

Single Case – General Neurology

Coexistence of Hereditary Spastic Paraplegia Type 4 and Narcolepsy: A Case Report

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Keywords

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Abstract

Spastic paraplegia type 4 (SPG4) is the most common type of hereditary spastic paraplegia (HSP) caused by the mutations in the *SPAST* gene, which encodes a microtubule-severing protein named spastin. Spastin regulates the number and mobility of microtubules and is essential for axonal outgrowth and neuronal morphogenesis. Herein, we report a patient with SPG4 harboring a novel donor splice site mutation in the *SPAST* gene (c.1616+1dupG). Although SPG4 usually manifests itself as a pure form of HSP, this patient exhibited a slow progressive cognitive decline and also developed narcolepsy type 2 (narcolepsy without cataplexy) prior to the onset of SPG4. Recently, cognitive decline has attracted attention as a main non-motor symptom of SPG4. However, this is the first reported case of a patient developing both SPG4 and narcolepsy, although it remains unclear whether the manifestation of the two diseases is a coincidence or an association. In this report, we describe the clinical symptoms and genetic background of the patient.

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Introduction

Hereditary spastic paraplegias (HSPs) are a rare, heterogeneous group of monogenic neurodegenerative disorders characterized by progressive spasticity and weakness of the lower limbs. So far, nearly 80 genetic loci have been linked to HSPs. HSPs can be transmitted by all classical modes of inheritance, including autosomal dominant and recessive, X-linked, and mitochondrial transmission. Traditionally, HSP has been classified into two clinical forms based on the phenotype: pure and complicated. In principle, symptoms of the pure HSP form are limited to pyramidal signs associated with spastic paraplegia; however, some patients can also present with a mild reduction in vibration sensations in the lower limbs, urinary bladder dysfunction, mild upper limb involvement, or pes cavus [1]. In contrast, the complicated HSP form is characterized by the symptoms present in the pure form of HSP, alongside other severe neurologic findings, such as ataxia, dysarthria, mental retardation, dementia, epilepsy, peripheral neuropathy, or optic neuropathy. The estimated prevalence of all HSPs is 0.9 per 100,000 people in Japan. Spastic paraplegia type 4 (SPG4) is the most frequent subtype of autosomal dominant HSP, which accounts for more than 25% of all HSP cases and 40–60% of all autosomal dominant HSP cases [2, 3]. SPG4 is caused by mutations in the *SPAST* gene which encodes a microtubule-severing protein named spastin [4]. SPG4 has been considered one of the pure forms of HSP; however, recent studies have revealed that some SPG4 patients could present with some phenotypic features of the complicated form. In recent years, it has also become clear that SPG4 patients can present with non-motor manifestations such as autonomic dysfunctions, depression, and cognitive impairment. In particular, cognitive impairment in SPG4 has attracted the attention of many researchers [5].

We encountered a Japanese patient with SPG4 associated with slowly progressive cognitive impairment and identified a novel donor splice site mutation in the *SPAST* gene. This patient manifested severe excessive daytime sleepiness (EDS) and was diagnosed with narcolepsy prior to the SPG4 symptoms. Narcolepsy is a chronic sleep disorder characterized by varying degrees of EDS and clinical symptoms of rapid eye movement (REM) sleep abnormalities, such as sleep paralysis, hypnagogic hallucinations, and cataplexy (sudden loss of muscle tone triggered by strong emotions such as pleasure, laughing, surprise, and anger). In the late 1990s, the discovery of two neuropeptides, hypocretin-1 and hypocretin-2 (also called orexin-A and orexin-B, respectively) and of their receptors, HCRTR1 and HCRTR2, enabled a breakthrough in elucidating the cause of narcolepsy. Hypocretin-1 and hypocretin-2 are derived from hypocretin, a neuropeptide precursor protein synthesized by a small number of neurons in the lateral hypothalamus [6, 7]. The actions of hypocretin-1 and hypocretin-2 are heavily involved in the sleep-wake cycle in humans and some animals. In the 3rd Edition of the International Classification of Sleep Disorders (ICSD-3) [8], narcolepsy is classified into two subtypes, narcolepsy type 1 (NT1) and narcolepsy type 2 (NT2), based on the advances in the research of hypocretin system. NT1 is narcolepsy with cataplexy and/or very low levels of hypocretin-1 in the cerebrospinal fluid (CSF). Hypocretin deficiency because of the severe loss of hypocretin-producing neurons is the hallmark of NT1. NT2 simply represents narcolepsy without cataplexy. NT2 symptoms are generally less severe than those of NT1, and nearly 90% of the patients with NT2 have normal hypocretin-1 levels in the CSF. Our patient was classified into NT2 because he did not manifest cataplexy and did not agree with the hypocretin-1 measurement in the CSF. The estimated prevalence of NT1 is 1 per 600 people in Japan and about 1 per 2,000 people in the United States and Europe. However, the exact prevalence of NT2 is

unclear because of the non-specific nature of the symptoms and lack of useful biomarkers for NT2.

