

[CASE REPORT]

Novel *SPG11* Mutations in a Patient with Symptoms Mimicking Multiple Sclerosis

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Abstract:

We describe the cases of two sisters with spastic paraplegia 11 (SPG11). The younger sister developed relapsing lesions in the brain white matter with enhancement during the acute phase that mimicked multiple sclerosis (MS). The elevation of myelin basic protein in the cerebrospinal fluid (CSF) suggested demyelination, but a normal IgG index, the absence of oligoclonal bands, and the ineffectiveness of steroid treatment indicate that an autoimmune mechanism may not have been involved. In these affected sisters, we identified novel compound heterozygous mutations in the *SPG11* gene. Our cases indicate the possible existence of a broader phenotypic spectrum of *SPG11* mutations.

Key words: hereditary spastic paraplegia, SPG11, multiple sclerosis, white matter lesions, mutations

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Introduction

Hereditary spastic paraplegia (HSP) is a heterogeneous disorder characterized by the progressive degeneration of the corticospinal tract resulting in progressive lower limb spasticity and weakness. Spastic paraplegia 11 (SPG11) is one of the most common complicated forms of autosomal recessive HSP with thin corpus callosum (TCC) that leads to cognitive impairment, peripheral neuropathy, ataxia, extrapyramidal symptoms and other conditions (1). We herein describe the cases of two sisters with SPG11, the younger of whom showed relapsing attacks with white matter lesions in the brain that mimicked multiple sclerosis (MS).

Case Reports

Case 1 (II-3)

The patient was a fifteen-year-old girl who showed normal motor and psychological milestones, but who developed left-side hemiparesis. Head MRI showed a thin corpus callo-

sum and some scattered white matter lesions around the ventricles on T2-weighted imaging (T2WI). A cerebrospinal fluid (CSF) analysis revealed elevated myelin basic protein (MBP) 624 pg/mL. She was diagnosed with MS and intravenous steroid pulse treatment was administered (1 g intravenous methylprednisolone for three days) (IVMP). However, this was ineffective, and her spastic paraplegia and cognitive decline slowly progressed. She developed facial nerve palsy and bilateral oculomotor disturbance twice at 20 and 22 years of age. Head MRI revealed new lesions in the white matter and brain stem; one showed ringed gadolinium enhancement. A CSF analysis revealed that her MBP level was elevated again. IVMP was ineffective, but the symptoms improved slowly during rehabilitation and the brain lesions became obscure. Oral steroid treatment was initiated. Thereafter, a wide variety of symptoms, including sensory disturbance and weakness, appeared with new white matter lesions of the brain (Figure H). Periventricular white matter changes and moderate diffuse cortical atrophy appeared. Her gait became impaired and she required a cane to walk. At twenty-four years of age, she was admitted to our hospital because of left-side hemiparesis. Her mini mental state ex-

