PSEUDOBULBAR AFFECT IN MULTIPLE SCLEROSIS PATIENTS

Viktor Vidović[1], Merisanda Časar Rovazdi[1], Oto Kraml[1] and Vanja Bašić Kes[2]

[1]Lipik Special Hospital for Medical Rehabilitation, Lipik; [2]University Department of Neurology, Sestre milosrdnice University Hospital Center, Zagreb, Croatia

SUMMARY – The aim of the study was to determine the prevalence of pseudobulbar affect (PBA) in patients with multiple sclerosis (MS) and to analyze the link between PBA and patient age, sex, clinical course of MS, disease duration and degree of disability. The study was conducted on 79 MS patients that underwent inpatient rehabilitation at the Lipik Special Hospital for Medical Rehabilitation in the period from August 15, 2014 to February 15, 2015. PBA is a term used for an emotional disinhibition syndrome characterized by sudden and involuntary episodes of crying or laughing which are not in proportion to the stimulus applied or occur without stimulus. The condition can be present in patients with various neurological disorders, such as amyotrophic lateral sclerosis, Alzheimer's disease, Parkinson's disease, patients having recovered from stroke, or following traumatic brain injury. The estimated prevalence in patients with MS ranges from 10% to 46.2%. As a measuring instrument in the study, we used the Center for Neurologic Study-Lability Scale (CNS-LS), where a sum ≥17 denoted positive finding. The total number of respondents was 79, of which 33 (41.8%) met the CNS-LS criteria for the diagnosis of PBA. There was no statistically significant correlation between PBA, age and degree of disability, although PBA was more common in women and in patients with a secondary progressive form of the disease. We found that 42.4% of respondents with positive CNS-LS criteria for PBA did not inform their neurologist on the presence of sudden mood changes. The high frequency of PBA and the fact that a significant proportion of patients did not inform the neurologist on their affective disturbances call for an active approach to diagnosis and treatment.

Key words: *Multiple sclerosis – complications; Pseudobulbar affect; CNS-LS*

Introduction

Pseudobulbar affect (PBA) is a term used for an emotional disinhibition syndrome characterized by sudden and involuntary episodes of crying or laughing, where such episodes are not in proportion to the stimulus applied or occur without stimulus[1]. Although the pathophysiology has not yet been fully elucidated, PBA has been linked to lesions in the frontal lobes and descending pathways to the brain stem, the base of the pons and cerebellum, which in turn leads to disorders in the system that is believed to participate in the motor control of emotional expression[2-4]. The synonyms frequently used for pseudobulbar affect in scientific literature are the terms of involuntary emotional expression disorder, emotional lability, emotional incontinence, and pathological laughing and crying[5], which makes it difficult to estimate the prevalence of the syndrome[2,6]. It is thought that PBA is inadequately identified in clinical practice, and may be misdiagnosed as a mood disorder such as depression[5,7-9]. PBA and depressive disorders may co-exist, but recent research has shown a high incidence of depression in patients with PBA[9,10-17]. The

Correspondence to: *Viktor Vidović, MD*, Lipik Special Hospital for Medical Rehabilitation, Marije Terezije 13, HR-34551 Lipik, Croatia
E-mail: viktor.vidovic@bolnica-lipik.hr

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condition may be present in a variety of neurological disorders. It is most common in patients with amyotrophic lateral sclerosis (44.8%-60%)[18-21], Alzheimer's disease (29.3%-39%)[11,18], in persons having recovered from stroke (11%-53%)[14,18,22-24], those with Parkinson's disease (4.7%-42.5%)[9,12,13,17,18], and after a traumatic brain injury (5%-52.4%)[18,25,26]. In patients with multiple sclerosis (MS), the estimated prevalence is 10%-46.2%[6,18,27]. Given that the studies use different criteria for diagnosing the syndrome, the prevalence varies significantly, even in terms of individually analyzed diseases. More recent studies have used the Center for Neurologic Study-Lability Scale (CNS-LS), validated for patients suffering from amyotrophic lateral sclerosis and MS, for evaluation and quantification of PBA symptoms[28,29]. The CNS-LS consists of a scale for laughter (4 questions) and crying (3 questions). Each answer is scored 1 to 5 (1 = never through 5 = almost always), depending on the frequency of the symptoms tested. The total sum varies from 7 (no symptoms) to 35 (maximum expressed symptoms). When validating a scale for MS patients, the recommended threshold is ≥17 for establishing a diagnosis of PBA[29]. In the validation process, a threshold ≥17 coincided with a clinical diagnosis in 89% of cases, accompanied by a sensitivity of 0.94 and specificity of 0.83. According to the recommendation of the American Academy of Neurology (AAN), the CNS-LS can be used for screening the existence of PBA[30], where the recommendation is based on a study in which the validation was conducted[29]. In some studies, estimates of the prevalence of PBA in MS patients are considered a positive finding if the sum is ≥13[6,18], which is the validated threshold for the diagnosis of PBA in those suffering from amyotrophic lateral sclerosis. Also, a more restrictive threshold of ≥21[6,18] has been used for moderate and severe forms of the disorder, for which, however, validation has not been conducted. A threshold of ≥13 on the CNS-LS for patients with MS has a sensitivity of 0.96 and specificity of 0.55 for the diagnosis of PBA, which also leads to false-positive findings[29]. The aim of the study was to determine the prevalence of PBA in MS patients and analyze the relationship between PBA and patient age, sex, clinical form of MS, and time elapsed from MS diagnosis.

