Two Brothers with Horizontal Gaze Palsy with Progressive Scoliosis

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ABSTRACT

Horizontal gaze palsy with progressive scoliosis (HGPPS) is a rare autosomal recessive disorder, which results in complete absence of horizontal eye movements. Convergence is typically intact and pendular low amplitude nystagmus is a common presentation in patients with this condition. In 2015, the first reported Australian cases presented to an Ophthalmology Department in Melbourne. The two Chinese siblings were diagnosed with HGPPS and an absence of all forms of horizontal gaze, including saccadic, smooth pursuit and vestibule-ocular responses. The patients demonstrated the presence of pendular nystagmus, however convergence remained unimpaired. The two sibling's rare genetic findings are compared with similar presentations located in literature worldwide.

Keywords: horizontal gaze palsy, progressive scoliosis, nystagmus, convergence, ROBO3

INTRODUCTION

Horizontal gaze palsy with progressive scoliosis (HGPPS) is a rare autosomal recessive disorder caused by homozygous or compound heterozygous mutations in the ROBO3 gene on chromosome 11.[1] HGPPS is a congenital disorder resulting in complete absence of horizontal eye movements including saccadic, smooth pursuit and vestibulo-ocular responses.[1-8] Convergence is intact and patients may have low amplitude horizontal pendular nystagmus.[1-11] HGPPS was first reported in 1974 though it was not until 30 years later that the gene responsible ROBO3 was discovered.[7,10,11] As of 2016, there have been 33 different ROBO3 mutations described that are related to HGPPS.[12] They can be from either consanguineous or non-consanguineous pedigrees and may or may not be associated with strabismus. The majority of these cases have been documented in patients from Middle Eastern, African and European backgrounds. On reviewing the literature, it is noted that this case report of two brothers of Hokkien descent, aged eight and six years who have migrated from China, may be the first published cases in Australia.

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CASE REPORTS

After recently arriving in Australia, two brothers, aged 8 years and 6 years, presented to the eye clinic after being referred by their paediatrician with a query of congenital bilateral VI cranial nerve palsy with horizontal nystagmus. It was also documented by the paediatrician that they were being managed for scoliosis. Both brothers were born to non-consanguineous parents and are the youngest two of four siblings. The older two female siblings have no signs of horizontal gaze palsy or scoliosis. Both brothers had normal cognitive function and were learning English as a second language.

The older brother had visual acuity of 3/9.5 each eye using a LogMAR chart. There was no movement on cover test at distance or near. He had horizontal, low amplitude, pendular nystagmus. Ocular movements showed no saccadic, pursuit or doll's head movement on horizontal gazes, though vertical movements, both elevation and depression, were intact. Convergence near point was 4 cm. Fusion was not demonstrable using a 20 PD base-out prism and stereo acuity was 200" of arc on the Lang II. Fundus examination was normal and there was no significant refractive error on retinoscopy.

The younger brother had visual acuity of 3/6 each eye using single optotype Kay Pictures. There was no eye movement on cover test at distance or near. He had horizontal, low amplitude, pendular nystagmus. Ocular movements showed no movement on horizontal gazes, though vertical movements were intact. Convergence near point was 4 cm. Fusion was not demonstrable with a 20 PD base-out prism

Table 1. Comparison of published HGPPS cases

Ethnicity	Horizontal eye movements	Vertical eye movements	Convergence	Nystagmus	Strabismus	Reference
Turkish x 3	Absent	Restricted	Not stated	Horizontal, head tremor	Straight	Dretakis & Kondoyannis 1974[10]
Chinese x4	Absent	Normal	Intact	Pendular, low amplitude horizontal	Straight	Sharpe et al 1975[11]
Irish/German	Absent	Normal	Not stated	Pendular horizontal, left head tilt	Straight	Chan et al 2006[4]
English/Irish	Absent	Normal	Intact	Low amplitude	15$^{\Delta}$ esotropia	Chan et al 2006[4]
Saudi x 5 Sudanese x 1	Absent	Normal	Intact	Three of the six had nystagmus	Straight	Abu-Amero et al 2009[1]
Indian	Absent	Normal	Intact	Not stated	Straight	Ng et al 2011[15]
Turkish	'Limited'	Normal	Intact	Horizontal pendular	40$^{\Delta}$ esotropia	Volk et al 2011[8]
Turkish	Absent	Normal	Intact	Horizontal, pendular, slight rotational	24$^{\Delta}$ exotropia	Volk et al 2011[8]
Saudi	Absent	Normal	Intact	Nil	Microtropia	Volk et al 2011[8]
Turkish	Absent	Normal	Intact	Horizontal	14$^{\Delta}$ exotropia	Volk et al 2011[8]
Serbian	Absent	Normal	Intact	Small amplitude, horizontal, pendular	Straight	Abu-Amero et al 2011[2]
Afghani x 4	Absent	Normal	One had no convergence	One had no nystagmus	Mild esotropia	Abu-Amero et al 2011[3]
Iraqi	Absent	Normal	Intact	Upbeat	Straight	Samolades et al 2013[7]
Moroccan x 4	Absent	Normal	Intact	Low amplitude horizontal	Straight	Handor et al 2014[5]
Saudi	Absent	Normal	Intact	Nil	35$^{\Delta}$ esotropia	Khan & Abu-Amero 2014[14]
Turkish	Limited	Normal	Intact	Nil	40$^{\Delta}$ exotropia	Bozdogan et al 2017[12]
Cape Verdean x 2	Absent	Normal	Intact	Nil	Straight	Mendes Marques et al 2017[6]

