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Comprehensive Characterization of Spastic Paraplegia in Korean Patients: A Single-Center Experience over Two Decades

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Purpose: Hereditary spastic paraplegia (HSP) refers to a group of genetic neurodegenerative diseases marked by gradually worsening spasticity and hyperreflexia in the lower extremities. This study aimed to describe the clinical and genetic characteristics of Korean patients with spastic paraplegia.

Materials and Methods: We retrospectively reviewed medical records of 69 patients with spastic paraplegia from 54 unrelated families between 2002 and 2024. Genetic, clinical, electrophysiological, and radiological features were comprehensively analyzed.

Results: Causative genes were identified in 34 (63%) of 54 unrelated families; *SPAST*, detected in 26 families, was the most prevalent. Seven novel pathogenic variants were identified. Clinically, the median age of symptom onset was 25 years [14.0–37.0]. Out of 69 patients with spastic paraplegia, 51 (74%) presented with the pure form of spastic paraplegia, which included all patients with SPG4. Spastic gait was a universal feature in all patients. Urinary dysfunction was present in 42 (61%) patients. Additional neurologic manifestations included peripheral neuropathy 9 (13%), cognitive impairment 5 (7%), upper limb weakness 4 (6%), dysarthria 4 (6%), dysphagia 3 (4%), ataxia 3 (4%), and scoliosis 1 (3%). Brain MRI findings demonstrated a thin corpus callosum in two patients with SPG11; all patients with SPG4 had normal findings. Spine MRI revealed spinal cord atrophy in 16 (27%) patients, including 6 (21%) patients with SPG4.

Conclusion: The study comprehensively reviewed genetic and clinical spectra of spastic paraplegia in Korean patients, emphasizing the predominance of *SPAST* as the causative gene and underscoring the genetic and phenotypic heterogeneity of spastic paraplegia.

Key Words: Spastic paraplegia, hereditary; diagnosis; spastic paraplegia type 4; spastic paraplegia type 11; genetic variation; clinical relevance

INTRODUCTION

Hereditary spastic paraplegia (HSP) refers to a group of clinically and genetically heterogeneous neurodegenerative disorders that primarily affect the corticospinal tracts. These disorders are defined by slowly progressive spasticity, hyperreflexia, and an extensor plantar response, predominantly affecting the lower extremities. The genetic inheritance patterns of HSP encompass autosomal recessive, autosomal dominant, X-linked, and maternal patterns, with 13%–40% of cases occurring sporadically without any family history.[1-3] The prevalence of HSP

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is estimated to be between two and five cases per 100000 individuals.[4,5]

Clinically, HSP is broadly categorized into pure and complicated forms. The pure form of HSP predominantly manifests as a slowly progressive spastic gait disturbance. Spasticity may exhibit slight asymmetry, with or without motor weakness. While the upper extremities typically remain unaffected by spasticity and motor weakness, hyperreflexia is occasionally observed.[6] Urinary symptoms are frequently observed and may result from detrusor instability or detrusor-sphincter dyssynergia.[7] Asymptomatic or mildly symptomatic impairments of vibration sensation are occasionally observed, though pain and touch sensation are less affected.[1,4,5] However, a complicated form of HSP is distinguished by both spastic paraplegia and additional neurological impairments, including upper limb weakness, dysarthria, dysphagia, ataxia, cognitive dysfunction, seizures, extrapyramidal symptoms, peripheral neuropathy, and chorioretinal dystrophy.[1] Complex HSP is more frequently associated with autosomal recessive inheritance patterns than autosomal dominant inheritance.[2,8]

To date, approximately 80 causative genes have been identified (www.musclegenetable.fr). Among the subtypes, SPG4, resulting from pathogenic variants in *SPAST*, represents the most prevalent form of autosomal dominant HSP, followed by SPG3A (*ATL1*) and SPG31 (*REEP1*).[6,8,9] SPG11, caused by pathogenic variants in *SPG11*, is the most common autosomal recessive HSP.[4] However, the distribution of HSP subtypes varies by ethnicity and geographic region. Additionally, the cardinal clinical feature of HSP, progressive spastic paraparesis, is also found in other monogenic neurologic diseases, including adrenomyeloneuropathy and adult-onset Krabbe syndrome.[10,11]

Several studies have demonstrated the genetic and clinical spectra of HSP in the Korean population.[12-15] However, comprehensive datasets on HSP remain scarce. This study aims to comprehensively characterize the clinical, electrophysiological, radiological, and genetic features of Korean patients with spastic paraplegia seen at a single referral center over a two-decade period.

