



Case Series

A case series of hereditary spastic paraplegia

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ABSTRACT

Hereditary spastic paraplegia is a spectrum of disorders with progressive spasticity of lower limbs with clinical and genetic heterogeneity. Harding classified HSP into pure and complicated forms. Currently classification is largely based on genetics. Around 87 genetic loci were identified till date. We have studied 44 patients presented with spastic ataxia with or without additional neurologic or non-neurological features from February 2021 to February 2024. Out of 44 spastic ataxia cases studied over period of 3 years, 17 patients were positive for SPG genes with 21 variants detected by NGS method. New phenotypic representation of SPG 28 as it can present with spastic paraparesis and distal upper limb amyotrophy, i.e., Silver Syndrome. We found SPG 11 to be the most common inherited cause of hereditary spastic paraplegia in our study. SPG 7 is next common HSP type found. In conclusion, SPG 11 should be tested in cases presenting with spastic paraparesis before second decade, with thin corpus callosum, ear of lynx on MRI along with other neurological features like cognitive decline. With gene specific therapy on the horizon diagnosing HSP cases based on NGS should be considered.

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1. Introduction

Hereditary spastic paraplegia is a spectrum of disorders with progressive spasticity of lower limbs being a common finding, with clinical and genetic heterogeneity. Prevalence of HSP was found to be 3.6 per 1, 00,000 population all over the world.¹ Harding classified HSP in to pure and complicated forms based on the presence of UMN paraparesis alone and in combination with other features respectively. Now classification is largely based on genetics. Around 87 genetic loci were identified till date.

2. Materials and Methods

We have studied 44 patients presented with spastic ataxia with or without additional neurologic or non-neurological features from February 2021 to February 2024. Deep phenotyping with a detailed pedigree charting was done.

MRI brain and spine study was done in all patients. NCS, EEG studies were done wherever appropriate. Genetic studies (WES by NGS, PCR for repeat disorders) were done based on phenotype and investigations. Out of 44 spastic ataxia cases studied over period of 3 years, 17 patients were positive for SPG genes with 21 variants detected by NGS method. Patient with mutation in SPG loci were studied further to understand clinical and genetic spectrum.

3. Results

Out of 44 spastic ataxia cases, a total of 17 genetically confirmed cases of hereditary spastic paraplegia were studied. Out of 17, 13 were male (76.47%) and 4 (23.53 %) were female patients (Figure 1). Most common age of onset was found to be 2nd and 3rd decade (47 %). Late onset hsp was found in 3 cases in our study. One Patient presented at 5th decade, with onset of symptoms at 48 years of age. Two patients presented in 4th decade with 33- and 35-years age

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of onset.

Third degree Consanguinity is found in 5(29.41%) cases in our study. (Figures 2 and 3). Positive Family history was found in 6 patients (35.29%). Family history is autosomal recessive like in all these patients .Among the patients with positive family history, five families had patient and their siblings affected. Only in one family, father and son were affected.

In our cohort, Pure HSP is seen in 3 (17.64%) cases, complicated HSP in 14 (82.35 %) cases. Out of 14 complicated HSP cases, 6 had cognitive decline (35%) along with spasticity. Likewise, dysarthria in 3 (17.6%), Extrapyrarnidal involvement in 3(17.64%) (2 had dystonia, 1 had parkinsonian features), ataxia in 1 (6.67%) patient was found.

On imaging studies, specific pattern corresponding with HSP was found in 8 patients. MRI brain and spinal cord done in all patients, out of which, thin corpus callosum is seen in 4 patients, Ear of lynx sign is seen in 2 patients; all of them were found to be SPG 11. Cervicodorsal cord atrophy seen in SPG 10 and SPG 30. Bilateral periventricular hyperintensities were seen in 2 cases. Cerebellar atrophy seen in 2 cases, that is SPG 15 and 35. MRI was normal in 5 cases. Electrophysiology studies showed neuropathy in 2 patients and amyotrophy (motor neuron disease) in 1 patient.

