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HEREDITARY SPASTIC PARAPLEGIA DUE TO *NIPA 1* GENE MUTATION: CASE REPORT

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Palabras clave: Paraplejía espástica hereditaria; Mutación; Genética.

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RESUMEN

Introducción. La paraplejía espástica hereditaria (PEH) es un grupo de trastornos neurológicos caracterizados por espasticidad progresiva y debilidad muscular de miembros inferiores. Su etiología es genética y se ha asociado con mutaciones en más de 60 genes. La PEH es poco frecuente y puede ser útil en el diagnóstico diferencial de la parálisis cerebral.

Presentación de caso. Adolescente masculino de 16 años con diagnóstico de PEH por mutación del gen *NIPA1*: c. 316G>A (p. Gly106arg), correspondiente a una PEH tipo 6 (SPG6). El paciente presentó signos clínicos de síndrome de motoneurona superior progresivos en miembros inferiores como espasticidad, hiperreflexia y paraparesia, asociados a epilepsia de inicio focal diagnosticada a los 11 años y tratada satisfactoriamente con ácido valproico. El manejo de la espasticidad fue complejo e incluyó baclofeno oral, toxina botulínica intraoperatoria, terapia física y cirugía ortopédica multinivel para manejo de deformidades musculoesqueléticas en miembros inferiores.

Conclusión. El presente caso demuestra la importancia de realizar un diagnóstico temprano de la SPG6 (variante más común de la PEH) para realizar intervenciones oportunas en estos pacientes, prevenir complicaciones y evitar un mayor nivel de discapacidad.

ABSTRACT

Introduction: Hereditary spastic paraplegia (HSP) is the term for a group of neurological disorders characterized by progressive spasticity and muscle weakness in the lower limbs. Its etiology is genetic and has been associated with mutations in more than 60 genes. HSP is rare and may be useful in the differential diagnosis of cerebral palsy.

Case presentation: 16-year-old male with a diagnosis of HSP due to mutation of the *NIPA1* gene:c.316G>A (p. Gly106arg), which corresponds to HSP type 6 (SPG6). The patient presented with clinical signs of progressive upper motor neuron syndrome in the lower limbs, such as spasticity, hyperreflexia and paraparesis, associated with focal onset seizures diagnosed at age 11 and successfully treated with valproic acid. Spasticity treatment was complex and included oral baclofen, intraoperative botulinum toxin, physical therapy, and multilevel orthopedic surgery for the management of musculoskeletal deformities.

Conclusion: This is a rare case of complex HSP, associated with epilepsy, due to the mutation of the *NIPA1* gene (SPG6), the most common pathogenic variant within this type of mutation. The present case demonstrates the importance of making an early diagnosis of GSP6 to perform timely interventions in these patients, prevent complications, and avoid a higher level of disability.

INTRODUCTION

Hereditary spastic paraplegia (HSP) is a group of hereditary neurological disorders characterized by progressive spasticity, lower limb paresis, and hyperreflexia, caused by neurodegeneration in the corticospinal tract, resulting in axonopathy depending on the extension of the injury. These disorders may be autosomal dominant, autosomal recessive, or X-linked (1-5). Variants associated with mutations in more than 60 genes have been identified so far.

HSP is an orphan disease, with a prevalence between 0.5 and 5.3 cases per 100 000 people for the autosomal dominant type and between 0.0 and 5.3 cases per 100 000 people for the autosomal recessive type (6).

Currently, there is no effective treatment to prevent gait disturbances in these patients and the management of spasticity is symptomatic with physiotherapy. Pharmacological treatment includes oral or intrathecal baclofen, botulinum toxin and tizanidine injections, and oral benzodiazepines (5).

This report describes the case of an adolescent with HSP caused by a mutation of the *NIPA1* gene and associated with seizures.

CASE PRESENTATION

Male patient from a low-income household who was taken for the first time to an outpatient physiatry consultation in a tertiary care center at the age of 8 due to frequent falls with loss of stability in bipedal position, paraparesis, toe walking, and spasticity. On that occasion, it was also reported that he presented with pain in the feet attributed to flat foot at the age of 5.

The patient was the result of a second pregnancy between non-consanguineous parents, and the mother received proper antenatal care throughout her pregnancy; he was born at term by vaginal birth, with a weight of 3 050g and length of 49cm, and his TORCH screen was negative. No perinatal diseases were reported, and psychomotor and language development patterns were normal.

