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Mood disorders and cognitive impairment in the course of increasing disability in patients suffering from amyotrophic lateral sclerosis

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Summary

Amyotrophic lateral sclerosis is a progressive, incurable, multi-system degenerative disease which leads to physical disability and cognitive impairment as well as depression resulting in physical and mental suffering.

Aim: The aim of this paper was to evaluate the incidence rate of mood disorders in the form of depression and cognitive impairment in the course of exacerbating motor disorders during a six-month observation of ALS patients.

Material: The study covered 20 people (5 women, 15 men), 10 with bulbar-onset ALS and 10 with limb-onset ALS.

Methods: The patients were examined three times with 3-month intervals during a six-month period. Physical fitness, cognitive functions and depression were subject to evaluation. Mira Stambak's line-drawing test and the 10-meter walk test were used to evaluate fitness. The evaluation of cognitive functions was based on a psychometric screening test – *DemTect*. *The Beck Depression Inventory* (BDI) was used for the diagnosis of depression.

Results: The analysis of the results showed that impaired physical fitness is accompanied by cognitive impairment, with a tendency to progression over a six-month period. Depression also presented a relationship with motor disability; however, the intensity was transient in the course of ALS.

Conclusions: (1) The gradually developing motor neuron loss of the anterior horns of the spinal cord is reflected in physical fitness impairment in the ALS patients. (2) The exacerbation of cognitive impairment accompanies the intensifying physical disability. (3) The exacerbation of depression in the course of amyotrophic lateral sclerosis is of transient nature.

Key words: amyotrophic lateral sclerosis, depression, cognitive impairment

Introduction

Amyotrophic lateral sclerosis (ALS) is a degenerative, multi-system and multi-factor disease of unknown origin and pathogenesis. It is linked to neuron damage, both of the central and peripheral nervous system, as well as other nerve cells. From the histopathological point of view, the unit is determined as degeneration of the upper and lower motor neuron [1, 2]. ALS comes under various names: Charcot disease, motor neuron disease, while in the USA also Lou Gehrig's disease named after the famous American baseball player Henry Lou Gehrig, who died of ALS in 1941. ALS is a rare disease, and the incidence rate worldwide is estimated to amount to approx. 7 in100 thousand. The disease affects the middle-aged and the elderly – the peak incidence rate applies to people aged 65; 20% of the cases have its onset after the age of 70, 10% before the age of 40 and 5% even before 30. The problem affects men more often than women (1.5:1). Most of the ALS cases are of sporadic nature (SALS, sporadic amyotrophic lateral sclerosis), 5–10% constitute familial cases (FALS, familial amyotrophic lateral sclerosis) [3, 4]. The disease has a latent onset, rarely subacute one. The clinical image is characterized by multiple symptoms originating from various anatomical regions. The symptoms include the loss of muscle strength and amyotrophy. In the case of a well-developed disease, there are spastic symptoms of lower extremities with hyperactive deep reflexes and bilateral Babiński sign and fasciculation. Moreover, bulbar and pseudo-bulbar signs are observed in the form of dysarthria and difficulty swallowing as well as breathing problems, which may appear in various phases of the disease [2, 4].

Classical descriptions of amyotrophic lateral sclerosis perceive it exclusively as a motor neuron disease. Contemporary research shows that ALS is a consequence of changes in many systems, i.e., neocortex, olfactory brain and cingulate gyrus. The consequences of the changes are cognitive impairment and executive function disorders observed in 35–55% of the cases, but not dementia. The disorders concern the sphere of emotions, weakened memory and executive functions. Patients have difficulty focusing attention, recollecting some words or phenomena, as well as impaired word fluency, planning or organization abilities. There may also be visual and spatial disorders.

Cognitive disorders may precede or follow the exposure of motor neuron damage symptoms [5–7]. ALS may also accompany other neurodegenerative diseases, including dementia, most often frontotemporal dementia, more rarely the patients present changes typical of Alzheimer's disease. In the case of SALS, dementia is present in approx. 5% of the cases, in FALS in 15% of the cases [8, 9]. Epidemiological studies in recent years show a significantly increased rate of ALS patients with observed cognitive function disorders and dementia. Bulbar signs of the disease dominate in majority of the patients with concomitant dementia. Intensified dementia correlates with the exacerbations of motor neuron damage symptoms [10, 11].

