Clinico- radiological profile of genetically proven Complicated Hereditary Spastic Paraparesis: A case Series

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Abstract

Complicated Hereditary Spastic Paraparesis (HSP) is a group of heterogenous neurodegenerative disease characterized by progressive spastic paraparesis with additional features like cognitive impairment, seizures, movement disorders, visual loss, deafness, peripheral neuropathy, and pes cavus. There have been few case series reported in literature from India. We herein report four cases of complicated HSP. Four (three females and 1 male) patients of genetically confirmed HSP with a mean age of onset 10.5 years were recruited. There was mean delay of 8 years in reaching diagnosis. MRI brain showed thinning of corpus callosum in three patients and Ear of lynx sign in two patients. Next Generation Clinical Exome Sequencing confirmed mutations in SPG11 gene in three patients and SLC2A1 in one patient. SPG11 gene mutations were the most frequent genetic abnormality with SLC2A1 gene mutation in single patient. Genetically confirmed diagnosis helps in prognostication and genetic counselling.

Key words: Hereditary Spastic Paraparesis, HSP, Complicated, Atypical, SPG11, SLC2A1, Ear of lynx.

Introduction

Hereditary Spastic Paraparesis (HSP) is a group of clinically and genetically heterogenous neurodegenerative disease. It is classified according to the clinical phenotype (pure or typical HSP and complicated or atypical HSP)[1] or the mode of inheritance (autosomal dominant, autosomal recessive, X- linked or mitochondrial). The atypical or complicated forms are usually inherited as autosomal recessive traits. In addition to spastic paraparesis, other features like cognitive impairment, seizures, cerebellar ataxia, choreoathetosis, dystonia, optic atrophy, retinopathy, peripheral neuropathy, deafness, icthyosis and pes cavus have also been described.[2]

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Case Report

In this study we report four cases of complicated Hereditary Spastic Paraparesis. Three cases were females while one was a male. All the four cases were born out of non-consanguineous marriages. None of the patient had family history of similar complaints. The mean age at onset of symptoms was 10.5 years (range 5-15 years) while mean age at presentation was 18.25 years (range 14-25 years).

All of them had progressive difficulty in walking with severe spasticity of both lower limbs and cognitive impairment in the form of poor scholastic performance. Behavioral problems like frequent inappropriate smiling were found in two patients while excessive laughter or crying (pseudobulbar affect) and excessively stubborn nature were noted in each patient. Spastic paraparesis was the first manifestation of the disease in three patients while cognitive impairment was the initial manifestation in one patient. Urinary complaints i.e., urgency and incontinence were seen in two patients. One patient had of atrophy of both hand and foot muscles. Foot deformity in the form of pes cavus were noted in single patient. Spastic dysarthria was seen in one patient (Table 1).

MRI of brain and spinal cord was done in all patients. In three cases thinning of the corpus callosum were found. In two of them, there were T2/FLAIR hyperintense signals at the tip of the frontal horns of the lateral ventricles (Figure 1). The brain MRI was normal in one patient. MRI of the spinal cord did not reveal any significant abnormality in any of these patients. NCS showed pure motor axonal pattern in one patient while one had bilateral anterior optic pathway dysfunction on VEP. All the four patients underwent Next Generation Clinical Exome Sequencing confirming that they harbored genetic mutations known to be associated with complicated forms of HSP. In three of them, mutations were found in SPG11 gene and in one patient, splicing mutation was found in Exon 2 of SLC2A1 gene (Table 1). CSF/ blood glucose ratio was lowered (0.4) in the same patient. Oral baclofen and tolperisone were prescribed to reduce the lower limb spasticity and ketogenic diet therapy was initiated in single patient with consultation of dietitian. Efficacy of ketogenic diet could not be assessed due to non-compliance of ketogenic diet. The prognosis was explained to the parents and advised for genetic counselling.

