HORIZONTAL GAZE PALSY WITH PROGRESSIVE SCOLIOSIS: CASE REPORT

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ABSTRACT
Purpose: horizontal gaze palsy with progressive scoliosis (HGPPS) is an autosomal recessive disorder characterized by congenital absence of horizontal gaze, progressive scoliosis, and failure of the corticospinal and somatosensory axon tracts to decussate in the medulla. Case description: man with sporadic HGPPS, 26 years old, of non-consanguineous parents. Pupils were normal and there was full vertical motility. Horizontal saccades and pursuit movements were absent, and vestibulo-ocular reflex testing produced no horizontal eye movements. While in his adolescence, the patient presented scoliosis and underwent surgical treatment to avoid its progression. Conclusions: the HGPPS is a rare syndrome. Any patient with absence of horizontal gaze should be evaluated comprehensively to rule out other syndromic associations.

Keywords: Scoliosis; Horizontal gaze palsy.

PARALISIA DO OLHAR HORIZONTAL COM ESCOLIOSE PROGRESSIVA: RELATO DE CASO

RESUMO
Objetivo: escoliose progressiva com paralisia do olhar horizontal (EPPOH) é uma doença autossômica recessiva caracterizada pela ausência congênita do olhar horizontal, escoliose progressiva e falha na decussação de fibras motoras e sensitivas no bulbo. O objetivo desta revisão consiste na descrição de um relato de caso de um paciente com esta patologia. Descrição do caso: paciente do sexo masculino, 26 anos de idade, sem familiares com EPPOH. Seu exame neurológico não apresentava alterações pupilares. A movimentação vertical do olhar estava preservada e o movimento sacádico horizontal e de busca ausentes. O teste do reflexo vestíbulo-ocular não produzia movimento horizontal dos olhos. Durante a adolescência, o paciente cursou com escoliose progressiva e necessitou de artrodese para evitar a progressão da mesma. Conclusão: a EPPOH é uma síndrome rara e deve ser suspeitada quando qualquer paciente apresente paralisia do olhar horizontal e escoliose.

Palavras-chave: Escoliose; Paralisia do olhar horizontal.

INTRODUCTION

Horizontal gaze palsy with progressive scoliosis (HGPPS) is a rare disorder characterized by congenital absence of horizontal conjugate eye movements with a progressive scoliosis that develops in childhood and adolescence. 1 HGPPS is included in the group of ocular congenital cranial dysinnervation disorders (CCDDs).[3]

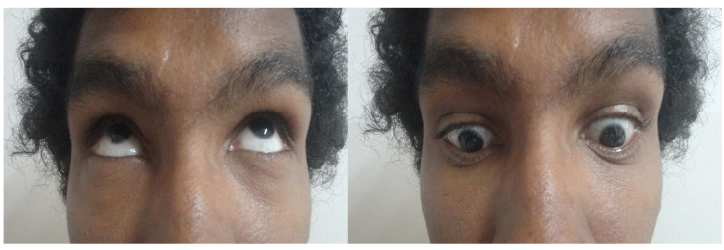
CASE REPORT

Male, 26 years old, comes to our medical service looking for neurologic evaluation to a headache. The patient was evaluated for his complaints and received a comprehensive approach. He received treatment for his disease as well as orientations to come back to our service when in need and for revaluations. The patient authorized the use of the case here presented for scientific purposes, as well as the usage of his pictures and imaging exams. During his evaluation was noticed absent bilateral horizontal gaze. (Picture 01) According to him, this problem started when he was a teenager. Also in his adolescence he noticed progressive and marked thoracic scoliosis and, after orthopedic evaluation, he underwent a thoracic-lumbar arthodesis in order to avoid scoliosis progression. (Picture 02, 03) Associated to these clinical findings was observed left ear malformation and bilateral hearing impairment, but without the necessity to use hearing devices. (Picture 04)

Neither his parents nor other relatives have ocular or musculo-skeletal diseases. His pregnancy was normal. He was born at term by, at the time, his 35-year-old primigravida mother by cesarean.

Spine X-rays at 25 years of age showed a severe scoliosis convex to the left at the thoracic level. Cervical CT scan has found cervical vertebrae anomalies with a C5-C6 and C7-T1 fusion similar to Klippel-feil Syndrome. (Picture 05) Brain CT scan showed anomalous calcification on the external occipital protuberance extended to the nuchal line. Other alterations on brain TC scan were not found. (Picture 06)

Picture 1 - pacient with HGPPS demonstrating absent horizontal eye movement but with normal upward and downward vertical gaze



