

Amyotrophic lateral sclerosis autosomal dominant due to a mutation in the TARDBP gene (ALS10)

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ABSTRACT

Introduction: The pathophysiology of amyotrophic lateral sclerosis (ALS), for the most part, is of unknown origin. However, it is known that in worldwide parameters, mutations of the superoxide dismutase 1 gene (SOD1) occupy about 20% of the cases of familial ALS, and mutations related to the TARDBP gene are responsible for 1–5% of SOD1-negative familial cases, as well as in some cases of sporadic ALS. Several studies have discussed TARDBP mutations in patients with ALS, or even in cases of frontotemporal dementia. At present, the search remains to clarify whether patients with ALS and with TARDBP mutations have a particular clinical presentation, with frequent or exceptional frontotemporal dementia, and whether, as for SOD1, some mutations may have an influence on the phenotype.

Case Report: We report a case of 48-year-old man, retired police officer, without comorbidities. He had received a diagnosis of Amyotrophic lateral sclerosis in 2019, after a possible picture of multifocal motor

neuropathy (NMM) with conduction block (greater than 30% and less than 50%) in the right median nerve between wrist and elbow. After genetic testing, we identified the genetic variant TARDBP with autosomal dominant pattern with or without association with Frontotemporal Dementia. This variant, LAS10, can be considered a mutation of exon 6, c.1147>G (p.ile383Val).

Conclusion: Although there are several clinically significant differences between patients carrying the TARDBP mutation, it is not possible to differentiate between sporadic and familial cases. It is believed that genetic parameters and their study can lead to a better understanding of the mechanisms of ALS degeneration and subsequently individualized therapeutic strategies.

Keywords: Amyotrophic lateral sclerosis, ALS10, Autosomal dominant, TARDBP gene

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INTRODUCTION

Amyotrophic lateral sclerosis (ALS), also called motor neuron disease (MPD), is a progressive, neurodegenerative, and inexorable disease that affects the neurons of the anterior tip of the spinal cord and lateral funiculus [1]. The incidence in the population is heterogeneously reported and ranges from 0.73 to 1.89

cases per 100,000 persons per year in South Asia and Northern Europe, respectively [2, 3]. In other words, it is a degeneration of the motor system at various levels: bulbar, cervical, thoracic, and lumbar [4].

The pathophysiology of ALS, for the most part, is of unknown origin. However, at present it is known that in worldwide parameters, mutations of the superoxide dismutase 1 (SOD1) gene occupy about 20% of familial ALS cases, with mutations related to the TARDBP gene accounting for 1–5% of SOD1-negative familial cases, as well as in some cases of sporadic ALS—40% to 50% of familial ALS and ≈10% of sporadic ALS [5].

As of the year 2008, mutations in the TARDBP (TAR DNA binding protein) gene have been found in both sporadic and familial ALS, now called ALS10 (OMIM 612069). Since this description, several genes have been correlated in amyotrophic lateral sclerosis, such as fused in sarcoma/translocated in liposarcoma (FUS/TLS), vasolin-containing protein (VCP), optineurin (OPTN), and recently a hexanucleotide repeat on chromosome 9 [6].

TAR-DNA binding protein 43 (TDP-43) had recently been qualified as the major protein in abnormal neuronal and glial cell inclusions in the sporadic and familial forms of amyotrophic lateral sclerosis. TDP-43 consists of two RNA and a C-terminal glycine-rich domain [7]. It is included in the regulation of expression, and in other cellular processes such as microRNA biogenesis, apoptosis, and cell division. All but one of the mutations identified (D169G) reside in exon 6 of the TARDBP gene, which codes for the glycine-rich C-terminus. In their entirety, they are missense alterations, inherited in a dominant fashion with the exception of one mutation (Y374X) at the C-terminal end [8, 9].

