Neurol Ther (2024) 13:739–747
https://doi.org/10.1007/s40120-024-00605-w

ORIGINAL RESEARCH

Chinese Translation and Validation of the Center for Neurologic Study Lability Scale

Lu Chen · Shan Ye · Davan Murphy · Jieying Wu · Hui Zhang · Hong Liu · Boliang Zou · Guanghao Hou · Nan Zhang · Tielun Yin · Richard A. Smith · Dongsheng Fan

Received: January 30, 2024 / Accepted: March 15, 2024 / Published online: April 16, 2024

ABSTRACT

Introduction: Pseudobulbar palsy is a common symptom in patients with amyotrophic lateral sclerosis (ALS), but it is often underdiagnosed or misdiagnosed as other diseases. The Center for Neurologic Study Lability Scale (CNS-LS) is a self-report scale consisting of seven questions designed for evaluating pseudobulbar affect (PBA). The current study aimed to validate a Chinese version of the CNS-LS.

Methods: The Chinese version of the CNS-LS was obtained through a standardized forward–backward translation and cultural adaptation. A total of 105 patients with ALS were recruited from the ALS database of Peking University Third Hospital in Beijing, China, to complete the CNS-LS. The reliability of the Chinese ver-

Prior Presentation: A poster summarizing our research was presented at the NEALS annual meeting on October 4th, 2023. Prior to this, a version of our research was published as an abstract in "Proceedings of the 22nd Annual Meeting of the Northeast ALS Consortium" (*Muscle and Nerve*, October 2, 2023).

Richard A Smith and Dongsheng Fan are co-corresponding authors.

L. Chen · S. Ye · J. Wu · H. Zhang · H. Liu · B. Zou · G. Hou · N. Zhang · T. Yin · D. Fan (✉)
ĆDepartment of Neurology, Peking University Third Hospital, Haidian District, 49 North Garden Road, Beijing 100191, China
e-mail: dsfan2010@aliyun.com

S. Ye
e-mail: yeshanbysy@163.com

J. Wu
e-mail: dazhi_jieying@163.com

H. Zhang
e-mail: 2441358498@qq.com

H. Liu
e-mail: 15901557272@163.com

B. Zou
e-mail: blz0369258147@hotmail.com

G. Hou
e-mail: 1710301241@pku.edu.cn

N. Zhang
e-mail: 13520985887@163.com

T. Yin
e-mail: yintl716@sina.com

L. ChenĆDepartment of Neurology, Yan'an Hospital of Traditional Chinese Medicine, No. 26 Xuan Yuan Road, Bridge Ditch Street, Bao Ta District, Yan'an 716000, Shaanxi Province, China
e-mail: chenlu88@bjmu.edu.cn

D. Murphy · R. A. Smith (✉)ĆCenter for Neurological Study in La Jolla, 7590 Fay Avenue, Suite 517, La Jolla, CA, USA
e-mail: cnsonline@ymail.com

D. Murphy
e-mail: dmurphy@ucsd.edu

sion was determined by the test–retest method, and receiver operating characteristic (ROC) analysis was performed for criterion validity.
Results: Of 105 patients with ALS, 37 had symptoms of PBA and were diagnosed with that condition by neurologists. Forty-two patients completed the CNS-LS twice, and there was no statistically significant difference between the scores (Z = -0.896, p=0.37). The Spearman correlation coefficient between the test and retest scores was 0.940 (p<0.0005), and the Cronbach alpha coefficient was high (α=0.905, n=105). Scores of 12 or higher on the CNS-LS identified PBA with sensitivity of 0.919 and specificity of 0.882. The area under the ROC curve was 0.924.
Conclusion: The Chinese version of the CNS-LS demonstrated good sensitivity and specificity in the group of patients with ALS enrolled in this study. The CNS-LS should be a useful instrument for clinical and research purposes for patients in this language group.

Keywords: Pseudobulbar palsy; Pseudobulbar affect; Center for Neurologic Study Lability Scale

Key Summary Points

The diagnosis of pseudobulbar affect (PBA) is clinically based on the occurrence of inappropriate emotionality principally manifested by tearfulness and/or laughter. It is often misdiagnosed as depression or ignored by healthcare providers.

The Center for Neurologic Study Lability Scale (CNS-LS) is a self-report scale consisting of seven questions designed for the evaluation of PBA. The English version of the scale has been translated into numerous languages, but heretofore has not been available for clinical or research use involving Mandarin Chinese speakers.

