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Van der Woude syndrome: a review. Cardinal signs, epidemiology, associated features, differential diagnosis, expressivity, genetic counselling and treatment

Maria Rizos and Meropi N. Spyropoulos
Department of Orthodontics, University of Athens, Goudi, Greece

SUMMARY Congenital pits of the lower lip constitute a rare developmental malformation, transmitted by an autosomal dominant mode, with considerable heterogeneity as regards the expression of the disorder. They are present in van der Woude syndrome (VWS), in which clefts of the upper lip and/or palate are often observed. Literature related to the various parameters associated with and relevant to the disorder is extensive. The purpose of this review is to cover, synthesize and categorize the existing knowledge into distinct entities, in order to facilitate understanding of the aetiopathogenesis of the malformation, its clinical manifestations and histological features, the epidemiology of the syndromic situation and the fundamental approach to an integral differential diagnosis. Special emphasis is given to the rationale underlying the treatment modalities that have been suggested, and the necessity for appropriate genetic counselling, as the disorder shows a high affinity with clefts and a familial type of occurrence.

Introduction

Lip pits may be divided into three types relative to their location: commissural, midline upper lip and lower lip (Nagore *et al.*, 1998). Lower lip pits are the most frequently occurring congenital malformations (Watanabe *et al.*, 1951; Cervenka *et al.*, 1967). They were originally described by Demarquay in 1845 (cited by van der Woude, 1954), by De Nancrede (1912) and reviewed extensively by van der Woude (1954). Van der Woude was the first to combine lower lip pits with cleft lip (CL) and/or cleft palate (CP), introducing a new clinical entity, while she also described its mode of heredity. Van der Woude syndrome (VWS) is the most frequent form of syndromic clefting, accounting for 2 per cent of all cleft lip and palate (CLP) cases (Schutte *et al.*, 1996). Furthermore, it is remarkable that both CLP and CP can be combined with lower lip pits in the same pedigree.

VWS

Cardinal signs

VWS, the most frequent form of syndromic clefting, is a rare developmental, congenital malformation with autosomal dominant inheritance, high penetrance and variable expressivity. Lower lip pits, CL with or without CP, and isolated CP are its cardinal signs (Figure 1). Phenotypic expression of clefts ranges from incomplete unilateral CL, submucous CP, bifid uvula, to complete bilateral CLP. The cardinal signs found in cases reported in the literature are summarized in Table 1. Familial occurrence has been verified in 61 per cent of patients, 47 per cent of whom present bilateral lip pits, while 18 and 35 per cent present mixed types of various morphology and microforms (i.e. conical elevations on the lips), respectively (Rintala and Ranta, 1981). A special variety (11 per cent) consisting of a lateral transverse groove or ridge on the mucosal side of the lip has previously been misinterpreted as double lip (Rintala and Ranta, 1981).

According to Schinzel and Kläusler (1986), the pits are associated with clefts in about half the patients. Among these, two-thirds have CL or CLP and one-third have CP alone, similar to the proportions observed in non-syndromic oral clefts.

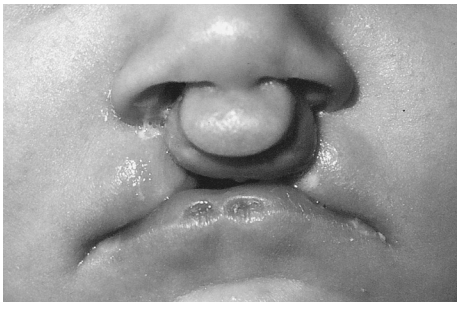

Figure 1 Bilateral symmetrical lower lip pits combined with a bilateral cleft of the upper lip.

Table 1 Van der Woude syndrome and associated features.