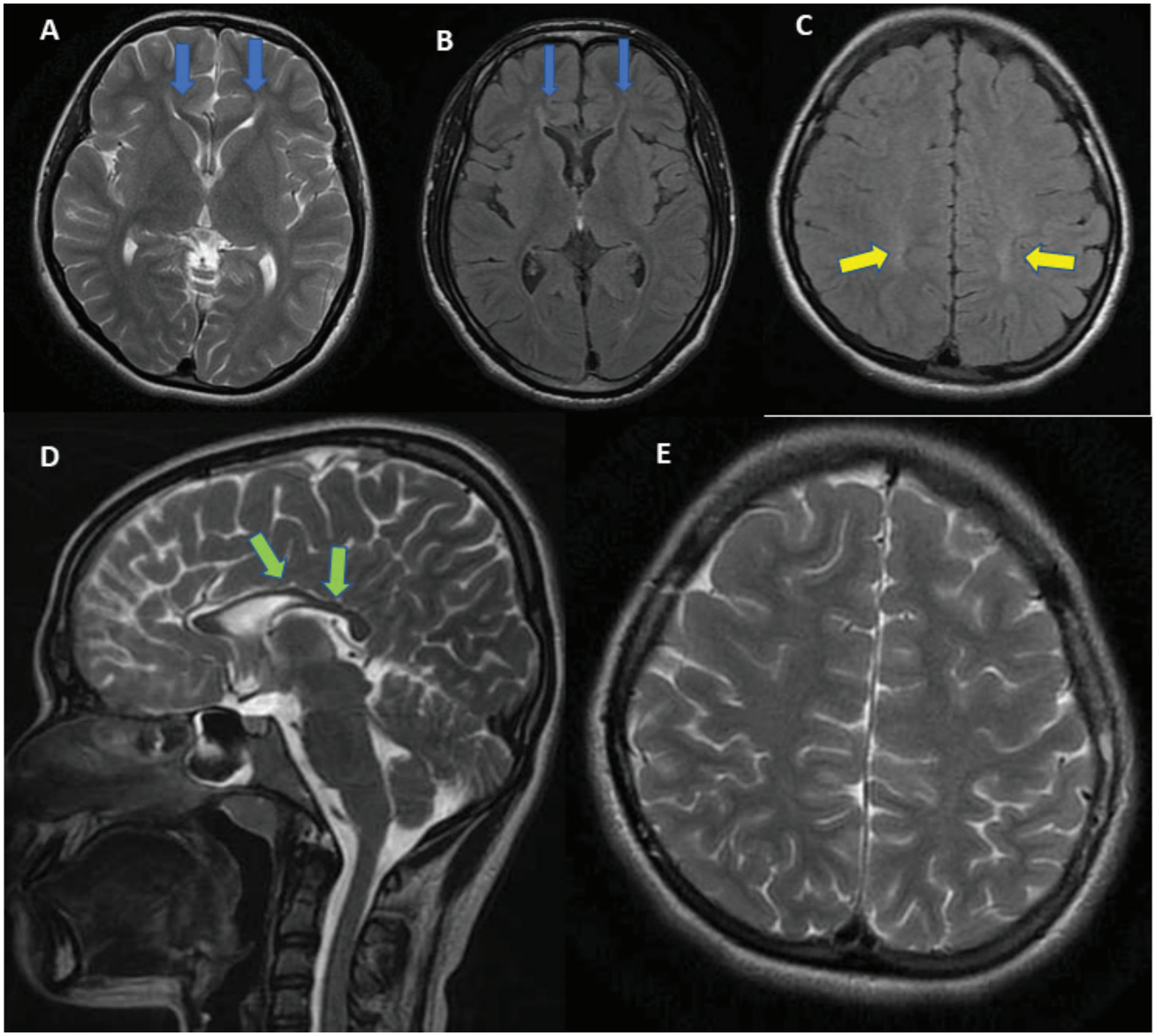

Figure 1- Axial T2 weighted (A, E), axial FLAIR (B,C) and sagittal T2 weighted MR images of brain (A) and (B), High signal intensity can be seen along the ends of the frontal horn of bilateral lateral ventricles involving the forceps minor of the genu of corpus callosum similar to the ears of the lynx. [blue arrows] There is hyperintense signal in bilateral centrum semiovale [yellow arrows in (C)] with thin corpus callosum [green arrows in (D) and widened sulci in bilateral cerebral hemisphere (E) which represents, cerebral atrophy

Table 1: Demographic, Clinico-radiological, electrophysiological, laboratory and genetic profile of complicated HSP patients

