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Case Report

A 5-year-old girl case of spastic paraplegia type 56, a mutation in the CYP2U1 gene

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ABSTRACT

This case report details the presentation, diagnosis, and management of a 5-year-old girl from Saudi Arabia with Spastic Paraplegia Type 56 (SPG56) resulting from a novel mutation in the CYP2U1 gene. SPG56, a rare form of hereditary spastic paraplegia, exhibits genetic variability, impacting neurological and extra-neurological functions. The patient's clinical course involved a fall at age 2, subsequent motor deterioration, cognitive delays, and spasticity. Comprehensive diagnostic evaluations, including genetic testing, identified a homozygous likely pathogenic variant in CYP2U1. Despite outpatient therapy, the patient underwent a four-week intensive rehabilitation course to address spasticity and enhance daily living activities. This case highlights the challenges in diagnosing and managing SPG56 and underscores the importance of genetic testing in complex neurodegenerative cases.

Keywords: CYP2U1 gene mutation, Case reports, Hereditary spastic paraplegia, Spastic paraplegia type 56

INTRODUCTION

Hereditary spastic paraplegia (HSP) is a rare neurodegenerative disease characterized by progressive spasticity and weakness in the lower extremities bilaterally. Approximately 60 mutant genes have been recognized for over 70 distinctive genetic loci that comprise the HSPs, making them one of the neurologic illnesses with the largest genetic variability.[1] Spastic paraplegia-56 (OMIM#615030) is among the recently identified hereditary spastic paraplegias (HSPs), initially documented in 2012 by Tesson et al.[2] Additionally, individuals with SPG56 may exhibit various neurological symptoms, such as dystonia and developmental delays. HSP encompasses over 50 genetic variations. It impacts individuals across diverse ethnicities, with prevalence estimates ranging from 1.2 to 9.6 per 100,000 people.[3] A newly recognized autosomal recessive complex type of Hereditary spastic paraplegia is Spastic paraplegia type 56, resulting from CYP2U1 gene mutations on chromosome 4.[4] Limited studies currently exist on this "orphan" enzyme, which is primarily expressed in the brain and thymus. It exhibits a bimodal targeting mechanism, directing it to both the endoplasmic reticulum and mitochondria.[5] CYP2U1 plays a role in the metabolism of long-chain fatty acids, facilitating the hydroxylation of arachidonic acid to produce 19- and 20-hydroxy-modified arachidonic acids (19- and 20-HETE). Additionally, it is involved in the metabolism of docosahexaenoic acid (DHA) and other long-chain fatty acids.[5]

Hereditary spastic paraplegia is categorized into two main groups based on the presence of additional neurological and extra-neurological signs and symptoms: complicated and uncomplicated HSP. Additional manifestations can include intellectual disability, ataxia, seizures, peripheral neuropathy, and visual problems.[6]

Some genetic types are linked to either complicated or uncomplicated HSP, while others can be associated with both. Uncomplicated HSP is commonly inherited dominantly, whereas autosomal recessive inheritance is more prevalent in complicated forms. Populations with a high rate of consanguineous marriages tend to have higher rates of autosomal recessive inheritance.[7] Mutations in the CYP2U1 gene have been identified in families with complicated HSP. Citterio et al evaluated 150 patients diagnosed with complicated hereditary spastic paraplegia. They investigated mutations in CYP2U1/SPG56, DDHD2/SPG54, and GBA2/SPG46. Within the cohort, they identified a mutation in each gene, with a CYP2U1 mutation found in a single family. The patient with the CYP2U1 mutation experienced disease onset at 18 months, exhibiting symptoms such as spasticity, weakness, intellectual disability, thin corpus callosum, and periventricular white-matter hyperintensities.[8] In a separate report by Masciullo et al a case of SPG56 was described in a 6-year-old girl with early-onset spastic paraplegia and mild mental retardation. Spinal MRI revealed hydromyelia, leading the authors to categorize this case within the complicated phenotype of SPG56.[9] Leonardi et al reported a family with three affected members, all carrying a homozygous mutation in CYP2U1. These individuals developed visual impairment and spastic paraplegia in their twenties or thirties. Ophthalmological investigations revealed pigmentary degenerative maculopathy in all three patients.[10] A limited number of cases have been documented thus far. Presently, we report the case of a 5-year-old girl diagnosed with spastic paraplegia-56 (SPG-56), which is attributed to a novel mutation in the CYP2U1 gene. This study received approval from the institutional review board, and informed consent was obtained from the parents of the child.

