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REVIEW

Apathy as Non-Motor Manifestation in Amyotrophic Lateral Sclerosis

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Although the term of amyotrophic lateral sclerosis (ALS) is often used interchangeably with motor neuron disease, ALS is universally accepted as a multisystem disorder. Cognitive impairment is an acknowledged feature of ALS, affecting language, memory and behaviour, and apathy is considered to be the prevalent behavioural alteration in ALS. It can be divided in three subtypes: executive, emotional and initiation apathy. Out of the three subtypes, initiation apathy is common among patients with ALS. Even in patients that do not meet the criteria for ALS with frontotemporal dementia, low-key neuropsychiatric and cognitive changes can be observed. Apathy has also been found to be systematically associated with disruptions in medial frontal cortex and subcortical structures in several neuroimaging studies that confirm the pre-existing brain lesions in the early stages of this disease. Thus, there is a growing body of evidence that motor signs and symptoms are accompanied or even preceded by cognitive and behavioural alterations, and screening for non-motor signs and symptoms can be clinically relevant.

Keywords: amyotrophic lateral sclerosis, non-motor manifestation, apathetic syndrome, depression

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Introduction

Amyotrophic Lateral Sclerosis (ALS) is an uncurable relentlessly progressive neurodegenerative disorder causing muscle weakness and culminating in fatal dysphagia and respiratory failure [1]. It is no longer believed to be a pure motor system degeneration. Cognitive impairment is an acknowledged feature of ALS and it affects emotion processing, social cognition, executive functions and behaviour. They are all identified and described as extra-motor signs and symptoms of the disease [2,3].

Screening for Non-Motor Manifestations

According to several recent studies, more than 50% of patients with ALS experience cognitive dysfunctions over the course of the disease (i.e., changes in language, behaviour, memory, social cognition) [4]. About 30%-40% of patients with cognitive dysfunctions present with cognitive impairment alone, 10% have only behavioural impairment, and 10-15% reach criteria for frontotemporal dementia (FTD) [5].

In order to quantify these non-motor manifestations a new assessment instrument was developed by Abrahams et al. (2014) - the Edinburgh Cognitive and Behavioural ALS Screen (ECAS), a screening test developed specifically for ALS patients. Its design allows assessing cognitive performance irrespective of physical disability, which may be a confounder in ALS [6,7]. ECAS is considered the gold standard for the assessment of cognition and behaviour in ALS and it is widely used as a screening tool for ALS-specific (executive functions, verbal fluency, and language tests) and ALS non-specific subtests (memory and visuospatial tests) [8], and a carer behaviour screen of five domains pertaining to FTD [7].

The Apathetic Syndrome

Apathy is acknowledged as the prevalent behavioural alteration in ALS and other neurodegenerative diseases[9]. Studies show that it occurs in 30–60% of ALS patients[10]. Marin (1996) defines apathy as "lack of motivation or decreased motivation towards goal-directed behaviours" [11]. He also refers to the symptom of apathy as loss of motivation as a result of disruption in intellect, emotion, or level of consciousness [12], suggesting thus its multidomain structure.

Strong et al. (2017) revised the criteria for ALS with behavioural impairment and included apathy as a main symptom [13]. Apathy was conventionally measured as a unidimensional symptom [10]. Nevertheless, recent findings suggest that apathy in ALS can be divided in three subtypes that can be measured using a specifically designed instrument, the Dimensional Apathy Scale (DAS): (1) executive apathy, referring to planning, attention or organization impairments, (2) emotional apathy, concerning emotion integration deficits, and (3) initiation apathy, pertaining to impaired self-generation of behaviours or cognition [10,14].

Initiation apathy, which is associated with impaired origination of thoughts or actions, has been found to be the most common subtype in patients with ALS. It is also associated with poor results on verbal fluency tests [15], which have been employed as highly sensitive instruments to measure executive dysfunction in clinical settings [3]. Thus test results show patients are lacking intrinsic response generation, planning and goal management strategies [16].

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Apathy has been found to be systematically associated with disruptions in medial frontal cortex and subcortical structures in several neuroimaging studies [17]. Femiano et al. (2018) aimed to prove a potential association between brain microstructural damage and apathy in the early stages of ALS. They used diffusion tensor imaging (DTI), which is able to investigate white matter integrity, and King's clinical staging system, a validated staging system for ALS. Their findings revealed that, in early stages of disease, ALS patients without cognitive or behaviour dysfunctions may present with microstructural changes in motor and respectively, extra-motor white matter tracts, namely corticospinal tracts, midbody of corpus callosum and bilateral anterior cingulate bundles [9].