These patients also suffer from emotional lability, being a sign of pseudobulbar affect, with inadequate laughter or, more often, crying. It may be wrongly perceived

as reactive depression in the course of the underlying disease. Emotional lability is perceived as a sign of disinhibition of the complex reflexes participating in emotional expression [2].

ALS patients may also present mood disorders. Symptoms of depression of transient nature are observed in nearly half the patients, while depression in approx.10% [12–15]. The percentage of patients with depression as the death of the patient approaches does not increase. The terminal phase of the disease includes sleep disorders, anorexia, the feeling of hopelessness and fatigue. Very often, the declared willingness to accelerate death in the terminal stage of the disease is related to the lack of hope of recovery, therapeutic nihilism or poor belief, rather than the presence or exacerbation of depression [16, 17].

ALS diagnosis is based on the clinical image, neurological examination and electrophysiology study, and in some cases also MRI and MR tractography [2]. Currently, the clinical classification of ALS includes the modified El Escorial criteria dating back to 1998 [18].

There is no effective treatment which would allow to inhibit the development of the disease; the only medication of proven minor effectiveness in prolonging the life in ALS patient is Riluzole [3]. The disease is of a chronically progressive nature, with varied duration (on average 5 years). Along with the development of the disease, and so the increasing motor function damage, there is a gradual impairment of the independent functioning of the patients in everyday life. Due to the above, the quality of the patients' lives is greatly affected [19–21]. Additionally, it is affected by the concomitant depression, which also shortens their life.

Aim

The aim of the study was to assess the presence of mood disorders in the form of depression and cognitive impairment in the course of intensifying motor function impairment during a six-month observation of ALS patients.

Material

The study included people who reported to the Neurology Ward for diagnostic purposes as regards amyotrophic lateral sclerosis and later for the monitoring of the course of the disease. The study included 20 patients with clinically proven or probable ALS, determined based on the El Escorial criteria. Among the patients, there were 5 women and 15 men aged 43–85 (mean age 65.5, $SD \pm 13$). Patients presented no other ailments that would impair their physical fitness.

The patients were informed about the scope of the clinical study and the types of tests to which they orally gave their consent.

Methods

A written enquiry was made to the Bioethics Committee as regards the methodology of research. In accordance with the determinations, the consent of the committee to perform the study was not required, since it was only diagnostics and aimed at monitoring the course of the disease, rather than an experimental study.

All patients underwent a complete neurological examination along with the assessment of the upper and lower motor neuron, the assessment of manual dexterity, gait, cognitive functions and mood. Based on the clinical assessment, the patients were divided into two groups: (a) bulbar-onset ALS patients (predominant bulbar signs, i.e., dysarthria, dysphagia); (b) limb-onset ALS patients (predominant symptoms included the weakening of the muscle strength in limbs).

The examinations were performed by the authors three times over a six-month period. Measurement A was a preliminary one, measurement B took place after three months, and measurement C after another 3 months. The clinical study and all the tests were performed for the whole group and separately for bulbar-onset ALS patients and limb-onset ALS patients.

A test aimed at the evaluation of limb lateralization in children and teenagers was used to assess the manual dexterity of the patients, i.e., Mira Stambak's line-drawing test [22]. In the course of every test, the more dexterous hand was selected, and its result was compared to the control group of 20 healthy (in terms of motor skills) patients aged 20–85 (mean age 59.5, *SD* ± 18). In the case of Mira Stambak's test, the higher the result of the patient, the greater the dexterity of upper limbs.

Gait was assessed with the application of the 10-meter walk test [23]. Also in this case, the results were compared with the control group, the same one as in the case of Mira Stambak's test. In the case of the 10-meter walk test, the lower the result, the better the gait.

The Beck Depression Inventory (BDI) was used to evaluate the mood of the patients. The results were compared to the generally assumed standards for the scale [24]. Two types of analyses were performed in relation to this test: the first one took into account the normal condition and depression of the patient without categorizing its severity, while the other analysis considered the severity of depression of the patient (mild, moderate and severe depression). The more points the patients obtained in the test, the greater the severity of depression.

