

Clinico-Investigative Profile of Hereditary Spastic Paraplegia in Children

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Abstract

Introduction: Hereditary spastic paraplegia (HSP) is a group of neurogenetic disorders seen mainly in adults. With the advancement in genetics, more than 78 types of HSP have been identified, with increasing identification of HSP in children. However, there is scant literature on this from India. **Materials and Methods:** Retrospective chart review of patients with HSP diagnosed in the last 6 years was done. The data were extracted and analyzed. **Results:** A total of 11 patients had a diagnosis of HSP (genetically confirmed), with mean age of presentation at 21.7 months. The main symptom at the time of presentation was delayed walking and/or abnormal gait in the form of tip-toeing and scissoring of limbs. The mean delay in diagnosis was 5.2 years after initial presentation. MRI of the presented children showed mainly thinning of corpus callosum and white-matter changes. All of them had gradual worsening spasticity, despite physiotherapy and drugs. Except one, all children had recessive form of spastic paraplegia. Child with autosomal dominant spastic paraplegia had heterozygous mutation in *SPAST* gene, which is known to present in the first 2 years of life. **Conclusions:** HSP is probably not uncommon. Recessive form of HSP is more frequently seen in children. Because of lack of awareness, there is delay in reaching the final diagnosis.

Keywords: Hereditary spastic paraplegia, magnetic resonance imaging, genetics

INTRODUCTION

Hereditary spastic paraplegia (HSP) is a group of neurodegenerative disorders, mainly characterized by progressive spasticity of the lower limbs. These disorders are both clinically and genetically very heterogeneous, thereby complicating their diagnoses.^[1] Length-dependent, retrograde axonal degeneration of the corticospinal fibers is the main pathophysiology in most of these disorders. HSP is rare, with prevalence estimates ranging from 1.2 to 9.6 per 100,000.^[2] HSP is classified as pure (uncomplicated) and complicated. In pure HSP, spastic paraparesis is the main clinical finding, occasionally accompanied by mild sensory deficits in the lower limbs and bladder dysfunction; whereas in complicated HSP, spastic paraparesis is accompanied by variable combinations of other manifestations, such as extra-pyramidal disturbances, ataxia, epilepsy, cognitive deficits, peripheral neuropathy, and neuroimaging abnormalities.^[1,2]

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 and none from our country.^[3-7] This often results in delay in diagnosis, failed opportunity for prenatal diagnosis, and stress in the parents. The purpose of this study is to describe our experience with pediatric HSP in a tertiary care center in southern India. We report here the clinical and genetic findings in our patients and aim to offer insights into the diagnostic difficulties of childhood-onset disease.

MATERIALS AND METHODS

A retrospective review of studies on children with a diagnosis of HSP was done from January 2012 to June 2018. The diagnosis

was confirmed by genetic analysis. The presenting features which included details of perinatal events, developmental milestones, and family history, as well as the neurological examination details in all patients were extracted and entered in predesigned proforma. Children were called for follow-up and their current status was noted. Siblings and parents were also examined. The details of the workup done (including metabolic and electrophysiology investigations), neuroimaging details, and the delay in the diagnosis of the disease from the onset of symptoms were also noted. Informed written consent was obtained from the patients' parents.

RESULTS

In total, 17 children were clinically suspected of HSP; out of them 11 children who had genetically confirmed HSP (details given in Tables 1 and 2) were included in this study. The remaining had other causes such as cranio-vertebral junction anomalies, human immunodeficiency virus infection, arginase deficiency, and mild spastic paraplegia secondary to premature

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Table 1: Clinico-radiological features of hereditary spastic paraplegia

Patient	Gender	Age at onset (in months)	Presenting symptoms	Age at diagnosis (in months)	Clinical findings			MRI findings
					Lower limbs	Upper limbs	Others	
1	F	18	Gait abnormality	108	Spasticity, hyperreflexia	Spasticity, hyperreflexia	ADHD, speech delay	Thin CC, paucity of WM
2	M	24	Gait abnormality	144	Spasticity, Achilles contracture	Spasticity, hyperreflexia	ADHD, dysarthria, optic atrophy	Thin CC, paucity of WM
3	M	30	Gait abnormality	72	Spasticity, dystonia, hyperreflexia	Spasticity, dystonia, hyperreflexia	Sialorrhea	WM hyperintensities
4	F	36	Gait abnormality	132	Spasticity, hyperreflexia	Hyperreflexia	None	WM hyperintensities
5	F	18	Delayed walking, leg pain	48	Spasticity, hyperreflexia	Dystonia, hyperreflexia	Bladder incontinence	Normal
6	F	10	Global developmental delay	60	Spasticity, hyperreflexia	Hyperreflexia	Optic atrophy	Paucity of WM, thin CC
7	F	10	Global developmental delay	72	Spasticity, hyperreflexia	Hyperreflexia	Congenital cataract, deafness	Thin CC
8	M	36	Gait abnormality	156	Spasticity, Achilles contracture	Spasticity, hyperreflexia	ID	Normal
9	M	36	Gait abnormality	48	Spasticity, hyperreflexia	Hyperreflexia	None	WM hyperintensities
10	F	12	Global developmental delay	48	Spasticity, hyperreflexia	Spasticity, hyperreflexia	Microcephaly, epilepsy, sialorrhea	Cerebellar atrophy
11	M	9	Global developmental delay	48	Rigidity	Spasticity, hyperreflexia	Sialorrhea, nystagmus, pontocerebellar hypoplasia-9	ACC, hypoplasia of cerebellum

