Amyotrophic lateral sclerosis
Considerations on diagnostic criteria

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ABSTRACT
Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder, compromising the motor neuron, characterized by progressive muscle weakness, with reserved prognosis. The diagnosis is based on inclusion and exclusion clinical criteria, since there is no specific confirmation test. The objective of this research is to critically examine the main diagnosis instrument - El Escorial revisited, from the World Federation of Neurology (1998). Of the 540 patients with initial ALS diagnosis, either probable or definite, seen at UNIFESP-EPM, 190 underwent thorough investigation, following regular clinical and therapeutic treatment for over two years. Thirty patients (15.78%) had their diagnosis completely changed. The false-positive diagnoses were related to: early age, clinical presentation of symmetry, weakness greater than atrophy, symptomatic exacerbation. In addition, three patients with myasthenia gravis developed framework for ALS, suggesting the post-synaptic disability as a sign of early disease.

Key words: amyotrophic lateral sclerosis, correct diagnosis, El Escorial revisited.

Esclerose lateral amiotrófica: considerações sobre critérios diagnósticos

RESUMO
Esclerose lateral amiotrófica (ELA) é uma doença neurodegenerativa, que compromete o neurônio motor, caracterizada por fraqueza muscular progressiva, com prognóstico reservado. O diagnóstico é baseado na inclusão e exclusão de critérios clínicos, uma vez que não existe um teste de confirmação específica. O objetivo desta pesquisa é analisar criticamente o instrumento de diagnóstico principal - El Escorial revisited, da Federação Mundial de Neurologia (1998). Dos 540 pacientes com diagnóstico inicial de ELA, seja provável ou definitiva, vistos pela UNIFESP-EPM, 190 foram submetidos a investigação aprofundada, após tratamento clínico e terapêutico regular há mais de dois anos. Trinta pacientes (15,78%) tiveram seu diagnóstico mudado completamente. Os diagnósticos falso-positivos foram relacionados à idade precoce, a apresentação clínica da simetria, a fraqueza superior a atrofia, exacerbação sintomática. Além disso, três pacientes com miastenia gravis desenvolveram quadro de ELA, sugerindo a lesão pós-sináptica como um sinal precoce da doença.

Palavras-chave: esclerose lateral amiotrófica, diagnóstico correto, El Escorial revisited.

Motor neuron diseases (MND) constitute a group of neurodegenerative disorders characterized by loss of neurons in the motor cortex, brainstem, and ventral horn of the spinal cord. The clinical presentation depends on the involvement of upper motor neurons – UMN (weakness, spasticity and hyperreflexia) or lower motor neurons – LMN (weakness, absent or diminished deep reflexes and fasciculations). MND’s evolution can compromise both upper and lower limbs, as well as areas innervated by bulbar nerve fibers. MND patient survival is low, and is dependent on the initial involvement. Death usually occurs in 3 to 5 years after the onset of symptoms, mainly as a result of respiratory failure.1
The disorders include: progressive muscle atrophy (PMA), represented by a pure involvement of LMN; primary lateral sclerosis, characterized by progressive involvement of pyramidal tract; progressive bulbar palsy (PBP), defined as the onset in the bulbar region; amyotrophic lateral sclerosis (ALS), as described by Charcot in 1874, showing deterioration of UMN and LMN.

The latter accounts for the most frequent clinical presentation (80% of total cases) and as a result many centers use the name ALS for the diseases with impairment of motor neuron.

The causes of motor neuron injury in MND/ALS remain incompletely understood. There are several mechanisms that may be involved in its development and a multifactorial disease is considered. The mechanisms related to ALS include the toxic effects caused by the mutation of superoxide desmutase1, inclusion of abnormal protein aggregation, intermediary filaments disorganization, anterograde and retrograde axonal transport change, microglial activation, excitotoxicity mediated by glutamate, abnormalities in regulation of intracellular calcium and others.

The diagnosis is based on clinical aspects. Therefore, we do not have a real biomarker for MND diagnosis.

**Diagnosis**

For many years, the only published criteria for the recognition of MND / ALS were done by Lambert, established through electroneuromyography (ENMG). In 1990, guidelines set by different researchers have been incorporated within the diagnostic criteria formulated by a Subcommittee on ALS of the World Federation of Neurology (WFN), which culminated in the meeting and editing of the diagnostic criteria in El Escorial, Spain, in 1994.

