RESEARCH PAPER

Laughter, crying and sadness in ALS

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ABSTRACT

Background Pseudobulbar affect (PBA) is prevalent in amyotrophic lateral sclerosis (ALS), but there is limited information on its associations and course.

Objectives Explore prevalence, associations, course and manifestations of PBA in outpatient cohort of patients with ALS and examine its relationship to depression.

Methods Self-reported measures of PBA and depression (Center for Neurologic Study-Lability Scale (CNS-LS) and Patient Health Questionnaire (PHQ-9), respectively) were obtained from consecutive patients with ALS using tablet devices in waiting rooms (Knowledge Program).

Results PBA (CNS-LS ≥13) was seen in 209/735 patients (28.4%). PBA was associated with bulbar onset and dysfunction, upper motor neuron dysfunction, cognitive impairment, depression and lower quality of life. A multivariable model that included lower bulbar and gross motor subscores, female gender, younger age and shorter duration of disease predicted PBA with 74% accuracy. CNS-LS scores increased only slowly with time. Women with PBA reported more crying than men. Crying (but not laughter) correlated with depression, and crying was associated with poorer quality of life. Exploratory factor analysis of pooled questions of CNS-LS and PHQ-9 identified three underlying factors (laughter, crying and depression) loaded on appropriate questions of the respective instruments.

Conclusion This study identifies associations of PBA and additionally finds PBA (especially crying-predominant PBA) more prevalent in women with ALS. Although the two self-report instruments (CNS-LS and PHQ-9) discriminate well between PBA and depression, there is significant overlap between depression and crying in PBA. Studies of PBA should stratify for gender, examine crying and laughter as separate outcomes and adjust for depression.

INTRODUCTION

Pseudobulbar affect (PBA) is a treatable but under-recognised neuropsychiatric phenomenon observed in a wide range of neurological disorders.[1] PBA manifests with uncontrollable episodes of laughter or crying that are excessive for or incongruent with the underlying emotion and situation. Depression, on the other hand, is a pervasive disorder of mood characterised by sadness, anhedonia, worthlessness, suicidal thoughts and cognitive and somatic symptoms. Depression as well as PBA is typically diagnosed by a formal or structured interview and/or direct observation, and guidelines assist clinicians to differentiate the two conditions.[2] Additionally, various self-report instruments may be used to screen for these conditions.[3–7] Both states are prevalent in amyotrophic lateral sclerosis (ALS), where estimates range from 15% to >50%,[1 8] and both negatively affect quality of life (QoL).[1 9] There is little information on the interplay or overlap of these phenomena.

The aim of this study of a large cohort of patients with ALS using self-report measures of PBA and depression is threefold: (1) examine the prevalence, associations and course of PBA in ALS; (2) explore associations, if any, that differentiate laughter from crying in PBA; and (3) examine the relationship of PBA and depression, and if self-report instruments effectively distinguish these two phenomena. A previous report describes the prevalence and associations of depression in this cohort.[9]

METHODS

This was an exploratory observational study of PBA and depression in ALS, specifically addressing questions listed above. The cohort consisted of consecutive patients with ALS seen at a neuromuscular centre between August 2006 and January 2015.

Data source, participants and measures

Under a quality initiative called *Knowledge Program* (KP),[10] all neurology patients at our institution are requested to provide patient-reported outcomes (PROs) during routine clinic visits using wireless tablet devices in waiting rooms. Live data thus obtained inform clinical care. The practice of collecting PROs is standard of care in neurology at our institution, and no additional consent is sought. These data accumulate in the KP Data Registry that also includes some discrete elements of the patient's electronic health record. Disease-specific instruments used for ALS include a self-administered version of the *Revised ALS Functional Rating Scale* (ALSFRS-R)[11] and *Center for Neurologic Study-Lability Scale* (CNS-LS). ALSFRS-R is a widely used 12-question five-level instrument that measures function in ALS in the domains of bulbar, fine motor, gross motor and respiratory function (three questions each),[12] with a score of 48 representing normal function. CNS-LS is a seven-question five-level measure of PBA that includes four questions about laughter and three questions about crying.[5] Total CNS-LS score can range from 7 to 35, with a score of ≥13 implying clinically identifiable PBA (sensitivity 0.84 and specificity 0.81 in ALS).[5] Generic outcomes measured in all neurological disorders include *Patient Health Questionnaire (PHQ-9)* and EuroQol five dimensions questionnaire (*EQ-5D*). PHQ-9 is a nine-question four-level instrument that incorporates *Diagnostic and Statistical Manual for Mental Disorders*, Fourth Edition criteria for major depressive disorder.[4] Total PHQ-9

