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Wildervanck Syndrome – a review of the "triad" and its variations

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Summary

The first case of cervico-oculo-acoustic (COA) syndrome was described by Wildervanck in 1952. The "Wildervanck syndrome" is characterised by the triad of fused cervical vertebrae (Klippel-Feil anomaly), retracted eyeballs with sixth nerve palsy (Duane syndrome) and congenital deafness. Since that original paper, there have been further, rare reports mentioning this triad, either completely or incompletely. However, there has been scattered and sparse reports of additional variations of the syndrome besides the triad reported in previous publications. Herein, we present a short review of the available literature on this entity, while reporting a further case of the syndrome, with the aim of compiling and discussing the phenotypic, genetic, clinical and radiological spectrum of the disorder.

Keywords: *Wildervanck, Klippel-Feil, mirror movements, hearing loss, Duane syndrome, Sprengel shoulder, neuroschisis*

Key messages

We emphasise collation of the yet known manifestations of this rare genetic disorder so as to aggregate our knowledge of this syndrome. This will add to the sparse literature regarding the triad and the additional manifestations of this uncommon disorder.

Introduction

Wildervanck syndrome, also known as cervico-oculo-acoustic syndrome, constitutes a triad of Klippel–Feil anomaly (fusion of >1 cervical vertebra), Duane retraction syndrome, and hearing deficits with a ten-fold female to male preponderance [1].

The KF anomaly essentially comprises a variety of bony deformities of the cervical spine, usually involving fusion, which clinically appears as a short, webbed neck with a limited range of head and neck movements and a low posterior hairline [2].

Retraction syndrome comprises narrowing of the palpebral fissure and eyeball retraction on adduction with widening of the palpebral fissure on attempted abduction and apparent lateral rectus palsy. Duane pointed that there is often limitation of abduction (more marked), as well as limitation of adduction [2].

The hearing loss in Wildervanck syndrome may be sensorineural, conductive, or mixed, arising from a variety of malformations in the auditory apparatus [3].

Almost 90 cases of this disorder have been reported in the medical literature since its original description in 1952, only half of them manifesting the complete classic triad. Hence, there have been phenotypic variabilities in 50% of the patients. The Online Mendelian Inheritance in Man (OMIM) database has estimated the prevalence to be <1/1,000,000. Some reports, in fact, state that nearly one percent of hearing impaired females may be affected by Wildervanck syndrome [4].

We herein discuss one of our patients diagnosed with this disorder, and retrospectively review the literature for variability in the manifestations of this rare genetic disorder. This will help clinicians diagnose, investigate, prognosticate and offer possible treatment for these patients.

Case history

An 11-year-old Indian-origin female, born out of a non-consanguineous marriage, with history of developmental delay in the form of delayed speech acquisition and below par scholastic performance in school, presented with her father, who for last 3 years had noticed involuntary symmetric movements simultaneously appearing on the contralateral side whenever she performed voluntary movement on one side. He gave a childhood onset history of her being the shortest in her class with poor speech output, diminished hearing and reduced neck movements. There was no family history of such congenital anomalies or other neurological disorders.

On physical examination, vital signs were stable, her anthropometric measurements revealed short stature (height 118 cm; <3rd percentile), weight 30.5 kg, head circumference 50 cm, short neck with restricted movements, abnormally high placed right scapula (fig. 1, panel D) and a low hairline. Facies was noticeable for micrognathia, abnormal dentition and small, low set external ears.

Extraocular movements were significantly restricted, more for abduction than adduction, on both sides and the patient

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had to turn her head for saccadic and pursuit movements (video 1). There was no associated ptosis, and the pupils were bilaterally equal and reactive with normal vision and fundus.

Mirror limb movements were apparent in the upper limbs, most obviously in movements of the fingers where involuntary symmetrical movements of the contralateral hand simultaneously appeared on attempted voluntary action of one side (video 2).

Rest sensory, motor, cerebellar, and gait testing was unremarkable.

Investigations revealed normal visual evoked potentials, and audiometric tests revealed mild bilateral conductive hearing loss. X-rays were suggestive of elevation of the scapula on the right side (Sprengel's deformity) and fused cervical vertebrae (KF anomaly). Routine blood test results were within normal limits, including levels of growth hormone, and thyroid and parathyroid hormones An ultrasound scan showed normal bilateral kidneys, bladder and urethra. The electrocardiogram was also normal.

Magnetic resonance imaging (MRI) of the brain was normal. MRI of the cervical spine showed non-segmented and fused C2-C3 cervical vertebrae and early signs of C5-C6 vertebral fusion (fig. 1, panels A and B). Cervico-medullary neuroschisis (fig. 1, panels C and E) was evident in axial sections of the cervical cord.