MATERIALS AND METHODS

Patients

We conducted a retrospective review of medical records for patients with spastic paraplegia who were referred to Gangnam Severance Hospital between January 2002 and September 2024. A total of 69 patients from 54 unrelated families were included. Patients were eligible if they presented with slowly progressive spastic paraparesis without structural spinal cord lesions on MRI, and if there was no clinical history, laboratory evidence, or neuroimaging findings suggestive of inflammatory, infectious, or vascular etiologies. This clinical definition was used to identify patients with spastic paraplegia. Our study retrospectively analyzes cases of spastic paraplegia over a span of more than 20 years, encompassing a wide range of diagnostic methods. Conventional Sanger sequencing of the *SPAST* and *ATL1* genes was conducted in 15 families (F2, F4, F6, F7, F8, F9, F10, F11, F13, F14, F19, F20, F41, F44, and F47), primarily during the early years of the study when next-generation sequencing (NGS) technologies were not widely accessible. Using this method, pathogenic variants in SPAST were identified in six patients. For the remaining 39 families and nine undiagnosed families, targeted sequencing of neuromuscular disorder-associated genes or whole-exome sequencing was employed, which became available later and provided broader genetic coverage. Additionally, for patients in whom exome sequencing indicated potential exonic deletions or duplications, multiplex ligation-dependent probe amplification (MLPA) was performed to confirm these findings with precision.

Phenotype analysis

Clinical and laboratory data were retrospectively reviewed from medical records. The collected clinical information included the onset age of symptoms, age at diagnosis, spastic gait, urinary dysfunction, lower limb hypesthesia, upper limb weakness, dysarthria, dysphagia, ataxia, cognitive impairment, seizures, extrapyramidal involvement, peripheral neuropathy, and scoliosis. Electrophysiologic assessments included nerve conduction studies with needle electromyography as well as somatosensory evoked potential (SEP) of the median and posterior tibial nerves, performed in 65, 47, and 49 patients, respectively. Additionally, brain and spine MRI was conducted in 50 and 59 patients, respectively.

Ethics statement

This study was approved by the Institutional Review Board of Gangnam Severance Hospital, Korea (approval number: 3–2024–0379). Written informed consent was obtained in accordance with the study protocol, and the study was conducted in compliance with the principles of the Declaration of Helsinki.

RESULTS

Genetic spectrum of Korean families with spastic paraplegia

Among a total of 54 families, 21 families demonstrated autosomal dominant inheritance, one exhibited autosomal recessive inheritance, and 32 had no reported family history (Fig. 1 and Supplementary Fig. 1, only online). Causative genes were identified in 34 (63%) of 54 unrelated families. Until 2015, when genetic testing was performed using Sanger sequencing, the diagnostic yield was 40% (6 out of 15 families). In contrast, with the application of NGS, the diagnostic yield increased to 67% (26 out of 39 families). Furthermore, among 9 families in

whom no causative variant was identified by Sanger sequencing, additional testing using NGS revealed pathogenic variants in 2 families (22%).