The validation of the Mandarin version of the CNS-LS will potentially facilitate the evaluation and treatment of patients with common and rare neurological disorders involving a large segment of the world's population.

Scores of 12 or higher on the CNS-LS identified PBA with sensitivity of 0.919 and specificity of 0.882 in the group of Chinese patients with amyotrophic lateral sclerosis (ALS) enrolled in this study.

INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is the most common motor neuron disease and mainly involves the anterior horn cells of the spinal cord, the motor nuclei of the brain stem, and the pyramidal tract [1, 2]. It is characterized by simultaneous damage to upper and lower motor neurons [1, 2]. Currently, it is estimated that the number of patients with ALS in China is as high as 40,000 [3]. Because of the rapid progression and poor prognosis of ALS, [1, 2] this condition imposes great economic and psychological burden on the patients themselves, their families, and society.

A common symptom of ALS is pseudobulbar palsy, which includes dysphagia, slurred speech, salivation, and pseudobulbar affect (PBA) [4]. PBA has been described as exaggerated or inappropriate episodes of uncontrolled laughing and/or crying without an apparent motivating stimulus [5, 6]. Although the cause is still unclear, approximately 38.5% of patients with ALS show symptoms of PBA [6]. Diagnosis of PBA is usually by clinical examination and the

D. FanĆKey Laboratory for Neuroscience, National Health Commission/Ministry of Education, Peking University, 38 Xueyuan Road, Haidian District, Beijing 100191, China

D. FanĆBeijing Key Laboratory of Biomarker and Translational Research in Neurodegenerative Diseases, Beijing 100191, China

complaints of the patients, which results in significant underdiagnosis of the condition [7]. Effective and accurate evaluation of PBA is of great significance for patient care and the design of clinical trials.

The Center for Neurologic Study Lability Scale (CNS-LS) is a self-report scale consisting of seven questions designed for evaluating PBA [4, 7, 8]. Validation of this scale has been undertaken in subjects with multiple sclerosis (MS) and ALS in many countries [4, 7, 8]. Further, the CNS-LS has been widely used in clinical trials and patient screening [9]. Before this tool was adopted for the evaluation of Chinese patients, the validity and reliability of the Chinese version needed to be confirmed.

The aim of this study was to translate the CNS-LS into Mandarin Chinese and to validate the Chinese version of this scale in Chinese patients with ALS.

METHODS

CNS-LS

The CNS-LS is a validated self-report measure of pathological laughing and crying that consists of seven questions, answered using a five-point Likert scale. The score for each question was rated from 1 ("never applies") to 5 ("applies most of the time"). Responses across questions were summed as the total PBA score. The highest possible score on the CNS-LS is 35, and the lowest is 7. In a previous study in patients with ALS, a cutoff value of 13 or above was used in the diagnosis of PBA, with sensitivity of 0.84 and specificity of 0.81 [4]. The senior author of the English version of the Center for Neurologic Study Lability Scale, Dr. Richard Smith, is one of the corresponding authors of this research, and he has given us permission to translate and validate the scale in Chinese.

Translation of the CNS-LS

Two bilingual neurologists translated the scale into Mandarin Chinese. A back-translation to English was performed by an English language specialist. After these procedures, the back-translated scale was deemed substantially similar to the original. Thus, the Chinese version of the CNS-LS was created, and this scale was then administered to patients with ALS. The Chinese version of the CNS-LS is shown in Table 1.

Patient Recruitment from the ALS Database of Peking University Third Hospital

Peking University Third Hospital (PUTH) established a longitudinal ALS cohort in 2003, and this institution is currently one of the largest centers for ALS treatment in Asia. All patients with ALS who visited PUTH were recruited for the cohort, and patients who visited PUTH in 2022 were recruited into the study. Patients with ALS were diagnosed and classified by two board-certified neurologists according to the revised El Escorial diagnostic criteria [10, 11] If the patients had symptoms of PBA, they were assigned to the PBA group, and the others were assigned to the non-PBA group. The two neurologists made diagnoses for each patient independently, with any divergence between them resolved by a third senior neurologist. At the time of recruitment into the cohort (i.e., the first visit to the ALS center in PUTH), patients with ALS needed to complete the Chinese version of the CNS-LS and a case report form (CRF), which contained demographic and epidemiological information. All CRFs and scales were completed and checked by two neurologists independently.