Out of 21 mutations detected in SPG loci, 9 were Likely pathogenic cases (percentage), 2 patients had Pathogenic and 10 patients had variant of unknown significance mutations. (Figures 5 and 6). Out of these 21 SPG loci mutations detected, 10 missense mutations, 6 frame shift mutations (2 AMINO ACID SUBSTITUTIONS, 2 DELETIONS ,1 LOSS OF FUNCTION), 3 nonsense mutations and 2 deletions were seen. We have seen the inheritance pattern to be compound heterozygous autosomal recessive in 11, homozygous autosomal recessive in 6, autosomal dominant in 4. Out of 14 complicated hsp cases, recessive pattern of inheritance is seen in 12 and dominant in 2. Of the 3 pure hsp cases in our study, 2 have autosomal recessive pattern of inheritance and 1 has dominant inheritance.

Out of 21 SPG loci detected, we found c.3623C>T (p. Pro1208Leu) mutations common in 2 different unrelated patients i.e., in 22-year-old female patient from Uttar Pradesh and an 18-year-old male patient from Maharashtra. Another Homozygous autosomal recessive nonsense mutation at chr15:44865850G>A c.6100C>T p. Arg2034Ter loci is found in 2 unrelated patients. Autosomal dominant mutation was found in SPG17/ SPG 73, SPG 42, SPG 30, SPG 10/ SPG 7. 15 novel mutations were found in our study (Figure 4).

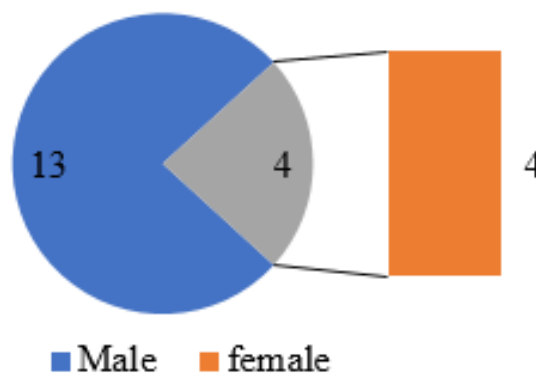


Figure 1: Gender distribution in our study

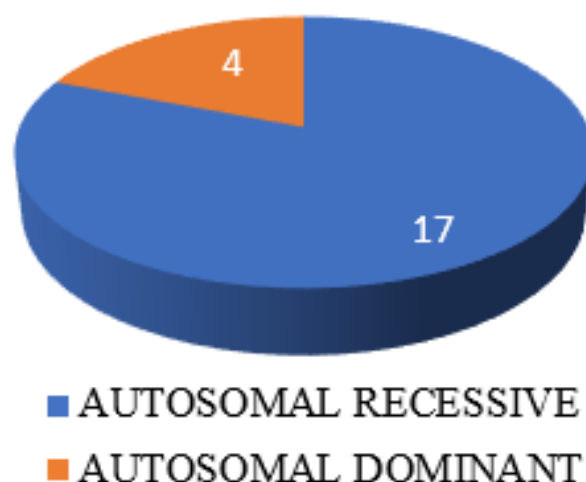


Figure 2: Number of autosomal recessive and dominant inheritance all 21spg variants

4. Discussion

In our study, we found HSP more commonly in 2nd and 3rd decade (7-50 Y) with male predilection (Tables 1 and 2). Age of onset and sex predilection was in concordance with another Indian study i.e., Narendiran S. et al.³ (3-22 Y). Similar age of presentation is found in Kara et al.⁶(3-39). Stevanin G et al.⁵study found to have more female preponderance with 2nd and 3rddecade presentation (2 to 27). Positive Family history is found in 6 patients. Most of the patients with family history had their siblings affected in same generation (5 patients). While in only one family, Father and son were affected with similar phenotype. Consanguineous marriage increases the frequency of AR HSPs in the community. Study by Arun Meyyazhagan et al.⁹ found that European and north American population had predominance of autosomal