Reference	Gender	Lip pits				Cleft lip	Cleft palate	Cleft lip and palate	Hypodontia
		BS	BA	M	UL				
De Nancrede (1912)	M, F	?					√	√	
Ruppe and Magdeleine (1927)	F	√		√	√	√	√	√	
Ludy and Shirazy (1937)	M, F	√							
Gurney (1940)	M, F	√						√	
Mason *et al.* (1940)	M		√						
Watanabe *et al.* (1951)	M, F	√					√	√	√
Carter and Johnson (1952)	M	√							
Warbrick *et al.* (1952)	M, F	?			?	√	√	√	
Calnan (1953)	M	√					√		
Van der Woude (1954)	M, F	√	√			√	√	√	√
Wang and Macomber (1956)	M, F	√	√	√	√	√	√	√	
Neuman and Shulman (1961)	M, F	√	√		√		√		
Baker (1964)		√							
Hall (1964)	M		√				√		
Csiba (1966)	M		√					√	
Soricelli *et al.* (1966)	M, F	√					√		
Taylor and Lane (1966)	M, F	√	√			√		√	
Cervenka *et al.* (1967)	M, F	√	√	√	√	√	√	√	√
Phillips (1968)	M, F	√		√		√		√	√
Gordon *et al.* (1969)	M, F	√	√		√	√	√	√	
Rintala *et al.* (1970)	M, F	√	√	√	√	√	√	√	
Hoffman (1971)	M, F	√	√		√	√	√	√	
Schneider (1973)	M, F	√	√		√			√	√
Rintala and Lahti (1973)	M			√				√	
Glass *et al.* (1979)	M, F	√	√	√	√		√	√	
Janku *et al.* (1980)	M, F	?	?		√		√	√	√
Pauli and Hall (1980)	M	√	√				√	√	
Shaw and Simpson (1980)	M, F	√			√			√	
Shprintzen *et al.* (1980)	M, F	√	√		√		√	√	
Rintala (1981)	M				√				
Rintala and Ranta (1981)	M, F	√	√	√	√	√	√	√	
Ranta and Rintala (1982)	F, M	√	√	√	√	√	√	√	√
Ranta and Rintala (1983)	M, F	√	√	√	√	√	√	√	√
Leck and Aird (1984)	M	√			√			√	
Ortega-Resinas *et al.* (1984)	M, F	3 pits							
Ranta (1985)	F, M	√	√	√	√	√	√	√	
Cheney *et al.* (1986)	M, F		√			√		√	
Ranta (1986)	M, F	√	√	√	√	√	√	√	√
Burdick *et al.* (1987)	M		√		√			√	√
Chewning *et al.* (1988)	M	√							
Küster and Lambrecht (1988)	F	√						√	
Menko *et al.* (1988)	M, F	√		√		√	√	√	
Srivastava and Bang (1989)	M, F	√	√				√	√	
Franceschini *et al.* (1993)	F		√						√
Mutaf *et al.* (1993)	M, F	√			√	√		√	
Sander *et al.* (1993)	M, F	?	?			√	√	√	√
Kulkarni *et al.* (1995)	F	?						√	
Lacombe *et al.* (1995)	M	√					√	√	√
Onofre *et al.* (1997)	M, F	√	√	√	√	√	√	√	
Silengo *et al.* (1997)	F	√					√		√
Lekkas *et al.* (1998)	M	√						√	
Möhrenschlager *et al.* (1998)	M, F	√							
Nagore *et al.* (1998)	M, F	√	√				√	√	
Vignale *et al.* (1998)	F		√			√		√	√
Kokitsu-Nakata *et al.* (1999)	F	√					√		
Wong *et al.* (1999)	M, F	√	?	?	?	√	√	√	√

This table summarizes the presence of lip pits, clefts and hypodontia in van der Woude syndrome patients presented in the respective literature. Note that hypodontia is a feature not commonly mentioned and most probably overlooked by many authors. A question mark implies that the author does not comment on the symmetry, number or location of lower lip pits.
BS, bilaterally symmetrical; BA, bilaterally asymmetrical; M, medially symmetrical; UL, unilaterally symmetrical.

