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Poor emotional well-being is associated with rapid progression in amyotrophic lateral sclerosis

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ABSTRACT

The study aimed to determine the impact of emotional well-being on disease aggressiveness and survival in amyotrophic lateral sclerosis (ALS). In 224 patients with ALS (without significant cognitive deficits) the revised ALS Functional Rating Scale (physical function), the ALS Assessment Questionnaire (ALSAQ-40) for health-related Quality of Life and survival data were collected. Data analysis comprised logistic regression, Kaplan-Meier curves analyses and Cox regression model. Most patients reported to be worried about how the disease will affect them in the future and 67% reported to feel depressed. Patients with good emotional well-being were characterized by better physical function (higher ALSFRS-R) and lower disease aggressiveness. The association between high emotional well-being and lower disease aggressiveness was confirmed in the univariate analysis and also after adjustment for known predictors of disease progression. In the Kaplan-Meier survival curve analysis the overall 1-year, 2-year and 3-year mortality did not significantly differ between patients with poor and good emotional well-being. Our study demonstrates an association between emotional well-being and disease progression. Knowing that subjective well-being is neither a necessary nor a sufficient cause of health, longitudinal studies are necessary to explore when well-being does and does not influence disease progress and survival in ALS.

1. Introduction

Amyotrophic lateral sclerosis (ALS) is a multi-systemic neurodegenerative disorder that is characterized by motor neuron degeneration and several non-motor symptoms [1,2]. To date there is no cure and treatment mainly aims to improve or sustain quality of life (QoL) for the patients. Various factors influence QoL and health-related QoL in ALS, including disease progression, depression, anxiety, pain and dysphagia [3–6]. There is a link between mental health and physical health, and many studies showed that psychological factors are related to the course and severity of several physical diseases [7]. In particular, emotional well-being was found to predict the prognosis of physical illness in common disorders such as osteoporosis, coronary heart disease, diabetes and cancer [8–13]. In psychological research, there is pre-eminent definition or approach to well-being [14]. The “subjective well-being” describes how individuals evaluate or appraise their own lives. These evaluations can be either in terms of cognitive reflections (cognitive well-being) or can be in terms of affect (emotional well-being) [15]. Emotional well-being characterizes the presence of positive affects and the absence of negative affects. Cognitive and emotional well-being are distinctive constituent parts of subjective well-being and should be analyzed separately [15]. With the current study we aimed to answer if emotional well-being may play a protective role for survival and disease progress in ALS.

2. Methods

In this observational prospective study, 250 patients with a diagnosis of definite, probable, laboratory-supported probable, or possible ALS (as determined by the revised El-Escorial criteria) [16] were consecutively recruited from the Department of Neurology, Jena University Hospital between January 2012 and March 2016. Written informed consent was obtained from all participants and the study was approved by the local Ethics committee of the Jena University Hospital (#3633–11/12). The study has been performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and

Abbreviations: ALS, Amyotrophic Lateral Sclerosis; ALSAQ-40, Amyotrophic Lateral Sclerosis Assessment Questionnaire; ALSFRS-R, Amyotrophic Lateral Sclerosis Functional Rating Scale Revised; QoL, quality of life

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its later amendments or comparable ethical standards.

During the first or second visit in our specialized outpatient hospital or neurological ward the following assessments were performed: The revised ALS Functional Rating Scale (ALSFRS-R) was used to quantify physical impairment [17]. Health-related QoL was measured using the ALS Assessment Questionnaire (ALSAQ-40) [18] which queries the domains of mobility, activities of daily living (ADL), eating, communication, and emotional well-being, with higher scores indicating poorer health-related QoL. The instrument has a 0–4 Likert-type scaling. Dimension scores are coded on a scale of 0 (perfect health as assessed by the measure) to 100 (worse health as assessed by the measure). All 40 items are also used to calculate an overall ALS index score (summary index). The domain emotional well-being (10 items) addresses various emotional problems, such as feeling lonely, bored, depressed, feeling embarrassed in social situations and feeling worried about the future disease course [18]. Patients with significant cognitive deficits according to the reported cut-off scores of the German version of the Edinburgh Cognitive and Behavioral ALS Screen (ECAS) were excluded [19,20].