Table 1: Clinical features and genetics

S.No	Age of onset	Age of presentation	Sex	Description	Consanguinity	Other features	Family history	MRI	NCS
1	25 Y	29 Y	F	UMN Type of weakness of both L/L and bladder/Bowel dysfunction	Non consanguinous	Nil	No	Normal	Normal
2	3 Y	10 Y	M	Progressive quadriparesis	Non consanguinous	Delayed milestones	No	Dorsal cord atrophy	Peripheral neuropathy
3	25 Y	25 Y	M	B/L L/L UMN Weakness	Non consanguinous	Nil	No	Periventricular hyperintensities	Normal
4	17 Y	22 Y	F	UMN B/L L/L Weakness	Non consanguinous	Cognitive involvement seizures	No	Thin corpus callosum	Normal
5	48 Y	50 Y	F	B/L L/L UMN Type of weakness	Non consanguinous	Backward falls, Weight loss	No	Dorsal cord atrophy	Peripheral neuropathy
6	16 Y	19 Y	M	B/L L/L UMN Weakness	Non consanguinous	Cognitive decline	Brother affected	Ear of lynx	Normal
7	14 Y	19 Y	M	B/L UMN Weakness and imbalance while walking	Consanguinous	Cognitive decline, Parkinsonism, pseudo bulbar	2 brothers affected	Thin corpus callosum	Normal
8	33 Y	37 Y	M	B/L L/L UMN Weakness with urinary urgency, Dysarthria	Non consanguinous	Urinary urgency, Dysarthria	No	Dorsal cord atrophy	Normal
9	21 Y	25 Y	M	Dystonic myoclonic tremors, spasticity of bpoth l/l , ataxia	Consanguinous	Dystonic myoclonic tremors	No	Cerebellar atrophy	Normal
10	25 Y	28 Y	M	B/L U/L Distal UMN Weakness since 3 years, L/L Weakness since 1 year	Non consanguinous	U/L Distal amyotrophy	No	Normal	Normal
11	5 Y	18 Y	F	B/L L/L UMN Weakness	Non consanguinous	Cognitive decline	Elder sister effected	Normal	Normal
12	35 y	40 Y	M	LBA , B/L UMN Weakness	Non consanguinous	Nil	Son affected	Normal	Normal
13	2 y	20 Y	M	B/L L/L UMN Weakness	Non consanguinous	Poor scholastic performance	Elder brother effected	Normal	Normal
14	8 Y	18 Y	M	B/L L/L UMN Weakness	Consanguinous	Cognitive decline	No	Thin corpus callosum	Normal
15	13 Y	23 Y	M	B/L L/L UMN Weakness, Urinary retention	Non consanguinous	Dysarthria, Urinary retention	No	Ear of lynx	Normal
16	5 Y	7 Y	F	B/L LIMB Ataxia, B/L L/L UMN	Consanguinous	Dystonia in L/L, Flat foot	No	B/l Periventricular hyperintensities	Normal
17	2 Y	6 Y	MALE	B/l l/l Stiffness and imbalance while walking	Consanguinous	Ataxia,flat foot	younger brother affected	Cerebellar atrophy	Normal

