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Case Report

First SPG48 case report in India with a novel mutation

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ABSTRACT

The hereditary spastic paraplegias (HSP) are a large group of inherited neurologic disorders that share the primary symptom of difficulty in walking due to weakness and spasticity in the lower limbs. Spastic paraplegia-48 (SPG48) is an autosomal recessive neurologic disorder characterized by spasticity of the lower limbs resulting in gait difficulties. Biallelic mutations in AP5Z1 are known to cause this complex form of hereditary spastic paraplegia (HSP) referred to as SPG48 (MIM#613647). Most patients have onset in mid- or late-adulthood, although childhood onset has been reported in 1 patient. Additional features may include parkinsonism, urinary incontinence, neuropathy, and mild cognitive impairment. We report a 49-year-old male with SPG48 with a novel mutation. This is the first SPG48 case report in an Indian patient and to the best of our knowledge this mutation is the first to be reported worldwide.

1. Introduction

The hereditary spastic paraplegias (HSP) are a large group of inherited neurologic disorders that share the primary symptom of difficulty in walking due to weakness and spasticity in the lower limbs.[1] Various types of HSP are classified according to a) the mode of inheritance (dominant, recessive, X-linked, maternal); b) the gene in which the mutation occurs; and c) the clinical syndrome (pattern of symptoms and neurologic findings). There are more than 80 genetic types of HSP. The chromosome locations ("loci") of HSP genes are designated "SPastic parapleGia, loci ("SPG") and numbered in order of their discovery (for example, SPG1 through SPG80).[1]

Spastic paraplegia-48 (SPG48) is an autosomal recessive neurologic disorder characterized by spasticity of the lower limbs resulting in gait difficulties. Biallelic mutations in AP5Z1 are known to cause this complex form of hereditary spastic paraplegia (HSP) referred to as SPG48 (MIM#613647). Most patients have onset in mid- or late-adulthood, although childhood onset has been reported in 1 patient. Additional features may include parkinsonism, urinary incontinence, neuropathy, and mild cognitive impairment.[2]

Adaptor proteins (AP 1–5) are ubiquitously expressed protein complexes that facilitate vesicle-mediated intracellular sorting and trafficking of selected transmembrane cargo proteins (1). AP-5 has been shown to associate in a stable complex with two other proteins, spatacsin (SPG11) and spastizin (SPG15). In patients with hereditary spastic paraplegia, mutations in SPG11, SPG15 and SPG48 (AP5Z1) have been seen and described. SPG48 patients have some clinical features similar to those of SPG11 or SPG15 patients, including spastic paraplegia, retinal abnormalities and parkinsonism, but the clinical spectrum of AP5Z1 patients is still being defined.[3]

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We report a 49-year-old male with SPG48 with a novel mutation. This is the first SPG48 case report in an Indian patient and to the best of our knowledge this mutation is the first to be reported worldwide.

2. Case History

A 49-year-old male patient presented for evaluation after he developed difficulty in walking as well as standing along with parasthesias in both legs since last 3 years. This gradually worsened to the point where he started walking with support. There is no evidence of any family history.

On examination, the patient exhibited prominent lower extremity spasticity with weak plantar flexion bilaterally. Deep tendon reflexes showed brisk in the upper limbs, brisk knee reflex and absent ankle reflex. Sensory examination revealed reduced vibration sense in bilateral feet distally. Otherwise, position sense, touch and pain/ temperature were normal.

NCS was performed which showed absent CMAPs in bilateral tibial nerves and rest of the findings were normal. MRI of Brain was normal. MRI of spine did not show anything significant. His Whole Genome Sequencing detected a heterozygous missense variation in exon 17 of the AP5Z1 gene.

3. Discussion

Hereditary spastic paraplegias (HSP) are a group of heterogeneous neurodegenerative disorders with an estimated prevalence of 3–10/100,000 in most populations.[3] They are characterized by an insidiously progressive weakness and spasticity of the lower extremities as their core defining clinical features.