To the best of our knowledge, the coexistence of SPG4 and narcolepsy has not been previously reported in the literature. In this report, we describe the clinical and genetic findings of the patient.

Case Report

Our patient is a 71-year-old Japanese man. He was very good at judo, swimming, and baseball when he was a teenager. Because his school grades were average, we assumed that his intellect was within the normal range during his teens. He started working as a lathe operator in an ironworks at the age of 19. However, after middle age, he showed slowly progressing gait disturbance and needed a cane to walk after he turned 60.

At the age of 61, he was admitted to a neurology hospital. Neurological examinations revealed spasticity and increased deep tendon reflexes in his lower extremities. No ataxia, peripheral neuropathy, or bladder dysfunction were observed at that time. However, mild cognitive impairment was suspected based on the results of several neuropsychological assessment tests. Brain magnetic resonance imaging did not reveal a thin corpus callosum.

The parents of the patient were first cousins. We had no precise information on the walking ability of his father, who died of pancreatic cancer at the age of 54. His mother, who died of senile decay in her 80s, did not develop a spastic gait in her lifetime. His elder brothers also showed slowly progressive spastic paraplegia (Fig. 1). The eldest brother (II-1) developed a gait disturbance in his 30s, and the second eldest brother (II-3) developed a gait disturbance before the age of 10. We had no specific information on the cognitive function of these two brothers.

After obtaining written informed consent, the patient's blood sample was sent to the Japan Spastic Paraplegia Research Consortium for genetic analysis of the HSP-related genes [9]. As a result, a novel single-nucleotide duplication was identified in a donor splice site of the *SPAST* gene (NM_014946.3:c.1616+1dupG), the responsible gene for SPG4.

Soon after being discharged from the neurology hospital, the patient was referred to our hospital to pursue outpatient treatment and to undergo periodical in-hospital rehabilitation. Over the next 10 years, his neurological symptoms, including both pyramidal signs and cognitive impairment, had gradually deteriorated. He had been using a wheelchair to get around for the last several years. At the age of 61, his scores on the Mini-Mental State Examination (MMSE) and frontal assessment battery (FAB) were 22/30 (normal >23/30) and 13/18 (normal >16, under the age of 65), respectively. At the age of 70, his scores on the MMSE and FAB had dropped to 18/30 and 10/18, respectively.

Other than HSP, this patient developed severe hypersomnia. He began to experience EDS in his 20s. Since then, he has had many car accidents due to EDS while driving. He was fired because of frequent nodding off during working hours at the age of 49. He visited a sleep medicine specialist for a detailed examination for his serious EDS at the age of 57. At that time, his Epworth Sleepiness Score was 12, which indicated the presence of strong daytime sleepiness. The nocturnal polysomnography revealed a short sleep latency and sleep-onset REM period (4 min) in the patient. Fragmented nocturnal sleep and frequent periodic limb movements were also observed; however, he did not show any signs of cataplexy. Although a multiple sleep latency test was not performed because of unavailability, he was diagnosed with

narcolepsy based on these highly specific polysomnography findings including nocturnal sleep-onset REM period. Modafinil was used for the treatment of his narcolepsy, and the drug noticeably improved his EDS. No other family member of his manifested EDS.

Later, we genotyped his class II human leukocyte antigen (HLA) genes and found that he carried one *HLA-DQB1*06:02* allele, which has a very strong association with the occurrence of NT1. After that, we suggested a hypocretin-1 concentration measurement in his CSF; however, he did not consent to this. When he was 70 years old, we carried out a genetic analysis once again because a significant number of HSP-related genes had been newly reported and the possibility of autosomal recessive HSP could not be completely ruled out. We analyzed 57 genes associated with HSP using a next-generation sequencer and a multi-disease exome panel (TruSight One, Illumina), but no pathogenic variant was found except for the previously identified variant, c.1616+1dupG, which is located at the exon 14-intron 14 junction in the *SPAST* gene (Fig. 2). Since we were unable to analyze the mRNA of the *SPAST* gene in this patient, we performed in silico analyses to evaluate the effects of the variant on splicing using two different splice site prediction algorithms: the Berkeley Drosophila Genome Project (BDGP) splice site predictor and the Human Splicing Finder (HSF) v.3.1. Both BDGP and HSF predicted a shift of the donor splice site from the canonical site to the one base downstream position. This splice site alteration results in a frameshift and a premature stop codon in exon 15 (Fig. 3). Therefore, we determined this variant to be “pathogenic” according to the American College of Medical Genetics guidelines [10]. We also analyzed the exome panel data for *HCRT*, *HCRTR1*, and *HCRTR2* genes, but did not find pathogenic variants in these hypocretin system-related genes. Written informed consent of the patient was obtained for all the genetic analyses performed.

