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Case study

Early-onset or rapidly progressive scoliosis in children: Check the eyes!

M. Kurian [a,*,g], C. Megevand [a,g], R. De Haller [b], L. Merlini [c], C. Boex [d], A. Truffert [d], A. Kaelin [e], L. Burglen [f], C.M. Korff [a]

[a] Pediatric Neurology, Child and Adolescent Department, University Hospitals, Geneva, Switzerland
[b] Ophthalmology, University Hospitals, Geneva, Switzerland
[c] Radiology, University Hospitals, Geneva, Switzerland
[d] Neurology, University Hospitals, Geneva, Switzerland
[e] Pediatric Orthopedic Surgery, University Hospitals, Geneva, Switzerland
[f] AP-HP, Department of Genetics and Reference Center for Cerebellar Malformations, Armand Trousseau Hospital, Paris, France

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ABSTRACT

Horizontal gaze palsy with progressive scoliosis (HGPPS) is a rare autosomal recessive disorder characterized by the absence of conjugate horizontal eye movements, and progressive scoliosis developing in childhood and adolescence, caused by mutations in the *ROBO3* gene which has an important role in axonal guidance and neuronal migration. We describe two female children aged 12 years and 18 months, with progressive scoliosis, in whom the neurological examination showed absent conjugate horizontal eye movements, but preserved vertical gaze and convergence. Cerebral Magnetic resonance imaging findings included pontine hypoplasia, absent facial colliculi, butterfly configuration of the medulla and a deep midline pontine cleft, while Diffusion tensor imaging (DTI) maps showed the absence of decussating ponto-cerebellar fibers and superior cerebellar peduncles. Somatosensory and motor evoked potential studies demonstrated ipsilateral sensory and motor responses. The diagnosis was confirmed by the identification of biallelic mutations in the *ROBO3* gene.

1. Introduction

Horizontal gaze palsy with progressive scoliosis (HGPPS) is a rare autosomal recessive disorder characterized by the absence of conjugate horizontal eye movements, preservation of vertical gaze and convergence, and progressive scoliosis, developing in childhood and adolescence. The syndrome includes a distinctive brain stem malformation and defective crossing of brain stem neuronal pathways.[1] The gene involved encodes the protein ROBO3, which plays a role in axonal

* *Corresponding author*. Pediatric Neurology, Hôpital des Enfants, 6 Rue Willy Donzé, 1211 Genève 14, Switzerland. Tel.: +41 22 382 45 72; fax: +41 22 382 54 89.
E-mail address: mary.kurian@hcuge.ch (M. Kurian).
[g] Kurian M and Megevand C contributed equally to the work.
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guidance mediating major fibers crossing the midline during embryogenesis of the spinal cord.[2] A systematic examination of the oculomotricity in young patients presenting with a rapidly progressive scoliosis may lead to early diagnosis which enables precise genetic counseling on recurrence risk and prenatal testing. We report two patients diagnosed with HGPPS at the age of 12 years and 18 months respectively, with bi-allelic mutations in the *ROBO3* gene.

