development. In these children with obvious delay in speech and language development, *speech therapy* is initiated. For children following special education in Flanders, the speech therapy can usually be provided at school. A six monthly assessment of the speech and language development is recommended to adjust further therapy. Speech therapy can be continued in children showing good progress. Speech and language problems often persist during the further life. Older children may benefit from continued speech and language therapy in order to maintain the obtained level of speech and language. In children without obvious improvement after speech therapy, objective evaluation of the velopharyngeal function by videofluoroscopic investigations will be indicated. If this radiological investigation demonstrates velopharyngeal insufficiency, a *pharyngoplasty* is proposed. Speech therapy remains necessary postoperatively. To our knowledge, no standardized studies on the efficacy of speech therapy or surgery for velopharyngeal insufficiency in patients with a del22q11 have been published. A recent study on speech in VCFS patients only report on the frequency and the severity of articulation difficulties, velopharyngeal impair-

ment and the level of speech intelligibilty (34).
Besides this regular assessment of the speech and language development, we also recommend an annual evaluation of the general cognitive development and behavior, as well as a medical check-up because these factors may influence the outcome of the speech therapy. In some VCFS children the protocol needs to be adapted because of mental retardation or behavior problems. In those patients, the educational psycholgist and the psychiatrist play an important role.

7.4. PERSPECTIVES

During the past ten years, the foundations have been laid for a better diagnosis, treatment and follow-up of ENT manifestations in individuals with the VCFS. This was mainly achieved through a better description and categorization of these manifestations, and has resulted in a number of standardized protocols. These protocols will form the basis for future research, to answer remaining questions such as the optimal timing and most suited type of surgical intervention.

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SHORT CURRICULUM VITAE

Greet Vantrappen was born in Leuven on May 14th 1963. After receiving a classical (Latin-Mathematics) secondary school training at the 'Paridaens' Institute in Leuven, she entered medical school at the Catholic University Leuven in 1981, where she graduated as Master Doctor ('Doctor in de Genees-, Heel-, en Verloskunde), greatest distinction, in 1988. Under supervision of J. Tyberghein, MD PhD, and L. Feenstra, MD PhD, she started her specialist training in Oto-Rhino-Laryngology, Head and Neck Surgery in 1988 at the University Hospitals of the Catholic University Leuven. During her training, in 1990, she has been working during six months at the 'St-Radboud' Hospital of the Catholic University Nijmegen, under supervision of P. van den Broek, MD PhD. She became certified in Oto-Rhino-Laryngology in 1992. From 1992, she was trained in Revalidation for Speech- and Hearing Disorders at the University Hospitals of the Catholic University Leuven under supervision of L. Feenstra, MD PhD. She became certified in Revalidation for Speech- and Hearing Disorders in 1996. During this training she completed a postgraduate course of hospital management at the Center for Health Services and Nursing Research and Department of Applied Economics of the Catholic University Leuven and presented a thesis entitled 'The hospital costs and outcome of cochlear implants in the department of Oto-Rhino-Laryngology, Head and Neck Surgery of the University Hospitals Leuven' under supervision of K. Kesteloot, PhD.

From august 1992 she has been working as part-time consulent at the department of Oto-Rhino-Laryngology, Head and Neck Surgery of the University Hospitals Leuven. Since 1995, she participated as specialist in Oto-Rhino-Laryngology in the multidisciplinary consultation for Velo-Cardio-Facial Syndrome, Center for Human Genetics, University Hospitals Leuven. Her concurrent scientific and clinical work lead to the current PhD thesis.

Besides her job at the University Hospitals Leuven, she is working as specialist in Oto-Rhino-Laryngology in her private practice situated in Heverlee-Leuven.

SUMMARY

The Velo-Cardio-Facial syndrome is caused by a submicroscopic deletion on the long arm of one of the chromosomes 22 in band 22q11 (del22q11). The most constant features of this syndrome are velopharyngeal dysfunction with or without cleft palate, congenital heart defects, learning and behavioral difficulties, and characteristic facial features. However, the clinical expression is highly variable, and many additional features have been described. Fortunately, a suspected clinical diagnosis can nowadays be confirmed by means of a specific cytogenetic test based on Fluorescence in Situ Hybridization (FISH), to demonstrate the microdeletion in chromosome 22q11.
During the last 10 years, it has become clear that the Velo-Cardio-Facial syndrome is one of the most frequent genetic disorders, with an estimated incidence at birth of 1/4000. Given its frequent occurrence and the multiple clinical problems of individuals with VCFS, a multidisciplinary team for the Velo-Cardio-Facial syndrome was formed in 1994 at the University Hospital Leuven, in order to provide optimal care. The team included an Ear-Nose and Throat (ENT)-surgeon, a speech- and feeding therapist, an educational psychologist, a geneticist, a pediatric cardiologist and a psychiatrist. All patients diagnosed with a del22q11 at the Leuven department were seen by this multidisciplinary team and in many instances, a longitudinal follow-up could be organized. Depending on the presence and severity of specific problems, this follow-up was personalized.
The multidisciplinary team also provided a framework for further research into the clinical and genetic aspects of this syndrome. The current thesis is the result of research in the various ENT manifestations of the Velo-Cardio-Facial syndrome.

Chapter 1 presents the evolution of our knowledge on the Velo-Cardio-Facial and DiGeorge syndrome since their original description up to the identification of their common genetic cause. Based on the literature, the oto-rhino-laryngological manifestations of the Velo-Cardio-Facial syndrome are reviewed.

Chapter 2 describes the aims and outline of the study.

