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Late-Onset Hereditary Spastic Paraplegia With a Novel SPAST Intronic Variant

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Introduction

Hereditary spastic paraplegia (HSP) is an inherited neurodegenerative disorder characterized by progressive lower-limb spasticity and weakness. Mutations in the SPAST gene are the most common cause of autosomal dominant HSP, known as spastic paraplegia type 4 (SPG4). The reported median age at onset of SPG4 is approximately 30 years, and most patients develop progressive gait disturbance. The clinical severity varies considerably and the relationship between mutation location and disease phenotype has not been fully clarified. In particular, the contribution of intronic SPAST variants to atypically late-onset or mild clinical presentations remains unclear.

Case Presentation

A 69-year-old female presented with a progressively worsening gait disturbance. Approximately 10 years prior to her first visit to our hospital, she initially noticed a vague sense of discomfort while walking without any preceding trauma or medical illness. At that time, she described her symptoms as “leg stiffness” and a feeling that her gait was “awkward.” Despite these symptoms, she was able to perform activities of daily living and ambulate independently, and no further evaluation was undertaken.

Over time, her symptoms gradually progressed. Approximately 5 years prior to presentation, gait disturbance became more pronounced, making independent ambulation increasingly difficult, and she reported frequent falls. One year prior to presentation, due to continued worsening of gait disturbance, she visited the outpatient clinic of the Department of Rehabilitation Medicine at Daegu Fatima hospital for the first time. At that time, ambulation was possible only with a quad cane.

Family history was notable for similar symptoms in the patient’s deceased mother and maternal grandfather, both of whom had experienced progressive gait difficulty. Among her siblings, two were affected, whereas one was asymptomatic, suggesting autosomal dominant inheritance.

On admission for inpatient rehabilitation, neurological examination revealed no gross or focal weakness in the upper extremities. In the lower extremities, manual muscle testing demonstrated generally preserved strength (grade G) without focal weakness. However, spasticity was evident in both lower limbs, particularly involving the hip adductors and knee extensors. The most severe spasticity was observed in the hip adductors (Modified Ashworth Scale [MAS] grade 2). Gait analysis revealed a narrow-based, short-step pattern with scissoring and reduced gait stability.

The patient underwent a comprehensive rehabilitation program for approximately six weeks, including gait training, stretching and strengthening exercises. Pharmacological management for spasticity was also initiated, with oral baclofen gradually titrated up to 40 mg/day and oral tizanidine increased to 4 mg/day.

Following inpatient rehabilitation, spasticity of the hip adductor muscles improved to MAS grade 1, accompanied by a reduction in scissoring gait and improved gait stability. Functionally, the patient showed improvement of indoor gait without assistive devices, outdoor gait with mono-cane, and resulting in fewer falls compared with before.

Results

Genetic testing identified a heterozygous intronic deletion in the SPAST gene(NM_014946.4:c.1494-6_1494-3del) located in intron 12, immediately upstream of exon 13. No other pathogenic variants related to HSP were detected. SpliceAI predicted acceptor and donor loss (Δ scores 0.61 and 0.7), suggesting exon 13 skipping. cDNA analysis confirmed an additional shorter transcript in the patient that was absent in a healthy control, and Sanger sequencing verified exon 13 skipping, indicating aberrant pre-mRNA splicing caused by the intronic deletion.