Characteristics	Case 1	Case 2	Case 3	Case 4
Age/sex	17/ Female	25 / Female	14/ Female	17/ Male
Age of onset	10 years	15 years	12 years	5 years
Inheritance	Autosomal recessive	Autosomal recessive	Autosomal recessive	Autosomal recessive
Family history	No	No	No	No
Clinical Features	Spastic paraparesis Moderate Cognitive impairment Socially inappropriate smile for 5 years Urinary urgency and incontinence for 3 years Bilateral wasting of the hand and foot muscles for 1 year	Spastic paraparesis Mild Cognitive impairment Socially inappropriate smile for 2 years. Urinary urgency and incontinence for 2 years Bilateral pes cavus	Spastic paraparesis Mild Cognitive impairment	Spastic paraparesis Moderate cognitive impairment Behavioral problems like stubborn nature and impulsiveness. Dysarthria
MRI Brain	Thin corpus callosum	Normal	Thin corpus callosum, "Ear of the Lynx" sign	Thin corpus callosum, "Ear of the Lynx" sign
MRI Spinal Cord	Normal	Normal	Normal	Normal
EDX findings	pure motor axonal neuropathy	Normal	Normal	VEP - Bilateral anterior optic pathway dysfunction
Other Investigations	S. CPK - 453.7 U/L	NAD	CSF/Blood glucose ratio = 0.4	NAD
Gene	SPG 11	SPG 11	SLC2A1	SPG 11
Chromosomal coordinates	chr15:44912482	chr15:44912482	Chr1:43396879	chr15:44912482
Exon	15	15	2	4 and 36
Variant	c.2740C>T p.Gln914Ter	c.2740C>T p.Gln914Ter	NM_006516.2:c.115-2A>G	c.6658_6659del (p.met2220AspfsTer27) c.6658_6659del (p.met2220AspfsTer27)
Type of mutation	Nonsense	Nonsense	Splice site mutation	Deletion
Zygosity	Homozygous	Homozygous	Heterozygous	Heterozygous
Significance	Likely Pathogenic	Likely Pathogenic	Variant of uncertain significance	Pathogenic

Discussion

HSP is rare disease with an overall prevalence of 1.8/100,000.[3] In 1981, it was further classified by Harding into pure and complex HSP.[1]There is scarcity of data regarding its prevalence in India with limited case reports and series reported in literature[4-6]. Pure HSP is more commonly reported from Northern Europe, Japan, and North America[7, 8]whereas the complicated forms are more commonly reported from the Mediterranean countries.[9]

Onset of HSP is usually subtle with slow progression leading to delay in diagnosis, as there was around eight years delay in diagnosis in our series. SPG11 mutation is associated with pes cavus, neuropathy, and UL spasticity as

these findings were observed in two of our patients. MRI-Brain showed thinning of corpus callosum in three patients. HSP with thin corpus callosum (HSP-TCC) was earlier considered specific for SPG11 as 75 % cases of HSP-TCC had this mutation.[10] But now other genotypes like SPG 15, SPG35 and SPG48 are also known to cause thinning of corpus callosum.[11]"Ear-of-the-lynx sign", seen in two patients, is a cone shaped T2W-FLAIR hyperintensity and T1W-hypointensity at the tip of the frontal horns of the lateral ventricles. It has been described as a classical sign associated with SPG11 and less frequently with SPG15.[12] We found that the patient with SLC2A1 mutation had both of these classical neuroimaging features on MRI-brain i.e., thinning of corpus callosum and Ear-of-the-lynx sign. SLC2A1 related HSP has not been previously reported to have both of these neuroimaging feature in single patient. MRI brain was normal in one of our cases as found in a study in which patient had normal MRI brain, although spectrum of neuroimaging findings may be found[13]. MRI spine did not show any abnormality in any of our patients as spine MRI can be normal in HSP patients[13].

At present, approximately 80 genes have been associated with HSP phenotypes. In the literature SPG11 is most frequent gene associated with complicated HSP as found in our series with three out of four cases having same mutation.[14]SPG11 encodes spatacsin, a ubiquitous protein in the nervous system deemed essential for survival of neurons, mutation of which leads to premature truncation of the protein.[15]

SLC2A1 mutations have been most commonly associated with Glut1 deficiency syndrome and variant phenotypes like paroxysmal choreoathetosis with spasticity also known as dystonia 9 (DYT9). Complex HSP without associated movement disorder as seen in our patient, represent only 1.4% of *SLC2A1* mutations.[16]Our patient carried splice site variant in heterozygous state in SLC2A1 gene (c.115-2A>G). This is a novel variant as per the gnomAD database and has not been reported in Clinvar database. CSF/blood glucose ratio was lowered in our patient with SLC2A1 mutation. CSF/blood glucose ratio is suggested in HSP patients where no pathogenic variants or variant of unknown significance is found as it is a reliable biomarker for diagnosing a treatable variant of HSP[16, 17]. SLC2A1 mutation with lower CSF/blood glucose ratio in HSP is a treatable disorder in which brain uses ketones as alternative source of energy through ketogenic diet.

Conclusion

To conclude, SPG11 gene mutations were the most frequent genetic abnormality in our case series. A novel mutation in SLC2A1 gene was found, which is a very rare and treatable variant of complicated HSP.

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