Woolley et al. (2011) aimed to determine whether apathy in ALS relates to structural changes associated with the degenerative process, also using DTI with fractional anisotropy. Their results are consistent with the previous study, confirming that there are neuroanatomical grounds for apathy in non-demented ALS patients [18]. The anterior cingulum is known to be involved in both the regulation of goal-directed and socioemotional behaviours and inhibitory control, explaining thus the strong association between the altered anterior cingulum bundle and apathy in ALS [9,19].

The inferior parietal lobule is another region believed to be involved in movement intention and movement perception, and thus disruptions in this area may be related to the occurrence of apathy [20]. Tumati et al. (2018) concluded that altered neural input from this region may affect intentional goal-directed actions. Patients find it difficult to initiate behaviour and they need instructions to perform regular or habitual actions [21].

Apathy and Depression

Depression is considered to be a marker of global neurodegeneration, albeit a nonspecific one [22]. Nevertheless, depression in patients with ALS may be an underdiagnosed comorbidity, mainly because clinical signs of cognitive impairment may confound depressive symptoms [23,24].

Caga et al. (2016) examined the relationship between apathy levels, mortality and survival time. They also assessed the link between specific symptom clusters of depression and apathy. Depression symptoms were categorised as follows: depression with demoralization and depression with anhedonia. Their results showed there was no significant association between the level of apathy and depression with demoralization (feelings of worthlessness and hopelessness). In contrast, depression with anhedonia (loss of interest or pleasure) was more frequent in patients with mild and moderate to severe apathy [25].

Differentiating between apathy and anhedonia is challenging. Abnormalities in the anterior cingulate circuits are thought to be implicated in the pathophysiology of both apathy and depression [25]. Another study identifies the ventromedial sectors of the prefrontal cortex as the neural pathways underlying depression [26], nevertheless lesions in the dorsolateral sector of the prefrontal cortex remain a common structural marker for both apathy and depression [25].

Apathy as a Premorbid Condition

As mentioned before, recent findings suggest that patients with ALS, who do not make up for the 10 to 15% diagnosed with FTD, also present with low-key neuropsychiatric and cognitive changes [27], apathy being most often reported. Mioshi et al. (2014) study results confirm the hypothesis that neuropsychiatric symptoms precede classic motor features of ALS [27]. In another study, they also prove that significant cortical atrophy is present in patients with ALS and neuropsychiatric symptoms. However, this cortical alteration lacks in those who only exhibit motor symptoms [28]. Their results support the conclusions of the abovementioned studies of Femiano and Woolley that confirm the pre-existing brain lesions correlated with apathy in the early stages of the disease.

Interestingly enough, in the ALS context, apathy used to be consistently misread as patients being unusually compliant [6]. Mehl et al. (2017) surveyed the physicians' assessment of the personality structure of their ALS patients. The authors' endeavour was motivated by several studies and reviews on ALS where physicians described patients as "genuinely pleasant", "pleasant and warm", or "unusually stoic". They used a multidimensional personality questionnaire (the shortened version of the "NEO Five-Factor Inventory"), and they concluded that helpfulness and compliance seem to be prevalent in ALS patients' perceived behaviour [29].

Grossman et. al. (2006) conducted a caregiver-based study where ALS patients were rated a lower score on "openness" as a premorbid personality trait compared to patients with other chronic medical conditions (lung cancer, multiple sclerosis or brain glioma). Openness describes individuals with conventional values, who would follow the advice of their physicians and comply with medical treatment. Their results suggest that there may be premorbid personality features that are common among patients with ALS [30].

Conclusions

Although the term of amyotrophic lateral sclerosis is often used interchangeably with motor neuron disease, ALS is universally accepted as a multisystem disorder. There is a growing body of evidence that motor signs and symptoms are accompanied or even preceded by cognitive and behavioural changes. Notwithstanding the inexorable progress and fatal outcome of ALS, screening for non-motor signs and symptoms can be clinically relevant, allowing optimal clinical approach and treatment tailored to the needs of each patient.

Given the impact of being diagnosed with an incurable disease, is there a chance that behavioural alterations be

erroneously considered a reasonable response to the diagnosis? Do lack of motivation and loss of interest manifest as a consequence of such diagnosis or are they actually a tell-tale sign of early behavioural impairment? Is apathy a prodromal phase of ALS? To what extent are the non-motor signs and symptoms concealed by physical deficits? Can we buy ALS patients more time? These are questions that remain to be addressed.

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AM (Conceptualization; Supervision; Writing – review & editing)
IO (Conceptualization; Investigation; Writing – original draft)
RB (Supervision; Validation; Visualization)

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