Original Article

Access this article online
Website: www.afrjpaedsurg.org
DOI: 10.4103/0189-6725.129235
Quick Response Code:

Van der Woude syndrome: A review of 11 cases seen at the Lagos University Teaching Hospital

Olutayo James, Wasiu L. Adeyemo[1], Christian I. Emeka[1], Mobolanle O. Ogunlewe[1], Akinola L. Ladeinde[1], Azeez Butali[2]

ABSTRACT

Background: Van der Woude syndrome (VWS), an autosomal dominant condition associated with clefts of the lip and/or palate and lower lip pits and is caused by mutations in interferon regulatory factor six gene. It is reported to be the most common syndromic cleft world-wide. Non-penetrance for the lip pit phenotype is found in at least 10% of affected individuals and those without the pits are phenocopies for non-syndromic clefting. The aim of this study is to present the phenotypic characteristic of VWS seen at the Lagos University Teaching Hospital (LUTH) cleft clinic. **Materials and Methods:** A review of cases of patients with VWS that attended the cleft lip and palate clinic at the LUTH Idi-Araba, Lagos, from January 2007 to December 2012 was conducted. Data analyses included sex of affected patients, types of cleft, presence of lower lip pits and history of lower lip pits/cleft in the family. **Results:** A total of 11 cases were seen during the period (male = 4; female = 7). Age at presentation ranged between 1 week and 12 years, with majority (n = 10) less than 2 years of age. Bilateral cleft lip and palate (BCLP) was seen in six patients, isolated soft palatal cleft (n = 3) and unilateral cleft lip and alveolus (n = 1) and cleft of hard and soft palate (n = 1). Bilateral lower lips were presented in 10 out of the 11 cases. The mother of the only patient without lip pits presented with bilateral lower lip pits. No family history of cleft/lip pits was elicited in 10 other cases. **Conclusion:** Most of the cases of VWS presented with BCLP and lower lip pits. Non-penetrance for the lip pits was seen in one out of 11 cases. Our study emphasizes the need to screen family members in all cleft cases, especially clinically diagnosed non-syndromic cases who may be VWS with no lip pits. Future studies are required to investigate the genetic causes of this syndrome in our population.

Key words: Cleft lip, cleft palate, lip pits, Van der Woude syndrome

Departments of Oral and Maxillofacial Surgery, Faculty of Dental Sciences, College of Medicine, University of Lagos, [1]Lagos University Teaching Hospital, Lagos, Nigeria, [2]Department of Oral Pathology, Radiology and Medicine, College of Dentistry, University of Iowa, Iowa, USA

Address for correspondence:
Dr. W. L. Adeyemo,
Department of Oral and Maxillofacial Surgery, Faculty of Dental Sciences, College of Medicine, University of Lagos, Lagos, Nigeria.
E-mail: lanreadeyemo@yahoo.com

INTRODUCTION

Lower lip pit(s) and cleft lip and palate form an entity known as Van der Woude syndrome (VWS).[1] The association between congenital fistulas of the lower lip and cleft lip and/or palate was first described by Anne Van der Woude in 1954.[1,2] The world-wide disease incidence ranges from 1:100,000 to 1:40,000. VWS is the most common form of syndromic orofacial clefting and individuals with this syndrome account for 2% of all cleft cases.[3-5] VWS is inherited as an autosomal dominant disease caused by a mutation in a single gene encoding interferon regulatory factor 6 (IRF 6).[3,4] No significant difference between sexes is reported as regards the prevalence of the syndrome.[6] 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.[3,7] Approximately, 88% of VWS patients has been found to display lower lip pits, and in about 64% of cases lip pits are the only visible defect.[7]

Other features frequently associated with VWS include hypodontia, narrow arched palate, congenital heart disease, heart murmur and cerebral abnormalities, syndactyly of the hands, polythelia, ankyloglossia and adhesions between the upper and lower gum pads.[8] VWS is an autosomal dominant condition that is highly penetrant. The risk of clefts in a family with VWS increases from 3% to 5%. Furthermore, the cleft features in VWS are phenocopies for non-syndromic clefts. Therefore, it is important to clinically evaluate individuals who appear as non-syndromic clefts for

features of VWS. In addition, family history of clefts is suggestive of VWS until the features are clinically excluded.

The aim of this study is to present the phenotypic characteristic of VWS seen at the cleft clinic of the Lagos University Teaching Hospital (LUTH).

MATERIALS AND METHODS

A review all patients with features suggestive of VWS attending the cleft lip and palate clinic of the LUTH Idi-Araba, Lagos, from January 2007 to December 2012 was done. All children and their parents were clinically examined to confirm the diagnosis of non-syndromic clefts and VWS. Data included in the analysis were: gender of patients, age at presentation in the clinic, types cleft deformity, presence or absence of lower lip pits and any other associated congenital anomalies.

RESULT

A total of 400 patients presented to the cleft clinic during the study period. Age at presentation ranged between 1 week and 12 years, with majority ($n = 10$) less than 2 years of age [Table 1]. Eleven (2.7%) of these patients were presented with features of VWS. Table 1 shows the phenotypic expression of cleft and lower lip pits. Most of the patients (63.6%, $n = 7$) were females. Bilateral lower lips were presented in 10 (90.9%) out of the 11 cases. The mother of the only patient without lip pits presented with bilateral lower lip pits. No family history of cleft/lip pits was elicited in 10 other cases. Cleft phenotypes displayed in the study population included isolated cleft palate, complete unilateral or bilateral cleft lip and palate (BCLP). Six patients (54.5%) had BCLP, one patient (9.1%) had left unilateral cleft lip, one patient (9.1%) had cleft of hard and soft palate while three patients (27.3%) had isolated cleft soft palate Figures 1 and 2 show different phenotypic expression of VWS.

