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Case Report

Hereditary spastic paraplegia associated with a rare endoplasmic reticulum lipid raft-associated protein 2 mutation

Sai Chandar Dudipala*, Naveen Reddy Cheruku, Krishna Chaithanya Battu

Department of Pediatric Neurology, Star women and Children Hospital, Karim Nagar, Telangana, India

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***Correspondence:**
Dr. Sai Chandar Dudipala,
E-mail: drsaichander@gmail.com

ABSTRACT

Hereditary spastic paraplegia (HSP) is a clinically and genetically heterogeneous group of neurological disorders that are characterized by progressive spasticity of the lower extremities. It can present as pure form or complex form. It can be present from infancy to adulthood, but majority in adult population. Childhood onset HSP must be differentiated from common conditions like cerebral palsy, neurodegenerative disorders and metabolic disorders. Many patients with pediatric HSP are mistakenly diagnosed with cerebral palsy. In children with spastic paraplegia in whom no acquired cause identified, HSP should be considered. Here we diagnosed a 6-year-old boy with HSP who presented with progressive spastic paraplegia, intellectual disability, seizures, joint contractures and cataract. His genetic study revealed exonic deletion of endoplasmic reticulum lipid raft-associated protein gene, which is associated with complicated Autosomal recessive HSP 18 (SPG18). HSP 18 was rarely described in literature.

Keywords: Cerebral palsy, Endoplasmic reticulum lipid raft-associated protein 2, Gene, Spastic paraplegia

INTRODUCTION

Hereditary spastic paraplegia (HSP) is a genetically and clinically heterogeneous group of disorders in which the main clinical feature is progressive lower limb spasticity secondary to pyramidal tract dysfunction.[1] HSP can present as a pure form only with pyramidal symptoms, or as a complex form associated with other symptoms. HSP may be inherited as an autosomal dominant, autosomal recessive, or X-linked disease. Adolf von Strümpell and Sigmund Freud were among the first to describe the condition towards the end of the 19th century.[2,3] HSP is rare, with prevalence estimates ranging from 1.2 to 9.6 per 100,000.[4] Although the age of symptom onset varies widely from infancy to late adulthood, mostly adult case series dominate the literature. There have been only a few studies in children. Childhood onset HSP needs to be differentiated from more common conditions like cerebral palsy and other mimicking neurodegenerative disorders. Clinical examination is unspecific and diagnosis requires confirmation by DNA analysis. Because of these issues, clinicians have little knowledge about HSP and diagnosis is often delayed. Improving knowledge of HSP would lead to earlier diagnosis, rehabilitation, isolate genetic causes, and develop therapeutic strategies.

We describe the case of a patient who was diagnosed with HSP based on the results of gene testing; the disease-causing gene was determined to be endoplasmic reticulum lipid raft-associated protein 2. HSP related to endoplasmic reticulum lipid raft-associated protein 2 (ERLIN2) gene mutations is very rarely observed in practice.

CASE REPORT

A 6-year-old boy born of 3rd degree consanguineous marriage presented to pediatric neurology clinic with complaints of progressive spasticity and speech delay. Pregnancy and birth history were uneventful with no indication of intrauterine or perinatal hypoxia or other

neonatal complications. Early motor milestones were achieved within the normal limit up to 18months of age. From the age of 18 months, a significant discrepancy of the boy's gait, compared with his peers was noted. At 24 months parents noticed a progressive tightening of his lower extremities which progressed to the upper extremities at 5 years of age. Now the child was completely bedridden. The child had speech delay; his expressive language never progressed beyond 5-10 words. Seizures were first noted at 5 years of age and controlled with medications. There was no history of hearing and visual problems. His family history was significant for minimal gait abnormalities with onset after age 35, occurring in the patient's maternal grandfather; he had never sought medical attention.

General examination revealed normal anthropometric parameters including head circumference. Ophthalmological examination revealed a blue dot cataract with normal fundus. He had moderate intellectual impairment and dysarthric speech. Examination of the lower extremity showed a bilateral equinovarus deformity, paraparesis, severe spasticity, hyperreflexia with clonus of both ankles, and positive babinski. Upper extremities also have spasticity with brisk deep tendon reflexes.