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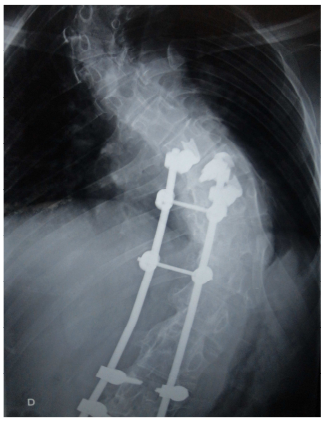
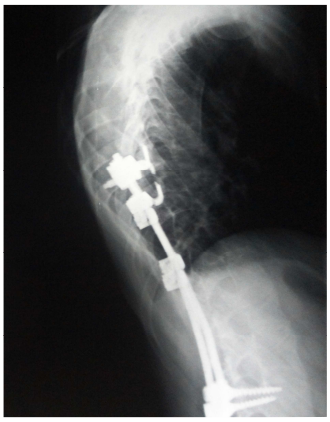
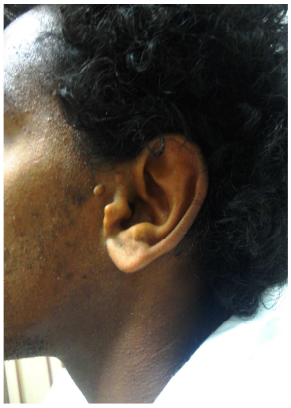
Picture 2 - Chest X-ray, anteroposterior view, showing thoracic-lumbar artrodesis.



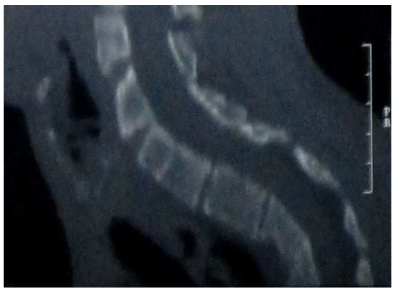
Picture 3 - Chest X-ray, lateral view, showing thoracic-lumbar arthrodesis.



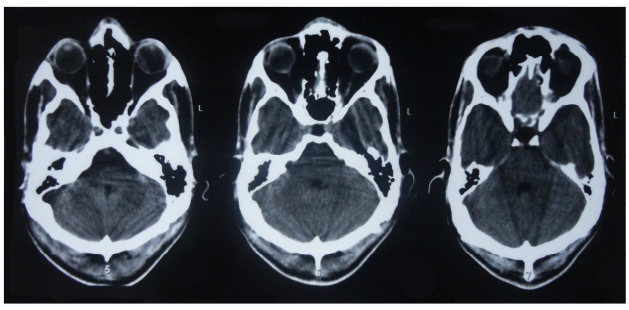
Picture 4 - unilateral malformation of the outer ear.



Picture 5 - Cervical CT scan showing sagital incidence-vertebrae fusion in C5-C6 and C7-T1.



Picture 6 - Cranial CT scan showing nuchal ligament calcification.



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DISCUSSION

Ocular congenital cranial dysinnervation disorders (CCDDs) refers to disorders of innervation of cranial musculature.3The ocular CCDDs are also included in the category of complex or incomitant strabismus, in which the degree of misalignment of the eyes varies with the direction of gaze.[3] Duane syndrome is the most common of the ocular CCDDs. Ocular CCDDs include the following:

- *Duane syndrome* is a strabismus syndrome characterized by congenital non-progressive horizontal ophthalmoplegia (inability to move the eyes) primarily affecting the abducens nucleus and nerve and its innervated extraocular muscle, the lateral rectus muscle. [3] At birth, affected infants have restricted ability to move the affected eye(s) outward (abduction) and/or inward (adduction).1 In addition, the globe retracts into the orbit with attempted adduction, accompanied by narrowing of the palpebral fissure.[1] Most individuals with Duane syndrome have strabismus in primary gaze but can use a compensatory head position to align the eyes, and thus can preserve single binocular vision, avoiding diplopia.[1] Individuals with Duane syndrome who lack binocular vision are at risk for amblyopia. [3] Approximately 70% of individuals with Duane syndrome have isolated Duane syndrome, i.e., they do not have other detected congenital anomalies.[1]
- *Congenital fibrosis of the extraocular muscles (CFEOM*) refers to at least seven genetically defined syndromes: CFEOM1A, CFEOM1B, CFEOM2, CFEOM3A, CFEOM3B, CFEOM3C, and Tukel syndrome[1,3] CFEOM is characterized by congenital non-progressive ophthalmoplegia (inability to move the eyes) that is restrictive and includes some limitation of vertical gaze. It often, but not always, includes ptosis (droopy eyelids).[1,3] It typically results from aberrant development of all or part of the oculomotor nucleus and nerve (cranial nerve III) and its innervated muscles (superior, medial, and inferior recti, inferior oblique, and levator palpebrae superioris) and/or the trochlear nucleus and nerve (cranial nerve IV) and its innervated muscle (the superior oblique).[1,3] In general, affected individuals have severe limitation of vertical gaze and variable limitation of horizontal gaze.[1,3] Individuals with CFEOM frequently compensate their ophthalmoplegia by maintaining abnormal head positions at rest and by moving their heads rather than their eyes to track objects. Individuals with CFEOM3A may also have intellectual and social disability, facial

weakness, and/or a progressive axonal peripheral neuropathy (a form of Charcot-Marie-Tooth disease).[1,3] Individuals with CFEOM3C also have intellectual disability and facial dysmorphism reminiscent of Albright hereditary osteodystrophy-like syndrome.[1,3]Individuals with Tukel syndrome also have postaxial oligodactyly or oligosyndactyly of the hands.[1,3]