score can range from 0 to 27, with a score of ≥10 implying at least moderate depression. EQ-5D is a brief five-question three-level generic QoL index that includes a visual analogue scale (VAS) component.[13] For this study, the KP Data Registry was queried by dates (2006–2015), diagnosis (International Classification of Diseases, ninth version, code 335.20) and department/centre evaluated (Neuromuscular) to obtain the dataset for analysis. Corresponding patient charts were manually reviewed for additional information including date of onset of weakness, site of onset (bulbar or extremity/other), clinical impression of cognitive dysfunction and clinical syndrome, namely typical ALS, upper motor neuron (UMN)-predominant disease or lower motor neuron (LMN)-predominant disease. ALSFRS-R 'pre-slope'[14] was computed by dividing (initial ALSFRS-R minus 48) by months from weakness onset.

Statistical methods

Distribution of CNS-LS scores and prevalence of PBA (CNS-LS ≥13) were described. Univariate associations of PBA with categorical and continuous variables were examined using Pearson's χ^2 test and Wilcoxon rank-sum test, respectively. Logistic regression with bootstrap validation was used for multivariable prediction of PBA. In patients with repeated measures, change in CNS-LS over time was estimated using a mixed model that included a time term. The relative prevalence of laughter and crying was explored by centring and scaling corresponding subscores by population means and SD, respectively (z-scores).[15] Patients with PBA were empirically classified into those who cried more (crying-z-score > laughter-z-score), and those who laughed more (laughter-z-score > crying-z-score), and associations of these subgroups were examined. The association between CNS-LS/PBA and PHQ-9/Depression/major depressive disorder(MDD) was examined in a subset of patients who scored CNS-LS and PHQ-9 on the same day. Spearman's correlation between questions of CNS-LS and PHQ-9 was estimated with bootstrap confidence intervals. Cronbach's alpha was used to report internal consistency of CNS-LS and PHQ-9, and discriminant validity of these instruments was examined by exploratory factor analysis of pooled questions. A significance threshold of 0.05 was used. Sensitivity analyses involved (1) excluding patients with duration of weakness >2 years, (2) using alternative thresholds of CNS-LS, (3) using an alternative empirical way of classifying PBA patients as laughter/crying-predominant (adjustment of raw subscore by question number, 4 and 3, respectively)[15] and (4) alternative factor extractions in factor analysis. The R platform[16] with additional packages (rms,[17] lme4[18] and psych[19]) was used for data visualisation and analysis.

RESULTS

Population characteristics and prevalence of PBA

Of 1067 patients with ALS seen between August 2006 and January 2015, 735 had CNS-LS records with available question-level responses. Population characteristics of this cohort are reported in column 2 of table 1. Forty-three per cent of patients were women. Median age of onset was 60.4 years. Twenty-eight per cent had bulbar onset, and 18% had clinically evident cognitive dysfunction. Seventy-nine per cent (n=575) had typical ALS (with UMN and LMN dysfunction). Of 83 UMN-predominant patients, 25 (30%) were diagnosed with primary lateral sclerosis (PLS), and of 71 LMN-predominant patients, 12 (17%) were diagnosed with progressive muscular atrophy (PMA). Histograms of the CNS-LS total score, individual questions, laughter subscore (sum of answers 2, 4, 5 and 7) and crying subscore (sum of answers 1, 3 and 5) are presented in figure 1. Mean (SD) CNS-LS score was 10.86 (4.49), whereas median score was 9, and first and third quartiles were 7 and 13, respectively. The reported threshold for diagnosing PBA in ALS (13 points) that we used for further analyses was reached or exceeded by 209 of 735 patients (28.4%). In total, 293 (39.9%) reached a liberal threshold of 11 points, but only 95 (12.9%) and 37 (5%) reached stringent thresholds of 17 and 21 points, respectively. The prevalence of PBA remained similar if we excluded patients with longer duration from onset (>2 years).

