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Case Report

Syringomyelia: A New Phenotype of *SPG11*-Related Hereditary Spastic Paraplegia?

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HIGHLIGHTS

- We present a case of hereditary spastic paraplegia (HSP) type 11 with biallelic pathogenic variants in *SPG11*.
- This case contributes to a rare imaging finding associated with HSP type 11.

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Conflict of Interest
The authors have no potential conflicts of interest to disclose.

ABSTRACT

Hereditary spastic paraplegia (HSP) refers to a group of neurodegenerative disorders affecting motor neurons in the central nervous system. HSP type 11 is the most frequent subtype of autosomal recessive HSPs. Caused by pathogenic variants in *SPG11*, HSP type 11 has a heterogeneous clinical presentation, including various degrees of cognitive dysfunction, spasticity and weakness predominantly in the lower extremities among other features. An 8-year-old boy visited our rehabilitation clinic with a chief complaint of intellectual impairment. Motor weakness was not apparent, but he exhibited a mild limping gait with physical signs of upper motor neuron involvement. Next generation sequencing revealed biallelic pathogenic variants, c.2163dupT and c.5866+1G>A in *SPG11*, inherited biparentally which was confirmed by Sanger sequencing. Brain imaging study showed thinning of corpus callosum, consistent with previous reports, however whole spine imaging study revealed extensive syringomyelia in his spinal cord, a rare finding in HSP type 11. Further studies are needed to determine whether this finding is a true phenotype associated with HSP type 11.

Keywords: Hereditary Spastic Paraplegia; Genetic Disorders; Syringomyelia

INTRODUCTION

Hereditary spastic paraplegia (HSP) is a heterogeneous group of neurodegenerative diseases, both genetically and clinically, affecting motor neurons. More than 80 genes causative of HSP have been described to date, with all patterns of Mendelian inheritance reported [1,2]. The only symptom common to all forms of HSP is spasticity and weakness of the lower limbs. Clinically, HSPs have been classified into pure (or uncomplicated) or complex (or complicated) forms [3]. Signs of upper motor neuron impairment alone, clinically presenting as spasticity, weakness, and hyperreflexia predominantly in the lower limbs, are categorized as pure. Complex or complicated forms are characterized by additional neurological signs, such as ataxia, intellectual disability, cognitive impairment, extrapyramidal disturbance, and peripheral neuropathy among others [4].

While autosomal dominant HSP is the predominant form of the disorder, autosomal recessive HSPs are most frequently associated with complex forms. HSP arising from *SPG11*

Author Contributions

Conceptualization: Jang DH; Data curation: Kim GH, Jang DH; Formal analysis: Kim GH, Song T, Lee J; Investigation: Kim GH, Song T, Lee J; Supervision: Jang DH; Writing - original draft: Kim GH; Writing - review & editing: Kim GH, Jang DH.

variants represents the most common subtype of autosomal recessive types, accounting for approximately 20% of autosomal recessive HSP patients [5]. Located on chromosome 15q21.1, *SPG11* encodes the spatacsin protein which is extensively expressed in the central nervous system, especially in cortical and spinal motor neurons. This protein, required for axonal growth, development, and intracellular transport, is thought to have a major impact on neuronal viability [6]. Pathogenic variants of *SPG11* are often linked to complex forms of HSP, with various phenotypes from involvement of both upper and lower motor neurons. In most cases, the associated phenotype comprises a combination of cognitive deterioration, progressive spastic gait accompanied by weakness of the limbs, peripheral neuropathy, with typically a thin corpus callosum seen on brain magnetic resonance imaging (MRI) [4]. Onset usually occurs during infancy or adolescence, and the disease progresses rapidly, often leaving patients wheelchair-bound within one to 2 decades of its onset.

Although the broad clinical spectrum makes diagnosis difficult, given the clinical presentation, these patients are often studied with MRI imaging to detect disorders affecting the brain. In 90% of HSP type 11 patients, a thin corpus callosum (TCC) is apparent on brain imaging, and this sign has come to serve as a characteristic abnormality for this disorder [7]. However, abnormalities of the spinal cord have rarely been reported in association with HSP type 11. Herein, we describe a patient diagnosed with HSP type 11 via targeted next-generation sequencing, with a rarely seen radiological presentation in the spinal cord.