Cognitive functions were analyzed with the use of a screening test called *DemTect*, used to detect mild cognitive function disorders and dementia. The test evaluates a wide scope of cognitive functions despite the fact that it has only five tasks (a word list, a number transcoding task, a word fluency task, digit span reverse and delayed recall of the word list) [25]. The obtained results were referred to the test standards. The higher the result, the less impaired the cognitive functions or they are not impaired. Also in this case, one analysis was performed with a differentiation between a normal condition and cognitive impairment without specifying the severity and

another analysis took into account the normal condition, mild cognitive impairment and dementia.

Descriptive methods and methods of statistical inference were applied in the statistical analysis of the obtained results. An arithmetic mean (X) was calculated to characterize the average value for quantitative features, while standard deviation (SD) was assumed as statistical dispersion.

In the case of Mira Stambak's test and the 10-meter walk test – owing to the compatibility of dependent variables distribution with the normal distribution – a parametric variance analysis was used in an intra-group scheme (ANOVA for repeated measurements). The Bonferroni correction was used for multiple *post hoc* comparisons.

In the case of *the Beck Depression Inventory* and *the DemTect*, owing to the lack of compatibility of distribution of explained variables with the normal distribution, the statistical study used a non-parametric two-way Friedman variance analysis (Friedman ANOVA). *Post hoc* analyses were performed with the use of the Wilcoxon signed-rank test for a group of variables with the Bonferroni correction. All the analyses had a maximum permissible type 1 error assumed $\alpha = 0.05$; $p \leq 0.05$ was considered statistically significant.

Results

In the preliminary measurement, as regards own standards created in the control group, the majority of patients (60%) obtained inaccurate results as regards Mira Stambak's test and a great majority (80%) presented inaccurate results in the 10-meter walk test.

The analysis of the BDI results in the first measurement showed that the majority of the patients (85%) achieved an accurate result, while 15% of the cases included the feeling of depression (Table 1).

Table 1. **The structure of accurateness of test results in the preliminary measurement and over a six-month period in the studied group (N = 20)**

Type of test	Time of measurement	Inaccurate value N	Inaccurate value % of total	N	X	SD
Beck Depression Inventory	A	3	15.00	20	11.05	5.45
	B	8	40.00	20	14.50	7.09
	C	4	20.00	20	11.75	6.08
DemTect	A	9	45.00	20	13.75	2.75
	B	9	45.00	20	13.20	3.09
	C	9	45.00	20	12.35	2.94
Mira Stambak's line-drawing test	A	12	60.00	20	111.30	33.21
	B	15	75.00	20	102.25	32.19
	C	15	75.00	20	97.55	30.37

table continued on the next page

Type of test	Time of measurement	Inaccurate value N % of total		N	X	SD
10-meter walk test	A	16	80.00	20	14.20	3.99
	B	17	85.00	20	15.65	4.73
	C	20	100.00	20	17.70	4.88

N – number; X – mean; SD – standard deviation; A – preliminary measurement; B – measurement after 3 months; C – measurement after 6 months

The severity of depression was then evaluated. All the patients diagnosed with depression had the feeling of depression of mild intensity. No patient experienced moderate or severe depression (Table 2).

Table 2. **The structure of severity of depression according to the Beck Depression Inventory and cognitive impairment according to the DemTect in the preliminary measurement and over a six-month period in the studied group (N = 20)**

Type of test	Time of measurement	Severity of impairment	Incorrect value N % of total	
Beck Depression Inventory	A	No depression	17	85.00
		Mild depression	3	15.00
		Moderate depression	0	0.00
		Severe depression	0	0.00
	B	No depression	12	60.00
		Mild depression	5	25.00
		Moderate depression	3	15.00
		Severe depression	0	0.00
	C	No depression	16	80.00
		Mild depression	4	20.00
		Moderate depression	0	0.00
		Severe depression	0	0.00
DemTect	A	No cognitive impairment	11	55.00
		Mild cognitive impairment (MCI)	9	45.00
		Dementia	0	0.00
	B	No cognitive impairment	11	55.00
		Mild cognitive impairment (MCI)	9	45.00
		Dementia	0	0.00

