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Two siblings with horizontal gaze palsy and *ROBO3* gene mutation: A double case study

[1]Sibgatullah Ali Orak, [2]Mustafa Erdogan, [1]Celil Yilmaz, [1]Asli Kubra Atasever, [1]Cisil Cerci Kubur, [1]Muzaffer Polat

[1]Department of Child Neurology and [2]Department of Ophthalmology, Manisa Celal Bayar University, Manisa, Turkey

Abstract

Horizontal gaze palsy along with progressive scoliosis (HGPPS) is rare and autosomal recessive disease related to the mutations in the *ROBO3* gene located on chromosome 11q23-25. We present here two siblings from parents of consanguineous marriage, who were diagnosed with bilateral horizontal gaze restriction and scoliosis associated with homozygous mutation within *ROBO3* gene and at the same time having neuroimaging findings. With HGPSS's typical findings, we detected a homozygous c.1366G> T (p.Gly456Ter) variant in the *ROBO3* gene in our patients. HGPPS should be confirmed by *ROBO3 gene* analysis, and the brain MRI may be the first diagnostic technique.

Keyword: ROBO3, genetic, gaze palsy, progressive scoliosis, children

INTRODUCTION

Horizontal gaze palsy along with progressive scoliosis (HGPPS) is a rare and an inherited autosomal recessive disease. HGPPS was first detected in 5 children of 2 families by Dretakis and Kondoyannis in 1974.[1] The disorder is related to the mutations within *ROBO3* available in chromosome 11q23-25.

Function loss develops due to the mutation in this gene, and has been was shown that the cortico-spinal and dorsal colon medial lemniscus pathways were not crossed.[2] HGPSS presents with congenital horizontal gaze limitation where vertical gaze is preserved; there is progressive scoliosis that developed since childhood. In this syndrome brain magnetic resonance imaging (MRI) typically shows medulla's butterfly-like configuration, a flattened pontine tegmentum, markedly reduced both pons and medulla diameter, and midline division on ridge part of the pons.[3]

In this report, we present the phenotypic ophthalmologic and neuroimaging characteristics of the two-sibling HGPPS cases related to the *ROBO3* gene mutation. A written consent was obtained from the patients and their parents for this case report.

CASE REPORT

A 2-years-old male, born from parents out of consanguineous marriage was referred to us with the complaint of lateral gaze limitation in the eyes. It was found that when he was 3 months old, he was evaluated for torticollis but no pathology was found. The visual acuity was 20/30 in both eyes using single Allen pictures. Cycloplegic refraction on both eyes was +1,50 diopter. Patients vertical eye movements were unremarkable, but horizontal eye movements were absent (Figure 1). No abnormal head position and nystagmus were observed. Strabismus was not detected with the Hirschberg test. Pupillary reactions, and examination of the anterior and posterior segments were normal.

Neuro-motor developmental stages were found to be slightly delayed. Scoliosis had began to progress (Figure 2). In brain MRI, the pons hypoplasia, enlarged fourth ventricle dimensions, and a butterfly-like figure were observed at the level of the medulla oblongata (Figure 3).

Our patient's affected 15-year old sister had been followed up due to horizontal gaze limitation noticed since her childhood. Pendular horizontal nystagmus of low amplitude was seen and the best corrected visual acuity (BCVA)

Address correspondence to: Mustafa Erdogan, Celal Bayar Üniversitesi Hafsa Sultan Hastanesi, Göz Hastalıkları Ana bilim Dalı, Yunusemre /MANİSA, 45030 Turkey. Tel: +905326908573, email: doctormustafa@hotmail.com