The patient had the following family history: a maternal cousin diagnosed with epilepsy at the age of 14 under treatment with valproic acid, and a sister with epilepsy caused by neurocysticercosis.

On physical examination performed at the first physiatry assessment, when he was 8 years old, the patient was alert with reactive pupils; facial symmetry; normal lower cranial nerves; upper limbs without alterations; left clubfoot with plantar flexion at 10°; increased muscle tone (Ashworth scale 2/4) predominantly distal and in hip adductors; muscle strength of 4/5 in dorsiflexion, plantarflexion and bilateral knee flexors, and 2/5 in hip extensors and flexors; patellar hyperreflexia; bilateral Achilles tendinitis; scissor gait; limping due to left clubfoot discrepancy; and normal sensation in all four limbs. The patient understood simple commands and communicated efficiently with clear, coherent, and fluid language; bilateral ophthalmoscopy was normal.

The patient's IQ was 82 points (low average). During this assessment by physiatry, the patient also presented the reports of the following tests: computed tomography of the skull, magnetic resonance imaging (MRI) of the brain and lumbar region, very long chain fatty acid measurement, plasma amino acid test, urine amino acid test, blood copper test, vitamin B12 test, and creatine phosphokinase test, all with normal results. In addition, he had a negative human T-cell lymphotropic virus type 1 and 2 antibody test. Given the findings and based on hereditary spastic paraplegia panel in which a mutation in the *NIPA1* gene was reported (c. 316G>A [p. Gly106arg]), the patient was diagnosed with HSP type 6 (SPG6) at the age of 8 years.

The patient's progress since the time of his first seizure, as reported in the medical records, is described below:

At age 11, the patient had his first focal seizure with right-sided motor involvement (ictal phase semiology: blurred vision, altered state of consciousness with tonic seizures in the right side of the head, right side of the body, and involuntary eye movements on the same side), which was treated with valproic acid. After the treatment was completed, a follow-up electroencephalogram (EGG) was performed, showing normal results.

At age 12, he underwent a computerized gait analysis that reported decreased knee (crouched gait) and hip mobility, femoral anteversion, bilateral foot drop, and paralytic stable valgus flat feet. A 6-minute walk test (distance: 188m, speed: 0.52m/s) and a Timed Up & Go test without orthoses (15.12 seconds) were also performed.

When he was 13 years old, somatosensory evoked potentials studies were carried out, in which a somatosensory pathway impairment was found in the right lower limb causing absolute conduction block through the posterior pathway at distal point C7. In addition, electromyography and nerve conduction studies were performed, and the findings allowed ruling out peripheral neuropathy. However, a decrease in the amplitude of the bilateral tibial and peroneal nerves was observed.

Due to the patient's condition, the dose of oral baclofen (started at 11 years of age with a dose of 20mg/day) was adjusted to 40 mg/day, although it was finally discontinued 3 months later since the desired effect on spasticity was not achieved. Since lower limb spasticity, hyperreflexia, and bilateral Achilles clonus persisted, the patient was instructed to use walking aids and multilevel surgery was proposed to put the feet in plantigrade position. Likewise, the pediatric neurology service indicated to progressively reduce the dose of valproic acid until it was completely discontinued due to the risk of bleeding during surgery, so treatment with carbamazepine was initiated. However, this drug was replaced by levetiracetam because the patient presented with drug dermatitis as an adverse reaction.

At 14 years of age, he underwent multiple reconstructive surgeries of the lower limbs during which botulinum toxin was applied bilaterally to the iliopsoas,

ischiotibial, and gastrocnemius muscles; no complications were reported. At postoperative week six, after removing both casts, the use of knee immobilizers in extension at night and floor reaction ankle-foot orthoses were indicated; additionally, the patient was ordered to walk on elbow crutches.

The alignment of the patient's lower limbs improved three months after surgery; in addition, although he had limited hip abduction on the left side, he was able to perform full knee extension: bilateral 120° flexion.

Although physical therapy was interrupted for a short period, after a year of clinical follow-up, the patient presented hip adduction, marked deformity due to hip flexion contracture, and valgus collapse when walking.