They can present as pure or complex forms with all classical modes of monogenic inheritance reported. HSP syndromes are classified as "uncomplicated" when symptoms are confined to leg weakness and spasticity and urinary urgency.[1] HSP syndromes are classified as "complicated" when leg weakness and spasticity are accompanied by other neurologic and non-neurological manifestations such intellectual impairment, cerebellar signs, amyotrophy, peripheral neuropathy, optic atrophy, cognitive decline, deafness, retinopathy or cataract.[1,4–6] Herein, we report a case of complicated HSP, as the patient presented with spasticity along with other manifestations such as neuropathy.

SPG48 is a neurologic disorder characterized by spasticity of the lower limbs resulting in gait difficulties. The reported patient had gait difficulties along with spasticity of lower limbs. Most patients have onset in mid- or late-adulthood, although childhood onset has been reported in 1 patient.[2] The symptoms started in his late middle age for the patient. Additional features may include parkinsonism, urinary incontinence, neuropathy, and mild cognitive impairment. Hirst et al. (2015) stated that one of the patients reported by Slabicki et al. (2010) had neuropathy. Patient had diminished ankle reflex and reduced vibration sense in bilateral feet distally. NCS of the patient showed predominantly motor axonal neuropathy. Rest of the features were not present in the patient.

MRI of Brain shows clinical variability in the patients with SPG48. Slabicki et al. (2010) reported 2 French sibs with progressive spastic paraplegia, where one had normal cerebral MRI, whereas the other had spinal hyperintensities in the cervical spine. Pensato et al. (2014) reported a 51-year-old woman, whose Brain MRI showed severe thin corpus callosum and mild white matter hyperintensities at the frontal horns of the lateral ventricles.[2] The reported patient's MRI Brain showed no abnormality in the brain parenchyma.

To date, there are more than 100 loci/88 spastic paraplegia genes (SPG) involved in the pathogenesis of HSP. New patterns of inheritance are being increasingly identified in this era of huge advances in genetic and functional studies. Biallelic mutations in AP5Z1 are known to cause a rare, autosomal-recessive, complex form of hereditary spastic paraplegia (HSP) referred to as SPG48 (MIM#613647).[3] Autosomal recessive spastic paraplegia-48 (SPG48) is caused by homozygous or compound heterozygous mutation in the AP5Z1 gene (613653) on chromosome 7p22. Until now, SPG48 cases have not been reported in India and hence, this might be the first case report.

According to an extended analysis of all SPG48 patients by Breza et al. (2021), 21 AP5Z1 variants (SPG48) from 18 families have been identified in the literature.[7] Some examples include Slabicki et al. (2010) who identified a homozygous truncating mutation in 2 affected French sibs (613653.0001). Another patient with sporadic disease was heterozygous for another truncating mutation (613653.0002). In a 51-year-old woman with adult-onset SPG48, Pensato et al. (2014) identified compound heterozygous truncating mutations in the AP5Z1 gene (W441X, 613653.0003 and R138X, 613653.0004). A 7-year-old boy with early-onset SPG48 was homozygous for a missense mutation (R206W; 613653.0005). In a man with adult-onset SPG48, Hirst et al. (2015) identified a homozygous truncating mutation in the AP5Z1 gene (Q578X; 613653.0006).[7] Whole Genome sequencing in the reported patient detected a new allelic variant- a heterozygous missense variation in exon 17 of the AP5Z1 gene (chr7:g.4791281G>A;Depth:201x) that results in the amino acid substitution of Methionine for Valine at codon 774 (p.Val774Met; ENST00000649063.2). To the best of our knowledge, this is a novel mutation and has not been reported anywhere in the world.

There are no specific treatments to prevent, slow, or reverse HSP. Symptomatic treatments used for spasticity,

such as muscle relaxants, are sometimes helpful. Regular physical therapy is important for muscle strength and to preserve range of motion. The prognosis for individuals with HSP varies. Some individuals are very disabled and others have only mild disability. The majority of individuals with uncomplicated HSP have a normal life expectancy. [8]

4. Conflict of Interest

The authors declare no relevant conflict of interest with respect to research, authorship and or publication of this article

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