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CLINICAL CASES

# Amyotrophic Lateral Sclerosis as a phenotypic form of the SPG11 gene mutation spectrum. A case report.

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## Abstract

*Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease that affects to both the upper and lower motor neuron. We reported a rare presentation of ALS with SPG11 mutation with heterozygous state, contrary to the classic autosomal recessive form of ALS associated with this mutation, thus documenting the third case found with probable association with said pattern of inheritance, and the first of related ALS a mutation of SPG11 in Mexico. This allows us to reaffirm the genetic heterogeneity of ALS and the prognostic importance of the determination of such rare mutations with less lethal course to the classical form.*

***Keywords:*** *Amyotrophic lateral sclerosis. SPG11. Motor neuron disease. Mutation. Gene.*

## Introduction

The term motor neuron disease encompasses a group of neurodegenerative diseases where there is damage to the upper motor neuron (UMN) and/or lower (LMN) or both, highlighting in the latter group for its frequency and popularity ALS. Phenotypically it is characterized by muscle weakness, atrophy, fasciculations, spasticity and hyperreflexia. The classical form has a maximum incidence between the sixth and seventh decade of life. However, there is a way in which the initial symptoms occur before the age of 25 known as juvenile-onset ALS (JALS)[1]. In addition to age, another difference between JALS and classical ALS is its causality. In the classical form it is considered that 90% occurs sporadically and 10% can be attributed to mutations in a genetic locus, while in the JALS the sporadic form comprises 60% of cases, while genetic mutations acquire relevance up to 40%. In 90% of genetic cases the classical form is attributed to the mutation of 4 genes (SOD1, C9orf72, TARDBP and FUS), with the advent of genetic sequencing tests more than 100genes involved have been identified[2].

Among the rest of the genes involved linked to non-sporadic ALS is SPG11, responsible for encoding a protein known as spactacsin, whose protein, among other functions, is responsible for axonal transport.

Classically its mutation results in the development of Hereditary Spastic Paraparesis (HSP), acquiring relevance because it is the most frequent form in AR[3] transmission.

Clinical overlap between ALS and HSP led to the identification of SPG11 mutations in patients with a rare form of JALS AR with long survival.

Most of the case reports in which this ALS-linked mutation is found come from regions with a high rate

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of consanguinity, due to their typical AR inheritance pattern, such as some regions in Europe[4].

We present the case of a patient with ALS at the beginning with spastic paraparesis, however, during its evolution, dysphagia and fasciculations appear. as evolution. LMN damage data corroborated by electromyography (EMG) were added in whom, due to their atypical age, a genetic study was carried out where SPG11 mutation was found, however, with a single allele mutation. Acquiring importance since it would be the first national case of ALS associated with SPG11 mutation and third worldwide along with two other cases previously reported in an Irish cohort of 3 patients with possible AD pattern of inheritance contrasting with the classic AR pattern classically reported.

## Case presentation

Right-handed woman, 37 years old, originally from Sonora with no personal and family history of neuromuscular diseases, nor history of consanguinity. She goes to an assessment for chronic evolution of onset 2 years ago characterized by spasticity of pelvic limbs that progressed to cause frequent falls and limitation of ambulation; involving 1 year later weakness in thoracic limbs gradually; in addition to mild dysphagia, fasciculations and occasional cramps. Denying sensory, cognitive alterations or autonomic affection. Clinically, upper, and lower motor neuron syndrome was integrated simultaneously. The basic laboratory studies, thyroid profile, cerebrospinal fluid analysis was normal, viral and rheumatological panel negative. Magnetic resonance imaging (MRI) which showed hypointense lesion in T1, hyperintense in FLAIR and T2, without modification after the administration of contrast medium, of frontal subcortical location right or, without lesions at the level of the craniocervical junction (Fig. 1). Nerve conduction studies without documenting sensory affection, electromyography showed data of active and chronic denervation, as well as re-innervation in bulbar, cervical, thoracic, and lumbosacral segments. The diagnosis of ALS was established according to the Escorial criteria (Table 1) with more than 3 affected regions with upper and lower motor neuron data. Finally, due to the age of presentation of the disease lower than the classic onset and the notorious predominance of spasticity in the lower limbs a genetic sequencing study carried out by a private laboratory was compiled in which the main genes associated with motor neuron disease were analyzed, however an extended panel is not carried out due to limited financial resources (see figure 2 for methodology) in which SPG11 mutation was reported with variant (c_704_705del (p.His235Argfs*12)(Table 2). After diagnosis, symptomatic treatment with baclofen began. In the follow-up visit to 6 months she remained with progression of weakness showing atrophy in addition to the tenar musculature of left predominance.

