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Wildervanck's syndrome and mirror movements: a congenital disorder of axon migration?

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Abstract

Cell outgrowth and migration in the developing nervous system result from guidance cues, whose molecular bases and clinical correlates are only partly known. We describe a patient with brain stem malformation, paroxysmal left sided lacrimation when eating ("crocodile tears") and mirror movements in addition to Wildervanck's cervico-oculo-acusticus (COA) syndrome, which encompasses Klippel–Feil anomaly, congenital hearing loss and Duane's syndrome. The unique symptom constellation has not been reported in that combination before and can be discussed in

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the context of congenital disordered axonal migration based on dysfunction of signalling pathways. However, mutations in some recently discovered genes, associated with single findings also present in our patient, were not found. Therefore, we suppose that the disturbance of an as yet unknown regulatory factor may explain the congenital malformation syndrome of our patient. In general, only a few human disorders have yet been found to result from defects in axon guidance. Nevertheless, disorders of axon guidance can certainly be regarded as a new category of neurodevelopmental disorders.

Keywords

Wildervanck's syndrome; Mirror movements; Duane syndrome; Klippel–Feil syndrome; Axonal disorder

Case report

A 36-year-old male storage worker of Turkish origin presented with subacute left facial weakness. From childhood he had experienced left-sided lacrimation while eating. There was no family history of neurological disorders or congenital anomalies. His parents were unrelated. On examination he measured 152 cm and showed aplasia of the right pectoralis muscle. His neck was short and its motion restricted with slight right torticollis and a low hairline. Hearing tests revealed 80 db hearing loss in the right ear. Ocular motor exam showed bilaterally impaired abduction without diplopia as well as narrowing of the palpebral fissures on adduction, corresponding to Duane's syndrome (Fig. 1a and Supplementary video). Whenever the patient performed distal voluntary movements on one side, involuntary mirror-symmetric movements simultaneously appeared on the contralateral side. This was most obvious in the fingers, but also occurred with wrist, forearm and toe movements (Supplementary video). Apart from left facial weakness, his cranial nerves, muscle strength, reflexes, coordination, sensory findings and higher cerebral functions were normal. X-ray showed elevation of the right scapula (Sprengel's deformity), extensive right convex thoracic scoliosis, fused cervico-thoracic vertebrae (Klippel–Feil anomaly) and failed fusion of the posterior arch at S1. CT-scans revealed bilateral cochlear dysplasia and a median split anomaly of the occipital bone. MR-imaging demonstrated neuroschisis with a dorsal cleft of 5 cm length affecting the upper cervical chord (Fig. 1b). Focal transcranial magnetic stimulation of the motor cortex hand area was performed with a figure-of-eight coil 5 cm lateral from the vertex. On recording from both thenars, the patient showed bilateral simultaneous EMG responses of short latency, irrespective of which hemisphere had been stimulated, suggesting the presence of a variant, ipsilateral corticospinal pathway with fast, monosynaptic conduction [1]. Within 2 weeks of hospitalisation, the patient's left facial palsy which was considered idiopathic, improved with conservative treatment and subsequently cleared.

The findings may be summarized as an extended variant of Wildervanck's cervico-oculo-acoustic (COA) syndrome [2], which encompasses Klippel–Feil anomaly, congenital deafness and Duane's syndrome [3]. Its co-occurrence with spinal vertebral malformations, cervicomedullary neuroschisis, congenital left-sided paroxysmal lacrimation ("crocodile tears" [4]) and mirror movements has not been reported before [5, 6] and may be discussed with respect to disorders of axonal guidance and neuronal migration in the developing nervous system [7]. As to aberrant ocular motor or corticospinal axon pathfinding some genes were identified recently: the human *ROBO3* transmembrane receptor protein was found to be essential for the regulation of midline crossing in the hindbrain and spinal cord. Patients exhibiting mutations in the *ROBO3* gene suffer from a multisystem disorder including structural brainstem alterations with absent pyramidal and lemniscal decussations

