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ORIGINAL COMMUNICATION

Motor and non-motor symptoms in blepharospasm: clinical and pathophysiological implications

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Abstract

Introduction Patients with blepharospasm in addition to involuntary contraction of the orbicularis oculi muscle also have non-motor symptoms (psychiatric, sleep, cognitive, and ocular). In this paper, we investigated the relationship of non-motor with motor symptoms and the total burden of non-motor symptoms in patients with blepharospasm. Results were compared with those of age- and sex-matched healthy controls.

Methods We enrolled 60 patients with blepharospasm and 40 age-matched healthy controls. In all patients, the severity of blepharospasm was assessed clinically with the Blepharospasm Severity Rating Scale. All the participants underwent a psychiatric, sleep, cognitive, and ocular symptom evaluation. We investigated the correlations between motor, non-motor symptoms, and patients' clinical and demographic features.

Results The frequency of psychiatric, sleep, and cognitive disorders and ocular symptoms was higher in blepharospasm patients than in healthy controls. Non-motor symptoms coexisted in the majority of patients and there was no correlation between non-motor and motor symptoms. The total burden of non-motor symptoms did not associate with motor symptoms and demographic features in blepharospasm.

Conclusions Non-motor symptoms are independent of motor features and likely belong to the clinical spectrum of blepharospasm. The presence of non-motor symptoms possibly reflects a complex network disorder of blepharospasm.

Keywords Blepharospasm · Dystonia · Non-motor symptoms · Depression · Cognitive

Introduction

Blepharospasm (BSP) is a focal dystonia characterized by an increased activity of the orbicularis oculi (OO) muscles, associated with increased blinking and, sometimes, with apraxia of eyelid opening [1–3]. BSP is clinically heterogeneous as suggested by the presence of different subtypes identified on the basis of the duration of OO muscle spasms [4, 5]. In addition to motor symptoms, BSP patients may have non-motor features [3, 6, 7], including psychiatric problems [8, 9], sleep difficulties [10, 11], cognitive impairment [12, 13], and ocular symptoms [14, 15]. Previous studies on BSP patients have focused on the investigation of individual non-motor symptoms but did not assess the possible coexistence, the relationship with motor symptoms, and the total burden of psychiatric, sleep, cognitive, and ocular symptoms.

To this aim in this paper, we investigated in a sample of 60 patients with BSP non-motor symptoms including

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psychiatric, sleep, cognitive disorders, and ocular disturbances which are considered the most frequent non-motor symptoms in BSP [3] and their relationship with motor symptoms. Severity of motor symptoms was assessed by using a validated clinical scale. The overall burden of non-motor symptoms in individual BSP patients was also investigated.

Methods

We consecutively enrolled 60 patients with BSP (21 men and 39 women aged 65.7 ± 10.2 years) diagnosed according to the validated diagnostic criteria [2]. Seventy percent of patients were affected by focal BSP and 30% by BSP as a segmental dystonia. Age at dystonia onset was 55 ± 9.3 years and disease duration was 10.9 ± 6.7 years. All the BSP patients came from the outpatient movement disorders clinic of the Department of Human Neurosciences, Sapienza University of Rome. We also enrolled 40 healthy control subjects of similar sex (16 men and 24 women) and age (64.3 ± 9.4 years). To exclude any confounding effects due to botulinum toxin (BoNT) injections, the clinical assessment was performed at least 4 months after the last BoNT treatment. The experimental procedure was approved by the local institutional review board and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from each participant.

Blepharospasm assessment

BSP patients underwent a video-recorded neurological assessment. Video recordings performed according to a standardized procedure [5], were reviewed by two independent experienced movement disorder specialists who scored the severity of BSP using the Blepharospasm Severity Rating Scale (BSRS) [5]. The BSRS is based on: the type of OO spasm; the presence or absence of apraxia of eyelid opening; the presence of OO spasms that occur while writing; the average duration of prolonged OO spasms with complete rim closure; the frequency of brief spasms and blinks; the frequency of prolonged OO spasms with complete rim closure. Mean severity score of BSP in our patient population was 8.08 ± 4.03. Cohen's Kappa statistics yielded a high inter-rater agreement between the two neurologists who scored the videotapes ($K = 0.85$).