Table 2: Continue table-1: Clinical features and genetics

S.No	GENE	EXON	Variant	Type of mutation	Pathogenic/VOUS	Novel/ Known	Inheritance pattern	HSP
1	CPT1C, BSLC2	EXON 18, EXON 7	C.1994C>T (p.Ser66GLeu), C.754T>C (p.Phe252Leu)	Missense, missense	VOUS, VOUS	Known, novel	Heterozygous autosomal dominant, heterozygous autosomal dominant	SPG73, SPG17
2	KIF1A	EXON 45	C.4781C>T p.Ser1594Leu	Missense	VOUS	Known	Heterozygous autosomal dominant/recessive	SPG 30/ Hereditary sensory neuropathy type IIC
3	CACNA1G, PNPLA6	EXON 13, EXON 25	C.2860G>A (p.Val954Met), c.2962G>A (p.Ala988Thr)	Missense, missense	VOUS, VOUS	Novel, novel	Heterozygous autosomal dominant, heterozygous autosomal recessive	SCA42, SPG39
4	SPG11	EXON 21	C.3623C>T (p.Pro1208Leu)	Missense	VOUS	Novel	Heterozygous autosomal recessive	SPG11
5	KIF5A, SPG 7	Intron 26, EXON 3	C.2993-1G>A, c.322C>G (p.Gln108Glu)	Frameshift, missense	Likely pathogenic, VOUS	Novel, novel	Heterozygous autosomal dominant, heterozygous autosomal dominant	HSP10, HSP7
6	SPG11	EXON 31	C.5939del(p.Leu1980Argfs*78)	Frameshift	Likely pathogenic	Novel	Heterozygous autosomal recessive	SPG11
7	SPG11, SPG11	EXON 32	C.6658_6659delat p.Met2220fs*27, c.6100C>T p.Arg2034*	Frameshift, nonsense	Likely pathogenic, Pathogenic	Novel, novel	Heterozygous autosomal recessive, heterozygous autosomal recessive	SPG11, SPG11
8	SPG7	EXON 6	C.778A>T p.Met260Leu	Missense	VOUS	Novel	Heterozygous autosomal recessive/autosomal dominant	SPG7
9	RAPGEF2, ZFYVE26, ZFYVE26	EXON 7	C.4411C>T p.Pro1471Ser, c.6744_6746delgaa p.Lys2248DEL, c.1093delc p.Leu365Serfs*16	Missense, inframe deletion, frameshift	VOUS, VOUS, Likely pathogenic	Known, novel, novel	Heterozygous autosomal dominant, heterozygous autosomal recessive, heterozygous autosomal recessive	Familial adult myoclonus 7, SPG 15, SPG15
10	HSPB3, DDHD1	EXON 1	C.224T>A p.Leu75Gln, c.424delg p.Glu142fs*18	Missense, frameshift	VOUS, Likely pathogenic	Known, novel	Heterozygous autosomal dominant, homozygous autosomal recessive	HMN2C, SPG 28
11	SPG11	EXON 32	Chr15:44865850G>A c.6100C>T p.Arg2034Ter	Nonsense	Pathogenic	Known	Homozygous autosomal recessive	SPG11
12	SPG7	EXON 2	Chr16:89576947T>A c.233T>A p.Leu78Ter	Nonsense	Likely pathogenic	Known	Homozygous autosomal recessive	SPG7
13	GBA2	EXON 9	C.1460T>C p.Leu487Pro	Missense	Likely pathogenic	Novel	Homozygous autosomal recessive	SPG 46
14	SPG11	EXON 21	C.3623C>T p.Pro1208Leu	Missense	VOUS	Known	Homozygous autosomal recessive	SPG11
15	SDHA, SPG11, SCN4A	EXON 21-24	Chr5:251555G>A c.1766G>A p.Arg589G1, chr15:c.3520+1_3521-1_(4161+1_4162-1)del, chr17:62022916C>T c.3524G>Ap.Ser1175aSN	Missense, deletion, missense	Likely pathogenic, Likely pathogenic, VOUS	Known, novel, known	Heterozygous dominant/Recessive, heterozygous autosomal recessive, heterozygous dominant/Recessive	SDHA, SPG11, CMS/hyperpp, hypopp
16	SPG11, FLVCR1	EXON 15	C.2626A>A/G p.Lys876Glu, c.49C>C/G p.Pro17Ala	Missense	VOUS, VOUS	Known, known	Heterozygous missense autosomal recessive, heterozygous missense autosomal recessive	SPG11, Posterior column Ataxia withrp
17	FA2H /SPG 35	EXON 6	C.815duptp.Val275fs*38	Frameshift	Likely pathogenic	Novel	Homozygous autosomal recessive	FA2H / SPG35

