Clinico-aetiological profile of hereditary spastic paraplegia in children attending a tertiary care hospital in India

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INTRODUCTION

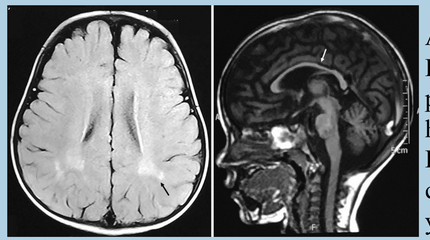
- Hereditary spastic paraplegia (HSP)- a heterogeneous group of disorders characterized by spasticity and hyperreflexia with over 80 causative genes.
- Pure HSP occurs mainly because of the involvement of the long tracts, while Complex HSP has additional features- cognitive deficits, dystonia, ataxia, epilepsy, peripheral neuropathy.
- Though it is known to have onset in infancy and childhood, adult cases are profound in literature with scarcity in paediatric data, more so from India.
- This leads to diagnostic delay and a missed opportunity for prenatal diagnosis.

OBJECTIVES

1. To identify the common types of hereditary spastic paraplegia visiting our hospital
2. To describe the clinical, radiological, and genetic characteristics of HSP.

MATERIALS AND METHODS

- Period: 2013 to 2023 (retrospective + prospective).
- Diagnosis by whole exome sequencing.
- Detailed history- presenting features, perinatal, birth, developmental, and family history, and neurological examination, neuroimaging details entered in a proforma.
- Delay in the diagnosis of the disease from the onset of symptoms were noted.
- Children were followed up, current status noted.



A: MRI- Posterior predominant WM hyperintensities
B: Thin corpus callosum (age 2 yrs)

RESULTS

- 23 children included: 7 F, 16 M (Table).
- Mean age of presentation: 23.8 mon (5-120 mon). Presentation was gait abnormality in 11 and developmental delay in 13.
- Neuroimaging: thin corpus callosum, white matter hyperintensities, and normal in 10, 5, and 6 cases respectively.

4 had mutations in FA2H, 4 in AP4 group of genes, 2 each in DDHD2 and CYP2U1.

- Mean delay in genetic confirmation of diagnosis: 3.1 yrs (0.5-10 yrs). All but 4 cases had a recessive mode of inheritance.
- Of the 10 cases on follow-up, 2 continue to be ambulatory at 17 years, 2 are ambulatory with support at 10 years, 4 never attained walking and 3 lost ambulation (2 after 5 years, 1 after 9 years)- all with FA2H mutation.

DISCUSSION

Diagnosis of HSP in children may be missed in the absence of a positive family history, but, as most paediatric cases are sporadic, it must be kept in mind after ruling out structural, neurodegenerative, and neuro-metabolic disorders.

Cerebral palsy (CP) is the most common cause of spasticity in children. Many cases are misdiagnosed as CP. The slow progression of HSP in children also promotes misdiagnosis of CP, depriving parents of the opportunity for prenatal diagnosis.

In our study, all children showed very slow progression in accordance with other pediatric series of HSP.

Battini et al. reported normal gross motor milestones in their patients. In contrast, our series showed GDD in >1/3rd of children suggesting that pediatric HSP often manifests very early even during infancy, and may present with developmental delay as the 1^{s} manifestation.

HSP in most cases (75%) is known to have autosomal dominant inheritance, but majority of our patients (82.6%) had a recessive inheritance, probably due to high rate of consanguinity (69.5%).

MRI findings are nonspecific - thin corpus callosum, white-matter hyperintensities, abnormal T2 signal in the posterior limb of the internal capsule, and atrophy of the brain/spinal cord. Many cases can also have a normal neuroimaging as seen in 6 of our cases.

Case	Sex	CM	FH	Presenting symptoms	Age at onset (mon)	Age at diagnosis (mon)	Clinical features (other than Spasticity)	MRI	Gene
1	M	N	N	Abnormal gait	120	156	Hemangioma, migraine	Normal	NIPA1
2	M	Y	N	GDD	9	48	Dystonia, PCH, microcephaly	Agenesis of CC, PCH	AMPD2
3	M	Y	N	Abnormal gait	18	132	ID, speech delay	Thin CC, WM abnormality	ERLIN2
4	M	Y	N	GDD, Stiffness of limbs	8	48	Microcephaly, speech delay	Cerebral atrophy, paucity of WM, thin CC, PCH	AP4S1
5	M	Y	Y	Abnormal gait	36	48	-	Parieto-occipital WM changes	FA2H
6	F	Y	Y	Abnormal gait	36	38	Speech abnormality	Normal	FA2H
7	M	Y	Y	Abnormal gait	36	38	Speech abnormality, ichthyosis	Normal	FA2H
8	M	N	N	DD, limb stiffness	10	120	Seizures, OMD, microcephaly	Thin CC	AP4S1
9	F	Y	N	GDD, Abnormal gait	30	72	Congenital cataract, deafness	Thin CC	RAB3GAP2
10	M	Y	N	GDD, Stiffness of limbs	6	14	Congenital cataract, congenital ptosis	Cerebral atrophy-dilated ventricles	KIF1A
11	M	Y	N	Abnormal gait	18	32	-	Transitional S1 vertebra, minimal subarachnoid space prominence around optic nerve	CYP2U1
12	M	Y		DD	5	11	Equino-varus, microcephaly	Thin CC	AP4B1
13	F	Y	N	Abnormal gait	36	132	-	WM hyper intensities	FA2H
14	F	Y	N	GDD	10	60	Ataxia	Thin CC, paucity of WM	AP4M1
15	M	N	N	Abnormal gait	36	156	ID	Normal	USP8
16	M	N	N	DD, limb stiffness	6	12	-	Thin CC, paucity of WM	CYP27A1
17	M	Y	N	GDD	9	120	Microcephaly, autistic features	Normal	KIF1A
18	M	N	N	GDD, exaggerated startle	18	192	ID, cognitive regression	Deep WM hyperintensities with diffusion restriction	PCYT2
19	F	Y	Y	Abnormal gait	18	108	ADHD, speech delay	Thin CC, paucity of WM	DDHD2
20	M	Y	Y	Abnormal gait	24	144	ADHD, dysarthria	Thin CC, paucity of WM	DDHD2
21	M	Y	N	Abnormal gait	30	72	Drooling	WM hyper intensities	AP5Z1
22	F	Y	N	DD	18	48	Bladder incontinence	Normal	CYP2U1
23	F	N	N	GDD	12	48	Microcephaly, seizures, drooling	Cerebellar atrophy	SPAST

CM- consanguineous marriage, FH- family history, GDD- global developmental delay, MRI- magnetic resonance imaging, CC- corpus callosum, WM – white matter, Y-yes, N- no

CONCLUSION

- There is clinical and genetic heterogeneity in childhood-onset HSPs.
- HSP-35 caused by FA2H mutation - most common gene implicated, with severe presentation with loss of ambulation and death in our cohort.
- Developmental delay is a common presentation in children, along with gait abnormality.
- Recessive forms and complex HSP are more common in children.
- Lack of awareness → delay in diagnosis and missed opportunity for genetic counselling.
- Labeling as 'CP' or 'HSP' is important as prognosis varies greatly.

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