Lower lip pits

Over the last decades, the literature related to clefts has been extensive, covering their manifold aetiology, the underlying genetics and the long-lasting, complicated and laborious treatment. This is not the case, however, where lower lip pits are concerned. In this article, lower lip pits, which are the principal trait of VWS, will be reviewed, in an effort to reveal fully the features related to their location, morphology, symptomatology, aetiology and histopathology.

Location. The classical type of lower lip pits is the bilateral paramedian sinuses of the lower lip, placed symmetrically on either side of the midline (Figure 1). They can also be unilaterally, medially or bilaterally asymmetrical. A single median or paramedian lesion is considered as an incomplete expression of the trait.

The unilateral type occurs mostly on the left side (Watanabe *et al.*, 1951; Neuman and Shulman, 1961; Rintala *et al.*, 1970; Hoffman, 1971; Schneider, 1973) and rarely on the right side (Ruppe and Magdeleine, 1927; Hoffman, 1971; Kulkarni *et al.*, 1995). Three types of lip pit have also been reported (Hall, 1964; Ortega-Resinas *et al.*, 1984). Lip pits are usually circular or oval, but can also be transverse, slit-like or sulci. Sometimes it is difficult to decide whether they are truly median or paramedian. The transverse mucosal ridges, the conical elevations (nipple-like) and/or openings with no depth, presumably represent microforms of lower lip pits. The elevations may rarely fuse in the midline, producing a snout-like structure (Oberst, 1910, cited by Gorlin *et al.*, 1990).

The sinuses are located on the upper border of the lower lip or on any site from the vermilion border to the mucosal side of the lip in an antero-posterior direction. Most of them are located in the lip vermilion and on the mucocutaneous line at a distance of about 5–25 mm from each other (Csiba, 1966). The base of the sinus tract is embedded in skeletal muscle bundles, whose fibres, in some sections, have been so orientated as to suggest a peristaltic projection of the mucous secretion upon contraction (Taylor and Lane, 1966).

Morphology. The lip pits form canals, lined by labial mucosa, which extend inside the orbicularis oris muscle, their length being between 1 and 25 mm. Fistulography has shown that the fistula is long with bifurcated tracts, of 5–6 cm in length, ending blindly under the skin, beyond the orbicularis oris muscle (Ortega-Resinas *et al.*, 1984). Occasionally the fistulas diverge, and, in rare instances, they converge to form a single sinus tract (Taylor and Lane, 1966). A median lower lip sinus that was bipartile, like a pair of trousers, was described by Rintala and Lahti (1973).

The orifice may be flush with the lower lip, form a depression (surrounded by a fold of epithelium), be located at the apex of a nipple-like elevation, or two nipple-like protrusions may be found with no sinus openings at their apices (Wang and Macomber, 1956). The contour of the surrounding lip is normal (Warbrick *et al.*, 1952). The canals always end as blind sacs surrounded by mucous glands. The orifice may be so small as to barely admit a hair probe or as large as 6 mm in diameter (De Nancrede, 1912; Wang and Macomber, 1956).

Symptomatology. Lower lip pits are usually asymptomatic (Shprintzen *et al.*, 1980); the only symptom might be the continuous or intermittent drainage of watery or salivary secretions (Nagore *et al.*, 1998), occurring spontaneously or caused by mastication and 'fear or apprehension' (Soricelli *et al.*, 1966). The mucous accumulation occurs more rapidly before and during mealtimes (Carter and Johnson, 1952), or in relation to crying, when infants are concerned (Csiba, 1966). In a patient described by Chewning *et al.* (1988), the secretion worsened in the winter months, resulting in constant chaffing and excoration of the lower lip, while in another patient the pits became painful when he had a cold (Gurney, 1940). Occasional collection of food particles in the sinuses has also been a source of complaint (Hoffman, 1971).