The SPSS software package (version 25.0; IBM Corporation, USA) was used for all statistical analyses. Prior to statistical analysis, data were checked for outliers. Disease aggressiveness was calculated using the D50 model [21,22]. Here, the D50 value is a summative descriptor of the individual disease aggressiveness and it references the estimated time (in months) for a patient to lose 50% of his/her functionality (equivalent to an ALSFRS-R score of 24). Patients were stratified according to their D50 value in a group with lower (D50 > 40) and higher disease aggressiveness (D50 < 20). In addition the disease progression rate (ΔFS) was calculated as follows: ΔFS = 40 − ALSFRS/disease duration (months) [23]. Mean and percentages of clinical variables for group comparison were compared using *t*-test or $\chi 2$-test corrected for multiple comparisons (Bonferroni correction). A general linear model with backward selection was used to analyze the association between the emotional well-being sum score (dependent variable) and its 10 items (independent variables) (Akaike information criterion). A binary logistic regression model was used to study the association between emotional well-being and disease aggressiveness (forward selection). Survival data were expressed as median with interquartile range (IQR), and analyses were performed with the Kaplan-Meier method. Survival curves of patients with good and poor emotional well-being (based on the ALSAQ-40 domain) were compared with the log-rank test. A Cox regression model was utilized to study the association between emotional well-being and survival. For all the analyses, *P*-values < .05 were considered significant.

Anonymized data from this study will be shared with qualified investigators on request.

3. Results

Detailed clinical data is given in Table 1, complete assessments were available from 224 patients without significant cognitive deficits. The worst health-related QoL was observed in the ALSAQ-40 domains ADL, communication, and mobility. Because there is no cut off for high and low health-related QoL we used the median of the emotional well-being domain (30, IQR 33) to categorize patients into a group with high/good and low/poor emotional well-being. Patients with high emotional well-being were characterized by better physical function (ALSFRS-*R* = 35.0 +/− 9.5 [95%CI 33.2–36.7] vs. 30.8 +/− 9.6 [95%CI 28.9–32.7] in the group with worse emotional well-being, *P* = .001) and lower disease aggressiveness (D50 = 56.5 ± 81.9 [95%CI 41.2–71.7] vs. 36.9 +/− 48.8 [95%CI 27.5–46.4] in the group with worse emotional well-being, *P* = .036) (Fig. 1). Both groups did not significantly differ in terms of age, gender, disease duration and mean survival time since symptom onset (Table 1).

Eighty-eight percent of patients reported to be worried about how the disease will affect them in the future and 67% reported to feel depressed (Fig. 2). The strongest predictor of poor emotional well-being was item 37 (I have felt angry because of the disease) and item 33 (I have felt embarrassed in social situations) ($F(37, 186) = 2675.29$, $P < .001$) (Table 2).

Good emotional well-being was associated with lower disease aggressiveness in the univariate analysis and also after adjustment for ALSFRS-R and known predictors of disease progression, namely disease duration and presence of bulbar symptoms (sum of ALSFRS-R items 1 to 3) [24] (Table 2).

Survival data were available for up to three years ($n = 174$ subjects, 50 lost to follow up) after symptom onset. The median survival for the entire cohort was 32 (IQR = 23) months. The Kaplan-Meier survival curve analysis revealed that the overall 1-year (Fig. 3), 2-year and 3-year mortality did not significantly differ between patients with poor and good emotional well-being (log rank $P = .56$, $P = .66$, $P = .36$, respectively). Accordingly, in the univariate Cox regression analyses for mortality the ALSAQ-40 emotional well-being domain was not significantly associated with mortality after one, two and three years.

4. Discussion

Our study demonstrates an association between poor emotional well-being and higher disease aggressiveness in ALS. However, this association is weak in comparison to other factors that are known to be associated with rapid disease progression. There is evidence from other chronic disorders that psychological well-being is related to slower disease progression [25]. In particular, the importance of physical health for emotional well-being has been reported in a number of studies [26]. It is known that depression is a strong predictor of QoL in ALS [4]. We did not find that depressed feelings (item 38) are the strongest predictors of poor emotional well-being. Therefore, we hypothesize that other neuropsychological disturbances might contribute to the observed association between well-being and progression. This should be evaluated in future studies by using specific questionnaires for depression and anxiety.

We did not observe an effect of poor emotional well-being on survival. Although, we analyzed a large cohort of patients with ALS, this might be explained by sample specific characteristics or the missing correction for other common predictors of survival. Therefore multicentre studies taking into account other prognosis biomarkers (e.g. frontal dysfunction, C9orf72 mutation, forced vital capacity) could help to answer the question if good emotional well-being has a beneficial effect on survival in ALS [27].