Given the recurrence of hip and knee mobility alterations, which in turn severely affected gait and involved significant energy expenditure, a new computerized gait analysis was performed, finding crouched gait and bilateral calcaneal spur (distance: 157m, energy expenditure index: 1.05, and speed: 0.43 m/s). Since the patient had a score of 2 points on the Ashworth scale for muscle tone and good selective motor control of the lower limbs, including dorsiflexion, he was considered a candidate for treatment with intrathecal baclofen pump to improve performance in the 6-minute walk test (target improvement of 50m) and reduce the degree of spasticity. It was then decided, on the one hand, that if spasticity improved, management would focus on the use of external aids, and, on the other hand, that if it did not improve, further surgery would be necessary.

At 15 years of age, the patient presented with a new seizure with ictal phase semiology similar to the one described above. Therefore, an electroencephalogram (EEG) was performed, showing generalized interictal epileptiform discharges. It is important to mention that, at that time, the patient was being treated with levetiracetam 2 000mg daily divided into 3 daily doses, but based on the EEG findings, valproic acid 250mg (every 12 hours) was restarted and the dose of levetiracetam was progressively decreased.

Unfortunately, when the patient was 16 years old, the COVID-19 pandemic was declared and, due to the human mobility restriction and social distancing measures implemented to slow its spread, it was not possible to initiate treatment with intrathecal baclofen pump.

DISCUSSION

HSP is classified into complex and pure forms depending on the clinical phenotype. The latter are characterized by spasticity (especially in the ischiotibial, quadriceps, gastrocnemius, soleus, and adductor muscles) and slow and progressive weakness of the lower limbs (mainly in the iliopsoas, ischiotibial, and anterior tibial muscles) (3,6), clinical manifestations that were observed in the reported patient. Variable hypertonic urinary disturbances and mild reduction in lower limb vibration sense and proprioception are also symptoms of the pure forms(6).

On the other hand, complex forms of HSP are characterized by the presence of additional neurological or non-neurological symptoms (6) such as neuropathy, seizures, parkinsonism, cognitive impairment, amyotrophy, short stature, visual disturbances (optic atrophy, retinal alterations), among others (5).

The SPG6 variant, identified in the patient described in this report, is caused by mutations in the *NIPA1* gene, located at 15q11.2, and accounts for 1% of all autosomal dominant HSP cases (7); it encodes a magnesium transporter involved in neuronal development and maintenance. Long-term endoplasmic reticulum stress in this variant has been associated with several neurodegenerative disorders, such as Parkinson's disease or amyotrophic lateral sclerosis (ALS) (7).

The pathogenic nonsense variants of the *NIPA1* gene associated with HSP are c.316G>A p. (Gly106Arg), c.316G>C p. (Gly106Arg), c.134C>G p. (Tyr45Arg), c.298G>A p. (Ala100Thr), and c.731A>G p. (Gln244Arg) (7,8). The case described here had the most common variant, c.316G>A p. (Gly106Arg).

Mutations of this gene have been reported in 10 families with pure autosomal dominant HSP (with an age of disease onset between 8 and 35 years), of which recurrent mutations have been reported in 9: c.134C>G and c.316G>C or c.316G>A (8). In this sense, it has been described that, in the mutant protein, a nonpolar neutral glycine is changed to a polar-charged arginine, which strengthens the claim that the mutation is pathogenic (9).

There are several proteins associated with the different types of HSP that regulate the signaling pathways that are important for axon function. A compelling candidate for this function that cuts across all types of HSP and widely involved in the development of neurodegenerative diseases is bone morphogenetic protein (BMP) signaling (5). *NIPA1* usually acts by inhibiting synaptic overgrowth at the neuromuscular junction; its function is to inhibit BMP signaling by binding to the BMP type II receptor and to promote endocytosis and lysosomal degradation. *NIPA1* mutations associated with autosomal dominant HSP alter trafficking of BMP type II receptor and are less efficient at promoting BMPRII degradation than wild-type *NIPA1*. The hallmark pathological change is the abnormal accumulation of tubulovesicular membranous organelles in axonal and dendritic nerve endings as the earliest abnormality (10).

Although clinical manifestations of HSP can occur at any age, the first symptoms and signs occur mainly before age 40 (11). However, most cases of HSP are of juvenile or early adult onset (8 to 35 years), with a pure phenotype and urinary disturbances (2,8).