CASE REPORT

A 5-year-old female from Hafer al Batin, Saudi Arabia, was born naturally through spontaneous vaginal delivery, had an uncomplicated pregnancy, and was discharged home in good health. There were no admissions to the neonatal intensive care unit. The patient had previously been healthy and had met all of her developmental milestones, with the exception of delayed speech. She started saying "mama" and "baba" at the age of 1.5 years and walking at the age of one. At the age of two, the patient fell while being held by her sister, resulting in a fractured left arm. The fracture was treated with surgical reduction. Following the surgery, the patient's parents noticed that she frequently fell while walking. Over the course of three months, her condition deteriorated, affecting her gait. She eventually began walking on tiptoes before becoming unable to walk due to lower limb stiffness and spasticity. There were no reported changes in upper-limb power or tone. Furthermore, the patient demonstrated delayed cognitive and behavioral function, hyperlexia, delayed speech and language, and fair to good upper body gross motor function. The patient's parents sought medical attention, while brain and spine magnetic resonance imaging (MRI) was performed, with unremarkable results. The neurology team also performed other tests, such as electromyography (EMG) and nerve conduction studies, to determine a proper diagnosis. These tests only revealed decreased amplitude in the evaluation of the left and right peroneal motor nerves (Figure 1).

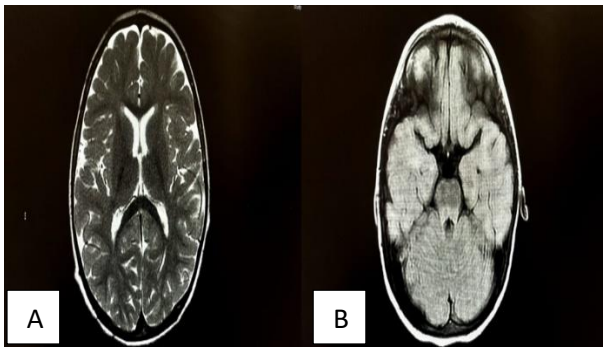

Figure 1: (A-B) Neuroradiological characteristics: axial MRI sequence using fast-field-echo T2-weighted imaging.

However, the electrodiagnostic study found no evidence of large-fibre peripheral neuropathy. The low peroneal compound muscle action potentials (CMAPs) may be due to her foot posture rather than an underlying neurogenic pathology. Her main medical issues are spasticity, aphasia, urinary and bowel incontinence, cognitive impairment, imbalance, and weakness. A whole-exome sequencing test was performed, and the results revealed a homozygous likely pathogenic variant in the CYP2U1 gene, which supports the genetic diagnosis of autosomal recessive spastic paraplegia type 56. Since her diagnosis, the patient has been undergoing outpatient physical therapy with no significant improvement.

As a result, the patient was admitted to the physical medicine and rehabilitation department for a four-week intensive rehabilitation program. The primary objectives of this course are to improve spasticity, sitting and standing balance, and independence in activities of daily living (ADL). upon admission, the patient was assigned to the care of a physiatrist consultant. She was assessed by a multidisciplinary rehabilitation team that included a physical therapist, occupational therapist, speech therapist, cognitive therapist, and swallowing team. Spasticity management was one of the primary goals upon admitting the patient, who had bilateral spasticity in the upper and lower limbs which resulted in gait dysfunction involving crouching and tiptoeing. The patient had bilateral elbow flexors with a Modified Ashworth Scale (MAS) score of 1 that did not interfere with her ADLs. In the lower limb, the patient had bilateral hamstring MAS 3, bilateral adductor MAS 2, and solus MAS 2. The patient received an onabotulinumtoxinA (BOTOX) injection in the hamstring (30 milliliters bilaterally), 30 milliliters bilaterally in the

adductors, and 25 milliliters bilaterally in the soleus, for a total of 170 milliliters of botox injection. The procedure was completed successfully with no immediate complications and using an aseptic technique. The patient's family was educated on the importance of following the home exercise program and wearing the orthosis correctly. In addition to the Botox injection, the patient received extensive physical therapy sessions as part of the specialty care. According to the physical therapy team's initial assessment, the patient had -3 power in the upper and lower limbs, with normal tone of the muscles in the head and trunk. The functional status was independent in rolling to the right or left. The patient needed moderate assistance in lying to sit and sitting to lie, crawling was modified independent, and kneeling required a contact guard. In terms of static and dynamic sitting balance, the patient had poor balance because her posture was an extension battle on her legs, causing her to be unable to sit upright and require support. The patient required moderate assistance when sitting to stand, and her standing balance was poor both statically and dynamically, with the posture of tiptoeing, extension button with scissoring.

Table 1: Functional independence measure (FIM) at admission and discharge.

