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RESEARCH ARTICLE

Horizontal Gaze Palsy with Progressive Scoliosis Syndrome: A Concise Synopsis from the Ophthalmologist's Perspective

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ABSTRACT

The aim of this article is to provide a concise synopsis of Horizontal Gaze Palsy and Progressive Scoliosis syndrome and give the ophthalmologist's perspective.

Horizontal Gaze Palsy and Progressive Scoliosis is a rare autosomal recessive genetic condition. It has been described in both consanguineous and non-consanguineous families. It is caused by mutations in the round-about guidance receptor 3 (ROBO3) gene. Based on our literature review, to date, roughly 100 patients with this rare syndrome and 55 round-about guidance receptor 3 gene mutations have been reported. The age of onset of symptoms varies from 2 months up to 60 years, but usually start in early childhood. Musculoskeletal symptoms include scoliosis and difficulties with posturing. Mental retardation and global developmental delay may also ensue. Ophthalmological manifestations include convergent squint, pendular nystagmus and horizontal gaze palsy. Vertical and convergence eye movements are preserved. Lid position, pupillary reflexes and fundus examination are usually normal as well. Brain neuroimaging reveals striking radiological findings, including brainstem hypoplasia with an anterior and dorsal pontine cleft and a butterfly shaped medulla and absence of the normal promontories of the facial colliculi.

To date, there is no definitive treatment of this condition. Convergent squint can be corrected with prisms or surgery. Spectacles are used to correct any significant refractive error. Patching or atropine drops can be used for the treatment of amblyopia.

This rare syndrome is a systemic condition that requires a multidisciplinary team to treat the patients with a holistic approach, address their needs and alleviate the emotional burden. It should always be included in the differential diagnosis in patients who present with skeletal anomalies and ocular motility disorders.

Introduction

Horizontal gaze palsy with progressive scoliosis (HGPPS) is a rare syndrome inherited in an autosomal recessive pattern[1]. The first cases were described by Crisfield 49 years ago[2]. Since that initial publication, several other case reports, or case series of patients with this rare syndrome have been published[3-14]. With this manuscript, our main aim is to provide a concise synopsis of this rare disease and give the ophthalmologist's perspective regarding its management.

This brief article aims to answer the following questions:

1. What is the incidence and prevalence of this rare disorder?
2. What is the genetic background of HGPPS?
3. What are the radiological findings of neuroimaging studies of patients with HGPPS?
4. What are the clinical manifestations of this condition?
5. What are the treatment options?

Epidemiology

According to Yi et al[1], approximately 100 patients with HGPPS have been described in the literature. Due to the scarcity in numbers of HGPSS, no large prospective longitudinal epidemiological studies exist to describe accurately the incidence and prevalence of this genetic condition[14]. As it is an autosomal recessive condition, there is no sex predilection and therefore both females and males can be equally affected. According to Xiu et al[15], most cases originated from consanguineous families, although HGPSS can occur in non-consanguineous families as well[5-7, 14].

Genetics

Horizontal gaze palsy with progressive scoliosis (HGPPS) exhibits an autosomal recessive mode of inheritance. It has been identified that the responsible gene implicated in the manifestation of HGPSS is called ROBO-3 gene (round-about guidance receptor 3, MIM#608630)[16, 17]. ROBO-3gene is situated in chromosome 11q23-q5[16, 17]. This gene encodes a protein that plays a pivotal role in the physiological formation and crossing of axonal neuronal fibers during embryological development[1, 7, 18]. Mutations in ROBO-3 gene result in aberrant crossing of axonal neuronal fibers and subsequent clinical manifestations of HGPPS.