Type of test	Time of measurement	Severity of impairment	Incorrect value N % of total	
DemTect	C	No cognitive impairment	11	55.00
		Mild cognitive impairment (MCI)	7	35.00
		Dementia	2	10.00

N – number; A – preliminary measurement; B – measurement after 3 months; C – measurement after 6 months

The evaluation of *the DemTect* results showed that slightly over half the patients (55%) had an accurate result, while 45% an inaccurate one (Table 1). The analysis of the severity of cognitive impairment in this measurement showed that all the people with cognitive impairment presented mild cognitive impairment (MCI), and no dementia was found (Table 2).

A statistical analysis of Mira Stambak's test and the 10-meter walk test over a period of six months in the group subject to evaluation showed statistically significant differences between measurements as regards both the tests. Variance analysis in the intra-group scheme showed that the result of Mira Stambak's test in the measurement A was higher than in the measurement B ($p = 0.005$) and the measurement C ($p = 0.007$) (Figure 1).

In the case of the 10-meter walk test, multiple comparisons showed that the result in the people subject to the preliminary measurement A was lower than in the measurement B ($p < 0.001$) and in the measurement C ($p < 0.001$), and it was lower in the measurement B than in the measurement C ($p < 0.001$) (Figure 2).

Also, the two-way analysis of the BDI results over a period of six months showed statistically significant differences between the measurements. It has been shown that the result of the test in the measurement B was higher than in the measurement A ($p = 0.001$) and the measurement C ($p = 0.002$) (Figure 3). In the measurement B, 25% of the patients had mild depression, 15% moderate depression, while 60% had no mood disorders. None of the patients suffered from severe depression. In the measurement C, 80% of the patients did not suffer from depression, while the remaining 20% suffered from mild depression – at that time there was no case of moderate and severe depression (Table 2).

The analysis of *the DemTect* results over a six-month period in the surveyed group showed statistically significant differences between particular measurements. In the measurement C, the test result was lower than in the measurement A ($p = 0.002$) and the measurement B ($p = 0.01$) (Figure 4). The evaluation of the severity of cognitive impairment demonstrated that in the measurement B – as in the preliminary measurement A – 55% of the respondents did not suffer from cognitive impairment, while 45% had mild cognitive impairment (MCI). In the measurement C, 35% of the respondents had mild cognitive impairment (MCI), 10% suffered from dementia, while the remaining study participants reported no disorders (Table 2).

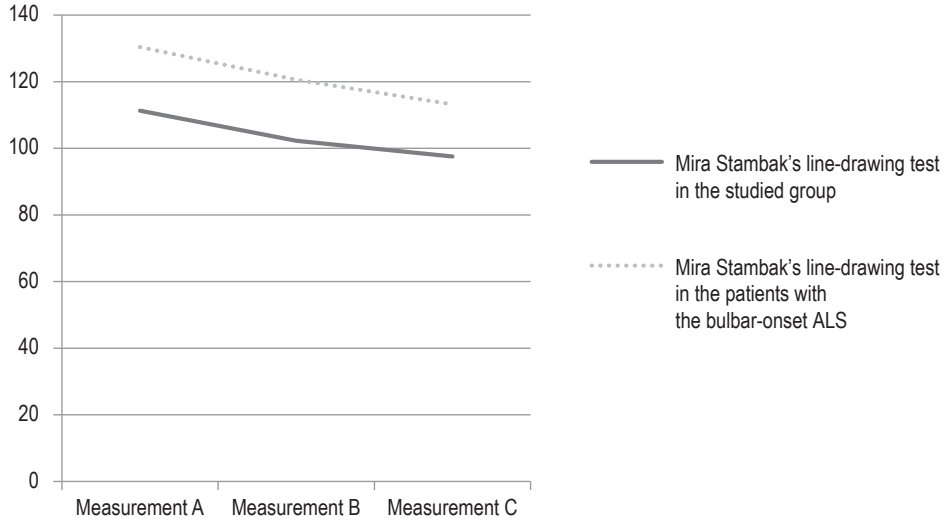

Figure 1. **Average result of Mira Stambak's line-drawing test over a six-month period in the studied group and in patients with bulbar-onset ALS**