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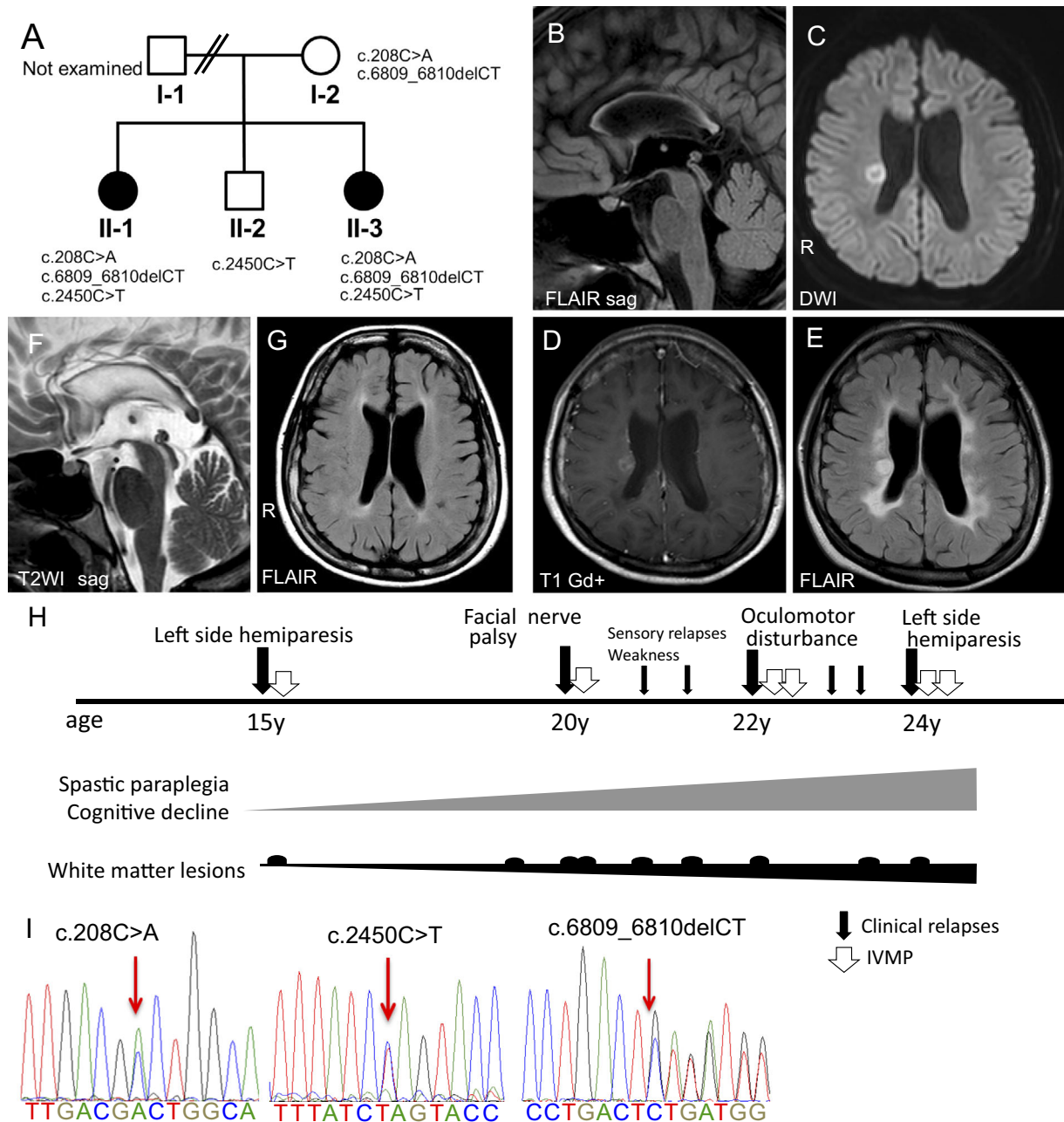


Figure. The family pedigree, head MRI of the sisters, clinical course of case 1 and the DNA sequence chromatogram. (A) The pedigree of the family carrying the *SPG11* mutations. (B-E) The brain MRI features of case 1 (II-3) at 24 years of age. (B) FLAIR imaging (sagittal section) shows a thin corpus callosum (TCC). (C) Diffusion weighted imaging (axial section) shows hyperintense periventricular lesions, (D) with gadolinium ring enhancement. (E) FLAIR imaging (axial section) shows hyperintensity of the periventricular white matter. (F, G) The brain MRI features in case 2 (II-1) at 30 years of age. (F) T2WI (sagittal section) shows TCC. (G) FLAIR imaging (axial section) shows slight hyperintensity of the periventricular white matter. (H) Clinical course of case 1. Black arrows indicate the clinical relapses, and white arrows indicate intravenous methylprednisolone (IVMP). The neurological symptoms and brain white matter lesions were exacerbated. (I) The sequence chromatogram of DNA extracted from the peripheral blood. Heteroplasmic mutations (c.208C>A, c.2450C>T and c.6809_6810delCT) were found in the *SPG11* gene (arrows).

amination score was 18/30, and a beside frontal assessment battery revealed a score of 7/18. She showed saccadic eye movements, facial paresthesia, dysarthria and spastic paraplegia. The results of laboratory examinations, including the patients levels of anti-nuclear, anti-aquaporin 4, and myelin

oligodendrocyte glycoprotein, and anti-HTLV1 antibodies, vitamin 12, and folic acid were within normal ranges. A CSF analysis showed neither oligoclonal bands (OCBs) nor an increased IgG index; however, the patient's MBP level was elevated (211 pg/mL). Head MRI revealed new lesions

with enhancement in the periventricular white matter (Figure B-E). Typical findings of MS, such as periventricular ovoid lesions perpendicular to the ventricles, so-called Dawson's fingers, juxtacortical lesions, and T1 black holes were not detected. Spinal cord MRI and magnetic resonance spectroscopy revealed no remarkable findings. Two further courses of IVMP showed no clear effect. The patient became wheelchair-bound.

Case 2 (II-1)

The patient was the sister (six years older) of the patient in Case 1 (Figure A). She had normal motor and psychological milestones but developed tremor in her right hand and general convulsion at fifteen years of age. A neurological examination revealed cerebellar ataxia and lower leg spasticity. Head MRI showed TCC and moderate cerebral atrophy with slight hyperintensity of the periventricular white matter on T2WI (Figure F and G). Spinal MRI revealed no spinal cord lesions. Subsequently, her academic performance declined, her spastic paraplegia slowly worsened, and she became wheelchair-bound.

