Case Report

Spastic Paraplegia-56 due to a Novel CYP2U1 Truncating Mutation in an Indian Boy: A New Report and Literature Review

Indar K. Sharawat*, Prateek Kumar Panda*, Lesa Dawman1

Pediatric Neurology Division, Department of Pediatrics, All India Institute of Medical Sciences (AIIMS), Rishikesh, Uttarakhand, India, 1Department of Pediatrics, Post Graduate Institute of Medical Education and Research (PGIMER), Chandigarh, India

Spastic paraplegia-56 is a rare autosomal recessive disorder, caused by homozygous or compound heterozygous mutations in the CYP2U1 gene, located on chromosome 4. Till date, only 28 patients with this disorder have been reported in the literature. We report a new case of CYP2U1-related spastic paraplegia-56. We also reviewed previously published patients with this condition from various databases. Next-generation sequencing in the index child detected a novel homozygous two base pair deletion in exon 2 of the CYP2U1 gene that results in a frameshift and premature truncation of the protein 19 amino-acid downstream to codon 361. Together with the presented case, 29 were available for analysis. The mean age at the diagnosis was 17.84 ± 6.86 years. Intellectual disability/cognitive dysfunction and delayed walking or gait disturbance were the most common presenting features. Around half of the patients had neuroregression in between 1 and 2 years. It is clinically imperative to suspect this disease in children with early-onset spastic paraparesis, especially in cases accompanied by baseline development delay or cognitive impairment and consanguinity.

Keywords: CYP2U1 gene, hereditary spastic paraplegia, neurodegeneration, spasticity, SPG56

INTRODUCTION

Hereditary spastic paraplegias (HSP) are a heterogeneous group of genetically diverse neurological disorders, characterized by progressive spasticity and weakness of the lower limbs.[1] Pathologically retrograde axonal degeneration of the corticospinal tracts and posterior columns is often identified. Spastic paraplegia-56 (OMIM#615030) is one of the recently described HSPs, first reported in 2012 by Tesson et al.[2] It has autosomal recessive inheritance, caused by homozygous or compound heterozygous mutations in the CYP2U1 gene, located on chromosome 4. Only a few cases have been reported so far. Here we are reporting a 4-year-old Indian boy with spastic paraplegia-56 (SPG-56) caused by a novel mutation in the CYP2U1 gene. The study was approved from the institutional review board and informed consent was taken from the parents of the child.

CASE REPORT

A 4-year-old boy firstborn to third-degree consanguineous parents of north Indian origin presented with progressive spasticity of lower limbs and regression of acquired motor milestones from 1 year of age. The child had an uncomplicated antenatal and perinatal period and had no affected family members. He attained motor, adaptive, social, and language milestones appropriately till 1 year of age. Before the onset of illness, he was able to walk with one handheld, attained mature pincer grasp, used to wave bye-bye, and was able to speak two meaningful words. Initially, he developed gait instability, toe walking, and...
frequent falls during walking, without any diurnal fluctuation. By 2 years of age, he stopped walking and had significant difficulty in standing up independently, with a crouch at the knee. By that time, he had also developed tightness in bilateral lower limbs at the knee and ankle. Thereafter, the child continued to gain social and language milestones, but at a slower pace than his peers. While presenting to us at 4 years, he had a vocabulary of 10–20 words and was able to indicate bowel and bladder needs, although required assistance to complete these activities. He also had difficulty in performing tasks with upper limb requiring fine skills and slurring of speech. In lower limbs, he had Ashworth grade III spasticity, hyperreflexia, positive Babinski sign, and dynamic flexion contractures at ankles. In bilateral upper limbs, grade I spasticity, exaggerated deep tendon reflexes, along with spastic dysarthria was found. Anthropometry and physical examination were otherwise within normal limits. Magnetic resonance imaging (MRI) of the brain and spine were unremarkable. He did not have any favorable clinical response to a clinical trial of levodopa/carbidopa combination for 4 weeks, in an escalating dose of 1–5 mg/kg/day. Nerve conduction study was also normal. Next-generation sequencing detected a novel homozygous two base pair deletion in exon 2 of the CYP2U1 gene (c.1080_8081delTT [p.Leu361AlafsTer19]) that results in a frameshift and premature truncation of the protein 19 amino-acid downstream to codon 361. The in silico prediction of the variant was damaging by PolyPhen-2, SIFT, and MutationTaster2. A diagnosis of SPG-56 was concluded.

**Discussion**

A systematic literature search in PubMed and Google Scholar yielded a total of 29 cases (including the presented case). Clinical presentation and genetic/other investigation findings of reported cases are shown in Tables 1 and 2, respectively. Most of the cases presented with loss of acquired motor milestones, starting from 1 to 3 years of age. Initially, gait instability and frequent falls and later on progressive spasticity in bilateral lower limbs ultimately progressed to nonambulatory status followed by contractures in most of the children. A proportion of children also had baseline developmental delay, mild-to-moderate intellectual disability, variable spasticity and weakness of upper limb and truncal muscles, dystonia (often action induced), mild cerebellar signs, and evidence of subclinical axonal neuropathy in lower limbs. A rare proportion also showed some neuroimaging abnormalities, among which periventricular white matter hyperintensity in T2-weighed sequences has been the most commonly reported finding. Other less frequently documented findings include thinning of the corpus callosum, delayed myelination, white matter hypodensity in globus pallidus, dorsal hydromelia and mild atrophy of brain stem, and cerebellum. The majority of affected patients had consanguineous parents, with homozygous variants. Although around half of pathogenic variants reported in the CYP2U1 gene are protein-truncating variants including frameshift mutations caused by base-pair deletions and nonsense mutations, a considerable proportion also had missense and splice site variants. These pathogenic variants ultimately lead to a truncated protein or nonsense-mediated RNA decay, suggesting loss of function as the underlying mechanism of disease causation.

