

DOI: 10.21767/2576-392X.100017

Van der Woude Syndrome and Implications in Dental Medicine

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Abstract

There are many types of genetic anomalies that affect the development of orofacial structures. Van der Woude syndrome (VWS), also known as cleft palate, lip pits or lip pit papilla syndrome, is a rare autosomal dominant condition being considered the most common cleft syndrome. It is believed to occur in 1 in 35,000 to 1 in 100,000 individuals, based on data from Europe and Asia.

It is characterized by the congenital association of lip sinuses with cleft lip and palate. These are the main traits of VWS and occur in 88% of affected individuals. Another common signal/symptom is hypodontia.

Diagnosis of VWS can be done clinically, based on the presence of lip pits and/or other orofacial anomalies that can be present all together or isolated. Most of the development anomalies are congenital so, in most cases, clinical diagnosis can be done immediately after birth.

Almost all cases of VWS are linked to a locus in chromosome 1 (q32-q41) also known as VWS locus 1. The *IRF6* gene is located at this critical location and encodes the interferon regulatory factor 6. This gene is expressed in the palate, teeth, hair follicles, external genitals and skin. Mutations in this gene are responsible for the development of this pathology.

Treatment of patients with this syndrome includes all surgical and multidisciplinary procedures for the correction of the presented anomalies.

Keywords: Treatment; Chromosome; Syndrome; Mouthpiece

determined that this pathology has a complex heritage, with a single gene involved, with high penetrance but variable expressivity. The variety of symptoms can go from fistulas of the lower lip with lip and palate cleft to invisible anomalies [2].

It is a rare congenital malformation with an autosomal dominant transmission consisting of 2% of all cases of cleft lip and palate, with an incidence of 1 in 35,000-100,000 [3-5].

Lip pits were the most common manifestation present in affected individuals, occurring in 88% of patients [6,7].

Materials and Methods

For this work, a systematic bibliographic search was performed using the research gates PubMed and Research Gate, without time or language limitations and books as a complement.

The search was performed using the following words: VWS, Van der Woude syndrome, cleft lip, cleft palate, lip pit syndrome, *IRF6*, hypodontia.

Clinical manifestations

The most frequent phenotypic traits in the VWS are the orofacial congenital anomalies that include the pits in the lower lip [6-9]. These small pits in the lower lips may appear moist due to the presence of mucous and salivary glands in these pits. They represent small fistulas that connect to the salivary glands. They can also be presented as a small amount of tissue in the lower lip [6].

Fistulas are located in the upper border of the lower lip, in any area of the red border on the mucous portion of the lip, with an anterior posterior direction. Major part of the pits is in the lip and in the mucocutaneous line with a distance of 5 to 25 mm between each other [10]. The base of the fistula can be found incorporated in skeletal muscle bundles, which fibers, in some sections, are oriented suggesting a peristaltic projection of the mucous secretion when contracted [11].

Previously described changes are associated to cleft lip with or without cleft palate, or cleft palate alone in half of the patients [9,12]. Among these, two thirds have cleft lip or cleft lip and palate and one third have only cleft palate [13,14]. The phenotypic expressions of the clefts range from incomplete unilateral cleft lip, submucous cleft palate, bifid uvula, to complete bilateral cleft palate.

Introduction

Van der Woude syndrome (VWS) is also called cleft palate, lip pits or lip pit papilla syndrome. The first case of lip pits was described by Demarquay in 1845. The name of this syndrome comes from the first scientist, Anne Van der Woude, that, in 1954, described the association between congenital pits of the lower lip and lip and palate cleft [1]. In this study, it was

According to Janku et al. [6], lip pits were present in 88% of affected individuals, being the only phenotypic manifestation in 64% of them. Cleft lips and palate occurred in 21% and in this study, penetrance was 96,7% [6].

Bilateral pits in the lower lips were registered in a family of 4 generations [15]. The combination of only cleft lip and lip pits is very rare [16].

One of the most unusual characteristics observed in VWS is the presence, in the same family, of different types of clefts, with vertical or horizontal direction [17]. When different types of clefts are present in the same patient, the term "mixed type" is used.

A recent study reported a rare case of this syndrome of a 10-year-old male patient having a single median lower lip pit and a repaired bilateral cleft lip and cleft palate, together with microstomia, hypodontia and clubbing of the left foot with syndactyly of the same foot [18].

Another symptom in VWS patients includes, besides the orofacial cleft, hypodontia [6,14]. Missing teeth are frequently the upper second pre-molars, the bottom second pre-molars and upper laterals [6,14].