CASE DESCRIPTION

An 8-year-old boy with intellectual impairment was referred to a rehabilitation clinic. He was born via spontaneous vaginal delivery at 38 weeks of gestation with a birth weight of 3,160 g (70th percentile). There were no perinatal complications, and his family history was non-contributory. At birth, his eyesight and hearing were determined to be within normal ranges. At time of referral, the patient's height was 140 cm (97th percentile) and his body weight was 45 kg (99th percentile). His parents reported that he showed no particular developmental problems until age four, after which his cognitive development seemed to lag.

The patient presented with attention deficit and cognitive function impairment. Upon physical examination, he had a mild limping gait, and while he showed no apparent motor weakness, he had bilaterally increased knee jerk reflexes with an ankle clonus of 2–3 Hz. Speech and language evaluations were performed. His Preschool Receptive-Expressive Language Scale (PRES) scores revealed receptive language skills of 5.5 years and expressive language skills of 4 years. His Receptive & Expressive Vocabulary Test (REVT) results revealed receptive vocabulary of below 7 years (< 10th percentile, −2 SD to −1 SD) and expressive vocabulary of below 5 years (< 10th percentile, below −2 SD). Using the Korean Wechsler Intelligence Scale-IV, he was determined to have a borderline intellectual functioning level, with a Full-Scale Intelligence Quotient (FSIQ) of 74.

To rule out mitochondrial dysfunction and metabolic disorders, laboratory tests were performed and revealed results within normal ranges. Due to a suspected central nervous system pathology, electroencephalogram, brain and whole-spine MRI were performed. His electroencephalogram showed normal results, while brain MRI revealed a hypoplastic genu of his corpus callosum with no other definite parenchymal abnormalities (**Fig. 1**). Notably, whole-spine MRI revealed diffuse extensive syringomyelia in the thoracic and lumbar levels of his spinal cord (**Fig. 2**).

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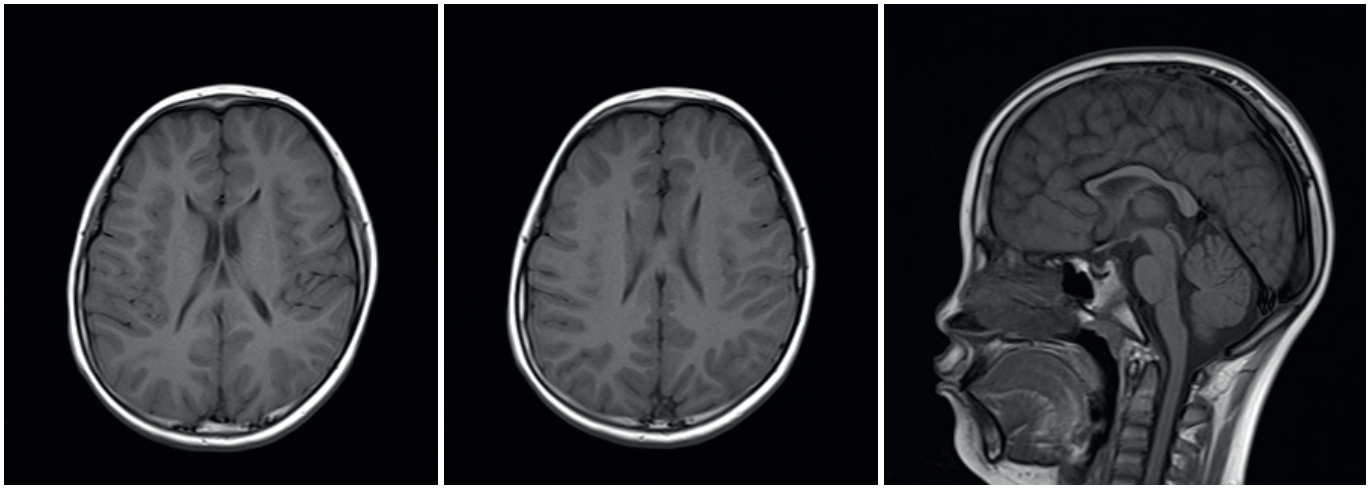

Fig. 1. Axial and sagittal T1-weighted magnetic resonance imaging shows hypoplastic genu of the corpus callosum. No other abnormalities were noted.