Morphogenesis. In the very first report on lower lip pits, Demarquay (1845, cited by Burdick *et al.*, 1987) attributed their formation impressions made on the lower lip to the upper central incisors, and many patients tend to adopt this hypothesis even now (Menko *et al.*, 1988). Numerous other theories were synopsized by Wang and Macomber (1956) and cover the phylogenetic, epithelial or glandular, compensatory and embryonic origins. However, all of the above theories, except the embryonic one, have no scientific background. The theory of embryonic origin supports the concept that a defective gene is partially responsible for the formation of CLP, by retardation or inhibition of a certain phase in the normal development of the lower lip.

Modern research gives new insight, as far as the embryology of the syndrome is concerned. The most prevalent theory on the mechanism of formation of lower lip pits during intrauterine development was described by Warbrick *et al.* (1952), based on serial sections (5–16.1 mm) of human embryos. The whole of the lateral sulcus is obliterated in the normal manner, with the exception of the cephalic end, which becomes deeper as growth proceeds. At the same time, the edges of the furrow become more prominent and ultimately fuse together, and thus convert the furrow into a tubular canal open at its upper end. This canal is then incorporated into the substance of the lower lip, as this separates from the main mass of the mandibular arch and remains as a congenital fistula. This theory, however, does not explain the frequent openings of these sinuses

on well-marked conical elevations (Srivastava and Bang, 1989).

According to Kitamura (1989), in a 32 day embryo, the lower lip consists of four growth centres, divided by one median and two lateral grooves. In the 38 day embryo, the lateral grooves disappear, except in the case of impeded mandibular process growth that results in the formation of a lip pit. If a cyst derived from the remnant of the epithelial wall is communicated to the duct of labial glands, a congenital fistula of the lip is formed. The development of lip pits starts at day 36 of development, CL at day 40 and CP at day 50. The periods of liability of these three tissues probably vary in length and even in sequence, and perhaps they also overlap.

Histopathology. Histopathological examination of the pits reveals extensive depression in the central part, well surrounded by elevated borders (Vignale *et al.*, 1998). The stratified epithelium of the borders and the central area is thinned, while most of the basal cells are vacuolated, with displacement of the nucleus (Mason *et al.*, 1940; Nagore *et al.*, 1998; Vignale *et al.*, 1998; Onofre *et al.*, 1999), resembling immature epithelial cells (Watanabe *et al.*, 1951). Csiba (1966) added the presence of acantholysis and hydropic degeneration in the fistulous epithelium, while Ruppe and Magdeleine (1927) observed spongiosis. The superficial dermis has a diffuse interstitial oedema, slight dilation of the dermal papillae and congested capillaries. Between the lateral wall and the bottom of the depression, a small columnar sector of parakeratotic cells is observed. The muscle and the nerve fibres do not present any significant change, relevant to quality, quantity and disposition (Figure 2).

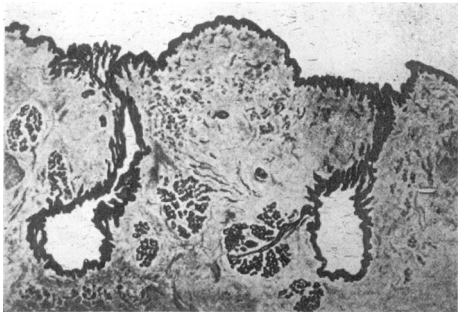

Figure 2 Histological section of a lower lip with bilateral fistulae. Note the epithelium lining the tracts and the acini of mucous glands communicating with them. Originally published by Hilgenreiner (1924) in Deutsch. Zeitschr. Chir 188: 273.

Epidemiology of VWS

Prevalence. The prevalence of VWS varies from 1:100 000 to 1:40 000 still born or live births (Cervenka *et al.*, 1967; Gordon *et al.*, 1969; Janku *et al.*, 1980; Rintala and Ranta, 1981; Burdick, 1986).