Ranta and Rintala [19] analyzed microforms of VWS in cases of cleft palate. Data showed presence of hypodontia in 40,8% of cleft palate cases having conic elevations and in 24,7% of clefts without conic elevation [19].

Most problems associated with submucous cleft palate are eating disturbances of newborns, usually associated with nasal escape [20], slow development of speech, disease of the middle ear and changes in facial growth [21].

Diagnosis

VWS diagnosis can be done clinically, based on the presence of lip pits and/or other orofacial anomalies that can be together or isolated. As mentioned before, most of the development anomalies are congenital, so the clinical diagnosis can be done right after birth.

This clinical diagnosis requires a detailed examination of family members so other people with the syndrome can be identified. This is particularly important as a guide to the genetic counselling since, due to VWS penetrance, the risk of cleft in the family is high [22].

The variability in phenotypic expression must be taken into account when diagnosing patients. Clinical phenotypic variability in VWS described in literature is very vast and for the cases non-diagnosed after birth, dentists represent the front line in helping identify this syndrome. For this reason, it is important that they have some knowledge concerning phenotypic variations that can be present in affected individuals. Following this idea, the goal of the study of Lam et al. [2] was to describe the range of clinical presentations in 22 individuals with VWS to help in its diagnosis [2].

Phenotypic characteristics of VWS are essential for differential diagnosis, since there are symptoms frequently associated to VWS alone. Hypodontia é considered a typical

sign of VWS and it has been observed in 10-81% of all VWS patients [4-23], where the number of missing teeth in the maxilla is almost twice the number of the missing teeth in control groups [24].

As referred before, VWS diagnosis is primarily clinical. However, since the syndrome does not show complete penetrance, genetic tests can be done to detect mutations of the *IRF6* gene [25]. Genetic diagnosis can help in counselling of families with clefts [2,14,26-28].

Since the phenotype of this syndrome may not be easily recognized, as is the case of the submucous cleft palate that can be easily confused with normal palate at birth, it is very important the role of the dental doctor in VWS diagnosis [21].

Moreover, experts in speech therapy have also a very important role in identifying patients with minimal clinical signs, such as a sub mucous cleft palate [14,29].

Etiology

Genes involved: VWS is a disorder known for quite a long time, however, only recently its cause was identified. Almost all cases of VWS have demonstrated to be linked to a region in chromosome 1(q32-q41) known as VWS locus 1. It was in 2002, when the *IRF6* gene was cloned, that mutations in this gene were associated with the development of this pathology. *IRF6* gene is in the VWS critical region (q32-q41) and codes a regulator factor of interferon 6, being expressed in palate, teeth, hair follicles, external genitals and skin. For this reason, clinical manifestations of this pathology affect essentially these organs [30,31].

The regulator factor of interferon 6 (*IRF6*) is a protein that belongs to a family of 9 transcription factors that share a highly conserved helix-loop-helix domain of DNA binding and a less conserved domain involved in attachment to proteins. A big part of IRFs regulate the expression of interferon α or β after viral infection, but *IRF6* function was not yet established [30,31].

It is intriguing that mutations in only one gene can lead to such a variability of phenotypes. It seems that the phenotype presented by VWS patients is related with the type and location of the mutation.

Several mutations in the *IRF6* gene were found in families with VWS, showing that this is the main locus involved in this pathology.

Bocian and Walker [32] were the first to describe a deletion in chromosome 1 (q32-q41) in a VWS patient.

In 2005, a new mutation in exon 2 (region of DNA binding) of *IRF6* gene (p. Arg84Gly) was found in two brothers with VWS of a Turkish family as well as in their mother [33]. This study suggested a dominant negative effect of this mutation in both patients. Moreover, as the mother is asymptomatic, it also suggests the absence of VWS penetrance in this woman [33].

Tan et al. [34] analysed this gene in three families. This work identified a nonsense mutation and a missense mutation in

exon 9 of this gene in a family from Malaysia having five affected individuals but with different symptoms. The first mutation involves a C>T substitution in position 1234 that converts codon of arginine into a stop codon. The second mutation, 23 bp downstream of the first one, was a G>A change that leads to a shift of arginine to histidine. In this study, no mutations were found in exons 3, 4, 7 and 8 that were the most affected in other studies [34]. Still in the same work, the analysis of another family allowed to identify, in one of the descendants, a C>T substitution in the third exon that leads to change of arginine to tryptophan in position 45 of the protein (inside the DNA binding domain). However, it is possible the existence of another genetic defect, since the mother and the twin sister of the child had the same mutation, without any symptoms [34].

Moreover, Gowans et al. [35] observed that mutations in exons or splice sites were nonrandomly distributed among the nine exons of *IRF6* gene, with 92% of those mutations present in exons 4 and 7.

