http://dx.doi.org/10.5607/en.2013.22.2.128
Exp Neurobiol. 2013 Jun;22(2):128-131.
pISSN 1226-2560 • eISSN 2093-8144

Case Report

Experimental Neurobiology

Hereditary Spastic Paraplegia with a Novel *SPAST* Mutation Misdiagnosed with Subacute Combined Degeneration

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Autosomal dominant hereditary spastic paraplegia (AD-HSP) is due to mutations in the "spastin" gene (*SPAST* gene) encoding the AAA protein. The main clinical features of "pure" HSP are progressive lower-limb spasticity with corticospinal tracts and dorsal column degeneration without peripheral neuropathy. Here we report the case of HSP with novel *SPAST* gene mutation that misdiagnosed with subacute combined degeneration initially. A 58-year-old man with gait disturbance came to our hospital. He was unable to regulate his steps by himself. The impaired gait began 3 years after he had undergone subtotal gastrectomy and chemotherapy for 6 months. Thereafter, he started feeling tingling sensations in the hands and feet and acquired gait difficulties. He denied having a family history of abnormal gait or developmental problem. We diagnosed him with subacute combined degeneration on the evidence of history of gastrectomy, lower normal limit of vitamin B12 (363 pg/ml), apparent absence of vibration sensations and paresthesia in the feet. He was intramuscularly administered cyanocobalamin regularly. However, there was no improvement in his condition. We reconsidered his symptoms and signs, decided to examine the *SPAST* gene, which is the most common mutation in HSP. The *SPAST* gene, c.870+1delG, heterozygote, splicing mutation is detected from the gene sample. There was no previous information of this polymorphism or mutation at this locus. We examined his two children, and the same mutation was founded in his son. We report a patient of novel *SPAST* gene mutation with AD-HSP which is misdiagnosed with SCD.

Key words: hereditary spastic paraplegia, SPAST protein, subacute combined degeneration

INTRODUCTION

Hereditary spastic paraplegia (HSP) is a clinically and genetically heterogeneous group of neurodegenerative diseases that predominantly involves the lower extremities. The essential features are insidiously progressive spastic leg weakness associated with corticospinal tract and dorsal column degeneration [1]. HSP is classified according to the mode of inheritance (autosomal dominant, autosomal recessive, or X-linked), clinical symptoms ("pure" or "complicated"), and specific gene locus ("SPG1" through "SPG17") [1]. Autosomal dominant HSP (AD-HSP) is the

Received April 22, 2013, Revised June 13, 2013,
Accepted June 14, 2013

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most prevalent mode and includes approximately 70% of cases. Approximately 40-45% of AD-HSP patients have pathogenic mutations in the spastin gene (*SPG4* or *SPAST* gene), which causes predominantly "pure" HSP [2]. Pure HSP is characterized by severe progressive spasticity limited to both legs, which is eventually accompanied by urinary urgency (reported in up to 50% of cases in later disease stages) and mildly impaired vibration sense resulting from "dying back" degeneration affecting axonal transport of the longest fibers that innervate the lower extremities [2]. Pure HSP can be confused with other diseases involving the corticospinal tract and dorsal column. Therefore, clinicians should consider this when they encounter patients who do not show improvement in gait disturbance, although they receive appropriate treatment. Here, we report the case of a patient who was initially misdiagnosed with subacute combined degeneration (SCD), but in fact had HSP with a novel *SPAST* mutation.

CASE REPORT

A 58-year-old man with gait disturbance came to our hospital on Oct 30, 2011. He did not complain of lower extremity weakness or leg pain. He was unable to regulate his steps by himself, and his acquaintances reported he walked with a slight limp. The impaired gait began 3 years after he had undergone subtotal gastrectomy and chemotherapy for 6 months. Thereafter, he felt tingling sensations in the hands and feet and acquired gait difficulties. He denied having a family history of abnormal gait or developmental problems. He had quit smoking and drinking alcohol many years prior to his diagnosis.

Upon neurological examination, his muscle strength was normal. The limbs did not reveal any spasticity or rigidity. He responded normally to pin prick and thermal stimulation. However, there was a severely decreased response to vibration in both big toes, particularly in the left. The ankle jerk reflexes were bilaterally decreased, whereas the reflexes of other joints were normal. Both toes showed extensor toe signs. Other pathologic reflexes were not observed. Cranial nerve and cerebellar functions were normal. He did not exhibit scissoring or spastic gait, but rather a limping gait. Thus, he had mixed neurological signs that involved the upper motor neuron and peripheral nerves.

Considering his previous medical history, we investigated his brain, spinal cord, meninges, and peripheral nerve by using magnetic resonance imaging (MRI), cerebrospinal fluid (CSF) analysis, blood tests, and electrodiagnostic studies. Notable results included the lower-normal limit of serum vitamin B12 (363 pg/ml; reference range 200-1,000 pg/ml) and generalized sensory dominant polyneuropathy with axonal involvement. Blood tests, including those for syphilis, HIV, diabetes, connective tissue disease, vasculitis, and renal and liver function, were normal. CSF chemistry and cell counts were also in the reference range. Mild small vessel disease and a small amount of chronic subdural hematoma were observed in the left cerebral convexity. Whole-spine MRI revealed normal signal intensity in the cord, except for disc extrusion with mild cord indentation, which did not seem relevant to the exhibited neurological symptoms. Nerve conduction studies showed mild sensory dominant peripheral polyneuropathy with axonal involvement.

