

Van Der Woude syndrome

Introduction

The Van der Woude syndrome is an autosomal dominant syndrome and was originally described by Van der Woude in 1954, as a dominant inheritance pattern with variable penetrance and expression, even within families. Even monozygotic twins may be affected to markedly different degrees.¹

Etiology

The syndrome has been linked to a deletion in chromosome 1q32-q41, but a second chromosomal locus at 1p34 has also been identified. The exact mechanism of the interferon regulatory factor 6 (IRF6) gene mutations on craniofacial development is uncertain. Chromosomal mutations that cause van der Woude syndrome and are associated with *IRF-6* gene mutations. A potential modifying gene has been identified at 17p11.2-p11.1. Los et al stated that most cases of Van der Woude syndrome are caused by a mutation to interferon regulatory factor 6 on chromosome I.² They describe a unique case of the two syndromes occurring concurrently though apparently independently in a girl with Van der Woude syndrome and pituitary insufficiency associated with clefts before correctly diagnosing Turner syndrome.² Typical blind fistulas of the lower lip, combined with bilateral cleft upper lip and palate. Cleft, lips, alveolar ridges and palates are among the most common birth defects. The cleft occurrence is result of interaction of multiple genes and environmental factors. Several thousand of different discovered mutations are responsible for syndromes, but still numerous phenotypic cases are of unknown genetic origin. Today easier access to genetic counseling and the lower cost of DNA testing can lead to new findings on the causes of complex malformations.³ The Interferon Regulatory Factor 6 gene has been associated with syndromic and nonsyndromic orofacial clefts. Gowans LJ et al.⁴ carried out Sanger Sequencing on DNA from 184 patients with nonsyndromic orofacial clefts and 80 individuals with multiple congenital anomalies that presented with orofacial clefts. They sequenced all the nine exons of IRF6 as well as the 5' and 3' untranslated regions. Their results show that exons 4 and 7 of IRF6 are mutational 'hotspots' in sub-Saharan Africans cohort. In Africa population, prevalent of the porofacial clefts with variable penetrance and expressivity is induced by IRF6 mutants. Their observations are relevant for detection of high-risk families as well as genetic counselling.⁴ The etiology of nonsyndromic cleft palate remains elusive, but it has been suggested that causative genes of syndromic CL/P might also contribute to NSCL/P. Recently, GRHL3 was identified as another VWS causative gene. Thus, it may be a novel candidate gene for NSCL/P. In the study by Wang Y et al, they genotyped 10 tag SNPs covering GRHL3 and performed association analysis with NSCL/P in 504 cases and 455 healthy controls. They also stated that further, the robustness of association between GRHL3 and NSCL/P should be further validated in expanded cohorts.⁵ Common to van der Woude and Popliteal pterygium syndrome syndromes is that they are autosomal dominantly inherited disorders caused by heterozygous mutations in IRF6. Busche A et al.⁶ present a three generation family with tremendous intrafamilial phenotypic variability. The newborn index patient had a diagnosis of popliteal pterygium syndrome. The

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mother presented with a classic Van der Woude Syndrome, while the maternal grandfather had Van der Woude Syndrome as well as minor signs of popliteal pterygium syndrome. In all three affected the known pathogenic mutation c.265A>G, p.Lys89Glu in IRF6 was identified. While inter- as well as intra-familial variability has been described in IRF6-related disorders, the occurrence of a typical Van der Woude Syndrome without any other anomalies as well as a diagnosis of Popliteal pterygium syndrome in the same family is rare.⁶

Epidemiology

The van der Woude syndrome affects about 1 in 100,000-200,000 individuals, in general and about 1-2% of patients with cleft lip or cleft palate have van der Woude syndrome. Differences among races have not been described.

Clinical features

Patients with Van der Woude syndrome typically present with cleft lip, cleft lip and palate, or with cleft palate only. Cleft or bifid uvula and hypernasal voice may be present as possible isolated finding in certain individuals with van der Woude syndrome. In some cases lip pits may be the only abnormality. In contrast to non-syndromic cleft lip and/or palate, this syndrome typically is characterized by bilateral, paramedian lower-lip pits. Minimal findings, such as absent teeth or trivial indentations in the lower lips, which are asymptomatic, are present within 25% of the cases with van der Woude syndrome. The blind fistulas are represented as two cavities placed symmetrically on the vermilion of the lower lip on each side of the medial plane. The fistulas may be: circular, or rarely, in the form of transverse cracks. The recesses are openings of the blind fistulae which penetrate through the m. m. orbicularis oris, with a length of 5mm - 2.5cm. Often lip pits are associated with accessory salivary glands that empty into the pits. Viscous secret is excreted from the blind fistulas, which occasionally leads to embarrassing visible discharge. Seventy percent of cleft palate cases are nonsyndromic, characterized by isolated orofacial cleft without any known syndrome. Hypodontia is present in 10-81% of affected individuals. Most upper and/or lower second premolars are frequently absent. An association of van der Woude syndrome