A recent study, identified the change of arginine to stop codon (R412X; 1234C>T) in 3 members of the same family and a change of glutamate to lysine (E404K; 1210G>A) in two other families [36].

In another case, without family history of VWS, a child having a *de novo* deletion covering the full *IRF6* gene was identified. This case of haplo-insufficiency caused failure of orofacial development but without changes in other organs. This child also presented deletion of, at least, other five genes [34]. There are other four described cases of mutation by deletion of the *IRF6* gene [32,37-39].

Birkeland et al. [40] identified three new mutations in this gene in VWS patients of a population from Honduras. In one family, VWS affected mother and daughter presented mutation p. Asn88Ile, in the DNA binding region of *IRF6* protein. In a second family, a unique mutation p. Lys101GlnfsX15 was detected in a VWS patient, that leads to change in the reading frame and premature appearance of a stop codon. The third identified mutation was p. Gln208X in exon 6 [40]. In this study, a nonsense mutation in exon 9 was also identified (p. Arg412X), that had previously been identified in Brazilian and north of Europe populations [41].

In 2013, Wu-Chou et al. [42] identified five new mutations in the *IRF6* gene: substitution A>G in codon 290 that leads to change of amino acid p. Tyr97Cys; deletion of 16 bp between codons 360-375 that results in protein change p. Gln120HisfsX24; insertion of adenine between codons 411 and 412 (p. Glu136fsX3); substitution A>C in codon 871 (p. Thr291Pro); and substitution G>A in codon 969 (p. Trp323X) [42].

Other loci were also suggested as being responsible for the high variability of clinical expression of VWS [43]. Results of this study suggest that a gene located in chromosome 17 (p11.2-p11.1), associated with *IRF6* gene, increases the probability of symptoms development in patients having changes in both genes simultaneously [43].

Another locus in chromosome 1 (p34) was also associated with the development of VWS syndrome, but the responsible gene was still not identified [44].

Leslie et al. [45] determined association between mutations in the DNA binding domain of *IRF6* and limb defects (including pterygia). These researchers identified several genes that could modify the VWS phenotype, including *FOXE1*, *TGFB3*, and *TFAP2A*. It is believed that some of these genes are part of the *IRF6* gene regulatory network [45].

Prevalence and incidence: Prevalence of VWS varies between 1:100.000 and 1:40.000 live births [3-7,14,46] being present in 2% of patients with facial clefts [2].

No significant differences seem to exist between the incidence in men and women [3-48]. However, many authors believe that there is a higher prevalence of this syndrome in women that might result from their most frequent medical appointments due to esthetical changes [49-52]. Opposite results were observed by Csiba [10] that saw that the syndrome in men is twice more frequent than in women.

VWS has been reported as having almost complete penetrance, varying between 80% and 100% [2-53].

Genetic counselling: All VWS patients should be informed about their 50% risk of having a child with cleft lip and/or cleft palate due to the type of transmission of this syndrome [54]. Due to the high penetrance of this gene, individuals that received the mutated gene will have high probability of developing the phenotype, being possible the presence of big differences in developed symptoms.

In patients with isolated cases of clefts it is essential the study of the family history for a good genetic counselling [55].

For a VWS patient, the relative risk of transmission of cleft is between 11,0% and 22,4% [3,5,6]. The relative risk of transmission of only lower lip pits or not being penetrant is 24,7% to 42,7% [3,5,6].

VWS patients rarely have clefts without pits. These cases represent a small group of patients with cleft with high risk of recurrence. It is important to emphasize the need for detailed examination of the lip pits, including microforms, in relatives with clefts, during genetic counselling [13].

According with Menko et al. [56], in patients with cleft lip and palate, a detailed exam of their lower lip must be done as well as in their relatives until the third generation [14,29].

Results

The first surgical intervention is performed by a plastic surgeon and is characterized by queiloplasty (surgery in the lip and palate). Usually, surgeries are done after the age of 3 months (always taking into consideration the hygiene of the child), starting with the queiloplasty, and when the child is 1 year old, palate surgery is done [57].

Surgeries may vary according with the type (severity) of the cleft.

The intervention of a speech therapy specialist is very important and starts in the maternity, guiding mothers on how to feed their newborns, and after that the follow-up after the cleft palate surgery, with exercises and most of all guiding parents in patients stimulation.

The child must be accompanied by a pediatrician and parents should be oriented by a member of a multi-disciplinary team, since guiding and orientation as well as trips to the hospital are frequent and patients must adhere to the treatment as much as possible [58-60]. A study from Fadeyibi et al. [61] demonstrated that patients with clefts usually present high incidence of anxiety and depression that can be more pronounced between 6 to 12 years of age.