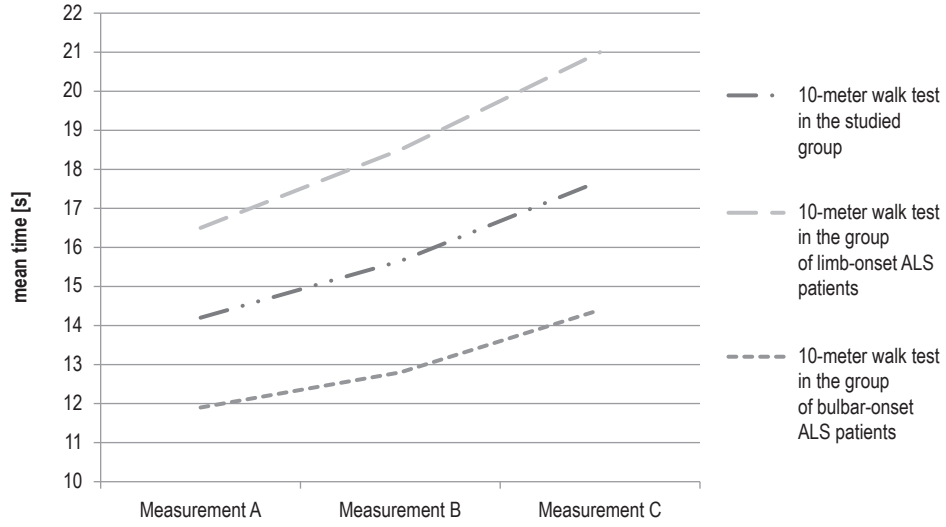

Figure 2. **Average result of the 10-meter walk test over a six-month period in the studied group and in the case of limb-onset and bulbar-onset ALS patients**

In the case of limb-onset ALS patients, the analysis of Mira Stambak's test results over a six-month period showed no statistically significant differences between the measurements. On the other hand, this group showed statistically significant differences

between the measurements as regards the 10-meter walk test. In the measurement A, the test result was lower than in the measurement B ($p < 0.001$) and the measurement C ($p < 0.001$), and in the case of the measurement B, it was lower than in the measurement C ($p < 0.001$) (Figure 2). The evaluation of the BDI results in these patients showed statistically significant differences between the measurements. Multiple comparisons showed that the test result in the measurement B was higher than in the measurement A ($p = 0.022$) and the measurement C ($p = 0.043$) (Figure 3).

The analysis of *the DemTect* results over a six-month period also showed statistically significant differences. The test result in the measurement C was lower than in the measurement A ($p = 0.042$) (Figure 4).

Yet, in the case of bulbar-onset ALS patients, the same analysis showed statistically significant differences between particular measurements as regards Mira Stambak's test and the 10-meter walk test. In the case of Mira Stambak's test, the result in the measurement A was higher than in the measurement B ($p = 0.015$), and in the case of the 10-meter walk test, in the measurement A the result was lower than in the measurement B ($p = 0.012$) and than in the measurement C ($p < 0.001$), and in the measurement B it was lower than in the measurement C ($p = 0.003$) (Figure 1 and 2).

The analysis of the BDI and *the DemTect* results also showed statistically significant differences between particular measurements. Multiple comparisons of the BDI results showed that in the measurement B, the result was higher than in the measurement A ($p = 0.024$), and in the case of *the DemTect*, the result of the measurement C was lower than in the measurement B ($p = 0.028$) and the measurement A ($p = 0.033$) (Figure 3 and 4).