Table 3: Comparison of clinical features in our study and SHI et al study²

Clinical features	Our study	SHI et al., Study ²
Cognitive decline	6 (35.29%)	6 (22.2%)
Extrapyramidal	3 (17.64%)	3 (11.1%)
Dysarthria	2 (11.7%)	9 (33.3%)
Peripheral neuropathy	2 (11.7%)	3 (11.1%)
Ataxia	1 (5.8%)	3 (11.1%)
Seizure	1 (5.8%)	2 (7.4%)

Table 4: 3: MRI findings in our study

S.No. of patients	MRI Findings
1	Normal
2	Dorsal cord atrophy
3	Periventricular hyperintensities
4	Thin Corpus Callosum
5	Dorsal cord atrophy
6	EAR OF LYNX
7	Thin Corpus Callosum
8	Dorsal cord atrophy
9	Cerebellar atrophy
10	Normal
11	Normal
12	Normal
13	Normal
14	Thin Corpus Callosum
15	EAR OF LYNX, Thin Corpus Callosum
16	B/L Periventricular hyperintensities
17	Cerebellar atrophy

Table 5: Comparison of our study with other Indian and international studies

	Our study	Narendiran et al. ³ (2022)	Kamate et al., ⁴ (2019)	Stevanin et al. ⁵ (2008)	Kara et al. ⁶ (2016)	Ishiura et al. ⁷ (2014)	Luo et al. ⁸ (2014)	Elert-Dobkowska et al. ² (2019)
Ethnicity	India	India	India	France	UK	Japan	China	Poland
Cohort	44 (17)	57 (25)	11	76	97 (48)	129 (46)	201	30
Age	2-50 Y	3-22 Y	21.7 months.	2 to 27	16 (3-39)	10-50	SPG4 - 11-41 Non SPG4 5-34	NA
Gender M:F	13: 4	40:17	6:5	18:20		75:54	134:67	NA
Pure or complicated	3/14	15/42	4/7	0/38		0/97	130/71	16/14
Inheritance	AR	AR	AR 10/ AD 1	AR (65%)	AR	AD	AD	AR
GENE	SPG11	SPG11	DDHD2	SPG11				

M: Male, F: Female, AD- Autosomal dominant, AR - Autosomal recessive, NA - Not applicable

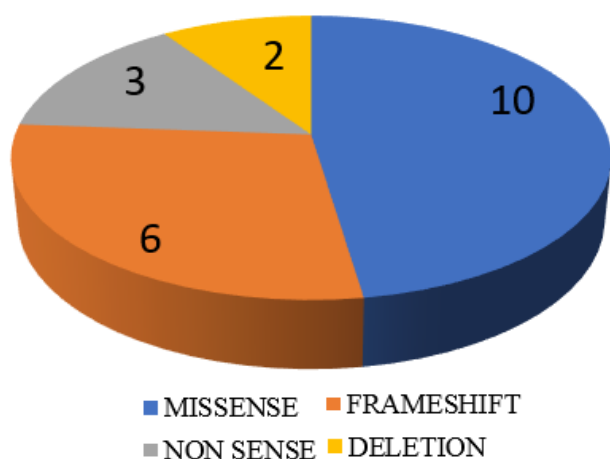


Figure 3: No of missense, frameshift, non-sense, deletion mutations.

