Clinical and Genetic Analysis of a Korean Family with Hereditary Spastic Paraplegia Type 3

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Abstract. Hereditary spastic paraplegia (HSP) is a neurodegenerative disease characterized by progressive spasticity in the lower extremities. Mutations in the atlastin GTPase 1 (ATL1) gene cause approximately 10% of autosomal dominantly inherited HSP. For many subjects with an ATL1 mutation, spastic gait begins in early childhood and does not significantly worsen, even over many years; such cases resemble spastic diplegic cerebral palsy. Herein we report a heterozygous R239C mutation in the ATL1 gene in a Korean family. The family members exhibited early onset pure spastic paraplegia and had been previously diagnosed with the diplegic form of cerebral palsy. We suggest that spastic paraplegia type 3 (SPG3A) be included in the differential diagnosis of early onset spastic paraplegia. To the best of our knowledge, this is the first report of a genetically confirmed family affected with SPG3A in Korea.

Keywords: hereditary spastic paraplegia, atlastin GTPase 1, ATL1 mutation

Introduction

Hereditary spastic paraplegia (HSP) comprises a group of inherited neurodegenerative disorders that cause progressive weakness and spasticity, predominantly affecting the lower extremities. HSP is due to a length-dependent retrograde degeneration of the corticospinal tracts and fasciculus gracilis [1]. Conventionally, patients with HSP are classified into pure and complicated types based on the absence or presence of accompanying extra-neurological features, such as retinopathy, dementia, deafness, ataxia, and mental retardation [2], and on the mode of inheritance (autosomal dominant [AD], autosomal recessive [AR], or X-linked recessive). At least 41 spastic paraplegia gene loci have been mapped and 17 affected genes have been identified to date [3].

Spastic paraplegia 3 (SPG3A; OMIM 182600) is caused by mutations in the atlastin GTPase 1 (ATL1) gene, which is also known as the SPG3A gene, located on chromosome band 14q22.1. The SPG3A form of HSP typically presents with a pure phenotype, early onset, and a benign prognosis. For many subjects with an ATL1 mutation, spastic gait begins in early childhood and does not significantly worsen, even over many years. Such cases resemble spastic diplegic cerebral palsy, which is the most common cause of spastic paraplegia affecting infants. However, spasticity characterized by progressive gait impairment may also be the first sign of infantile onset HSP [4,5].

In Korea, there is a report demonstrating that SPAST gene mutations are the most common cause of HSP, as in other ethnic groups [6]. However, although the ATL1 gene has been known to be the
second most common cause of HSP in other populations, there have been no reports of a Korean
HSP patient with an ATL1 gene mutation. In the
present study, we report a point mutation in the
ATL1 gene in a Korean family with infantile onset
spastic paraplegia whose members were originally
diagnosed with the diplegic form of cerebral palsy.
To the best of our knowledge, this is the first report
of a genetically confirmed, SPG3A affected family
in Korea.

Materials and Methods

Patients. The proband (Fig. 1, III-1) was a 28-yr-old woman
with slowly progressive leg spasticity and weakness, which
began in infancy. She was born to nonconsanguineous parents
after an uncomplicated pregnancy and delivery. At one mo of
life, she developed respiratory distress and a fever, which led
to an initial diagnosis of cerebral palsy at a university hospital.
She had normal development except for her lower extremities
and an abnormal tiptoeing gait, which was identified at two
yr of age. At seven yr of age, at a different regional hospital,
the patient underwent tendon release surgery in both Achilles
tendons to improve her walking ability and to reduce her
spasticity under a presumptive diagnosis of spastic cerebral
palsy. At the same hospital, the patient again underwent
tendon release surgery in both Achilles tendons at age 21.

