Frontotemporal dementia in amyotrophic lateral sclerosis: from rarity to reality?

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Amyotrophic lateral sclerosis (ALS) was initially described in 1869 by Jean-Martin Charcot.[1] ALS is a progressive neurodegenerative disease that affects motoneurons in the cortex, medulla, and spinal cord.[2,3] The lesion of Upper Motor Neuron (UMN) generates spasticity, weakness, and hyperreflexia. The affection of Lower Motor Neuron (LMN) justifies the observed fasciculation, fatigue and weakness. In the presence of bulbar dysfunction, it is seen dysarthria, dysphagia, weakness and tongue fasciculations.[4,5] Commonly, it leads to death by respiratory failure a few years after onset of first symptoms.[6]

ALS is a multifactorial disorder, which involves both glial cells and neurons. According to Moura MC and colleagues (2016), the main known pathogenesis mechanisms include oxidative stress with damage to RNA, mitochondrial dysfunction, impairment of axonal transport and glutamate excitotoxicity. There are also described: protein aggregation, endoplasmic reticulum (ER) stress, abnormal RNA processing, neuroinflammation and excitability of peripheral axons.[7]

Genetic and environmental factors may play an important role, influencing the susceptibility to ALS due the interactions between them and epigenetics effects, which leads to a phenotypic individuality. Approximately 90-95% of patients have sporadic ALS, and the remaining 5-10% of them has familial ALS.[8]

According to El Escorial and Airlie House Criteria, a definitive diagnosis of ALS requires the following features: clinical, electrophysiological or neuropathological examination that identifies LMN degeneration. By clinical examination of UMN, degeneration and progression of the motor syndrome within a region or to other ones are necessary. Besides, it is fundamental to rule out possible imaging, electrophysiological or pathological evidence of another disease that may justify clinical signs of UMN or LMN deterioration.[9,10]

The neurophysiological investigation should include nerve conduction studies, electromyography, and, less commonly, transcranial magnetic stimulation.[11] Electromyography and nerve conduction are useful for the identification of LMN loss and illustrates LMN loss (*i.e.*; fibrillation potentials, positive sharp waves, and chronic neurogenic changes).[5,12]

Regarding neuroimaging, some of them have been used to aid in the diagnosis of ALS, but its success is still variable. Studies with magnetic resonance imaging (MRI) show motor system atrophy, especially in pyramidal tract. At a more advanced stage, changes might be seen already in motor cortex.[13] Diffusion tensor imaging (DTI), also known as tractography, arises as a promising method. Considering its higher sensitivity to evaluate microstructural function and integrity of white matter fibers, DTI would evince the early damage of UMN. Those signs might be subtle and hamper the definitive diagnosis of ALS. However, since the current findings are non-specific, and imaging is more useful to discard diseases that mimic ALS, MRI studies have not been established as a routine use yet.[14,15]

The relationship between ALS and dementia dates back in 1950 when it was linked to aphasia and Pick's disease.[16,17] In 1960s, the first studies describing the association of ALS and Parkinsonism-Dementia Complex (PDC) were published, referring to the indigenous Chamorro population, native inhabitants of Guam.[18,19] The higher incidence of the disease among patients' relatives compared to control ones launched the basis of the familiar aspect of ALS+PDC.[20] Forty years after the former reports, greater risk persisted, being the new cases among patients' relatives even in greater number than expected.[21] Furthermore, tau pathological features found both in cases of ALS and ALS+PDC patients seal the relation between ALS and dementia development.[22]

Following this reasoning, the overlap of ALS and Frontotemporal Dementia (now referred to as frontotemporal lobar degeneration – FTLD) was also registered through punctual and prospective analysis of FTLD patients with no known diagnosis of ALS or family history of ALS.[22] It is worth remembering that ubiquitin-positive neuronal inclusions have been found both in some cases of ALS and in FTLD related to motor neuron disease, whose findings tends to arise promptly, endorsing the hypothesis of a spectrum binding both diseases.[23,24] TAR DNA-binding protein of 43 kDa (TDP-43), a nuclear factor that works in transcriptional expression and exon skipping, was proved to be present in neuronal cytoplasmic inclusions and dystrophic neuritis in the hippocampal region and temporal cortex of FTLD-Motor Neuron Disease (MND) and FTLD-MND-type cases. These inclusions and neuritis were comparable to that of ubiquitin-positive inclusions and neuritis. In the spinal cord of the ALS and FTLD-MND cases, skein-like inclusions were positive for ubiquitin and also for polyclonal and monoclonal antibodies to TDP-43.[24] Some mutations involving TDP-43 have been identified, for instance, the missense mutation A315T within a highly conserved region of exon 6 with an autosomal dominant pattern of inheritance.[25] Recently, this mutation was demonstrated to induce ER stress-mediated apoptosis besides autophagy, as a self-protection to neuronal toxicity *in vitro*.[26]