We diagnosed him with SCD. He was intramuscularly administered cyanocobalamin regularly for 6 months. However, there was no improvement in his condition. After reconsidering his abnormal neurological signs and laboratory tests, we examined HSP mutations in his genomic DNA. As a result, the *SPAST* mutation was detected from the gene sample of the proband (Fig. 1). The mutation, a novel splicing mutation, is c.870+1delG (IVS5; heterozygote). The deletion of 188 bp of exon 5 was confirmed by RT-PCR. We compared this result with the mutation database (http://hgmd.cf.ac.uk/ac/index.php), and there was no previous information of this polymorphism or mutation at this locus.

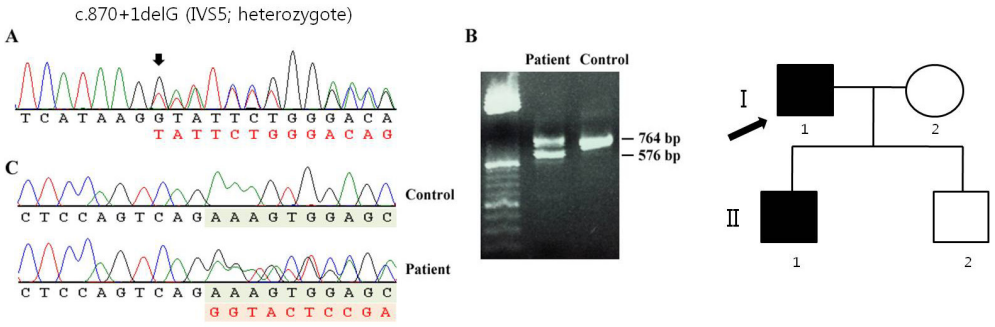

Fig. 1. Results of sequence analysis for the mutation identified in the patient at both DNA and RNA level. (A) The invariant splice site mutation, c.870+1delG (denoted with arrow) was identified in the patient. An abnormal band of smaller size (576 bp) was identified in RT-PCR (B) and subsequent sequence analysis (C) revealed that the transcript (on red background) was resulted from skipping of exon 5.

Table 1. Clinical findings of HSP family

	Patient (I-1)	Son (II-1)
Age at onset (years)	55	27
Lower extremities		
Weakness	-	-
Hyper-reflexia	-	+ (both)
Spasticity	-	+
Sensory ataxia	+	-
Ankle clonus	-	+ (both)
Extensor plantar reflex	+ (both)	+ (both)
Sensory impairment	+	-

We brought his children into the clinic for neurological examination. His 32-year-old son complained of subjective gait difficulty, even though there was no abnormality in his walking. However, he showed hyper-reflexic knee jerks, ankle clonus, and bilateral extensor toe signs. His 29-year-old daughter with an intellectual disability of unknown origin did not have any abnormalities upon examination. Genetic tests revealed that his son had the same *SPAST* mutation. The symptoms and signs of the patient and his son were different and are described in Table 1. Other relatives were not available to perform genetic analyses.

DISCUSSION

As described, we misdiagnosed this patient with SCD, which is distinct from HSP, because of atypical neurological signs and previous medical history. A genetic test revealed a novel splicing mutation in the *SPAST* gene that confirmed HSP. Genetic analysis of his son indicated the same result.

Genetically, HSP is classified according to the mode of inheritance and various gene loci. Among the several autosomal dominant HSP loci, mutations in *SPAST* are responsible for the largest share (about 40%) [2]. Since the first mutation in the *SPAST* gene was identified in 1999 [3], at least 300 different pathogenic mutations have been detected. *SPAST* is composed of 17 exons, encodes the spastin protein, and belongs to the ATPases Associated with various cellular Activities (AAA) family [2]. In the *SPAST* gene, the AAA domain in the C-terminal region (amino acids 342 to 599) and the microtubule interacting and trafficking (MIT) domain in the N-terminal region play important roles [2]. A large number of mutations are located in the AAA domain and are related with microtubule-severing and membrane-binding properties. It is thought that the AAA domain directly affects axonal and other intracellular transport. Furthermore, the MIT domain is involved in microtubule dynamics, such as intracellular organelle trafficking and endocytosis [4]. All pathogenic mutations appear to act via loss of function (haploinsufficiency) [4].

In Korea, there are 4 previous reports of novel *SPAST* mutations: One report involved a large genetic study of *SPAST* and *ATL1* mutations among several families. Of 8 different *SPAST* mutations, 7 novel mutations were identified in this study. Most mutations are located between exons 7-17, in the AAA domain, and 1 mutation is located in intron 11. Only one was a splicing mutation; the others were missense mutations, in-frame deletions, and frame-shift mutations [5]. Unlike in our patient, the clinical manifestations in the patients in these reports typically corresponded to pure AD-HSP. It is to be remained whether our HSP patient should be classified as having a rare "complicated" AD-HSP with a *SPAST* gene mutation or "pure" AD-HSP, combined with nutritional-deficiency peripheral neuropathy.

CONCLUSION

In conclusion, we report a novel splicing mutation, c.870+1delG (IVS5), in a Korean family with autosomal dominant-inherited HSP. We confirmed the deletion of exon 5 by using RT-PCR and segregation of the *SPAST* gene among family members by direct sequencing.

ACKNOWLEDGEMENTS

This research was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology (2010-0011008).

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