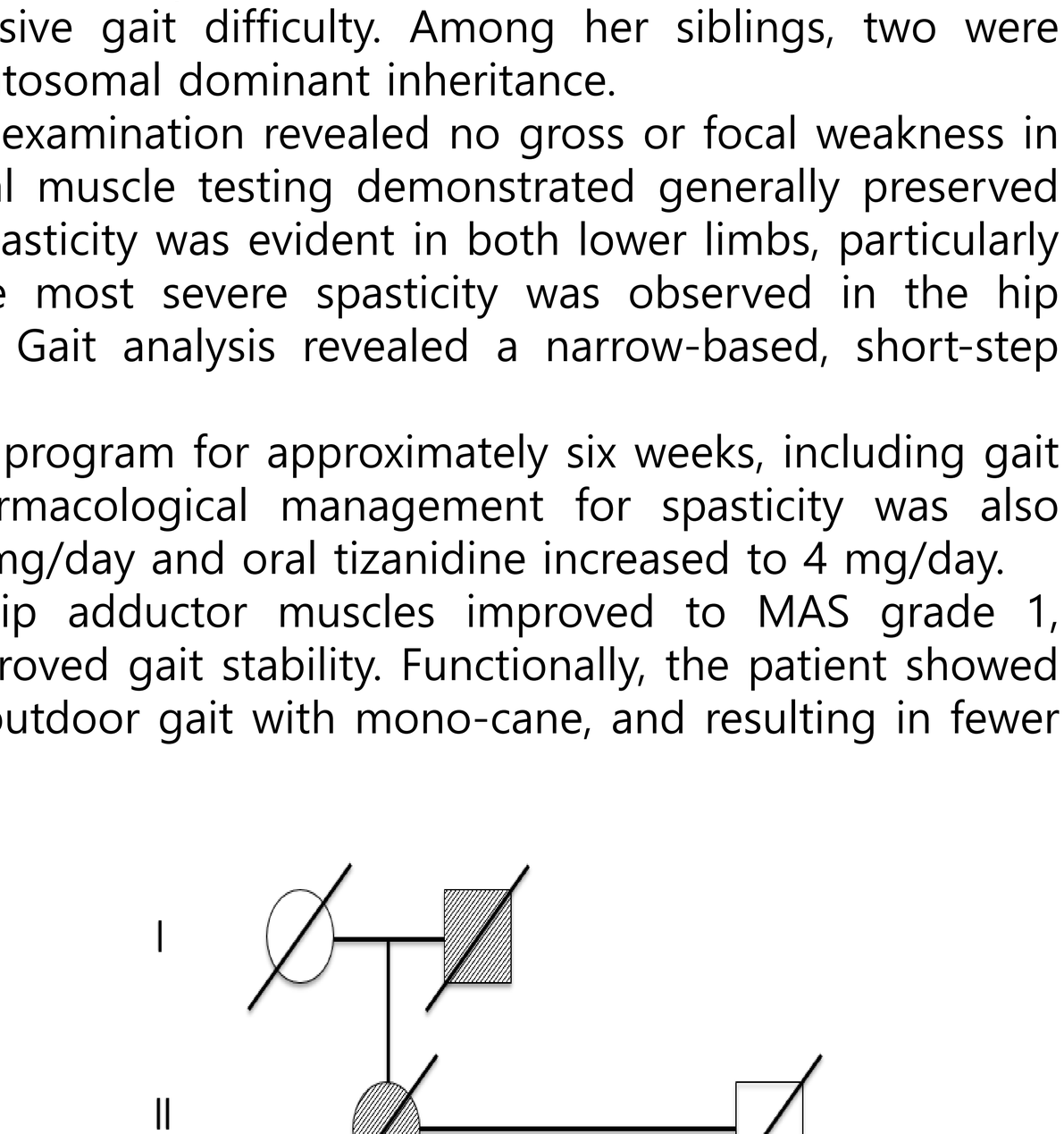

Figure 1. Pedigree of a Family with an SPAST Intronic Variant. The pedigree demonstrates an autosomal dominant inheritance pattern with vertical transmission across generations.

Conclusion

This family showed late-onset autosomal dominant HSP associated with an intronic SPAST variant. Compared with the typical age of onset for SPG4, which is around 30 years old, this patient’s symptoms began in their sixth decade; the clinical course was relatively mild, and the patient responded well to rehabilitation therapy. Functional evidence of exon 13 skipping suggests that partial alteration of spastin function may contribute to the attenuated phenotype observed in this family.