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CASE REPORT

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Adult-Onset Hereditary Spastic Paraplegia 15 in a Saudi Patient with A Compound Heterozygous Variant in the *ZFYVE26* Gene

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ABSTRACT

Hereditary spastic paraplegia (HSP) 15 is an autosomal recessive neurodegenerative disease caused by homozygous or heterozygous point mutations in the ZFYVE26 *gene that encodes the spastizin protein, located on chromosome 14q22-q24. Hereditary spastic paraplegia has been rarely reported in Saudi Arabia. In this article, we reported a rare case of adult-onset HSP 15 with a pure form of the disease in a Saudi patient with a compound heterozygous variant in the* ZFYVE26 *gene. The present case suggests that a compound heterozygous mutation in the* ZFYVE26 *may be associated with a later-onset disease and a milder phenotype. Given the low prevalence of the disease as well as heterogenicity and variability of its presenting symptoms, HSP 15 may be difficult to diagnose. However, early diagnosis is important to prevent unnecessary extensive investigations, facilitate early symptomatic management and provide genetic counseling for family planning to those affected and their first and second-degree relatives.*

Keywords: *ZFYVE26*, hereditary spastic paraplegia 15, autosomal recessive, mutation, Saudi Arabia.

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INTRODUCTION

Hereditary spastic paraplegia (HSP) refers to a group of genetically heterogeneous Mendelian disorders clinically characterized by progressive lower-limb spasticity, weakness and loss of the vibratory sense (1). It is classified into pure and complicated forms based on the clinical phenotype. The pure form includes cases whose symptoms are confined to lower limb spasticity and weakness with bladder involvement. The complicated form occurs when spasticity is accompanied by additional neurological features including intellectual disability, major neurocognitive impairment, behavioral disturbances, extrapyramidal abnormalities, and cerebellar ataxia or non-neurological symptoms such as pigmentary retinopathy, deafness, ichthyosis, and autoimmune hemolytic anemia/thrombocytopenia (2). Hereditary spastic paraplegia is considered a rare disease, with an overall prevalence of approximately 2–7.4/100,000. The age of onset is highly variable ranging from early childhood to 70 years of age, although most cases occur between the second and fourth decade of life (3). Genetically, HSPs are classified by the mode of inheritance into autosomal dominant, autosomal recessive, X-linked, and mitochondrial/maternal transmission with over 70 gene mutations identified (4). Hereditary spastic paraplegia 15 is an autosomal recessive neurodegenerative disease caused by homozygous or heterozygous point mutations in the *ZFYVE26* gene that encodes the spastizin protein, located on chromosome 14q22-q24 (5). Hereditary spastic paraplegia has been rarely reportedin Saudi Arabia. In this article, we report a novel compound heterozygous variant in the *ZFYVE26* gene in a Saudi male with autosomal recessive HSP 15. ❑

CASE REPORT

The proband is a 40-year-old Saudi male who presented to the neurology clinic with a five-year history of gait impairment and urinary disturbance. Initially, his symptoms started as pain associated with numbness and weakness in both lower limbs. His symptoms gradually progressed to the point where he needed crutches to facilitate walking. There was no history of seizures, dysarthria, dysphagia, learning difficulties, or gastrointestinal or cardiac symptoms. The patient denied any headache, hearing loss, tinnitus, vertigo, hoarseness, or limb incoordination. Past medical history included long-standing end-stage renal disease due to vesicoureteral reflux for which he had regular hemodialysis. In addition, he gave history of hepatitis C virus infection, which was cured by medical therapy. Family history was unremarkable (Figure 1). Neurologic examination revealed a conscious, alert and oriented patient. Higher mental functions and cranial nerves were normal. Examination of the sensory system showed impaired light touch, pinprick, and vibration in the lower extremities. Motor examination revealed spasticity in both lower extremities with distal weakness at 3/5 of hip flexors and 4+/5 of hip extensors on the Medical Research Council scale for muscle strength. Patellar and ankle deep tendon reflexes were reduced bilaterally with extensor plantar responses (Babinski sign). Gait examination showed spastic and out-toeing gait. Systemic examination was unremarkable. He had signs of renal osteodystrophy in both hands and feet (Figure 2). Laboratory investigations were unremarkable, except for an abnormal renal profile. Magnetic resonance imaging (MRI) of the brain showed a subtle T2 hyperintensity in the motor cortex, internal capsule, and juxtacortical callosal area (Figure 3), while the MRI of the cervical and thoracic spine was unremarkable for spinal cord or root pathology. A spine X-ray revealed the Rugger Jersey spine, which indicates osteosclerosis due to long-standing (untreated) hyperparathyroidism in chronic kidney disease (Figure 4). Nerve conduction study and electromyography were normal. Genetic testing was performed using whole-exome sequencing, and sequence analysis detected a heterozygous variant in the *ZFYVE26* gene c.5417G>A p. (Arg1806Lys) in exon 27 and a heterozygous