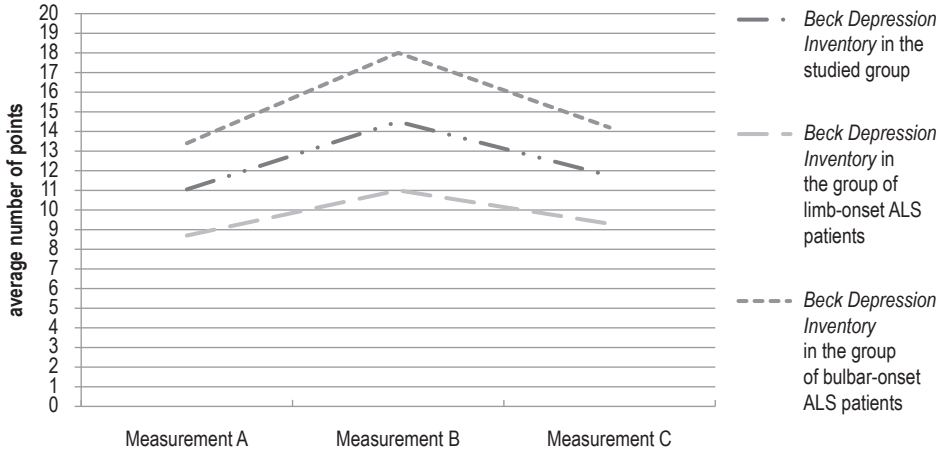

Figure 3. **Average result of the Beck Depression Inventory over a six–month period in the studied group and in the case of limb-onset and bulbar-onset ALS patients**

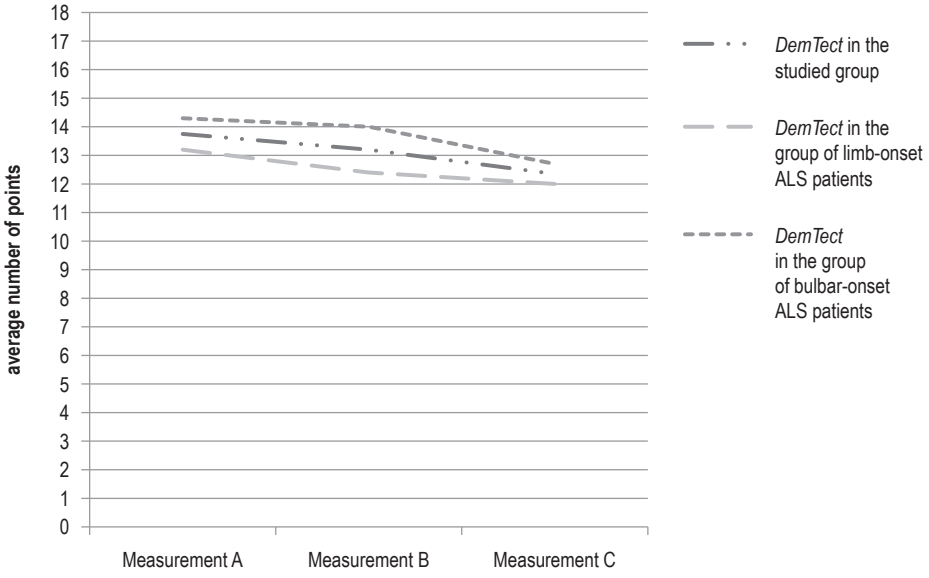

Figure 4. **Average result of the DemTect over a six–month period in the studied group and in the case of limb-onset and bulbar-onset ALS patients**

Discussion

Patients suffering from amyotrophic lateral sclerosis, in the majority of cases, feature various degrees of clinical physical dexterity impairment resulting from motor neuron damage. Moreover, symptoms of damage to other regions of the nervous system, such as cognitive impairment, or depression are also observed in this group of patients.

Couratier et al. [21] used several scales to clinically assess the dexterity of patients suffering from amyotrophic lateral sclerosis, i.e., *ALS Functional Rating Scale* (ALSFRS), *ALS Severity Scale* (ALSSS), *Appel Scale* (AS), *Norris Scale* (NS), and *Honda Scale* (HS). In own studies, the authors of this work used Mira Stambak's test and the 10-meter walk test to assess the physical fitness of the patients. Similarly, Harkema et al. [23] used the 10-meter walk test to assess the progress of rehabilitation in chronically ill patients with incomplete spinal cord impairment.