Patients and Methods

The study included 79 patients with MS that underwent inpatient rehabilitation at the Lipik Special Hospital for Medical Rehabilitation in the period from August 15, 2014 to February 15, 2015. Participating in the study were patients older than 18 and diagnosed with MS according to the revised McDonald criteria[31]. The exclusion criterion was serious cognitive impairment, and accordingly, five patients were not included in the study. Data on patient age, sex, clinical course of MS, and time elapsed from MS diagnosis were collected. The diagnosis of PBA was made by use of the CNS-LS[28], where a sum ≥17 denoted positive finding. The degree of disability for all study subjects was based on the Expanded Disability Status Scale (EDSS)[32], and assessment of cognitive status was performed using the Mini Mental Status Exam (MMSE)[33]. Patients with a CNS-LS sum ≥17 were asked whether they had informed their neurologist on the sudden and involuntary mood changes. The study was approved by the Hospital Ethics Committee and patients were required to provide written consent for their participation.

Statistical analysis was performed using the SOFA Stats. Comparison of the variables was conducted using the Student's T-test and Pearson's correlation test.

Results

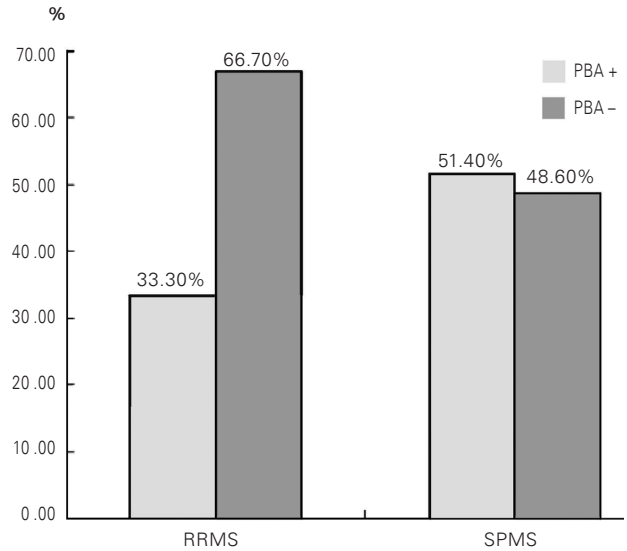
The study included 79 patients, 48 (60.8%) female and 31 (39.2%) male, mean age 48.9 years, age range 21-71 years. The mean time elapsed from MS diagnosis was 11.5 years (range, 6 months to 32 years). The relapsing-remitting course of the disease (RRMS) was experienced by 42 (53%) and secondary progressive MS (SPMS) by 37 (47%) patients. The mean EDSS was 4.7, range 1 to 9. Out of 79 study patients, 33 (41.8%) patients were diagnosed with PBA. Study patients were divided into two groups according to the presence/absence of PBA (Table 1). There were no statistically significant differences between the groups with and without PBA according to age (P=0.915), disease duration (P=0.374) and degree of disability measured by EDSS (P=0.6). The PBA positive group showed a significantly higher female predominance (P=0.066). The distribution of PBA prevalence in the

Table 1. Characteristics of patients with and without pseudobulbar syndrome

Characteristic	PBA+	PBA-
n (%)	33 (41.8)	46 (58.2)
Age (yrs), $\bar{x}$ ±SD	48.7±10.96	49.0±11.69
Female, n (%)	24 (72.7)	24 (52.2)
Male, n (%)	9 (27.3)	22 (47.8)
EDSS, $\bar{x}$ ±SD	4.9±1.85	4.64±2.02
Time elapsed from MS diagnosis (yrs), $\bar{x}$ ±SD	12.5±8.49	10.8±8.00

PBA = pseudobulbar affect; EDSS = Expanded Disability Status Scale; MS = multiple sclerosis

two clinical courses of MS indicated it to be higher in patients with SPMS (19 of 37 or 51.4% were PBA positive; 18 of 37 or 48.6% were PBA negative) than in those with RRMS (14 of 42 or 33.3% were PBA positive; 28 of 42 or 66.7% were PBA negative) (Fig. 1). Furthermore, 14 of 33 PBA positive patients (42.4%) had not informed their neurologist on the presence of sudden mood changes.



PBA = pseudobulbar affect; RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis

Fig. 1. Prevalence of PBA positive and PBA negative patients in two clinical courses of multiple sclerosis.