Reliability

The reliability of the Chinese version was determined by the test–retest method; the paired rank–sum test and the Spearman correlation coefficient were used to verify the consistency of the results of the test and the retest. Cronbach's alpha coefficient was used to test the internal consistency of the scale. In 42 patients with ALS, the CNS-LS was scored twice at an interval of 5–10 days to determine the consistency of the scores.

Table 1 Chinese version of the CNS-LS

项目 **Question**	从不 **Never**	极少 **Rarely**	偶尔 **Occasionally**	经常 **Frequently**	绝大部分时间 **Most of the time**
1. 有时1分钟前我还感觉很好，但随后就会因为一些小事或无缘无故地流泪 There are times when I feel fine one minute, and then I'll become tearful the next over something small or for no reason at all					
2. 别人评价，我看起来很容易被逗乐，或者我看起来会因为一些根本不有趣的事而发笑 Others have told me that I seem to become amused very easily or that I seem to become amused about things that really aren't funny					
3. 我很容易哭泣 I find myself crying very easily					
4. 我发现即使我努力控制自己的大笑，我仍然经常无法控制 I find that even when I try to control my laughter, I am often unable to do so					
5. 即使我没有在想任何快乐或搞笑的事情，我的脑海也会突然控制不住地被快乐或搞笑的想法所占据。 There are times when I won't be thinking of anything happy or funny at all, but then I'll suddenly be overcome by funny or happy thoughts					
6. 我发现即使我努力控制自己的哭泣，我仍然经常无法控制 I find that even when I try to control my crying, I am often unable to do so					
7. 我发现我会控制不住地大笑 I find that I am easily overcome by laughter					
总分 Total score					

CNS-LS Center for Neurologic Study Lability Scale

Table 2 Clinical features of the patients in the study

	Group with PBA	Group without PBA	*p*
Number (*n*, %)	37	68	
Age (years, median, IQR)	53 (16.5)	56 (17.5)	0.634
Gender (*n*, %)			0.056
Male	15 (40.5)	40 (58.8)	
Female	22 (59.5)	28 (41.2)	
Time interval from onset to completion of the scale (months, median, IQR)	27.0 (31.50)	14.0 (19.75)	<0.0005
Revised El Escorial category			0.095
Definite	6 (16.2)	6 (8.8)	
Probable	16 (43.2)	21 (30.9)	
Laboratory-supported probable	7 (18.9)	26 (38.2)	
Possible	8 (21.6)	15 (22.1)	
Score of CNS-LS (median, IQR)	16 (7)	8 (4)	<0.0005
Score of Question 1 (median, IQR)	2 (2)	1 (1)	<0.0005
Score of Question 2 (median, IQR)	3 (2)	1 (0)	<0.0005
Score of Question 3 (median, IQR)	3 (1)	1 (1)	<0.0005
Score of Question 4 (median, IQR)	3 (2)	1 (0)	<0.0005
Score of Question 5 (median, IQR)	2 (2)	1 (0)	<0.0005
Score of Question 6 (median, IQR)	2 (2)	1 (0)	<0.0005
Score of Question 7 (median, IQR)	3 (1)	1 (1)	<0.0005

PBA pseudobulbar affect; *CNS-LS* Center for Neurologic Study Lability Scale; *IQR* interquartile range

Validation

Validation of the CNS-LS scale was performed in 105 patients with ALS. The diagnosis of PBA was made by board-certified neurologists who had experience with motor neuron diseases. Receiver operating characteristic (ROC) analysis was performed for criterion validity.

Ethics Approval

This study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments. The protocol was approved by the institutional ethics committee of PUTH (IRB No. 00006761), and written informed consent was obtained from each patient.

Data Availability Statement

The data that support the findings of this study are available from the database of the Neurology Department, PUTH, Beijing, China. All the anonymized data and the Chinese version of the CNS-LS within this article will be shared by the corresponding authors upon request from any qualified investigator.

RESULTS

A total of 105 patients with ALS participated in the study, of whom 42 patients completed the CNS-LS twice at an interval of 5–10 days. Of these patients, 55 (52.38%) were male and 50 (47.62%) were female; 37 (35.24%) patients had symptoms of PBA. The clinical features of the patients are shown in Table 2. No significant differences in age, gender, or El Escorial category were found between the PBA and non-PBA groups. The median time interval from onset to completion of the scale was significantly longer in the PBA group than in the non-PBA group ($p<0.0005$). The total scores and the scores for each question were significantly higher in the PBA group than in the non-PBA group (all $p<0.0005$).