ALS diagnosis is defined within the evidence of signs of impairment of lower motor neuron, by means of clinical examination, electrophysiological or neuropathological changes, associated with clinically proven impairment of upper motor neuron, with chronic and progressive development. It is still necessary, for diagnosis, the absence of electrophysiological and pathological findings characteristic of other diseases that explain the degeneration of motor neurons, as well as changes in neuroimaging to justify the electrophysiological signals.

There has been, however, consensus among researchers, since certain clinical pictures and, above all, certain electrophysiological findings left doubt about the completion of diagnosis in some specific situations. General neurologists and specialists in neuromuscular diseases claimed additional difficulties for the necessary ALS early diagnosis.

The diagnostic criteria in El Escorial were reformulated in 1998, at the World Federation of Neurology ALS meeting in Airlie House, Warrenton, Virginia, U.S. This revised document, known as El Escorial Revisited, was published by the WFN-ALS on the Web, with an aim at refining the diagnosis.

New methods of electrophysiology, neuroimaging, immunohistochemistry and genome analysis were added for accuracy of diagnosis. The document El Escorial Revisited has been regarded as an important step to alleviate the difficulties in producing the diagnosis.

In a recent meeting, held in Japan, researchers improved the diagnostic criteria and formulated “Awaji criteria”. There was a reformulation of electromyography, adding fasciculation with signal of neuronal damage, and inclusion new methods of diagnosis with transcranial magnetic stimulation, voxel based morphometry and diffusion tensor imaging.

Despite the diagnostic criteria established by the WFN, aided by more refined laboratory tests for diseases that mimic ALS, accompanied by recent advances in imaging techniques, incorrect diagnosis is not infrequent. In previous studies, 45% of ALS patients presented initial wrong diagnosis and 25% of these were performed by neurologists.

In addition, there is a long waiting period between the onset of symptoms and the diagnosis. In an international multicenter study named ISIS Survey, with 201 ELA-diagnosed patients, median time required to confirm diagnosis was 14 months, with a 2-month waiting period for the first appointment. It took 8 months for the first appointment with the neurologist and it took another 4 months for neurologist’s diagnosis observation and re-evaluation.

Systematic reviews of ALS patients, in the last decade, have shown 9 to 10% of false-positive ALS diagnosis. These, primarily included in the group of ALS at El Escorial Revisited, have unusual developments, with a break of the progression of chronic and progressive motor involvement and the appearance of signs and symptoms uncommon in clinical course, leading to a careful review diagnostic, pointing to other diseases such as multifocal motor neuropathy (MMN) and Kennedy disease.

The objective of this study is a critical analysis of the ALS diagnostic criteria based on clinical presentations of patients with atypical presentation of motor neuron disease.

**METHOD**

The Motor Neuron Disease Unit at the Neuromuscular Diseases Clinic in UNIFESP-EPM, running regularly since 1999, has sought to follow the development of diagnostic criteria for MND / ALS. The current diagnostic criteria are those defined by the El Escorial Revisited, in which patients are subjected to a memorandum of clinical research in the WFN, previously cited.
The outpatient monitoring is carried out under regular (at least quarterly) periodic consultations encompassing multidisciplinary orientation therapy. To the best characterization of the goals, these patients’ medical records were analyzed in retrospect, with an aim at especially identifying the following medical conditions: patients with ALS initial clinical diagnosis, with an illness history longer than two years, classified as probable or defined ALS, with different clinical course from the initial diagnosis, then ruling out MND / ALS diagnosis. Patients characterized, initially, with other neuromuscular diseases, evolving, later on, to classic aspects of MND / ALS.

**RESULTS**

Of the 540 patients registered in the Clinic, 190 patients met the MND / ALS diagnostic criteria, complemented with laboratory research in compliance with both research protocols and regular monitoring. Thirty of these patients (15.78%) had their diagnosis completely changed, during the clinical observation development period (Table 1).

On the other hand, three patients with initial symptoms and diagnosis of other neuromuscular diseases developed features typical of MND / ALS during the clinical evolution. They are male, aged between 55 and 58 years old, whose characteristics are described in Table 2.

The Motor Neuron Disease Unit is a reference service, and last months, has been receiving a great number of patients with defined ALS, which reduces the number of false negative diagnosis in this work.

