JCN Open Access ORIGINAL ARTICLE

pISSN 1738-6586 / eISSN 2005-5013 / J Clin Neurol 2022;18(3):343-350 / https://doi.org/10.3988/jcn.2022.18.3.343

Hereditary Spastic Paraplegia in Koreans: Clinical Characteristics and Factors Influencing the Disease Severity

Jong Geol Do[a]
Byoung Joon Kim[b]
Nam-Soon Kim[c,d]
Duk Hyun Sung[a]

[a]Department of Physical and Rehabilitation Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea
[b]Department of Neurology, Neuroscience Center, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea
[c]Rare Disease Research Center, Korea Research Institute of Bioscience and Biotechnology, Daejeon, Korea
[d]Department of Functional Genomics, Korea Research Institute of Bioscience and Biotechnology School of Bioscience, University of Science and Technology (UST), Daejeon, Korea

Background and Purpose Hereditary spastic paraplegia (HSP) progresses over time and is associated with locomotive dysfunction. Understanding the factors affecting disease severity and locomotive function is important in HSP. This study investigated the factors influencing disease severity and ambulation status of HSP.

Methods We consecutively enrolled 109 Korean patients (64 males, and 45 females)from 84 families with a clinical diagnosis of HSP. HSP was primarily diagnosed based on clinical criteria including clinical findings, family history, and supported by genetic studies. Epidemiological and clinical features of the patients were analyzed, and the Spastic Paraplegia Rating Scale (SPRS) score and ambulatory status were used to evaluate disease severity.

Results Ninety-two (84.4%) patients had pure HSP, and 55 (50.4%) had a dominant family history. Thirty-one (28.4%) patients required a mobility aid for locomotion. A Kaplan-Meier analysis showed that HSP patients lost their independent gait ability after a median disease duration of 34 years. Those with an age at onset of ≤18 years had a longer median independent walking time. Pure HSP is characterized by predominant bilateral lower extremity weakness and spasticity, whereas complicated HSP presents more complex neurological findings such as ocular and bulbar symptoms, ataxia, and cognitive impairment. Complicated HSP was significantly correlated with the SPRS mobility score (β=3.70, 95% confidence interval=0.45−6.94). The age at onset and disease duration were significantly correlated with disease severity, and they were significant predictors of the use of a mobility aid (p<0.05).

Conclusions These findings suggest that a later age at onset and longer disease duration are significant factors affecting the disease severity and ambulatory function in patients with HSP. These findings can help clinicians to identify subjects at risk of locomotive impairment.

Keywords hereditary spastic paraplegia; spastic paraplegia; locomotion; Korea.

INTRODUCTION

Hereditary spastic paraplegia (HSP) is a genetic disorder characterized by lower extremity spasticity and gait disturbance, and has a reported incidence rate of 1.27−9.6/100,000 births.[1] HSP is genetically heterogeneous, being associated with at least different 79 genes.[2-4] HSP-related symptoms are due to degeneration of the corticospinal tract axons and dorsal column.[5] The common pathological features are bilateral lower leg spasticity, hyperreflexia, and extensor plantar responses.[4,6] HSP is classified into pure HSP and complicated HSP.[7] Pure HPS is characterized by progressive spasticity and weakness of the lower limbs, with or without impaired vibration sense and urinary incontinence.[8] Complicated HSP is characterized by the presence of additional clinical features such as ataxia, intellectual disability, seizures, peripheral neuropathy, and optic defects.[9,10]

HSP is not life-threatening, but it is associated with functional disability and decreased

Received July 1, 2021
Revised September 8, 2021
Accepted September 8, 2021

Correspondence
Duk Hyun Sung, MD, PhD
Department of Physical and Rehabilitation Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul 06351 Korea
Tel +82-2-3410-2818
Fax +82-2-3414-2832
E-mail yays.sung@samsung.com

quality of life,[11] and represents a significant burden on the affected families. Although the disease progresses over time, such as worsening of the gait, the rate of severity progression varies among affected individuals.[12] However, little is known regarding the demographic and clinical factors that affect the severity of HSP. Since there are no curative treatments for HSP, a better understanding of the factors affecting disease severity and locomotive function is an important concern of patients and their families.

The Spastic Paraplegia Rating Scale (SPRS) has been developed to quantify the functional severity and progression of HSP using 13 items.[13] The SPRS subscales are not used routinely to evaluate clinical impairment, but could be useful for understanding the characteristics of disease severity and measuring locomotive function.

This cross-sectional, multicenter study investigated the clinical characteristics of HSP and assessed the factors influencing the disease severity and ambulation status of HSP patients in a Korean population using the SPRS.