Non-motor symptom assessment

BSP patients and healthy controls underwent a full psychiatric evaluation. The Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) was used to determine major mental disorders, while the Structured Clinical Interview for DSM-IV Axis II Disorders (SCID-II) was used to determine personality disorders. The Hamilton Rating Scale for Anxiety (HAM-A) (a score of 17 or more indicates mild anxiety severity) [16] and the Hamilton Rating Scale for Depression (HAM-D) (a score of 7 or more indicates mild depression severity) [17] were administered to evaluate the severity of anxiety and depressive symptoms, respectively. The quality and pattern of sleep were assessed by means of the Pittsburgh Sleep Quality Index (PSQI) [18], a questionnaire that differentiates "poor" from "good" sleep by measuring seven aspects: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medications, and daytime dysfunction over the last month (a score of 5 or more indicates a poor quality of sleep). Both BSP patients and healthy controls underwent an evaluation to detect any cognitive impairment by means of the Montreal Cognitive Assessment (MoCA) [19], which investigates cognitive domains such us memory recall, visuospatial abilities, multiple aspects of executive functions, attention, concentration, working memory, language, spatial, and temporal orientation (a score of 26 or less indicates cognitive impairment). Ocular symptoms including burning sensation, grittiness, dryness of the eye, and red eyes were investigated in all the BSP patients and healthy controls by administering a standardized questionnaire [14].

In each patient and healthy control, we also calculated the overall burden of non-motor symptoms, which was defined as the sum of abnormal non-motor domains (1 = abnormal; 0 = normal) among the domains tested. For psychiatric domain, we used the SCID I (1 = presence of psychiatric diagnosis; 0 = absence of psychiatric diagnosis); for sleep domain, we used the PSQI total score which provides a comprehensive assessment of sleep quality (1 = ≥ 5; 0 = < 5); for cognitive domain, we used total MoCA score (1 = ≤ 26; 0 = > 26); and for ocular symptom domain, we used a standardized questionnaire (1 = presence of ocular symptoms; 0 = absence of ocular symptoms).

Statistical analysis

Data are expressed as mean ± standard deviation (SD) unless otherwise indicated. The statistical analysis was performed using the SPSS software version 25. Groups were compared by Mann–Whitney *U* test, one-way analysis of variance (ANOVA), Chi-squared test, and Fisher test as appropriate. Univariate and multivariate linear regression models were computed to analyze associations

Table 1 Clinical and demographic data of patients with blepharospasm and healthy controls

	Blepharospasm patients (*n*. 60)	Healthy control subjects (*n*. 40)	*P*
Age (mean ± SD years)	65.7 ± 10.2	64.3 ± 9.4	> 0.05
Number of women (%)	65%	60%	> 0.05
Psychiatric disturbances:			
SCID I (%)	23 (38.3%)	8 (10%)	< 0.001
SCID II (%)	4 (6.6%)	–	0.001
HAM-D score (mean ± SD)	5.8 ± 5.4	1.06 ± 3.3	< 0.001
HAM-A score (mean ± SD)	6.4 ± 5.9	1.03 ± 2.7	< 0.001
Sleep disorders (%)	34 (56%)	7 (18%)	< 0.001
PSQI score (mean ± SD)	6.1 ± 3.4	5 ± 2.6	< 0.001
MoCA score (mean ± SD)	23.03 ± 4.5	26.6 ± 2.9	< 0.001
Ocular symptoms (%)	43 (71.6%)	2 (5%)	< 0.001

Data are expressed as mean ± SD and as the number and the percentage of patients and healthy controls

among variables. A value of $p < 0.05$ indicated statistical significance.

Results

Patients and control subjects did not differ in age and gender (Table 1).

