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Original Research Paper

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A RARE CASE REPORT OF INFANTILE ONSET ASCENDING HEREDITARY SPASTIC PARALYSIS

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ABSTRACT **Background:** Infantile-Onset Ascending Hereditary Spastic Paralysis (IAHSP) is a rare, progressive neurodegenerative disorder caused by mutations in the ALS2 gene. It typically presents during infancy with delayed developmental motor milestones, hypertonia, and lower limb spasticity, progressing to involve the upper limbs and resulting in severe motor impairment. Cognitive function is usually preserved, and MRI findings are often normal, making genetic testing essential for diagnosis. **Case Presentation:** We report the case of a 4½-year-old girl presenting with delayed motor development and progressive spasticity, initially affecting lower limbs and later extending to the upper limbs. Diagnostic workup, including MRI and nerve conduction studies, was unremarkable. Whole-exome sequencing revealed a homozygous nonsense variant in the ALS2 gene, confirming the diagnosis of IAHSP. Symptomatic treatment, including physiotherapy, syndopa (levodopa + carbidopa) and anti-spasticity medications, was initiated with limited success. **Conclusion:** IAHSP is a rare genetic disorder with a poor motor prognosis. Early diagnosis through genetic testing is crucial for management, and multidisciplinary care plays a vital role in improving the quality of life, although significant motor improvement remains unlikely.

KEYWORDS : Infantile spastic paralysis

INTRODUCTION:

Infantile-Onset Ascending Hereditary Spastic Paralysis (IAHSP) is a rare autosomal recessive neurodegenerative disorder caused by mutations in the ALS2 gene. The disorder is part of a group of hereditary spastic paraplegias (HSPs) characterized by progressive weakness and spasticity, predominantly affecting the lower limbs before ascending to involve the upper limbs and bulbar muscles. Clinical features typically present in infancy, with delays in motor milestones such as sitting and walking, hypertonia, and brisk reflexes.

Though the disease's onset and progression are well-documented, it remains exceedingly rare, with around 30 cases reported globally. Diagnosis is primarily based on genetic testing, as neuroimaging such as MRI often fails to show significant abnormalities. Treatment focuses on symptom management, with physiotherapy and anti-spasticity medications playing key roles in managing the condition, though motor function continues to deteriorate. Here, we report a rare case of IAHSP in a 4½-year-old girl, highlighting the clinical presentation, diagnostic challenges, and the importance of early genetic confirmation.[1,2]

Case Report:

Case Presentation:

A 4 1 2-year-old girl, the first child of non-consanguineous parents with no family history of neurological disorders, was born at full term via spontaneous vaginal delivery, weighing 2.75 kg. The pregnancy was uneventful, with the mother taking routine prenatal supplements, and there were no complications during delivery or need for a NICU stay.

During the first year of life, her mother noted delays in motor devlopmental milestones. The child achieved sitting with support at 8 months and had difficulty pulling to stand and cruising, which was achieved only by 16 months. Despite these delays, her cognitive and social development remained normal. However, by 22 months of age, concerns about her motor development led to a referral to a pediatric neurologist.

Upon neurological assessment, the child exhibited bilateral lower limb hypertonia and brisk reflexes, with clonus present at the ankles. Initial investigations, including an MRI of the brain and spine as well as a nerve conduction study (NCV), were normal. Physiotherapy was initiated, but her motor condition showed no significant improvement.

By the age of 4½ years, the spasticity had ascended to involve the upper limbs, and dystonia became evident. The child also developed spastic speech, although her cognition remained unaffected. On further evaluation, a genetic investigation using whole-exome sequencing confirmed a homozygous nonsense variant in the ALS2 gene, leading to the diagnosis of Infantile-Onset Ascending Hereditary Spastic Paralysis (IAHSP). Both parents were found to be heterozygous carriers of the pathogenic variant.

Table 1: examination findings

Examination Findings	Age	
	22 months	4.5 year
General examination	• No dysmorphic facial features • Bilateral talipes-equinovalgus foot deformity (Image 1)	• No dysmorphic facial features • Bilateral talipes-equinovalgus foot deformity
Cognition	Normal	Normal
Tone	• Bilateral Lower limb spasticity • Upper Limb Normal	• Spastic Quadriparesis (lower limb > upper limb)
Power	• Lower limb: Bilateral weakness in dorsiflexion foot	• Lower limb: Bilateral weakness dorsiflexion of foot • Upper limb: Normal

	• Upper limb: Normal	
Deep tendon reflex	Brisk at ankle and knee joint and bilateral ankle clonus is present	All deep tendon reflex is Brisk and bilateral ankle clonus is present
Babinski sign	Positive	Positive
cranial nerve	Intact	Intact
Speech	Normal	Spastic
Involuntary movements	Absent	Generalized dystonia present
Gait	• Steppage gait/ Tendoachilles spasticity	• Steppage gait/ Tendoachilles spasticity
Systemic examination (GI)	No hepatosplenomegaly	No hepatosplenomegaly

- **Investigation:**

Table 2: Investigation during admission

Investigation	22 months of age	4.5 years of age
Creatine-kinase MB (<5 ng/ml)	3.09	-
Nerve conduction velocity-NCV study	Normal	Normal
MRI brain with whole spine screening	Normal	Normal
Tandem mass spectrometry	-	Normal
Whole exome sequencing	-	ALS2 mutation