Associations of PBA

Univariate associations of PBA are reported in columns 3–5 of table 1. PBA (CNS-LS ≥13) was significantly associated with female gender (37.8% vs 21.4% in males), bulbar onset (42.6% vs 23.2% in non-bulbar onset), lower ALSFRS-R score (especially bulbar subscore) and more rapidly progressive disease. Prevalence of PBA increased with increasing UMN dysfunction (10%, 29% and 39% for LMN-predominant disease, typical ALS and UMN-predominant disease, respectively). Only 1 of 12 (8%) patients with PMA had PBA compared with 10 of 25 (40%) patients with PLS. PBA was more prevalent in patients with cognitive dysfunction (37.9%) than those without (26.1%). Significant dysarthria/dysphagia (bulbar subscore ≤9) was observed in 69% of patients with PBA compared with only 31% of those without. Additionally, PBA was significantly associated with poorer objective (EQ-5D) and subjective (VAS) QoL, and with more prevalent use of dextromethorphan-quinidine, antidepressants and baclofen. For a higher threshold of PBA (CNS-LS ≥17), several univariate associations were similar. An optimal multivariable logistic regression model for PBA (CNS-LS ≥13) is presented in figure 2 and online supplementary table S1 . Female gender, lower bulbar and gross motor ALSFRS-R subscores, lower age and shorter disease duration significantly increased odds of PBA; the effect of decreasing bulbar subscore was non-linear, steep between 12 and 9 and relatively blunted for values <9. This model has an acceptable goodness of fit and predicts the presence of PBA with 74% accuracy.

Course of PBA

In total, 416 patients had at least one repeated CNS-LS measure. There were 1198 repeated measures ranging widely in interval from the initial measure (2–2141 days, median 248 days). Using a mixed model, the estimated average rate of change of CNS-LS was small but significant at a 0.67-point increase per year (95% CI 0.06 to 1.28).

Crying versus laughter

Fewer patients scored higher on laughter questions than on crying questions (figure 1). Overall mean (SD) laughter and crying subscores in all patients with ALS were 5.45 (2.78) (normal=4) and 5.41 (2.72) (normal=3), respectively, and corresponding median values were 4 and 5, respectively. Among patients with PBA, mean (median) total score, laughter subscore and crying subscore were 17.10 (16), 8.53 (8) and 8.57 (9), respectively. By our empirical definition (z-score comparison), 100/209 patients with PBA (47.8%) laughed predominantly, although by the alternative definition (subscores adjusted by number of questions), only 61/209 with PBA (29.2%) laughed predominantly. Associations of predominant laughter/crying are presented in table 1, columns 6–8. Gender had a strong association; 64.7% of women with PBA cried predominantly, whereas 64.4% of men laughed predominantly. Additionally,

Table 1 Population characteristics, univariate associations of PBA and univariate associations of laughter/crying-predominant PBA*