SCID I (Table 1) showed that 23 of the 60 BSP patients enrolled (38.3%) had psychiatric disorders: 8 (13%) had a generalized anxiety disorder, 4 (6.6%) had undefined anxiety disorder, 2 (3.3%) had major depression, 3 (5%) had dysthymia, 4 (6.6%) had adjustment disorder associated with depressed mood, 1 had affective psychosis (1.6%), and 1 had a post-traumatic stress disorder (1.6%). In contrast, only four (10%) healthy controls were diagnosed with a psychiatric disorder on the basis of the SCID I: one subject had major depression (2.5%), two (5%) had an unspecified anxiety disorder, and one had panic attacks (2.5%). The SCID II (Table 2) revealed the presence of a histrionic personality disorder in four BSP (6.6%) patients and in none of the healthy controls.

Sleep disturbances (Table 1) were significantly more frequent in BSP patients than in healthy controls—34 of the 60 BSP (56%) patients and 7 of the 40 controls (18%).

The global MoCA score was higher in BSP patients than in controls—42 of the 60 BSP (70%) patients and 8 of the 40 controls (20%) (Table 1). Analyzing the sub-domains investigated by the MoCA, the BSP patients showed an altered score compared to the healthy controls with regard to the visuospatial domain ($p < 0.001$), the attention ($p = 0.012$), and the recall ($p = 0.026$).

Table 2 Distribution of non-motor symptom domains in 60 patients with blepharospasm

	No. patients (%)
Total number of patients (%)	60 (100%)
Patients with isolated non-motor symptoms:	17 (28.3%)
Psychiatric disturbances alone	1 (5.8%)
Sleep disturbances alone	5 (29.4%)
Cognitive disturbances alone	3 (17.6%)
Ocular disturbances alone	8 (47.0%)
Patients with multiple non-motor symptoms:	43 (71.6%)
Psychiatric and sleep disturbances	14 (32.5%)
Psychiatric and cognitive disturbances	16 (37.2%)
Psychiatric and ocular disturbances	18 (41.8%)
Sleep and cognitive disturbances	24 (55.8%)
Sleep and ocular disturbances	25 (58.1%)
Ocular and cognitive disturbances	25 (58.1%)

Data are expressed as the number of patients with blepharospasm and the percentage in parenthesis

The prevalence of ocular symptoms was significantly higher in patients with BSP than in the healthy controls (Table 1)—43 of the 60 BSP (71%) and 2 of the 40 (5%) healthy controls. In 38 of the 43 BSP patients with ocular symptoms, the symptoms appeared before the onset of BSP, whereas in the remaining 5 patients, they appeared approximately 3 years later.

When the total burden of non-motor symptoms was investigated by means of standardized measurements (SCID-I, PSQI, MoCA, questionnaire for ocular symptoms), the BSP patients exhibited abnormalities in 1.9 ± 1.04 non-motor measurements (range from 0 to 4; 0 = no abnormality, 4 = abnormalities in all the clinical non-motor measurements). Psychiatric, sleep, cognitive, and ocular domains were affected in isolation in a minority of patients, whereas multiple non-motor symptoms domains were involved in most BSP patients (Table 2). Patients with isolated and multiple non-motor symptoms did not differ for disease duration ($p = 0.4$). No statistically significant association was found among the various non-motor symptoms (all $p > 0.05$).

When we classified BSP patients in the clinical phenotypes according to the type and duration of OO muscle spasm [4, 5], they did not differ in terms of non-motor symptoms, with a similar extent and severity of such symptoms being observed in each phenotype group (all values of $p > 0.05$).

Two linear regression models using the BSRS score as the dependent variable were computed to assess the relationships between motor and non-motor symptoms. The first model assessed the relationships between the BSRS

score and age, sex, disease duration, and the mean number of affected non-motor domains per BSP patients (Table 1 Supplementary material). The second model assessed the relationships between the BSRS score and age, sex, disease duration, the total score of HAM-D, HAM-A, and MoCA (Table 1 Supplementary material). In both these models, univariate and multivariate linear regression analyses did not disclose significant relationships between the variables examined (Table 1 Supplementary material). Likewise, no relationships could be observed between the number of affected non-motor domains per BSP patient (dependent variable) and age, sex, disease duration, and severity of motor symptoms tested by BSRS (Table 1 Supplementary material).