## Discussion

ALS is the prototypical model of motor neuron disease in which classically combined findings of damage in UMN and LMN can occur both sporadically and associated with genetic mutation[5]. To date, more than 30 genes have been implicated in a reproducible way, while more than 120 have been proposed as potentially related to ALS, although most still have uncertain significance and often have not been replicated. Epigenetic influences may also play an important role[6]. The genetic causality of ALS is even greater the lower the age of onset (known as a juvenile form when you have a debut under 25 years). In a study done in China in patients with ALS of juvenile onset 44 patients carrying one or more variants were identified, mutations in SPG11, ALS2 and SETX were the most frequent, followed by FUS variants. Other prevalent genes such as SOD1, TARDBP and C9ORF72 were relatively rare in juvenile-onset patients[7].

Although this division seems to be simple in some cases, its clinical distinction is not so easy since the phenotypes between one disease and another overlap.

In this case, although the first clinic initially suspected HSP due to the severe spastic condition of the pelvic limbs as it evolved, the presence of dysphagia and fasciculations was added, in addition to the presence of atrophy in thoracic limbs, these data compatible with the LMN condition, which was also corroborated by EMG, integrating by criteria of the El Escorial modified for ALS. Due to the age of the patient at the onset of symptoms outside the classical age for ALS, genetic determination was requested in which heterozygous mutation was found in SPG11 (Table 2).

The SPG11 gene is a gene that is located on chromosome 15q21, has 100 982 coding nucleotides, is responsible for the coding of the protein espacsin. Such a protein is ubiquitously expressed in the nervous system, particularly in the cerebellum, cerebral cortex, and hippocampus. It is found diffusely in the cytosol with a higher concentration in the mitochondria and in the endoplasmic reticulum functionally related to neuronal transport[8].