Boutry *et al.* (1) state that the initial symptoms of HSP are subtle and patients usually complain of frequent falls, stiff legs, cramps, and abnormal or unstable gait, which were evident in the patient reported since he was 5 years old, when gait disturbances began. Additionally, de Souza *et al.* (2) describe a complicated phenotype in a large British family that includes adult-onset generalized tonic-clonic seizures and postural tremor in the upper limbs (2).

The progression of HSP is usually slow, but often results in the patient requiring assistance with canes, walkers, or wheelchairs as their gait becomes increasingly spastic and other symptoms appear (1).

In 2011, Svenstrup *et al.* (8), in a study of 52 unrelated HSP patients in Sweden, found that a patient with the *NIPA1* mutation (c.316G> A) belonged to a family that segregated HSP and epilepsy through three generations; this patient was diagnosed at age 11 (normal brain MRI and abnormal EEG. It was presumed that she had idiopathic generalized epilepsy [IGE]). Similarly, although it is unknown whether there is a family history related to HSP in the present case, the patient was diagnosed with epilepsy (focal type) at age 11, with normal brain MRI and abnormal EEG.

In a study conducted in Alberta, Ontario, and Quebec (Canada) between 2012 and 2015, including 526 patients with HSP, Chrestian *et al.* (6) found that seizures were one of the least frequent symptoms and were reported in only 3% of cases.

Likewise, microdeletions of the 15q11.2 region (including the *NIPA1* gene) have been described in patients with IGE, suggesting that changes in one or more genes within this region predispose to this type of epilepsy. Furthermore, the fact that the c.316G> A/C mutation has also been described in patients with autosomal dominant HSP suggests that additional genetic or environmental factors are important for the development of epilepsy (8).

HSP is a rare entity, and this is the first SPG6 case reported in Colombia. In Latin America, Munhoz *et al.* (12) published in 2006 the report of a Brazilian family with the same genetic variant; it is noteworthy that in that case the mean age of onset of symptoms was 23.75 ± 2.98 years. Worldwide, Chen *et al.* (13) reported cases of two independent Chinese families with two mutations linked to the SPG6 locus, c.316G> C and c.316G> A, while Martinez-Lage *et al.* (14) made a neuropathological description *postmortem* of a woman with the same genetic variant who presented with lower limb spasticity, bladder dysfunction, and lower limb weakness at age 13; she also developed dysphagia, facial weakness, and cognitive impairment at age 53 years. This patient had no known family history, but the anatomopathological study showed round neuronal cytoplasmic inclusions in the spinal cord.

Although SPG6 phenotypes associated with epilepsy have been described in the literature, their pathophysiological relationship is still unclear (12-14). Tanti *et al.* (7), by describing the case of a 32-year-old patient with HSP, epilepsy and ALS, reported the first case of a family with *NIPA1* pathogenic variants and ALS segregation; they concluded that *NIPA1* pathogenic variants, particularly c.316G>A p.(Gly106Arg), are associated with pure and complex HSP.

There is no specific treatment for SPG6, so it currently focuses on the management of spasticity using baclofen (both oral and intrathecal) and tizanidine. It has also been established that botulinum toxin type A injections may be useful for relaxing specific muscles, reducing pain, and improving mobility and thus

self-care; benzodiazepines may relieve spasms, but should be used with caution because they generate pharmacodependence; and drugs that include oxybutynin or trospium chloride regulate detrusor overactivity and sphincter dyssynergia (15).

In the same way, it has been determined that an individualized strength training program of 2 sessions per week should be implemented for patients with GPS6, as this favors the maintenance of muscle strength and skills in activities of daily living and posture (16). After surgery, when the patient reaches a walking speed of 0.43 m/s, the use of devices other than or additional to elbow crutches is suggested. In this regard, Van Lith *et al.* (17), in a study in which they analyzed 109 questionnaires completed by patients with pure HSP, found that 35% of them required aids for walking indoors, while 46% required them for walking outdoors; regarding falls, the authors reported that 57% of participants stated that they fell at least twice a year and that 51% had had at least one injury for this reason.

CONCLUSIONS

Reporting this first case of GSP6 in Colombia, the most common pathogenic variant among all HSP, demonstrates the importance of early diagnosis in order to perform timely pharmacological and rehabilitation interventions to prevent complications, improve the quality of life of patients, and minimize their disability.

ETHICAL CONSIDERATIONS

The patient's father signed an informed consent form granting permission for publishing this case report.

CONFLICT OF INTEREST

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