**Table 1: Demographic variables and clinical presentation of reported cases with spastic paraplegia 56 in the existing literature**

| Characteristics                                      | Distribution in reported cases (n = 29) |
|-------------------------------------------------------|----------------------------------------|
| Total no. of families reported over the world          | 18 (13 had homozygous and 5 had compound heterozygous variants) |
| Total no. of cases reported from India                | 3                                      |
| Age at diagnosis                                      | 17.84 ± 6.86 years                     |
| Median age at onset of symptoms                       | 1 year (IQR 1-3 years)                 |
| Presence OD developmental delay since birth           | 5(17%)                                 |
| Neuroregression between 9 months and 2 years         | 17(58%)                                |
| Predominant symptoms                                  |                                        |
| Delayed walking/unable to walk                        | 14(48%)                                |
| Unsteadiness/frequent falls and spastic gait          | 12(41%)                                |
| Vision impairment                                     | 4(13%) (adult onset)                   |
| Intellectual disability/cognitive impairment          | 17(58%)                                |
| Predominant clinical findings                         |                                        |
| Lower limb spasticity                                 | 29(100%)                               |
| Lower limb hyperreflexia and positive Babinski sign   | 29(100%)                               |
| Upper limb spasticity                                 | 13(44%)                                |
| Upper limb hyperreflexia                              | 19(65%)                                |
| Dysarthria                                            | 13(44%)                                |
| Dystonia                                              | 6(20%)                                 |
| Mild cerebellar signs                                 | 4(13%)                                 |
| Seizures                                              | 2(7%)                                  |
Table 2: Abnormalities in neuroimaging, genetic testing, and ophthalmic evaluation in the reported cases of spastic paraplegia 56

| Investigations                | Distribution of different findings in reported cases (n = 29) |
|-------------------------------|---------------------------------------------------------------|
| MRI brain                     |                                                               |
| White matter signal change    | 10(34%)                                                       |
| Thinning of the corpus callosum| 3(10%)                                                       |
| Globus pallidus hypointensity  | 3(10%)                                                       |
| Delayed myelination           | 2(7%)                                                        |
| Mild brain stem and cerebellar atrophy- | 1(3.5%)                                                  |
| Normal                        | 19(65%)                                                      |
| MRI spine                     |                                                               |
| Dorsal hydromyelia            | 1(3.5%)                                                      |
| Normal                        | 28(96.5%)                                                    |
| Nerve conduction study        |                                                               |
| Subclinical axonal neuropathy | 12(41%)                                                      |
| Normal study                  | 17(59%)                                                      |
| Fundus evaluation             |                                                               |
| Pigmentary degenerative       |                                                               |
| maculopathy                   | 4(13%)                                                       |
| Mutations (variants) reported | 23                                                            |
| Missense                      | 8/23(34.5%)                                                  |
| Nonsense                      | 4/23(17.5%)                                                  |
| Framesift                     | 7/23(30.5%)                                                  |
| Splice site                   | 4/23(30.5%)                                                  |

Due to the small number of cases reported in the literature and the presence of novel variants in most of the cases, no definite genotype–phenotype correlation regarding severity and variability of symptoms could be established until now. Symptom severity often varied widely, even within the same family. Surprisingly, four cases detected in adulthood, with onset in the third decade or early fourth decade of life presented with visual impairment, due to pigmentary maculopathy, often starting before motor symptoms.[8,9] Although Leonard et al.[10] reported this as a novel clinical finding and variability of the clinical spectrum of CYP2U1 variants, some contributed this to age-dependent variability rather than genetic heterogeneity.

Pathogenic variants in CYP2U1 had been found to result in alteration of mitochondrial architecture in vitro, leading to increased oxidative stress.[10] Reduced ATP levels and increased cytosolic hydrogen peroxide was shown in these cells as compared to controls. Accumulation of these reactive oxygen species ultimately might result in neurodegeneration. Fibroblasts harboring CYP2U1 mutations showed structural abnormalities, most probably due to a defect in mitochondrial membrane organization.[4] Also, CYP2U1 catalyzes the hydroxylation of arachidonic acid and other related long-chain fatty acids, which are mediators of signaling pathways of various hormones and neurotransmitters. Variants of the DDHD1 gene also implicated in another type hereditary spastic paraparesis (SPG28) perturb with the same pathway related to fatty acid metabolism, disrupting mitochondrial function.[4,16] Thus at least a proportion of patients with hereditary spastic paraparesis may have mitochondrial dysfunction and may benefit clinically from a trial of vitamins, which act as mitochondrial cofactors.

**CONCLUSION**

Children with SPG-56 present with delayed walking, varying degrees of gait disturbance, starting from 1 to 3 years of age. It is clinically imperative to suspect this disease in children with early-onset spastic paraparesis, especially in cases accompanied by baseline development delay or cognitive impairment and consanguinity.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

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