After obtaining informed consent from all participants, we extracted genomic DNA from the patients' peripheral blood according to the standard procedures, performed a polymerase chain reaction (PCR) to screen for mutations. In the two affected sisters (II-1, II-3), compound heterozygous mutations were identified in the *SPG11* gene: c.208C>A p.Trp70Thr in exon 1, c.2450C>T p.Trp817* in exon 14 and c.6809_6810delCT p.Thr2270Thrfs*68 in exon 37 (Figure D). Segregation of the genetic variants was validated in other family members who were not symptomatic: the mother (I-2) carried heterozygous c.208C>A p.Trp70Thr and c.6809_6810delCT, while her brother (II-2) carried heterozygous c.2450C>T p.Trp817.

Discussion

We reported the cases of two sisters with novel compound mutations in the *SPG11* gene. We considered that c.208C>A and c.6809_6810delCT were on the same allele and that c.2450C>T was on the other allele. We could not investigate the divorced father (I-1) but expect that he would have c.2450C>T. Mutations c.2450C>T and c.6809_6810delCT which were not present in the Exome Aggregation Consortium database-leading to a premature stop codon. c.208C>A is not considered to be a pathogenic mutation (ClinVar / NCBI). The combination of c.2450C>T from the father and c.6809_6810delCT from the mother may result in a truncated protein or reduced transcript levels, suggesting that the clinical symptoms of SPG11 arise through a loss-of-function mechanism. Although the two sisters have the same mutations in the *SPG11* gene, only the younger sister showed relapsing attacks with white matter lesions. Indeed, no genotype-phenotype correlation has been shown in SPG11 patients. Other factors, such as environmental, genomic, or epigenetic factors, are suggested to influence intra-familial

phenotypic variability (2, 3).

The *SPG11* gene encodes a protein called spatascin, which interacts with the proteins involved in membrane-trafficking, playing a role in intracellular trafficking and endolysosomal homeostasis (4, 5). The pathological examination of a patient with SPG11 revealed myelin pallor of the white matter in the cerebral hemispheres and a demyelination of the corpus callosum. Astrogliosis and abnormally abundant lipofuscin-positive granules in supratentorial neurons were thought to suggest lysosomal impairment (6). On the other hand, brain ¹H-MR spectroscopic imaging shows significantly lower n-acetyl acetate (NAA)/Cr values throughout the whole white matter periventricular regions of SPG11 patients. This finding might suggest the presence of pronounced neuro-axonal damage and/or loss (7). It is unclear whether or not elevation of MBP in CSF is usually observed in the SPG11 patients. However, these pathological and radiological observations indicate that the lysosomal dysfunction and lipid metabolism impairment caused by *SPG11* gene mutations may lead to neuro-axonal degeneration in the bilateral periventricular white matter, resulting in the elevation of MBP in the CSF and white matter lesions.

It was reported that brain MRI of SPG11 patients showed TCC (95-100%), cortical atrophy (81-90%) and bilateral hyperintensity of the periventricular white-matter on T2WI (47-90%), but that subtentorial lesions were unusual (1, 8-10). White matter lesions without clinical relapse are considered to be important for the differentiating SPG11 from MS. Laurencin et al. (11), reported the case of a nineteen-year-old man with SPG11 harboring compound heterozygous mutations in c.5255delT/p.Phe1752SerfsX86 (in exon 30) and c.6754+2_6754+3dupTG (in intron 36), who experienced relapsing episodes with multiple white-matter lesions. Similarly to our case, some lesions were gadolinium-enhanced, and a CSF analysis showed no OCB and a normal IgG index. However, in contrast to our findings, they reported that IVMP was effective in the acute phase and that natalizumab prevented relapses for a year, and then concluded that MS and SPG11 coexisted in the same patient. As noted above case 1 showed relapses of cerebral white matter lesions with enhancement during the acute phase. The elevation of MBP in the patient's CSF suggested demyelination, but the normal IgG index, the absence of OCBs, and the ineffectiveness of several courses of steroid treatment indicated that an autoimmune mechanism was not involved. We hypothesize that the clinical relapses of the neurological symptoms may be a part of a broader phenotypic spectrum of *SPG11* mutations. Further consideration of the validity of immunotherapy is needed.

Conclusion

We herein described the cases of two sisters with novel compound heterozygous mutations of the *SPG11* gene. One sister showed relapses of MS-like white-matter lesions; however, a CSF analysis and the ineffectiveness of steroid therapy were inconsistent with an autoimmune mechanism. Our

cases indicate a broader phenotypic spectrum of *SPG11* mutations.

The authors state that they have no Conflict of Interest (COI).

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