Reliability

A paired rank–sum test was performed on the scores of each patient who completed the instrument twice. Among the 42 patients with ALS who completed the retest, 21 were male and 21 were female. The median age at the time of testing was 53.5 [interquartile range (IQR) 16.25] years. No statistically significant difference was found between the scores ($Z=-0.896$, $p=0.37$). The Spearman correlation coefficient between the test and retest was 0.940 ($p<0.0005$). Cronbach's alpha coefficient was high ($\alpha=0.905$, $n=105$), indicating the good internal consistency of the scale.

Validation

The median of the scores of the patients with PBA was 16 (IQR, 7), while that of the patients without PBA was 8 (IQR, 4). The difference in the CNS-LS scores was significant between the groups with PBA and without PBA ($p<0.0005$). Significant differences were found between the two groups for each question in the scale.

Using ROC curve analysis (Fig. 1), the patient's CNS-LS score was compared with the physician's diagnosis. The sensitivity and specificity for each possible cutoff point were calculated (Table 3). The area under the ROC curve (AUC) was high (AUC=0.924, $p<0.0005$), which indicated that the overall predictive accuracy of the Chinese version of the scale was good.

The upper-leftmost points in the ROC curve correspond to CNS-LS scores of 11.5 and 12.5. The sensitivity and specificity of the CNS-LS were 91.9% and 88.2%, respectively, using a cutoff of 11.5. At 12.5, they were 89.2% and 88.2%. A CNS-LS score above 11.5 as the cutoff for PBA had the best sensitivity and specificity. Because the scale is composed of whole numbers, a cutoff of 12 was chosen.

DISCUSSION

Since it was first published in 1997, the CNS-LS has been translated into many languages and is widely used in many countries. However, before the present study, the Chinese version of this scale had never undergone rigorous statistical verification. In this article, we document the successful translation of the English version of the CNS-LS into Mandarin Chinese in

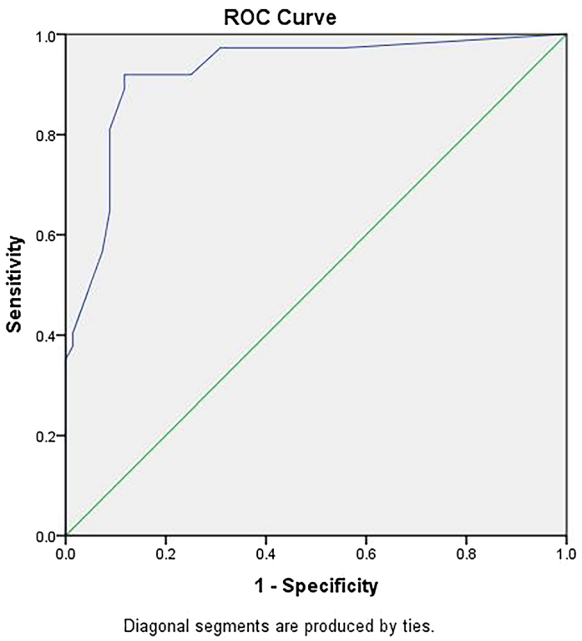

Fig. 1 Receiver operating characteristic (ROC) curve of the Chinese version of the Center for Neurologic Study Lability Scale

Table 3 Sensitivity and specificity levels of scores

Positive if greater than or equal to	Sensitivity	Specificity
6.00	1.000	0.000
7.50	0.973	0.441
8.50	0.973	0.574
9.50	0.973	0.691
10.50	0.919	0.750
11.50	0.919	0.882
12.50	0.892	0.882
13.50	0.811	0.912
14.50	0.649	0.912
15.50	0.568	0.926
16.50	0.486	0.956
17.50	0.405	0.985
18.50	0.378	0.985
19.50	0.351	1.000
20.50	0.324	1.000
21.50	0.189	1.000
22.50	0.135	1.000
25.00	0.081	1.000
27.50	0.054	1.000
29.00	0.000	1.000

cooperation with the corresponding author of the original publication. Because China is a populous country with 1.4 billion people speaking Mandarin, the validation of the Chinese version of the CNS-LS is of great significance for Chinese patients with PBA. The Chinese version of the CNS-LS showed high internal and external construct validity as well as good test–retest reliability. The cutoff value for the diagnosis of PBA was 12 in Chinese patients with ALS.