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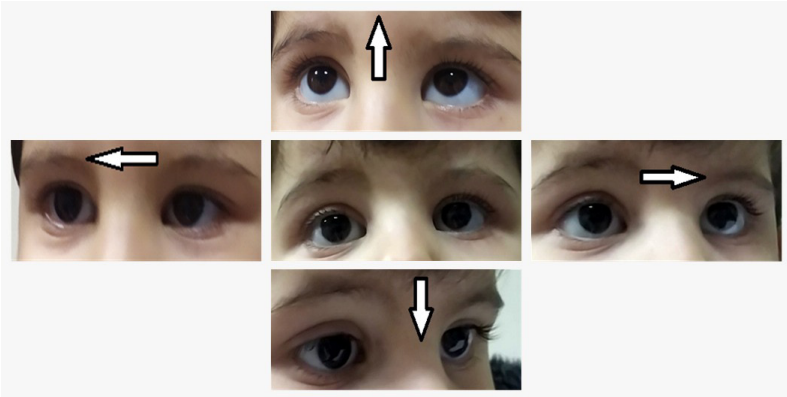

Figure 1: Vertical eye movements are robust but horizontal eye movements are absent. (arrows show the directions to be looked at)

was 20/20 in both eyes. (Snellen visual chart) Cyclorefraction was +1.50 (+2.00×90°) for her right eye, and +1.00 (+2.00×90°) for the left eye. Horizontal eye movements were absent and there was no limitation in vertical eye movements (Figure 4). She had no abnormal head position. Pupillary reactions, and examination of the anterior and posterior segments were normal. Without refractive correction, she had 15 prism diopter esodeviation at both distance and near in primer, superior and inferior gaze positions. She had orthotrophic with refractive correction in all positions. Patient had convergence. Suppression was detected in the right eye in the worth 4 point test. Her visual field examination was found to be within normal limits.

She has been evaluated preoperatively for spine correction surgery due to the progressive scoliosis started from early childhood. (Figure 5) Pons hypoplasia, midline cleft in the pons, enlarged fourth ventricle size and a butterfly-like figure at the level of the medulla oblongata were detected in the cranial MRI taken (Figure 6). Due to clinical and radiological findings suggesting HGPSS, all coding regions of the *ROBO3* gene were analyzed. As in her sibling, homozygous

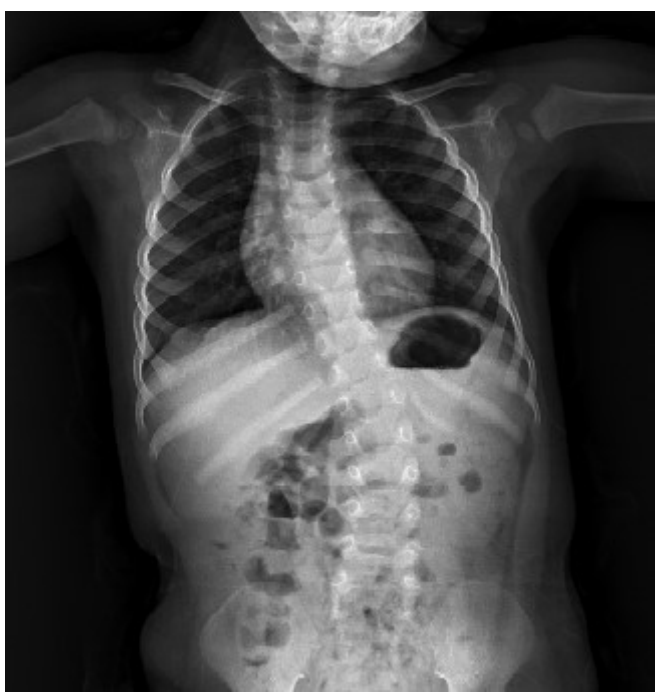

Figure 2. Onset of thoracolumbar scoliosis.