Amyotrophic lateral sclerosis inevitably leads to progressive disability. This results from amyotrophy, which leads to manual dexterity impairment of the patients and gait disorders [3, 19]. Tarvonen-Schröder et al. [20] reported that amyotrophic lateral sclerosis leads to a significant deterioration in motor skills of the patients, and it impairs their independent functioning in everyday life [20]. Jawdat et al. [1] showed that in the bulbar-onset ALS patients, the progression of the disease is faster than in the case of the limb-onset ALS patients.

Our results showed abnormalities in the majority of patients as regards both the above tests and development of the abnormalities in the course of the disease, which confirms the earlier findings. On the other hand, a separate analysis of the bulbar-onset and limb-onset ALS patients showed no significant differences in the course of disability in both groups, which is inconsistent with the previous results.

Due to the limited fitness and word fluency in the course of motor neuron damage in patients suffering from ALS, to assess cognitive functions, it is recommended to apply tests omitting such dysfunctions. Poletti et al. [26] used a new test in the evaluation of the ALS patients, which consists in the Eye-Tracking technology adjusted to the mentioned disability. In own studies, we used a Polish language version of *the DemTect* to assess cognitive functions [27].

In the case of the ALS patients, cognitive impairment is diagnosed increasingly more often, from mild cognitive impairment (MCI) to dementia [8]. Rippon et al. [10] showed that mild cognitive impairment is more common in ALS patients, while dementia is rare. Our analysis confirms these findings.

According to Chenji et al. [11], who used ALSFRS to assess fitness, and Addenbrooke's Cognitive Examination (ACE) to assess cognitive functions, the increasing physical disability is accompanied by the increasing cognitive impairment. In own material, the authors obtained similar results using completely different tests to monitor the development of the disease, both in the motor and cognitive spheres. In turn, the analysis of own results does not correspond to the findings of Ringholz et al. [9], according to which the severity of cognitive impairment shows no relation to the exacerbation of physical disability in ALS patients, nor is it dependent on the length of the disease. In turn, Xu et al. [28] identified a relationship between motor skills impairment and the severity of cognitive impairment, which meant that the more physically unfit patients had more severe cognitive impairment, which was at a constant level for the period of 6 months or maybe longer. The results partly correspond to our research.

It should be borne in mind that depression is also observed quite frequently in the case of the ALS patients [13]. To diagnose depression and its severity, our analysis utilized a worldwide popular test – *the Beck Depression Inventory* (BDI) [29]. Wei et al. [12] assessed that episodes of severe depression are rarely present in the course of ALS. Also Averill et al. [17] reported that the clinically severe depression in patients is not as common and intense as it could be expected. Patients present hopelessness resulting from the approaching death, rather than depression.

The analysis of the obtained results of the Beck Depression Inventory showed that patients presented mild and moderate depression, which confirms earlier findings. Moreover, it was observed that the severity of depression in a six-month observation was transient. Also, according to Hillemacher et al. [16], depression appears to be a reaction to the ALS diagnosis, later its severity decreases; the authors also reported no relationship between intensified motor skills disorders and depression. A contrary opinion to these findings was presented by Oh et al. [30], who – using the ALSFRS to assess the physical fitness of the ALS patients, and the BDI to assess depression –

reported that the increase in physical fitness impairment is accompanied by increased depression.

Previous analyses concerning both cognitive impairment and depression indicate that they are more severe in the case of bulbar-onset ALS patients than in limb-onset ALS patients [10, 16]. The analysis of our studies showed that cognitive impairment and depression greatly intensified in the course of the disease in the same way in both groups; however, in the case of depression the severity was transient.

The authors would like to note that both motor function impairment and cognitive impairment as well as depression are common in the course of amyotrophic lateral sclerosis and have a negative impact on the functioning of the patients and their caregivers. That is why an early diagnosis of the impairments and the introduction of an appropriate therapy is so important, as this may improve the quality of life of those patients in the course of a terminal disease, such as amyotrophic lateral sclerosis.

Conclusions

1. The gradually developing loss of motor neurons of the anterior horns of the spinal cord is reflected in physical fitness impairment in the ALS patients.
2. The exacerbation of cognitive impairment accompanies the intensifying physical disability.
3. The exacerbation of depression in the course of amyotrophic lateral sclerosis is of transient nature.

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