Discussion

By assessing multiple non-motor domains simultaneously, we have observed that non-motor symptoms are more frequent in BSP patients than in healthy controls, and that in the majority of BSP patients (71%), there is the coexistence of different types of non-motor symptoms, including psychiatric disturbances, sleep disorders, cognitive impairment, and ocular symptoms. There was no relationship between non-motor symptoms and motor symptoms severity, as assessed by BSRS. Furthermore, when we classified BSP patients according to the type and duration of OO muscle spasms [4, 5], we found that the frequency and severity of non-motor symptoms were similar in all the three clinical subtypes of BSP.

One important question is whether non-motor symptoms are secondary to motor symptoms or are part of the clinical spectrum of BSP. An association between motor and non-motor symptoms severity would suggest that non-motor symptoms are the consequence of motor manifestations. In our cohort of patients, however, we have demonstrated that the individual and global burden of non-motor symptoms were not associated with severity, duration, and clinical subtype of motor manifestations. In keeping with these observations, previous studies, investigating only single non-motor symptom domain, reported that non-motor symptoms did not correlate with motor symptoms in the different types of focal dystonias [8–11, 13, 20, 21]. Furthermore, non-motor symptoms sometimes precede the onset of motor symptoms [9], can be present in asymptomatic carriers of gene mutations associated with dystonia [22] or in unaffected relatives of dystonic patients [23]. In addition, unlike motor symptoms, non-motor symptoms do not improve after BoNT therapy [20, 24]. Overall, these observations suggest that non-motor symptoms are independent features from motor manifestations and should be considered as part of the clinical spectrum of BSP.

From a pathophysiological prospective, BSP, as well as other focal dystonias, is now considered to be due to an involvement of a brain network including different cortical and subcortical circuits [25, 26]. This hypothesis received recent support by studies examining brain connectivity patterns. BSP patients have an altered functional connectivity in basal ganglia, cerebellum, primary/secondary sensorimotor cortex, and visual areas [27]. There is also an altered connectivity between the basal ganglia and supplementary motor area [28], and among the sensorimotor cortex, supplementary motor area, premotor cortex, precuneus, and parietal cortex [29, 30]. This extensive abnormal connectivity would explain the wide impairment in multiple motor and non-motor domains in BSP [31]. A striatal-corticolimbic pathway dysfunction may underlie the psychiatric disorders, whereas a connectivity dysfunction between the basal ganglia and the cingulate, precuneus, and frontal areas may underlie the cognitive impairment. Recent findings have shown that the mesolimbic dopamine pathway is also involved in sleep regulation [32] and that the ventral tegmental area and nucleus accumbens play a crucial role in this pathway [32]. It is, however, important to stress out that in most of our patients we found the coexistence of different non-motor symptoms. This suggests that, although each single non-motor disorder may reflect the activity of a specific circuit, there is a pathophysiological crossroads of motor and non-motor manifestations, likely represented by basal ganglia. Indeed, basal ganglia are involved in motor as well non-motor domains, and this involvement reflects the presence of parallel loops implicated in motor, cognitive, and behavioral functions [31, 33].

As cross-sectional studies may be subject to bias, we took several precautions to ensure the reliability of the data that we gathered. The recruitment of consecutive BSP patients in a single-center setting provided a case series resembling the general population. The control group was unselected in terms of exposure of interest and almost matched the BSP patients in terms of place of origin and degree of medical surveillance. The level of agreement between the two neurologists, both with considerable experience in movement disorders, who blindly and independently evaluated the videotapes to assess the clinical subtypes and disease severity was high. The psychiatric assessment was performed by an experienced psychiatrist using the SCID I and SCID II, which are validated clinical tools. To exclude any confounding effects due to BoNT injections, the clinical assessment was performed at least 4 months after the last BoNT treatment.

Our study has some limitations. Data from BSP patients were compared with those of healthy subjects and we did not compare the results with those obtained from a second control group of patients with a different chronic illness. Therefore, the possibility that psychiatric disturbances may

be secondary to the chronic disease per sè cannot be fully excluded. Since there are not standardized scales for the overall burden of non-motor symptoms in dystonia, we introduced a score calculating normal/abnormal finding for each single domain. This approach might have underestimated the weight of psychiatric disturbances.