According to Yi et al[1], prior to the publication of their manuscript, 55 mutations in ROBO-3 gene were identified[1]. According to the same report[1], these included 23 missense mutations, 11 nonsense mutations, five splicing mutations, 15 frameshift mutations, and one in-frame deletion[1]. Yi et al. described 2 additional novel mutations in a Chinese boy that led to an abnormal splicing in the ROBO-3 gene that resulted in intron retention[1]. Furthermore, Yi et al conducted an in-house review of their own data base and identified 5 more variants that could potentially be pathogenic[1]. Yi et al suggest that their findings will allow the expansion of the spectrum of ROBO-3 gene mutations and shed more light in the process of RNA sequencing for rare intronic variants that may affect splicing[1].

Radiological Findings of Hgpss

Magnetic Resonance Imaging (MRI) of the brain of HGPPS patients demonstrates very striking radiological features. These include brainstem hypoplasia with an anterior and dorsal pontine cleft and a butterfly shaped medulla and absence of the normal promontories of the facial colliculi (Figures 1 and 2)[19-22]. Interestingly, similar findings have been reported in animal models[23].

Clinical Manifestations

Mutations of ROBO-3 gene result in aberrant crossing of axonal neuronal fibers. As a result, the horizontal eye movements are predominantly affected[24]. There is bilateral horizontal gaze palsy and marked esotropia (convergent squint)[4, 7, 14, 24]. As the sixth nerve nucleus is hypoplastic or absent, the lateral recti muscles are very weak and the medial recti are overacting, resulting in a large angle esotropia[14]. The esotropia may remain constant or may become worse. In most cases, horizontal gaze palsy precedes scoliosis[1]. Scoliosis usually gets progressively worse. Nevertheless, ocular motility disorders at older age have also been described[24]. Pendular nystagmus can also be present[14, 25]. Other clinical manifestations include sensorineural hearing loss, stroke, and head bobbing[16, 26-29]. Vertical and convergence eye movements are usually preserved[3, 4, 14, 16]. Lid position, pupillary reflexes, confrontational visual fields, and fundus examination are usually unremarkable as well[14, 16].

