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Clinical, histomorphological and therapeutic features of the Van der Woude Syndrome: literature review and presentation of an unusual case

ABSTRACT

Background *Van der Woude syndrome (VWS), an autosomal dominant condition associated with lower lip pits and/or cleft palate, is caused by mutations in the interferon regulatory factor 6 gene (IRF6 gene). The genetic alterations identified to date that contribute to expression of the syndrome are chiefly mutations located on chromosome 1 (the largest of our chromosomes), mutations at p36 that codifies the gene GRHL (grainy-head transcriptor factor) and mutations involving IRF6 (interferon regulatory factor). With frequency ranging from 1:35,000 to 1:100,000, depending on ethnicity, gender, and socio-economic status, the syndrome accounts for about 2% of orofacial clefts. The clinical and histomorphological aspects of VWS are studied, and a case of heterozygous female twins of whom only one was affected with VWS is reported.*

Conclusion *This very rare case (no similar case has been reported to date) contributes further evidence on modifying factors in the expression of this condition.*

Keywords *Heterozygous female twins; Van der Woude syndrome.*

Introduction

Van der Woude syndrome (VWS) is a rare autosomal dominant developmental disorder, usually associated with lower lip pit(s) and cleft lip and palate. It was first described in 1954 by Anne Van der Woude, who detailed the association between congenital pits of the lower lips and cleft lip and palate [Natarajasundaram et al., 2008]. The disease incidence ranges from 1:35,000 to 1:100,000, making VWS the most common syndromic orofacial clefting; individuals with this syndrome account for 2% of all cleft cases. No significant difference in prevalence between sexes is reported [Arangannal et al., 2002]. Congenital lip pits are developmental defects that occur on the paramedial portion of the vermilion border of the lower lip, with or without excretion. Lip pits are depressions of the lower lip that contain the orifice of mucous glands or minor salivary glands. They may be unilateral or bilateral, and may occur as an isolated condition or in association with cleft lip and or cleft palate [Kaul et al., 2014].

VWS is inherited as an autosomal dominant disease that shows high penetrance but variable expressivity amongst carriers. The gene responsible for this disorder has been mapped to the long arm of chromosome 1 at q32 to q41 [Wojcicki et al., 2016]. This gene encodes interferon regulatory factor 6 (IRF 6). However, some affected individuals have shown linkage to a second chromosomal locus (VWS locus 2) which is located at 1p34 [Wojcicki et al., 2016]. The disease has high penetrance, at about 96%, but the phenotypic expression varies from lower lip pits with cleft lip and cleft palate to no visible abnormalities. Approximately 88% of VWS patients has been found to have lower lip pits, and in about 64% of cases lip pits are the only visible defect. Other anomalies frequently associated with VWS include hypodontia, ankyloglossia, narrow arched palate, syndactyly, congenital heart disease, heart murmur and cerebral abnormalities, ankyloblepharon, polythelia and, rarely, congenital adhesion (synechiae) between different parts of the oral cavity [Wilkie and Morriss-Kay, 2001; Kernahan, 1971; Rossell-Perry, 2009].

Diagnosis of VWS can be made clinically. However, due to the genetic non penetrance or high penetrance of the condition, genetic investigations may be appropriate. A clinical diagnosis of VWS requires additional examination of family members to identify other members with the syndrome, due to its high penetrance. This will also be a valuable guide for counseling, since VWS is highly penetrant, and the family risk for clefts is increased. Management of VWS mainly focuses on surgical and

cosmetic correction of clefts and lip pits.

A case is presented of heterozygous female twins, of whom only one was affected with VWS. To the authors' knowledge such a case has not previously been reported, and it contributes further evidence for modifying factors in the expression of this condition.

Case report

A 4 year-old girl was referred to the Department of Oral Pathology and the Department of Pedodontics of the Italian Stomatology Institute (Milan, Italy) with a persisting pit on the right lower lip (Fig. 1). Medical history was unremarkable; family history revealed no similar case among immediate or distant relatives. She was symptom-free and had a heterozygous female twin. Extraoral examination revealed the presence of a unilateral lower lip pit of 3 mm in diameter, with no exudation, present since birth with no sign of regression in size. Diagnostic probing was used to assess the depth and patency of the lip pit. Intraoral examination showed a normal hard palate and deciduous dentition. The patient was scheduled for surgical correction of the pit on the right lower lip as soon as she was old enough to collaborate.

FIG. 1 Clinical aspect of the lesion on the right site of lower lip.