Chromosomal study revealed a karyotype of 46, XY without anomalies. No significant microdeletion or duplication was detected on the chromosomal microarray test. Next generation sequencing (NGS) analysis of a multigene panel consisting of 985 genes related to delayed development was performed. Genomic DNA was extracted from peripheral blood. Libraries were prepared with the Truseq DNA kit (Illumina Inc., San Diego, CA, USA), and sequencing was performed using the Illumina™ Nextseq platform. After demultiplexing, the reads were aligned to the human reference genome hg19 using the Burrows-Wheeler Aligner (BWA) algorithm. Duplicate reads were then removed, and the variants were called by haplotype caller of GATK.

NGS test revealed two heterozygous variants in *SPG11* (NM_025137.3): a frameshift variant in exon 11 (c.2163dupT) and an intronic variant in intron 30 (c.5866+1G>A), which were validated by Sanger sequencing. The variant c.5866+1G>A is expected to cause aberrant splicing, leading to truncated protein synthesis. Family gene analysis revealed that his parents were heterozygous carriers of each variant. The c.2163dupT variant was inherited from the mother, while the c.5866+1G>A variant was inherited from the father (**Fig. 3**).

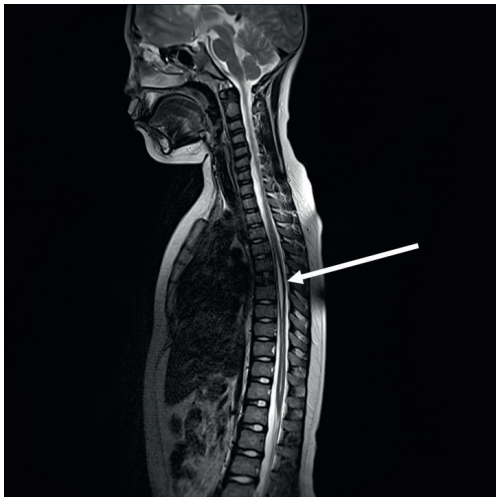

Fig. 2. Whole-spine magnetic resonance imaging of the patient, showing syringomyelia in the thoracic and lumbar levels of the spinal cord (marked by an arrow).

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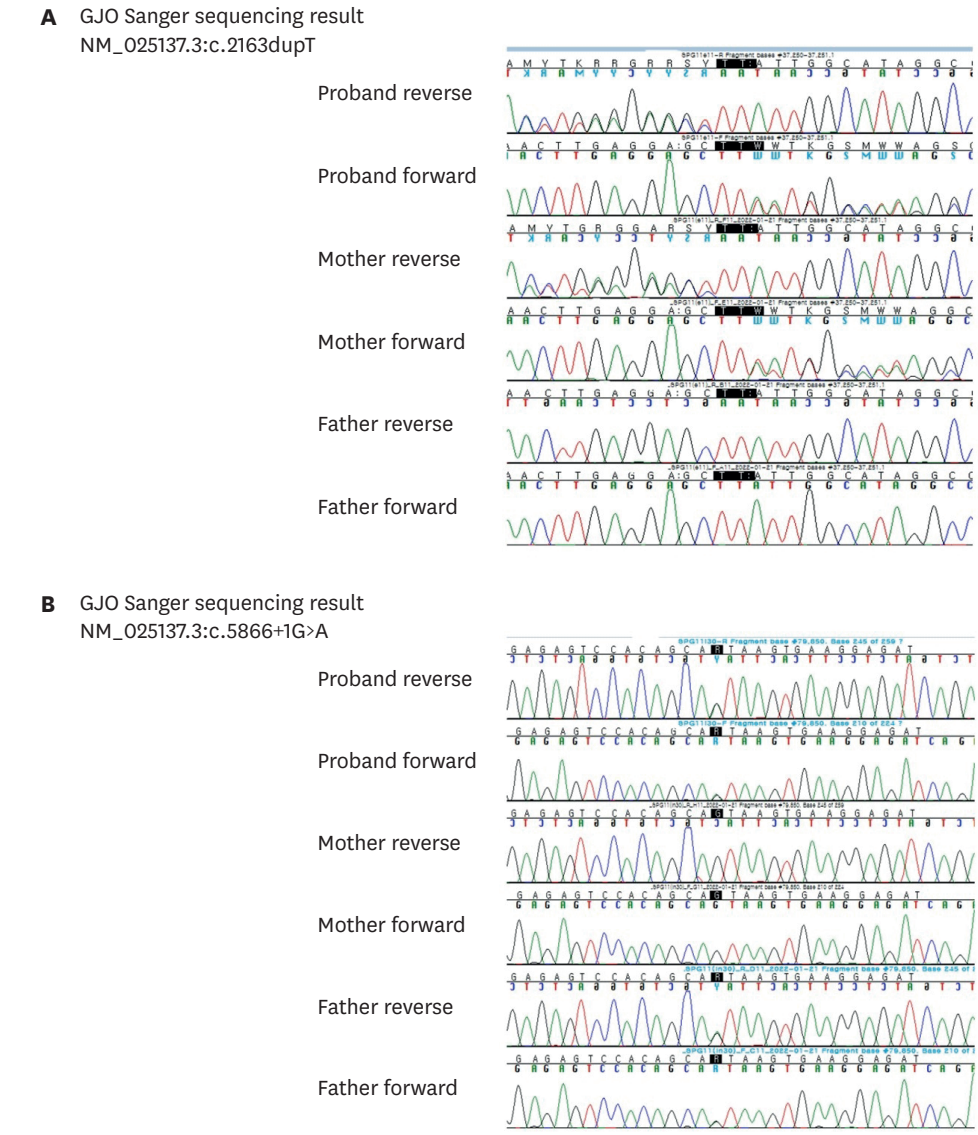