- *Moebius syndrome* is characterized by sixth and seventh nerve palsies, resulting in abduction defect and facial weakness. The vast majority of individuals with Moebius syndrome are simplex cases (i.e., single occurrence in a family) and many are associated with additional developmental defects of lower cranial nerves and distal extremities.[1,3]
- *Hereditary congenital facial paresis* is characterized by the isolated dysfunction of cranial nerve VII. It may be confused with Moebius syndrome if it is coincidentally accompanied by strabismus.[3]
- *Horizontal gaze palsy with progressive scoliosis* is characterized by congenital horizontal gaze palsy (no horizontal eye movements) accompanied by progressive scoliosis.[3] HGPPS is inherited in an autosomal recessive manner and is caused by mutations in *ROBO3*.4 Compound heterozygous *ROBO3* mutations have also been identified in children of non-consanguineous parents.[5] Neuroimaging and neurophysiology studies of individuals with HGPPS found that the axons that make up the major motor and sensory pathways for communication between the brain and the spinal cord fail to cross the midline in the hindbrain.

Patients with this syndrome presents with horizontal gaze palsy was fully penetrant, present at birth, and total or almost total in all affected individuals.[8] Convergence, ocular alignment, congenital nystagmus, and vertical smooth pursuit defects were variable between individuals.[8] All patients developed progressive scoliosis during early childhood. [8] The scoliosis progresses when the children begin to walk.[9] Even when they are treated with physiotherapy or brace, they often require early operation.[9]

The first description of a family who had scoliosis associated with progressive external ophthalmoplegia was performed by Dretakis in 1970.[2] Crisfield in 1974 observed 4 (2 male, 2 female) of 11 siblings with severe scoliosis and progressive external ophthalmoplegia.[6] Weakness of trunk muscles or other neurologic diseases were not detected. Sharpe in 1975 reported further on this Chinese family of Hakka extraction.[7] All 4 siblings had paralysis of horizontal (i.e., lateral) gaze, that developed in their first decade of life.[7] They also showed

pendular nystagmus and progressive scoliosis.[7] The oldest sibling developed, in his 20s, bilateral facial myokymia and continuous contracture of the facial muscles. [7] The site of the neurologic lesion was thought to be the supranuclear areas of the pons.[7] Other case reports were performed by Jen et al. and Bosley at al. more recently.[4] Jen et al. identified 10 different mutations in the ROBO3 gene.[4] Each of the mutations were found in homozygosity and included 1 nonsense, 1 splice site, 2 frameshift, and 6 missense mutations, 4 of which resulted in nonconservative changes to amino acid residues that are evolutionarily conserved. It was found that ROBO3 is required for hindbrain axon midline crossing, explaining the horizontal gaze palsy in this condition.[4] MRI in patients with HGPPS show abnormal flattening of the basis pontis, and hypoplasia in the pontine tegmentum are evident on sagittal sections. [4] The structural alterations in caudal pons suggests potential involvement of the abducens nuclei, the medial longitudinal fasciculus, and the pontine paramedian reticular formation.[4] The medulla appeared abnormally butterfly-like, with anterior flattening and an unusual midline cleft.[4] The abducens nerves were visualized bilaterally in the extra-axial space, and orbital MRI demonstrated normal extraocular muscle configuration and size, as well as the presence of apparently normal intraorbital motor nerves to the medial and lateral rectus muscles. [4]

Somatosensory evoked potential studies in patients usually show abnormally reversed lateralization of these responses, indicating uncrossed ascending dorsal column-medial lemniscal sensory pathways.[4]

Motor evoked potential studies in these patients show abnormally ipsilateral muscle responses, reflecting uncrossed descending corticospinal motor pathways.[4] Uncrossed corticospinal and dorsal column-medial lemniscal pathways and the abnormal midline cleft in the medulla observed in these patients suggested the absence of pyramidal and internal arcuate decussations and a role for the HGPPS gene in hindbrain axon pathway crossing and morphogenesis. [4] Horizontal gaze palsy with progressive scoliosis does not present treatment for horizontal gaze palsy but the progressive scoliosis may require surgical stabilization. Physical therapy can be beneficial.

CONCLUSIONS

Horizontal gaze palsy with progressive scoliosis is a rare disorder characterized by congenital absence of horizontal conjugate eye movements with progressive scoliosis that

develops in childhood and adolescence. Duane syndrome is the most common of the Ocular congenital cranial dysinnervation disorders and must be a differential diagnosis.

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