Surgical procedure

At age 5 years 7 months, the patient was operated under local anaesthesia (Mepimynol, mepivacaine chloridrate 30mg/mL, Curaden Healthcare, Saronno, Italy) without general anesthesia, nor oral analgesia. The surgical operation began under cannulation, with a blunt probe placed through the fistula. Complete excision was performed with a scalpel blade 11, reaching the lower labio-gingival groove along the inner face of the lip mucosa (Fig. 2). After surgical removal of the fistula (Fig. 3), the continuity of the inferior orbicularis muscle was reconstructed with Vicryl 5-0 reabsorbable sutures. Externally, the inferior labial mucosa and vermilion were sutured with Vicryl 5-0 reabsorbable sutures. Surgery was concluded with the placement of Z-shaped plastic suture to reduce labial mucosa tension.

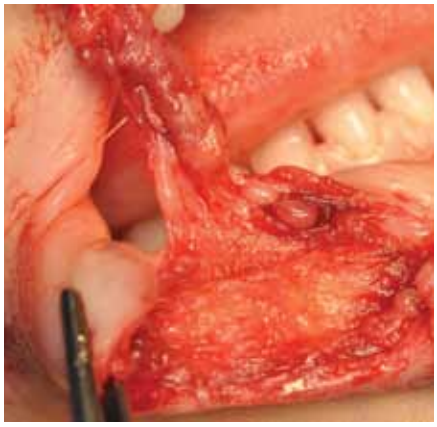

FIG. 2 Intraoperative photograph during the isolation of the fistula.

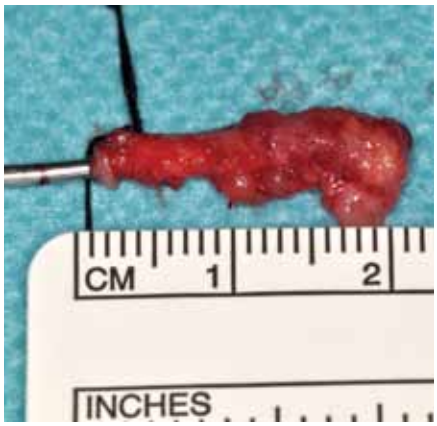

FIG. 3 Macroscopic photograph of the lesion after surgical removal.

Postsurgical procedure

The resulting surgical wound healed by second intention, despite its depth. No antibiotics were prescribed. Paracetamol tablets, 500 mg, were prescribed: half tablet as needed, up to 3 tablets per day. Chlorhexidine was applied as a gel (0.2%) to the surgical zone twice daily to maintain good postoperative oral hygiene. Follow-up at 21 days showed perfect wound healing. The patient was carefully monitored until the final follow-up, at age 9 years 10 months (Fig. 4).

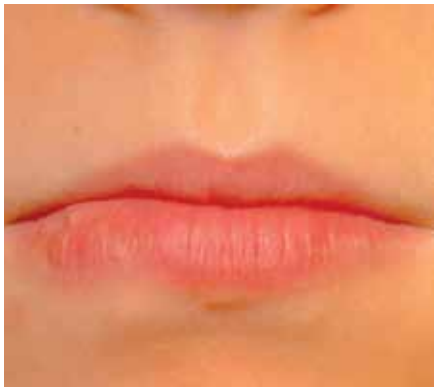

FIG. 4 Lower lip after 4 years of follow up.

Histology

The surgical sample was fixed in formalin and

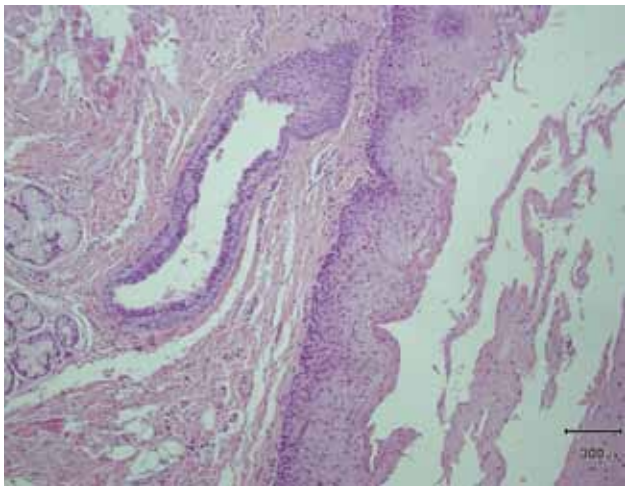

FIG. 5 Microscopic photograph revealed a soft tissue lesion covered by stratified squamous epithelium that was hyperkeratotic and spongiotic. The histologic diagnosis was of epithelial inclusion cysts. Original magnification 20 X hematoxylin and eosin.

enbebbed in paraffine cut into 3-µm-thick sections and stained with hematoxylin and eosin. Microscopic examination revealed a soft tissue lesion covered by stratified squamous epithelium that was hyperkeratotic and spongiotic, in the subepithelial connective tissue, numerous blood vessels of various diameter with thickened wall, and glandular lobules with acines in part were dilated. The histologic diagnosis was of epithelial inclusion cysts (Fig. 5).

