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Characterization of a case of chromosome 21 SOD1 mutation in a patient with familial amyotrophic lateral sclerosis: Discussion on the topic

Thaiana Duarte Celento, Marco Orsini, Regina Maria Papais Alvarenga, Antônio Marcos da Silva Catharino

ABSTRACT

Introduction: Amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease, Charcot's disease, and motor neuron disease (MPD), is a progressive, neurodegenerative, and relapsing disease that affects the neurons of the anterior horn of the spinal cord and lateral funiculus. Although the gene defect and pathogenesis of familial ALS is still poorly elucidated, genetic studies point to the involvement of chromosome 21 linkage mutations in the superoxide dismutase 1 (SOD1) gene in approximately 20% of familial ALS cases.

Case Report: We report the case of a 52-year-old woman, with no comorbidities. She had been diagnosed with ALS about eight years ago. She began with episodes of paresis in the right lower limb and melting of the right foot. Fasciculations and unmotivated cramps in the right calf complemented the clinical picture. The right side of the body was initially impaired, with later dissemination of paresis and amyotrophy of the trunk and left side. After a genetic test, the SOD1 genetic variant was identified. The exome analysis corroborated the diagnosis of ALS.

Conclusion: Superoxide dismutase 1 in the context of ALS represents only a fraction of the cases; however, as several neurodegenerative conditions are caused by abnormal protein folding, the study of a protein disorder with incorrect folding confers elucidation on the molecular basis of other diseases. This is important in terms of management and conduct, since the approach based on this hypothesis may favor the design of drugs that stabilize the SOD1 dimer and prevent misfolding.

Keywords: Amyotrophic lateral sclerosis, ALS10, Autosomal dominant, SOD1 protein

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INTRODUCTION

Amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease, Charcot's disease, and motor neuron disease (NMD), is a progressive, neurodegenerative, and inexorable disease that affects the neurons of the

anterior horn of the spinal cord and lateral funiculus [1]. Neurodegeneration occurs especially at the level of the motor cortex, brainstem, and spinal cord. The incidence in the population is heterogeneously marked and ranges from 0.73 to 1.89 cases per 100,000 people per year in South Asia and Northern Europe, respectively. In other words, it is the degeneration of the motor system at various levels: bulbar, cervical, thoracic, and lumbar [2, 3].

The pathophysiology of ALS, for the most part, is of unknown origin. It is observed that in worldwide parameters, about 90% of the ALS cases are sporadic, while about 5–10% are of familial origin. Regarding the molecular component, the first gene associated with ALS was the superoxide dismutase 1 (SOD1) gene, identified in 1993, and in early 2014, more than 20 genes were discovered as a driver of, or overly related to, ALS [4].

As of 2014, seven additional genes have been congruent to ALS, such as MATR3, CHCHD10, TBK1, TUBA4A, NEK1, C21orf2, and CCNF. All recognized by genome-wide association studies, whole genome searches or exome sequencing technologies. These genes encode proteins related to one or more molecular pathways involved in ALS [5]. These pathways comprise disturbances in global protein homeostasis arising from irregular protein aggregation or a failure of the protein clearance pathway, mitochondrial dysfunction, deranged RNA metabolism, impaired cytoskeletal integrity, altered axonal transport dynamics, and accumulation of DNA damage due to defective DNA repair [6].

Although the gene defect and pathogenesis of familial ALS is still poorly elucidated, genetic studies point to the involvement of chromosome 21 linkage mutations in the superoxide dismutase 1 (SOD1) gene in approximately 20% of familial ALS cases [7].

Therefore, the aim of the present study is to present a case report about a presentation of ALS due to a mutation in chromosome 21 of the SOD1 gene, and to undertake a theoretical discussion about the toxic mechanisms of this gene in the context of ALS, as well as the potential implication of this mechanism [8].

