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Case Report

A case of horizontal gaze palsy with progressive scoliosis☆,☆☆

Hassan Ali AlSayegh, MBBS[a,*], *Zahraa Ahmed AlSubaie, MBBS*[b], *Hesham Jassim AlRamadhan, MBBS*[c], *Qasem Mohammed AlAlwan, MBBS*[a], *Hani Ali Almohammed Ali, MD, Ssc-Rad, EBIR*[a], *Jaafar AlObaid, MBBS, SB-Rad, SF-NR*[a]

[a] *Department of Radiology, King Fahad Hospital Hofuf, 36441 Prince Salman St, Eastern Province, Saudi Arabia*
[b] *King Fahad Hospital Hofuf, 36441 Prince Salman St, Eastern Province, Saudi Arabia*
[c] *Department of Paediatrics, Maternity and Children's Hospital, Hofuf 3424, Eastern Province, Saudi Arabia*

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ABSTRACT

Horizontal gaze palsy with progressive scoliosis is a rare entity with few cases in the literature. Despite the fact the patient will not present with typical symptoms of this syndrome, clinical suspicion should be raised particularly in terms of imaging findings. Imaging findings are characteristic to flag the possibility of this syndrome. Keeping in mind such congenital abnormalities on magnetic resonance imaging particularly for radiologists might help in the management process. Multidisciplinary teams play a crucial role in terms of communication to find the clinical, radiological and genetic studies to reach the diagnosis.

Introduction

Horizontal gaze palsy with progressive scoliosis (HGPPS) is a congenital disorder characterized by the absence of normal horizontal eye activity associated with progressive scoliosis during the period of adolescence or early childhood [1]. It is associated with preservation of the vertical gaze and convergence activity and normal behavioral or neurological activity [2]. It is an autosomal recessive syndrome [1]. The first record of this syndrome was in 1974, by (Sharpe and Silversides JL) [3]. By the early 2000s, it was found that the location of mutation at the chromosome 11q23–25 of ROBO3 gene in various genetics studies [4]. ROBO3 gene encodes a responsible protein for neuronal migration and axonal guidance [5]. Mutations of the ROBO3 gene give rise to crossing disturbance in brainstem neuronal pathways that would ordinarily cross over during embryonic time [5]. It is found that this gene is crucial for the nerve decussation of ascending as well as descending neural tract [6,2]. For horizontal activity of the eye, it is mainly controlled by medial and lateral rectus muscles altogether. Each of these muscles are innervated by a corre-

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* Corresponding author.
E-mail address: Has.alsayegh@gmail.com (H.A. AlSayegh).

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sponding cranial nerve, that originates from their nerve nucleus. The oculomotor nerve takes control of the medial rectus whereas, on the other hand, the abducens nerve takes control of the lateral rectus muscle [6,2]. Thus, to have a coordinated conjugate horizontal eye activity, normal functioning oculomotor nerve, abducens nerve and normal morphology of their nucleus is a must. Furthermore, the abducens nucleus controls the smooth horizontal gaze movement. It stated that the abducens nucleus has two samples of internuclear neurons: the first one innervates the lateral rectus muscle on the same side directly and the other type projects through the medial longitudinal fasciculus (MLF) to the nucleus of the oculomotor nerve in the other side of the brain. Thus, it innervates the medial rectus muscle of the contralateral eye. At the level of the floor of the fourth ventricle in the lower part of the pontine tegmentum, the abducens nuclei are found [7]. As stated before, HGPPS is also associated with progressive scoliotic deformity of the spine, the degree and patterns of which broadly differ based on the unique cases reported by various authors. The deformity recorded in most of the literature is right thoracic or thoracolumbar deformity [8]. Moreover, the pathophysiology of progressive scoliosis, a rather consistent feature of this disorder, remains unclear. Disturbances in the regulation of the muscle tone of paraspinal muscles, initiated by some descending tracts have been suggested [4,9].