Activities of daily living	Abilities on admission	Abilities on discharge
Feeding	3	5-supervision/ setup
Grooming	1	3-moderate assistant
Bathing	1	1-dependent
Dressing (upper body)	1	2-maximum assistant
Dressing (lower body)	1	1-dependent
Toileting	1	1-dependent
Transfer-bed, chair, W/C	1	1-dependent
Transfer-toilet	1	1-dependent
Transfer-tub/shower	1	1-dependent

The patient was dependent on transfer, and crawling was his primary mode of locomotion. Her gait and walking required assistive devices such as ankle foot orthoses with moderate assistance, and the pattern was tiptoeing extension with scissoring; additionally, the walking distance was less than 20 meters with poor endurance. The patient was completely dependent when climbing stairs. the admission goals were divided into short and long-term categories using the SMART method. Short-term goals for two to three weeks included improving sitting balance and posture to fair, reducing lower limb spasticity, being able to transfer from bed to chair and vice versa with moderate assistance, and facilitating the flexion pattern, which included knee kneeling, short sitting, and four-point kneeling. Long-term goals for 4-5 weeks included increasing lower limb muscle power, being able to sit to stand using a walker and an AFO with minimal assistance, transferring with minimal assistance, and walking for 20 meters with a walker and an AFO with minimal assistance. In addition to physical therapy treatment, the patient was referred to the orthosis team for proper ankle-foot orthosis to aid in walking and support the patient's gait, as she received bilateral ankle-foot orthosis and a knee gaiter to facilitate gait positions. Following discharge, the patient was able to sit and stand using a walker and Ankle Foot Orthosis with minimal assistance due to muscle power improvement in the lower limbs from -3 to 3. The patient was unable to walk for 20 meters with a walker and an AFO. During the sessions, new goals were established, including the ability to manage transfers with moderate assistance from bed to chair, chair to chair, and vice versa, as well as climbing up and down furniture with minimal assistance. According to the occupational therapy team, the patient was alert and oriented to people, playful, and capable of following instructions. The patient presented with delayed cognitive and behavioral function, as well as fair to good upper body gross motor ability. The patient has a functional pen grasp but is delayed in pre-writing skills. The patient engages in constructive and symbolic play and interacts with her siblings. Functionally, the patient's function status was assessed using the Functional Independence Measure (FIM) at admission and discharge, as shown in (Table 1). Cognitive skills are assessed. The patient's color, size, number, alphabet, and shape recognition were impaired, as were his visual-spatial perception, memory, problem-solving, and attention/concentration skills. The occupational team established treatment goals upon admission, with the goal regarding the patient being able to feed herself with set up/supervision, groom with set up/supervision, dress her upper and lower bodies with moderate assistance, and complete toileting with moderate assistance all within two weeks. Furthermore, the goals included the prescription of a wheelchair and commode, as well as proper training on how to use them to improve mobility and reduce the burden of care. At discharge, the patient met some of the goals but did not complete toileting training because she did not participate in the task. According to the swallowing unit assessment impression, the patient presented with normal swallow function and no overt signs or symptoms of aspiration. During the speech-language pathology assessment, the patient was not fully cooperative and required frequent redirections to complete assigned tasks. She was easily distracted and paid adequate attention. According to the assessment results, the patient has severe expressive language delay and mild to moderate receptive language delay. In terms of speech, the patient had functional orofacial musculature but had significant difficulty articulating to produce sounds or words. She was unable to imitate words, despite numerous attempts. Apraxia of speech was suspected in the assessment. The Plan is to be seen in four therapy sessions with the goals of family education, initiating an AAC system to enable the patient to communicate her needs, identifying nouns and verbs when presented with pictures in a set of three with 100%

accuracy, using minimum cuing, and imitating functional simple words such as mama and baba with 50% accuracy, using maximum verbal, visual, and tactile cues. Furthermore, a clinical nutrition assessment was performed. Showed that the patient was undernourished, so measurable goals were set to support weight gain and improve nutritional health status.

DISCUSSION

A 5-year-old girl from Saudi Arabia diagnosed with spastic paraplegia type 56 (CYP2U1) presented with a history of normal development until a fall at age two led to a left arm fracture. It was a rare form of hereditary spastic paraplegia resulting from mutations in the CYP2U1 gene. It presents with progressive spasticity and weakness due to a novel mutation in the CYP2U1 gene. Subsequent deterioration in motor function, cognitive delays, and spasticity prompted medical attention. Extensive diagnostic evaluations, including MRI and genetic testing, revealed a homozygous likely pathogenic variant in the CYP2U1 gene. Despite outpatient physical therapy, the patient showed limited improvement, leading to a four-week intensive rehabilitation course to address spasticity and enhance daily living activities.