	Missing data	Population (n=735) Median (IQR) or counts	Not PBA CNS-LS<13 (n=526)	PBA CNS-LS≥13 (n=209) (28.4%)	p-Value	PBA crying-predominant (n=109)	PBA laughter-predominant (n=100)	p-Value
Age (years)		60.4 (52–68.9)	60.2	60.8	ns	62.0	57.1	<0.05
Female		315	196	119 (37.8%)	<0.0001	77 (64.7%)	42 (35.3%)	<0.0001
Male		420	330	90 (21.4%)		32 (35.6%)	58 (64.4%)	
Bulbar onset	2	202	116	86 (42.6%)	<0.0001	39	47	ns
Non-bulbar onset		531	408	123 (23.2%)		70	53	
Days from onset		399 (243–727)	399	411	ns	383	423	ns
ALSFRS-R	165	38 (32–42)	39	35	<0.0001	35	34	ns
Bulbar subscore	167	10 (8–12)	11	8	<0.0001	9	8	<0.05
Fine motor subscore		9 (7–11)	9	9	<0.01	8	9	ns
Gross motor subscore		8 (6–10)	9	7	<0.001	6.5	8	ns
Respiratory subscore		11 (9–12)	12	10	<0.0001	11	10	.099
Pre-slope ALSFRS-R†	165	−0.64 (−1.13 to −0.35)	−0.56	−0.96	<0.0001	−1.00	−0.80	ns
ALS (UMN+LMN)	6	575	409	166 (28.9%)	<0.001	88	78	ns
UMN-predominant		83	51	32 (38.6%)		16	16	
LMN-predominant		71	64	7 (9.9%)		4	3	
Cognition normal	10	593	438	155 (26.1%)	<0.01	83	78	ns
Cognitive impairment		132	82	50 (37.9%)		25	25	
Dysarthria/dysphagia (−)	167	334	286	48 (14.4%)	<0.0001	32	16	<0.05
Dysarthria/dysphagia (+)		234	129	105 (44.9%)		50	55	
EQ-5D	10	0.71 (0.60–0.82)	0.75	0.68	<0.001	0.60	0.69	<0.05
EQ-5D VAS	332	60 (42.5–88)	66.5	50	<0.0001	49	56	.085
Dextromethorphan-quinidine		102/735	41	61	<0.0001	31	30	ns
Any antidepressant		413/735	265	148	<0.0001	77	71	ns
Riluzole		505/735	366	139	ns	71	68	ns
Baclofen		194/735	114	80	<0.0001	32	48	<0.01