There are multiple theories that explain the altered morphologies associated with this syndrome, which will be discussed in more detail in the coming sections. These theories include uncrossed medial longitudinal fasciculus (MLF) [10,11], abnormality in the paramedian pontine reticular formation (PPRF) [11], absence of facial colliculi due to selective agenesis of abducens nuclei [12], loss of normal decussation of corticospinal tract [2,13], prominent inferior olivular nuclei of medulla oblongata [2,10], uncrossed dorsal column-medial lemniscal sensory ascending pathways [4,14], hypoplastic cerebellar peduncles as well as loss of normal decussation of superior cerebellar peduncles [10] and normal corpus callosum [6]. The diagnostic approach to this syndrome is achieved by neurological, neurophysiological and physical examination along with radiological imaging play a vital role to reach the precise location of the lesions in this syndrome. Brain magnetic resonance imaging (MRI) has several characteristic findings for this syndrome including, split pons sign and medulla oblongata butterfly configuration. Also, absence of facial colliculi with a fourth ventricle tent-shaped, brainstem hypoplasia and inferior olivary nuclei prominence in relation to pyramids of the medulla oblongata [15,16]. The split pons sign found in MRI has been suggested to be a result of abnormally developed medial longitudinal fasciculus and abducens nuclei, and the butterfly appearance of the medulla oblongata is due to uncrossed corticospinal tracts [2,11]. The inferior olivary nuclei prominence in relation to pyramids of the medulla oblongata might be explained by the absence of cuneate and gracilis nuclei, while the tented-shaped fourth ventricle is presumed to be due to facial colliculi protrusion [15,17].

White matter tracts abnormal course, decussation failure, and presence of ectopic tracts are all suggestive of axonal guidance disorders. Previously, examination of neural fiber connectivity depended mainly on post-mortem neuroanatomical studies by using tracers in animals [18]. In addition to conventional MRI, advanced neuroimaging techniques nowadays like functional MRI, diffusion tensor imaging, and fiber tractography, and neurophysiological studies like motor and somatosensory-evoked potentials are suitable investigational tools to detect morphological abnormalities in connectivity and decussation of neuronal fibers.

These imaging techniques are non-invasive tools that play a crucial role in the analysis of brain anomalies involving specific neural tracts and nuclei in humans. [17]. These diagnostic tools and the expected morphologies found in this syndrome will be discussed more clearly in the discussion section.

Case report

An 11-year old female known to have congenital atretic tricuspid and pulmonary valve with hypoplastic right heart since birth and underwent multiple cardiac surgeries, the last of which was fenestrated extracardiac Fontan at the age of 8 years.

The patient is also known to have infantile thoracolumbar scoliosis which was diagnosed in infancy and showed progression as she got older, for which she underwent vertical expandable prosthetic titanium ribs at age of 9 years old (Figs. 1 and 2). The patient was also noticed to have left lower limb spasticity and walking on the lateral aspects of her left foot.

Her family brought her to our emergency with a history of acute alteration in level of consciousness and one attack of generalized tonic convulsion that lasted for one minute. There was no associated history of fever, headache, photophobia, or recent head trauma. There was no history of a similar event before.

On examination, she was found to be drowsy and irritable, with a given Glasgow coma scale of 13 out of 15.

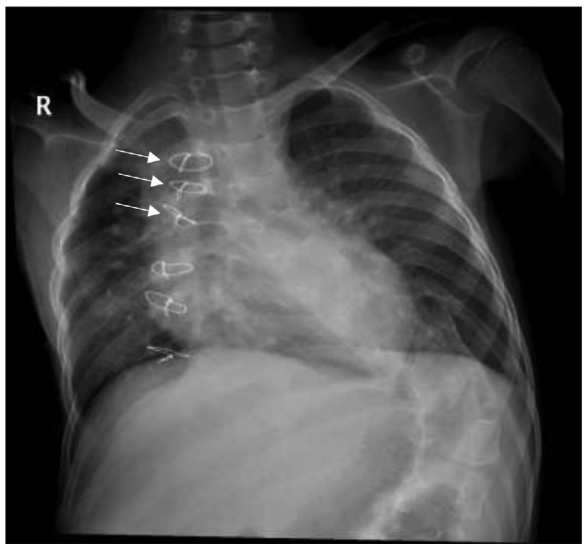

Fig. 1 – Frontal chest radiographs show thoracolumbar levoscoliosis and sternotomy wires (white straight arrows) at age of 8.