Sex ratios. No significant difference between sexes is reported as regards the prevalence of the syndrome (Cervenka *et al.*, 1967; Janku *et al.*, 1980; Burdick *et al.*, 1985, 1987; Schinzel and Kläusler, 1986). Many authors believe that there is a higher prevalence of the syndrome in females, which may partly be due to the fact that women visit a doctor more frequently as a consequence of cosmetic defects (Watanabe *et al.*, 1951; Wang and Macomber, 1956; Rintala *et al.*, 1970; Onofre *et al.*, 1997). On the contrary, Csiba (1966) found the syndrome to be twice as frequent in males compared with females.

Associated features of VWS and differential diagnosis

Apart from the major signs, there are other features that are often associated with VWS. Hypodontia is considered a cardinal associated feature and has been observed in 10–81 per cent of all VWS patients (Schneider, 1973; Rintala and Ranta, 1981; Schinzel and Kläusler, 1986), with the number of teeth missing in the upper jaw almost double that in corresponding control groups (Ranta and Rintala, 1982). The teeth missing in sequence of frequency are the upper second premolars, the lower second premolars, and the upper lateral incisors.

Other frequently associated anomalies include syndactyly of the hands, polythelia, ankyloglossia and symblepharon (Neuman and Shulman, 1961; Cervenka *et al.*, 1967; Burdick *et al.*, 1987), club foot (Ludy and Shirazy, 1937), thumb hypoplasia (Wong *et al.*, 1999), congenital heart disease (Pauli and Hall, 1980), congenital strand-like adhesions (oral synechiae) between the upper and lower gum pads (Neuman and Shulman, 1961; Shaw and Simpson, 1980), commissural pits (Chewning *et al.*, 1988; Menko *et al.*, 1988), tapering fingers (Burdick *et al.*, 1987) pre-auricular sinuses (Phillips, 1968), lower CL (Möhrenschlager *et al.*, 1998; Lekkas *et al.*, 1998; Lo and Noordhoff, 1999), heart murmur and midline cerebral abnormalities (Lacombe *et al.*, 1995), double lower lip (Calnan, 1953), ectodermal dysplasia and central nervous system malformation (Silengo *et al.*, 1997). Patients with Kabuki make-up (Niikawa-Kuroki) syndrome and VWS were also described by Franceschini *et al.* (1993) and Kokitsu-Nakata *et al.* (1999).

A review of the literature reveals a variety of other anomalies from which VWS should be differentially diagnosed:

1. Commissural and upper lip pits (Baker, 1966; Gorlin *et al.*, 1990; Ohishi *et al.*, 1991; Neville *et al.*, 1995).

Commissural pits occur at the site of the horizontal facial cleft and may represent defective development of this embryonic fissure (Shafer *et al.*, 1983). Congenital sinuses rarely occur in the upper lip and its fraena (Ludy and Shirazy, 1937; Wang and Macomber, 1956; Mahler and Karev, 1975; Ortega-Resinas *et al.*, 1984; Özgur and Tunçbilek, 2000) (Figure 3).