CASE REPORT

We report the case of a 52-year-old woman, with no comorbidities. She had been diagnosed with ALS about eight years ago. She complained of episodes of paresis in the right lower limb and melting of the right foot. Fasciculations, cramps in the right calf and severe generalized amyotrophy, uniquely affecting the palm (Figure 1) complemented the clinical picture. The right side of the body was impaired initially, with subsequent dissemination of paresis and amyotrophy of the trunk and left side. The neurophysiological findings showed an axonal lesion affecting the second motor neuron, in spinal and suprasegmental topographies, with characteristics of current damage, together with typical elements of motor unit remodeling, integrity of the first motor neuron, and laboratory tests and biochemistry without noteworthy alterations. After genetic testing, the SOD1 genetic variant was identified (Figure 2). Exome analysis corroborated the diagnosis of ALS and magnetic resonance imaging of the brain with tractography without significant alterations. Clinical picture had worsened until the electroneuromyography revealed fibrillations, positive waves, and fasciculations in the upper and lower limbs, in addition to motor unit action potentials with increased amplitudes in the same; videoendoscopy of normal deglutition. On physical examination we found the patient to be collaborative, and the MRC (Medical Research Council) strength scale was used, which showed: Left biceps brachii strength grade 4, right biceps brachii strength grade 3; left triceps strength grade 3, right triceps strength grade 3; left radial extensor carpus strength grade 1, right radial extensor carpus strength grade 2; right flexor digitorum strength grade 4, left flexor digitorum strength grade 4; quadriceps left strength grade 3, quadriceps right strength grade 3; tibialis anterior left strength grade 2, tibialis anterior right strength grade 2, extensor hallux longus right strength grade 3, extensor

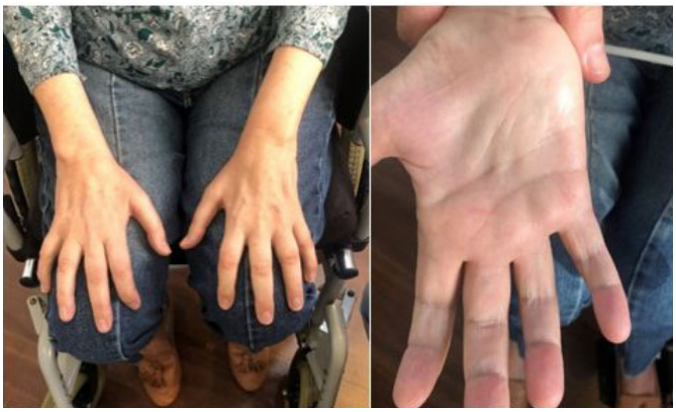

Figure 1: Accentuated amyotrophy in palms and dorsum of hands.

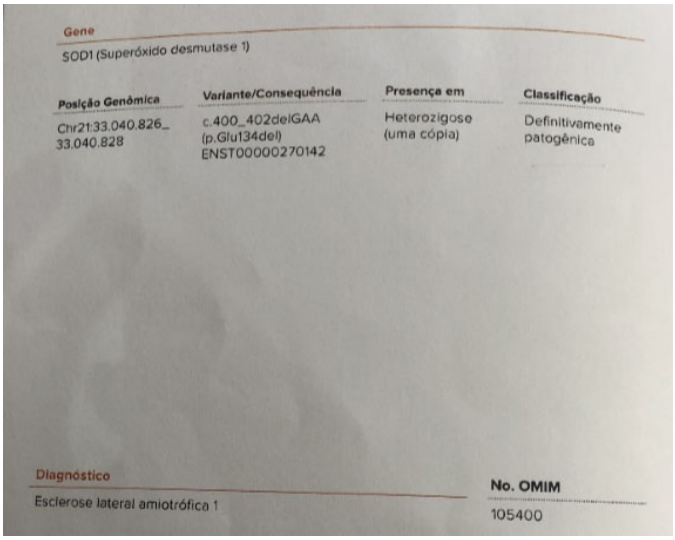

Figure 2: Genetic test showing SOD1 variant.

hallux longus left strength grade 2; psoas left strength grade 1, psoas right strength grade 1. Bicipital reflex left +, right +; radial reflex left +++, right ++; finger flexor reflex left ++, right +++; tricipital reflexes abolished; patellar reflexes abolished; achilles reflex abolished, presence of Babinski's sign at right, absence of Hoffmann's sign, under use of Riluzol, Methylcobalamin (intra-muscular) 2× a week; Escitalopram and Edaravone.