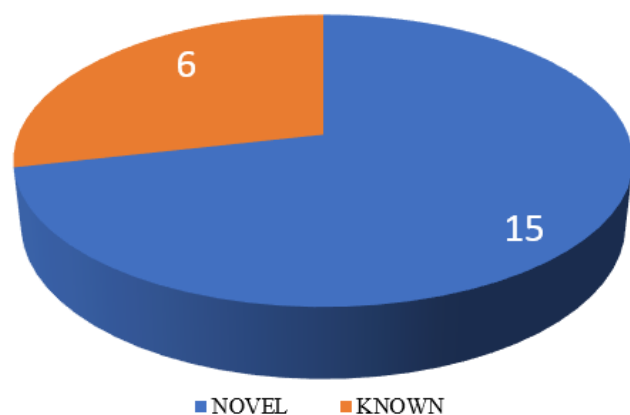


Figure 4: Number of novel and known mutations in allspg variants.

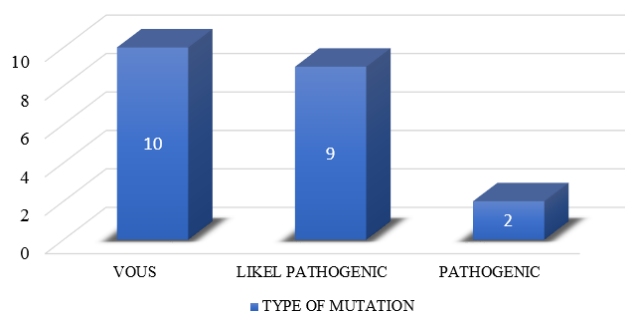


Figure 5: Type of mutation in allspg patients

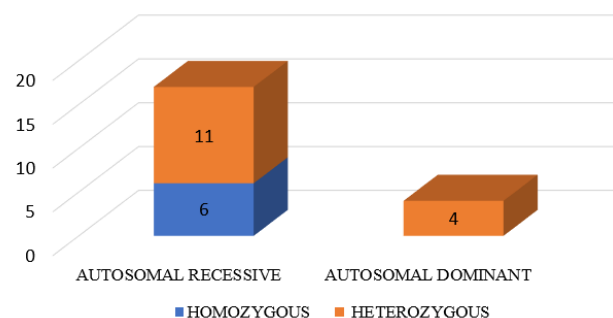


Figure 6: Inheritance pattern among 17 patients

dominant HSP whereas middle eastern and American amish groups had predominant autosomal recessive inherited hsp, attributed to the higher prevalence of consanguinity in these populations.

PURE HSP in our study is seen in 3 (17.64%), COMPLICATED HSP in 14 (82.35 %) cases. This is Corroborated by an Indian study by Narendiran S. et al.,³ where they found 17 complicated HSP and 7 pure HSP cases out of 24 genetically confirmed hsp cases. Unlike a chinese study by Cao, Y et al.,¹⁰ of a total of 270 patients, they found 67% of patients with pure HSP, and 33% with complicated HSP. European study by Elert-Dobkowska E et al.,² in Poland, found pure HSP in 16 and complicated HSP in 14 out of 30 cases studied. In our study, predominance of complicated HSP is probably due to greater number of autosomal recessive HSP compared to autosomal dominant HSP.

We found cognitive decline to be the next most common clinical feature after spasticity of limbs, seen in 6 patients, extra pyramidal involvement in 3, dysarthria in 3, ataxia in 1 patient, Peripheral neuropathy is seen in 2 and upper limb distal amyotrophy in one patient. In Shi Y et al study,¹¹ dysarthria and cerebellar ataxia were detected in 9(33.3%) and 3(11.1%) of patients with HSPs, respectively. Comparison of clinical features with Shi Y et al. study¹¹ is shown in Table 3. Harding found urinary symptoms, sensory followed by ataxia to be the most common in the descending order of frequency. A 28-year-old male, born of non-consanguineous parents presented with 3 years progressive spastic paraparesis and upper limb distal amyotrophy. WES revealed DDHD 1 mutation, in SPG 28 loci. HSP with amyotrophy is not described in SPG 28 till date. All over world, only 3 cases of spg 28 reported to the best of our knowledge. Tesson et al. (2012)¹² reported 3 patients from 2 unrelated families with SPG28. Two Turkish brothers, born of consanguineous parents, showed progressive spastic gait with onset around adolescence. An unrelated 62-year-old French woman had spastic paraplegia since infancy and had an axonal neuropathy. None of them were reported to have amyotrophy. Spastic paraparesis with distal amyotrophy is called as silver syndrome. Phenotype of silver syndrome

was described in SPG 17, SPG 38 and in few SPG 4 cases. We therefore describe a new phenotypic representation of SPG 28 i.e., spastic paraparesis with distal amyotrophy, called as silver syndrome.