2. Clefts with no pits, due to variable expressivity of VWS (Gorlin *et al.*, 1990).
3. Popliteal pterygium syndrome (PPS), which includes popliteal web, CL and/or P, lower lip pits in 60 per cent of cases [71 per cent according to Audino *et al.* (1984)], anomalies of the genitourinary system, such as cryptorchidism and bifid scrotum in males and hypoplastic labia majora and uterus in females (Klein and Franceschetti, 1962; Gorlin *et al.*, 1968, 1990; Rintala and Lahti, 1970; Leck and Aird, 1984; Herold *et al.*, 1986). Soekarman *et al.* (1995) found 23 families who exhibited PPS, while seven of them showed a clinical picture indiscernible from VWS in prior generations, with CLP, lip pits and hypodontia only. The characteristics of VWS may all be found in PPS. The hypothesis is that they are both allelic variants of the same condition and genetic counselling must include the possibility that people with VWS have a risk of giving birth to offspring with PPS. Lees *et al.* (1999) proved that the two disorders are allelic by genotyping three families for markers flanking and within the critical region of 1q32-41 within 1.6 cM, and obtaining a LOD score of 2.7 with no evidence of recombination.
4. Aganglionic megacolon combined with CP and lip pits (Hirschsprung's disease) (Schwarz *et al.*, 1979; Goldberg and Shprintzen, 1981; Gorlin *et al.*, 1990).
5. Oro-facio-digital syndrome type 1, an X-linked dominant trait, lethal in males, with striking orodental, facial, digital, renal and central nervous system abnormalities. Orodental signs include CP, bifid tongue, hypodontia, and median cleft of the upper lip, while Salinas *et al.* (1991) added lip pits to the wide clinical variability. The exclusion of this syndrome should be based on the orodigital findings (Schinzel and Kläusler, 1986).
6. Ankyloblepharon filiform adnatum (Srivastava and Bang, 1989).

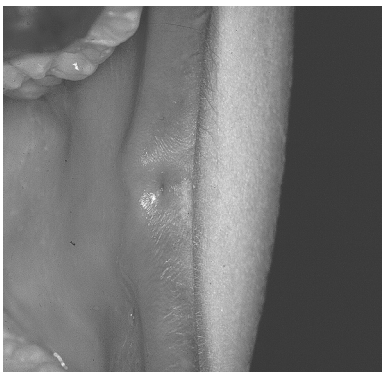

Figure 3 A commissural lip pit.

Expressivity of VWS and genetic counselling

The expressivity of the syndrome is variable; all of the signs can be present, either alone or in combination, or no abnormalities can be detected clinically. In a seven-generation kindred investigation (Janku *et al.*, 1980), lip pits occurred in 88 per cent of those affected by VWS and were the only manifestation in 64 per cent, while clefts occurred in 21 per cent. Ludy and Shirazy (1937) presented a family with five members with lip pits only, in which there was familial occurrence of the deformity. The reported prevalence of lower lip pits among cleft patients ranges from 0.37 to 6 per cent (van der Woude, 1954; Fogh-Andersen, 1961; Shprintzen *et al.*, 1980; Rintala and Ranta, 1981; Onofre *et al.*, 1997).

Bilateral lower lip pits with no cleft were reported in a four-generation family by Baker (1964). The combination of CL and lip pits alone in the same pedigree is very rare (Lacombe *et al.*, 1995). One of the unusual features of VWS is that different forms of clefts occur in the vertical and horizontal directions in the same pedigree (Fogh-Andersen, 1961; Sander *et al.*, 1993).

When various types of pit occur in the same patient, the term 'mixed type' is used. Microforms of VWS occur as conical elevation on the lips, transverse fissure on the lip, median depression and hypodontia (Rintala *et al.*, 1970; Rintala, 1981; Ranta and Rintala, 1983; Ranta, 1985).

Genetic counselling, a procedure highly recommended for this abnormality, includes information on the likelihood of gene transmission, and possible ways of expression and penetrance. A full family history is essential before counselling can be given to patients of isolated cases of clefts (Stricker *et al.*, 1990).

The complex is inherited as if due to a single gene of variable expressivity. The affected person is capable of transmitting the anomalies to approximately one half of his or her offspring. There is significant association between the types of cleft in parents and their children (Cervenka *et al.*, 1967). A severely affected parent appears to have more severely affected offspring than the mildly affected parent (van der Woude, 1954; Burdick *et al.*, 1985). On the other hand, a non-affected parent with familial history of the defects may have severely affected offspring (van der Woude, 1954). Mildly affected individuals have passed on severe forms of the trait (Cheney *et al.*, 1986).

