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A Novel c.4822>T Mutation on SPG11 in an Iranian Patient Marked by Hereditary Spastic Paraparesis and Skeletal Deformity: An Incidental Finding or a True Association

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ABSTRACT

Hereditary spastic paraplegias are highly heterogeneous neurodegenerative disorders with some special mutations. We report on a patient with pescavus, distal a myotrophy, hyper extended fingers, and pectus excavatum. Neurological examination showed that he had proximal lower limbs weakness with a positive Gower sign, exaggerated lower limbs deep tendon reflexes with spasticity, distal muscle was ting, bilateral horizontal nystagmus (direction change), and positive Romberg sign. A novel mutation in SPG11/spatacsin was detected through genetic analysis. Magnetic resonance imaging showed normal whole spine and brain anatomy.

Keywords: Spastic Paraplegia, Hereditary; Genotype; Mutation

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Introduction

Hereditary spastic paraplegias (HSPs) are highly heterogeneous neurodegenerative disorder distinguished by progressive spasticity and weakness of the lower limbs. The key symptoms of spastic paraparesis of the lower

limbs include cognitive decline, optic atrophy, cerebellar ataxia, peripheral neuropathy, and seizure. The most common mutations for pure autosomal recessive HSP are SPG7 and SPG5mutations. Mental deterioration and thin corpus callosumrevealed bymagnetic resonance imaging are indicative of SPG11 and SPG15 mutations.

Case Presentation

A 31-year-old male who suffered from insidious progressive lower limbs weakness from the age of 7, disequilibrium, and early fatigability for a period of a year was admitted. He was otherwise healthy. One of his brothers died during childhood because of a seizure without any specific diagnosis. His parents had a consanguineous marriage. General examination showed that the patient suffered from pescavus, distal amyotrophy, hyper-extended fingers, and pectus excavatum. A neurological examination indicated that he had proximal lower limb weakness with positive Gower sign, exaggerated lower limb deep tendon reflexes with spasticity, distal muscle wasting, bilateral horizontal nystagmus (direction change), and positive Romberg sign.

Neuro imaging (brain and whole spinal MRI) was normal. Electrophysiological testing of peripheral nerves and an electroencephalogram (EEG) was normal. Laboratory tests indicated that his vasculitis profile, serum B12, vitamin E, and folate levels were normal. The enzyme-linked immune-sorbent assay for human T-cell lymphotropic virus types I was also negative.

Genetic consultation and testing was performed: SPG/spatacsin mutation analysis for hereditary spastic paraplegia genes by the NGS method was conducted for the following genes: CYP7B1, SPG7, SPG11, ZFYVE26, SPG20, SPG21,L1CAM,PLP1,SLC16A2,ATL1,SPAST, N1PA1, KIAA0196, KIF5A, HSPD1, BSCL2, REEP1, and ZFYVE27.

Using a Targeted Next Generation Sequencing method, we detected one heterozygous variant, c.4822>T(p.Leu1608Phe), on the SPG11 gene of sample 14D1171535. This variant had not been reported in literature, and thus, its clinical significance was unknown. The frequency is 0 in both the 1000 genomes and BGIs database. Bio informatic analysis indicated that the variant is predicted to be tolerated by the Sorting Intolerant From Tolerant (SIFT) method and is probably damaged by polyphen. The SPG11 gene is associated with spastic paraplegia11, which is autosomal and recessive. Segregation and functional study of the variant c.4822C>T(p.Leu1608Phe) on the SPG11 gene has been proposed for our patient.

The patient had two healthy brothers. Both of them were examined, and mutation analysis of that specific mutation was performed, so it was clear that it was an incidental finding andc.4822>T(p.Leu1608Phe) on the SPG11 gene was not etiology of spastic paraparesis and skeletal deformities in our patient.

Discussion

SPG11 is presumably the most common type of autosomal recessive HSP and accounts for 20% of cases (1,2). SPG11 typically manifests in the first three decades of life. Spastic paraplegia is frequently accompanied by progressive cognitive deficits (80%), dysarthria (80%), and atrophy of thenar and hypothenar muscles (50%) (3). Cerebellar signs may occur later in the

disease course. The mean progression rate is higher in SPG11 than in nonSPG11 HSP, leading to earlier requirement of a wheelchair (4,5). A thin corpus callosum is the MRI hallmark of SPG11, often accompanied by white matter alterations and cortical atrophy. Sensory motor peripheral neuropathy (axonal type) is common (3). If the typical phenotype, a particularly thin corpus callosum, and cognitive problems are present, SPG11 is present in 59% of autosomal recessive or apparently sporadic HSP patients (6). This case presented clinical signs of spastic paraplegia, but we could not prove a diagnosis of HSP in the genetic study. Note that another clue in this case is the absence of mental retardation and brain imaging findings consistent with typical SPG11 mutation. In autosomal recessive juvenile amyotrophic lateral sclerosis (ALS) long-term survivors, fulfilling the revised El Escorial criteria for the diagnosis of ALS, Orlacchio *et al.* recognized SPG11 mutations in 40% (11/25) of cases. None of the affected had the cognitive impairment or MRI abnormalities typical for SPG11 (3,6). Parkinsonism might be the first presenting symptom in SPG11 (7). Although in all reported cases, a thin corpus callosum was present in the images obtained from the MRI and Parkinsonis msymptoms were followed by lower limb spasticity within a few years of disease onset (3).

Conclusion

In this case, we detected a novel variant mutation on the SPG11/spatacsin gene, but we proved that this mutation on this locus was an incidental finding.

Conflict of Interest

Authors have no conflict of interest.

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