Another 10-year-old male presented with progressive spastic quadriparesis along with peripheral neuropathy. On WES by NGS method, revealed mutation at KIF1A gene at c.4781C>T p.Ser1594Leu loci which can cause both SPG 30 and HEREDITARY SENSORY NEUROPATHY TYPE IIC. Mutation at one locus, with overlapping clinical manifestation is seen in this case.

Another patient presented with predominantly dystonia and dystonic tremors, associated with spasticity of lower limbs. WES by NGS method, revealed likely pathogenic mutation in gene ZFYVE26, causing SPG 15. Ebrahimi-Fakhari et al.¹³ described focal dystonia in patients with SPG 15. NGS is helpful in diagnosis in such cases considering the overlap of the neurological symptoms (which is seen in Stevanin G et al. study, Narendiran S. et al. study).^{3,5}

On MRI brain with spine study (Table 4), thin corpus callosum is most commonly found in our study (4 cases 23.52%). We found TCC only in SPG11 cases. It is consistent with a comprehensive genetic evaluation of an Italian cohort of patients, da Graça FF et al study.¹⁴ In that study, patients with HSP-TCC (n = 61) were studied and found SPG11 to be the most frequent subtype (26.2%), followed by SPG15 (14.8%), SPG35 (5%), and SPG48 (3%) (13). Other less frequent causes of HSP-TCC are SPG 4, 7, 18, 21, 46, 47, 49, and 54.

The most classic neuroimaging finding “ear-of-the-lynx sign” is characterized by hyperintense on T2-FLAIR-weighted and hypointense on T1-weighted images at the forceps minor of the corpus callosum (genum fibres). This radiological sign may also be present in SPG 15, another form of complicated AR HSP. We have seen Ear of lynx sign in 2 (11.7%) patients, who are SPG 11, consistent with the other studies by da Graça FF et al.¹⁴ and Stevanin G et al.⁵ Dorsal spinal cord atrophy, next most common finding in MRI in our cohort, found in 3 (17.64%) patients, (SPG 7, SPG 10 and SPG 30). Dorsal spinal cord atrophy is characteristic but not exclusive for HSP.

In our study, we identified SPG gene loci mutation to be *vous* in 10, Likely pathogenic in 9, pathogenic in 2 patients. Based on WES by NGS method, patients with hsp phenotype were diagnosed as pathogenic in 40 % (10/25), with *vous* in 28% (7/25). WES is negative in 8 (31%) cases. In a polish study by Elert- Dobkowska E et al.,² 18 pathogenic and likely pathogenic variants in spastic paraplegia probands, as well as six variants of uncertain significance were found. Cao, Y et al.¹⁰ studied a total of 270 patients with HSP phenotype. According to this study, 60 percent diagnoses could be made out of 270 patients, of whom 132(48 percent) cases were diagnosed on NGS and remaining 30 cases were diagnosed with

MLPA analysis. In our study, VOUS and WES negative cases could not be further confirmed by MLPA analysis, familial cosegregation or RNA sequencing due to financial constraints. It is a fallacy of our study.