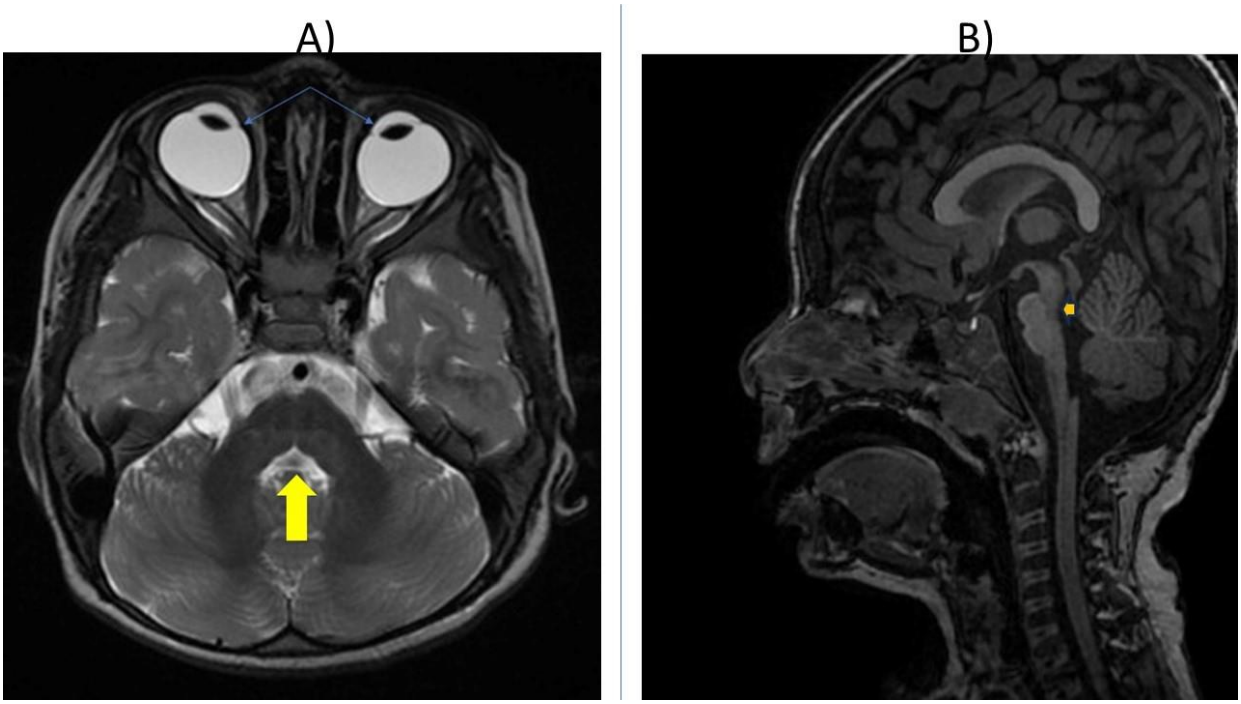

Figure 1: From left to right: A) Axial T2 MRI brain of HGPPS patient. Note the thin blue arrows showing marked esotropia (convergent squint). In addition, note the presence of dorsal pontine cleft and absent facial colliculus (Yellow arrow) B) Sagittal T1 Sequence MRI of brain of HGPPS patient. The small orange arrow with thin blue outline demonstrates the presence of hypoplastic brainstem with depression of the fourth ventricle.