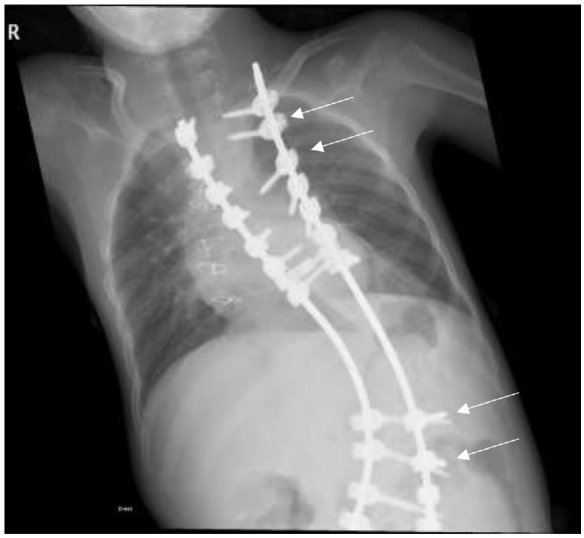

Fig. 2 – Frontal chest radiographs show thoracolumbar improved levoscoliosis and sternotomy sutures and posterior spinal fixation (white straight arrows) of thoracolumbar spine at age of 9 years old.

Neurological examination showed mild left side weakness with a power of four out of five in both upper and lower extremities, with slightly exaggerated deep tendon reflexes on that side. Cranial nerve examination was normal including intact extraocular movement (preserved horizontal and vertical gaze) and normal pupils.

The systematic examination was within expectation for her status. Complete blood count and metabolic panels that included serum electrolytes, renal function and liver function were all within expected. The patient admitted initially to our pediatric intensive care unit with the impression of ischemic stroke. An emergency computed topography (CT) scan of the brain without contrast was reported to be normal. She was observed for several hours and then shifted to the general pediatric ward. Magnetic resonance imaging scan of the brain was done later, and it showed an overall small brainstem, in particular a small pons, with abnormal dorsal concavity, midline brainstem cleft and butterfly-like appearance of the medulla. The floor of fourth ventricle is tent-shape with missing facial colliculi and thinning of corpus callosum (Fig. 3). Note is made of left basal ganglia old insult (Fig. 3) in which HGPPS possibility was raised by the neuroradiologist. Patient reviewed by cardiologist and was stable regarding cardiology status (echocardiography shows patent Fontan pathway with no clots). The case was discussed between a pediatric cardiologist, a hematologist, and a neurologist and their decision was to start a therapeutic dose of enoxaparin. Over the following days, the Patient shows improvement in her level of consciousness, and the seizure did not reoccur. After that, the plan was to transfer the patient to tertiary hospital care for further management and to perform genetic studies. The possibility of HGPPS was suggested based on clinical history, specifically the progressive thoracolumbar scoliosis, and MRI findings of the brain. The patient was transferred for confirmatory genetic study.

Discussion

HGPPS is defined as progressive scoliosis during early childhood and adolescence along with the congenital absence of normal horizontal eye activity with preservation of the vertical gaze and convergence activity and normal behavioral or neurological activity [1,2]. It is found to be associated with ROBO3 gene mutation. ROBO3 gene encodes a responsible protein of neuronal migration and axonal guidance [5]. Mutations of ROBO3 gene give rise to crossing disturbance in brainstem neuronal pathways that would ordinarily cross over during embryonic time [5]. It is found that this gene is crucial for the nerve decussation of ascending as well as descending neural tract [6,2]. Ordinarily, the motor movements are fundamentally innervated by the contralateral side of the motor cortex in the brain. The pyramidal or corticospinal tracts are the major neural fiber communicating between the primary motor cortex in the cerebral hemispheres and the spinal cord through the medulla oblongata [19]. For the horizontal activity of the eye is mainly controlled by medial and lateral rectus muscles altogether. Each of these muscles is innervated by a corresponding cranial nerve, that originates from their nerve nucleus. The oculomotor nerve takes control of the medial rectus whereas, on the other hand, the abducens nerve takes control of the lateral rectus muscle [6,2]. The motor nuclei of the cranial nerves receive impulses from the cerebral cortex through the corticobulbar fibers. These fibers originate from the precentral gyrus and from the adjacent part of the postcentral gyrus. The corticobulbar fibers descend through the corona radiata and internal capsule. They pass through the midbrain just medial to the corticospinal fibers and end by synapsing either directly within the cranial nerve nuclei or indirectly through the interneurons " internuncial neurons." The majority of the corticobulbar fibers which is going to the motor cranial nerve nuclei cross the median plane before reaching the nuclei. Bilateral connections are also present for all the cranial motor nuclei except for part of the facial nucleus and hypoglossal nucleus [20]. Thus, to have a coordinated conjugate horizontal eye movement, normal functioning oculomotor nerve, abducens nerve and normal morphology of their nucleus is a must. Furthermore, the abducens nucleus controls smooth horizontal gaze movement. It stated that the abducens nucleus has two samples of internuclear neurons: the first one innervates the lateral rectus muscle on the ipsilateral side directly, and the other type projects through the medial longitudinal fasciculus (MLF) to the nucleus of the oculomotor nerve in the other side of the brain. Thus, innervates the medial rectus muscle of the other eye. At the level of the floor of the fourth ventricle in the lower part of the pontine tegmentum, the abducens nuclei are found [15]. In fact, cases without esotropia or atrophy in lateral rectus muscle and show conjugate horizontal eye movement paralysis supports the site of the lesion to be at the MLF rather than on the abducens nuclei [3]. There are multiple theories that suggest the morphologies associated with this syndrome. First theory: uncrossed medial longitudinal fasciculus (MLF). In this disorder, the internuclear nucleus axons of the sixth nerve nucleus do not cross the midline to ascend in the medial longitudinal fasciculi to synapse with the neurons within the nucleus of the oculo-