*Defined by which z-score subscore was higher.
†Preslope ALSFRS-R = (Initial ALSFRS-R at first assessment − 48)/months from onset of weakness.
Counts and median values are reported for categorical and continuous variables, respectively. Wilcoxon rank-sum test and Pearson's χ^2 test are used to compare continuous and categorical variables, respectively.
ALSFRS-R, Revised ALS Functional Rating Scale; CNS-LS, Center for Neurologic Study-Lability Scale; EQ-5D, EuroQol five dimensions questionnaire; LMN, lower motor neuron; ns, not significant; PBA, pseudobulbar affect; UMN, upper motor neuron; VAS, visual analogue scale.
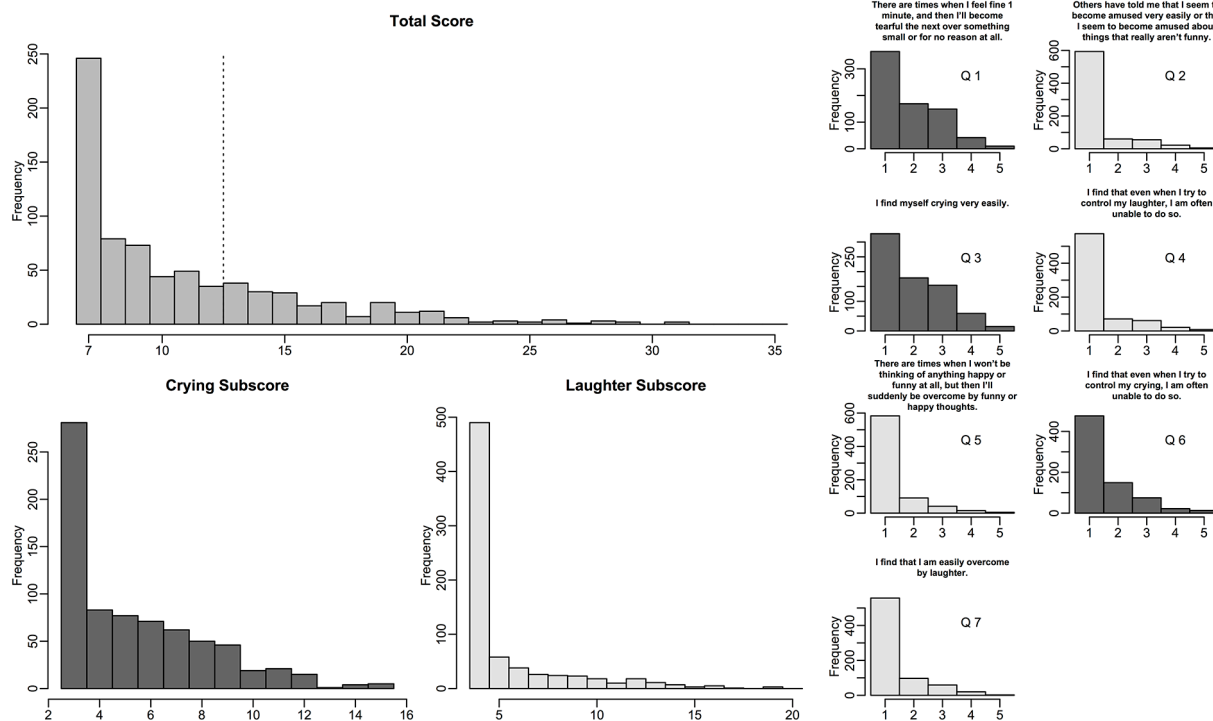
Figure 1 Histograms of Center for Neurologic Study-Lability Scale total score (panel top left), crying and laughter subscores (panel bottom left) and individual questions (panel right).
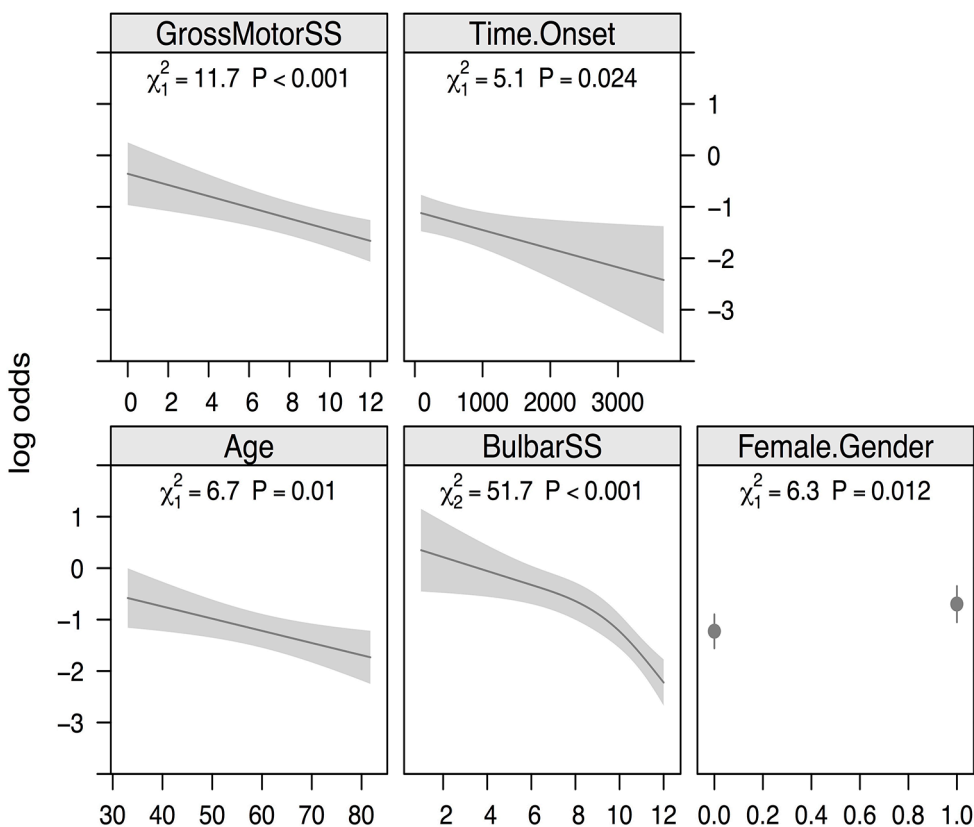

Figure 2 Optimal multivariable predictive model of pseudobulbar affect (PBA) (Center for Neurologic Study-Lability Scale ≥13) includes five variables. Log odds of PBA are on the y-axis for different values of individual predictors, while other predictors are set at their means or most frequent values. Corresponding function of the linear predictor is displayed in online supplementary table S1. Note that bulbar subscore has a non-linear effect on log odds of PBA (modelled using a restricted cubic spline function), while other variables have a linear effect. The C statistic of predictive accuracy (area under the ROC curve) of this model derived from bootstrap internal validation is 0.74. BulbarSS, bulbar subscore; GrossMotorSS, gross motor subscore. ROC, receiver operating characteristic.