Since it was first reported in 1837 in a patient with multiple infarctions, PBA has been found in many conditions that damage bilateral corticobulbar pathways, such as ALS, MS, and cerebral infarction [12]. Although clinical features were used as the gold standard for the evaluation of the scale, the symptoms of PBA might be atypical in some patients, as the severity of PBA may vary greatly. Based on clinical symptoms alone, PBA has been underdiagnosed or misdiagnosed as other diseases, such as depression [4, 7]. Accordingly, the use of the CNS-LS is a valuable clinical tool [7] This conclusion has been affirmed in numerous studies, with the CNS-LS demonstrating high sensitivity and specificity in identifying PBA. A further advantage is the brevity of the scale, which includes only seven questions, making it easy for patients to understand and complete [4, 7]. Finally, we consider an abnormal CNS-LS score to confirm the presence of upper motor neuron involvement of the nervous system, which from a diagnostic point of view is useful to us for establishing the presence of exaggerated reflexes or a positive Babinski sign.

The cutoff value of the Chinese version of the CNS-LS was 12, which is one point lower than that of the English version [4]. Chinese patients with ALS have little understanding of the symptoms of PBA. Some patients and their families deliberately suppress the symptoms of PBA or interpret PBA as a rational response to their illness. In daily clinical work, our study team found that the number of patients with PBA symptoms or signs was significantly greater than the number of patients who complained of PBA. On the other hand, the time interval from disease onset to completion of the CNS-LS was significantly shorter in the PBA group than in the non-PBA group, which suggested that the symptoms of PBA were one of the reasons many patients sought medical attention [4]. Accordingly, the Chinese version of the CNS-LS should facilitate earlier detection of PBA by both physicians and patients, perhaps providing comfort to patients and their families who do not realize that PBA is a medical versus psychiatric condition.

Both the total scores and the scores for each question were significantly higher in the PBA group than in the non-PBA group in our study. After translation into Chinese, the CNS-LS still had high internal consistency and test–retest reliability. In addition, the high sensitivity and

specificity of the Chinese version of the CNS-LS suggested that it can successfully predict neurologists' diagnoses of PBA and that the scale is suitable for disease assessment and enrollment in clinical trials. In addition, this scale can help researchers better understand PBA and improve research on the prevalence and incidence of this syndrome in patients with ALS as well as those with other diseases, such as MS and stroke. Because it is simple and easy to complete, this scale is suitable for regular self-evaluation by patients and follow-up by their clinicians to track disease progression. In the era of highly developed modern means of communication, patients can be assisted in completing the scale regularly using a mobile phone.

This study has several limitations. First, the Chinese version of the CNS-LS was validated only in patients with ALS, and the cutoff value cannot be generalized to other diseases, such as MS, Parkinson's disease (PD), and stroke. Further validation in these diseases is needed. Second, the sample size of the study was relatively small. However, because ALS is an orphan disease, studies of patients with ALS face similar challenges in general, and the sample size of our study is comparable to those of other ALS studies [4, 7]. Larger studies with more patients can be completed in the future.

CONCLUSION

In this study, we translated and validated the Mandarin Chinese version of the CNS-LS in Chinese patients with ALS. The Chinese version of the CNS-LS demonstrates good internal consistency and test–retest reliability. Scores of 12 or higher on the CNS-LS identified PBA with high sensitivity and specificity in Chinese patients with ALS enrolled in this study. Based on our findings, the CNS-LS should be suitable for use as a clinical research tool in persons whose native language is Mandarin Chinese.

ACKNOWLEDGEMENTS

Medical Writing and Editorial Assistance. The initial edition of this manuscript was edited by the American Journal Experts.

Author Contributions. Lu Chen and Ye Shan translated the scale into Chinese and collected, analyzed and made the interpretation of the data; Richard Smith provided the CNS-LS; Richard Smith and Davan Murphy confirmed the equivalence and made revisions of the Chinese version; Jieying Wu, Hui Zhang, Hong Liu, Boliang Zou, Guanghao Hou, Nan Zhang and Tielun Yin collected the data; Dongsheng Fan and Richard Smith reviewed and approved the manuscript; Dongsheng Fan had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Dongsheng Fan and Richard Smith designed the study and finally made the decision to submit the manuscript for publication. Final approval of manuscript: all authors.

Funding. Dongsheng Fan has received the funding from the National Natural Science Foundation of China (NSFC) under Grant [Number 81873784; 82071426; 82001350]. The Rapid Service Fee was funded by the NSFC funding.