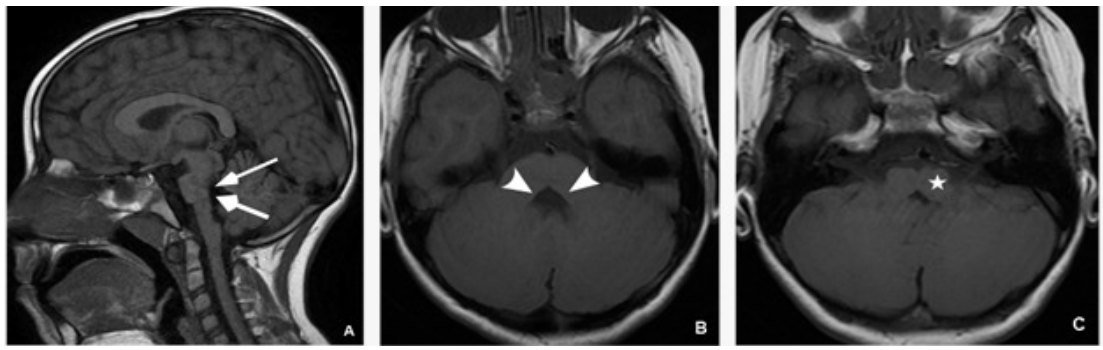

Figure 3. A. On sagittal T1 MRI the followings are seen; the depression on the fourth ventricular base (arrow) and the reduced medulla and pons diameters. B. The midline cleft in Pons (arrow) and the absence of the surface contour of the facial collicules. C. On axial T1 MRI the butterfly-like configuration of the medulla.

c.1366G>T (p.Gly456Ter) variant was established in the *ROBO3* gene (NM_022370.4). This variant is classified as pathogenic using the American College of Medical Genetics and Genomics 2015 criteria.[4]

DISCUSSION

A *ROBO3 gene* with normal function is important in axon guidance activity and helps regulation of the posterior brain axon midline crossing.[5] There are few scientific studies on features associated with progressive scoliosis in patients with HGPPS. Majority of studies report that it starts in early childhood and should be treated surgically.[6] As in our case, torticollis symptom was reported in a few babies with HGPPS, previously.[7] Most of the patients reported in the literature seem unaffected neurologically; however, a small proportion show delayed motor and cognitive development. While our case had a mild developmental delay, the neuromotor development in her sister was normal.

In a systematic review Pinero-pinto *et al*. found the presence of consanguineous marriage between parents in 48.4% of HGPSS cases.[8] In all cases or case series described so far, it was reported that vertical gaze movement was preserved as an ocular disorder, but horizontal gaze limitation or absence was seen. Although there are no published histopathological reports on HGPSS patients in recent studies, it is thought that hypoplasia of the supranuclear abducens nerve in the pontine tegmentum or abnormal innervation of the medial longitudinal fascicle is responsible for the clinical abnormality.[9] In the ophthalmological evaluation of our patients, typical findings were observed. However, refractive esotropia and low amplitude conjugated pendular nystagmus was also found in our 15-year-old patient. This can be regarded as a another manifestation of the neurologic impairment.

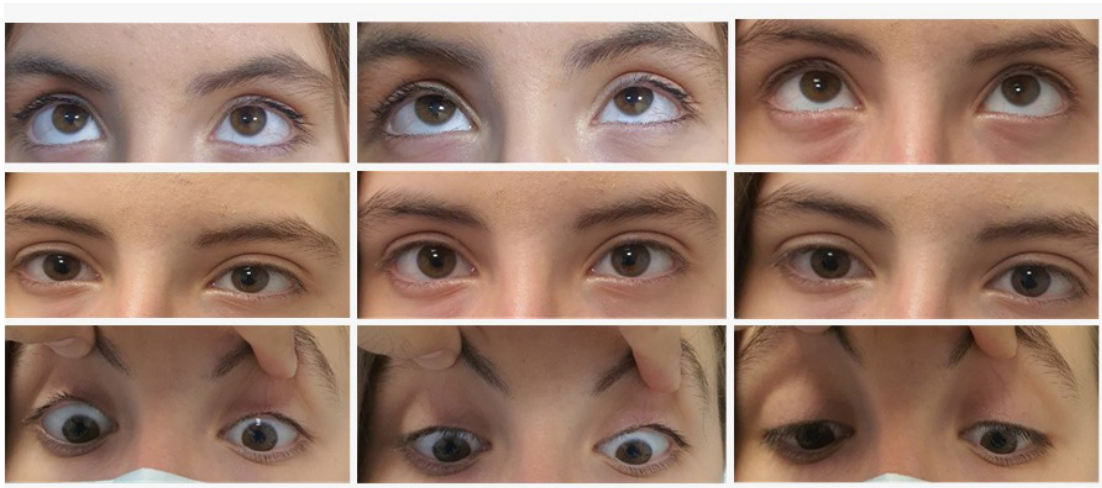

Figure 4. Vertical eye movements are intact but horizontal gaze is absent.

