Van der Woude Syndrome with Variable Family Presentation

Síndrome de Van der Woude com Apresentação Familiar Variável

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Van der Woude syndrome (VWS) is characterized by pits and/or sinuses in the lips, a cleft lip and/or cleft palate or both. It is an autosomal-dominant disorder with a variable expressivity and a high degree of penetration. Because of it, the clinical presentation differs widely in the affected families.[1] VWS accounts for 2% of all cleft lip and cleft palate cases, and in 64% of the cases isolated lower lip pits can be the only manifestation.[1] Hypodontia is also a common finding and rarely extraoral manifestations like congenital heart defects or hand syndactyly can be seen.[2]

Congenital lip pits are rare developmental defects, in VWS it usually occurs in the vermillion border of the lower lip. They are mostly asymptomatic, although salivary drainage or infection may occur when fistulas into accessory salivary glands are present.[2] The morphology, location and severity of the pits varies according to the gene expression.

Most cases of VWS have been associated with mutations in the *IRF6* (interferon regulatory factor 6) gene, located on chromosome 1q32-q41.

We report the case of a full-term female newborn (37+6 weeks 'gestational age; 2625 g of birth weight), delivered by vaginal birth, after an uneventful pregnancy, presented at birth with an isolated midline inferior lip pit (Fig. 1). A "V" shaped invaginated deformity of the lower lip, with soft consistency and apparently asymptomatic was noticed. Examination revealed no other congenital abnormalities. Family history of cleft lip and/or cleft palate was present in the mother, grandmother, and great-grandfather of the newborn. Breastfeeding occurred without difficulties. She was referred for a surgery consultation and genetic counseling, under suspicion of VWS. Screening of the *IRF6* gene was performed to the newborn and her mother and revealed a rare heterozygous mutation of this gene.

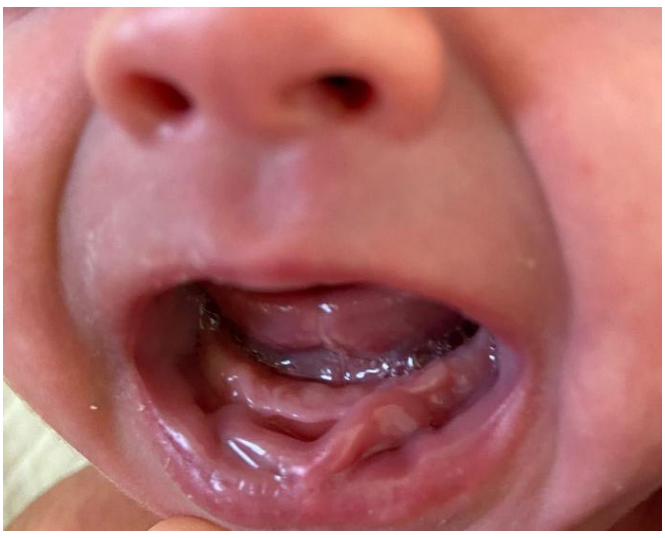

Figure 1. Isolated lower lip pits

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The IRF6-related disorders range from isolated cleft clip and palate, VWS or a more severe phenotype named popliteal pterygium syndrome (PPS), that combines VWS signs with syndactyly, nails and genital anomalies, popliteal webs, syngnathia, ankyloblepharon and others.[3] The missense mutation detected in our patient, in the *IRF6* gene – c.65T>C p. (Leu22Pro), has been only described in literature in one family with individuals clinically diagnosed with VWS and PPS.[4] Due to this lack of information, this pathogenic variant was initially considered of unknown clinical significance. However, the posterior genetic screening performed to her mother revealed the same mutation. This familial transmission reinforces its pathogenicity and, furthermore, a functional study suggests that this variant might have a negative impact on protein function.[5]

The presence of isolated lip pits, without other congenital abnormalities (including in the relatives with cleft lip/palate), makes VWS the most likely diagnosis in this family.

In this newborn, the rarity and the size of the deformity along with the family history of cleft lip/palate were helpful for the diagnostic suspicion. Identification of these syndromes is important for genetic counseling, due to the 50% risk of recurrence in the offspring.

Lip pits may need supportive/symptomatic treatment. Although commonly asymptomatic, for aesthetic reasons, intermittent drainage/infection or speech problems, surgical excision is usually performed. Feeding and speech therapy, and orthodontia treatments may also be required.[3]

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