On laboratory investigations, complete blood picture, blood sugar, renal function tests, creatinine, thyroid profile, lactate, ceruloplasmin, and vitamin B12 were normal. Tandem mass spectrometry was normal. His nerve conduction study was normal. MRI of the brain revealed symmetrical periventricular white matter lesions on T2 and FLAIR images. MRI of the spine was unremarkable.

After all diagnostic work-up, on the ground of the family history and the clinical features, the diagnosis of hereditary spastic paraplegia was considered. DNA sequencing with next-generation sequencing platform revealed a pathogenic mutation ERLIN 2 gene which causes an AR HSP (SPG 18). The mutation has previously been reported in literature rarely. Family screening and genetic counseling were advised.

DISCUSSION

HSP is a clinically and genetically heterogeneous group of neurological disorders that are characterized by progressive spasticity that typically affects the lower extremities.[1] Clinically, they are classified as "pure" when spastic paraplegia exists in isolation and as "complicated" when other major clinical features such as mental retardation, optic atrophy, retinopathy, ichthyosis, ataxia, deafness, cerebellar signs, muscle wasting, epilepsy, and extrapyramidal symptoms are present.[5]

The age of symptom onset varies widely from infancy to late adulthood, but mostly adult case series dominate the literature. There have been only a few studies in children.[6-9] Spastic paraplegia (SP) is a very common problem in regular practice of pediatricians and pediatric neurologists. SP generally caused by perinatal asphyxia or brain infections early in life resulting in cerebral palsy (CP). In addition, SP caused by so many disorders includes structural abnormalities, tumors of the brain or spinal cord, metabolic diseases such as arginase deficiency, vitamin B12 deficiency, leukodystrophies, and genetic disorders.[6,10] Only a small minority cases of SP due to HSP, hence many patients with childhood onset HSP are mistakenly diagnosed with CP. Our patient also treated as CP up to now.

In children with SP in whom no acquired cause can be identified, HSP should be considered. A positive family history aids with the diagnosis. In our case, there was no antecedent event and the child had mildly affected family member, so suspected HSP along with other causes of SP. Routine laboratory investigations were unremarkable, and hence considered genetic testing. The American Academy of Neurology recommends that metabolic and genetic testing should be considered in children with spastic paraplegia if their clinical record or Neuroimaging findings are insufficient for establishing a specific diagnosis, or if there are other additional atypical features in their history or clinical examination.[11]

The genetics of HSP is complex, and all modes of inheritance (Autosomal dominant, Autosomal recessive, and X-linked recessive) have been described.[12] AD inheritance is most commonly associated with pure forms, whereas AR inheritance is associated with several well-defined severe syndromes.[13] To date, at least 79 distinct loci (SPGs) and 67 causative genes have been identified.[14] In our case, DNA analysis with NGS revealed ERLIN 2 gene mutation. ERLIN2 gene mutation causes AR HSP 18 (SGP18), which is a complicated form of HSP. In literature, rare case series reported with this gene mutation.[15-17]

MRI findings of HSP are nonspecific, including thinning of corpus callosum, nonspecific white matter lesion, abnormal T2 hyperintensity in the posterior limb of the internal capsules, and atrophy of the brain/spinal cord.18 Brain and spinal MRI are usually used to rule out other differential diagnoses of HSP. In our case report, MRI brain showed symmetrical periventricular white matter lesions on T2 and FLAIR images, which was non-specific and MRI spine was normal. At present, there are few therapeutic options are available for treatment of HSP. Still rehabilitation therapy, physical therapy for the maintenance of muscular strength and coordinated movement are mainstay of treatment. Some medications like baclofen (oral and intrathecal), trihexyphenidyl and diazepam can relieve spasticity to some degree.[19]

CONCLUSION

HSP is a rare disease among children, but not uncommon. Cerebral palsy is an important differential diagnosis for

HSP. The suspicion of HSP diagnosis strongly depends on the age at onset, course of the disease, associated clinical features, and family history. Genetic studies using next generation sequencing techniques are very helpful in reaching the diagnosis. Early diagnosis is crucial for HSP patients. In addition, identification of gene mutations among family members of HSP patients is beneficial for the early detection of non-symptomatic mutation carriers and the timely implementation of intervention measures to slow disease progression and genetic counseling.

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