SPAST was identified as the most frequent causative gene, found in 26 unrelated families, followed by *SPG11* in three families, *SPG9* in one family, *SPG10* in one family, *SPG31* in one

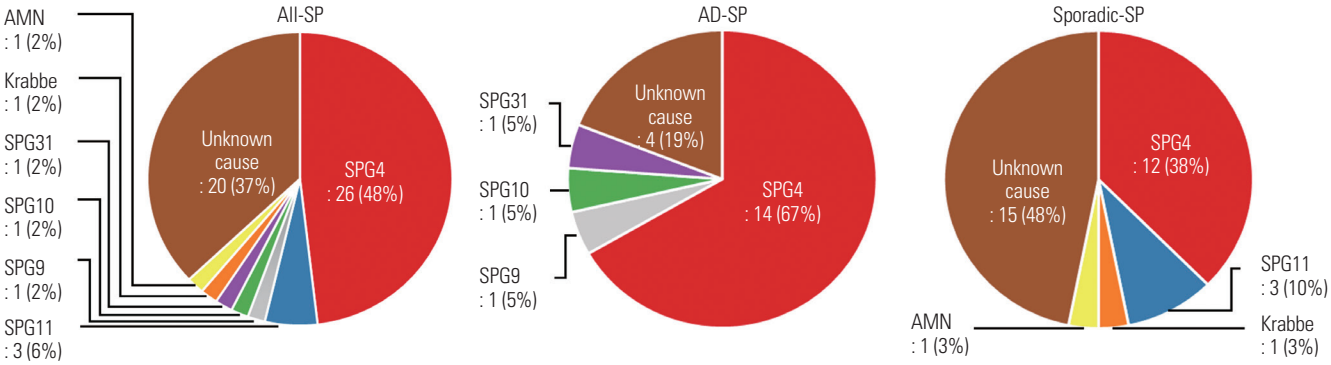

Fig. 1. Distribution of patients with SP by mode of inheritance. SP, spastic paraplegia; AMN, adrenomyeloneuropathy; AD, autosomal dominant.

Table 1. Pathogenic and Likely Pathogenic Variants in Genes Associated with Spastic Paraplegia

Gene	Reference sequence	Exon	Variant	Families	PMID	Phenotype
SPAST	NM_014946	2	c.443G>A (p.Trp148Ter)	F7, F42	20932283	SPG4
		5	c.870G>A (p.Lys290=)	F40	18701882	
		6	c.936del (p.Asp313ThrfsTer2)	F46	Novel	
		9	c.1196C>T (p.Ser399Leu)	F47	18701882	
		IVS9	c.1245+1G>A	F6, F19	18701882	
		10	c.1291C>T (p.Arg431Ter)	F36	18701882	
		IVS10	c.1322–1G>C	F41	Novel	
		11	c.1378C>T (p.Arg460Cys)	F38	18701882	
		11	c.1379G>A (p.Arg460His)	F45	18701882	
		11	c.1384A>C (p.Lys462Gln)	F28	Novel	
		11	c.1412G>A (p.Gly471Asp)	F39	17560499	
		IVS11	c.1413+4A>G	F51	30375765	
		IVS11	c.1414–2A>G	F10	11843700	
		12	c.1474C>T (p.Leu492Phe)	F37	20932283	
		12	c.1486del (p.Val496PhefsTer34)	F16	Novel	
		13	c.1495C>T (p.Arg499Cys)	F25	11039577	
		15	c.1649C>T (p.Thr550Ile)	F24	10699187	
		15	c.1685G>A (p.Arg562Gln)	F14	11843700	
		17	c.1741C>T (p.Arg581Ter)	F43	20562464	
		17	c.1751A>T (p.Asp584Val)	F48	16009769	
			Deletion of exons 5–16	F20	Novel	
			Deletion of exons 16–17	F23	17098887	
			Duplication of exons 9–16	F44	Novel	
SPG11	NM_025137	11	c.2163dup (p.Ile722TyrfsTer10)	F26	19513778	SPG11
		IVS18	c.3291+1G>T	F1, F26, F27	19513778	
		IVS30	c.5866+1G>A	F27	26671123	
		37	c.6832_6833del (p.Ser2278LeufsTer61)	F1	20110243	
KIF5A	NM_004984	8	c.611G>A (p.Arg204Gln)	F13	25008398	SPG10
REEP1	NM_022912	5	c.337C>T (p.Arg113Ter)	F5	29629531	SPG31
ALDH18A1	NM_002860	7	c.755G>A (p.Arg252Gln)	F54	26297558	SPG9
ABCD1	NM_000033	7	c.1747_1749del (p.Val583del)	F52	Novel	AMN
GALC	NM_000153	7	c.683_694delinsCTC (p.Asn228_Ser232delinsThrPro)	F53	38515343	Krabbe disease
		16	c.1901T>C (p.Leu634Ser)		35571021	

AMN, adrenomyeloneuropathy.