Discussion

VWS is an autosomal dominant syndrome characterised by cleft lip or palate, distinctive pits at the lower lips, or both. It is the most common syndrome associated with cleft lip or palate. The degree to which individuals carrying the gene are affected varies widely, even within families. Variable manifestations include lower lip pits alone, teeth agenesis, or isolated cleft lip and cleft palate of varying severity [Richardson and Khandeparker, 2017]. Hypodontia has been increasingly recognised as a frequently associated anomaly, and has been observed in 10-81% of all VWS cases; hypodontia is more frequently in the upper jaw [Nawa et al., 2008].

Although the lip pits are inherited as an autosomal dominant trait, their pathogenesis is not clearly understood. They are thought to develop from notching of the lip at an early stage of labial development, with fixation of the tissue at the base of the notch, or from failure of complete union of the embryonic lateral part of the lip to take place; this appears to persist and ultimately to develop into the typical pits.

The surface opening of the lip pit may present as a circular or transverse slit; the depth of the pits ranges from 1 to 25 mm [Busche et al., 2016]. These depressions can be blind, or may have minor salivary glands within them. The presence of minor salivary glands, or of communication with salivary ducts, is readily recognised by the spontaneous or pressure-induced discharge of saliva or mucus. The pits pass through the orbicularis oris muscle, and some fibers of this muscle are orientated so that, upon contraction, they induce the peristaltic ejection of mucous secretion; thus the fistula may secrete a mucin-like fluid [Suzuki et al., 2000]. Chronic discomfort (due to inflammation caused by the salivary excretions and/or bacterial penetration) and poor aesthetics are common reasons cited for surgical removal of lip pits. Although the cleft lip and palate are the most serious esthetic problems for these patients, exudation of mucus from the lip pits onto the lower labial skin is a source of embarrassment. The case reported here presented a lip pit approximately 3 mm in diameter with no exudation.

This is a rare case, and the studies published to date, report no other such cases; the prevalence of the only cleft lip clinical phenotype is also low. Most cases of Van der Woude syndrome have been linked to a deletion in chromosome 1q32-q41; however a second chromosomal locus at 1p34 has also been identified (VWS locus 2). The mutation responsible has been identified in the interferon regulatory factor 6 (IRF 6) gene, but the exact mechanism of this mutation's effect on craniofacial development is uncertain. Demonstrating the presence or absence of an IRF6 mutation can be helpful when distinguishing between uncomplicated cleft lip and/or cleft palate and VWS [Tassabehji et al., 1992; Kim et al., 2003]. A wide variety of chromosomal mutations that cause VWS and are associated with IRF6 gene mutations have been described [Lidral and Moreno, 2005]; a potential modifying gene has been identified at 17p11.2p11. Because of the variability of this syndrome, it is important to obtain a detailed family history in diagnosing VWS. All VWS-affected relatives should be cautioned that they carry a 50% risk of having a child with cleft lip and/or palate, due to the autosomal dominant transmission mode. However, some VWS cases arise as a *de novo* mutation. The present case showed no relevant family history.

A single study has suggested that males with the syndrome may have poorer cognitive function than females [Jugessur et al., 2009]. Congenital lower lip pits also occur in three other syndromes: the Popliteal pterygium syndrome (lower lip pits, oral clefts, syngnathia, toenail dysplasia, syndactyly of the toes, congenital heart disease, and genital abnormalities); oro-facial-digital syndrome type I (lip pits, oral clefts, oral frenula, hypoplasia of nasal cartilages, malformations of the hands, hypertelorism, and psychomotor retardation); and the Kabuki make-up syndrome (postnatal growth retardation, dysmorphic

face, skeletal abnormalities, mental retardation, and unusual dermato-glyphic patterns) [Gorlin, 1968].

Conclusion

VWS is a rare clinical entity. Although Congenital Lip Pit (CLP) associated with Cleft Palate (CP) is the typical pattern of the disease, expressivity varies widely and careful clinical examination of parents and relatives may be necessary. Physical examination of relatives, close examination of family photos, or interviews with older relatives may be necessary to identify minimally-affected family members. Genetic counseling is strongly recommended.

The case reported demonstrates the complexity of the expression of the VWS phenotype, and reinforces the need for further studies on modifier genes, epigenetics, and environmental factors.

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The patient's parents signed an informed written consent for the publication of the manuscript and figures.

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