Table 3 Spearman's correlation between CNS-LS total score, laughter and crying subscores, and PHQ-9 total score

*	CNS-LS laughter subscore	CNS-LS crying subscore	PHQ-9 total score
CNS-LS total score	0.73	0.91	0.39
CNS-LS laughter subscore		0.45	0.18
CNS-LS crying subscore			0.43

*All correlations are significant (p<0.05).
Correlation between individual questions of the two instruments, total scores and subscores along with bootstrap confidence intervals are available in online supplementary figure S1.
CNS-LS, Center for Neurologic Study-Lability Scale; PHQ-9, Patient Health Questionnaire.

laughter-predominant patients were slightly younger, had better QoL, had more frequent bulbar dysfunction and used baclofen more often compared with crying-predominant patients. The alternative laughter versus crying definition yielded similar associations (see online supplementary table S2). Women on the average scored about 1.4 points higher on the crying subscore and 1.5 points higher on the total score after adjusting for bulbar onset (p<0.0001). Significant gender effects persisted even after adjusting for depression.

Depression and PBA

Table 2 reports measures of depression and their association with PBA in 705 patients who completed CNS-LS and PHQ-9 on the same day. Examined were PHQ-9 total score, number of patients exceeding the threshold for moderate depression (10 points) and number of patients diagnosed with MDD on the basis of PHQ-9 responses (information available in 650 patients). There was a highly significant association between PBA, especially crying-predominant PBA, and depression. Laughter-predominant PBA, on the other hand, was not associated with depression. Table 3 reports Spearman's rank correlation between PHQ-9 and CNS-LS total scores as well as laughter and crying subscores of the latter. For the full correlation matrix of individual questions from these two instruments, total scores and subscores, along with confidence intervals, please see online supplementary figure S1. Moderate-to-strong internal correlation within questions of PHQ-9 and within questions of CNS-LS was borne out by Cronbach's alpha values for these instruments of 0.82 and 0.87, respectively. Cronbach's alphas for laughter and crying subscales of CNS-LS were 0.90 and 0.89, respectively. There was modest correlation between CNS-LS questions 1, 3 and 6 related to crying and PHQ-9 questions, but poor/absent correlation between CNS-LS questions 2, 4, 5 and 7 related to laughter, and PHQ-9 questions. Within PHQ-9,

questions 8 (moving or speaking slowly) and 9 (death wish) correlated less well with other questions and the total score, but no clear separation was observed between 'somatic' and 'psychological' questions. Question 8 of PHQ-9 correlated weakly with all CNS-LS questions, likely reflecting confounding by bulbar symptoms. Exploratory factor analysis of pooled PHQ-9 and CNS-LS questions suggested an optimum of three orthogonal factors corresponding to depression, laughter and crying, loaded appropriately on corresponding questions of PHQ-9, CNS-LS (laughter) and CNS-LS (crying), respectively (online supplementary table S3). Additional clinically meaningful factors (such as somatic and psychological dimensions of depression) were not identified on alternative factor specifications.

DISCUSSION

We found PBA in almost 30% of our unselected outpatient population with ALS, a prevalence slightly lower than 34% from a population-based study that employed CNS-LS,[20] but considerably lower than 45% in ALS from a cross-sectional study of multiple populations[1] that may not necessarily have enrolled consecutive patients or confirmed the presence of PBA clinically. This study confirms previously described and clinically recognised associations of PBA in ALS, including bulbar onset, and worse bulbar and UMN dysfunction. More than half (18/33) of patients with UMN-predominant disease and significant dysarthria/dysphagia (ALSFRS-R bulbar subscore ≤9) had PBA. In contrast, <10% of patients with LMN-predominant disease had PBA. Baclofen use (a surrogate for UMN dysfunction) was more common with PBA (38%) than without (22%). Almost 43% of patients with PBA had bulbar-onset ALS, and 69% had significant dysarthria/dysphagia. Like others,[20] we found an association with more severe disease and more rapidly progressive disease. Impaired executive function in association with PBA in ALS has been found by some[21 22] but not others[23]; similar deficits are reported with PBA in multiple sclerosis (MS).[24] The association with female gender has not been previously reported with ALS, although a weak trend was noted in two studies.[1 20] Women with acquired brain lesions[25] including stroke[26] are more likely to have emotional lability. As discussed herein, excessive crying may drive this excess of PBA in women, and this gender effect persists (OR 1.7) in the optimal multivariable predictive model of PBA. In fact, this model, which incorporates four other predictors (younger age, shorter duration of disease, lower bulbar subscore and lower gross motor subscore), can correctly predict the presence of PBA 74% of the time. We suspect that gross motor subscore is a surrogate for UMN dysfunction, a notion supported by higher use of baclofen in patients with lower gross motor subscores. Higher use of dextromethorphan-quinidine and antidepressants is to be expected because those agents are used to treat PBA. Lastly,

