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SPG4 유전자 변이에 의한 유전경직하반신마비를 보인 가족 1예

서울보훈병원 신경과

조정선 · 김두응 · 김정미 · 한영수 · 하상원 · 박상은 · 한정호 · 조은경

One Family with Hereditary Spastic Paraplegia due to SPG4 Gene Mutation

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Strümpell, in 1880, was the first to describe familial case of spastic paraplegia characterized by progressive weakness and spasticity of the lower limbs with little or no involvement of the upper extremities. This syndrome is heterogeneous in inheritance, age of onset, severity and associated signs. We present one family with autosomal dominant hereditary spastic paraplegia (HSP) due to SPG4 (spastin) gene mutation which is confirmed by genomic DNA isolated from peripheral blood.

Key Words: Hereditary spastic paraplegia (HSP), SPG4 (spastin)

Hereditary spastic paraplegia comprises a heterogeneous group of disorders characterized by progressive weakness and spasticity of the lower limbs with little or no involvement of the upper extremities. This is often accompanied by urinary urgency and subtle impairment of the vibratory sense. HSP has been classified traditionally as 'pure' or 'complicated'. Depending on whether spastic paraplegia is the only symptom or whether it is found in association with other neurological abnormalities, such as optic neuropathy, retinopathy, extrapyramidal symptoms, dementia, ataxia, mental retardation and deafness.[2] We recently confirmed one family with autosomal dominant pure hereditary spastic paraplegia with SPG4 gene mutation which was verified by genomic DNA isolated from peripheral blood.

Case report

A 21-years old male was admitted to our hospital because of the gait disturbance. He was born a normal baby. He walked at a normal age, but on his toes. He repeated fall and walked slower than other children. His gait was deteriorated in his high school days. After his high school days, he walked with dragging feet. On neurologic examination, both upper limbs exhibited no weakness. The deep tendon reflexes were hyperreflexia in both upper limbs. The Hoffmann sign was not presented. Both lower limbs represented with weakness, grade IV+ by manual muscle testing, and hyperreflexia. The ankle clonus was expressed in both sides. Babinski sign or extensor plantar response was not presented. No sensory disturbances were found. The muscle bulks of all extremities were intact. Korean version Mini-Mental State Examination score was 30/30. Brain MRI view demonstrated no abnormal focal lesion

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in whole brain parenchyma except 6.8 mm incidental intraventricular nodular lesion on the anteromedial wall of left lateral ventricle. In neuroelectrophysiologic study test, there was no definite electrophysiological evidence of motor neuron disease, peripheral neuropathy or myopathy.

In family history (Fig. 1), his mother and his younger sister also had gait disturbance. His mother had one brother and five sisters. His mother was the only one person with gait difficulty in her family. She walked at a normal age, but repeated fall. At 35-years old, her gait was deteriorated. She dragged his feet but walked by herself. At that time, she visited hospital. Muscle biopsy and EMG were done. The reason for her gait deficiency was not founded. At 43-years old, she walked with stick. In these days, she could not leave far from the house. But she had no difficulties in both upper limbs' movements.

His younger sister is 19 years old. She was born normally. She was grown up without abnormalities. From the elementary school days, she walked slower than other children and slightly dragged her feet. Until a recent date, she dragged her feet but she walked without other help. But she used her upper extremities without difficulties.

We suspected familial autosomal transmitted disease with progressive lower limbs weakness. So, all of the patient's families had been taken peripheral blood test to look for the gene mutation. We confirmed autosomal dominant hereditary paraplegia with SPG4 gene mutation by genomic DNA isolated from peripheral blood.

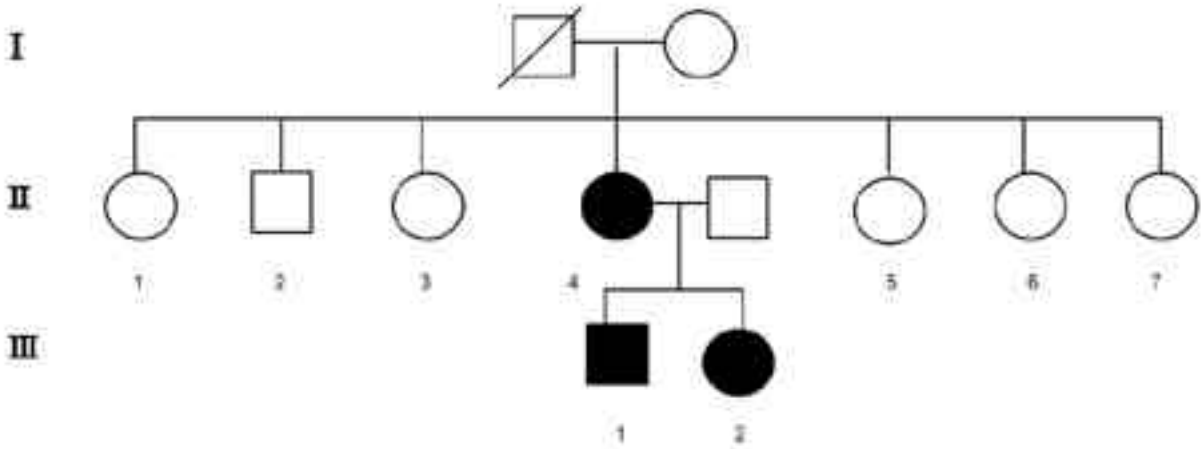

Figure 1. Pedigree of family. Filled symbols indicate affected members. Slanted line indicates deceased members. II-4: patient's mother, III-1: patient, III-2: patient's sister.