METHODS

Subjects and clinical assessment

One hundred and nine patients (64 males and 45 females) from 84 families with a clinical diagnosis of HSP were recruited from 4 medical centers in Korea between April 2011 and February 2017. HSP was clinically diagnosed based on the following published criteria: 1) pure spastic paraplegia, 2) spastic tetraparesis with earlier and greater severity in the lower limbs, or 3) spastic paraplegia as an early prominent sign (within the first 3 years of the disease) of a degenerative disease affecting several parts of the nervous system.[13,14]

Genetic assessments were performed to support the clinical diagnoses. Direct nucleotide sequence analysis of *SPG4* and/or *SPG3* was performed in pure-HSP patients. Next-generation sequencing was applied to patients in whom mutations were not detected by direct nucleotide sequence analysis. Variants were classified according to American College of Medical Genetics and Genomics criteria.[15] Diagnosis was primarily based on clinical criteria, and HSP was included irrespective of their genetic identification. The exclusion criteria were a family history of another neurological disease, psychiatric illness, focal or diffuse brain damage, inflammatory lesion in the central nervous system, life-threatening disease, orthopedic problem, or cardiovascular disease that affects the locomotive function.

Data on demographics features (sex, age at onset, and age at examination), family history, and clinical features (leg weakness, bladder dysfunction, and ankle clonus) were collected after written consent was obtained from all participants, as were blood samples for use in genetic analysis. Other clinical conditions were also assessed, such as sensory impairment, cognitive impairment, ataxia, and ocular motor deficits. Additional investigations were performed were possible, such as magnetic resonance imaging (MRI) of the brain/spinal cord, electrophysiological studies, and metabolic studies. Peripheral neuropathy was identified in an physical examination by abnormal pinprick or soft-touch discrimination, and by nerve conduction studies when available. Complicated HSP was defined in the present study as ocular or auditory problems, bulbar symptoms, ataxia, symptoms or signs of peripheral nerve involvement, and cognitive impairment. The mode of inheritance was classified as autosomal dominant (AD) when HSP was reported in more than one generation. Families with several affected members in one generation only were classified as having autosomal recessive (AR) HSP. Cases with no known family history were classified as having sporadic HSP.[12,16]

Spastic Paraplegia Rating Scale

We assessed disease severity using the SPRS, which is a reliable and valid measure for evaluating functional impairment.[17] Each 13 item of the SPRS is scored from 0 to 4, giving a maximum total score of 52. The SPRS is a composite measure for assessing gait, spasticity, weakness and contractures, pain, and bladder dysfunction.[13] We divided the 13 items into 6 subscales. The mobility subscale measured mobility function and comprised items 1−6 of the SPRS: walking distance without pause, gait quality, maximum gait speed, climbing stairs, speed of stair climbing, and rising from a chair. The spasticity subscale comprised items 7 and 8: hip adductor spasticity and knee flexion spasticity. The weakness subscale comprised items 9 and 10: hip abduction weakness and foot dorsiflexion weakness. The contracture subscale was represented by item 11: contracture of the lower limbs. The pain subscale was represented by item 12: pain due to spastic paraplegia-related symptoms. The bowel and bladder subscale was represented by item 13: bladder and bowel function.

Statistical analysis

Descriptive statistics were used to characterize the demographic and clinical variables. Continuous variables are reported as mean and standard deviation (SD) values. Frequency counts and percentages are provided for categorical variables. Groups were compared using the independent *t*-test or Mann-Whitney U test for continuous variables, and Fisher's exact test or the chi-square test for categorical variables. Pearson's correlation analysis was used to investigate the relationships of the SPRS score with age at onset, age at examination, and disease duration. We used linear regression analysis to assess the as-

sociations of the SPRS score with sex, age at onset, disease duration, and complicated HSP. Multivariable logistic regression was used to evaluate the associations of the ambulatory status with sex, age at onset, disease duration, and complicated HSP.

Ambulatory status was divided into independent gait and use of a mobility aid. The independent-gait group comprised patients who walked without an assistive device, while the mobility-aid group comprised patients who needed a cane, walker, or wheelchair for locomotion. Kaplan-Meier analysis was used to evaluate the curve of the disease duration before needing to use of a mobility aid for locomotion. The patients were divided into subgroups according to their age-at-onset quartiles: Q1, ≤18 years; Q2, >18 and ≤31 years; Q3, >31 and ≤40 years; and Q4, >40 years. We also compared between patients with ages at onset of <20 and ≥20 years.[18]

Data were analyzed using SPSS Statistics (version 24.0; IBM Corp., Armonk, NY, USA). A p value less than 0.05 was considered statistically significant. The study protocol was approved by the Institutional Review Board of Samsung Medical Center (approval number 2014-09-052-018). All procedures involving human participants were performed in accordance with the ethical standards of the institutional and/or national research committee, and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. All patients were informed about the aim and experimental procedures before enrollment, after which written informed consent was obtained from all of them.