Upon admission to our hospital, the patient's
neurological examination showed increased knee jerk and
ankle jerk reflexes, positive Babinski sign, and ankle clonus.
Her lower extremity motor strength was poor to good, and
sensory examination revealed no abnormal findings. Her
lower extremities were spastic and gait analysis revealed
excessive pelvic anterior tilt, stiff knees during the swing
phase, and abrupt reversal of ankle movement direction from
dorsiflexion to plantarflexion in the sagittal plane during the
mid-stance phase. These findings are characteristics of a
spastic paretic gait. However, the patient could walk indoors
and outdoors and climb stairs while holding a railing. She had
no cerebellar ataxia, sensory symptoms, or urinary bladder
urgency, and she had normal intelligence and language
function. She underwent brain and spine magnetic resonance
imaging (MRI) studies, with normal results.

The family history revealed that the patient's maternal
grandmother (age 80 yr, I-2), mother (age 51 yr, II-3),
deceased maternal aunt (II-5), deceased maternal cousin (III-
3), and maternal uncle (age 38 yr, II-6) also had gait
disturbances beginning in childhood (Fig. 1). All affected
family members could walk without support, except the
grandmother who had been wheelchair-bound since 75 yr of
age. The patient's mother (II-3) was affected in a similar
manner and showed minimal gait abnormalities, such as
intermittent dragging of her feet for the past 7 yr and
progressive lower extremity weakness, which had only been
recognized recently. Her neurological examination at age 50
yr revealed a stiff knee gait, positive Babinski sign, and
increased deep tendon reflexes in the lower extremities.
However, her gait disturbance was unremarkable during slow
walking and became apparent only when she was running or
moving quickly.

Detailed medical information of the patient's maternal
aunt (II-5) and cousin (III-3) could not be obtained because
they had died in a car accident 15 yr ago. The patient's
maternal uncle (II-6) was diagnosed as having a diplegic form
of cerebral palsy at two yr of age. A mild regression in his
motor ability had been noticed since early adulthood. At the
age of 28 yr, he underwent Achilles tendon release surgery at
a university hospital, which did not improve his walking
capacity. Although he exhibited some characteristics of a
spastic paretic gait, such as bilateral stiff knee gait, he did not
require supportive devices. Other family members and their
offspring did not have any histories of gait abnormalities.

Genetic analysis. To identify the genetic defect, we performed
molecular genetic testing for the SPA3A and SPG4 forms of
HSP. After we obtained informed consent, blood samples
were collected from the patient, her mother, and her maternal
uncle. The maternal grandmother was unavailable for study.
Genomic DNA was isolated from peripheral whole blood
leukocytes using the Wizard Genomic DNA Purification Kit
(Promega, Madison, WI) following the manufacturer's
directions. All coding exons and their flanking intronic
sequences of the ATL1 and SPAST genes were amplified using
the polymerase chain reaction (PCR) in a thermal cycler
(Model 9700; Applied Biosystems, Foster City, CA) with
primers designed by the authors (available upon request).
Direct sequencing was performed using the same primer sets
and the BigDye Terminator Cycle Sequencing Ready
Reaction kit (Applied Biosystems) on the ABI Prism 3130
genetic analyzer (Applied Biosystems). To identify sequence
variations, the subject's sequences were compared with
reference sequences for the ATL1 and SPAST genes (GenBank
NM_015915.4 and NM_014946.3, respectively) using
Sequencher software (Gene Codes Corp., Ann Arbor, MI).

Fig 1. Pedigree of proband and her family.
Results

Direct sequencing analyses of the *ATL1* and *SPAST* genes were performed and revealed a missense mutation in the *ATL1* gene. This mutation caused a C-to-T substitution at nucleotide position 715 in exon 7, replacing arginine with cysteine in codon 239 (c.715C>T; p.Arg239Cys) (Fig. 2). Except for an intronic SNP (rs2934684) where the patient was homozygous for major alleles in Asian samples according to HapMap data (http://www.hapmap.org; http://www.ncbi.nlm.nih.gov/projects/SNP), no other sequence variations were observed in the *ATL1* and *SPAST* genes.