The study is not free of limitations. We cannot answer if the observed disturbances of emotional well-being are disease inherent and probably related to the known multisytemic structural and functional changes in the brain of patients with ALS or if they occur secondary, i.e. due to functional/social impairments. Due to the cross-sectional design we cannot make a statement about causality. To answer this question in longitudinal studies would help to explore if modulation of emotional well-being (e.g. pharmacological) might have a protective effect on disease progression and survival in ALS. Moreover, the subdomain of emotional well-being in the ALSQ-40 only covers negative affect, such as feelings of anger, sadness, stress, and worry. A comprehensive analysis including positive affects may show a much more impressive association between aggressiveness, survival and emotional well-being in ALS.

5. Conclusion

Higher levels of emotional well-being are associated with slower disease progression but not with better survival in ALS. Knowing that subjective well-being is neither a necessary nor a sufficient cause of health [15], longitudinal studies are necessary to explore when well-being does and does not influence disease progress and survival in ALS.

Table 1
Patient demographics and clinical parameters.

	Entire cohort (n = 224)		Good emotional well-being (n = 117)		Poor emotional well-being (n = 107)	
Age [mean, SD]	62.5	11.5	61.3	11.7	63.9	11.2
Disease duration [mean, SD]	18	21	17.3	21.4	17.9	20.1
Female [n, %]	93	41.5	46		47	
Bulbar onset [n, %]	50	22	23			27
Disease progression rate [mean, SD]	1.09	3.91	0.9	3.3	1.3	4.5
D50 [mean, SD]	46.8	68.4	56.5	82.0	37.0	48.8
Survival time since onset [mean, SD]	35	20	35.8	17.5	34.8	22.0
Physical function						
• ALSFRS-R total [mean, SD] (item 1–12, max 48)	33	10	35	9.5	30.9	9.7
Health-related quality of life [mean, SD]						
• ALSAQ-40 Summary index	37.39	19.57	25.8	15.2	50.1	15.6
• ALSAQ-40 Mobility	39.33	29.89	30.3	27.9	49.2	28.9
• ALSAQ-40 Activity of daily living	41.64	31.44	32.1	31.3	52.1	28.2
• ALSAQ-40 Eating	21.96	28.94	13.8	22.0	30.9	32.9
• ALSAQ-40 Communication	40.49	35.92	30.0	32.5	52.0	36.1
• ALSAQ-40 Emotional well-being	33.67	23.21	15.5	9.5	53.6	16.4

Abbreviations: Disease aggressiveness (D50), revised ALS Functional Rating Scale (ALSFRS-R), ALS Assessment Questionnaire (ALSAQ-40).

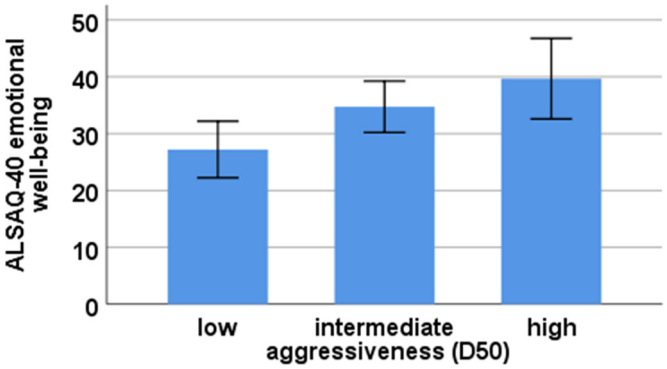

Fig. 1. Group comparison of emotional well-being among different types of disease aggressiveness (D50) (means and 95% confidence interval).

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Ethical approval

All procedures performed were in accordance with the ethical standards of the local Ethics committee of the Jena University Hospital (#3633–11/12) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Declaration of Competing Interest

The authors have no conflicts of interest to declare.

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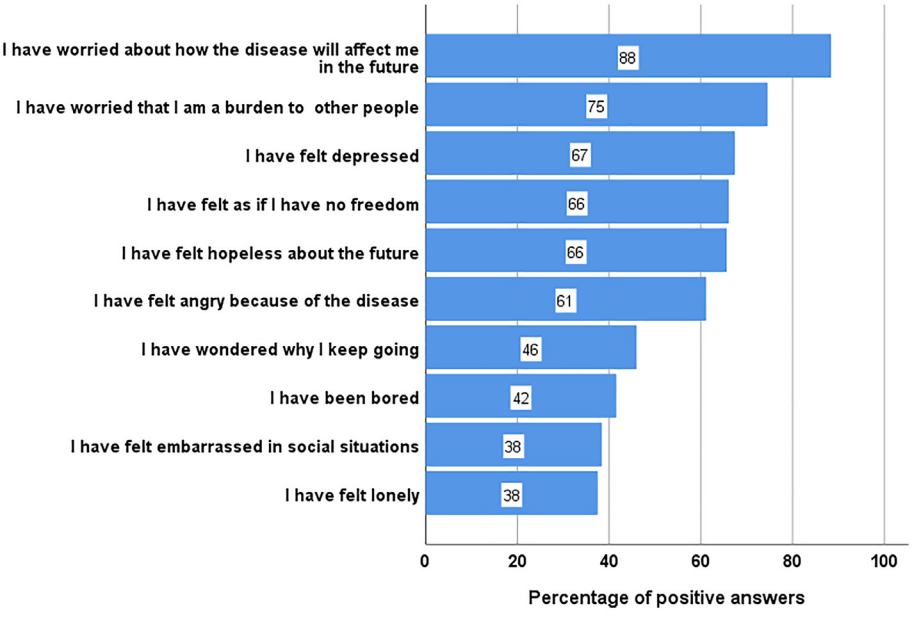

