Case Series of Autosomal Recessive Hereditary Spastic Paraplegia in Adults

Sir,

Hereditary spastic paraplegia (HSP) is a heterogeneous group of familial neurodegenerative disorders which are characterized by progressive lower limb spasticity. HSP is rare, with prevalence estimates ranging from 1.2 to 9.6 per 100,000.[1] However, there is scant literature from India. HSP was first classified by Harding, into pure and complicated HSP. Genotype and phenotype heterogeneity are a hallmark of this group of diseases. Genetic testing is helpful in confirming the clinical diagnosis of HSP and in determining the genetic type of HSP. Brain and spinal MRI is done to rule out other diagnosis and see for the various abnormalities described in HSP.

We evaluated 12 patients presenting with gradually progressive spastic paraparesis from January 2019 to December 2019. Out of them five genetically confirmed patients [Tables 1 and 2] were included in this study.

Out of five patients, three had mutation for SPG11, one each had mutation in SPG7 and SPG46. Autosomal dominant inheritance is the commonest in HSP; however, in our study all five patients had recessive inheritance.

There was no history of consanguinity but family history was significant in two cases. Out of five cases two were from Maharashtra and three were from Uttar-Pradesh but with different ethnic background. There was no founder effect. In one family with SPG11 two siblings of same generation were affected. In another family with SPG7 two generations were affected (father and son). Heterozygotes are typically asymptomatic in autosomal recessive inheritance. The only known exception to this rule is SPG7, where pseudo-dominant inheritance may be seen.[2]

SPG11 is the most common autosomal-recessive HSP. In one study, SPG11 mutation was found to account for 18.9% of all recessive cases.[3] These patients classically present with severe lower limb spasticity with cognitive decline. In general, onset is in childhood/early teenage years with walking problems and spasticity, severe bladder problems, ataxia, neuropathy, parkinsonism and/or cognitive problems, muscular atrophy, epileptic seizures, upper limb hyperreflexia, pseudobulbar affect. Atypical phenotypes have additional retinal manifestations, slowly progressive amyotrophic lateral sclerosis, dystonia-parkinsonism.[4] MRI features found in our patients with SPG11 were corpus callosal atrophy and periventricular hyperintensities [Figure 1a and b]. SPG11 is found in 75% of all types of HSP who have

Table 1: Clinical and investigative profile of HSP patients

Features	Age of onset	Current age	Sex	Additional features	Birth and developmental history	MRI features	NCV-EMG
Patient 1	15 yrs	18 yrs	Female	Hammer toes, moderate cognitive decline, aggressive behavior, emotional lability,	Normal	Thin corpus callosum, periventricular hyperintensities	Sensory-motor axonal neuropathy
Patient 2	5 yrs	18 yrs	Female	Bladder involvement, moderate cognitive decline, upper limbs hyperreflexia	Normal	Thin corpus callosum in both sisters	Normal
Patient 3	35 yrs	40 yrs	Male	Impairment of joint position sense	Normal	Dorsal spinal cord atrophy	Normal
Patient 4	8 yrs	18 yrs	Male	Cognitive decline, bilateral congenital squint, upper limb hyperreflexia	Birth Normal Delayed speech development	Periventricular mild hyper intensity, spine normal	Normal
Patient 5	2 yrs	20 yrs	Male	Mild cognitive decline- poor score in studies, Upper limb hyperreflexia	Normal	Normal	Normal

Table 2: Genetic findings in HSP patients

Features	Consanguinity	Family history	Inheritance	Gene involved	Zygosity	Variant	Clinical significance
Patient 1	No	Normal	Recessive	Exon 32 of SPG 11	Homozygous	chr15:44865850G >A c.6100C >T p.Arg2034Ter	Pathogenic
Patient 2	No	Younger sister affected	Recessive	Exon 16 of SPG 11	Homozygous	chr15:44907581A >C c.3018T >G p.Tyr1006Ter	Likely pathogenic
Patient 3	No	Son affected	Recessive	Exon 2 of SPG 7	Homozygous	chr16:89576947T >A c.233T >A p.Leu78Ter	Likely pathogenic
Patient 4	No	Normal	Recessive	Exon 21 of SPG 11	Homozygous	chr15:44892728G >A c.3623C >T p.Pro1208Leu	Uncertain significance
Patient 5	No	Normal	Recessive	Exon 9 of SPG 46	Homozygous	chr9:35739747A >G c.1460T >C p.Leu487Pro	Likely pathogenic