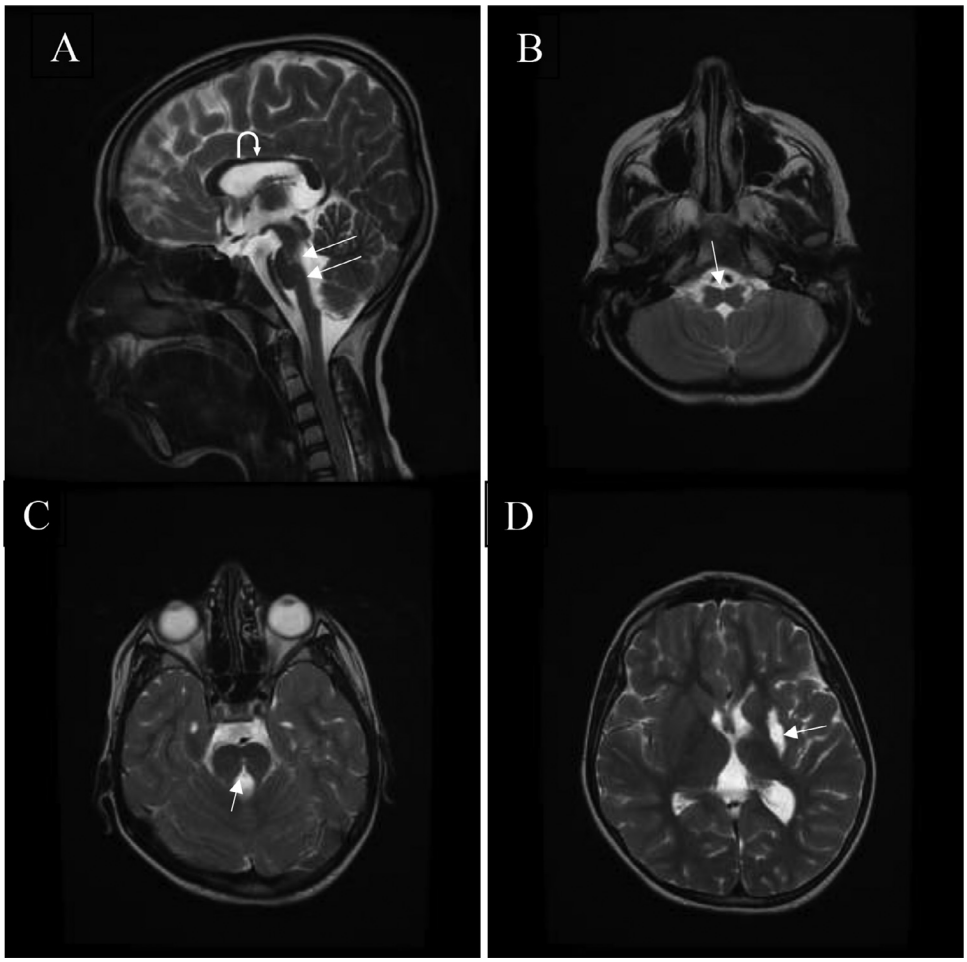

Fig. 3 – MRI midline sagittal T2-weighted Image of the brain (A) shows a small brainstem, in particular a small pons, with abnormal dorsal concavity (white straight arrows), thinning body of corpus callosum (curved white arrows). MRI Axial T2 weighted images through the pons and medulla (B and C) show the midline brainstem cleft (white straight arrow), butterfly-like appearance of the medulla. The floor of 4th ventricle is tent shaped with missing facial colliculi. MRI Axial T2 weight image (D) shows old insult in left basal ganglia (white straight arrow).