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family, *ABCD1* in one family, and *GALC* in one family (Table 1 and Supplementary Table 1, only online). However, no genetic cause was identified in 20 families. *SPAST*, associated with SPG4, was the most frequently identified gene in both autosomal dominant and sporadic HSP families (Fig. 1). However, a pathogenic variant in *ATL1*, associated with SPG3A, was not identified.

Among the identified pathogenic variants, seven were novel. Six of them were novel variants in *SPAST*. Three null variants (c.936del, c.1322–1G>C, and c.1486del) and two exonic deletions/duplications (deletion of exons 5–16 and duplication of exons 9–16) were classified as likely pathogenic variants based on PVS1 (null variant in genes with a known loss-of-function disease mechanism) and PM2 (not found in population databases). One missense variant (c.1384A>C) in *SPAST* was classified as a likely pathogenic variant according to the following evidence: PM1 (located in a mutational hotspot or critical domain), PM2, PM5 (a novel missense variant occurring at an amino acid residue where other missense changes, previously classified as pathogenic have been observed), PP3 (predicted deleterious by multiple in silico tools), and PP5 (reported as pathogenic in reputable databases). Additionally, one novel variant (c.1747_1749del) in *ABCD1* was classified as a likely pathogenic variant according to the following evidence: PS3 (increased serum content of very-long-chain fatty acids), PM1, PM2, and PM4 (protein length alterations caused by in-frame deletions within non-repeat regions or by stop-loss variants).

Clinical, electrophysiological, and radiological spectrum of Korean patients with spastic paraplegia

The clinical, electrophysiological, and radiological features of 69 Korean patients with spastic paraplegia and the subgroup of 33 patients with SPG4 are summarized in Table 2 and Supplementary Table 2 (only online). Most patients in both groups were male, accounting for 70% of the total cohort and 64% of the SPG4 group. The median age of symptom onset was 25 years [14.0–37.0] in the total group and slightly higher at 27 years [15.0–37.0] in the SPG4 group. The onset of symptoms in patients with spastic paraplegia significantly varied depending on the causative gene (Fig. 2). Among the patients with SPG4, the onset ranged widely, from childhood to their 60s. Additionally, the two patients with SPG9, who were from the same family, exhibited different symptom onset patterns. One developed spastic gait in their mid-20s, while the other (their son) experienced developmental delay and cataracts from birth. Meanwhile, patients with SPG11 and SPG31 showed a more consistent pattern, with symptoms typically appearing between the ages of 5 and 8 years. The median age at diagnosis was 46 years [33.0–56.0] overall and 50 years [43.0–56.0] in the SPG4 group. In clinical phenotypes, the majority of patients (74%) presented with a pure form of spastic paraplegia, with all patients in the SPG4 group (100%) classified under this category. Spastic gait was a universal feature, present in all patients with spastic paraplegia. Other clinical features were more variable: urinary dysfunction was observed in 61% of the total group compared to 55% of the SPG4 group. Additional features, including peripheral neuropathy (13%), lower limb hypesthesia (9%), cognitive impairment (7%), upper limb weakness (6%), dysarthria (6%), dysphagia (4%), and ataxia (4%) were identified in the total cohort but were absent in the SPG4 group. Scoliosis was identified in 1 patient (3%) within the SPG4 group. Seizures and extrapyramidal involvement were absent in both groups.