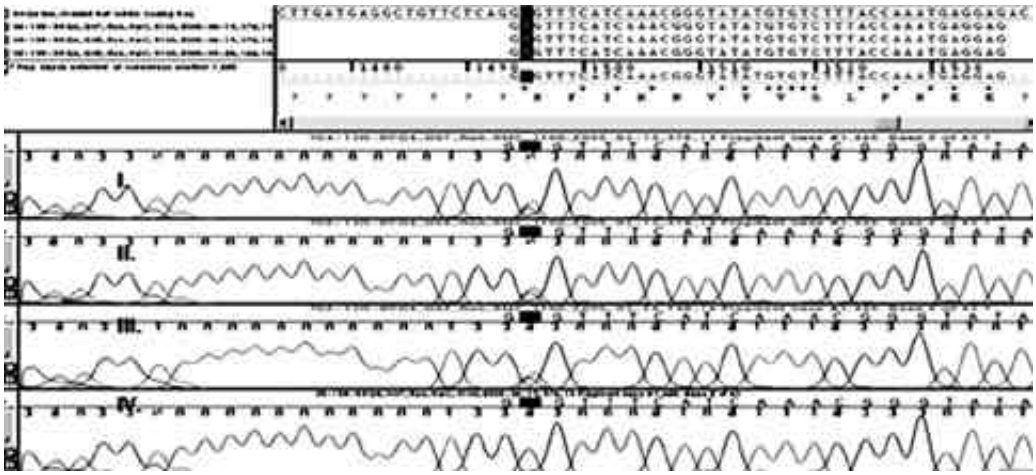

Figure 2. Genomic DNA isolated from the peripheral blood. SPG4 Gene on Chromosome 2p22-p21 point mutation was identified; the black line indicates Arg499Cys mutation. Line I: DNA isolation of patient, Line II: DNA isolation of patient's sister, Line III: DNA isolation of patient's mother, Line IV: DNA isolation of patient's father.

Discussion

The HSP is heterogeneous disorders in which the predominant clinical feature is gait disturbance due to lower extremities spasticity and weakness.

Diagnosis of HSP is made by the presence of (1) typical symptoms of gait disturbance (which range from childhood onset, essentially non-progressive spastic diplegia, to childhood-through-adult onset of insidiously progressive spastic weakness in the legs), which are often associated with urinary urgency; (2) neurologic findings of corticospinal tract deficits (spasticity, weakness, hyperreflexia, extensor plantar responses) that are limited to lower extremities (note, upper extremity reflexes may be brisk but not pathologically and muscle tone in the arms is normal) (3) family history of similar disorder that conforms to inheritance of an X-linked, autosomal dominant , or autosomal recessive disorder, and (4) careful exclusion of alternate disorders including multiple sclerosis, leukodystrophy, structural abnormalities involving the brain or spinal cord, and dopa-responsive dystonia.[2]

The degree of severity and manner of progression are often quite variable between different genetic type of HSP, and between affected subjects from the same family who share exactly the same HSP gene mutation. Presently, genetic loci (designated SPG1 through SPG28) have been identified for 10 autosomal dominant, 12 autosomal recessive, and 3 X-linked types of HSP (designations SPG18, SPG 22 and SPG 24 have been reserved for as yet unpublished loci).[3] The SPG4 HSP is the single most common cause of dominantly inherited HSP, representing approximately 40% of such cases.

Neuropathologic studies show that HSP involves axonal degeneration of selected motor (corticospinal tracts) and sensory (dorsal column fibers) within the spinal cord. Axonal degeneration is particular prominent in the distal aspects of these fibers. Anterior horn cells are generally preserved in uncomplicated HSP.[4]

In this case, a 21-years old male was admitted to our hospital because of slowly progressive gait disturbance from his childhood. His lower limbs presented spasticity and weakness, grade IV+. He had no sensory loss. He had no cognitive impairment and urinary urgency. His mother and sister also presented lower extremities spasticity and weakness without cognitive impairment. We suspected uncomplicated familial autosomal transmitted disease with progressive lower limbs weakness. From peripheral blood test for SPG gene, we confirmed autosomal dominant hereditary paraplegia with SPG4 gene mutation on Chromosome 2p22-p21 with point Arg499Cys mutation (Fig. 2).

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