RESULTS

Demographic and clinical features

The 109 enrolled patients had an age at onset of 29.8±16.5 years (mean±SD, range=1–64 years) and a disease duration of 15.3±11.8 years (range=1–62 years). Ninety-two (84.4%) patients had pure HSP. AD HSP was present in 51 (55.4%) of the 92 patients with pure HSP; their age at onset was 30.8±16.4 years (range=1–64 years), their disease duration was 15.9±12.4 years (range=1–62 years), and their SPRS total score was 17.0±11.0 points (range=2–42 points). AD HSP was present in 4 (23.5%) of the 17 patients with complicated HSP; their age at onset was 24.1±16.8 years (range=1–52 years), their disease duration was 11.8±7.1 years (range=2–23 years), and their SPRS total score was 16.9±9.0 points (range=6–36 points).

In addition to the core feature of spasticity, the most common clinical complaints were lower extremity weakness (68.8%), ankle clonus (60.6%), and bladder dysfunction (44.0%). The age at examination and inheritance type differed significantly between complicated-HSP and pure-HSP patients (p<0.05) (Table 1). The 17 patients with complicated HSP included 6 (35.3%) with peripheral neuropathy, 6 (35.3%) with bulbar symptoms, 4 (23.5%) with ataxia, 4 (23.5%) with cognitive impairment, and 3 (17.6%) with ocular problems. The family history showed that 55 (50.4%) patients had AD inheritance, 4 (3.7%) had AR inheritance, and 50 (45.9%) had sporadic inheritance. Fifty-eight (53.2%) patients were genetically diagnosed, and the most frequent genes were *SPG4* (n=37, 33.9%) and *SPG3A* (n=5, 4.6%), with other genes in n=16 (14.7%) patients. All of the *SPG4* patients had the pure-HSP phenotype. The *SPG4* patients had an age at onset of 30.4±14.9 years (range=1–54 years) and a disease duration of 15.2±12.4 years (range=1–55 years). Patients with *SPG4* was more likely to develop symptoms later compared with other HSP subtypes (20.2±14.9, p<0.05). Nine *SPG4* patients required a mobility aid (e.g., a cane or walker) for bipedal locomotion, and one

Table 1. Demographic and clinical characteristics of the included HSP patients

Characteristic	Total (n=109)	Patients with p-HSP (n=92)	Patients with c-HSP (n=17)	p
Age at examination (yr)	45.3±16.0 (3–83)	46.9±15.7 (3–83)	36.4±15.3 (17–59)	0.014*
Age at onset (yr)	29.8±16.5 (1–64)	30.8±16.4 (1–64)	24.1±16.8 (1–52)	0.150
Disease duration (yr)	15.3±11.8 (1–62)	15.9±12.4 (1–62)	11.8±7.1 (2–23)	0.400
Sex, male	64 (58.7)	52 (56.5)	12 (70.6)	0.279
Inheritance type				0.015*
AD	55 (50.4)	51 (55.4)	4 (23.5)	
AR	4 (3.7)	2 (2.2)	2 (11.8)	
Sporadic	50 (45.9)	39 (42.4)	11 (64.7)	
Genetically diagnosed	58 (53.2)	52 (56.5)	6 (35.3)	0.107
Leg weakness	75 (68.8)	61 (66.3)	14 (82.4)	0.190
Ankle clonus	66 (60.6)	56 (60.9)	10 (58.8)	0.525
Bladder dysfunction	48 (44.0)	42 (45.7)	6 (35.3)	0.429

Data are mean±SD (range) or n (%) values.
*p<0.05.
AD, autosomal dominant; AR, autosomal recessive; c-HSP, complicated HSP; HSP, hereditary spastic paraplegia; p-HSP, pure HSP; SD, standard deviation.

patient required a wheelchair.

Functional outcomes

The SPRS total score was 17.0±10.7 points (range=2–42 points). The SPRS total and mobility scores did not differ significantly between the pure-HSP and complicated-HSP phenotypes. Locomotive dysfunction did not differ significantly with the phenotype (Table 2). In univariable analyses, the SPRS total and mobility scores were significantly correlated with the age at onset, age at examination, and disease duration ($p<0.05$) (Table 3). The age at onset and disease duration were significantly correlated with the SPRS total and mobility scores in linear regression analysis (Table 4). Complicated HSP was significantly correlated with the SPRS mobility score (β=3.70, 95% confidence interval [CI]=0.45–6.94).