Fig. 3. DNA sequence chromatography of the patient and his parents. (A) c.2163dupT. (B) c.5866+1G>A.

The variant c.2163dupT was classified as pathogenic and the c.5866+1G>A variant as likely pathogenic by American College of Medical Genetics and Genomics (ACMG) Classification Standards and Guidelines for Genetic Variations [8]. Both variants have previously been reported in association with HSP type 11 [9-11]. Finally, the patient was diagnosed with HSP type 11 caused by biallelic pathogenic variants of *SPG11*, inherited biparentally.

This study was reviewed and approved by the Institutional Review Board (IRB) of Incheon St. Mary's Hospital, Catholic University of Korea (OC23ZISI0015). Informed consent was waived by the board.

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DISCUSSION

We have reported a patient with biallelic pathogenic variants, c.2163dupT and c.5866+1G>A in *SPG11* diagnosed with HSP type 11 with an atypical phenotype. He showed marked delays in language and cognitive function, along with mild gait impairment and physical signs of upper motor neuron involvement. Brain MRI revealed a hypoplastic corpus callosum. Although these features were generally consistent with the known phenotype of HSP type 11, an interesting feature in this patient was the presence of syringomyelia.

SPG11, located on 15q21.1 comprising 40 exons and spanning a genomic region of approximately 100 kb, is predicted to encode the spatacsin protein. Spatacsin is widely expressed in the nervous system, most prominently in the cerebellum, cerebral cortex, hippocampus, and pineal gland [12,13]. Specifically, the spatacsin protein is involved in lysosome recycling and clearance of gangliosides, and loss of function leads to ganglioside accumulation and neurodegeneration [14,15]. Over 180 types of pathogenic variants in *SPG11* have been reported thus far: missense, frameshift such as small insertions or deletions, splice site variants, and genomic deletions [7]. The variants result in premature termination of spatacsin protein, confirming a loss of function mechanism.

HSP from *SPG11* variants mostly present with a complex phenotype. Complex forms generally start earlier compared to pure forms, with diagnosis most often made in the second decade of life [16]. Oftentimes, the disorder manifests itself as subtle neurodevelopmental deficits in childhood, encompassing a wide range of symptoms from mild learning difficulties to severe intellectual impairments [17]. Due to the broad range of phenotypes, many patients miss diagnosis throughout early childhood when motor symptoms are subtle or are not yet present. Our patient showed uneventful development until age 4 after which cognitive development started to lag, and even at age 8, cognitive and language impairments were far more pronounced than motor symptoms.

A few studies have reported on genotype-phenotype correlations [5,7,16]. According to the German cohort of 608 patients published by Schule et al. [16], complicating symptoms of cognitive impairment (100%), dysarthria (> 70%), ataxia (up to 60%), peripheral motor and/or sensory involvement (> 30%), and dysphagia (20%) were reported. Du gathered data from 339 HSP type 11 patients originating from various European, African, East Asian, North and South American countries, and performed a systematic re-analysis [7]. Most presented with complicated forms (288/302, 95%). Frequent initial symptoms included gait disturbance (107/195, 55%), mental retardation (47/195, 24%) illustrated as learning difficulties in childhood, dysarthria (134/195, 69%), neuropathy (63%), sphincter disturbance (60/130, 46%), and ataxia (90/194, 46%). Du also reported on brain imaging abnormalities found in these patients: thinning of the corpus callosum (TCC) (173/190, 91%), followed by periventricular white matter changes (130/158, 82%). The most recent meta-analysis reported similar imaging findings: TCC (101/114, 89%) followed by white matter abnormalities (85/116, 73%) [5]. Mean age of onset of *SPG11*-HSP was 13.10 years [5,7]. Other than cognitive and language impairments including dysarthria, our patient exhibited no other definite abnormalities such as ataxia or peripheral nerve involvements.