Table 1: Summary of phenotypic expression of clefts and lip pits in the affected family

Sex	Age at presentation	Cleft type	Lip pits	Family history of pits
M	15 months	BCLP	−	+
F	1 month	Isolated soft palatal cleft	+	−
M	2 weeks	BCLP	+	−
F	2 weeks	BCLP	+	−
F	1 month	BCLP	+	−
F	12 years	Isolated soft palatal cleft	+	−
F	1 month	BCLP	+	−
F	2 weeks	UCL (left)	+	−
M	12 months	Isolated soft palatal cleft	+	−
M	12 months	Cleft of hard and soft palate	+	−
F	1 week	BCLP	+	−

BCLP-Bilateral cleft lip and palate, UCL-Unilateral cleft lip

DISCUSSION

The present study describes the clinical features of 11 individuals with VWS that presented to the LUTH. The prevalence of VWS among cleft populations has been reported in the literature to be 2% of orofacial cleft cases.[1,9-11] In the present study, we observed a prevalence of 2.7%, which is consistent with previous reports in the literature. The female preponderance of 63.6% recorded in this study is similar to the rate previously reported by Omo-Aghoja *et al*.[12] However, this is in contrast with earlier studies, which found no discernible difference in gender distribution of affected individuals.[1] The lip pits in VWS has been reported to be mostly bilateral and symmetrically placed on each side of the midline[1,5,13] and may sometimes be the only manifestation of this syndrome as seen in the mother of one of the presented case. All patients with lip pits in this series presented with bilateral paramedian sinuses of the lower lip, placed symmetrically on either side of the midline. Bilateral pits can also be unilaterally, medially or bilaterally asymmetrical.[13] A single median or paramedian pit has also been reported and is considered as an incomplete expression of the trait.[13] None of our patients in this series presented with unilateral lip pit.

Previous studies have reported variable expression of cleft phenotypes associated with VWS. Lam *et al*.[1] reported that approximately two-thirds in their series present with either BCLP or unilateral cleft lip and palate. Jones *et al*.[14] also reported than more than 50% of cases presented with either bilateral or unilateral cleft lip and palate. In this series, approximately 55% presented with BCLP. In agreement with previous reports[1,14] expression of only cleft lip deformity is low. The overall prevalence of characteristic lower lip pits in this study cohort was 90.9%. Hence, detection of the lower lip pits is vital for the correct diagnosis of VWS in the vast majority of affected individuals. The absence of cleft in the mother and the presence of lower lip pits in the mother and absence of lower lip pits in the child support the variable phenotypic variation of VWS reported in the literature.[3,7,15]

The diagnosis of VWS is primarily clinical. However, due to non-penetrance feature of the condition, genetic



Figure 1: (a) A 1-year-old boy with bilateral lower lip pits in association with isolated cleft of the soft palate

investigations may be appropriate. Mutations in the IRF6 gene are diagnostic of VWS and will assist in the counselling of families with clefts. Management of VWS is majorly focused on surgical and cosmetic correction of clefts and lip pits.[1,5-8] All patients in this series had undergone surgical repair of their cleft, no cosmetic repair of the lip was done as the lip pit were essentially asymptomatic.

Lower lip pit(s) and cleft lip and palate form an entity known as VWS.[1] Although, hypodontia is a frequently associated anomaly, hypodontia may not be obvious at presentation due the fact that many of the patients present during pre-eruption age.

Finally, it must be stated that a clinical diagnosis of VWS requires additional examination for family members to identify other members with the syndrome due to its penetrance nature. This will also be a valuable guide for counselling since VWS is highly penetrant and family risk for clefts is increased.

CONCLUSION

Most of the cases of VWS presented with BCLP and lower lip pits. Non-penetrance for the lip pits was seen in one out of 11 cases. Although rare, VWS must always be a consideration in families in which more than one individual is found with a cleft. The sample size in this study is relatively small and may not be truly representative of VWS in Nigeria. However, this is the first study of VWS conducted in Nigerian families and it provides a foundation for further research based on larger numbers of families. In addition, future studies on the genetic aetiology of VWS in the Nigerian population should be undertaken.



Figure 2: (a) A 15-month-old boy with repaired bilateral cleft lip (no lip pits). (b) The mother of the boy in Figure 2a with bilateral lower lip pits (no cleft deformity)

ACKNOWLEDGEMENTS

We are grateful to the families who voluntarily participated in this study, the resident doctors and nurses who assisted with data collection. We are also grateful to the SmileTrain organisation that fund cleft repairs in Nigeria. This study was support by NIH/NIDCR grant 5K99/R00-DE022378-02 (AB) sub-award to the College of Medicine, University of Lagos (WLA).

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Cite this article as: James O, Adeyemo WL, Emeka CI, Ogunlewe MO, Ladeinde AL, Butali A. Van der Woude syndrome: A review of 11 cases seen at the Lagos University Teaching Hospital. Afr J Paediatr Surg 2014;11:52-5.

Source of Support: Nil. **Conflict of Interest:** Nil.