MRI: Magnetic resonance imaging; ADHD: Attention deficit hyperactivity disorder; ID: Intellectual disability; CC: Corpus callosum; WM: White matter; ACC: Agenesis of corpus callosum

Table 2: Spastic paraplegia types and genetic findings

Patient	Consanguinity	Family history	Inheritance	Type	Gene	Zygosity	Variant (Mutation)
1	Yes	Yes	AR	SPG54	DDHD2	Homozygous	Chr8:g. 38103818G>T; c. 1125+1G>T
2	Yes	Yes	AR	SPG54	DDHD2	Homozygous	Chr8:g. 38103818G>T; c. 1125+1G>T
3	Yes	No	AR	SPG48	AP5Z1	Homozygous	Chr7:4823011A>G; c. 431A>G (p.Gln144Arg)
4	Yes	No	AR	SPG35	FA2H	Homozygous	Chr16:74753008C>T; c. 664G>A (p.Gly222Arg)
5	Yes	No	AR	SPG56	CYP2U1	Homozygous	Chr4:g. 108866415ATCTG>A; hrc. 782_785delTCTG
6	Yes	No	AR	SPG50	AP4M1	Homozygous	Chr7:99701748G>A; c. 577G>A (p.Glu193Lys)
7	No	No	AR	SPG69	RAB3GAP2	Homozygous	Chr1:220357438_220357439delAT; c. 1937_1938delAT (p.Tyr646Terfs)
8	No	No	AR	SPG59	USP8	Compound heterozygous	Chr15:50784955 C>C/A; c. 2292C>C/A (p.Asn764Lys) Chr15:50785016 A>A/G; c. 2353A>A/G (p.Thr785Ala)
9	Yes	Yes	AR	SPG35	FA2H	Homozygous	Chr16:74808384-?_74808653+?del, c.(?-1)_(270+1_271-1) del, (Exon 1 deletion)
10	No	No	AD	SPG4	SPAST	Heterozygous	Chr2:32323919 A>A/G; c. 641A>A/G
11	Yes	No	AR	SPG63	AMPD2	Homozygous	Chr1:110169406G>A; c. 752G>A (p.Arg251Gln)

AR: Autosomal recessive; AD: Autosomal dominant; SPG: Spastic paraplegia gene

delivery. The age of onset of the disease was difficult to ascertain in many cases. The mean of first symptoms (as appreciated by parents) was reported at 21.7 months (range: 9–36 months),

and the diagnosis of HSP was reached at 85 months (7.1 years; range: 48–156 months). The median delay in diagnosis was 72 months (6 years) after initial diagnosis. Five of them

were males. Six children presented with abnormal gait and difficulty walking, four with global developmental delay, and one with delayed walking and leg pain. One child showed gait difficulties immediately after walking skills were acquired, whereas the remaining five children developed abnormal gait later in childhood. Acquisition of motor milestones was delayed in five children while cognitive development was abnormal in four cases. Sensory deficit in lower limbs was not seen in any children, while one child had bladder dysfunction. Other symptoms included attention deficit hyperactivity disorder (two), speech problems (two), epilepsy (one), optic atrophy (two), deafness (one), congenital cataract (one), sialorrhea (three), and cerebellar signs (one) [Table 1]. Perinatal history was uneventful in all children. Parental consanguinity was seen in eight children. Family history was significant in two consanguineously married couple with two affected children (patient 1 and 2) in one family, while another patient (patient 9) had family history of sibling death by 9 years with the same symptomatology.

Neuroimaging details of all children are available in Table 1. Magnetic resonance imaging (MRI) of brain in six patients showed white-matter changes [Figure 1a], four patients had thin corpus callosum [Figure 1b], one patient had agenesis of corpus callosum with cerebellar hypoplasia, while one patient showed isolated cerebellar atrophy. MRI brain was normal in two children. Spinal MRI was done in all patients to exclude structural abnormalities/neurometabolic disorders. It was normal in all children. Nerve conduction tests were not done as none of them had sensory complaints and our diagnosis was made based on genetic studies.

