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Early-Onset Ataxia with Oculo-Motor Apraxia and Hypoalbuminemia – A Rare Case Report from South Indian Region

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Abstract:

Neurodegenerative diseases commonly manifest as progressive deterioration of neurological function in varied forms. Damage to the cerebellum disrupts the coordination of limb and eye movements, impairs balance, and decreases muscle tone. A 11-year-old male child born to consanguineous parents, developmentally normal until five years of age, presented with a history of frequent falls while walking and speech difficulty from the age of five years. On examination, bilateral ocular motor apraxia was seen with an ataxic gait and slurred speech. All the other cerebellar signs were present. Magnetic resonance imaging of the brain revealed severe cerebellar vermian hypoplasia with global cerebellar cortex atrophy. Suspecting an inherited cause of ataxia, whole exome sequencing was done, which revealed a frameshift mutation in the aprataxin gene with the diagnosis of Early-onset ataxia with oculomotor apraxia and hypoalbuminemia (EAOH). While evaluating a case of ataxia, EAOH should be kept as a differential diagnosis, as though it is a rare entity, it can prove to be a chronic disabling disorder for children requiring life-long physical rehabilitation and occupational therapy.

Key Words:

Aprataxin gene, early-onset ataxia, inherited cerebellar ataxia, oculo-motor apraxia

Key Message:

After ruling out common causes of cerebellar ataxia like post viral, post traumatic, stroke, and posterior fossa tumors, inherited causes must be thought of, as the prognosis is guarded and a detailed genetic workup is necessary, which will help in genetic counseling and pre-natal genetic diagnosis in future pregnancies.

Ataxia is a neurological disorder defined by the inability to make smooth, accurate, and coordinated movements.[1] The commonly encountered autosomal recessive cerebellar ataxias in children is Friedreich's ataxia (FA) worldwide, followed by ataxia-telangiectasia (AT). Early-onset ataxia with ocular motor apraxia and hypoalbuminemia (EAOH; Online Mendelian Inheritance in Man [OMIM]: 208920) is an autosomal recessive ataxia characterized by an early-age onset (3–12 years) of cerebellar ataxia with dysarthria and oculomotor apraxia. External ophthalmoplegia, choreiform movements of the limbs, facial grimacing, mental deterioration, and cerebellar atrophy are usually seen.[2]

Peripheral axonal neuropathy, hypoalbuminemia, and hypercholesterolemia are often associated with the later stage of the disease. EAOH was first reported in Japan in 1993.[3]

Here, we present the rare case of EAOH reported from the South Indian region.

Case Details

A 11-year-old male chid, second-born to second-degree consanguineous parents hailing from South India, presented with frequent falls while walking since the age of five years, which gradually progressed to difficulty maintaining balance in standing posture and an inability to walk independently.

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Child attained milestones in all domains appropriate for age until five years, when he had an episode of fever with a rash (varicella) following which the parents started noticing frequent unsteadiness of gait, which was associated with a change in the nature of speech. He was initially diagnosed as a case of post viral cerebellar ataxia by a general physician and was reassured. No history of giddiness, vomiting, convulsions, altered sensorium, memory disturbances, drooling of saliva, difficulty swallowing, visual disturbances, weakness in any limbs, sensory disturbances, or bowel bladder disturbances. The birth history was normal. There was no family history of any neurological disorders.

On general examination, the child was thin-built, alert, active, conscious, and oriented. The child's weight was 24 kg, height was 138 cm, and head circumference was 52 cm. He had bilateral ocular telangiectasia, bilateral pes cavus deformity, and scoliosis of the spine [Figure 1a and b]. Slurred speech and oculomotor apraxia were seen. Cranial nerve examination was normal. Motor and sensory examinations were normal. Ataxia and all cerebellar signs were present. Plantar reflexes were flexor bilaterally.

The complete hemogram, liver function tests, alpha-fetoprotein, and serum immunoglobulins were normal. Magnetic resonance imaging (MRI) of the brain showed severe cerebellar vermian hypoplasia with global cerebellar cortex atrophy [Figure 2].

Suspecting an inherited etiology, whole-exome sequencing was done, which was suggestive of EAOH. The report has been briefed in Table 1 and the figure of Integrative Genomics Viewer (IGV) has been given in Figure 3.