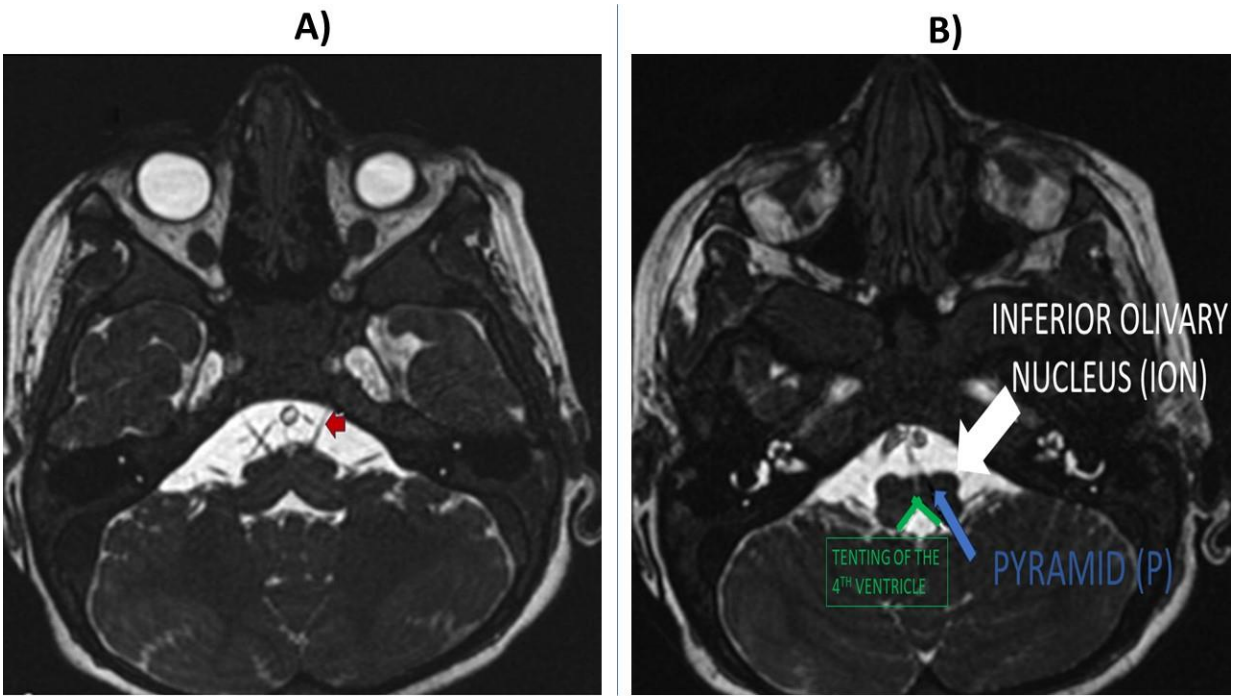

Figure 2: From left to right: A) Axial FIESTA Sequence MRI brain of HGPPS patient. The small dark red arrow demonstrates cisternal portion of the sixth (abducent) nerve. B) Axial FIESTA Sequence MRI brain of HGPPS patient showing butterfly configuration of the medulla with midline cleft. Note also the prominent Inferior Olivary Nucleus (ION) (Large Thick White Arrow) with respect to Pyramid (P) (Blue Arrow). Finally, the thick oblique green lines highlight the tenting of the fourth ventricle.

Regarding the extraocular manifestations of HGPPS, the most important symptom is the presence of scoliosis. Various reports suggest that the median age of onset for scoliosis in HGPPS is 6 years[12, 15, 24, 30-32]. The exact pathophysiological mechanism leading to scoliosis is yet to be determined. It has been suggested that the mutations in ROBO-3 gene and the aberrant crossing of nerve axons affecting the brainstem and the medulla oblongata affect important neuronal connections in the brain that play a significant role in the development of normal body posture[33]. In addition, a significant proportion of HGPPS patients may exhibit mental retardation, speech and global developmental delay and failure to thrive[1, 15].

In summary, HGPPS is a systemic condition that can affect the central nervous system, the eyes, and the musculoskeletal system. Therefore, as ophthalmologists, we recommend a multidisciplinary team approach to achieve a holistic management of such patients.

Treatment

There is currently no definitive cure for HGPPS. No gene therapy is available. Scoliosis can be managed using the input of physiotherapists and orthopedic surgeons. Developmental and speech delay may require the need for speech and language therapy.

Regarding the ocular manifestations, the convergent squint and nystagmus can be managed conservatively with prisms with the help of the orthoptics team. Cycloplegic refraction is also of paramount importance as it may unveil a significant refractive error that may require correction with spectacles. Strabismic or refractive amblyopia must be detected and treated promptly to maximize the visual potential of both eyes. The options of treatment of amblyopia include patching or atropine eye drops. Amblyopia treatment will require very good cooperation of the parents with the ophthalmology and orthoptic team. Furthermore, due to the developmental delay that many HGPPS patients have, it gets even more challenging to successfully treat amblyopia in this rare condition. Surgical correction of esotropia is also very challenging as it will require general anesthesia. HGPPS patients frequently have significant medical comorbidities, and they are not deemed fit enough to have general anesthesia and undergo squint surgery. If it is deemed safe to operate, surgical correction predominantly involves weakening of the medial recti muscles to alleviate the esotropia and aim to straighten both eyes. Meticulous pre-operative planning is required to avoid post-operative diplopia and post-operative exotropia (divergent squint) whilst operating on the medial recti muscles.

Conclusions

Horizontal gaze palsy with progressive scoliosis (HGPPS) is a rare systemic syndrome inherited in an autosomal recessive pattern. As ophthalmologists, we recommend that clinicians should include this rare syndrome in their differential diagnosis, especially in children who present with concomitant skeletal abnormalities and ocular motility deficits. HGPPS patients may have significant medical comorbidities. Therefore, a multidisciplinary team approach should be adopted with the contributions of clinicians (e.g., paediatric neurologists, orthopedic surgeons, ophthalmologists) and allied healthcare professionals (e.g., speech and language therapies, physiotherapists, orthoptists, psychologists, social services) to optimally manage their clinical symptoms and address their emotional needs. The contributions of the allied healthcare professionals are valuable so that these patients and their carers have enough practical and emotional support to be able to cope with the challenges involved with the day-to-day living with this rare condition.

Declaration

Both authors declare no conflicts of interest. In addition, they both declare that no funding was obtained for this work.

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