Genetic details are mentioned in Table 2. The inheritance pattern in all children was transmitted in autosomal recessive (AR) manner, except one who had heterozygous autosomal dominant (AD) mutation in *SPAST* gene (HSP type-4). Her parents, uncles, and aunts were examined clinically and found to be normal, while genetic testing was not done due to cost constraints. Nine patients with recessive inheritance showed homozygosity, while one had compound heterozygous mutation in *USP8* gene, classified as likely pathogenic and

his asymptomatic parents are heterozygous carrier of this pathogenic variation. Two unrelated patients (patient 4 and 9) had mutation in *FA2H* gene causing HSP type-35, while two siblings showed same mutation in *DDHD2* gene causing HSP type-54. All patients had pathogenic or likely pathogenic mutations, except in patient 3 and 4. They had homozygous mutations in *AP5Z1* and *FA2H* gene, respectively, and classified as variant of uncertain significance. To confirm the significance of these mutations, parental sequencing was done and same variation was detected in heterozygous condition in the unaffected parents of the index patients, indicating pathogenicity.

DISCUSSION

Diagnosis of HSP in pediatric cases can be difficult in the absence of a positive family history. Although the majority of childhood-onset HSP were sporadic cases, rendering HSP as a diagnosis of exclusion, once structural lesions, neurodegenerative, and neuro-metabolic disorders have been ruled out.^[4,6] Cerebral palsy is the most common cause of spasticity in children. Many patients are misdiagnosed with cerebral palsy, even when there is no antecedent history of perinatal event and no lesions detected on brain imaging.^[8] The nonprogress or very slow progression of the disease also justifies the diagnosis of cerebral palsy in many children. This deprives the parents an opportunity for prenatal diagnosis, and hence the urgency in reaching the correct diagnosis. Leukodystrophies, structural brain or spinal lesions, and rare neurometabolic disorders, including Segawa disease, arginase deficiency, and copper deficiency are other differential diagnosis of HSP.^[1,6,9] Diurnal fluctuations, neuroimaging, and metabolic screening can differentiate these disorders from HSP.

In our series, all children showed astatic or very slowly progressive course. These observations are in accordance with other pediatric series of HSP.^[4,7] Battini *et al.* reported normal gross motor milestones in all patients in his series. In contrast, our series showed global developmental delay in one-third of children.^[4] Our data suggest that pediatric HSP often manifest very early even during infancy, and may present with delay in development as first manifestation.

HSP can be transmitted in an AD, AR, or X-linked (XL) manner.^[1,2] It is mainly seen in adults compared to children and AD variety of HSP is most common, constituting around 75% of all cases.^[7] Majority of our patients have recessive mode of inheritance, while AD pattern of inheritance was seen in only one patient. Consanguineous union is the most likely cause for this observation, which was seen in 63.6% patients.

As described earlier, HSP is classified into two groups: pure and complicated forms. Pure form is mainly seen in adults as adult-onset AD HSP.^[7,10] In contrast, complicated form of HSP was seen in two-thirds of patients in this series, which correlates with other studies in children.^[4,5,7] Koul *et al.* mentioned that over a period of time, most of children with HSP invariably fall into the complicated group and reported

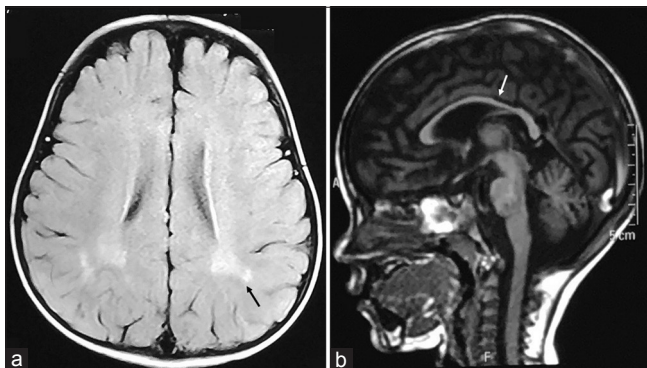


Figure 1: (a) Axial FLAIR sequence of brain of patient 8 at the age of 4 years shows predominant posteriorly white-matter patchy hyperintensities (black arrow). (b) Sagittal section of brain of patient 7 at the age of 2 years shows severe thinning of corpus callosum (white arrow)

complicated HSP in 81.1% of the children in their study.^[7] These observations conferred that complicated form of HSP is mainly seen in children and generally inherited as AR traits, while pure form dominates in adults as AD HSP.^[4,5,7,10]

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.^[11] However, normal neuroimaging findings are also seen in some patients like in our patient 5 and 8.^[11] Brain and spinal MRI are usually used to rule out other differential diagnosis of HSP.

To conclude, this study confirms the genetic and clinical heterogeneity of childhood-onset HSP. The absence of positive family history should not deter a clinician from considering HSP when more obvious etiologies have been excluded. Genetic studies using next generation sequencing techniques are very helpful in reaching the diagnosis. Pediatric HSP patients can present with delayed walking or variable gait difficulties even in toddlerhood. Investigating asymptomatic first-degree relatives would be sensible in both suspected and definitively diagnosed cases of HSP.

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Conflicts of interest

There are no conflicts of interest.

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