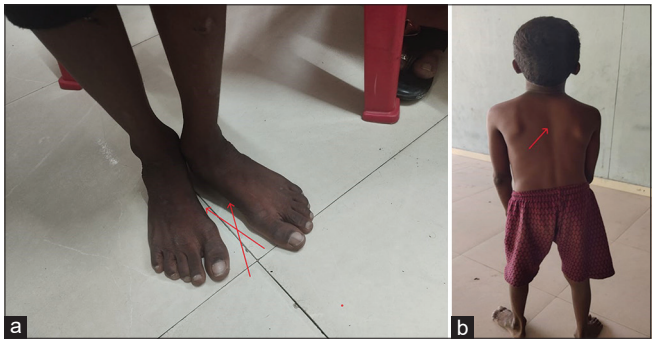

Figure 1: (a) Feet of the child showing bilateral pes cavus deformity (red arrow). (b) Back of the child – depicting scoliosis deformity of the spine (red arrow)

Discussion

While clinically diagnosing inherited cerebellar ataxia in children, though AT is more common, however history of recurrent infections and abnormal immunological parameters were not seen in our case, hence AT was a remote possibility.

A homozygote frameshift variant c.596delG in exon 6 of the aprataxin (*APTX*) gene that results in the premature termination of the protein p.Arg199fs*15 was identified in our patient. The observed variant has a minor allele frequency of 0.00002 in exomes and genomes, respectively. The severity of the impact of this variant on the protein is high, based on the effect of the protein and the REVEL score. Based on the literature evidence so far reported, pathogenic mutations in APTX have been predominantly frameshift mutations associated with severe phenotypes and our child has a frameshift mutation, which was reported earlier in three Indian patients.[4] There is a significant clinical correlation noted with the genotype, along with the age of onset, consanguinity, and MRI findings.

In our case, the age of onset of cerebellar ataxia was five years, which is similar to EAOH cases reported by Shimazaki *et al*.[2] (3–12 years). The youngest age for EAOH was given by Ito *et al*. from Japan (18 months). The pathognomonic manifestation of EAOH is oculo-motor apraxia, which as seen in our case, is also well described in other studies.[2,3] Sugawara *et al*.[5] explained that the loss of Purkinje cells in the cerebellar flocculus in brain biopsy samples of autopsied AOA1/EAOH adult patients may be the reason for oculo-motor apraxia.

Apart from intentional tremors, our case did not have any other involuntary movements; however, choreoathetoid and dystonic movements were reported in other studies. Peripheral neuropathies in the second decade of life have been reported in other studies, which in our case have not yet developed.[2,6]

Kato *et al*.[7] showed the laboratory and immunological abnormalities associated with EAOH in nine adult patients, where B or T lymphopenia, decreased CD4 and CD8 T-cells, and hypogammaglobulinemia were observed, similar to AT but milder. However, in our case, there was no such abnormality at this age; however, follow-up is needed as the child ages.

Our case had normal albumin and cholesterol levels, whereas hypoalbuminemia and hypercholesterolemia were reported at later ages (>20 years) in other studies.[2,3,7]

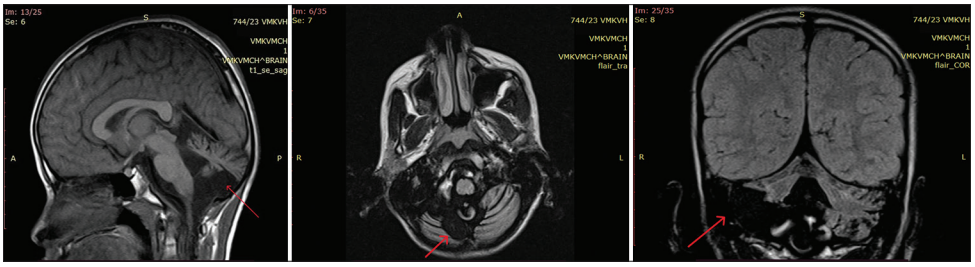

Figure 2: Sagittal, coronal, and axial sections of T1-weighted MRI of the brain of the case showing cerebellar vermian hypoplasia with global cerebellar cortex atrophy (red arrow)

Figure 3: IGV image of the genetic abnormality

Table 1: Whole-exome sequencing report for our case

Gene and transcript	Variant	Location	Zygosity	Disorder (OMIM)	Inheritance	Variant classification
APTX NM_001195248.2 Chr.9: 32984802 (AC/A)	c.596delG p.Arg199fs*15	Exon 6	Homozygous	Ataxia, early onset with oculomotor apraxia and hypoalbuminemia; EAOH: 208920	Autosomal recessive	Pathogenic

Table 2: Comparison of genetic mutation patterns of our case with similar cases from other populations

Study	No. of patients	Diagnosis	Zygosity	Type of mutation	Gene	Variant
Our case (2023)	One Indian adolescent male	EAOH	Homozygous	Frameshift	*APTX* NM_001195248.2 Exon 6	c.596delG p.Arg199fs*15
Yokoseki *et al*. (2011)[6]	Fifty-eight Japanese adults	EAOH	Homozygous Compound heterozygous	Frameshift Frameshift with missense	*APTX* gene	c.689_690insT c.689_690insT, p.Pro206Leu, or p.Val263Gly
Ito *et al*. (2005)[3]	Two Japanese adolescent females	EAOH	Compound heterozygous	Frameshift with missense	*APTX* gene in exon 5	689insT G692A
Bras *et al*. (2001)[11]	Eight Portugal families	AOA	Homozygous or compound heterozygous	-	PNKP	c.1123G>T (p.Gly375Trp)

The MRI findings of global cerebellar cortex atrophy with severe vermian hypoplasia reported in our case are similar to the MRI findings reported by Sugawara *et al*.[5]

A comparison of the genetic pattern of our study with other similar studies has been described in Table 2.