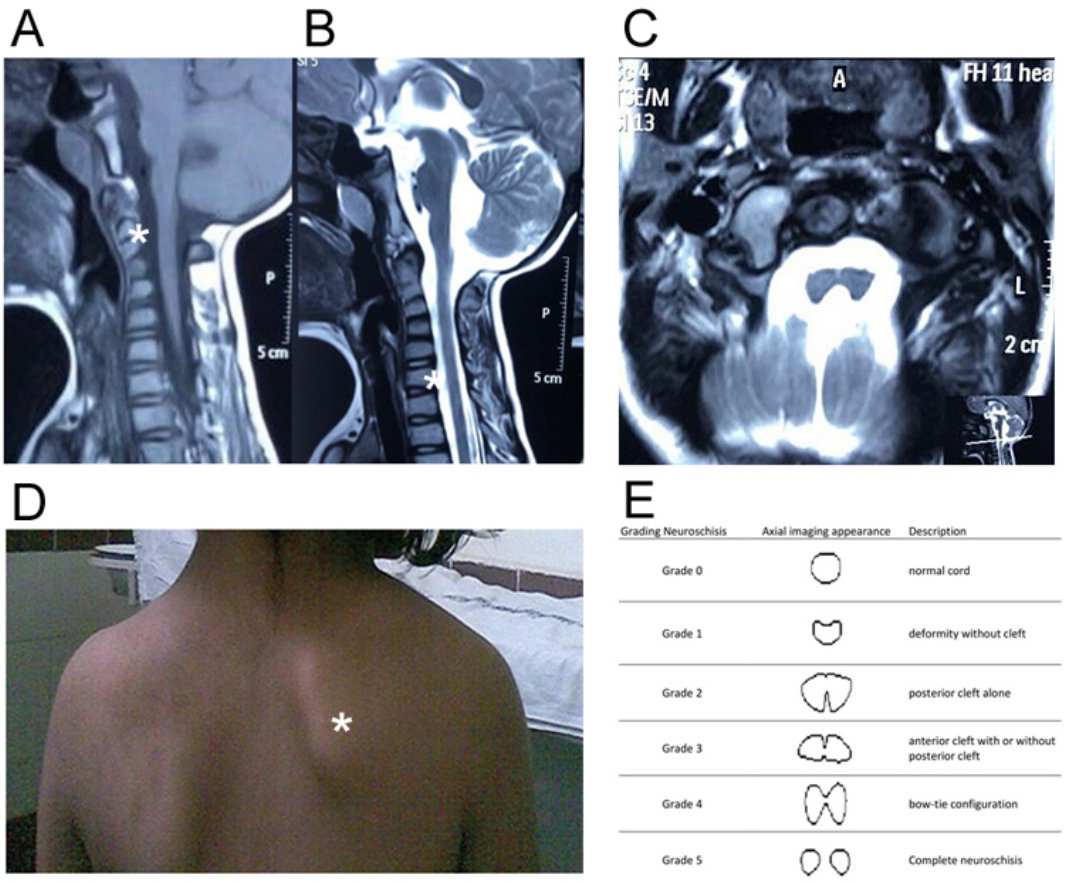
Thus, our patient had features of short stature, mandibular hypoplasia, Sprengel deformity on the right, components of the KF anomaly, bilateral horizontal gaze defects, bilateral conductive hearing loss, subnormal intelligence, mirror limb movements and neuroschisis of the cervical cord, leading to the diagnosis of cervico-oculo-acoustic or Wildervanck syndrome.

Genetic testing could made due to non-availability and financial constraints. The parents were counselled and reassured about the condition, and the child was regularly followed up to look for progression.

Discussion

Wildervanck syndrome, characterised in its prototypic form by the co-existence of the Klippel-Feil anomaly (congenital cervical vertebral fusion), Duane syndrome and congenital hearing loss, is a rare developmental defect of the cerebellum and brainstem and a segmental anomaly of the vertebrae [5]. However, various authors at different times have described certain additional features and variations in cases of this syndrome. (table 1)

Figure 1: Pictures of the case. A and B: MRI T1, T2 images of the cervical spine showing partial fusion of C2-C3, C5-C6 (asterisks) and partial occipitalisation of atlas. C: Grade 4 Neuroschisis of the cervicomedullary cord. D: Sprengel deformity of the right side (asterisk). E: Grading of cervico-medullary neuroschisis [14].



Genetics

Though the genetic transition of this disorder is not very precisely known, Wildervanck syndrome has been primarily observed in females (almost exclusively), and an X-linked dominant inheritance with high lethality in hemizygous males has been proposed [6]. Besides, dominant or polygenic inheritance with limitation to females [7], as well as multifactorial aetiology [1], cannot be excluded. Recently, occurrence of this syndrome and its components are being considered to be due to aberrancy of axonal guidance and neuronal migration in the developing nervous system [8].

Mutations in the human ROBO3 transmembrane receptor protein were found to cause structural brainstem alterations, deficient pyramidal and lemniscal decussations, and horizontal gaze palsy owing to ocular motor dysfunction. Missense mutations of the *CHN1* gene (encoding protein alpha-2-chimaerin), truncating mutations of homeobox gene (*HOXA1*), and aberrations in *DCC* and *GDF6* genes have been previously implicated in causation of various features of the syndrome. However, most recently, mutations of *FGF13* gene locus at Xq26.3, encoding a 216-amino acid protein that acts intracellularly in neurones throughout brain development, might cause Wildervanck syndrome [9].