Table 2. Summary of Clinical Features in all 69 Korean Patients with Spastic Paraplegia

Clinical findings	Value
Male	48 (70)
Age at symptom onset (yr)	25.0 [14.0–37.0]
Age at diagnosis (yr)	46.0 [33.0–56.0]
Clinical phenotype	
Pure form	51 (74)
Complicated form	18 (26)
Clinical features at diagnosis	
Spastic gait	69 (100)
Urinary dysfunction	42 (61)
Peripheral neuropathy	9 (13)
Hypesthesia	6 (9)
Cognitive impairment	5 (7)
Upper limb weakness	4 (6)
Dysarthria	4 (6)
Dysphagia	3 (4)
Ataxia	3 (4)
Scoliosis	1 (3)
Seizure	0 (0)
Extrapyramidal involvement	0 (0)
Electrophysiological study	
Nerve conduction study (n=65)	
Normal study	56 (86)
Polyneuropathy	9 (14)
Median SEP (n=47)	
Normal study	42 (89)
Central conduction defects	5 (11)
Tibial SEP (n=49)	
Normal study	39 (80)
Central conduction defects	10 (20)
MRIs	
Brain (n=50)	
Normal study	46 (92)
Thin corpus callosum	2 (4)
Non-specific white matter change	2 (4)
Spine (n=59)	
Normal study	43 (73)
Cord atrophy	16 (27)

SEP, somatosensory evoked potential.
Data are presented as mean [range] or n (%).

In electrophysiological studies, nerve conduction studies showed normal results in 56 (86%) patients and polyneuropathy in 9 (14%) of the total cohort. All tested patients in the SPG4 group showed normal results. Median-nerve SEPs showed no conduction defect in any of the 37 tested patients with a pure form of spastic paraplegia, whereas central conduction defects were identified in 5 (50%) of the 10 tested patients with a complicated form of spastic paraplegia. Tibial SEPs revealed central conduction defects in 4 (10%) of the 39 tested patients with a pure form of spastic paraplegia and in 6 (60%) of the 10 tested patients with a complicated form of spastic paraplegia.

Brain MRI findings demonstrated non-specific white matter changes in one patient with a complicated form of spastic paraplegia and in one patient with a pure form of spastic paraplegia. A thin corpus callosum was observed in two patients with SPG11 (Fig. 3A). In contrast, all participants (100%) in the SPG4 group exhibited normal brain MRI findings. Spine MRI revealed spinal cord atrophy in 16 patients (27%) of the total cohort and in 6 patients (21%) of the SPG4 group, as illustrated in Fig. 3B and C.

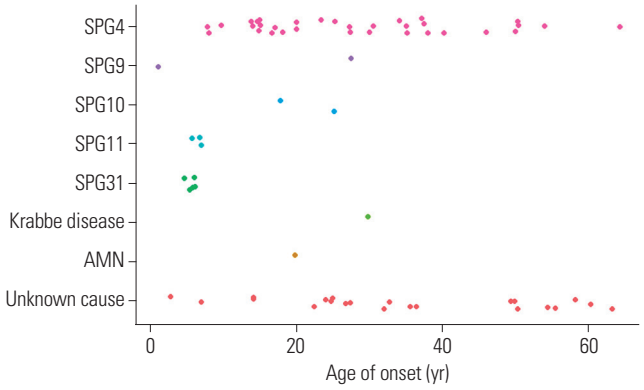

Fig. 2. Distribution of symptom onset age in spastic paraplegia, categorized by subtype. AMN, adrenomyeloneuropathy.

DISCUSSION

This retrospective study describes the clinical, radiological, electrophysiological, and genetic features of Korean patients with spastic paraplegia, based on more than 20 years of experience at a single neuromuscular center. All 69 patients were clinically diagnosed with spastic paraplegia based on predominant spasticity in the lower extremities without evidence of mechanical or metabolic etiologies. Initial genetic analyses were conducted using Sanger sequencing of *SPAST* or *ATL1*. With the advent of NGS, comprehensive analysis extended to whole exomes or targeted gene panels encompassing a broad range of genes associated with neuromuscular disorders. Pathogenic variants were subsequently classified following the American College of Medical Genetics and Genomics guidelines. We successfully identified causative genes in approximately two-thirds of the Korean families with spastic paraplegia.