In conclusion, BSP is characterized by motor and non-motor symptoms that belong to different psychiatric, sleep, cognitive domains and ocular symptoms. The independence of non-motor symptoms from motor signs and the coexistence of various types of non-motor symptoms may reflect the pathophysiology of BSP as characterized by the involvement of several brain networks entrained in the abnormal communication with a dysfunctional central node in the basal ganglia. Follow-up studies are needed to evaluate whether the type and/or intensity of non-motor disturbances change during the course of BSP.

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Compliance with ethical standards

Conflicts of interest All authors report no conflict of interests.

Ethical standards The research documented in this manuscript has been carried out in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

References

1. Conte A, Defazio G, Ferrazzano G, Hallett M, Macerollo A, Fabbrini G, Berardelli A (2013) Is increased blinking a form of blepharospasm? Neurology 80:2236–2241
2. Defazio G, Hallett M, Jinnah HA, Berardelli A (2013) Development and validation of a clinical guideline for diagnosing blepharospasm. Neurology 81:236–240
3. Defazio G, Hallett M, Jinnah HA, Conte A, Berardelli A (2017) Blepharospasm 40 years later. Mov Disord 32:498–509
4. Defazio G, Conte A, Gigante AF, Ferrazzano G, Pellicciari R, Dagostino S, Fabbrini G, Berardelli A (2017) Clinical heterogeneity in patients with idiopathic blepharospasm: a cluster analysis. Parkinsonism Relat Disord 40:64–68
5. Defazio G, Hallett M, Jinnah HA, Stebbins GT, Gigante AF, Ferrazzano G, Conte A, Fabbrini G, Berardelli A (2015) Development and validation of a clinical scale for rating the severity of blepharospasm. Mov Disord 30:525–530
6. Conte A, Berardelli I, Ferrazzano G, Pasquini M, Berardelli A, Fabbrini G (2016) Non-motor symptoms in patients with adult-onset focal dystonia: sensory and psychiatric disturbances. Parkinsonism Relat Disord 22:111–114
7. Stamelou M, Edwards MJ, Hallett M, Bhatia KP (2012) The non-motor syndrome of primary dystonia: clinical and pathophysiological implications. Brain 135:1668–1681
8. Fabbrini G, Berardelli I, Moretti G, Pasquini M, Bloise M, Colosimo C, Biondi M, Berardelli A (2010) Psychiatric disorders in adult-onset focal dystonia: a case–control study. Mov Disord 25:459–465
9. Lencer R, Steinlechner S, Stahlberg J, Rehling H, Orth M, Baeumer T, Rumpf HJ, Meyer C, Klein C, Muenchau A, Hagenah J (2009) Primary focal dystonia: evidence for distinct neuropsychiatric and personality profiles. J Neurol Neurosurg Psychiatry 80:1176–1179
10. Avanzino L, Martino D, Marchese R, Aniello MS, Minafra B, Superbo M, Defazio G, Abbruzzese G (2010) Quality of sleep in primary focal dystonia: a case–control study. Eur J Neurol 17:576–581
11. Paus S, Gross J, Moll-Müller M, Hentschel F, Spottke A, Wabbels B, Klockgether T, Abele M (2011) Impaired sleep quality and restless legs syndrome in idiopathic focal dystonia: a controlled study. J Neurol 258:1835–1840
12. Alemán GG, de Erausquin GA, Micheli F (2009) Cognitive disturbances in primary blepharospasm. Mov Disord 24:2112–2120
13. Romano R, Bertolino A, Gigante A, Martino D, Livrea P, Defazio G (2014) Impaired cognitive functions in adult-onset primary cranial cervical dystonia. Parkinsonism Relat Disord 20:162–165
14. Martino D, Defazio G, Alessio G, Abbruzzese G, Girlanda P, Tinazzi M, Fabbrini G, Marinelli L, Majorana G, Buccafusca M, Vacca L, Livrea P, Berardelli A (2005) Relationship between eye symptoms and blepharospasm: a multicenter case-control study. Mov Disord 20:1564–1570
15. Defazio G, Abbruzzese G, Aniello MS, Di Fede R, Esposito M, Fabbrini G, Girlanda P, Liguori R, Marinelli L, Martino D, Morgante F, Santoro L, Tinazzi M, Berardelli A (2012) Eye symptoms in relatives of patients with primary adult-onset dystonia. Mov Disord 27:305–307
16. Hamilton M (1959) The assessment of anxiety states by rating. Br J Med Psychol 32:50–55
17. Hamilton M (1960) A rating scale for depression. J Neurol Neurosurg Psychiatry 23:56–62
18. Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ (1989) The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res 28:193–213
19. Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, Cummings JL, Chertkow H (2005) The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc 53:695–699
20. Berardelli I, Ferrazzano G, Pasquini M, Biondi M, Berardelli A, Fabbrini G (2015) Clinical course of psychiatric disorders in patients with cervical dystonia. Psychiatry Res 229:583–585
21. Yang J, Shao N, Song W, Wei Q, Ou R, Wu Y, Shang HF (2017) Non motor symptoms in primary adult onset cervical dystonia and blepharospasm. Brain Behav 7(2):e00592
22. Heiman GA, Ottman R, Saunders-Pullman RJ, Ozelius LJ, Risch NJ, Bressman SB (2004) Increased risk for recurrent major depression in DYT1 dystonia mutation carriers. Neurology 63:631–637
23. Voon V, Butler TR, Ekanayake V, Gallea C, Ameli R, Murphy DL, Hallett M (2010) Psychiatric symptoms associated with focal hand dystonia. Mov Disord 25:2249–2252
24. Novaretti N, Cunha ALN, Bezerra TC, Pereira MAP, de Oliveira DS, Macruz Brito MMC, Pimentel AV, Brozinga TR, Foss M, Tumas V (2019) The prevalence and correlation of non-motor symptoms in adult patients with idiopathic focal or segmental dystonia. Tremor Other Hyperkinet Mov (N Y) 9:596
25. Jinnah HA, Berardelli A, Comella C, Defazio G, Delong MR, Factor S, Galpern WR, Hallett M, Ludlow CL, Perlmutter JS, Rosen AR, Investigators Dystonia Coalition (2013) The focal dystonias: current views and challenges for future research. Mov Disord 28:926–943

