Wildervanck syndrome: clinical case report

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ABSTRACT

Wildervanck syndrome (also known as cervico-oculo-acoustic dysplasia) is a very rare disease, characterized by the typical triad of cervical vertebral fusion or Klippel-Feil anomaly, Duane syndrome (paresis of the sixth cranial nerve), and hearing loss. Other vascular, cardiac, and musculoskeletal conditions have also been described.

In this case report, we describe a patient who met the cardinal triad and also presented additional clinical data that have not been previously reported, which contribute to broadening the disease phenotype. We have also reviewed the bibliography related to this syndrome.

**Keywords:** cervico-oculo-acoustic syndrome; Wildervanck syndrome; Klippel-Feil syndrome; hearing loss.

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INTRODUCTION

Wildervanck syndrome or cervico-oculo-acoustic dysplasia (OMIM 314600) is characterized by the presence of Klippel-Feil anomaly (fusion of cervical vertebra with butterfly vertebra), Duane syndrome (paralysis of the sixth cranial nerve with retraction of the eyeball in adduction), and conduction, sensorineural, or mixed hearing loss. In addition, other clinical features manifest with Wildervanck syndrome, such as facial asymmetry, cleft palate, bony prominences in the mandibular ramus, various vascular anomalies, heart malformations, and defects in the development of the spinal cord. In relation to radiological findings, different middle and inner ear malformations have been described, such as narrowing of the internal auditory canal, Mondini malformation, and vestigial remnants of the inner ear structures, as well as absence of the sixth cranial nerve. The first cases described date back to 1952 and, to date, 90 cases have been reported. Of these, most were female patients, with a 10:1 ratio. Because of this, it has been proposed that it has an X-linked dominant inheritance pattern, so the absence of a functional gene in the hemizygous state could cause a higher case fatality rate in male patients with the syndrome. Notwithstanding this, other types of inheritance patterns, such as autosomal dominant and polygenic, have been proposed. The case of a male patient with fusion of vertebral bodies, severe bilateral hearing loss, and cochlear dysplasia with narrow internal auditory canal has been reported in Mexico. Conventional karyotyping showed no structural or numerical alterations in any of the chromosomes.

At the moment, there is no defined locus for Wildervanck syndrome; however, in a recent report of a male patient with this syndrome, a 2 kb de novo microdeletion in the Xp26.3 region was discovered by array comparative genomic hybridization (aCGH), which cleaves a single gene in this region, the fibroblast growth factor 13 or FGF13 gene. It has been speculated that this gene is involved in embryogenesis, morphogenesis, cell growth, tissue repair, neural progenitor proliferation, neuronal migration, and growth cones. The loss or alteration of its gene structure may be associated with the lack of development of the sixth cranial nerve, the inner ear, the cervical spine, the limbs, among others.

The differential diagnosis may be intricate due to overlapping clinical manifestations with other more common syndromes, such as those described above or Goldenhar syndrome. However, hemifacial microsomia, ocular abnormalities, together with vertebral defects and the involvement of both sexes in the same proportion in Goldenhar syndrome serve to guide diagnosis.

In order to describe the typical characteristics of Wildervanck syndrome and provide new data to the phenotypic spectrum, here we describe the clinical case of a female patient who, in addition to having cervico-oculo-acoustic involvement, presented with malformation of the left upper limb and heart involvement not previously reported.

CASE REPORT

This was a 14-year-old female patient referred to the Department of Genetics with a diagnosis of multiple congenital anomalies and karyotype 46,XX,9qh+. She had a negative inherited family history and was the fourth child of non-consanguineous and healthy parents, with a normal pregnancy course with a vaginal delivery at 37 weeks of gestation. At birth, her weight and height were within normal parameters.

Her condition began at 4 months of age, with the presence of camptodactyly in the left hand, for which she underwent 2 surgeries. At the age of 4 years, she started with limitation of bilateral eye movements in adduction and convergent strabismus; she was diagnosed with Duane syndrome with amblyopia and hypermetropic astigmatism. At 5 years old, she showed signs of unilateral hearing loss and at 10 years old, she had evident thoracic scoliosis.