DISCUSSION

Amyotrophic lateral sclerosis is a neurodegenerative condition with inexorable prognosis, arising from the progressive loss of motor neurons [9]. To date, there are no efficient modifying treatments for the disease, and its heterogeneity, with respect to biochemical, genetic, and clinical features implies the identification of therapeutic targets. However, the present genetic discoveries have highlighted the main pathways of the disease, which in turn are therapeutically testable and amenable to potentiation [10].

Superoxide dismutase 1 is configured as the major constituent of protein deposits in certain familial and sporadic forms of ALS. This gene vulgarizes its misfolded composition as a prion, providing a plausible molecular basis for the focus and spread of paresis in ALS [11].

The human SOD1 gene (Entrez Gene ID 6647) is located on chromosome 21q22.11 and encodes the monomeric SOD1 protein (153 amino acids, molecular weight 16 kDa) [12]. According to the UCSC Genome Browser, the SOD1 gene inhabits from base pair 33,031,935 to base pair 33,041,241 with a genomic size of 9307 bp [13].

It stands out as a powerful antioxidant enzyme with the purpose of protecting cells against the harmful effects of superoxide radicals. Superoxide dismutase 1 binds the copper and zinc ions that are directly related to the deactivation of toxic superoxide radicals. The mutated SOD1 gene can achieve both gain and loss of function mutations [14]. The commonly observed mutations in SOD1 that affect the activity of the protein are D90A, A4V, and G93A. Damaging mutations alter the function of SOD1, promoting accumulation of highly toxic hydroxyl radicals. The accumulation of these free radicals causes nuclear and mitochondrial DNA degradation and protein misfolding, hallmarks associated with ALS [15].

The D90A mutation—aspartic acid at codon 90 modified to alanine—is the mutation most often associated with ALS and can be inherited as both a dominant and recessive trait, although in most cases it is recessive [16]. Alanine at codon 4 modified to valine (A4V) is the most common ALS-causing mutation (about 50%). Glycine 93 modified to alanine (G93A) is noted as a relatively rare mutation; however, it has been analyzed with caution, since it was the first mutation to be investigated in a transgenic mouse model capable of generating the motor neuron syndrome [17].

To date, an important number, about more than 180 various mutations have been described, including single point mutations, deletions, insertions, and truncation mutations along the five exons of the SOD1 gene [18]. It is emphasized that the deleterious effects of SOD1 are the consequence of protein missense [18].

Over the years, genetic screening has become more attainable and global in clinical practice, therefore understanding how a variant may cause disease in the context of the population may assist in procedural inductions about pathogenicity, especially when the family history of the disease is unknown [19].

CONCLUSION

Superoxide dismutase 1 in the context of amyotrophic lateral sclerosis represents only a fraction of the cases; however, as several neurodegenerative conditions are caused by abnormal protein folding, the study of a protein disorder with incorrect folding confers elucidation on the molecular basis of other diseases. This is important in terms of management and conduct, since the approach based on this hypothesis may favor the design of drugs that stabilize the SOD1 dimer and prevent misfolding. Conceiving, therefore, strategies aimed at correcting protein folding defects and, consequently, susceptible to prevention, or even interruption of these diseases.

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Author Contributions

Thaiana Duarte Celento – Conception of the work, Design of the work, Acquisition of data, Interpretation of data, Drafting the work, 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

Marco Orsini – Conception of the work, Analysis of data, Interpretation of data, Drafting the work, 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

Regina Maria Papais Alvarenga – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, 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, Interpretation of data, Drafting the work, 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

Guarantor of Submission

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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.