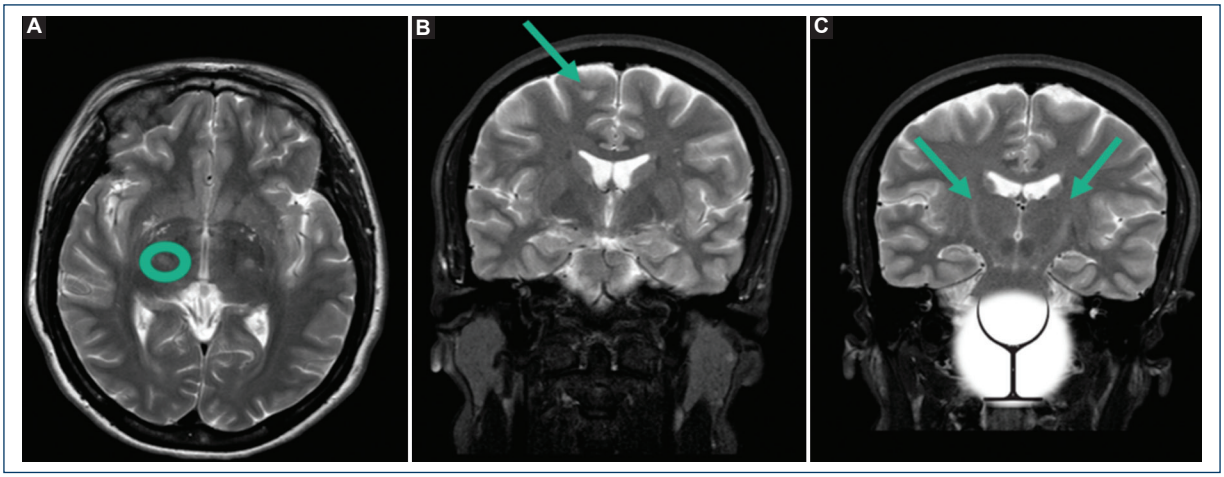


**Figure 1.** Imaging findings of motor neuron disease found in patient. **A:** hyperintensity of pyramidal route in posterior arm of internal capsule. **B:** hyperintense lesion in non-specific white matter. **C:** bilateral hyperintensity of the pyramidal route in coronal cut and similarity with wine glass.


**Figure 2.** Molecular genetic report of SNPGs-Array 46 Microarray.
Requested Study: Array46 750k.Genos Medical Reference: ARR127.21
Sample type: Peripheral blood.
It is based on CytoScan technology that allows observing copy number variations (CNV) of at least 400 Kb throughout the genome, which are correlated with imbalances in single nucleotide polymorphisms (SNP). This microarray contains more than 450 ml CNV markers, covering 80% of the RefSeq genes; with 200, 400 SNPs and 550,000 non-polymorphic markers.

It has relevance since it has been linked to the development of some cases of ALS,HSP,CMTX2.

The jointness of this case is the heterozygous form found with inheritance pattern in the forms that were linked was in an AR mode, in addition the age was described in forms of JALS, a form that by age exceeds the patient. However, there are clinical and MRI findings reported in families with this mutation that coincide with those found in this patient. By sharing with them absence of cognitive deficit, alteration in the fundus of the eye and severe bladder. As for MRI, there was also no evidence of thinning of the corpus callosum, and study of EMG showed acute and chronic denervation[9].

The heterozygous form found in the patient of SPG11 with variant (c_704_705del (p.His235Argfs*12) we consider that it does not rule out the attribution of the development of ALS, adding to the other 2 cases reported in an Irish observational cohort where the mutation variants were classified according to the SIFT as deleterious (c.7324G>C(p.[Ala2442Pro]) and c.4343G>A(p.[Cys1448Tyr]) with presumed mode of transmission AD thus encompassing it in the group of variants of low penetrance of mutation of putative genes for ALS[10].

**Table 1.** Regions affected in patient according to modified ¨El Escorial¨ criteria

| Segment | UMN | LMN |
|---|---|---|
| Cranio-bulbar | Glabellar and palmomental reflex | Tongue hypotrophy and fasciculations at rest and evoked |
| Cervical | Hyperreflexia, Hoffman's sign Spasticity Ashworth 2 in thoracic limbs | Distal paresis of thoracic limbs 4/5<br>Bilateral thenar hypotrophy<br>split sign |
| Thoracic | Absence of abdominal skin reflexes | Fasciculations in paraspinal muscles |
| Lumbo-sacral | Spasticity of pelvic limbs Ashworth 3 bilateral<br>Bilateral Achilles clonus<br>Proximal weakness 4+/5 | Fasciculations in bilateral quadriceps femoris<br>Bilateral extensor plantar response |

The El Escorial criteria classify into three levels of certainty of diagnostic suspicion according to the number of affected segments that are found with findings suggestive of damage in the UMN and LMN collected in the neurological examination at the level of four body segments (cranio-bulbar, cervical, thoracic, lumbo-sacral). In this case, the definitive clinical category was granted as more than three body segments were found with simultaneous findings of UMN and LMN. These findings were later supported with electromyography. UMN (upper motor neuron) LMN (lower motor neuron).