motor nerve complex innervating the medial rectus muscles in the other eye. This failure of decussation of the axons of the interneurons is suggested to be the primary cause of the defective control of horizontal eye activity [7]. Second theory: Absence of facial colliculi and selective agenesis of the abducent nucleus [21]. It is found that: this syndrome is associated with the absence of facial colliculi which is a paired prominence at the floor of the fourth ventricle and occurs from axons of the motor nuclei of the facial nerves passing dorsally around the abducens nerve nuclei. An absence of conjugate horizontal eye activity with facial colliculi not found on MRI with intact activity of facial and oculomotor nerves functions is tending to support the idea of selective agenesis of the abducens nuclei [21]. The third theory mentioned in the literature is the absence of normal decussation of the corticospinal tract [2]. The primary motor cortex, secondary motor area, and somatosensory cortex originate from the frontoparietal cortices which primarily originate from the corticospinal tract [22]. The corticospinal tracts then come together to form bundles, which travel through the posterior limb of the internal capsule and cerebral peduncles. The bundles then travel down to the brainstem [23]. When the corticospinal tract arrives at the pons, the bundles take on a more compact structure and continue to compress as they descend. As a result, the axonal structure of the corticospinal tract takes up more surface area in the upper part of the pons than the lower part of pons [24]. At the lowermost part of the medulla oblongata, most of the corticospinal fibers (around 90%) cross in the pyramidal decussation and form the lateral corticospinal tract at the level of the spinal cord. This pathway is controlling the individualized movement activities, especially of our hands and fingers. In this syndrome, the pyramidal tracts descend downwards straight without crossing [13]. Another morphology mentioned in the literature is prominent inferior olivular nuclei of medulla oblongata [2,10]. This defect could be due to hypoplasia of the medial lemniscus, which is located posterior to the pyramids, or the absence of the posterior prominence of the gracilis and cuneate nuclei is thought to explain

why the inferior olivary nuclei are unusual more prominent than the pyramids of the medulla [2,10]. Other morphological studies reported by use of physiological somatosensory evoked potential study is uncrossed dorsal column-medial lemniscal sensory ascending pathways [4,14]. The axons enter the spinal cord and turn upward, with no synapse Those fibers enter spinal cord to the fasciculus gracilis from legs and fasiculus cuneatus from arms, these tracts ascend the spinal cord and form the dorsal column. The first synapse in this pathway is found in two nuclei located in the lowermost part of the medulla, in the nuclei gracilis and cuneatus. After that, axons emanate from these two nuclei that decussate the midline as internal arcuate fibers. The fibers then group together to form the medial lemniscus which ascends through the brainstem to thalamus and then to the primary somatosensory cortex [24]. Other theory proposed that the lesion may arise from paramedian pontine reticular formation (PPRF). The PPRF is existed near to the abducens nucleus in the pontine tegmentum [11]. Afferent impulses are received from the parietal eye and frontal eye fields to PPRF. The regenerated impulses transmit through internal capsule of the brain and the cerebral peduncle. After that, it decussates to the contralateral side at the level of the midbrain. After that, it innervates the PPRF [25]. Furthermore, the impulses transmitted to the abducens nucleus through excitatory neurons within PPRF [26]. Abnormal supranuclear input into the abducens nucleus by axons originating from the PPRF that does not cross the midline could be the cause of conjugate horizontal gaze palsy [27].

Hypoplastic cerebellar peduncles as well as loss of normal decussation of superior cerebellar peduncles is another morphology found in a previous case [10]. The possible explanation is that the cerebellum is connected to the posterior aspect of the brainstem by three bundles of nerve fibers called the superior, middle, and Inferior cerebellar precancels. The superior cerebellar peduncles connect the cerebellum to the midbrain, the middle cerebellar peduncles connect the cerebellum to the pons and the inferior cerebellar peduncles connect the cerebellum to the medulla oblongata. The afferent fiber forms the greater part of the white matter and proceeds to the cerebellar cortex. Altogether enter the cerebellum mainly through the Inferior and middle cerebellar peduncles while the efferent leaves the cerebellum through the superior cerebellar peduncle and Inferior cerebellar peduncle. The cerebellum receives afferent information concerning voluntary movement from the cerebral cortex and from the muscles, tendons, and joints. Furthermore, it receives information concerning balance from the vestibular nerve and possibly concerning head position and movement. The cerebellum work as a coordinator of precise movements by comparing the output of the motor area of the cerebral cortex with the proprioceptive information received from the site of muscle action and makes necessary adjustments [28].