The retrospective design of our study presents limitations. However, it also enabled us to track the evolution of genetic diagnostic strategies over more than two decades. Until 2015, we primarily utilized Sanger sequencing for *SPAST* and *ATL1* in 15 families. As NGS became more accessible, targeted gene panels covering neuromuscular disorder-related genes and whole-exome sequencing were applied to 39 families. This advanced approach significantly improved the diagnostic yield by enabling the detection of variants across a wider range of genes. Furthermore, NGS facilitated the detection of exonal deletions and duplications that could not be identified by Sanger sequencing. However, due to concerns regarding the accuracy of NGS-based structural variant detection, we performed MLPA for confirmatory testing in relevant cases.

Our study showed the frequencies of causative genes in Korean patients with spastic paraplegia. SPG4 was identified as the most common subtype, representing 48% of the cases in our study (Table 3). Although SPG4 emerged as the most prevalent subtype, its frequency varied across populations. The frequency

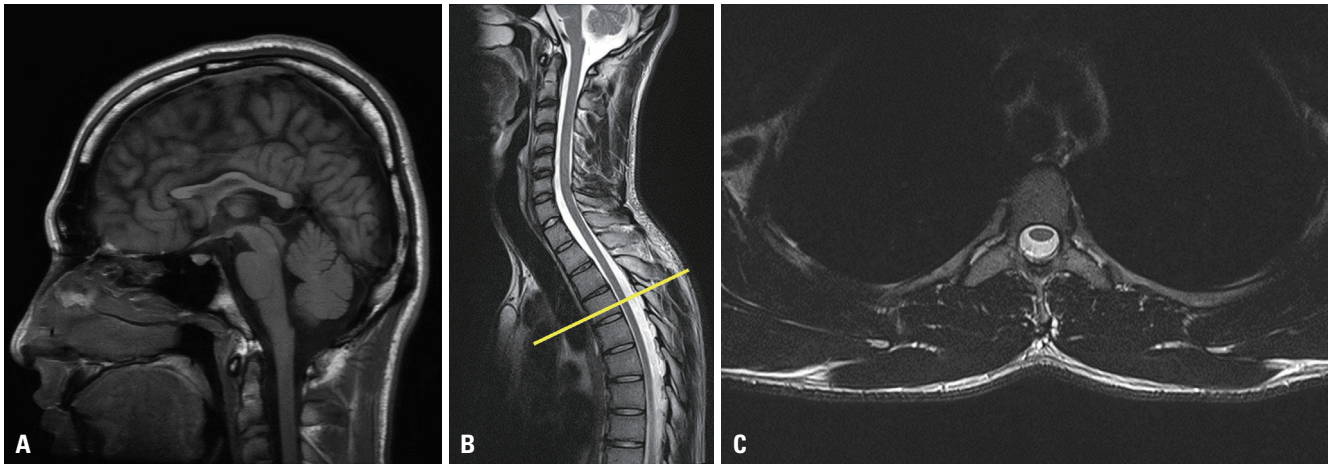

Fig. 3. Characteristic atrophy of the corpus callosum and spinal cord in *SPG11*. Magnetic resonance images of the brain and spinal cord revealed pronounced atrophy of the corpus callosum (A) and spinal cord (B and C) in a 22-year-old male patient (F27) with pathogenic variants in *SPG11*.

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Table 3. Comparison of Proportions of SPG4, SPG3A, SPG7, SPG9, SPG10, SPG11, SPG31, AMN, Krabbe Disease in Patients with Spastic Paraplegia in the Present and Published Datasets