Discussion

In our study, the prevalence of PBA in MS patients was 41.8%, and the diagnosis of PBA was based on the CNS-LS sum ≥17. We used this threshold because it was validated for patients with MS[29]. The prevalence of PBA in patients with MS varies significantly in published studies, ranging from 10% to 46.2%[6,18,27]; however, different thresholds on the CNS-LS and different measuring instruments were used on determining the prevalence rates. In the study by Feinstein *et al*., the prevalence of PBA was 10%[27], and the measuring instrument used was the Pathological Laughter and Crying Scale (PLACS)[15]. Work *et al*. have estimated that the prevalence of PBA in patients with MS was 46.2% based on the CNS-LS and using a threshold ≥13, and 9.8% when a sum ≥21 was used as the threshold[6]. In the PRISM study[18], the prevalence of PBA was 45.8% with a threshold on the CNS-LS ≥13 and 12.0% with a threshold ≥21. When we used a sum ≥13 on the CNS-LS as the threshold for diagnosing PBA in our study, the prevalence was 51.9%. In none of the earlier studies was the sum ≥17 on the CNS-LS used as the threshold for diagnosing PBA, hence a comparison of the prevalence rate with our study using this threshold is not possible.

A limitation of the study was the fact that using the CNS-LS does not set a definitive diagnosis of PBA, but provides screening instead. Therefore, positive patients require further neurological and psychiatric assessment. Furthermore, we did not evaluate the possible presence of psychiatric disorders, such as depression or bipolar disorder. Also, some of the symptoms described using the CNS-LS (e.g., crying) may be associated with the possible existence of another psychiatric disorder. The same limitation applies to other studies[6,18,27].

Statistically, PBA was more significantly present in women. In the PRISM study[18], PBA was also more common in women, and given that other factors that may have affected the difference in the prevalence rate depending on sex were not analyzed in these studies, the reason for the difference remains unknown.

In our study, there were no significant differences between the patient groups with and without PBA according to age and disease duration. The prevalence of the secondary progressive course of the disease was higher in the PBA positive group as compared with the PBA negative group. The same finding has been reported by Feinstein *et al*.[27], while other studies did not analyze the relationship between PBA and age, disease duration, degree of disability, and clinical

courses of the disease[6,18]. Considering that patients with the secondary progressive course of the disease due to pathological process have a larger number of cerebral regions affected, the higher prevalence in this group could be explained by the fact that those central nervous system areas that participate in the motor control of emotional expression are also more likely to be affected.

The absence of a link between the incidence of PBA and neurological deficit measured using EDSS could be due to the fact that on determining the degree of deficit measured by EDSS, the symptoms not linked to the affected brain regions the lesions of which cause PBA are also summed, e.g., the degree of sphincter control and sensory deficit.

Slightly less than half of the study patients (42.4%) diagnosed with PBA had not informed the neurologist on their emotional disorders.

Conclusions

In the present study, the prevalence of PBA based on the CNS-LS questionnaire in patients with MS was 41.8%. Given the high prevalence and the fact that a large proportion of patients did not inform the neurologist on their emotional disorders, there is a need to actively look for PBA symptoms in patients with MS.

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Sažetak

PSEUDOBULBARNI AFEKT KOD OBOLJELIH OD MULTIPLE SKLEROZE

V. Vidović, M. Časar Rovazdi, O. Kraml i *V. Bašić Kes*

Cilj rada je bio odrediti učestalost pseudobulbarnog afekta (PBA) kod oboljelih od multiple skleroze (MS) i analizirati povezanost PBA s dobi bolesnika, spolom, kliničkim oblikom MS, trajanjem bolesti i stupnjem onesposobljenosti. Studija je obuhvatila 79 oboljelih od MS koji su u razdoblju od 15. kolovoza 2014. do 15. veljače 2015. provodili stacionarnu rehabilitaciju u Specijalnoj bolnici za medicinsku rehabilitaciju Lipik. PBA je naziv za sindrom dezinhibicije emocionalne ekspresije obilježen iznenadnim i nevoljnim epizodama plača ili smijeha koje nisu u razmjeru s primijenjenim podražajem ili se javljaju bez njega. Može biti prisutan kod oboljelih od različitih neuroloških bolesti poput amiotrofične lateralne skleroze, Alzheimerove bolesti, Parkinsonove bolesti, kod osoba nakon preboljelog moždanog udara i nakon traumatskog oštećenja mozga. Procijenjena učestalost kod oboljelih od MS kreće se od 10% do 46,2%. Kao mjerni instrument u istraživanju koristili smo ljestvicu CNS-LS (*Center for Neurologic Study-Lability Scale)*, pričem je zbroj ≥17 značio pozitivan nalaz. Ukupan broj ispitanika bio je 79, od kojih je 33 (41,8%) ispunilo kriterije CNS-LS za dijagnozu PBA. Nije nađena statistički značajna povezanost između PBA, dobi i stupnja onesposobljenosti, dok je PBA bio češći kod žena i oboljelih od sekundarno progresivnog oblika bolesti. Utvrđeno je da 42,4% ispitanika s pozitivnim kriterijima CNS-LS za PBA nije obavijestilo neurologa o prisutnim naglim promjenama u raspoloženju. Visoka učestalost PBA i činjenica da značajan udio oboljelih ne iznosi neurologu smetnje u afektivnoj sferi zahtijeva aktivan pristup u dijagnostici i liječenju.

Ključne riječi: *Multipla skleroza – komplikacije; Pseudobulbarni afekt; Ljestvica CNS-LS*