In addition to lower limb spasticity, our patient exhibited HSP type 11-appropriate clinical features including intellectual disability, language impairment, mild gait disturbance with hypoplastic corpus callosum on brain MRI, however spine imaging study showed

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syringomyelia in his spinal cord. Syringomyelia is defined as the presence of abnormal, cerebrospinal fluid (CSF)-filled cavities within the spinal cord. Most syringomyelia cavities develop as the result of other anatomical abnormalities or lesions where normal flow of CSF around the lower brainstem or spinal cord is disturbed, such as Chiari malformations, spinal injury, spinal cord tumors, or tethered cord syndrome [18]. However in this patient, no other lesion that would seemingly disrupt the flow of CSF was observed in imaging studies which would explain the presence of syringomyelia.

To our knowledge, there has only been one previous report of syringomyelia associated with *SPG11*. In 2020, Kim et al. [19] reported a 36-year-old female patient with progressive weakness in the lower limbs for 10 years. She reported no other symptoms, such as dysarthria, cognitive impairment, or urinary sphincter problems. Her past medical and family history were non-specific. She was previously diagnosed with borderline Chiari 1 malformation and underwent decompression surgery, but her symptoms did not improve. Upon further examination, her spine MRI revealed syringomyelia along the thoracic spinal cord, and targeted gene panel sequencing revealed 2 heterozygous variants of *SPG11* (c.5410_5411delTG and c.5866+1G>A). The latter variant is shared by our case patient. Similar to our patient, this previously reported patient also did not report pain, sensory abnormalities, or bladder and bowel symptoms that may be related to syringomyelia. Syringomyelia has previously been found in a patient with *SPG56*-HSP [20], however other cases of *SPG11*-HSP sharing the same c.5866+1G>A variant do not seem to exhibit syringomyelia [9,21]. Due to the small number of patients, further studies are needed to identify whether syringomyelia is a true phenotype associated with this variant.

Syringomyelia has been reported in association with other neurodegenerative diseases of the central nervous system. Non-communicating syringomyelia has been described in various reports of patients with multiple sclerosis (MS) [22,23]. Authors of one study including nine MS patients with syringomyelia concluded that syringomyelia was not a coincidental finding but likely associated with MS pathophysiology, considering the low prevalence of syringomyelia in the normal population [24]. Syringomyelia was also recently reported in patients with amyotrophic lateral sclerosis (ALS) [25,26], while a study using MRI data to study CSF dynamics revealed different CSF hydrodynamics in ALS patients compared to healthy controls [27]. The mechanism behind syrinx formation in these patients is uncertain at this point, but drawing these findings together, one could hypothesize that the neurodegenerative change in nerve tissue might alter normal CSF drainage from the central canal. It is possible to draw parallels to HSP type 11 patients, especially in light of a recent neuropathological study in which brain and spinal cord autopsies were done on HSP type 11 patients [28]. The study confirmed cortical atrophy and demyelination of the pyramidal pathways and loss of motor neurons in medulla oblongata and anterior horns of the spinal cord, reminiscent of findings already observed in ALS. Taken together, there is a possibility that syringomyelia may be part of the phenotype in HSP type 11.

We reported a case of HSP type 11 resulting from biallelic pathogenic variants of *SPG11* inherited biparentally. This case was distinguished from those previously reported in that the patient had extensive syringomyelia in his spinal cord, a finding which has only been associated with the disorder once before. Because diagnosis of HSP type 11 is difficult to suspect clinically, especially at an early age when cognitive symptoms may be predominant, it would be important to gather clues from other perspectives when available. In addition to the typical brain imaging findings showing a thin corpus callosum, if more radiological

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signs were reported in association, it would help to suspect a genetic disorder and guide the diagnostic process in the right direction. Further studies are warranted to determine whether this finding is a true phenotype associated with HSP type 11 at this point.

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