Fig. 2. Prevalence of impaired emotional well-being in ALS (***n* = 224**). The percentage of positive items in the emotional well-being domain of the Amyotrophic Lateral Sclerosis Assessment Questionnaire - 40 is given (positive is defined as a rating above 0, indicating that the feeling occurs rarely (1), sometime (2), often (3), or always (4)).

Table 2
Summary of the general linear model (top) and the logistic regression model (bottom).

Emotional well-being items of the ALSAQ-40		β	*P* value
37	I have felt angry because of the disease	0.149	< 0.001
33	I have felt embarrassed in social situations	0.124	< 0.001
34	I have felt hopeless about the future	0.121	< 0.001
35	I have worried that I am a burden to other people	0.120	< 0.001
40	I have felt as if I have no freedom	0.106	< 0.001
32	I have been bored	0.093	< 0.001
38	I have felt depressed	0.082	< 0.001
39	I have worried about how the disease will affect me in the future	0.071	< 0.001
31	I have felt lonely	0.071	< 0.001
36	I have wondered why I keep going	0.065	< 0.001

Final predictors	Statistics					Final overall model			
	B	*SE*	*P* value	Exp(B)	95% CI for Exp(B)	Nagelkerke R^2	*P* value	Hosmer–lemeshow	Classification rate
Univariate									
EMO	−0.023	0.008	0.005	0.977	[0.96–0.99]	0.09	0.004	0.22	65%
Adjusted for cofactors									
EMO	−0.26	0.011	0.019	0.974	[0.95–0.99]	0.47	< 0.001	0.74	70%
Disease duration	0.08	0.019	< 0.001	1.086	[1.05–1.13]				
Bulbar symptoms	0.24	0.091	0.008	1.274	[1.06–1.52]				

Top: A general linear model was used to analyze the association between the emotional well-being sum score (dependent variable) and its 10 items (independent variables). The predictors are listed with decreasing impact on the emotional well-being sum score. Bottom: A binary logistic regression model was used to study the association between emotional well-being and disease aggressiveness. Dependent variable: high or low disease aggressiveness. Independent variables: Emotional well-being domain, ALSFRS-R, disease duration, presence of bulbar symptoms (sum of ALSFRS-R items 1 to 3). Abbreviations: EMO: emotional well-being. SE: Standard error. Exp(B): ratio of hazard rates that are one unit apart on the predictor. CI: Confidence interval.

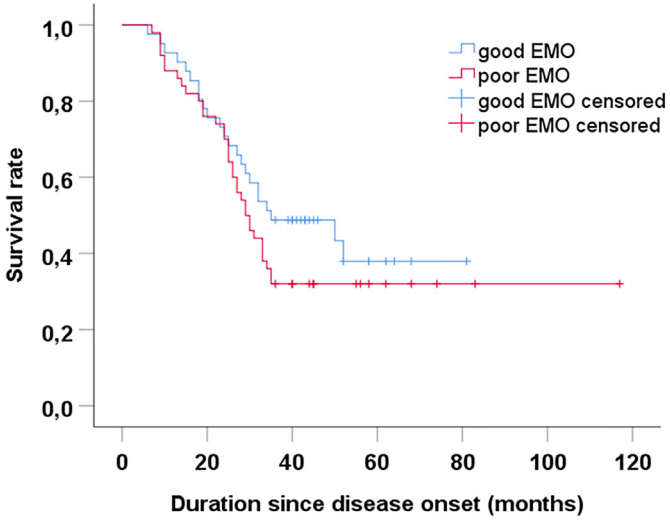

Fig. 3. Kaplan-Meier curve of patients with good and poor emotional well-being (EMO).

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