Date *et al*., in 2001, first found a new gene of the Histidine triad superfamily quoted as "*APTX*" encoding the aprataxin protein as the causative gene for EAOH.[8] Takahashi *et al*. hypothesized that the function of the aprataxin protein is to facilitate DNA single-strand break repair. In the *APTX* gene mutation, the aprataxin protein lacks this activity, leading to cerebellar atrophy.[9]

As there is no definitive treatment for EAOH, rehabilitation in the form of physiotherapy, speech therapy, and occupational therapy remains the mainstay of management. We have advised physiotherapy and speech therapy for our case.

Newer therapies like noninvasive cerebellar stimulation using anodal transcranial direct current stimulation and transcranial magnetic stimulation (TMS), have shown some benefits in ataxia for posture and gait. Drugs like riluzole have been under trial for FA.[10] Such options may be tried for EAOH too.

While evaluating a case of ataxia, EAOH should be kept, as a differential diagnosis as though it is a rare entity, it can prove to be a chronic disabling disorder for children requiring life-long physical rehabilitation and occupational therapy. Genetic counseling and prenatal genetic diagnosis play an important role.

Acknowledgement

We sincerely thank the parents of the child who gave consent for the publication of the details of the child's disease. The parents have permitted their child's case details and blinded photographs to be included in the manuscript.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest
There are no conflicts of interest.

References

1. Movement disorders. In: Kliegman RM, Stanton BF, St Geme JW, Schor NF, Ramirez-Montealegre D, Mink JW et al. editors. Nelson Textbook of Pediatrics. 21st ed. Philadelphia, USA: Sounders, Elsivier; 2019. p. 3150-67.
2. Shimazaki H, Takiyama Y, Sakoe K, Ikeguchi K, Niijima K, Kaneko J, *et al*. Early-onset ataxia with ocular motor apraxia and hypoalbuminemia: The aprataxin gene mutations. Neurology 2002;59:590-5.
3. Ito A, Yamagata T, Mori M, Momoi MY. Early-onset ataxia with oculomotor apraxia with a novel APTX mutation. Pediatr Neurol 2005;33:53-6.
4. Renaud M, Moreira M, Ben Monga B, Rodriguez D, Debs R, Charles P, *et al*. Clinical, biomarker, and molecular delineations and genotype-phenotype correlations of ataxia with oculomotor apraxia type 1. JAMA Neurol 2018;75:495–502.
5. Sugawara M, Wada C, Okawa S, Kobayashi M, Sageshima M, Imota T, *et al*. Purkinje cell loss in the cerebellar flocculus in patients with ataxia with ocular motor apraxia type 1/early-onset ataxia with ocular motor apraxia and hypoalbuminemia. Eur Neurol 2008;59:18-23.
6. Yokoseki A, Ishihara T, Koyama A, Shiga A, Yamada M, Suzuki C, *et al*. Genotype-phenotype correlations in early onset ataxia with ocular motor apraxia and hypoalbuminaemia. Brain 2011;134:1387-99.
7. Kato T, Tamura Y, Matsumoto H, Kobayashi O, Ishiguro H, Ogawa M, *et al*. Immunological abnormalities in patients with early-onset ataxia with ocular motor apraxia and hypoalbuminemia. Clin Immunol 2021;229:108776.
8. Date H, Onodera O, Tanaka H, Iwabuchi K, Uekawa K, Igarashi S, *et al*. Early-onset ataxia with ocular motor apraxia and hypoalbuminemia is caused by mutations in a new HIT superfamily gene. Nat Genet 2001;29:184-8.
9. Takahashi T, Tada M, Igarashi S, Koyama A, Date H, Yokoseki A, *et al*. Aprataxin, causative gene product for EAOH/AOA1, repairs DNA single-strand breaks with damaged 3'-phosphate and 3'-phosphoglycolate ends. Nucleic Acids Res 2007;35:3797-809.
10. Agarwal A, Garg D, Faruq M, Rajan R, Goyal V, Srivastava AK. Treating hereditary ataxias—where can we help? Ann Natl Acad Med Sci 2019;55:182-8.
11. Bras J, Alonso I, Barbot C, Costa MM, Darwent L, Orme T, *et al*. Mutations in PNKP cause recessive ataxia with oculomotor apraxia type 4. Am J Hum Genet. 2015 Mar 5; 96(3): 474-9.