26. Quartarone A, Hallett M (2013) Emerging concepts in the physiological basis of dystonia. Mov Disord 28:958–967
27. Jochim A, Li Y, Gora-Stahlberg G, Mantel T, Berndt M, Castrop F, Dresel C, Haslinger B (2017) Altered functional connectivity in blepharospasm/orofacial dystonia. Brain Behav. 8(1):e00894
28. NiMF HuangXF, MiaoYW LiangZH (2017) Resting state fMRI observations of baseline brain functional activities and connectivities in primary blepharospasm. Neurosci Lett 660:22–28
29. HuangXF ZhuMR, ShanP PeiCH, LiangZH ZhouHL, NiMF MiaoYW, XuGQ ZhangBW, Luo YY (2017) Multiple neural networks malfunction in primary blepharospasm: an independent components analysis. Front Hum Neurosci 11:235
30. BattistellaG Termsarasab P, Ramdhani RA, Fuertinger S, Simonyan K (2017) Isolated focal dystonia as a disorder of large-scale functional networks. Cereb Cortex 27:1203–1215
31. Graff-Radford J, Williams L, Jones DT, Benarroch EE (2017) Caudate nucleus as a component of networks controlling behavior. Neurology 89:2192–2197
32. OishiY Lazarus M (2017) The control of sleep and wakefulness by mesolimbic dopamine systems. NeurosciRes 118:66–73
33. Tremblay L, Worbe Y, Thobois S, Sgambato-Faure V, Féger J (2015) Selective dysfunction of basal ganglia subterritories: From movement to behavioral disorders. Mov Disord 30(9):1155–1170