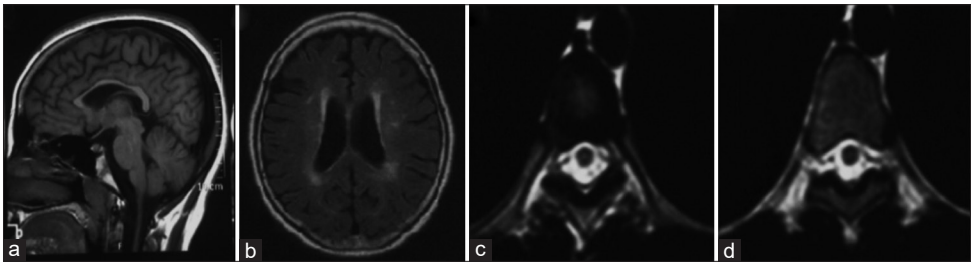

Figure 1: MRI brain shows (a) thinning of corpus callosum in T1W sagittal view, (b) periventricular hyperintensities in T2W/FLAIR axial image in a patient with SPG 11 mutation and MRI dorsal spine shows (c and d) thinning of dorsal cord in T2W axial images in a patient with SPG 7 mutation

thin or absent corpus callosum.[5] In our study, genetic analysis showed three variants in SPG11 gene. One of the identified variant chr15:44907581A > C c.3018T > G p.Tyr1006Ter in exon 16 seems to be a novel variant as it has not been previously reported in literature. Another variant chr15:44892728G > A (c. 3623C > T) is reported in gnomAD database with minor allele frequency of 0.0008% but it is not present in the 1000 Genomes database. The reference base is conserved across the species and in-silico predictions by Polyphen and SIFT are damaging. Based on the above evidence this variant has been classified as variant of uncertain significance. SPG11 gene encodes the protein spatacsin, which may play a role in neural development. Mutations in the SPG11 gene have been associated with SPG11, amyotrophic lateral sclerosis 5 (ALS 5) and Charcot-Marie-Tooth 2X. The identified homozygous nonsense substitutions in genes cause premature termination of the protein. The resultant protein likely result in loss-of-function.

SPG7 can present as a pure or complex phenotype. Our patient presented with pyramidal and posterior column involvement. MRI suggestive of dorsal cord atrophy [Figure 1c and d]. The complex phenotype shows clinical features like younger age of onset, optic nerve involvement, posterior column involvement, upper limb involvement, cognitive deficits, and peripheral neuropathy in addition to lower limb spasticity. Our patient had likely pathogenic variant in SPG7 gene. The SPG7 gene encodes a mitochondrial metalloprotease paraplegin protein, which plays a role in diverse cellular processes including membrane trafficking, intracellular motility, organelle biogenesis, protein folding, and proteolysis. Germline pathogenic variations in the SPG7 gene have been associated with SPG7 and progressive external ophthalmoplegia. It is a cause of undiagnosed ataxia in 18.6% in recently published case series.[6]

In one patient we had likely pathogenic variant of SPG46. He presented with mild spasticity in both lower limbs with mild cognitive decline. MRI brain and spine was normal in our patient. SPG46 is characterized by childhood onset slowly progressive spastic paraplegia and cerebellar signs. Some patients have cognitive impairment, cataracts, bladder dysfunction, pseudobulbar palsy, and hearing loss. It is a slowly progressive disease where patient becomes wheelchair bound at 40–50 years of age.[7] Imaging shows thinning of corpus callosum, mild cerebral and cerebellar atrophy**.** Boukhris *et al*.[7] Martin *et al*.[8] described SPG46 mutation from different Tunisian families. This mutation in SPG46 gene has not been described earlier in Indian literature. This gene encodes for GBA2 protein. The GBA2 protein is an enzyme of sphingolipid metabolism that is the source of a variety of mediators of cell signaling responses and of structural components of the plasma membrane involved in its dynamics. It has been associated with cerebellar ataxia and HSP.[8]

With no curative treatment known to date, current management of HSP is aimed at symptomatic relief. In general, it includes combination of pharmacologic (anti-spasticity drugs), physiotherapeutic, and devised-based (orthotics) treatment. A recent study substantiated the use of Miglustat, which inhibits glycosphingolipid synthesis, in human SPG11 neurons, and a zebrafish knockdown model.[9] This treatment resulted in improved lysosomal clearance and lipid accumulation in neurons and better locomotion in treated larvae. In SPG11, GSK3β in patient specific induced pluripotent stem cell-derived cortical neural progenitor cells have been identified as potential novel target for reversing disease phenotype.[10]

To conclude, in our case series SPG11 was the most frequent AR hereditary spastic paraplegia. We had one case each of SPG7 and SPG46. SPG11 classically presents with paraparesis and cognitive decline. MRI showed typical feature of thin corpus callosum and T2 high signal intensity in periventricular white matter. SPG7 presents as a complicated HSP, which may have pseudodominant inheritance and imaging showed dorsal cord atrophy. SPG46 is not previously described from India. The presentation is with mild spastic paraparesis and mild cognitive decline. Next generation sequencing for HSP genetic panel offered precise diagnosis in cases where mutations were identified. This helped in genetic counselling of families.

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Conflicts of interest

There are no conflicts of interest.

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