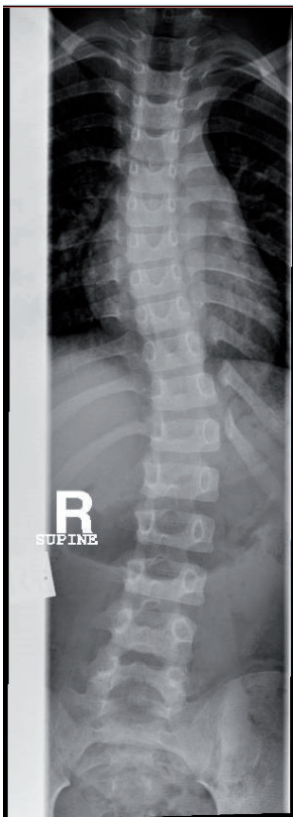

Figure 1. MRI demonstrating scoliosis of the older brother.

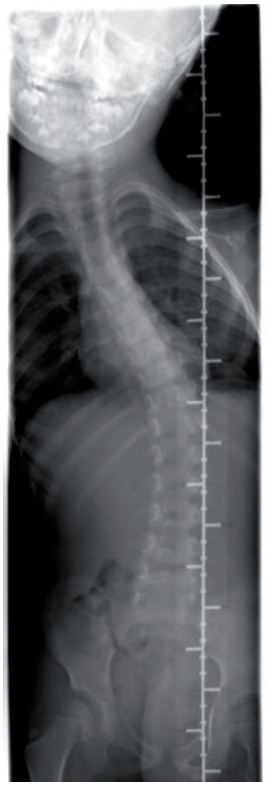

Figure 2. MRI demonstrating scoliosis of the younger brother.

and he only reported seeing monocular control picture on the Lang II stereoacuity test. He also had a mild left head tilt, which was due to his scoliosis. Fundus examination was normal and there was no significant refractive error on retinoscopy.

Genetic testing found that both parents are carriers of the faulty ROBO3 gene. There was no other history of any symptoms in other family members. It was confirmed that the older brother had a homozygous mutation of the ROBO3 gene with the nucleotide change being c.955G>A. The younger brother has not yet undergone genetic testing, as a negative genetic test would not alter his treatment and it was concluded by geneticists that both brothers had inherited the same diagnosis. It is unknown therefore, whether or not both boys have the same phenotype.

Spinal magnetic resonance imaging (MRI) of the older brother demonstrated 'mild biconcave scoliosis, convex to the right in the mid thoracic region and to the left at the thoracolumbar region,' as shown in Figure 1. Spinal MRI of the younger brother demonstrated 'biphasic scoliosis with the cervical curve convex to the right apex at the level of C7 and the more diffuse thoracolumbar curve convex to the left, maximal at the level of T12,' as shown in Figure 2.

Magnetic resonance imaging of the older sibling indicated slight asymmetry in volume of the pons with the right side appearing slightly smaller than that of the left. There was a small cleft in the dorsal pons. It was also found that he had spina bifida occulta at the level of sacral vertebra S1. The younger child's MRI was reported as 'unremarkable due to motion defect'. This project was approved by the Monash Health HREC (Project No. RES-17-0000-186Q) and consent obtained from the siblings' parent.

DISCUSSION

One of the very earliest cases of HGPSS documented four siblings of Chinese Hakka ethnicity. They were examined after immigrating to Toronto, Canada.[11] It was noted in this publication that all four children had full ocular movements in early childhood. The youngest was reported to have full ocular movements when examined at two years of age. By four years of age he had been diagnosed with scoliosis and partial limitation on lateral gazes. When examined again 10 years later at age 14 years, he had complete paralysis of horizontal gaze with pendular nystagmus.[11] However, as the first examination was not performed by an ophthalmic specialist, it could be suggested that the gaze paralysis may have been present at birth and not detected by either the family or general physicians given the difficulties of examining children.[9,11] No other authors have mentioned this progressive gaze paralysis.

Strabismus, either esotropic, exotropic or hypertropic deviations, was discussed in several of the reported cases.[1-4,8,9,12-14] Our brothers had no apparent deviation on cover test. One case described a 12-year-old boy from consanguineous parents who at four months of age had a 14 PD esotropia which increased to 40 PD at 2½ years old with a left micro hypertropia. With an initial diagnosis of bilateral Duane's retraction syndrome type 3, a bilateral medial rectus recession was performed to correct the strabismus. Although, his inability to abduct or adduct either eye remained. This boy had some intermittent head nodding and amblyopia. His sister who at 2½ years of age apparently had a 1 PD esotropia with binocular vision, which had changed to a 24 PD exotropia by the time of the authors' examination at 9 years of age.[8] Table 1 presents the strabismus and ocular findings of the other reported cases.