The high incidence of hypodontia in VWS patients has direct implications on dental doctors for an early diagnosis of the syndrome for a better plan of the treatment to be applied [14].

The congenital absence of teeth can contribute to the constriction of the dental arches, especially in the maxilla, that can result in malocclusion and skeletal discrepancy between arches that might need orthodontic and orthopedic intervention.

Concerning treatment of lower lip pits, despite that, in rare cases, may be registered its spontaneous shrinking [62,63], the main reasons why patients want their excision are aesthetics implications, mucous secretion and possible uncontrollable chronic inflammations.

Treatment is focused on manifestations present in each patient and may include surgery, speech therapy, orthodontics, physiotherapy and/or orthopedics care.

Fistula repair

Handling of labial fistulas included electrocoagulation or marsupialization [50]. However, current techniques usually involve simple surgical excision. Blocked resections have also been proposed [64]. Although surgical removal of the fistula is a seemingly simple process, ideal aesthetic results are rare [65].

The average age for the initial resection surgery of the lower lip fistula was 17 months (ranging from 3.5 to 35 months) [66]. After surgery there is an incidence of mucocellular formation in the lower lip of 100% [66].

In most cases, after surgery, additional procedures are required such as secondary repair of the cleft palate, revision of the cleft lip or repair of oronasal fistula [66].

In a study by Macedo et al. [67] the paramedian pits were removed with the removal of the minor salivary glands associated with the fistula, and the contour and lip aesthetics were preserved. After 2 months follow-up, no sensory and motor lesions were observed in the lower lip or recurrence of the secretion [67].

A recent study developed a classification of lip pits to help in surgical management. This classification is based on a difficulty index in the management of lower lip pits and can help in prediction of the treatment outcome before surgery [68].

Bertin et al. [69] made an overview of the surgical techniques currently available to treat labial pits. These authors state that fusiform excision with dissection of the entire pit is still the preferred procedure since it gives good functional and aesthetic result. However, the split-lip advancement technique and the inverted T-lip reduction are also good surgical alternatives [69].

Cleft repair

Despite the significant advances in the care of patients with cleft lip and palate, there is still a lack of consensus regarding the timing and specific techniques to be used during each stage of cleft reconstruction. In no other type of surgical problems, the effect of early procedure on growth is more apparent than in the treatment of cleft lip and palate deformations. It is necessary to understand the growth and development of the craniofacial skeleton to proceed with the planning of the process [70].

In many cases, waiting for more growth can bring disadvantages. Each stage of surgical reconstruction and the age to be performed are shown in **Table 1**.

Table 1 Reconstruction stages of cleft lip and palate deformations.

Procedure	Age for intervention
Repair of the cleft lip	After 10 weeks
Repair of the cleft palate	9-18 months
Pharyngeal flap or pharyngoplasty	3-5 years or later, taking into consideration the development of speech
Maxillary reconstruction/ alveolar with bone graft	6-9 years taking into consideration the teeth development
Orthognathic cleft surgery	14-16 years in girls, 16-18 years in boys
Rhinoplasty with cleft nose	After 5 years but preferably after skeletal maturity; after orthognathic surgery when possible
Lip cleft review	At any time since the initial remodelling and maturation of the scar is complete, but better after 5 years

As described in **Table 1** the repair of the cleft lip is usually performed at about 10 weeks of age. An advantage of waiting until the 10th to 12th week of child life is to allow a complete medical evaluation of the patient so that no congenital defect goes unnoticed (for example cardiac or renal anomalies) [71]. Repairs before this age are associated with a higher incidence of maxillary hypoplasia that develops later and shows no improvement in speech. For these reasons, many surgeons perform primary repair of the palate approximately at about 9-12 months of age [71].

Before the lip repair procedure elastic tape devices are placed on the face to apply a selective external pressure, which may allow improvement of the labial and nasal position.

The basis of the repair is to create the closure with 3 layers of skin, muscle, and mucosa that approximates normal tissue

and to remove hypoplastic tissue from the edges of the cleft. Primary nasal reconstruction can be performed at the time of lip repair to reposition the displaced lower lateral cartilages and alar tissue [71].

Since lip repair is performed so early in the child's growth and development, surgeons prefer to perform minimal surgical dissection due to the effect of scars on subsequent growth of these tissues. McComb [72] described a technique that became popular, which consists in dissecting the free lower lateral cartilages of the base of the wing of the nose and the surrounding connections through an incision in the wrinkle of the base of the wing of the nose [72-75]. This allows the nose to be reinforced and/or supported from within the nostril to improve symmetry [71].