An environmental aetiology, the so called "subclavian artery supply disruption sequence" (SASDS), an early embryonic interruption of blood supply in the subclavian arteries, the vertebral arteries and/or their branches, has also been hypothesised to produce predictable patterns of defects inducing a complex Wildervanck's syndrome-like phenotype [10].

Phenotypic components

Klippel-Feil (KF) anomaly is a bony anomaly clinically characterised by short neck, limitation of neck movements and a low hairline. Although the primary defect is fusion of two or more cervical vertebrae, three types of KF dysostosis are described [11]:

- KF type I: fusion of cervical and upper thoracic vertebrae,
- KF type II:isolated fusion of cervical vertebrae,
- KF type III: fusion of cervical vertebrae along with with fusion of lower thoracic and lumbar vertebrae.

Pterygium colli, scoliosis and Sprengel deformity were observed in several cases, along with short stature, microcephaly, facial asymmetry, mental retardation, and cleft palate [12]. Other spinal deformities (hemivertebrae, spina bifida occulta, fusion of the ribs, absent ribs, kyphosis) may coexist.

Duane syndrome, also called Stilling-Türk-Duane syndrome, is caused by aplasia/hypoplasia of the sixth cranial nerve nucleus with aberrant generation of the third nerve in many, but not all, cases [13], resulting in a combination of restricted eyeball abduction and retraction of eyeball on attempted adduction. This abducens paralysis is mostly unilateral, but may be bilateral in approximately 17% of the cases [7]. In addition to nuclear hypoplasia (neurogenic), underlying muscle fibrosis of the lateral rectus (peripheral) may also be seen [1]. Besides retraction syndrome, bilateral sixth nerve palsy [6], pseudopapilloedema [2] and heterochromia iridis are other reported manifestations.

The *hearing loss* may be conductive, sensorineural, or mixed in Wildervanck syndrome. Although no otological abnormality is characteristic, patients with this syndrome may have malformations of the external acoustic meatus, external auditory canal, ossicles and bony labyrinth [3, 6].

Mirror movements can be defined as movements wherein voluntary (active) movements in one extremity are concomitantly mimicked by involuntary (passive) movements in the other, with a central plane of symmetry [14]. Failure of pyramidal decussation in the cervical cord, leaving a direct connection between the motor cortex of each hemisphere and its respective contralateral spinal cord, is the best possible explanation [15]. Mirror movements are seen not only in Wildervanck syndrome, but are also observed in majority of KF syndrome patients, affecting mostly the hands, rarely the entire upper extremity and even the legs, tending to worsen with fatigue, and showing varying degrees of voluntary suppression [14].

Treatment [4]

Treatment of Wildervanck syndrome is symptomatic and supportive, with systematic and comprehensive planning for each affected child individually. These therapies require regular monitoring for neurological complications, surgical repair of certain abnormalities such as middle ear surgery for conductive hearing loss, ocular surgery for restricted eye movements, spine surgery for cervical cord compression or vertebral instability, and hence may warrant a coordinated team of paediatricians, neurologists, orthopaedic specialists, ophthalmologists, otologists, cardiologists and/or surgeons.

In addition, specialised hearing aids may benefit some individuals with hearing impairment. Physical therapy, spe-

Table 1: Varied reported manifestations of Wildervanck syndrome [1–15].

Musculoskeletal	**Klippel Feil anomaly*** Short stature, microcephaly, facial asymmetry, pterygium colli, scoliosis, Sprengel deformity, kyphosis hemivertebrae, absent ribs, fusion of the ribs, hypoplastic frontal sinus, webbed digits
Auditory	**Sensorineural, conductive, or mixed hearing loss***, Absent/deformed auricles, dysplasia of the middle or external acoustic meatus, preauricular tags, deformed ossicles, severe inner ear anomalies, bilateral Mondini deformities, anomalies of the vestibular and bony labyrinth, absent semicircular canals, absent or constricted internal auditory meatus.
Ocular	**Duane syndrome*** Pseudopapilloedema, bilateral lateral rectus palsy, epibulbar epidermoids,, subconjunctival lipoma, nystagmus, heterochromia iridis
Neurological	**Cervicomedullary neuroschisis*** Mirror movements, lower brainstem malformations, Chiari malformation, cerebellar hypoplasia, Dandy Walker syndrome, basilar invagination, occipital meningocele, triventricular hydrocephalus, mental retardation, crocodile tears, abducens paralysis
Visceral	Cleft palate*, agenesis of the internal carotid artery, absent or horse-shoe kidney.

* Denotes the most widely encountered entity in each category.

cial education, other medical, social, and/or vocational services are beneficial. Genetic counselling is recommended in families of affected individuals.

Supplementary material:

Video, recorded and published with the patient's consent, available on https://sanp.ch/online-only-content/post/wildervanck-syndrome-a-review-of-the-triad-and-its-variations.

Disclosure statement

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