In 2006, Morita and colleagues issued the results of a genome-wide linkage analysis of this association. They studied a four-generation, 50-member Scandinavian family, whose five individuals were diagnosed with ALS and nine with FTD. It was identified a new locus for ALS/FTD: chromosome 9p21.3-p13.3.[27] Still, DeJesus-Hernandez and colleagues (2011) detected the polymorphic GGGGCC hexanucleotide repeat in a noncoding region of chromosome 9 open reading frame 72 (C9ORF72) as the Chromosome 9p21-Linked familial FTD/ALS.[28]

This expansion comprises an intronic region of C9orf72 between non-coding exons 1a and 1b, which are alternatively spliced to generate three RNA variants. The hexanucleotide repeat expansion forms RNA is believed to sequester RNA-Binding Proteins (RBPs) and impair their function in RNA processing. The repeat expansion also undergoes translation that results in dipeptide repeat proteins (DPRs), which form inclusions in CNS. Finally, it induces the mislocalization and aggregation of TAR DNA-binding protein 43 (TDP-43).[29]

Byrne and colleagues (2012) verified that their sample of 39 ALS patients with more than 23 hexanucleotide repetitions represented a sub phenotype. This one was characterized by a lower age of onset, cognitive and behavioral impairment, specific neuroimaging changes (substantial non-motor cortex changes on high-resolution 3T structural MRI and reduced grey-matter volume), a robust family history of neurodegeneration and reduced survival. The repeat expansion was absent in patients who had sporadic ALS and no behavioral abnormalities and was present in high proportion in ALS patients with a predominance of executive cognitive impairment and behavioral change.[30] However, it must be remembered that repeat expansion was found both in familial as sporadic cases. Finish cohort of 402 ALS cases and 478 controls registered hexanucleotide repeat expanded in 113 (28.1%) patients, being calculated as 46.4% of familial and 21.0% of the sporadic cases.[31] Recent study among Italian patients confirmed the primary role of C9orf72 in increasing the risk of FTLD in ALS patients but also showed the importance of APOE 2 allele to a lesser extent to this relation.[32]

Radford and colleagues (2015) summarize the pathological protein inclusion that reinforces the continuum idea that bound ALS to FTLD. At one end, there is SOD1 inclusion, exclusively of ALS and positive in 2% of the cases. At the other end, there is Tau inclusion, exclusively of FTLD and positive in 40-45% of the cases; in the middle, there are TDP-43 inclusions, positive in 90-95% of ALS and in 45-50% of FTLD cases. It is highlighted the disturbance of microglial in both diseases. Loss of TREM2 protein function (exclusively expressed by microglia in the CNS) and mutations of progranulin (GRN, a neuroinflammatory modulator expressed by neurons and microglia) lead to dysfunctional microglial phagocytosis and altered inflammatory responses. They are implicated as risk factors for ALS, FTD, and Alzheimer's disease.[33]

Another important feature is the image study. The association ALS-FTD seemed to express higher atrophy ratings compared to ALS patients for the motor cortex, anterior cingulate, temporal and occipital lobes and a statistical trend for the orbitofrontal cortex.[34,35] DTI shows reduced white matter integrity relative in frontal and temporal regions when comparing to healthy older adults. Positron emission tomography (PET) and functional MRI (fMRI) reveals alterations in brain function and connectivity during executive task but also in resting state. Moreover, mutation in chromosome 9 is related to a greater frontal lobe thalamic, temporal lobe, insular, and posterior cortical atrophy than other mutations.[35] Thus employment of this MRI rating scale would serve as a complement clinical diagnostics of patients in the ALS-FTD continuum.

Nowadays, it would be a restrained practice to consider only the motor aspects of ALS, even though it is a widespread clinical and electrophysiological disease. Cognitive impairment may be already seen in the absence of dementia. Moreover, the association with dementia diagnosis has already been reported many decades ago. It should draw our attention for the atypical characteristic that preponderates in these cases of dementia: in the isolated indigenous population of Guam, the Parkinsonism-Dementia Complex became target of study among ALS patients. However, in general population, the fronto-temporal lobar degeneration turned into a prevalent association described in ALS cases.

The more we know about the possible symptoms and complementary assessment related to ALS, the better is the standard of care from doctors and health practitioners for this complex disease. Concerning the FTLD overlap, the researches have been advanced, allowing the discovery of special markers, as TDP-43 mutation and Cr9orf72 expansion. These mutations have a significant prevalence value in ALS, which might be useful as corroborative item in the diagnosis. Themolecular subtract also justifies the genetic counseling, especially in the at-risk group (*i.e.*, patients with evidence of cognitive and behavioral impairment or a family history of neurodegenerative disease). Fortunately, once there is an individualized molecular marker, many opportunities are created to the developing of new treatments, more target specific and possibly, more effective.

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