Data Availability. The data that support the findings of this study are available from the database of the Neurology Department, PUTH, Beijing, China. All the anonymized data within this article will be shared by request from any qualified investigator from the corresponding authors.

Declarations

Conflict of Interest. All the authors declare that they have no conflict of interest. Lu Chen has nothing to disclose. Shan Ye has nothing to disclose. Davan Murphy has nothing to disclose. Jieying Wu has nothing to disclose. Hui Zhang has nothing to disclose. Hong Liu has nothing to disclose. Boliang Zou has nothing to

disclose. Guanghao Hou has nothing to disclose. Nan Zhang has nothing to disclose. Tielun Yin has nothing to disclose. Richard A Smith has nothing to disclose. Dongsheng Fan has nothing to disclose.

Ethical Approval. This study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments. The protocol was approved by the institutional ethics committee of PUTH (IRB. No 00006761), and written informed consent was obtained from each patient.

REFERENCES

1. Kiernan MC, Vucic S, Cheah BC, Turner MR, Eisen A, Hardiman O, et al. Amyotrophic lateral sclerosis. Lancet. 2011;377(9769):942–55. https://doi.org/10.1016/S0140-6736(10)61156-7.

2. Shahrizaila N, Sobue G, Kuwabara S, Kim SH, Birks C, Fan DS, et al. Amyotrophic lateral sclerosis and motor neuron syndromes in Asia. J Neurol Neurosurg Psychiatry. 2016;87(8):821–30. https://doi.org/10.1136/jnnp-2015-312751.

3. Xu L, Chen L, Wang S, Feng J, Liu L, Liu G, et al. Incidence and prevalence of amyotrophic lateral sclerosis in urban China: a national population-based study. J Neurol Neurosurg Psychiatry. 2020;91(5):520–5. https://doi.org/10.1136/jnnp-2019-322317.

4. Moore SR, Gresham LS, Bromberg MB, Kasarkis EJ, Smith RA. A self report measure of affective lability. J Neurol Neurosurg Psychiatry. 1997;63(1):89–93. https://doi.org/10.1136/jnnp.63.1.89.

5. Trojsi F, Di Nardo F, D'Alvano G, Caiazzo G, Passaniti C, Mangione A, et al. Resting state fMRI analysis of pseudobulbar affect in Amyotrophic Lateral Sclerosis (ALS): motor dysfunction of emotional expression. Brain Imaging Behav. 2023;17(1):77–89. https://doi.org/10.1007/s11682-022-00744-4.

6. Nabizadeh F, Nikfarjam M, Azami M, Sharifkazemi H, Sodeifian F. Pseudobulbar affect in neurodegenerative diseases: a systematic review and meta-analysis. J Clin Neurosci. 2022;100:100–7. https://doi.org/10.1016/j.jocn.2022.04.009.

7. Smith RA, Berg JE, Pope LE, Callahan JD, Wynn D, Thisted RA. Validation of the CNS emotional lability scale for pseudobulbar affect (pathological laughing and crying) in multiple sclerosis patients. Mult Scler. 2004;10(6):679–85. https://doi.org/10.1191/1352458504ms1106oa.

8. Falconer R, Whitney D, Walters H, Rogers S. Prevalence of Pseudobulbar Affect (PBA) in Parkinson's disease: an underrecognized patient burden. Cureus. 2021;13(11): e19960. https://doi.org/10.7759/cureus.19960.

9. Patatanian E, Casselman J. Dextromethorphan/quinidine for the treatment of pseudobulbar affect. Consult Pharm. 2014;29(4):264–9. https://doi.org/10.4140/TCP.n.2014.264.

10. Chen L, Zhang B, Chen R, Tang L, Liu R, Yang Y, et al. Natural history and clinical features of sporadic amyotrophic lateral sclerosis in China. J Neurol Neurosurg Psychiatry. 2015;86(10):1075–81. https://doi.org/10.1136/jnnp-2015-310471.

11. Brooks BR, Miller RG, Swash M, Munsat TL. El Escorial revisited: revised criteria for the diagnosis of amyotrophic lateral sclerosis. Amyotroph Lateral Scler Other Motor Neuron Disord. 2000;1(5):293–9. https://doi.org/10.1080/146608200300079536.

12. Saleem F, Munakomi S. Pseudobulbar Palsy. 2023 Feb 12. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023. PMID: 31985953.