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Review Article

Nucleus accumbens changes in amyotrophic lateral sclerosis

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Abstract: Amyotrophic lateral sclerosis (ALS), a representative example of motor neuron disease, is a progressive and fatal neurodegenerative disorder. The nucleus accumbens (NA) is the ventral striatum's main part and is considered as a modulator of the human brain's reward network. The purpose of this article is to review the current knowledge regarding NA changes in ALS patients. The NA involvement in ALS includes volumetric, cellular and molecular changes. There are recent imaging and pathological studies revealing NA atrophy in ALS, a finding which seems to be related to neuronal loss and protein deposition in this area. The clinical significance of NA atrophy in these patients is not currently fully understood. Perhaps it could be correlated with apathy, behavioral disturbances and cognitive impairment that ALS patients sometimes manifest.

Keywords: Amyotrophic lateral sclerosis, atrophy, dopamine, nucleus accumbens

Introduction

Amyotrophic lateral sclerosis (ALS) is a rare progressive and fatal neurodegenerative disorder and a representative example of motor neuron disease [1-3]. Its clinical manifestations include muscle atrophy (predominately affecting the limbs) which causes severe movement difficulty and disability [1, 2]. Its pathogenesis remains unclear and its prognosis is bad, with the majority of patients dying within 3-5 years following symptoms' onset [1-3]. Central cholinergic system disturbance occurs in various neurodegenerative diseases such as ALS and is strongly related to the development of clinical symptoms [4]. The brain areas that demonstrate atrophy in ALS seem to be parts of three parallel circuits between the frontal lobe and subcortical structures, namely limbic, associative and motor circuits, suggesting probable diffuse frontal-subcortical dysfunction [5, 6]. The main clinical patterns of ALS include: 1) limb-onset ALS with combined limb signs upper and lower motor neuron; 2) bulbar-onset ALS, characterized by speech and swallowing difficulties, whereas limb findings develop later in the course of the disease; 3) primary lateral sclerosis with pure upper motor neuron involvement (less common); and 4) progressive muscular atrophy, with pure lower motor neuron involvement [2].

The distribution of the central nervous system's cholinergic neurons includes the nucleus accumbens (NA) [4]. The NA is the main part of the ventral striatum and a modulator of the human brain's reward network. It consists of two main parts; a core, laterally, which is mainly connected to the extrapyramidal motor system and a shell, medially, mainly connected to the limbic system. It is considered as a node between the reward network and executive control network through its projections to the limbic system and frontal cortex [7]. It has numerous connections with the limbic system and ventromedial prefrontal cortex and has a crucial role in various emotional and cognitive functions [7-9]. It is considered as the main pleasure center of the brain due to its role in motivation, reward and laughter [10, 11].

Given that ALS causes atrophy in limbic structures connected to the frontal lobe, one would expect that NA would be affected as well. But is this the case with ALS? Whereas involvement of the NA in other neurodegenerative disorders such as its atrophy in Parkinson's disease (the so called "Mavridis' atrophy") has been established [7, 11], data about NA changes in ALS are very limited. Under this prism, the aim of this review article is to summarize the current knowledge about the way that ALS affects the NA.

Nucleus accumbens involvement in amyotrophic lateral sclerosis

Volumetric changes

NA atrophy in ALS patients has been revealed by several studies. An imaging study using volumetric evaluation and diffusivity measurements in brain magnetic resonance images has shown that ALS patients present atrophy and altered diffusivity measurements in the NA area [12]. This is in accordance with a pathological study that correlated the third stage of ALS disease (as a TDP-43 [transactive-response DNA-binding protein 43 kDa] proteinopathy) with NA atrophy [13]. Another imaging study, with analysis of the subcortical nuclei shape in ALS, has also revealed NA atrophy affecting specifically the interior basal surface of the right NA [5]. Other authors have shown trend without statistical significance of NA atrophy in non-demented ALS patients [14].

Bede et al. (2013) [12] aimed to characterize in vivo the extent and nature of the involvement of basal ganglia in ALS genotypes and studied 39 patients suffering from ALS (30 were *C9orf72* negative and 9 carried expansion of the *C9orf72* hexanucleotide repeat). *C9orf72* repeat negative ALS patients showed significant reduction of the volume in the right NA, left caudate nucleus and hippocampus. The authors found that ALS is correlated with widespread involvement of the basal ganglia nuclei and supported caudate, hippocampal, and NA atrophy as key features of the disease. According to Bede et al. [12], malfunction of frontostriatal networks contributes to the distinct neuropsychiatric profile of ALS, dominated by apathy, executive dysfunction, and social cognition deficits. They also suggested that structures of the subcortical gray matter should be included in future studies of biomarkers in ALS [12].