Bilateral cleft repair may be one of the major challenges of technical procedures performed in children with clefts. Lack of quality tissue and widely displaced segments are great difficulties in achieving good results, but more refined techniques and adequate mobilization of tissue flaps generally allow excellent aesthetic results [71].

There are two main goals in repairing the cleft palate during childhood: (1) waterproof closure of whole oronasal communication involving the soft and hard palate; and (2) anatomical repair of the musculature through the soft palate that is critical for normal speech development [71]. Many techniques have been described to repair the palate [76-83].

Another common technique is reverse double zeta-plasty, which attempts to lengthen the palate using a nasal and oral mucosal zeta-plasty procedure [80-84].

In any case, comprehensive interdisciplinary care is required to achieve the best results including neurosurgery, ophthalmology, orthodontics, speech therapy and other members of the craniofacial team [71,85].

Discussion

Hypodontia

According to Pedro et al. [86] these are some important issues to take into account by dentists in the treatment of patients with fissures:

1. First, the orientation of parents to the importance of oral hygiene from birth is fundamental. Dental eruption in fissured patients follows the same chronology as any child, with the observation that it is delayed. In cases of cleft including the alveolar arch, the possibility of absence of a (lateral) tooth in the cleft should be noted. The canine tooth, on the cleft side, may not erupt because of lack of bone structure. Bad postures and gyrosynversion of the jaw are common, while the jaw teeth normally behave as to the position in the arch.
2. The use of appliances in the palate from the first months of life is controversial due to the difficulties in the elaboration of the child molds and the necessity of monthly exchange of apparatus due to growth. In

consultation with the specialist (orthodontist together with the surgeon) it will be decided to use a brace before the initial surgery or even after surgery.

3. Treatment in the dental office does not differ from any other patient: endodontics and periodontics procedures are performed without differentiation.
4. In patients with a fissure that reaches the alveolar arch, surgery (for bone grafting) is recommended around 7 years of age to facilitate the eruption of the canine and to achieve continuity of the alveolar arch.
5. Regarding dental medicine, treatment of the patient with cleft concerns orthodontics, since surgeries affect maxillary growth and might lead to severe changes on maxilla position, often requiring orthognathic surgery.
6. On average, orthognathic surgery should be performed after 16 years of age and with joint planning of the buccomaxillary surgeon and orthodontist. He should install the orthodontic appliance and seek to correct the dental misalignment before surgery.

Conclusion

VWS is an inherited pathology that affects the development of the face, characterized by the presence of pits and/or fistulas in the lower lip and cleft lip and/or palatine [8,9]. These are the main manifestations of VWS and occur in 88% of affected individuals. In 64% of registered cases this was the only detected symptom [6]. It is considered the most common cleft syndrome.

It is a rare malformation with congenital association of the inferior lip fistula with the cleft lip and/or palate. It is a condition with incomplete penetrance and variable expressivity ranging from pits of the lower lip with cleft lip and palate to not visible anomalies [2].

The main gene involved in VWS development is the gene coding for IRF-6 [7,54].

VWS diagnosis is usually performed by the identification of clinical characteristics, like lip pits and/or other orofacial anomalies. Clinical diagnosis can be made soon after birth due to the presence of those changes. This clinical diagnosis also requires detailed examination of family members in order to identify other carriers of the syndrome. However, due to its incomplete penetrance and variable expression, the pathology can be unnoticed in some individuals that can be transmit the syndrome to their offspring. In these cases, genetic tests should be performed [25].

Treatment is directed at the manifestations present in each patient and may include surgery, speech therapy, orthodontics, physiotherapy and/or orthopaedic care.

The first surgical intervention is performed by the plastic surgeon and involves lip-palatal plastic surgery (cheiloplasty). This first surgical intervention is usually performed from three months of age. At one year of age palate surgery is performed [57]. Performed surgeries vary according to the severity of the fissure.

It is very important the follow-up of the child by a paediatrician and parent's guidance by members of a multidisciplinary team, since the whole process is complex and time consuming with frequent hospital visits [58-60].

In any case, comprehensive interdisciplinary care is required in order to achieve the best possible results including neurosurgery, ophthalmology, orthodontics, speech therapy, and other members of the craniofacial team [71,85].

Although rare, VWS is a syndrome that has a large list of reported cases and available research for consultation. Thus, we can perceive that there are many signs/symptoms that characterize this syndrome and, consequently, improve its early diagnosis and, in this way, establish the best possible treatment, knowing that it is not only an intervention restricted to the dentist, but to a multidisciplinary team, where each one plays a different role, all extremely important to improve patient's quality of life.

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