Despite all the morphologies mentioned previously, it is found that normal inter-hemispheric connections in the corpus callosum were demonstrated [6]. Ultimately, brain MRI shows the characteristic congenital anatomical abnormalities of the brainstem. Several characteristic MRI findings of HGPPS have been reported in the literature including butterfly configuration of the medulla, midline pontine cleft (split pons sign) and brainstem hypoplasia with the absence of facial colliculi which were discussed earlier [15,16]. Functional MRI that directly or indirectly shows the complete or partial absence of decussation of some white matter bundles of the brainstem [15,17]. For example, performing a right-hand motor task show predominant right primary motor cortex activation while performing a left-hand motor task shows predominant left primary motor cortex activation. It is noticeable that cerebellar activation is ipsilateral when it is supposed to be contralateral activation [28]. The white matter organization and microstructure in vivo evaluation are achieved by an advanced neuroimaging technique that investigates called diffusion tensor imaging (DTI) [6]. DTI translates the information about the three-dimensional (3D) direction of diffusion of water in space and calculates the principal direction of diffusion within the brain. Graphical reconstruction of the white matter pathways is achieved by fiber tractography (FT) which is a post-processing tool that allows the DTI and tractography studies to prove a lack of the normal crossing of corticospinal descending tracts and superior cerebellar peduncles [6]. However, DTI tractography of the corpus callosum provided evidence of normal interhemispheric fibers [6]. Note that DTI tractography is not a sensitive modality to detect minor crossings [6]. In regards of electrophysiological evoked potential studies, (Amoiridis et al.) have reported that it can show both crossed and uncrossed tracts in HGPPS cases [30]. On the other hand, (Haller et al.) [19] have also recorded that somatosensory evoked potential (SSEPs) and motor evoked potential 'MEPs' can detect the uncrossed sensory and motor spinal tracts, and these appear to be partial and often asymmetric in their patients. All findings related to the sensory and motor system provided consistent results with dominantly ipsilateral fMRI motor activations in the primary sensorimotor area, and ipsilateral ascending and descending tractography without crossing fibers at the level of the brainstem and superior peduncle. Additionally, ipsilateral SSEPs and MEPs results are consistent with previous investigations [29].

Furthermore, there is a group of genetic diseases of the eye that have the identical characteristic to this syndrome and they are a part of the possible diagnoses that includes Möbius syndrome which those patients show facial paralysis partially or completely with paralysis of horizontal gaze movement because of devastation of abducens and facial nerve nuclei. Predominantly, there is a destruction in the other cranial nerves [11]. Other possible differential diagnosis is Duane's retraction syndrome is a syndrome that is characterized by abduction loss, palpebral narrowing during global retraction and fixation because of hypoplastic or absent motor neurons abducens nerve [10]. The predominant MRI findings of these syndromes include abducens and facial nuclei hypoplasia with hypoplasia of the pons and hypoglossal eminence is absent absence that shown in Möbius syndrome. On the other hand, abducens nerve aplasia shown in Duane's retraction syndrome [10]. Up to our knowledge, no reports described a split pons sign in association with Möbius syndromes or Duane's retraction syndrome [11].

Variability in the phenotypic expression of mutations in the ROBO3 gene awaits further verification. Despite the extensive neuroanatomic abnormalities present in HGPPS syndrome, affected patients have preserved motor and sensory

function. They do not demonstrate the severe ataxia and apraxia seen in other developmental disorder with uncrossed corticospinal tracts along with other white matter abnormalities [30]. While the symptoms of this syndrome are limited to horizontal eye movement paralysis and scoliosis. There is a real need to research other symptoms and association of this disease that were not reported before for the coming patients who will be diagnosed with this syndrome. Further studies of functional organization in conjunction with higher resolution structural imaging of fiber tracts are needed in human with HGPPS. Association with congenital heart disease is a possibility or could be incidental in our case.

Ultimately, understanding of the imaging characteristics of HGPPS and other possible differential diagnosis by radiologists is important and likely to be the initial step for clinical identification of this syndrome and further management will be warranted by multidisciplinary team.

Patient consent

Written informed consent was obtained from the guardians of the patient for publication of the case report and all imaging studies. Consent form on record.

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