Considering locomotive function, 27 (24.8%) patients required a cane or walker for bipedal locomotion and 4 (3.7%) patients were unable to walk. The Kaplan-Meier analysis revealed that, 6%, 27%, 39%, and 79% of patients required a mobility aid for locomotion after disease durations of 10, 20, 30, and 40 years, respectively. Half of the patients had lost their ability to walk independently after a disease duration of 34 years. The group with an age at onset of ≤18 years had a longer median independent walking time compared with other groups in a post-hoc analysis (Fig. 1). The SPRS total score and the scores on the SPRS subscales were significantly

Table 2. SPRS scores and ambulatory status in HSP patients

Parameter	Total (*n*=109)	Patients with p-HSP (*n*=92)	Patients with c-HSP (*n*=17)	*p*
SPRS total score	17.0±10.7 (2–42)	17.0±11.0 (2–42)	16.9±9.0 (6–36)	0.831
SPRS mobility score	9.4±6.3 (1–24)	9.2±6.2 (1–24)	10.7±6.6 (2–23)	0.332
SPRS spasticity score	2.9±2.0 (0–8)	3.1±2.1 (0–8)	2.4±1.5 (0–6)	0.292
SPRS weakness score	2.1±2.2 (0–8)	2.1±2.2 (0–8)	2.0±2.0 (0–6)	0.972
SPRS contracture score	1.1±1.2 (0–5)	1.1±1.3 (0–5)	1.0±1.0 (0–3)	>0.999
SPRS pain score	0.7±1.1 (0–4)	0.7±1.2 (0–4)	0.5±0.9 (0–3)	0.691
SPRS bowel and bladder score	0.7±1.0 (0–3)	0.7±1.0 (0–3)	0.4±0.8 (0–3)	0.113
Use of cane or walker	27 (24.8)	23 (25.0)	4 (23.5)	>0.999
Unable to walk*	4 (3.7)	3 (3.3)	1 (5.9)	>0.999
Use of mobility aid†	31 (28.4)	26 (28.3)	5 (29.4)	>0.999

Data are mean±SD (range) or *n* (%) values.
*Patients who needed a wheel chair for locomotion; †Patients who needed a cane, walker, or wheelchair for locomotion.
c-HSP, complicated HSP; HSP, hereditary spastic paraplegia; p-HSP, pure HSP; SPRS, Spastic Paraplegia Rating Scale.

Table 3. Correlations between clinical factors and disease severity

Factor	SPRS total score		SPRS mobility score		SPRS spasticity score		SPRS weakness score		SPRS contracture score		SPRS pain score		SPRS bowel and bladder score	
	r	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*
Age at onset	0.202	0.042*	0.216	0.029*	0.188	0.059	-0.047	0.637	-0.029	0.770	0.140	0.162	0.307	0.002*
Age at examination	0.392	<0.001†	0.403	<0.001†	0.325	<0.001†	0.107	0.277	0.103	0.294	0.148	0.131	0.371	<0.001†
Disease duration	0.386	<0.001†	0.350	<0.001†	0.254	0.010*	0.357	<0.001†	0.225	0.023*	0.086	0.388	0.183	0.066

*$p<0.05$; †$p<0.001$.
r, correlation coefficient; SPRS, Spastic Paraplegia Rating Scale.

Table 4. Results from the linear regression analysis of clinical factors and disease severity

Factor	SPRS total score		SPRS mobility score	
	Univariable crude model	Model 1	Univariable crude model	Model 1
Age at onset (yr)	0.11 (-0.02 to 0.24)	0.24 (0.11 to 0.37)†	0.09 (0.01 to 0.16)*	0.17 (0.09 to 0.24)†
Age at examination (yr)	0.27 (0.15 to 0.39)†		0.17 (0.10 to 0.24)†	
Disease duration (yr)	0.28 (0.11 to 0.45)*	0.43 (0.24 to 0.61)†	0.14 (0.04 to 0.24)*	0.25 (0.15 to 0.35)†
Sex, male	-0.34 (-4.69 to 4.01)	-1.22 (-5.20 to 2.76)	-0.35 (-2.89 to 2.19)	-1.03 (-3.30 to 1.24)
c-HSP phenotype	-0.51 (-6.56 to 5.53)	3.09 (-2.61 to 8.78)	1.36 (-2.16 to 4.88)	3.70 (0.45 to 6.94)*

Data are β (95% CI) values. Model 1: age at onset, disease duration, male, and c-HSP.
*$p<0.05$; †$p<0.001$.
c-HSP, complicated hereditary spastic paraplegia; CI, confidence interval; SPRS, Spastic Paraplegia Rating Scale.