and taurodontism (teeth with greatly enlarged pulp chambers)⁷ and dental fusion⁸ has been reported. Other oral manifestation symptoms include syngnathia (congenital adhesion of the jaws); narrow, high, arched palate; and ankyloglossia (short glossal frenulum or tongue-tie). A patient without lip pits, oral clefts, or hypodontia but with a heart-shaped mass of the lower lip has been described.⁹ Extraoral manifestations are rare but include limb anomalies, popliteal webs and brain abnormalities. Also, accessory nipples, congenital heart defects and Hirschsprung disease have been reported. Diagnosis of van der Woude syndrome is primarily clinical, but also chromosomal analysis may be appropriate. Using tissue that is easily obtained, transported and stored, such as a piece of fingernail, chromosomal analysis technology can be rapidly conducted and performed noninvasively.

Treatment management

Computed Tomography (CT) and Fistulography of lip pits are imaging studies that are used in the treatment management of van der Woude syndrome. CT scanning of oropharynx has to be done before planning surgical intervention. Despite thorough orofacial examination, general physical examination of the cardiovascular system, genitourinary system and limbs have to be done, because sometime associated anomalies are present. Genetic counseling and examination is suggested for families with a history of van der Woude syndrome. The American Academy of Pediatric Dentistry has released guidelines for the treatment of persons with special health care needs.¹⁰ Surgical repair of cleft lip and cleft palate or other anomalies sometimes are required. In some cases, reconstruction of the lower lip is conducted by dermal allograft.¹¹ Surgical excision of lip pits is performed for cosmetic reasons or to alleviate discomfort. Improving of the lip pits appearance and reducing of the mucous discharge are achieved with the surgical excision of the lip pits. Surgical removal of salivary tracts associated with lip pits may be difficult because they may be quite long and extending into other oral structures.¹² Treatment of children with van der Woude syndrome is best undertaken by multidisciplinary team of pediatric dentists, pediatric plastic surgeons, otolaryngologists, geneticists, genetic counselors, social workers and occupational, speech and physical therapists.

The orthodontic treatment of these patients comprehends all stages of the cleft palate management, and these fistulas are sometimes surgically treated if they are larger, and if they interfere with their acceptance by the patients. Over 500 different complex genetic disorders are associated with cleft defects. Nowadays, as genetic diagnostic and therapeutic methods advance, all syndromic form involving cleft lip and cleft palate may be proved with the early detection and even preventive therapy. The potential effects on unborn children are difficult to predict, due to variable phenotype expressivity, which may be of particular concern to parents. In the prenatally characterizing of the severity of the phenotype, high-resolution ultrasonography and fetal echocardiography are useful. Cleft palate may be very often be associated with feeding difficulties, voice disorders, frequent otitis media and hearing loss. Also, pediatric patients with syndromic cleft lip and/or palate may have obstructive sleep apnea.¹³ Tehranchi A et al.¹⁴ described their case report of girl with Van der Woude syndrome. Her genetic testing showed a known putative splice site mutation (c174+1G/A) as a prime cause of Van der Woude syndrome. They conducted comprehensive orthodontic treatment, secondary bone graft, distraction osteogenesis for deficient maxilla, secondary palatoplasty and excision of lower lip pits, as well as orthodontic and prosthetic procedures.¹⁴

Differential diagnosis

When distinguishing between uncomplicated cleft lip and/or cleft palate and van der Woude syndrome, demonstration of the presence or absence of an *IRF-6* mutation can be helpful. Popliteal pterygium syndrome shares features with Van der Woude syndrome, but, in addition, is characterized by a popliteal pterygium, genital anomalies, cutaneous syndactyly of the fingers and the toes, and a characteristic pyramidal fold of skin overlying the nail of the hallux.⁶ Pterygium is a wing-like growth that spreads over the cornea. In some patients oral synechiae are present. The blind fistulas are also seen as a characteristic symptom of Rett syndrome, X-linked, sex-linked, diagnosed only within girls. Rett syndrome belongs to a group of enzymopathies. Lip pits may be associated with other disorders, including popliteal pterygium syndrome and orodigitofacial dysostosis. Medical genetics's knowledge is necessary for an understanding of oro-facial diseases and disorders and for the conduction of complete health care for medical disadvantaged and disabled children patients. Pediatric dentists in their clinical practice are able to noted, recognize and diagnose genetic disorders sequence that affect the orofacial region. Many new insights about the role of genetic factors in the development of orofacial structures and the large numbers of genes responsible for dental, oral and craniofacial disorders and diseases imposes the need for introduction of a new subject in the program of undergraduate dental students. In that way they could follow the rapid advances in genetic research and would applied new findings in the proper care of the patient's oral health.

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None.

Conflicts of interest

The author declares there is no conflict of interest.

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