Although the attempt to distinguish sporadic from familial ALS is unequivocal, the clinical phenotype of ALS patients with SOD1 mutations has particularities when compared to patients with sporadic ALS [10]. In general no differences regarding age at onset, site of onset, duration of ALS, or sex ratio are markedly noted between sporadic and familial ALS cases. With regard to phenotype, SOD1 mutation-associated conditions have early onset and a predominance for lower limbs, and there is some interference with disease severity: A4V mutation cases have a course of less than 12 months, while in cases with G93C or D90A mutations the disease often lasts 5–10 years. No significant differences in the management of the condition have been described, either in sporadic or familial ALS [11].

Several studies have discussed TARDBP mutations in ALS patients, or even in cases of frontotemporal dementia. At present, the search remains to clarify whether ALS patients with TARDBP mutations have a particular clinical presentation, with frequent or exceptional frontotemporal dementia, and whether, as for SOD1, some mutations may have an influence on the phenotype [12, 13].

Therefore, the aim of this study is to present a case

report about a rare presentation of amyotrophic lateral sclerosis due to a mutation in the TARDBP gene (ALS10) and to undertake a theoretical discussion about the presence and frequency of mutations in this gene [14].

CASE REPORT

We report a case of a 48-year-old male, retired police officer, without comorbidities. He had been diagnosed with amyotrophic lateral sclerosis in 2019, after possible multifocal motor neuropathy (NMM) with conduction block (greater than 30% and less than 50%) in the right median nerve between wrist and elbow. He started pulse therapy treatment with solumedrol, believing it to be NMM, without obtaining functional improvements after 10 sessions. He suffered a ground level fall, with possible melting of the foot, alterations in the timbre and tone of his voice began to signal another disease; fasciculations and cramps complemented the clinical picture. The right side was impaired initially, with posterior dissemination of paresis and amyotrophy of the trunk and left dimidium. Respiratory difficulty is present, mainly in dorsal decubitus and through speech. He was using continuous positive airway pressure (CPAP) three times a day, already having extreme difficulty when using room air. The clinical picture had worsened until a new electroneuromyography result showed chronic preganglionic involvement suggestive of lower motor neuron lesion, without involvement of the bulbar muscles. After a genetic test, the TARDBP genetic variant was identified with an autosomal dominant pattern with or without an association with frontotemporal dementia. Such a variant, ELA10, can be considered a mutation of exon 6, c.1147>G (p.ile383Val). Complete blood count (CBC) was normal. At present, respiratory function test, polysomnography (all-night examination), ultrasonography of the diaphragm were suggested. The results of laboratory and imaging tests, such as immunomediated infections and diseases, and magnetic resonance imaging of the cervical spine ruled out other diseases. Lumbar puncture was normal. He will start treatment with methylcobalamin (intramuscular) 50 mg⁻²× a week; in addition to oral use of phenylbutyrate 3 g, tudca 1 g, l-serine 5 g every 12 hours, lamotrigine 25 mg, escitalopram 10 mg.

DISCUSSION

Amyotrophic lateral sclerosis is a neurodegenerative condition with inexorable outcome, resulting from the progressive loss of motor neurons. To date, there is no effective modifying therapy for the disease, and its heterogeneity, with respect to biochemical, genetic, and clinical features implies the identification of therapeutic targets. However, RNA dysregulation is known to be an important contributor to the pathophysiology of

ALS. Disease-related mutations have been identified in genes encoding multiple RNA-binding proteins and participating in RNA processing, among these, the TDP-43 protein [15].

Although mutations in the gene encoding TDP-43 (TARDBP) account for only a small proportion of the disease burden (1–5%), delocalization and accumulation of cytoplasmic TDP-43 are found in over 90% of individuals with ALS [16].