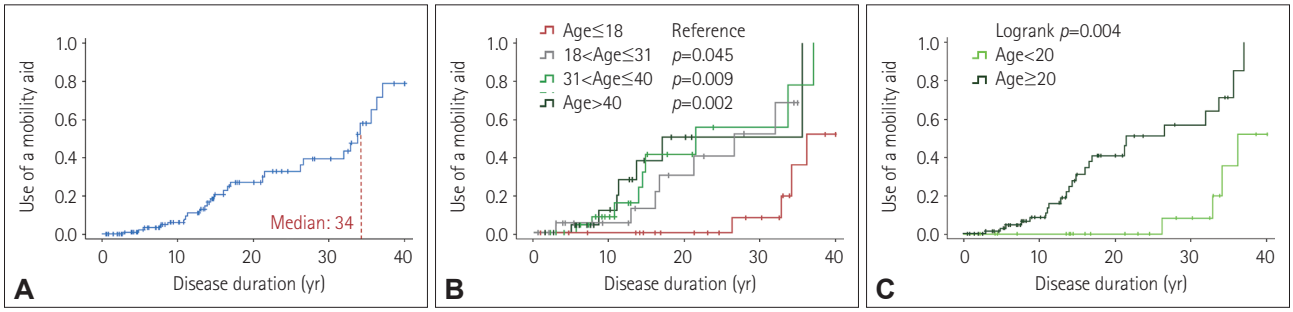

Fig. 1. Kaplan-Meier analysis of the disease duration before needing to use a mobility aid. A: Hereditary spastic paraplegia patients lost their independent gait ability after a median disease duration of 34 years. B: The patients were divided into four subgroups according to their age at onset: Q1, ≤18 years; Q2, >18 and ≤31 years; Q3, >31 and ≤40 years; and Q4, >40 years. Earlier onset was associated with a lower risk of having to use a mobility aid during the disease course (p<0.05). C: The median independent walking time was longer in patients with an age at onset of <20 years than in those with an age at onset of ≥20 years (p<0.05).

Table 5. Comparison of characteristics according to ambulatory status

Characteristic	Independent gait (n=75)	Use of a mobility aid (n=31)	p
Sex, male	45 (60.0)	17 (54.8)	0.68
Age at examination (yr)	41.7±16.4	53.8±12.3	<0.001
Age at onset (yr)	28.0±17.4	33.6±14.3	0.118
Disease duration (yr)	13.3±11.2	20.2±12.6	0.007
p-HSP phenotype	63 (84.0)	26 (83.9)	>0.999
Genetically diagnosed	41 (54.7)	16 (51.6)	0.832
Inheritance type			0.534
AD	41 (54.7)	13 (41.9)	
AR	3 (4.0)	1 (3.2)	
Sporadic	31 (41.3)	17 (54.8)	
SPRS total score	11.5±6.4	30.2±6.7	<0.001*
SPRS mobility score	6.2±3.6	17.3±3.8	<0.001*
SPRS spasticity score	2.3±1.7	4.5±1.9	<0.001*
SPRS weakness score	1.3±1.7	4.0±2.0	<0.001*
SPRS contracture score	0.7±0.9	2.0±1.4	<0.001*
SPRS pain score	0.6±0.9	1.1±1.5	0.095
SPRS bowel and bladder score	0.5±0.9	1.2±1.0	<0.001*

Data are mean±SD or n (%) values. Three patients were excluded from this analysis due to insufficient information about their ambulatory status.
*p<0.001.
AD, autosomal dominant; AR, autosomal recessive; p-HSP, pure hereditary spastic paraplegia; SPRS, Spastic Paraplegia Rating Scale.

Table 6. Results from the multivariable logistic regression analysis of predictors of the use of a mobility aid

Predictor	Univariable crude model	Model 1
Age at onset (yr)	1.02 (0.99 to 1.05)	1.05 [1.01 to 1.09]*
Age at examination (yr)	1.06 (1.02 to 1.09)*	
Disease duration (yr)	1.05 (1.01 to 1.09)*	1.09 [1.04 to 1.15]†
Sex, male	0.74 (0.31 to 1.79)	0.65 [0.25 to 1.69]
c-HSP phenotype	0.96 (0.28 to 3.29)	2.15 [0.53 to 8.70]

Data are β (95% CI) or adjusted odds ratio [95% CI] values.
*p<0.05; †p<0.001.
c-HSP, complicated hereditary spastic paraplegia.

higher in the mobility-aid group than in the independent-gait group (Table 5). In multivariable logistic regression analysis of the need to use a mobility aid, later age at onset (adjusted odds ratio [OR]=1.05, 95% CI=1.01–1.09) and longer disease duration (adjusted OR=1.09, 95% CI=1.04–1.15) were significant factors affecting locomotive dysfunction (Table 6).