	Total patients	SPG4 (%)	SPG3A (%)	SPG7 (%)	SPG9 (%)	SPG10 (%)	SPG11 (%)	SPG31 (%)	AMN (%)	Krabbe disease (%)	Total diagnosed (%)
Asians											
Korea, present study	69	33 (48)	0 (0)	0 (0)	2 (3)	2 (3)	3 (4)	5 (7)	1 (1)	1 (1)	47 (68)
Korea, 2014[12]	27	11 (41)	0 (0)	-	-	-	-	0 (0)	-	-	11 (41)
Korea, 2015[13]	206	49 (24)	3 (1)	-	-	-	-	-	-	-	52 (25)
Korea, 2021[14]	166	33 (20)	4 (2)	1 (1)	5 (3)	2 (1)	2 (1)	2 (1)	0 (0)	0 (0)	49 (30)
Japan, 2014[18]	129	32 (25)	2 (2)	0 (0)	-	0 (0)	5 (4)	2 (2)	-	-	41 (32)
China, 2015[16]	120	65 (54)	3 (3)	-	-	0 (0)	-	-	-	-	68 (57)
Caucasians											
Germany, 2016[1]	608	196 (32)	9 (1)	28 (5)	0 (0)	5 (1)	15 (2)	5 (1)	5 (1)	1 (0)	264 (43)
Insular Italy, 2014[22]	67	52 (78)	0 (0)	2 (3)	-	0 (0)	1 (1)	-	-	-	55 (82)
Spain, 2023[19]	562	150 (27)	14 (2)	56 (10)	-	21 (4)	22 (4)	11 (2)	11 (2)	-	285 (51)
Portugal, 2013[5]	418	92 (22)	14 (3)	-	-	-	26 (6)	-	-	-	132 (32)
Poland, 2015[20]	216	40 (19)	10 (5)	-	-	-	-	7 (3)	-	-	57 (26)
Russia, 2019[17]	122	38 (31)	10 (8)	-	-	-	-	-	-	-	48 (39)
Hungary, 2016[21]	58	10 (17)	1 (2)	5 (9)	-	0 (0)	2 (3)	2 (3)	1 (2)	-	21 (36)

AMN, adrenomyeloneuropathy; -, not reported.

of SPG4 in our study is similar to that in previous reports from Korean, Chinese, German, or Russian populations.[1,12,16,17] However, it is higher than the frequencies reported in other studies, including Korean, Japanese, Portuguese, Polish, and Hungarian populations,[13,14,18-21] and lower than that reported in the Italian population.[22] These discrepancies may be attributable to racial and ethnic differences but may also reflect variations in study methodologies and selection criteria, as many investigations are limited to a few representative centers. SPG11 and SPG10 were identified in fewer than 5% of patients in our study, consistent with previous results.[1,14,18,19,21] SPG31 was found in 5 (7%) patients, all belonging to a single family. Given this familial clustering, further research is necessary to accurately determine the proportion of SPG31 in Korean patients with spastic paraplegia. SPG3A, despite being recognized as the second most prevalent subtype in autosomal dominant HSP, was not identified in our study. This result suggests a potentially low prevalence of SPG3A in patients with spastic paraplegia, consistent with several previous studies.[1,12-14,18,19,21,22] Our study also identified pathogenic variants in *ABCD1* or *GALC* in two patients with spastic paraplegia. These two genes are responsible for distinct disorders, namely adrenomyeloneuropathy and Krabbe disease. However, when symptoms manifest in adults, the clinical presentation frequently resembles spastic paraplegia. This finding emphasizes the importance of comprehensive genetic testing that extends beyond HSP-associated genes to those implicated in other neuromuscular disorders. Additionally, identifying pathogenic variants in *ABCD1* is challenging due to the presence of *ABCD1* paralogs on chromosomes 2q11, 10p11, 16p11, and 22q11.2.[10] Therefore, measuring very-long-chain fatty acid levels in serum is crucial, especially in male patients with spastic paraplegia.

Our study showed the clinical characteristics of Korean patients with spastic paraplegia. Previous Korean studies have described the genetic landscape of HSP.[12-14] However, our study adds further value by incorporating detailed radiological and electrophysiological assessments, as well as reporting novel pathogenic variants. One prior study analyzed a larger Korean HSP cohort with a focus on disease severity and ambulation using the Spastic Paraplegia Rating Scale.[23] However, this study included patients with clinically suspected HSP without data on confirmed genotypes. In contrast, our study provides complementary insights through in-depth genotype-phenotype correlations and diagnostic yield analysis based on evolving sequencing methodologies. These distinctions enhance the understanding of HSP in the Korean population and justify the contribution of the present study to the existing literature.