and ocular motor dysfunction resulting in horizontal gaze palsy [8]. Missense mutations of *CHN1*, encoding the signalling protein α -2-chimaerin and previously implicated in the pathfinding of corticospinal axons in mice, were associated with aberrant innervation of the extraocular muscles causing Duane's retraction syndrome [9]. Truncating mutations of the homeobox *HOXA1* gene area disrupt brainstem and inner ear development resulting in horizontal gaze abnormalities, deafness and facial weakness [10]. Congenital mirror movements may be associated with mutations in the *DCC* gene, a diffusible extracellular receptor essential for guiding axons to cross the body's midline [11]. Interestingly, mutations in the *GDF6* gene, a growth differentiation factor, are associated with vertebral segmentation defects or mirror movements in Klippel–Feil syndrome [12]. To identify a genetic aetiology, DNA from saliva was extracted using purifier solution (DNA Genotek®, Canada) and amplified. We sequenced the coding exons and intron–exon boundaries of *ROBO3* [8], *CHN1* [9], *HOXA1* [10], *DCC* [11], and *GDF6* [12] without revealing mutations. In summary, the disturbance of an as yet unknown regulatory factor may explain this unique congenital malformation syndrome and emphasizes the importance of neuroimaging and genetic techniques to elicit such human disorders in the future.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

1. Danek A. The challenge of axonal path-finding. *Strabismus*. 2006; 14:95–99. [PubMed: 16760115]
2. Wildervanck, LS. The cervico-oculo-acusticus syndrome. In: Vinken, PJ.; Bruyn, GW.; Myrianthopoulos, NC., editors. *Congenital malformations of the spine and spinal cord. Handbook of clinical neurology*. Vol. 32. North Holland Publishing Co; New York: 1978. p. 123–130.
3. Duane A. Congenital deficiency of abduction, associated with impairment of adduction, retraction movements, contraction of the palpebral fissure and oblique movements of the eye. 1905. *Arch Ophthalmol*. 1996; 114:1255–1256. [PubMed: 8859088]
4. Ramsay J, Taylor D. Congenital crocodile tears: a key to the aetiology of Duane's syndrome. *Br J Ophthalmol*. 1980; 64:518–522. [PubMed: 7426566]
5. Balci S, Oguz KK, Firat MM, Boduroglu K. Cervical diastematomyelia in cervico-oculo-acoustic (Wildervanck) syndrome: MRI findings. *Clin Dysmorphol*. 2002; 11:125–128. [PubMed: 12002143]
6. Royal SA, Tubbs RS, D'Antonio MG, Rauzzino MJ, Oakes WJ. Investigations into the association between cervicomedullary neuroschisis and mirror movements in patients with Klippel–Feil syndrome. *AJNR Am J Neuroradiol*. 2002; 23:724–729. [PubMed: 11950676]
7. Engle EC. Human genetic disorders of axon guidance. *Cold Spring Harb Perspect Biol*. 2010; 2:a001784. [PubMed: 20300212]
8. Jen JC, Chan WM, Bosley TM, et al. Mutations in a human *ROBO* gene disrupt hindbrain axon pathway crossing and morphogenesis. *Science*. 2004; 304:1509–1513. [PubMed: 15105459]
9. Miyake N, Chilton J, Psatha M, et al. Human *CHN1* mutations hyperactivate alpha2-chimaerin and cause Duane's retraction syndrome. *Science*. 2008; 321:839–843. [PubMed: 18653847]
10. Tischfield MA, Bosley TM, Salih MAM, et al. Homozygous *HOXA1* mutations disrupt human brainstem, inner ear, cardiovascular and cognitive development. *Nat Genet*. 2005; 37:1035–1037. [PubMed: 16155570]
11. Srour M, Riviere JB, Pham JMT, et al. Mutations in *DCC* cause congenital mirror movements. *Science*. 2010; 328:592. [PubMed: 20431009]

12. Tassabehji M, Fang ZM, Hilton EN, et al. Mutations in *GDF6* are associated with vertebral segmentation defects in Klippel–Feil syndrome. *Hum Mutat.* 2008; 29:1017–1027. [PubMed: 18425797]

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Fig. 1.

a Findings on right lateral gaze (*top*), gaze straight ahead (*center*), and left lateral gaze (*bottom*): bilateral limitation of abduction with concomitant narrowing of the palpebral fissure of the adducting eye (Duane syndrome type III). **b** Magnetic resonance imaging demonstrates the neuroschisis with a dorsal cleft of the upper cervical cord. The image series starts at the level of the medulla (*uppermost left image*: pyramids and olives)