Her physical examination indicated she had a height of 1.47 meters (25th percentile), a weight of 46.5 kg (25th percentile), and a head circumference of 54 cm (25th percentile). She had a normal skull, low posterior capillary implantation, left hemifacial microsomia, wide nasal bridge, symmetrical eyes, right eye with severe limitation to abduction and adduction, left eye with severe limitation to abduction and mild limitation to adduction, mild enophthalmos in right eye adduction and moderate in left eye adduction. She had a short neck with limited arches of movement, short thorax, spine with scoliosis to the right, camptodactyly in left hand (Figure 1 A, B, C, D, E).

The following specialized tests were requested. Auditory evoked potentials revealed severe left hearing loss due to injury to the receptor.
The tone audiometry, speech audiometry, and tympanometry reported total deafness in the left ear with absence of cochlear reserve function and decreased middle ear function. The computed tomography (CT) of the left ear showed severe malformation of the inner ear, fusion of the bony labyrinth with vestigial remnants of the semicircular canals and cochlea (Figure 2. A).

**Figure 1.** Duane syndrome type I. A) Primary gaze with strabismus. B) Right gaze with limited abduction and moderate enophthalmos in the left eye. C) Left gaze with limited abduction and mild enophthalmos in the right eye. D) Low posterior capillary implantation. E) Camptodactyly in left hand

The echocardiogram reported mild anterior mitral valve prolapse. The magnetic resonance of the spine showed Klippel-Feil anomaly; fusion of C4 to C5 with butterfly vertebral bodies, causing dextroscoliosis (Figure 2. B and C). The kidney ultrasound did not show any structural alterations.

**Figure 2.** A) Computed tomography of the left ear. The arrow indicates the vestigial remnants of the cochlea, vestibule, and semicircular canals. B) Magnetic resonance of the cervical spine (axial section): fusion of C4-C5. C) Magnetic resonance of the spine (coronal section): scapular elevation, segmentation anomalies at the cervicothoracic level, and vertebral body deformity
DISCUSSION

Wildervanck syndrome is a rare genetic disease characterized by a phenotypic triad that includes Klippel-Feil anomaly, Duane syndrome, and congenital hearing loss.12 Here we describe the case of a female patient who met the diagnostic criteria of Wildervanck syndrome and who also had camptodactyly in the left hand as well as a structural alteration of the heart, characterized by mild mitral valve prolapse; the latter had not been previously described in other patients and, therefore, could be considered within the variable manifestations of Klippel-Feil anomaly.13 Like other sporadic cases reported in the bibliography, no family history or consanguinity were observed in this case.

Given that patients with Wildervanck syndrome have various dysmorphisms and visceral alterations, conventional karyotyping is the first diagnostic test requested to assess the chromosomal constitution, as reported in several patients, including our case.9,14

To date, a specific etiology for Wildervanck syndrome has not been elucidated; however, some candidate genes have been proposed, such as the FGF13 gene, involved in the processes of neural proliferation and migration,6 or the growth differentiation factors 3 and 6 genes (GDF3, GDF6), in which mutations associated with Klippel-Feil type 1 syndrome have been described, which are involved in the development of joint and heart malformations.13 The FGF3 and HOXA1 genes are associated with labyrinthine aplasia, which occurs during the third week of gestation; however, they are also related to other syndromes, such as labyrinthine aplasia, microtia, and microdontia (LAMM) syndrome and HOXA1 mutation syndrome, characterized by bilateral internal carotid artery aplasia, developmental delay, and gaze abnormalities.15 In our patient, the above may indicate a type of polygenic inheritance, given the joint and heart involvement together with the typical clinical features of the syndrome.

It would be advisable to consider diagnostic tests based on molecular cytogenetics or sequencing according to the published bibliography, which has shown alterations in candidate genes, FGF13, and microdeletion in the Xp26.3 region.6,10

The management of these patients includes surgical procedures in cases of structural alterations that compromise function and physical therapy to reduce the limitation caused by bone defects, as well as a multidisciplinary follow-up, depending on the needs of each patient, to guide them in terms of self-care.12

CONCLUSIONS

In patients with Klippel-Feil anomaly, it is important to purposefully investigate additional musculoskeletal alterations and heart malformations, as well as to perform ear and eye assessments to rule out Wildervanck syndrome. The integration of the typical triad of the Wildervanck syndrome allows a timely diagnosis and favors an early intervention, which will have an impact on patients' quality of life.

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