DISCUSSION

This cross-sectional, multicenter study analyzed the demographic and clinical characteristics of HSP, and evaluated the factors affecting the severity of HSP in a population of Korean patients using standardized and validated severity-rating scales, with a specific focus on ambulation status. The family history was revealed as AD inheritance, AR inheritance, and sporadic inheritance of the disease in 50.4%, 3.7%, and 45.9% of our Korean population, respectively. Thirty-one (28.4%) of the 109 included HSP patients required a mobility aid for locomotion.

Little is known about the factors associated with disease severity in patients with HSP. HSP is generally a progressive disease with high clinical heterogeneity, since the clinical course varies from mild gait disturbance in old age to severe gait disturbance at a young age. Moreover, HSP is a disease with a diverse symptom progression rates and levels of disability even for the same genetic type.[8] While HSP impairs the gait and affects the quality of life, it does not shorten the life expectancy.[11] There is no effective treatment to prevent gait disturbance in HSP, which makes it important to identify the factors influencing disease severity and ambulation status.

Few studies have focused on the functional outcome and associated epidemiological and clinical factors in HSP patients. We found that complicated HSP was significantly cor-

related with the SPRS mobility score. A previous Canadian study found that the mean SPRS score was higher in complicated-HSP patients (as indicated by abnormal brain MRI) than in those with normal brain imaging findings.[19] Our results are consistent with this: complicated HSP significantly affected the disease severity. Several studies have found complicating symptoms to be important in the severity of HSP. Abnormal brain MRI was positively correlated with disability severity, and cortical thickness was negatively correlated with SPRS scores.[19,20] In a large German HSP cohort, the presence of complicating features was associated with greater disease severity.[12] Furthermore, the health-related quality of life was reduced in patients with complicated HSP.[11] The correlation between complicated HSP and higher disease severity in our study supports the notion that this form of HSP is an important factor affecting the clinical disease severity. Because complicated HSP is important in the clinical diagnosis and prognosis, comprehensive assessments that include brain imaging are necessary in patients with HSP.

Locomotive function is essential to humans, since impairment therein affects many aspects of daily living and can be a burden for both the affected patients and their caregivers. The ambulatory status is also important when designing individual treatment plans and setting rehabilitation goals. Medications and physiotherapy can reduce the gait impairment and spasticity associated with HSP, but no current treatment is able to attenuate disease progression.[21-23] It is therefore important to identify the clinical factors that influence ambulatory function. Multiple factors are related to locomotive function, including the degrees of spasticity, muscle weakness, and contractures. A study of 46 HSP patients found that limitation in the active range of motion and increased spasticity were correlated with a reduced walking speed, and that the walking speed was negatively correlated with disease duration.[24] Furthermore, muscle paresis and passive stiffness were found to be associated with walking ability in HSP.[25] However, few studies have investigated locomotive function and its associated factors in patients with HSP.

We found that the disease duration was positively correlated with disease severity, which was a significant factor affecting the ambulatory function. A study of HSP in *SPG4* patients found that the disease duration was negatively correlated with cortical thickness and the Montreal Cognitive Assessment score.[20] An Italian pilot study similarly found a significant correlation between the SPRS score and disease duration (β= 0.408, p<0.01).[26] In contrast to the general conception that neurodegenerative disease are more progressed when symptoms begin to appear earlier, our results showed that a later age at onset significantly affected the disease severity and ambulatory dysfunction. This is in line with a study of 608 German patients finding that earlier disease onset was associated with less-severe disease, with the early-onset patients being able to maintain independent walking for longer.[12] When HSP begins in early childhood, symptoms may show a relatively nonprogressive course even over several decades. It is known that patients with *SPG3A* are typically younger at onset and have a slower average rate of disease progression,[4,8] and this can also be seen in *SPG4* patients.[5] Comparing only patients with early disease onset (age <20 years), the disease progression rate did not differ significantly between patients with *SPG4* and those with *SPG3*.[18] The Kaplan-Meier analysis performed in our study demonstrated that the median independent walking time was longer in those with an age at onset of ≤18 years, and longer in those with an age at onset of <20 years than in those with an age at onset of ≥20 years. Our study also suggests that for patients with HSP, an earlier onset results in less-severe disease.

HSP is a group of heterogeneous genetic disorders with a diversity of ages at onset and clinical features. This diversity of HSP makes molecular analysis essential, but achieving a genetic diagnosis can be difficult.[27] Genetic assessment is important for diagnosing the type of HSP. The overall diagnostic yield of HSP using next-generation sequencing with whole-exome sequencing and a targeted panel test has reportedly ranged from 25.0% to 52.5%.[19,28] We obtained a higher diagnostic yield of 53.2% using a comprehensive stepwise variant analysis protocol based on direct nucleotide sequence analysis, next-generation sequencing, and multiplex ligation-dependent probe amplification analysis of *SPG4*. Our high-yield molecular approach represents a major strength of our study that achieved the clear identification of factors associated with disease severity and predictors of ambulation.