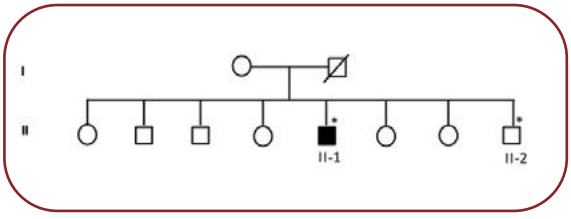

FIGURE 1. Family pedigree demonstrating the details of the proband's family. The asterisk sign (*) represents the available sample for the study

FIGURE 2. Patient's images showing signs of renal osteodystrophy in both hands and feet

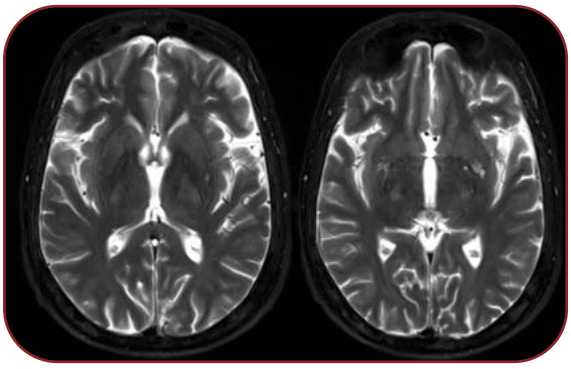

FIGURE 3. MRI of the brain showing a subtle T2 hyperintensity in the internal capsule

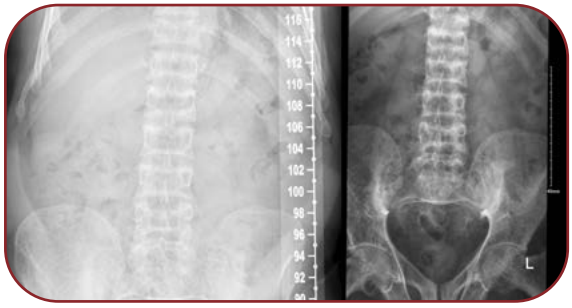

FIGURE 4. Spine X-ray showing Rugger Jersey spine

variant in the *ZFYVE26* gene c.7411A>G p.(Asn2471Asp) in exon 40, which are consistent with the diagnosis of HSP 15 (Figure 5). His symptoms were managed with baclofen and physiotherapy. ❑

DISCUSSION

In this study, we identified a previously unreported heterozygous variant in the *ZFYVE26* gene, c.5417G>A p.(Arg1806Lys) Chr14 (GRCH37):g.68238831C>T. According to recommendations of the American College of Medical Genetics, it has been classified as a variant of uncertain significance. We also detected a heterozygous variant in the same gene *ZFYVE26* c.7411A>G p.(Asn2471Asp) chr14(GRCH37):g.68217774T>C, and this variant has been detected in 75 cases, and one of them was in the homozygous state as well. The c.5417G>A has not been previously reported in either the literature or gnomAD database. The results of in-silico prediction software vary, with MutationTaster classifying it as "disease-causing" and PolyPhen2 as "benign". Current data suggest that these variants may play important roles in gene function leading to the result of the low prevalence of HSP 15 as well as heterogeneity and variability of its presenting symptoms. Our present case clearly represents that the compound heterozygous mutation in the *ZFYVE26* may be associated with a later-onset disease and a milder phenotype. Our observed variants as a compound heterozygous state are possibly con-