The case underscores the complexity of HSP and the challenges in managing its diverse manifestations. This case underscores the ongoing need for research to improve understanding and management of SPG56. A systematic literature search conducted on PubMed and Google Scholar identified a total of 29 cases, including the current case presented. Diagnosing SPG56 poses challenges due to its rarity and overlapping symptoms with other forms of hereditary spastic paraplegia. Initial signs included gait instability, frequent falls, and progressive spasticity in bilateral lower limbs, ultimately leading to non-ambulatory status and contractures in most children.[6] Additional manifestations encompassed baseline developmental delay, mild-to-moderate intellectual disability, variable spasticity and weakness in upper limb and truncal muscles, action-induced dystonia, mild cerebellar signs, and subclinical axonal neuropathy in lower limbs. Seizures and bladder incontinence were rarely reported in isolated cases.[9] In this case, the initial presentation included a left arm fracture followed by a decline in motor function, leading to spasticity, aphasia, and cognitive deficits.

Despite unremarkable results from brain and spine MRI, whole-exome sequencing proved essential in identifying a homozygous likely pathogenic variant in the CYP2U1 gene, highlighting the importance of advanced genetic testing in complex neurodegenerative cases. Most cases exhibited the onset of symptoms with the loss of acquired motor milestones between 1 and 3 years of age, as evident in the presented case of a 5-year-old girl with symptoms emerging after a fall at the age of 2. This variability emphasizes the need for individualized care and comprehensive assessments. Durant et al. also presented the case of two patients diagnosed with Spastic Paraplegia at the age of 2 and 14 months.[5] Genotype–phenotype correlation regarding symptom severity and variability could not be definitively established due to the small number of reported cases and the presence of novel variants. Symptom severity varied widely, even within the same family.[10,11] While Leonardi et al described it as a new clinical discovery and highlighted the diversity in the clinical spectrum of CYP2U1 variants, others attribute this variability to age-dependent factors rather than genetic heterogeneity. This perspective underscores the importance of exploring the impact of age-related influences on the clinical manifestations of SPG56.[10] Approximately half of the children displayed neuroimaging abnormalities, with periventricular white matter hyperintensity in T2-weighted sequences being the most commonly observed. Less frequent findings included thinning of the corpus callosum, delayed myelination, white matter hypodensity in the globus pallidus, dorsal hydromyelia, and mild atrophy of the brain stem and cerebellum.[5,6,11]

The majority of affected patients had consanguineous parents with homozygous variants. Pathogenic variants in the CYP2U1 gene were diverse, including protein-truncating variants, frameshift mutations, nonsense mutations, missense variants, and splice site variants.[2,8,12] These variants led to a truncated protein or nonsense-mediated RNA decay, indicating loss of function as the underlying mechanism. Pathogenic variants in CYP2U1 were associated with altered mitochondrial architecture, increased oxidative stress, reduced ATP levels, and elevated cytosolic hydrogen peroxide in vitro.[12] Fibroblasts harbouring CYP2U1 mutations exhibited structural abnormalities, possibly due to defects in mitochondrial membrane organization.[9] CYP2U1's role in catalyzing the hydroxylation of arachidonic acid and related long-chain fatty acids, critical in various signaling pathways, suggests a link to mitochondrial dysfunction. This aligns with findings in other types of hereditary spastic paraparesis, such as SPG28, where disruptions in fatty acid metabolism and mitochondrial function are implicated.[9] Consequently, a trial of vitamins acting as mitochondrial cofactors may offer clinical benefits to individuals with hereditary spastic paraparesis associated with mitochondrial dysfunction. Given the limited number of documented cases of SPG56, future research is crucial for understanding the underlying pathophysiology, natural history, and potential targeted interventions. Additionally, advancements in genetic testing technologies may contribute to earlier and more accurate diagnoses, facilitating timely interventions and improving the quality of life for individuals affected by SPG56.

CONCLUSION

The presented case contributes to the limited pool of documented SPG56 cases, emphasizing the complexity of its clinical manifestations and the significance of

advanced genetic testing in diagnosis. The age-dependent variability observed in symptom onset and severity adds nuance to the understanding of SPG56's clinical spectrum. The diverse neurological and developmental features, coupled with the rarity of the condition, underscore the need for individualized care and comprehensive assessments. Insights into the pathophysiology, such as altered mitochondrial architecture and fatty acid metabolism, suggest potential avenues for targeted interventions, including mitochondrial cofactor trials. As research in SPG56 remains sparse, ongoing investigations are essential for elucidating its natural history, pathophysiological mechanisms, and potential therapeutic strategies. Advances in genetic testing technologies offer promise for early and accurate diagnoses, thereby improving outcomes and the overall quality of life for individuals affected by SPG56.

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