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VAN DER WOUDE SYNDROME WITH ASSOCIATED SCAPHOCEPHALY: A RARE CASE REPORT

Leonardo Bezerra Feitosa[1], Cristiano Tonello[2], Eudemara Fernandes de Holanda[3] and Nivaldo Alonso[4]

[1]MD. PhD student. Plastic and Craniofacial surgeon. Universityof São Paulo. Specialist Member of the Sociedade Brasileira de Cirurgia Plástica; [2]MD, PhD. Craniofacial Surgeon of Hospital for Rehabilitation of Craniofacial Anomalies and Professor of Medicine. University of São Paulo; [3]MD. Plastic Surgeon. University of São Paulo; [4]MD, PhD. Craniofacial Surgeon of Hospital for Rehabilitation of Craniofacial Anomalies and Hospital of Clinics of Medicine Faculty. Professor of Medicine. University of São Paulo

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Corresponding author:
Leonardo Bezerra Feitosa

ABSTRACT

The purpose of this case is to provide a descriptive report of a rare combination of Van der Woude syndrome, recurrent in three generations of the same family, in a female patient with bilateral cleft lip and palate associated with a sagittal craniosynostosis (scaphocephaly).

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INTRODUCTION

Van der Woude syndrome (VWS; OMIM 119300) is a rare disorder, inherited with an autosomal dominant pattern. Although the prevalence is around 1 per 100,000 live births, it remains the most common form of syndromic orofacial cleft, accounting for approximately 2% of all cases. The main features of the syndrome include inferior lip pits, with or without cleft lip and palate and hypodontia. Other findings are rarely associated with the syndrome, such as limb deformities, genitourinary and cardiovascular abnormalities. While there have been prior studies investigating the high variability in phenotype of VWS, no case associated with craniosynostosis has been reported so far.

CASE REPORT

A female child was born uneventfully by cesarean delivery at 38 weeks gestation with a birth weight of 3445 grams, 48cm in length and Apgar scores of 9 and 10 at 1 and 5 minutes, respectively. Diagnosed at 20 weeks of gestational age with cleft lip through morphological ultrasound. During pregnancy, the mother, G2P2, did not use any drug, tobacco or alcohol. The child's family history includes a male sibling with cleft palate, her mother was born with bilateral cleft lip and palate and pits on the lower lip (Fig. 1), previously diagnosed with Van der Woude syndrome and maternal grandmother with bilateral cleft lip and also affected by the syndrome. She was first admitted to the craniofacial surgery department at 2-months-old. On physical examination, she had a bilateral trans-foramen cleft lip and palate, a projected premaxilla and two pits in her lower lip. In addition to the findings already expected for the Van der Woude Syndrome, clinical skull abnormalitieswere observed, such as anteroposterior elongation of the head, bitemporal narrowing, a prominent forehead and a palpable ridge over the sagittal suture (Fig. 2). Sagittal craniosynostosis was confirmed by computed tomography (Fig. 3). The patient underwent a cranial vault remodeling surgery at 6-month-old. Due to the significant projection of the premaxilla, it was decided to perform lip adhesion surgery on the right side at 9 months, followed by definitive cheiloplasty and closure of the anterior palate with a vomer flap at 14 months. Finally, she underwent posterior palatoplasty at 2 years old. She remains stable over 4 years of follow-up.

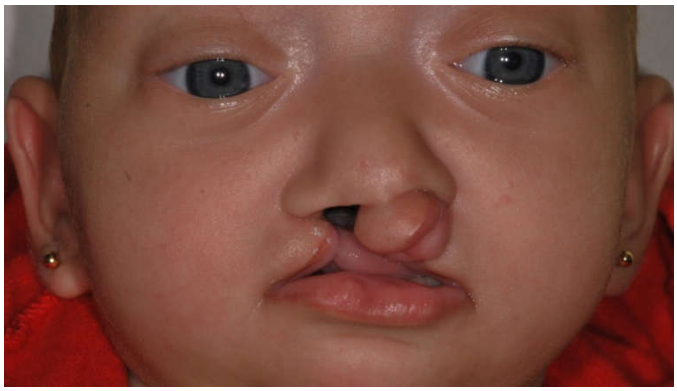

Fig.1 Girl with bilateral cleft lip and palate and pits on the lower lip

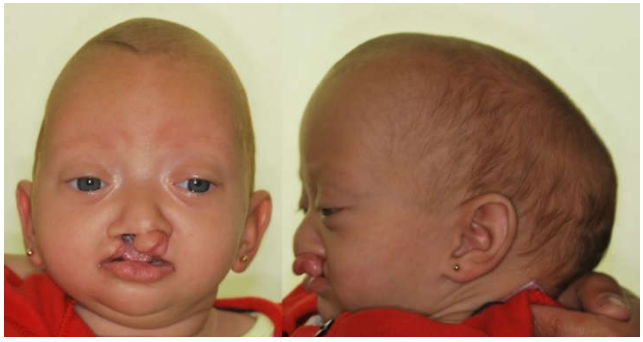

Fig. 2. Clinical findings with frontal bossing and bitemporal narrowing

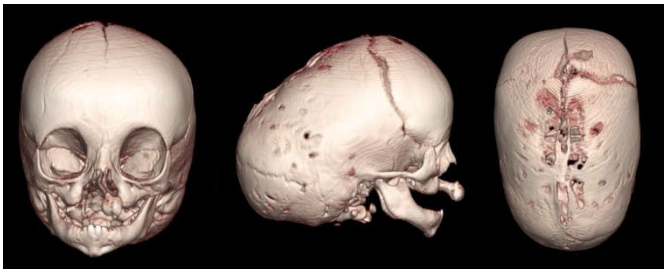

Fig. 3. CT study at 7 months of age. Imaging reveals scaphocephaly with a fused sagittal suture