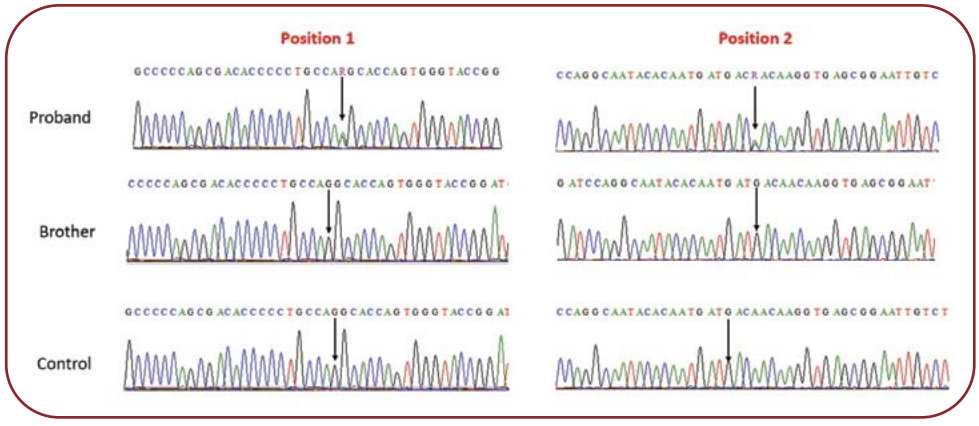

FIGURE 5. Representative chromograph of *ZFYVE26* Sanger sequencing read of the available family members. The proband II-1 is showing a heterozygous variant in the *ZFYVE26* gene at position one c.5417G>A p.(Arg1806Lys) in exon 27 and a heterozygous variant in the *ZFYVE26* gene exon 40 at position 2 c.7411A>G p.(Asn2471Asp), indicating a compound heterozygous mutation, whereas the II-2 a normal brother is showing wild type sequence at the same position

sistent with the diagnosis of HSP 15, and we believe this will further add to the literature concerning *ZFYVE26* mutations and their association with atypical phenotypes. Unfortunately, the parent samples were not available for further confirmation.

The *ZFYVE26* gene encodes a large protein that contains 2 539 amino acids known as Spastizin. The protein has three domains: leucine zipper, zinc finger and FYVE domain (6). The Spastizin protein has variable functions, including DNA repair, cytokinesis, autophagy, outgrowth and proper targeting of motor neuron axons. It is also responsible for autophagic lysosome reformation, which is an important prerequisite for generating new lysosomes (7). Moreover, *ZFYVE26* has a critical role during the development of the nervous system due to its wide expression in embryos, including hippocampal, cerebellar, spinal cord and cortical neuroepithelia (8). Autophagy is an intracellular process needed in the differentiation and degradation of cytoplasmic components and organelles to maintain the homeostasis and survival of the cells. It has multiple physiological functions including the removal of damaged organelles, degradation of misfolded proteins, and provision of nutrients during catabolism (9). Furthermore, autophagy is essential for neuron and motor neuron survival. Therefore, defects in any steps of autophagy will lead to abnormalities and disruption of neural function. The quantity and quality of lysosomes is pivotal in terminating the autophagy via their fusion with mature autophagosome to form autolysosomes which degrade autophagic components. In addition, Spastizin interacts with Beclin-1, a key regulator in autophagy, for proper autophagosomes maturation and clearance. Therefore, the cells lacking Spastizin may have impaired lysosomal biogenesis and autophagy defects which lead to immature autophagosome accumulation in neuronal cells. The net result of abnormalities in Spastizin protein synthesis is the degeneration of axons in the long ascending and descending corticospinal tracts. Even though the corticospinal tracts are mostly affected, the spinocerebellar tracts may also be involved (10).

Hereditary spastic paraplegia 15 has two different types: the pure phenotype (like our patient) and the complex phenotype. The complex form is characterized by heterogeneous features including white matter lesions, polyneuropathy, cognitive impairment, axonal neuropathy and pigmented retinopathy in addition to the pure phenotype (5). The onset of the disease is between the first and second decade of life (11). What makes our case interesting is the patient's late presentation, which may expand the age of presentation of HSP 15. There have been no published diagnostic criteria for HSP 15. However, the above-mentioned clinical manifestations may be suggestive of the disease. Our patient had progressive spastic paraplegia of both lower limbs (the pure form of HSP).

Neuroimaging abnormalities in patients with HSP 15 may include thinning of the corpus callosum, periventricular white matter signal changes, and cerebral and cerebellar atrophy (5). The only significant change seen in our patient was a subtle T2 hyperintensity in the motor cortex, internal capsule and juxtacortical callosal area suggestive of degeneration of the corticospinal tract. These findings are also identified in the neuroimaging of patients diagnosed with amyotrophic lateral sclerosis. ❑

CONCLUSION

We reported a rare case of adult-onset HSP 15 with a pure form of the disease in a Saudi patient with a compound heterozygous variant in the *ZFYVE26* gene. The present case suggests that a compound heterozygous mutation in the *ZFYVE26* may be associated with a later-onset disease and a milder phenotype. Given the low prevalence of the disease as well as the heterogenicity and variability of its presenting symptoms, HSP 15 may be difficult to diagnose. However, early diagnosis is important to prevent unnecessary extensive investigations, facilitate early symptomatic management and provide genetic counseling for family planning to those affected and their first and second-degree relatives. ❑

Conflicts of interests: none declared.
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