This study was subject to several limitations. First, it had a cross-sectional, observational design, and epidemiological, clinical, and functional data were obtained at a single time point, which prevented speculating about causality. Therefore, a prospective longitudinal follow-up study is needed. Nevertheless, the strength of this study of its relatively large sample provided a better understanding of the clinical characteristics of HSP. Second, the lower extremity weakness was measured using a manual muscle test. Evaluating lower extremity weakness in HSP patients is sometimes difficult because of lower limb spasticity and heel cord tightness. Third, we did not perform brain MRI routinely. Brain MRI is important for diagnosing HSP to identify structural, demyelinating, and degenerative lesions of the central nervous system. We performed brain MRI in patients with cognitive impairment, language problems, dysphagia, or ataxia, but not in some of the pure-HSP patients or family members. However, brain MRI was not performed in only six patients whose

genotype was not confirmed. Also, we did not apply routine screening tests for cognitive function, including the Mini Mental State Examination or the Montreal Cognitive Assessment. A large longitudinal study that comprehensively assesses complicating symptoms, including brain imaging, is needed in the future.

In conclusion, this study has revealed the epidemiological and clinical features of HSP in a Korean population. Complicated HSP, later age at onset, and longer disease duration are factors that significantly affect disease severity. These findings should enable clinicians to identify subjects at risk of locomotive impairment. Prospective longitudinal cohort studies are needed to assess the rate of disease progression.

Availability of Data and Material

The datasets generated and analyzed during this study are available from the corresponding author upon reasonable written request with a signed data-use agreement.

ORCID iDs

Jong Geol Do	https://orcid.org/0000-0001-8001-7782
Byoung Joon Kim	https://orcid.org/0000-0001-8424-881X
Nam-Soon Kim	https://orcid.org/0000-0001-7624-0690
Duk Hyun Sung	https://orcid.org/0000-0002-8261-7199

Author Contributions

Conceptualization: all authors. Data curation: Jong Geol Do, Nam-Soon Kim. Formal analysis: Jong Geol Do. Supervision: Duk Hyun Sung, Byoung Joon Kim, Nam-Soon Kim. Visualization: Jong Geol Do. Writing—original draft: Duk Hyun Sung, Jong Geol Do. Writing—review & editing: Duk Hyun Sung, Byoung Joon Kim, Jong Geol Do.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Funding Statement

This research was supported by the Collaborative Genome Program for Fostering New Post-Genome Industry of the National Research Foundation (NRF) funded by the Ministry of Science and ICT (MSIT) (grant numbers NRF-2014M3C9A2064620 and NRF-2014M3C9A2064619) and by the KRIBB Research Initiative Program in Korea (NTIS-1711134057).

Acknowledgements

The authors are grateful to all patients who participated in this study.