MRI : Magnetic resonance imaging

Table 3: Genetic report

Gene	ALS 2(-) (ENST00000264276.11)
Location	Exon 21
Variant	(p.Arg1139Ter)
Zygosity	homozygous
Disease	Infantile onset ascending hereditary spastic paralysis(OMIM#607225)
Inheritance	Autosomal recessive

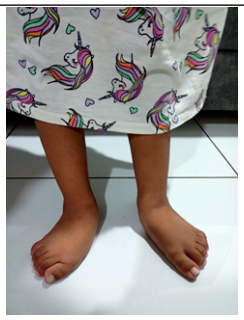

Image 1: Bilateral Talipes-equinovalgus due to Tendo-achilles spasticity

- **Treatment & Follow up:**

The patient was initially started on

1. Syndopa trial(levodopa 10mg+ carbidopa 2.5mg) 12 hourly, with weekly dose increment was started for dystonia management at the age of 4.5 years.

Following the failure of a two month trial with Syndopa, the medication was discontinued and the patient was started on

2. Syrup baclofen 1mg 8 hourly, weekly dose increments up-to 5 mg hourly and
3. Tablet trihexyphenidyl 0.5mg 8 hourly, weekly dose increments up to 1 mg 8 hourly. After 1 months of inadequate response patient was started on

4. Tablet clonazepam 0.0625 mg 12 hourly, with monthly dose increment to 0.125mg 12 hourly.

A multidisciplinary care approach was implemented, involving a team of specialists including a pediatric neurologist, physiotherapist, occupational therapist, and speech and language therapist. Regular physiotherapy sessions were emphasized to prevent contractures and improve motor function.

- **Follow Up:** On follow-up visit at 6 months, all the symptoms are static(unable to ambulate independently) with regular medications and physiotherapy. No side effects of baclofen, trihexyphenidyl, clonazepam or syndopa have been recorded.

DISCUSSION:

Infantile-Onset Ascending Hereditary Spastic Paralysis (IAHSP) is a rare autosomal recessive neurodegenerative disorder associated with mutations in the ALS2 gene, which encodes the ALSIN protein.[1] This protein is essential for neuronal development and function, influencing key processes such as axonal transport and neuronal structure.[2] It is a rare disease with at least 30 cases reported in the literature.[3] IAHSP is part of a collection of genetic diseases called hereditary spastic paraplegias and is characterized by ascending spastic paralysis that usually begins in the lower limbs (pure type) within the first 2 years of life and progressively affects the upper limbs and head and neck (complicated type).[4] Children have a normal examination at birth. Early manifestations of the disease include hyperreflexia and muscle twitching in the lower limbs, followed by tightness and weakness.[5] Although patients with the complicated type develop anarthria along with upper and lower limbs paralysis, their cognition remains preserved.[6]

Our case highlights several key aspects of IAHSP. The patient presented with early developmental delays and progressive spasticity, initially affecting the lower limbs and later involving the upper limbs, consistent with the disease's progression.[7] Despite normal MRI and nerve conduction studies, the diagnosis was confirmed through whole-exome sequencing, which identified a homozygous nonsense variant in the ALS2 gene.[8] This finding aligns with the typical genetic basis of IAHSP, where mutations in ALS2 lead to the characteristic neurodegenerative changes.

The differential diagnosis for this patient, presenting with spastic quadriparesis predominantly affecting the lower limbs, included several conditions. Juvenile Primary Lateral Sclerosis (PLS) and Juvenile Amyotrophic Lateral Sclerosis (ALS) were considered, but the absence of widespread upper motor neuron signs and neuroimaging findings, such as brain atrophy, helped rule them out.[6] Cerebral Palsy (CP), typically associated with early developmental insults, was excluded due to the lack of neuroimaging evidence like periventricular leukomalacia.[5] Pelizaeus-Merzbacher Disease, Canavan Disease, Purine Nucleoside Phosphorylase Deficiency are other differential diagnosis for this presentation.[7,8] Ultimately, comprehensive clinical assessment, neuroimaging, genetic testing, and biochemical evaluations confirmed the diagnosis of Infantile-Onset Ascending Hereditary Spastic Paralysis.[4]

Management of IAHSP focuses on symptomatic relief and improving quality of life. Although no curative treatment exists, symptomatic interventions, including antispasticity medications and multidisciplinary care, can help manage symptoms and enhance functional outcomes.[8] Physiotherapy and occupational therapy are crucial in addressing motor impairment and preventing complications, while assistive devices may be necessary as the disease progresses.[5]

The long-term prognosis for IAHSP is variable. Life expectancy is typically not shortened; however, quality of life is diminished due to the gradual loss of motor function, with

many patients eventually becoming wheelchair-bound.[8] Early intervention with supportive therapies can help in managing symptoms and prolonging functional independence.

CONCLUSION:

This case of a 4½-year-old girl with Infantile-Onset Ascending Hereditary Spastic Paralysis (IAHSP) underscores the value of early genetic testing, particularly when neuroimaging and other diagnostics are unremarkable. The patient's progressive spasticity, confirmed through a homozygous ALS2 mutation, highlights the typical clinical course of IAHSP. Despite symptomatic management and multidisciplinary care, motor function continued to decline, reflecting the poor prognosis of this condition. Early diagnosis and supportive care are crucial, though more research is needed to explore effective treatments.

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