SPG4 is caused by pathogenic variants in *SPAST*, which encodes spastin. Spastin plays a role in intracellular motility, membrane trafficking, organelle biogenesis, endosomal tubulation and fission, and protein folding.[3] In patients with SPG4, the age of symptom onset ranged from childhood to the sixth decade, consistent with previous results.[1] All patients with SPG4 showed the pure form of HSP, in accordance with a previous study on a large German SPG4 cohort, where fewer than 10% of the patients had other neurologic symptoms, including ataxia, peripheral neuropathy, extrapyramidal involvement, dysarthria, or dysphagia.[1]

SPG11 is the most prevalent autosomal recessive HSP, accounting for approximately 40% of autosomal recessive HSPs and up to 8% of all HSPs.[2,4] SPG11 is caused by pathogenic variants in *SPG11*, which encodes the SPG11 protein. SPG11 is essential for intracellular trafficking, neuronal axonal growth, and maintenance of neuronal function. The onset of SPG11 occurs

between 4 and 36 years of age.[24,25] SPG11 is clinically associated with not only spastic paraplegia and urinary dysfunction but also cerebellar ataxia, parkinsonism, dysphagia, pes cavus, neuropathy, intellectual impairment, and pigmented macular degeneration. Cognitive impairment usually emerges during the second decade of life.[26] In our study, three Korean patients with SPG11 had childhood-onset symptoms and cognitive impairment. However, none had a family history, which may be attributed to the rarity of consanguineous marriages in Korea.

SPG9 is caused by pathogenic variants in *ALDH18A1* and typically presents as a complicated form of HSP. It is frequently associated with cataracts, motor neuronopathy, short stature, developmental delay, and skeletal abnormalities.[27] Additionally, anticipation has been reported in SPG9.[28] In our study, one family with SPG9 was identified. The proband's son underwent surgery for cataracts and strabismus during infancy, and a significant gap in the ages of symptom onset within the family raised the suspicion of anticipation.

SPG10 is caused by pathogenic variants in *KIF5A*. This gene is associated not only with HSP but also with familial amyotrophic lateral sclerosis and axonal hereditary motor and sensory neuropathy.[29] In our study, a family with SPG10 also showed spastic paraplegia and peripheral neuropathy.

SPG31 is caused by pathogenic variants in *REEP1*. It usually presents as a pure form of HSP with a bimodal age-of-onset distribution, occurring either in individuals younger than 20 years or those older than 30 years.[30] In our study, all five patients with SPG31 from the same family exhibited childhood-onset symptoms and had a pure form of HSP.

Our study confirmed previous electrophysiological and radiological findings of spastic paraplegia. Central conduction defects were more frequently observed with the stimulation of legs than with the stimulation of arms, which is compatible with a previous study.[31] Brain MRI findings revealed a thin corpus callosum in patients with SPG11—a hallmark feature reported in previous studies.[32] Additionally, T2-weighted white matter hyperintensities were detected in two patients with unknown etiology: one with a pure form of HSP and the other with a complicated form of HSP. Spine MRI findings revealed spinal cord atrophy in approximately one-fourth of the patients, including those with SPG4, consistent with previous results.[33]

Our study has significant limitations. First, it is a retrospective, single-center investigation based solely on medical records. Second, although the dataset spans more than two decades, comprehensive longitudinal analysis is limited. Therefore, consistent data on long-term functional progression, ambulatory outcomes, and treatment response were not available. Despite these limitations, our institution serves as a leading referral center for neuromuscular disorders in Korea and manages many patients with spastic paraplegia, which lends credibility to our results. However, the discrepancies observed among several Korean studies underscore the necessity for further research. A multicenter prospective study is essential to comprehensively identify and validate the clinical and genetic characteristics of patients with HSP in the Korean population.

In conclusion, our study comprehensively reviewed the clinical and genetic spectra of spastic paraplegia in Korean patients, emphasizing the predominance of SPAST as a causative gene. Our study results highlighted the clinical and genetic heterogeneity of spastic paraplegia and emphasize the importance of comprehensive clinical phenotyping in the evaluation of patients with spastic paraplegia in Korea.

DATA AVAILABILITY

The data that supports the findings of this study are available in the supplementary material of this article.

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