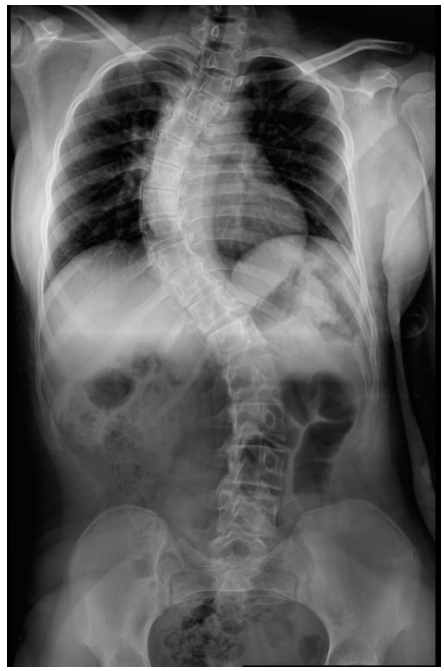

Figure 5. Apparent thoracolumbar scoliosis

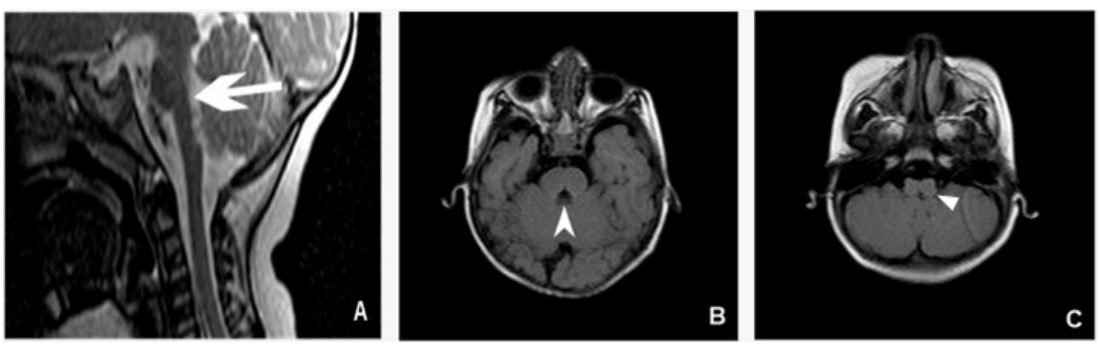

Figure 6. A. On sagittal T1 MRI, the followings are seen; depression of the fourth ventricular base (arrow) and reduced medulla and pons diameters. B. On pons (arrow) the midline cleft and the absence of the surface contour of the facial collicules. C. on axial T1 MRI, the butterfly-like configuration of the medulla.

To date, fewer than 50 disease-associated mutations in the *ROBO3* gene have been reported.[10] The variant detected in the family presented here, leads to a dysfunctional mutation because it causes a nonsense change. It seems that almost all of the variants resulting in loss of function are classified as pathogenic or likely pathogenic in databases.[11] Besides, the fact that the variant detected was never been found as heterozygous or homozygous in population frequency databases, it support its pathogenicity. This variant was previously reported in the ClinVar database to be related to the phenotype numbered RCV000002260.[12] In the light of all these data, this variant was thought to be the cause of the clinical picture stated in our patients.

Early HGPPS diagnose is important to prevent ocular and orthopedic problems associated with this pathology. In this respect, it is important to carefully examine eye movements in the systematic examination of a patient presenting with scoliosis and/or torticollis symptoms in early childhood and the first helpful technique in diagnosis may be a Brain MRI to determine the typical appearance.

DISCLOSURE

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Conflict of interest: None

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