Table 2 Associations of PBA (CNS-LS ≥13) and measures of depression reported on the same day

	705 cases Median (IQR) or counts (%)	No PBA 502 cases	PBA 203 cases	p Value*	PBA Crying-predominant 105 cases	PBA Laughter-predominant 98 cases	p Value*
PHQ-9	6 (3–10)	5	8	<0.0001	10	7	<0.01
PHQ-9<10	503	387	117		52	65	
PHQ-9≥10	202 (28.7%)	116 (23.2%)	86 (42.4%)	<0.0001	53 (50.5%)	33 (33.7%)	<0.05
No MDD	550	404	146		68	78	
MDD	100 (15.4%)	48 (10.6%)	52 (26.3%)	<0.0001	36 (34.6%)	16 (17.0%)	<0.01

*Wilcoxon rank-sum test used to compare continuous variables and Pearson's χ^2 test used to compare categorical variables.
CNS-LS, Center for Neurologic Study-Lability Scale; MDD, major depressive disorder; PBA, pseudobulbar affect; PHQ-9, Patient Health Questionnaire.

we confirmed that PBA (especially crying-predominant PBA) is associated with poorer QoL.

There is no prior report on the longitudinal course of PBA as identified by CNS-LS scores. We found that CNS-LS increases rather slowly at an annual rate of 0.67 points. Similar to a prior report,[20] a weak association between PBA and shorter duration of disease was seen, although we wonder if this is from earlier attrition of bulbar-predominant patients in the cohort because of shorter survival. Our findings suggest that PBA manifests early in the course of ALS and remains relatively static afterwards.

Few studies have compared laughter and crying in PBA. In agreement with two previous studies,[5 20] we found that the laughter subscore was approximately equal to the crying subscore in ALS patients with PBA. Adjusting for the number of questions, this suggests that more patients with PBA cry than laugh, or that patients cry more frequently than they laugh. Alternatively, it is possible that the crying questions of CNS-LS have lower thresholds. Distinguishing these possibilities would require analysis of reported frequencies of crying and laughter from patient diaries; however, these have been found to be highly skewed and may not permit ready comparison of their relative frequencies.[27–29] Direct observation of PBA[30] in 19 patients with ALS (mostly men) found that eight had only crying episodes, four had only laughing episodes and seven had both. However, more laughing (62) than crying (54) episodes were recorded. In MS patients with PBA (mostly women), crying episodes were more frequent (median 3.5 per week) than laughter episodes (median 1 per week) on a retrospective questionnaire.[31]

More importantly, laughter and crying in PBA have differing associations. Crying-predominant PBA was often associated with depression, whereas laughter-predominant PBA was not. Crying-predominant PBA had a greater negative effect of QoL. Women were more likely to be crying-predominant than men, who were more likely to be laughter-predominant. Additionally, women had a higher crying subscore than men even after adjusting for bulbar onset. If the crying subscore of women is adjusted down by 1.5 points, the prevalence of PBA drops in our study to 23%, and female predominance in PBA and crying-predominant PBA disappears. This implies that women reporting more crying drive gender differences in PBA. Indeed, earlier studies have reported that crying after acquired brain lesions is more common in women.[25 32] Although cross-cultural studies show that normal women cry more than men,[33] the cause (biological or social/cultural) is unknown. It is possible that this background gender difference influences emotional expression in PBA. Alternatively, the pathology underlying PBA may affect the genders differently. Yet another explanation is that men under-report crying, perhaps because of societal expectations and embarrassment. Additional information will be required to clarify this observation. Irrespective of the mechanism, gender differences need to be accounted for when interpreting CNS-LS scores and subscores.