Most of the reported cases demonstrated normal convergence, as did our brothers. However, one was a child with no convergence and no nystagmus.[3] This child had marked kyphoscoliosis, curvature of the spine in both coronal and sagittal planes.[3,5] This differs to our brothers who both had biconcave scoliosis. A few other cases were

reported where no nystagmus was evident, though no authors have presented explanations on this point.[1,6] There was also one case of upbeat nystagmus which occurred in a 27-year-old man.[7]

The greater number of cases, including our brothers, had hypoplasia of the pons and cerebellar peduncles with both or either anterior and posterior midline clefts of the pons and medulla. ROBO3 mutations may disturb brainstem morphogenesis by failing to promote decussation of long motor and sensory tracts in the pons and medulla. Impaired decussation of pontine oculomotor pathways could explain the absence of all horizontal eye movements. This gene encodes an axon-guidance protein, which is responsible for midline crossing of neurons in the medulla.[8,9,16,17] It can be hypothesised that convergence is intact due to the genetic mutation not affecting the midbrain vergence pathway in the majority of cases. The paramedian pontine reticular formation is the horizontal gaze centre, innervating the abducens nucleus. From the abducens nucleus, lower motor neurons via the ipsilateral abducens nerve innervate the lateral rectus muscle, and interneurons via the contralateral medial longitudinal fasciculus (MLF) innervate the oculomotor neurons controlling the medial rectus. Vertical gaze is intact due to the vertical gaze centre being located in the midbrain reticular formation which control the lower motor neurons in the oculomotor and trochlear nuclei.[18] Vestibular input to both horizontal and vertical gaze pathways is direct from the vestibular nuclei to the abducens, oculomotor and trochlear nuclei via the MLF, which indicates that the MLF fibres are not affected in this condition as vertical doll's heads are still intact.[18]

The ROBO3 gene mutation has been described as the likely cause of HGPPS. There has been one other case reported with the identical c.955G>A nucleotide change to that found in our case,[19] however this paper did not describe any clinical signs. One case has been described where the ROBO3 gene had no mutations, nor any other chromosomal deletion or duplication.[2] An 8-year-old boy of a non-consanguineous Serbian family presented for ophthalmic, neurologic and orthopaedic examinations. He was born at term, healthy and the third son, his parents and siblings had no ocular motility restriction or scoliosis. His cognitive and motor skills were normal. On ophthalmic examination, he had low amplitude pendular nystagmus, absence of horizontal gaze movements, with vertical movements and convergence intact. Progressive scoliosis was also noted, and relevant orthopaedic treatment was commenced. His spinal x-ray showed thoracolumbar kyphoscoliosis with both anterior and posterior clefts in the medulla and a posterior cleft in the pons. On genetic testing, no ROBO3 mutations were detected. It was hypothesised that some environmental or epigenetic factor might interfere with the action of ROBO3 or its protein product in the developing brainstem, or a phenotype identical to HGPPS might be caused by mutations of a gene other than ROBO3.[2]

As HGPPS is a rare condition not commonly seen in ophthalmology clinics, it can be misdiagnosed as a bilateral Duane's retraction syndrome type 3, though the differential clinical sign would be the absence of lid retraction.[8] Bosley-Salih-Alorainy syndrome, or Athabascan brainstem dysgenesis syndrome, may also be a differential diagnosis as a comparable congenital horizontal ocular motility abnormality, though these patients do not have scoliosis and usually have associated bilateral deafness, cardiovascular and cerebrovascular malformations.[1,2] Horizontal gaze restriction has also been described in Moebius syndrome, though this is usually associated with facial weakness.[2]

Few of these cases have been followed up long-term; two described cases of HGPPS in older patients. A 17-year-old Iranian female presented for scoliosis surgery as did a 22-year-old female from Turkey.[12,17] The 22-year-old had developmental delay, though it was unclear whether this was related to her being from a consanguineous pedigree. Patients with developmental delay were also described in other cases though there appeared no consistent pattern, so it is difficult to conclude that this is a distinct sign of HGPPS.[3,4,8,9,12]

It is of interest to look towards the future and the effect HGPPS may have on our two brothers. Older adults have been described. One 55-year-old from India, from a consanguineous pedigree, with HGPPS who presented with stroke, was diagnosed with ischaemic heart disease and given appropriate cardiac medication.[15] A 55-year-old female from Japan with HGPPS presented with a history of acute left hemiparesis. Computerised axial tomography (CT) and MRI were performed and showed a left putaminal haemorrhage and brain stem hypoplasia with uncrossed corticospinal tracts.[16] It is unclear if these cerebral vascular events had any relation to HGPPS or the ROBO3 mutation.

CONCLUSION

It has become clear that horizontal gaze palsy with progressive scoliosis may present with many different ophthalmic signs, possibly due to different nucleotide mutations. These two boys of Chinese descent are the first reported cases in Australia and can be added to the growing list of documented cases.

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