Discussion

We identified a novel donor splice site variant (c.1616+1dupG) in the *SPAST* gene in an HSP patient who manifested cognitive impairment. In silico, this variant was predicted to cause mis-splicing leading to a frameshift and a premature termination codon at the amino acid position of 542 in the AAA domain (Fig. 3). Spastin is a microtubule-severing protein belonging to ATPase associated with various cellular activities (AAA) family proteins. The *SPAST* gene produces two main isoforms, M1 and M87. M1 is the full-length 618-amino acid isoform, and M87 is the shorter isoform lacking amino acids 1 to 86 in the N-terminal. In humans, M87 is the most abundant isoform, widely expressed in various tissues, including the spinal cord and brain, while M1 is detectable only in the adult spinal cord, and not in the brain [11]. Spastin regulates the number and mobility of microtubules and is essential for axonal outgrowth and neuronal morphogenesis [12].

SPG4 is clinically classified as a pure form of HSP. However, some patients with SPG4 manifest non-motor symptoms. The index patient also showed slowly progressive cognitive impairment that could not be fully explained by aging. Although its pathogenesis has not yet been eliminated, cognitive impairment is now recognized as a main non-motor symptom of SPG4. The most characteristic feature of this patient was the manifestation of narcolepsy without cataplexy (NT2). From the viewpoint of pathogenesis, NT1 occurs due to the irreversible destruction of hypocretin-producing neurons in the lateral hypothalamus, probably by a T cell-mediated autoimmune mechanism which is very strongly linked to the *HLA-DQB1*06:02* allele. Almost all patients with NT1 have *HLA-DQB1*06:02* allele; however, the presence of this

allele is not sufficient for NT1 development since 12% of the healthy Japanese population and 30–50% of patients with NT2 are positive for this allele. On the other hand, the mechanism of NT2 has not yet been fully elucidated, and it is not clear if NT2 is just a mild stage of NT1 or comprises a different etiology than NT1.

Vascular malformations, strokes, and sarcoidosis in the hypothalamus and midbrain can cause narcolepsy (secondary narcolepsy), presumably by destroying HCRT neurons or the target cells of HCRT. However, these disorders were not found in this patient.

Although some familial cases have been reported in human narcolepsy, only one case of early-onset NT1 carrying a heterozygous p.Leu16Arg mutation in the signal peptide coding region of the *HCRT* gene has been reported so far [13]. In canines, exon skipping mutations in the *HCRTR2* gene was identified as the cause of narcolepsy [14]. In our case, no pathogenic variant was found in the *HCRT*, *HCRTR1*, or *HCRTR2* gene.

It has recently been reported that Parkinson's disease (PD), a progressive neurodegenerative disease characterized by the loss of dopaminergic neurons, is preceded or accompanied by narcolepsy-like symptoms. Interestingly enough, Thannickal et al. [15] found an increasing loss of HCRT neurons with the progression of PD and speculated that the loss of HCRT neurons was a cause of narcolepsy-like symptoms in PD. However, to this date, there is no evidence that mutations in the *SPAST* gene can cause narcolepsy by degeneration or loss of HCRT neurons or its targeting cells.

This is the first case report describing the coexistence of SPG4 and narcolepsy in the literature. However, it remains unclear whether the coexistence of these two rare diseases could be causally explained or is a coincidence. Until now, the relationship between SPG4 and sleep disorders has hardly been assessed. Larger studies are needed to clarify the association between SPG4 and narcolepsy.

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Statement of Ethics

Ethics approval was obtained from the National Hospital Organization Niigata National Hospital Institutional Review Board. Written informed consent was obtained from the patient for publication of this case report and any accompanying data.

Conflict of Interest Statement

The authors declare no conflict of interest associated with this case report.

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Author Contributions

T. Nagai wrote the manuscript draft. T. Nagai, Y.S., M.T., K.O., and T. Nakajima treated the patient. R.K., M.S., and O.O. performed the genetic analysis. H.F., K.G., and T.O. provided genetic counseling. T.O., the corresponding author of this case report, interpreted the results of the genetic analysis and reviewed and revised the manuscript.