2. Case 1

A twelve year-old girl of Eastern European (Kosovar) origin, known for a progressive scoliosis was admitted to our hospital for a multidisciplinary evaluation, before elective corrective orthopedic surgery. Pregnancy was uneventful and delivery was at term. Her psychomotor development was normal. Thoracic cyphoscoliosis was diagnosed at the age of seven years, initially managed with conservative methods (corset), without improvement. She progressively developed severe dorsal pain, in parallel with an increasing spine curvature. She was the fourth of five siblings of healthy parents who denied any history of consanguinity. The family history was unremarkable with respect to scoliosis and neurological diseases. On admission, the physical examination showed marked left thoracic scoliosis (curve T4-T12, Cobb's angle 125°) with left truncal translation and major vertebral and costal congenital malformations. Neurologic examination showed symmetric and reactive pupils, no limitation of visual fields, the examination of ocular motricity revealed preserved vertical gaze and convergence, but absent conjugate horizontal eye movements bilaterally. The rest of the neurological examination including the examination of cranial nerves V, VII, and VIII–XII remained normal. The patient neither showed mirror movement nor bimanual syncineses. The neuro-ophthalmologic examination revealed a left microstrabismus, anisometropic and strabismic amblyopia of the left eye, intact visual fields by confrontation and normal pupillary reactions. Ocular motility testing showed a severe impairment of conjugate horizontal eye movements to either side and synergistic convergence on abduction attempts of either eye. Vertical gaze movements and convergence were normal. A dysconjugate and irregular pendular nystagmus of low amplitude and high frequency was present. The vestibulo-ocular reflex induced by rotation of the head was present in the adducting eye (left eye by rotation to the left, right eye by rotation to the right), while no movement was present in the abducting eye. Conventional brain MRI 1.5 T (axial T2-weighted, coronal FLAIR and 3D SE T1-weighted) images of the brainstem showed a depressed floor of the fourth ventricle, a hypoplastic pons, absent facial colliculi, and anterior and posterior clefts of the pons and medulla oblongata (Fig. 1). Diffusion tensor imaging (DTI) color maps demonstrated the absence of decussating ponto-cerebellar fibers and superior cerebellar peduncles (absence of the midbrain "red dot") (Fig. 2), while fiber tract reconstruction showed separated pyramidal tract fibers and absence of the ventral segmental decussation (Fig. 3).

Somatosensory and motor evoked potential studies demonstrated ipsilateral sensory and motor responses. Sensory evoked potentials (SEP) were measured for median nerve stimulation (3.1 pps, 200 μs pulse duration; VikingSelect™, San Diego, CA, USA). Responses to 1000 stimuli were averaged to determine the latency of the primary somatosensory cortical responses (Filters: 3.2–1600 Hz). The response was observed on the left hemisphere for the left median nerve stimulation (N20: 20.92 ms), but not observed clearly on the left or the right hemisphere for the right median nerve. Using lateralized transcranial magnetic stimuli during a slight voluntary activity of both abductor digiti minimi (ADM) muscles, motor evoked potentials were elicitable from the hand ipsilateral to the stimulated hemisphere.

Direct sequencing of the *ROBO3* gene revealed a c.2108G > C homozygous mutation on exon 14 that leads to an Arginine substitution by a prolin (p.Arg703Pro) in the Fibrinonectin type III protein domain. Her father was shown to be heterozygous

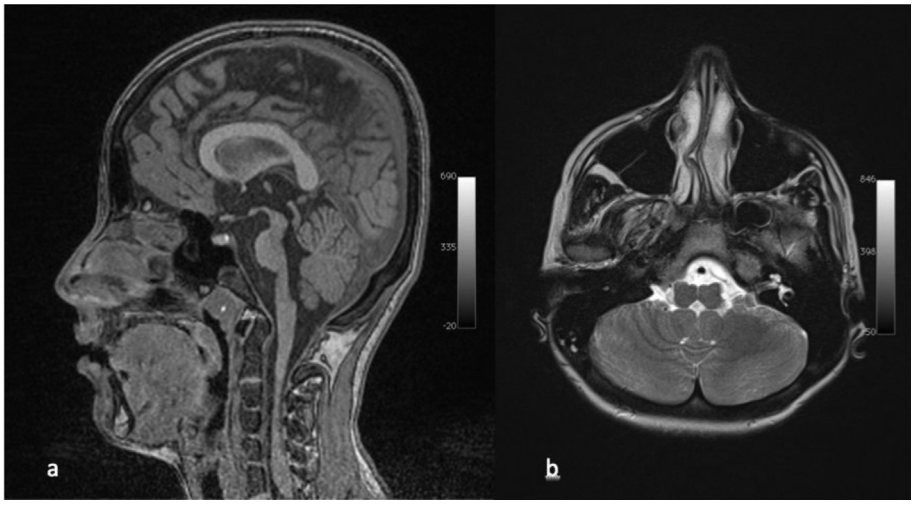

Fig. 1 – Conventional MRI: (a) T1-weighted 3D sagittal images demonstrate the hypoplastic pons and medulla, (b) Axial T2-weighted slices show a prominent midline cleft and the resulting characteristic "butterfly" configuration.