**Table 1. False-positive diagnosis: diagnosis review in patients who have amyotrophic lateral sclerosis with first diagnosis in tandem with El Escorial revisited criteria.**

<table>
<thead>
<tr>
<th>Gender</th>
<th>Starting age in years</th>
<th>Ethnicity</th>
<th>Disease evolution in years</th>
<th>Diagnosis</th>
</tr>
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<tbody>
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<td>Caucasian</td>
<td>5</td>
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<td>Inflammatory braquial plexitis</td>
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<td>48</td>
<td>Caucasian</td>
<td>9</td>
<td>Chronic inflammatory polineuropathy</td>
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<tr>
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<td>74</td>
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<td>Monoclonal gamopathy</td>
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<tr>
<td>Male</td>
<td>18</td>
<td>Afro-american</td>
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<td>Male</td>
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<td>Caucasian</td>
<td>25</td>
<td>Hexosaminidase A deficiency</td>
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DISCUSSION

Despite the recent refinement of the World Federation of Neurology Consensus for ALS diagnosis, erroneous diagnosis is not infrequent.

Even in an experienced ALS diagnostic service at the MND / ALS Clinic at UNIFESP-EPM, thirty patients out of a group of 190 with regular monitoring and laboratory research for complete characterization of ELA, have had their initial diagnosis changed over time. These patients’ clinical presentations display features that can help in ALS diagnosis, especially as to what regards a definitive diagnosis of this disease.

Age

The age of onset of first symptoms, usually at less than 30, increases the proportion of the differential MND / ALS diagnosis. The early onset, represented by 5 of the 30 patients with false positive diagnosis, displayed genetic abnormalities, including deficiency of the enzyme hexosaminidase A and B, lack of expression of proteins of the cytoskeleton of cortical spinal tract in hereditary spastic paraplegia, amendment of the suppressor gene expression in the formation of neurinomas in the peripheral nervous system in neurofibromatosis type I, or abnormalities of muscle protein constituents of the cytoskeleton such as disferlina.

Clinical forms of presentation

Unilateral/Bilateral – MND/ALS has, characteristically, unilateral initial presentation, involving most of the time limb distal regions, where roots C8-T1 and L5-S1 are the most commonly affected, with ipsilateral or contralateral progression to the other roots, in a progressive and cumulative manner.

Forms with peculiar clinical presentation as the monomelic atrophy of Hirayama, attended with atrophy of a limb, predominantly in the upper limbs, in youths, with self-progression or, in some cases, slow progression. In 12 (40%) of the 30 false-positive cases, we found monomelic atrophy, due to the specific motor involvement linked to immunoglobulins, in the associated cases of the multifocal motor neuropathy or monoclonal gammopathies related to autoimmune dyscrasies.

The involvement of bilateral and symmetrical limbs, at the beginning of the clinical picture, makes ALS diagnosis less likely, suggesting a multiradicular pattern more often found in polirradiculopathies with inflammatory motor predominance.

Proximal/Distal – Predominance of involvement of MND / ALS is distal, then, beginning with proximal limb forms, leaves room for doubt in diagnosis, especially if there are no signs of pyramid release. The forms called “flail in arms” or brachial paraplegia and the legs paraplegia, as early symptoms, have predominance of proximal involvement and presents blurry forms of spinal muscular atrophy of the adult form, which have variability progression and different prognosis. Kennedy’s disease, also called spinal bulbar atrophy, linked to the X chromosome, with typical symptoms of proximal atrophy associated with bulbar involvement, was found in two patients with false positive diagnosis in our study, and two other patients were diagnosed with an adult form of spinal muscular atrophy, type III, all of whom required more follow-up, since they have, until now, 6 years of tracking with localized forms of involvement. One patient with chronic neurogenic quadriiceps amyotrophy and another one with spastic paraparesis with dysarthria may later develop MND / ALS.

The motor and distal involvement presents other differential diagnoses such as multifocal motor neuropathy, characterized by MMSS asymmetric distal involvement, distal myopathies, hereditary motor neuropathies, which can provide the clinical motor aspects in a given moment, similar to MND / ALS.

Acute/Subacute/Chronic – The evolutionary pattern that characterizes the MND/ALS presents, in most of its forms, a chronic progressive decrease of motor function, bodily involvement with sum of the territories, ranging, on average, between three and five years.

The changes to this pattern, with acute or subacute evolution of motor deficits and stabilization of the disease with acute relapses are characteristic of autoimmune-driven diseases. Moreover, part of the slower evo-
lution, with onset of signs and symptoms over years of evolution, attests to other forms involving the degenerative motor neuron.