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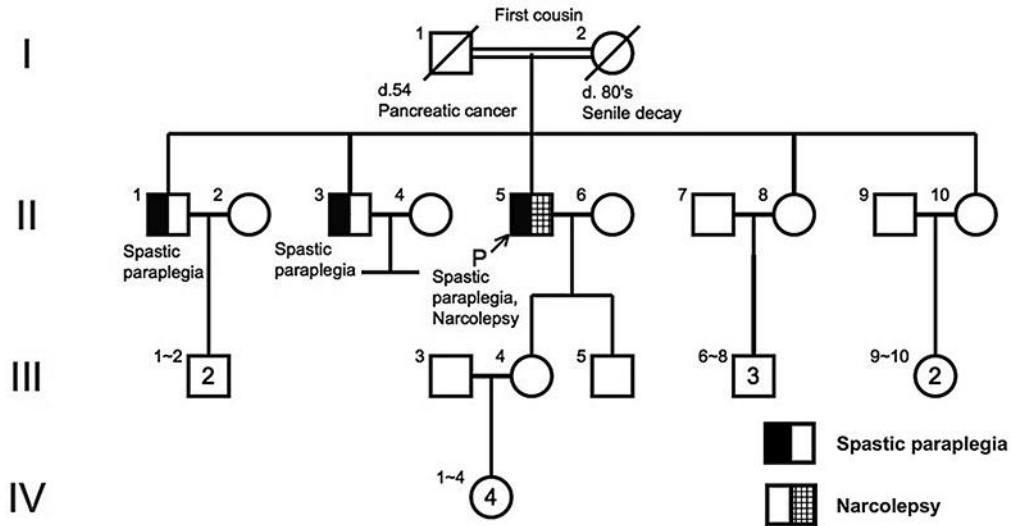


Fig. 1. Family tree of the patient. Square, man; circle, woman; diagonal black line, deceased; left side black-filled symbol, affected individual with spastic paraplegia; right side grid square symbol, affected individual with narcolepsy; empty symbol, unaffected individual; arrow with P, proband; double horizontal line, consanguineous marriage (first cousins).

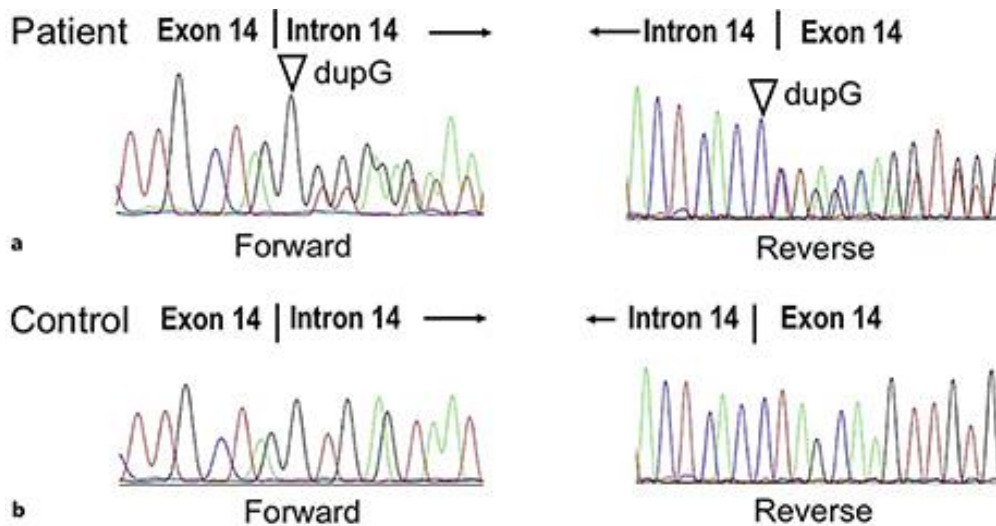


Fig. 2. Sanger sequencing results of the *SPAST* gene. Nucleotide sequences were read both from 5' to 3' direction (forward) and from 3' to 5' direction (reverse). **a** Electropherograms of the patient. A single nucleotide G (empty arrowhead) is duplicated in the donor splice site of exon 14-intron 14 boundary (NM_014946.3:c.1616+1dupG). **b** Electropherograms of the control.

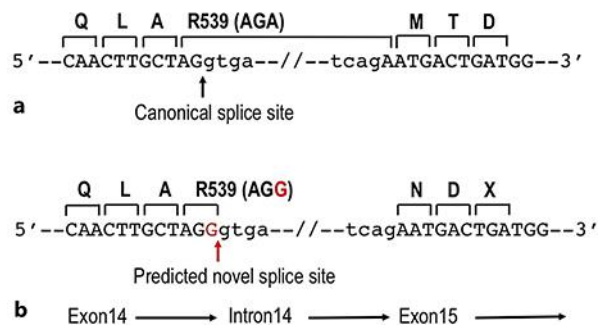


Fig. 3. Alteration of the splice site predicted by the two splice site prediction algorithms. **a** The black arrow indicates the canonical splice site. **b** The red arrow indicates the predicted novel splice site, which induces a premature stop codon (TGA) in exon 15.