Machts et al. (2015) [15] evaluated changes of the basal ganglia along the ALS-ALS-frontotemporal dementia (FTD) continuum by using multiple, complementary radiological techniques. Patients with ALS-FTD exhibited pathological changes of the NA (among other gray matter areas). Interestingly, NA volume showed negative correlation with the score of apathy in these patients [15].

Furthermore, a volumetric study comparing ALS patients to primary lateral sclerosis (PLS, a motor neuron disease type predominantly affecting upper motor neuron) patients, showed NA atrophy in both diseases [16]. In ALS patients there was a predominance of atrophy in the left NA and left pallidum. Regarding percentage of volume reduction, NA was the most affected area in PLS, and in ALS patients NA was the first and amygdala the second most affected area [16]. Other studies have also revealed NA atrophy in PLS patients [17, 18].

Given that NA controls aggression and impulsivity, its pathological changes can be related to behavioral disturbances of ALS patients [5, 15, 19]. Additionally, the relatively frequent presentation of apathy among PLS patients [18], might be attributed to NA atrophy, based on the fact that this nucleus normally regulates reward and motivation processing [15, 19].

Cellular changes

Kato et al. (1994) [20] used large brain sections to examine the topographic distribution of degenerative changes in five demented patients with sporadic ALS. The characteristics of dementia included impaired shifting from one thinking line to another, impaired perseveration, emotional disinhibition, and impaired cognition and judgment. Neuropathological examination showed loss of neurons in the NA, basolateral nucleus of the amygdala, and hippocampal subiculum, among other findings. The affected regions belong to the limbic system and its associated areas which are the sources of psychiatric problems, such as emotional disturbance, in patients suffering from ALS. The authors supported that psychological problems in ALS need further investigation under the prism of an affected limbic system [20].

Su et al. (1996) [21] reported a 72-year-old man affected by sporadic ALS who presented

Table 1. Summary of the NA involvement in ALS

- ► Macroscopic level: atrophy
- ► Cellular level: neuronal loss, amyloid plaques
- ► Molecular level: ↓ DA & DARs, TDP-43 deposition

ALS, amyotrophic lateral sclerosis; DA, dopamine; DARs, dopamine receptors; NA, nucleus accumbens; TDP-43, transactive-response DNA binding protein 43 kDa.

at 70 years with amyotrophy of distal upper limbs, which evolved to respiratory distress and gait disturbance. Neuropathological investigation revealed many amyloid plaques in the NA, neocortex, and amygdala, among other findings. Although he had no clinical findings of either parkinsonism or dementia, the final neuropathological diagnosis was sporadic ALS, Alzheimer's disease (AD), as well as incidental Lewy body disease [21].

Molecular changes

Fu et al. (2017) [3] studied 17 ALS patients who underwent ^{18}F-fallypride positron emission tomography/computed tomography scans and completed cognitive tests to assess the distribution of dopamine receptors in their brains. They found decreased binding affinity of ^{18}F-fallypride in the bilateral NAs, among other regions. They supported that the significantly decreased levels of dopamine receptors in specific areas may contribute to the manifestation of mild cognitive impairment in ALS patients [3].

In 15% of families, familial ALS is linked to mutated gene of the copper-zinc superoxide dismutase (*Cu/Zn-SOD*), a vital enzyme of cellular defense mechanisms against free radicals [22]. Kostic et al. (1997) [22] used a mouse model of familial ALS (transgenic G1H mice), based on the expression of mutated human *Cu/Zn-SOD*, to examine the influence that the transgene expression had on the dopaminergic neurons of the midbrain, cells rich in this enzyme. At the time that half of the spinal motor neurons were lost, simultaneous reduction of dopamine levels in the NA, caudate and putamen of transgenic mice was observed [22].

Another pathological study, comparing brains from patients with ALS and AD, demonstrated significant thinning of the subiculum, as well as astrocytosis, in ALS as opposed to AD. This thinning was often accompanied by TDP-43 deposition in the NA, entorhinal and transentorhinal cortices suggesting that these three areas may communicate [23].

Table 1 summarizes our current understanding of the NA involvement in ALS. We would mention as shortcoming of the present review article the fact that there is very limited published research on how does ALS affect the human NA. Future research is necessary in order to clarify the role of NA atrophy in the clinical manifestations of ALS, as well as its onset in the course of the disease.

Conclusion

Although the NA role in other neurodegenerative disorders is well known, the data regarding its involvement in ALS is limited. There are recent imaging and pathological studies revealing NA atrophy in these patients. NA atrophy seems to be related to neuronal loss and TDP-43 deposition in this area. The clinical importance of this atrophy has not been fully established yet. Perhaps it could be associated with apathy, behavioral disturbances and cognitive impairment that these patients sometimes present. Further research is mandatory in order to investigate these hypotheses and provide directions for future research.

Disclosure of conflict of interest

None.

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