**Table 2.** Results of the genetic sequence test performed on the patient. Test performed: Sequence analysis and deletion/duplication testing of the 141 genes

| Gene | Variant | Zygosity | Variant classification |
|---|---|---|---|
| SPG11 | c.704_705del(p.His235Argfs*12) | heterozygous | pathogenic |
| DST | Alternate transcript NM_015548:c11069A > G(p.Tyr3690Cys) | heterozygous | Uncertain significance |
| DST | c.4729G > A(p.Glu1577Lys) | heterozygous | Uncertain significance |
| GJC2 | c.1058T > C(p-Leu353Pro) | heterozygous | Uncertain significance |
| PLEKHG5 | c.649G > A(p.Gly217Arg) | heterozygous | Uncertain significance |
| PLEKHG5 | c.367G > A(p.Asp123Asn) | heterozygous | Uncertain significance |
| SACS | c.4900G > C(p.Glu1634Gln) | heterozygous | Uncertain significance |

This diagnostic test evaluates 141 gene(s) for variants( genetic changes) that are associated with genetic disorders. One pathogenic variant identified in SPG11.

Within the differential diagnosis of other diseases that occur with SPG11 mutation, in addition to JALS, there is a form of hereditary neuropathy and HSP. In this case, the main clinical differential was with HSP.

The best-known clinical form in which this genetic alteration has been implicated is HSP. However, the characteristics found in these patients with progressive signs of NMS, sensory neuropathy and absence of bulbar involvement distinguish this disease from the clinical presentation SPG11-JALS. In addition, HSP magnetic resonance imaging shows a thinning of the corpus callosum not found in SPG11-ALS j. SPG11- JALS mutations usually result in protein truncation, without a particular hotspot region being identified.

It appears that JALS has a greater propensity to involve neurodegeneration in multiple neural pathways, while clinical ALS is more limited to motor pathways. To date, there is no clear explanation for this in the literature, but it may be related to specific mutation locus[11].

It should be noted that in this case the MRI showed lesion of the white matter, a finding described in cases of mutation of the gene related to HSP[12]. I also reveal some classic signs of ALS such as the hyperintensity of the corticospinal pathway and the so-called cup sign found in coronal cuts[13].

This overlap of clinical findings between HSP and ALS found had already represented a previously described concern marking the complexity of the correct clinical differential diagnosis of diseases related to SPG 11 mutations.

Deducing in this case some proposals that could explain the reason for this overlap. One of them would be the low penetrance already mentioned of this heterozygous mutation to SPG11 that contrasts with the classic AR form of high penetrance linked to JALS already widely mentioned where due to its low penetrance did not show the most striking characteristics such as age less than 25 years, the thinning of the corpus callosum and cognitive impairment.

Another explanation supported by previous observations is about the importance of the recognition of rare variants with intermediate effects in the context of an orogenic model of the disease. According to this hypothesis, each concurrent variant alone could be tolerated, but when combined with a second variant it would exceed the threshold required for neurodegeneration. In this case, mutations of GCJ2 and PLEKHG5 (mutations related to the development of PHD type 44 and hereditary motor neuropathy, respectively) were also found in the genetic study, however in heterozygous forms. Certain variants may not cause the disease in isolation and concomitant analysis of the genes of the disease may prove very important. Genetic heterogeneity, pleiotropy and lack of penetration are problems that are not fully understood in ALS[10].

## Conclusion

The diagnosis and characterization of ALS in patients under 50 years of age is not always easy, since sometimes there are clinical phenotypes of other motor neuron diseases that overlap or predominate in early stages, mainly in those in the mutation of a gene, such as SPG11 that is linked to the development of different forms of both diseases becoming a diagnostic challenge. In these patients we suggest that complementation with genetic studies could serve for diagnostic clarification, prognostic determination for a clarifying of the heterogenetic and multifactorial mechanisms of this disease, which in the future could serve for the development of targeted gene therapy.

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## Conflicts of interest

The authors declare that they have no actual or potential conflicts of interest or unfair advantage at this time.

## Ethical disclosures

**Protection of humans and animals.** The authors declare that no experiments on humans or animals have been performed for this research.

**Confidentiality of data.** The authors declare that no patient data appear in this article.

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