In our cohort, total of 15 novel mutations were seen. In one study by Zeyu Zhu et al.,¹⁵ total of 34 different mutations in the SPAST gene were identified, of which 10 were novel. Our studied identified 15 novel mutations. Hereditary spastic paraplegia is a hereditary neurodegenerative disease, with a rapidly expanding list of genes causing it. Gene causing HSP has been named as SPG with number next to it, in the order of discovery. In our study, most common inherited HSP was found to be SPG 11 which has autosomal recessive inheritance. This similar pattern of was also observed in other studies of Elert-Dobkowska E et al.,² Stevanin G et al.,⁵ Narendiran S. et al.,³ Kara et al.,⁶ where SPG11 was found to be commonest (Table 5). Autosomal dominant inheritance found to be common in Ishiura H et al study.¹⁵ Luo Y et al.,⁷ studied autosomal dominant HSP and SPG 4 was seen as most common cause in china. Worldwide Autosomal dominant inheritance is studied to be the most common pattern of inheritance in HSP. In our study, the reason for more common autosomal recessive inheritance may be the cultural practice of consanguineous marriage in Indian ethnicity.

Two patients from different unrelated families (one was from Maharashtra, other from Uttar Pradesh) were detected with Mutation in SPG 11 gene at c.6100C>T p.Arg2034* in our study. In a study by Stevanin G et al.,⁵ same variant with mutation at c.6100C>T p.Arg2034* was found in 4 different north African families. This could be indicative of founder effect for this mutation. However, Haplotype analysis may be required for further confirmation.

One more similar mutation was found in 2 unrelated families. A novel missense autosomal recessive mutation in SPG11 gene c.3623C>T (p.Pro1208Leu) loci was found in 2 different patients, one from Maharashtra, other from Uttar Pradesh).

Of the 17 cases in our study, 7 were SPG 11 cases. On further analysis of these cases, age of onset was 1st decade in 3 patients, 2nd decade in 4 patients, ranging from 5 years to 17 years. In Stevanin et al. study,⁵ of the 38 patients from 20 families, age of onset was in the range from 2 to 27. We observed male predominance (M: F - 4: 3). In the study by Stevanin et al.,⁵ SPG 11 was seen in 18 Males and 20 female patients. Consanguinity is seen in 3 families and family history is found in 1 patients among these families.. Clinical features associated with lower limb weakness and gait disturbances were studied, more commonly observed were cognitive decline in 4, dystonia in 2, seizure in 1, dysarthria in 1 case. Comparing with Stevanin et al. study,⁵ of the 38 patients, most common associated neurological feature was cognitive decline in concordance with our study.

Dysarthria was frequently seen in their study (16/38). NCS was normal in all cases in our study, but in Stevanin et al. study, NCS showed neuropathy in 13 of 16 cases on follow up. MRI brain showed thin corpus callosum in 3 cases, ear of lynx in 2 patients, bilateral ventricular hyperintensities in 1 and normal in 1 case. More common thin corpus callosum and presence of characteristic ear of lynx sign in SPG 11, is in concordance with the Stevanin et al. study. So, in an HSP suspected case, with onset before 2nd decade, with cognitive decline and thin corpus callosum on mri brain, one should always suspect SPG11.⁵

5. Conclusion

In conclusion, there is a consider overlap of SPG genes with other neurological diseases like HSMN, HMN2C, FAMILIAL ADULT MYOCLONUS 7. SPG 28 can present with spastic paraparesis and distal upper limb amyotrophy, i.e., SILVER SYNDROME. Next generation sequencing method allowed us for confirming the diagnosis of HSP in patients with multiaxial neurological involvement. One should always suspect, SPG 11 in an HSP suspected case with onset before the second decade, cognitive impairment, and a thin corpus callosum on MRI brain.

This study of HSP highlights that genetic diagnosis can be reached with genetic testing by NGS method in patients with multiaxial neurological involvement and confirms the more common prevalence of complicated AR HSP in Indian population, predominantly at SPG 11 loci.

6. Limitations of study

The main limitation of the study is that parental segregation is not done, we have studied only proband and not studied parents.

7. Source of Funding

None.

8. Conflict of Interest

None.

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