Family analysis revealed that the two other affected individuals who participated in the molecular genetics study, the patient’s mother (II-3) and maternal uncle (II-6), were both heterozygous
for the same R239C mutation as was found in the proband (Fig. 2).

Discussion

Spastic paraplegia 3 (SPG3A; OMIM 182600) is caused by mutations in the **ATL1** gene. The ATL1 gene includes 14 exons spanning 69 kb and encodes atlastin-1, which is a member of the dynamin superfamily of large GTPases. Atlastin-1 is predominantly localized in the central nervous system, where it is enriched in pyramidal neurons in the cerebral cortex and hippocampus [7,8]. This protein has been implicated in vesicle formation, transport from the endoplasmic reticulum (ER) to the Golgi interface, maintenance of the Golgi apparatus, and ER morphogenesis [9,10].

The diagnosis of SPG3A is usually made based on genetic analysis. There are 27 disease-causing mutations reported in **ATL1** (Human Gene Mutation Database at http://www.hgmd.cf.ac.uk/ac/gene.php?gene=ATL1, last updated Jan 2010), including 25 missense/nonsense mutations and 2 small insertions. Furthermore, for professional subscribers, 39 mutations have been reported, and the Genetics Home Reference (http://ghr.nlm.nih.gov/gene/ATL1) currently states that there are more than 30 mutations in the **ATL1** gene that have been identified in SPG3A. In fact, **ATL1** mutations cause approximately 10% of autosomal dominantly inherited uncomplicated HSP. However, the mutation detection rate varies for each report and geographical origin, including Tessa et al [11] (1/8, 12%), Smith et al [12] (6/70, 9%), Abel et al [13] (1/12, 8%), Meijer et al [14] (1/70, 1.4%), and Souter et al [15] (5/13, 38%). Namekawa et al [16] reported that SPG3A is the most frequent HSP in patients with onset before ten yr of age and that it is twice as frequent as SPG4 in this age group. However, there have been no previous reports of genetically confirmed SPG3A in Korean HSP patients, and there has been only one previous investigation of SPG3A in AD-HSP. Park et al [6] reported a mutation analysis of the **ATL1** and **SPAST** genes in 18 Korean patients with dominantly inherited and uncomplicated HSP (SPG3A and SPG4). Although the samples analyzed included a small number of patients with AD-HSP who had not been selected for early age of onset, **ATL1** mutations were not found.

In this kindred, the members were unaware they had a genetically transmissible disease and had been provided no information regarding hereditary paraplegia. The patient's mother exhibited mild lower extremity symptoms and an unrecognized spastic gait. The patient's maternal uncle had lower extremity symptoms that were diagnosed as a diplegic form of cerebral palsy when he was two yr old, and the patient was incorrectly diagnosed by her original treating physicians. It has been reported that cases of infantile onset HSP can be misdiagnosed as spas tic diplegic cerebral palsy [17-19]. Progressive spasticity of lower extremities is a symptom commonly used to distinguish these two diseases and the other distinctions include no apparent underlying causes, minimal upper extremity symptoms, normal intelligence, and previous family history. However, some patients with SPG3A can have minimal worsening of their symptoms and a negative family history may be caused by mildly affected members who did not report any problems at the time of evaluation. SPG3A should be included in the differential diagnosis of early onset spastic paraplegia and genetic testing for the causative gene, **ATL1**, may be necessary to distinguish these two disease entities, which cause gait disturbances early in life.

In summary, we present a Korean family with SPG3A and a missense mutation in the **ATL1** gene. Their clinical phenotypes corresponded to the pure form of HSP with early onset of spastic paraplegia and the family members had previously been diagnosed with a diplegic form of cerebral palsy. To our knowledge, this is the first report of a genetically confirmed family affected with SPG3A in Korea. This report highlights the necessity of considering SPG3A in the differential diagnosis of early onset pure lower extremity motor impairment, particularly in patients without significantly worsening symptoms, even over many years.

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References