REFERENCES

1. Salinas S, Proukakis C, Crosby A, Warner TT. Hereditary spastic paraplegia: clinical features and pathogenetic mechanisms. *Lancet Neurol* 2008;7:1127-1138.
2. Ishiura H, Takahashi Y, Hayashi T, Saito K, Furuya H, Watanabe M, et al. Molecular epidemiology and clinical spectrum of hereditary spastic paraplegia in the Japanese population based on comprehensive mutational analyses. *J Hum Genet* 2014;59:163-172.
3. Schüle R, Schöls L. Genetics of hereditary spastic paraplegias. *Semin Neurol* 2011;31:484-493.
4. Shribman S, Reid E, Crosby AH, Houlden H, Warner TT. Hereditary spastic paraplegia: from diagnosis to emerging therapeutic approaches. *Lancet Neurol* 2019;18:1136-1146.
5. Fink JK. Hereditary spastic paraplegia: clinico-pathologic features and emerging molecular mechanisms. *Acta Neuropathol* 2013;126:307-328.
6. Agosta F, Scarlato M, Spinelli EG, Canu E, Benedetti S, Bassi MT, et al. Hereditary spastic paraplegia: beyond clinical phenotypes toward a unified pattern of central nervous system damage. *Radiology* 2015;276:207-218.
7. Finsterer J, Löscher W, Quasthoff S, Wanschitz J, Auer-Grumbach M, Stevanin G. Hereditary spastic paraplegias with autosomal dominant, recessive, X-linked, or maternal trait of inheritance. *J Neurol Sci* 2012;318:1-18.
8. Erfanian Omidvar M, Torkamandi S, Rezaei S, Alipoor B, Omrani MD, Darvish H, et al. Genotype-phenotype associations in hereditary spastic paraplegia: a systematic review and meta-analysis on 13,570 patients. *J Neurol* 2021;268:2065-2082.
9. Noreau A, Dion PA, Rouleau GA. Molecular aspects of hereditary spastic paraplegia. *Exp Cell Res* 2014;325:18-26.
10. Lo Giudice T, Lombardi F, Santorelli FM, Kawarai T, Orlacchio A. Hereditary spastic paraplegia: clinical-genetic characteristics and evolving molecular mechanisms. *Exp Neurol* 2014;261:518-539.
11. Klimpe S, Schüle R, Kassubek J, Otto S, Kohl Z, Klebe S, et al. Disease severity affects quality of life of hereditary spastic paraplegia patients. *Eur J Neurol* 2012;19:168-171.
12. Schüle R, Wiethoff S, Martus P, Karle KN, Otto S, Klebe S, et al. Hereditary spastic paraplegia: clinicogenetic lessons from 608 patients. *Ann Neurol* 2016;79:646-658.
13. Schüle R, Holland-Letz T, Klimpe S, Kassubek J, Klopstock T, Mall V, et al. The spastic paraplegia rating scale (SPRS): a reliable and valid measure of disease severity. *Neurology* 2006;67:430-434.
14. Harding AE. Classification of the hereditary ataxias and paraplegias. *Lancet* 1983;1:1151-1155.
15. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med* 2015;17:405-424.
16. Fink JK. Sporadically occurring neurologic disease: HSP genes and apparently sporadic spastic paraplegia. *Neurology* 2008;71:1468-1469.
17. Adry RA, Lins CC, Kruschewsky Rde A, Castro Filho BG. Comparison between the spastic paraplegia rating scale, Kurtzke scale, and Osame scale in the tropical spastic paraparesis/myelopathy associated with HTLV. *Rev Soc Bras Med Trop* 2012;45:309-312.
18. Loureiro JL, Brandão E, Ruano L, Brandão AF, Lopes AM, Thieleke-Matos C, et al. Autosomal dominant spastic paraplegias: a review of 89 families resulting from a portuguese survey. *JAMA Neurol* 2013;70:481-487.
19. Chrestian N, Dupré N, Gan-Or Z, Szuto A, Chen S, Venkitachalam A, et al. Clinical and genetic study of hereditary spastic paraplegia in Canada. *Neurol Genet* 2017;3:e122.
20. Lin JZ, Zheng HH, Ma QL, Wang C, Fan LP, Wu HM, et al. Cortical damage associated with cognitive and motor impairment in hereditary spastic paraplegia: evidence of a novel SPAST mutation. *Front Neurol* 2020;11:399.
21. Zhang Y, Roxburgh R, Huang L, Parsons J, Davies TC. The effect of hydrotherapy treatment on gait characteristics of hereditary spastic paraparesis patients. *Gait Posture* 2014;39:1074-1079.
22. Heetla HW, Halbertsma JP, Dekker R, Staal MJ, van Laar T. Improved gait performance in a patient with hereditary spastic paraplegia after a continuous intrathecal baclofen test infusion and subsequent pump implantation: a case report. *Arch Phys Med Rehabil* 2015;96:1166-1169.
23. Bertolucci F, Di Martino S, Orsucci D, Ienco EC, Siciliano G, Rossi B, et al. Robotic gait training improves motor skills and quality of life in hereditary spastic paraplegia. *NeuroRehabilitation* 2015;36:93-99.
24. Braschinsky M, Parts K, Maamägi H, Gross-Paju K, Haldre S. Functional assessment of lower extremities in hereditary spastic paraplegia. *Arch Phys Med Rehabil* 2009;90:1887-1890.
25. Marsden J, Ramdharry G, Stevenson V, Thompson A. Muscle paresis

and passive stiffness: key determinants in limiting function in hereditary and sporadic spastic paraparesis. *Gait Posture* 2012;35:266-271.
26. Martinuzzi A, Montanaro D, Vavla M, Paparella G, Bonanni P, Musumeci O, et al. Clinical and paraclinical indicators of motor system impairment in hereditary spastic paraplegia: a pilot study. *PLoS One* 2016;11:e0153283.
27. Trummer B, Haubenberger D, Blackstone C. Clinical trial designs and measures in hereditary spastic paraplegias. *Front Neurol* 2018;9:1017.
28. Burguez D, Polese-Bonatto M, Scudeiro LAJ, Björkhem I, Schöls L, Jardim LB, et al. Clinical and molecular characterization of hereditary spastic paraplegias: a next-generation sequencing panel approach. *J Neurol Sci* 2017;383:18-25.