For a VWS patient, the relative risk of transmitting a cleft is between 11.0 and 22.43 per cent (Cervenka *et al.*, 1967; Janku *et al.*, 1980; Burdick, 1986). The relative risk of transmitting lower lip pits only, or being non-penetrant,

is from 24.7 to 42.7 per cent (Cervenka *et al.*, 1967; Janku *et al.*, 1980; Burdick, 1986).

Relative to the phenotype of the patient, the risk of a cleft in a child (with 95 per cent confidence limits) having a parent with lip pits only, is 22 per cent. If the parent has lip pits and cleft, the risk is 39 per cent. If the parent has cleft only, but his/her parent or sibling has lip pits, the risk is 30 per cent (Cervenka *et al.*, 1967).

Kläusler found no difference in pedigrees, parental ages, birth orders, pregnancy histories, exposures to teratogens and birth weights between VWS carriers with or without clefts (quoted by Schinzel and Kläusler, 1986).

Because of the wide variability of expression of PPS as well and its probable aetiological heterogeneity, careful physical examination of available family members should be made, in all sporadic cases, to confirm the diagnosis in those presenting only minor manifestations and to identify less severely affected relatives of those with full expression (Audino *et al.*, 1984). Thus, patients with pits and clefts have a small risk of having offspring affected by popliteal pterygia and other signs of PPS, in addition to their parents' features (Schinzel and Kläusler, 1986). Pashayan and Lewis (1980) reported a father with a CP and lower lip pits, while two of his three offspring exhibited extensive involvement of PPS.

VWS patients may rarely show clefts without pits: these cases represent a small group of cleft patients with a high recurrence risk and underline the need for specific questions and examination for lip pits, including microforms, in relatives of cleft patients at genetic counselling (Schinzel and Kläusler, 1986). According to Menko *et al.* (1988), in patients with CLP, the lower lip should be actively examined in both the patients and their first-degree relatives. Furthermore, speech–language pathologists can play a major role in identifying patients who may have minimal clinical signs of VWS, such as a submucous cleft (Glass *et al.*, 1979).

Treatment of VWS

The treatment of VWS patients includes all necessary surgical and multidisciplinary procedures for the correction of serious anomalies including clefts. As far as the treatment of lower lip pits is concerned, although spontaneous shrinkage has been reported in rare cases (Ludy and Shirazy, 1937; Küster and Lambrecht, 1988), the reasons that make patients desire their excision are the minor cosmetic implications, the mucous secretion and the possible chronic uncontrollable inflammations. Secondary infections, although not frequently reported, are to be avoided and patients who do not undergo surgical correction should be instructed about meticulous hygiene care. Furthermore, a case of squamous cell carcinoma developing from a chronically inflamed lip sinus was reported by Bernier (1955, quoted by Soricelli *et al.*, 1966).

Watanabe *et al.* (1951) reviewed and categorized the surgical techniques available for the excision of lip pits. In all cases, excision of the sinus tract should be complete, because if some of the mucous glands attached to the fistula are left behind, this could allow a mucoid cyst to form (Wang and Macomber, 1956; Ortega-Resinas *et al.*, 1984). Looseness of the lip muscle has also been reported as a drawback of the operation (Wang and Macomber, 1956; Campus *et al.*, 1994).

When late post-operative results are evaluated, an aesthetically poor lip is often found, and treatment requires two or more operations, due to residual deformities (Bowers, 1972, quoted by Mutaf *et al.*, 1993).

Conclusions

VWS is usually underreported and frequently not diagnosed. The phenomenon that CLP and CP are regularly combined in the same pedigree makes it unique. A meticulous examination of a patient with lip pits may reveal a hidden form of a cleft, for example, submucous. Furthermore, the physical examination should include as many members of a VWS patient's kindred as possible. Genetic counselling is highly recommended.

Address for correspondence

Professor Meropi Spyropoulos
Department of Orthodontics
Dental School
University of Athens
2 Thivon str.
Goudi 11527
Athens
Greece

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