The presentation of typical clinical aspects of spinal muscular atrophy can display a wide variability in its evolution as well as in its clinical presentation and are excluded from their diagnosis, often for long periods with follow-up monitoring, and they may show signs of progress and bulbar involvement in 20 to 30 years of the onset of symptoms.

More accentuated weakness than atrophy – ALS diagnosis depends on clear evidence of both compromised lower motor neuron and upper motor neuron. The commitment of the LMN is clinically more easily identifiable through the presence of atrophy and fasciculations as well as electromyography analysis. We have evidence that UMN commitment is more unusual. Signs of pyramidal release are not always marked and, only recently, non-invasive tests to reveal cortical spinal tract commitment have been incorporated into the medical practice.

The MRI examination with sequences ST1 with MTC and transcranial magnetic stimulation (TMS) has identified abnormalities in the cortical spinal tract, thus becoming a useful tool in ALS diagnosis. In patients where there is no clinically defined involvement of motor tract, image and TMS analysis must be requested. In the absence of abnormalities, ALS diagnosis should be placed in suspicion. Moreover, the atrophy of the motor cortex, with severe loss of grey substance (cell body) and its brain connections are highlighted by recent advances in radiology and proton emission tomography (PET), which quantifies the metabolism of regional areas of motor cortex, associated with quantifying the volume by voxel, making early diagnoses possible. Transcranial magnetic stimulation has become an auxiliary method for early diagnosis through the quantification of the decrease in speed within the motor central nervous system in patients with MND / ALS.

Pyramidal signs and muscle atrophy – Characteristically in ALS, the signals of pyramidal release must be present at sites above the sites where the muscular atrophy is evident. The presence of muscle atrophy and signs of pyramidal release below the region of common cord nerve in the diagnosis, refer to a myelopathy, thus one should consider various causes, including spinal cord compression, tumor, syringomyelia, syringobulbia.

Temporal development – The abnormal temporal evolution, with a challenge in the chronic and progressive course of disease that involves the motor neuron can characterize changes in their etiology, and thus open therapeutic possibilities.

Time becomes a factor in the diagnosis in both false-positive and false-negative cases and should be seen in serial appointments, as well as abrupt changes in clinical signs, complaints of uncharacteristic symptoms typical of a motor neuron degenerative disease and the evolutionary course of the disease. Thus, the erroneous early diagnosis or lack of introduction of a feasible therapeutic measure would be deployed.

Electroneuromyography and nerve conduction studies (ENMG)

Due to the lack of a definitive marker for MND / ALS diagnosis, the ENMG study is a key element not only to detect abnormalities consistent with the disease diagnosis, showing activity of acute neuropathy damage and reinnervation, but also to rule out possible syndromes that mimic MND / ALS.

The examination must encompass all the spinal territories, that is, the four limbs plus the tongue (hypoglossal nerve), including the paravertebral, abdominal and thoracic muscles. In addition, there is search for conduction motor blocking, both distal and proximal, in upper and lower limbs. In the light of new findings, such as the emergence of sensory changes or sudden changes in the course of evolution of the clinical situation, the need for the repetition of ENMG examinations is not infrequent.

Considering clinical experience in outpatient clinic of motor neuron disease, attention must be drawn to these clinical features, which were identified and valued, without which many of our patients would have been attributed erroneous ALS diagnosis.

Differential diagnoses that mimic the MND/ALS present, as predominant syndromes, lower motor neuron involvement, in which the major diseases are multifocal motor neuropathy, spinal muscular atrophy, or diseases that affect the cortical spinal cord tract in its portion, such as neurofibromatosis type I and neoplasms of cervical spine, degenerative involvement associated with enzyme deficiencies, as hexosaminidase A and B and spastin (hereditary spastic paraparesis), among others.

The onset of unusual signs and symptoms in the clinical course, in the follow up also give way to other diagnoses, as well as long-time survival. Systemic involvement associated with endocrinal abnormalities, gynecomastia, insulin resistance and high levels of testosterone have led us to diagnose Kennedy disease.

In conclusion, patients who have had false-positive diagnosis presented certain clinical characteristics that would put the diagnosis in doubt. They are: [1] Age below 30 at the beginning of clinical manifestation; [2] Form of initial clinical presentation with: abrupt installation, bilateral and symmetrical muscular weakness, proximal compromising; [3] Clinical presentation with: muscular weakness without corresponding atrophy, absence of pyramidal signs in medullar regions below the region of com-

Albeit not specific, fatigue and fatigability can be early symptoms of MND/ALS, as seen in three patients.

REFERENCES