DISCUSSION

Van der Woude Syndrome (VWS) is characterized by the association between cleft lip and/or palate with congenital lower lip pits. It was first reported in 1954 by Anne Van der Woude and represents the most common syndrome among individuals with orofacial cleft, affecting 0.5% to 2% of them.[1,2,3,4,5]. VWS has an autosomal dominant patternwith high penetrance ranging from 61% to close to 100% when considering individuals with lip pits and submucous cleft palate. The gene mapped to the long arm of chromosome 1 at q32 to q41 encodes interferon regulatory factor 6 (IRF 6) and its mutation have been identified as the cause this disorder, interrupting orofacial development. However, some affected individuals have shown linkage to a second chromosomal locus (VWS locus 2) which is located at 1p34[2,3,5]. The most common presentation is two pits in the lower lip vermillion, equidistant from the midline; however, they may be asymmetric or single, and centrally or laterally positioned in relation to the midline[1,2]. Lip pits are depressions of the lower lip that contain the orifice of mucous glands or minor salivary glands[2,4]. The types of pits may vary in each family member with the syndrome. Also, mild expressivity may involve unilateral or bilateral conical elevations without secretion, called microforms, associated with submucous cleft palate and bifid uvula[1,2,4,5]. Other anomalies frequently associated with VWS include 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[2,4,5]. Craniosynostosis (from cranio - cranium + syn - together + ostosis - related to bone) is the second most common craniofacial anomaly after orofacial clefts. It results from the premature fusion of one or more cranial sutures that usually inhibits the growth of the bone that is perpendicular to the affected suture.It has a prevalence of 1 in 2250 live births and occurs in all ethnic groups[6,8]. In the majority of cases (85%), the disease is isolated and nonsyndromic and, in more severe cases, it might be complicated with increased intracranial pressure, visual impairment, hearing loss, sleep disturbances, choanal atresia, or psychomotor delay with intelectual disability[6]. Premature closure of the sagittal suture is the most common form of craniosynostosis, accounting for 55% to 60% of all cases. The vast majority of patients with sagittal craniosynostosis (SC) present at birth or in early infancy with a disproportionately long, thin head shape, known as scaphocephaly. Additional, but variable characteristics may include palpable bony ridge along the fused suture, mid-vault coronal depression, frontal bossing, bitemporal narrowing, occipital bulleting, cognitive déficits and/or language disabilities. There is significant phenotypic variability in the head shape in SC and some patients with more subtle changes may be identified later in childhood[7]. Some of the craniosynostosis syndromes, such as Crouzon, Apert, Pfeiffer, Muenke, and Saethre–Chotzen syndromes, were described based on clinical findings before the era of molecular testing[2]. The first locus related to craniosynostoses, 5q35.2, was identified by positional cloning analysis in a multigeneration family with Boston-type craniosynostosis[2]. In this family, mutations in the MSX2 gene located within this locus were described[2]. Later, mutations in genes encoding fibroblast growthfactor receptors 1, 2, and 3 (FGFR1, FGFR2, and FGFR3) and transcription factor TWIST1 (TWIST1) were found in syndromic patients[2]. The majority of syndromic craniosynostoses have autosomal dominant inheritance, although the clinical presentation might be variable due to incomplete penetrance of the disease. There are a few examples of autosomal recessive syndromic craniosynostosis that include Baller–Gerold syndrome, Carpenter syndrome and Antley–Bixler syndrome without genital abnormalities caused by mutations (homozygous or compound heterozygous) in the RECQL4, RAB23, and POR genes, respectively. Also, the cranioectodermal dysplasia (Sensenbrenner syndrome) that belongs to the clinically heterogenous group of ciliopathies should be mentioned as na example of genetic heterogeneity. Mutations in the IFTI22, WDR35, WDR19, IFT52, and IFT43 genes are responsible for this clinical condition[2]. In the current patient, the diagnosis of VWS and sagittal craniosynostosis was made by the genetics and craniofacial surgery team of a hospital specializing in craniofacial anomalies in Brazil. Even with the family history already established, a genetic investigation was carried out, including karyotype tests, in order to exclude other syndromes besides Van der Woude. The evaluation of patients with multiple congenital anomalies and the reporting of rare associations is very important, since the description of component anomalies in patients with multiple congenital anomalies may help in identifying new syndromes.There are still no reports in the literature of patients with Van Der Woude Syndrome and associated scaphocephaly.

CONCLUSION

Van der Woude syndrome and isolated sagittal synostosis may be familiar, and both seem to be transmitted as an autosomal dominant pattern. However, some cases tend to be sporadic in nature. There does not appear to be a direct correlation between both disorders, although this combination is rare and not yet reported in the literature. Hence, further studies would be necessary, and this will certainly have an important contribution to genetic counseling.

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