Covariance structure analysis of CNS-LS and PHQ-9 questions confirms internal consistency and discriminant validity of these two instruments as measures of three separate psychological constructs, namely laughter, crying and depression. These findings are similar to those reported in the original validation study,[5] wherein CNS-LS was compared with the Beck Depression Inventory. Our findings suggest that CNS-LS and PHQ-9 self-reports are indeed effective tools to distinguish PBA and depression in individual patients and populations with ALS. Given their brevity and low burden, and considering that PBA as well as depression is readily treatable and prevalent manifestations of ALS, we recommend that CNS-LS and PHQ-9

self-reports be routinely employed in the care of patients with ALS. Operative phrases in CNS-LS questions that effectively distinguish crying/tearfulness (a sudden/uncontrollable short-lived expression of emotion in PBA) from sadness (a more persistent emotion in depression) include '… feel fine 1 min … tearful the next …', '… crying very easily …' and '… try to control …unable …' in questions 1, 3 and 6, respectively. The interaction of PBA and depression, however, is complex. PBA and depression coexist more frequently than expected by chance in MS[34] and stroke.[35] Therefore, crying in PBA and depression may not be mutually exclusive and may be comorbidities. Moderate correlation between the CNS-LS crying subscore and PHQ-9 ($\rho=0.43$), and especially question 2 of PHQ-9 about sadness/hopelessness ($\rho=0.40$), suggests either that depression manifests with crying in the setting of PBA or that crying from PBA results in sadness and depression. Although it is believed that expression in PBA is unrelated to underlying emotional valence, direct observation indicates that patients with ALS do experience appropriate and intense emotions at the time of PBA episodes.[30] A study of emotionalism after stroke (predominantly uncontrolled crying) likewise found associations with sad/sentimental situations and depression.[36] The association between pathological crying and depression is neither unique to ALS[25] nor to the method employed to diagnose PBA/pathological crying.[23]

This study may be criticised for lack of external validation criteria for CNS-LS (such as direct observation or a diary of PBA episodes) and PHQ-9 (such as a structured interview to diagnose depression). However, the CNS-LS has been rigorously validated in ALS[5] as well as in MS.[31] One of the criticisms of using PHQ-9 (and other self-report depression instruments) in ALS is that motor decline confounds questions about somatic manifestations of depression. Our examination of responses to individual PHQ-9 questions, however, discloses acceptable internal consistency and unidimensionality of the scale in ALS, without evidence of an identifiable somatic subscale. PHQ-9 is validated in many neurological disorders, including some with prevalent PBA.[37 38] PHQ-9 has been successfully used in ALS as an indicator of depression.[9 39 40] Another criticism is the lack of standardised assessment of cognition (clinical impression inconsistently supplemented by brief cognitive instruments) and UMN dysfunction (clinical impression), not unexpected in a retrospective clinical cohort. There is also missing information as reported in column 1 of table 1; however, based upon the distribution of available variables, we feel that our cohort is a representative sample of patients with ALS seen in a tertiary centre.

The strengths of this study include the large number of unselected patients studied, associations examined, longitudinal data, comparison of laughter and crying subscores, examination of question-level data, correlation and discriminant validity of depression and PBA instruments, and new findings of associations between crying-predominant PBA, gender and depression. These latter findings have important clinical and research implications. Women with ALS should especially be screened for PBA. Additionally, patients with PBA and crying should be screened for depression, rather than assuming that crying is just a motoric expression of PBA without emotional correlate. Alternatively, patients with episodic crying should not automatically be assumed to be depressed but should be screened for PBA. Therapeutic studies of PBA should stratify by gender and assess outcomes of crying, laughter and depression separately. Further study into the relative prevalence of laughter and crying, and a possible causal effect of the latter on depression is needed in ALS and other conditions.

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