The nuclear RNA-binding protein TDP-43 is intimately involved in RNA processing. According to this core function, TDP-43 levels are tightly governed through a negative feedback system, whereby the nuclear protein distinguishes its own RNA transcript, destabilizes it, and reduces the manufacture of new TDP-43 protein [17]. In the neurodegenerative disorder, amyotrophic lateral sclerosis, the cytoplasmic mislocalization and accumulation of the protein prevent autoregulation. Moreover, ineffective autoregulation of TDP-43 may generate cytoplasmic deposition of TDP-43 and consecutive neurodegeneration [18]. Because TDP-43 performs a multifaceted function in maintaining RNA metabolism, its mislocalization and accumulation impedes several RNA processing pathways that, in turn, impair RNA stability and gene expression, contributing directly or indirectly to the pathogenesis of ALS [19].

Amyotrophic lateral sclerosis due to mutation in the TARDBP gene is often inherited in an autosomal dominant manner, that is, each child of a patient with TARDBP-related ALS has about a 50% chance of inheriting the pathogenic variant. Prenatal diagnosis for TARDBP-related ALS is possible if the pathogenic variant is identified in the family [20]. On rare occasions, an affected patient may have biallelic pathogenic variants in TARDBP, or even digenic pathogenic variants, that is, a variant with a coexisting repeat expansion in C9ORF72 [21].

Although typical ALS is the phenotype preponderantly associated with the pathogenic variants of TARDBP, patients with pathogenic variants of TARDBP may also have frontotemporal degeneration with motor neuron disease, and, rarely with frontotemporal dementia without motor neuron disease. In addition, extrapyramidal symptoms and Parkinsonism add to the clinical manifestations [22].

As with other forms of ALS, patients with the disease associated with the TARDBP mutation die of respiratory failure. This event occurs when the thoracic and phrenic motor neurons become severely compromised. However, the median survival for the disease is about 62 months, which is significantly longer than the survival of individuals without a known pathogenic variant of TARDBP [23]. Although the median survival is favorable, progression to death within one year is not uncommon [24].

Although clinically observed such trends, the range of age at onset, the pattern of symptoms, and the duration of the disease are very broad and overlap substantially

with all other causes of ALS. It is worth noting the significant differences for four criteria: sex ratio, age at onset, site of onset, and duration. As a result, phenotypic characteristics contribute little to inform whether genetic testing should be indicated [25].

Thus, in general, the diagnosis is often neglected by the medical community. This shows the unpreparedness for this condition, and even more so for this rare form. A detailed clinical evaluation is often enough to rule out other disorders. However, this is also the case with a certain frequency. Among the differential diagnoses of ALS are: multifocal motor neuropathy, cervical spondylosis, spinal muscular atrophy, Kennedy's disease, acquired and hereditary motor neuropathies—Charcot-Marie-Tooth disease, late onset GM2 gangliosidosis, among others [26].

CONCLUSION

Although there are several clinically significant differences between patients carrying the TARDBP mutation, it is not possible to differentiate between sporadic and familial cases. However, cases of TARDBP-associated ALS have a better prognosis with regard to survival, since these can extend for 50 years and the duration of the disease can spread over 15 years, making it an interesting issue in the management of ALS. In addition, describing the differential severity of TARDBP mutations according to their location in high glycine areas, differences in the site of onset between SOD1 and TARDBP cases may also help refine the strategy of genetic diagnosis. It is believed that genetic parameters and their study can lead to a better understanding of the mechanisms of ALS degeneration and subsequently individualized therapeutic strategies.

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Author Contributions

Marco Orsini – Analysis of data, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Jacqueline Fernandes do Nascimento – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Antônio Marcos da Silva Catharino – Analysis of data, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Luciana Armada – Acquisition of data, Analysis of data, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Marcos RG Freitas – Analysis of data, Drafting the work, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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Conflict of Interest

Authors declare no conflict of interest.

Data Availability

All relevant data are within the paper and its Supporting Information files.

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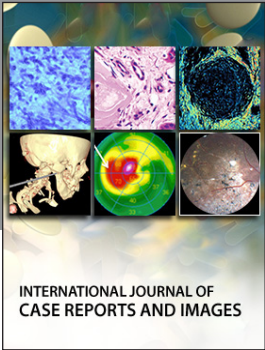
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