Chapter 3 describes the referral patterns, age and sex distributions and major clinical manifestations of the patients with a del22q11 diagnosed at the Center for Human Genetics in Leuven from 1993 to 1998.

In chapter 4, we address the ENT manifestations in the Velo-Cardio-Facial syndrome, more specifically the velopharyngeal function, the speech and feeding difficulties, the laryngeal malformations and the hearing problems. We propose guidelines for videofluoroscopy which should help in obtaining reliable and standardized information on the velopharyngeal valve function.

Chapter 5 describes novel genetic aspects of velopharyngeal insufficiency, including a family with autosomal dominant velopharyngeal insufficiency, and velopharyngeal insufficiency associated with mosaic trisomy 8.

In chapter 6, we propose a protocol for the ENT follow-up of persons with the Velo-Cardio-Facial syndrome based on our experience obtained during the last 8 years. These guidelines will allow a more rational approach in the diagnosis and treatment of these problems, and provide the basis for a long term follow-up of ENT manifestations in the Velo-Cardio-Facial syndrome.

Finally, in chapter 7, we summarize the findings of this work and present the final conclusions and prospects for future research in this field.

SAMENVATTING

Het Velo-Cardio-Faciaal syndroom wordt veroorzaakt door een submicroscopische deletie in de lange arm van één van de chromosomen 22 in band 22q11 (del22q11). De meest frequent voorkomende kenmerken van dit syndroom zijn velopharyngeale stoornissen al dan niet gekoppeld aan een gespleten verhemelte, congenitale hartafwijkingen, leer- en gedragsstoornissen, alsook karakteristieke gelaatstrekken. De kliniek is echter zeer gevarieerd en verschillende ander minder frequent voorkomende kenmerken werden beschreven. Tegenwoordig kan het klinisch vermoeden bevestigd worden door specifieke cytogenetische testen waarbij gebruik wordt gemaakt Fluorescence in Situ Hybridizatie (FISH) technieken die de microdeletie in chromosoom 22q11 aantonen.
De laatste 10 jaren, behoort het Velo-Cardio-Faciaal syndroom, met een incidentie van 1/4000 levend geborenen, tot één van de meest frequent voorkomende genetische aandoeningen. Gezien de relatieve hoge incidentie en de grote verscheidenheid in klinische problemen bij personen met het Velo-Cardio-Faciaal syndroom, werd in 1994 een multidisciplinair team voor het Velo-Cardio-Faciaal syndroom opgestart om zo te kunnen voorzien in een optimale zorgverlening. Verschillende specialisten met elk hun eigen deskundigheid maken deel uit van dit team: naast een Neus-Keel-en Oorarts en logopediste, maken een orthopedagoge, klinisch geneticus, kindercardioloog en kinderpsychiater deel uit van dit team. Alle patiënten waarbij in Leuven de diagnose gesteld werd van een del22q11 werden door dit multidisciplinair gezien en meestal kon voorzien worden in een longitudinale follow-up. Gezien de multidisciplinariteit kon deze follow-up, afhankelijk van de aard en de ernst van het specifieke probleem, individueel aangepast en bijgestuurd worden.
Het multidsiciplinaire team is een ideale uitvalsbasis voor verder onderzoek naar de verschillende klinische en genetische aspecten van dit syndroom. Zo is deze doctoraatsthesis het resultaat van onderzoek naar de verschillende Neus-Keel- en Oorsymptomen die deel uitmaken van het Velo-Cardio-Faciaal syndroom.

In hoofdstuk 1 beschrijven we de evolutie van het Velo-Cardio-Faciaal syndroom en het DiGeorge syndroom vanaf hun oorspronkelijke beschrijving tot

de ontdekking dat beide syndromen een identieke genetische basis hebben. Een literatuur overzicht beschrijft de verschillende Neus-Keel- en Oorsymptomen typisch voor het Velo-Cardio-Faciaal syndroom.

In hoofdstuk 2 wordt de doelstelling en de opzet van de studie uiteengezet.

In hoofdstuk 3 beschrijven we het verwijspatroon, de leeftijd- en geslachtsverdeling alsook de klinische symptomen van patiënten waarbij de diagnose van een del22q11 gesteld werd te Leuven in de periode van 1993 tot 1998.

Hoofdstuk 4 belicht de Neus-Keel- en Oor manifestaties van het Velo-Cardio-Faciaal syndroom meer in detail. Zo worden de velopharyngeale stoornissen, de spraak- en voedingsproblemen, de laryngeale afwijkingen en de gehoorproblemen verder uitgediept. We hebben richtlijnen voor de videofluorosopie uitgewerkt zodat dit radiologisch onderzoek betrouwbare en gestandardizeerde informatie omtrent de velopharyngeale klepfunctie geeft.

Hoofdstuk 5 haalt nieuwe genetische aspecten van velopharyngeale stoornissen aan. Zo beschrijven we een familie met een autosomaal dominante velopharyngeale insufficientie en een andere familie met velopharyngeale insufficientie geassocieerd met mosaic trisomie 8.

In hoofdstuk 6 wordt, op basis van onze ervaring de laatste 8 jaren, een protocol met betrekking tot de opvolging van patiënten met het Velo-Cardio-Faciaal syndroom geformuleerd. Deze richtlijnen beogen een meer uniforme en betrouwbare benadering in de diagnose en behandeling van patiënten met het Velo-Cardio-Faciaal syndroom en dienen als basis voor een lange termijn follow-up van de Neus-Keel- en Oor problematiek in het Velo-Cardio-Faciaal syndroom.

Tot slot, in hoofdstuk 7, vatten we onze bevindingen samen en geven tips naar verder onderzoek in deze topic.

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