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Motor and Psychiatric Features in Idiopathic Blepharospasm: a Data-Driven Cluster Analysis

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Abstract

Introduction: Idiopathic blepharospasm is a clinically heterogeneous dystonia also characterized by non motor symptoms.

Methods: We used a k-means cluster analysis to assess 188 patients with idiopathic blepharospasm in order to identify relatively homogeneous subpopulations of patients, using a set of motor and psychiatric variables to generate the cluster solution.

Results: Blepharospasm patients reached higher scores on scales assessing depressive- and anxiety-related disorders than healthy/disease controls. Cluster analysis suggested the existence of three groups of patients that differed by type of spasms, overall motor severity, and presence/severity of psychiatric problems. The greater severity of motor symptoms was observed in Group 1, the least severity in Group 3, while the severity of blepharospasm in Group 2 was between that observed in Groups 1 and 3. The three motor subtypes also differed by psychiatric features: the lowest severity of psychiatric symptoms was observed in the group with least severe motor symptoms (group 3), while the highest psychiatric severity scores were observed in group 2 that carried intermediate motor severity rather than in the group with more severe motor symptoms (group 1). The three groups did not differ by disease duration, age of onset, sex or other clinical features.

Conclusions: The present study suggests that blepharospasm patients may be classified in different subtypes according to the type of spasms, overall motor severity and presence/severity of depressive symptoms and anxiety.

Keywords

blepharospasm; depression; anxiety; cluster analysis

Introduction

Spasms of variable severity in the orbicularis oculi muscles are the core motor feature of idiopathic blepharospasm (BSP).[1] Additional manifestations may include apraxia of eyelid opening (AEO), sensory tricks, sensory symptoms (dry eyes,sensations of grit/sand in the eyes) and dystonia in other body parts.[1] There is an ongoing debate as to whether psychiatric symptoms (anxiety and depression),[1,2] are a primary phenotypic component or secondary sequelae of a chronic disorder. The phenomenological heterogeneity of BSP raises the possibility of distinct BSP subtypes. Accordingly, a recent data-driven cluster analysis identified three BSP subtypes, based on the type and severity of spasms.[3] In the current study, we analysed a larger international cohort of BSP patients to understand whether psychiatric symptoms are part of the phenotypic spectrum of BSP and to identify subpopulations based on motor and psychiatric manifestations.

Patients and methods

Data were acquired from the Dystonia Coalition (www.rarediseasesnetwork.org/dystonia/) project, “Diagnostic and Rating Tools for Blepharospasm”, a multicenter, observational study enrolling BSP patients across 10 sites in the USA and Europe. Each site recruited

about 20 patients;only 7/40 patients from two italian sites (Bari and Rome) were also included in the prior cluster study peformed 6 years earlier (3). Age 18 or more, any gender, and any racial-ethnic background were inclusion criteria for both cases and controls. Isolated idiopathic BSP was diagnosed by an experienced movement disorder neurologist, according to validated criteria.[4] Exclusion criteria were acquired BSP,[5] and co-existing medical conditions/surgical interventions that could confound BSP assessment. The last BoNT treatment session was performed at least 12 weeks prior to examination to ensure that the clinical hallmarks were detectable. Permission for the study and written informed consent were obtained. Details of age at BSP onset, disease duration, eye diseases, and sensory trick were collected through a standardized questionnaire. BSP severity was assessed by the validated blepharospasm severity rating scale (BSRS) that provides a composite score based on presence, frequency and duration of motor manifestations.[6] Brief spasms (lasting<3s) with complete rim closure and prolonged spasms (lasting <3s) leading to complete or incomplete rim closure were taken into consideration.[6] All patients were video-recorded according to a standardized protocol.[4] Six raters from the recruiting centers performed an independent evaluation of the videos, which yielded a satisfactory BSRS score agreement (Intraclass correlation coefficient=0.81,$p<0.0001$).

Psychiatric scales were the obsessive compulsive inventory-revised (OCI-R),[7] the Hospital Anxiety and Depression Scale (HADS)[8] and the Liebowitz Social Anxiety (LSAS).[9] The OCI-R is an 18-item self-reported instrument for assessing symptoms of obsessive–compulsive disorder rated on a 5-point scale (0–4; maximum severity score=72).[7] The HADS assesses self-reported severity of anxiety (HADS-A) and depression (HADS-D), with seven questions for both subscales, each yielding scores ranging 0–21 (maximum severity).[8] Finally, the self-reported LSAS is a 24-item scale that assesses both fear/anxiety symptoms and avoidance behaviour subcategories using a 4-point scale (0–3) for each item (maximum severity score=144).[9] All scales have good validity and reliability and were previously used in studies on dystonia. Standard scale cut-offs for defining clinically significant symptoms were: OCI-R>21; HADS-D/HADS-A>7; and LSAS>30.[7–9]

Scales were completed by BSP patients and a control group comprising 53 healthy subjects and 67 patients with BSP mimics (Bell’s palsy,hemifacial spasm,lid ptosis due to myasthenia or other conditions). Control subjects were collected and examined at the same sites which recruited BSP patients. Healthy and disease controls yielded similar scores on psychiatric scales (data not shown) and were therefore analysed as a whole group to gain power. Statistical analysis was performed using the Stata 11.0 package (Stata Corporation, College Station, TX, USA). Groups were compared by the chi-square test and one-way ANOVA and post hoc test, as appropriate. Non-hierarchical (k-means) cluster analysis using the Jaccard method for categorical data was performed on the BSP sample for two-, three- and four-cluster solutions;[3] the variables considered for the clustering included the three different types of spasm (brief spasms with complete rim closure and prolonged spasms leading to complete or incomplete rim closure), AEO, and presence of depression, anxiety and social anxiety as assessed by dichotomising HADS-D,HADS-A and LSAS according to standard scale cut-offs.[7–9] Calinski/Harabasz pseudo-F index stopping rule was used to determine the optimal number of clusters: the higher the Calinski/ Harabasz pseudo-F index value, the more distinct the clustering. We also investigated associations across the clusters

with variables not included in the cluster solution. Pearson correlation analysis was used to assess correlations between variables;statistical significance was set at 0.05.

Results

Study Population

One-hundred and eighty-eight patients partecipated in the study (128 women and 60 men aged 63.8±8.5 years; age at BSP onset, 52.5±9.9 years; disease duration 12.2±10.5 years). Control group included 80 women and 40 men aged 62.8±12.2 years. BSP patients and controls did not significantly differ for sex (p=0.95) and age (p=0.22). In the BSP group, brief spasms were present in 172/188 patients, prolonged spasms with partial rim closure in 78/188 patients, and prolonged spasms with complete rim closure in 51/188 patients. Additional symptoms included eye symptoms (166/188 patients),sensory trick (104/188 patients),AEO (55/188 patients),and dystonia in other body parts (121/188). Mean BSRS score was 7.1±3.8.

On psychiatric assessment,BSP patients yielded higher scores than controls on HADS-A (4.8±3.9 vs. 3.4±2.8,p=0.0004), HADS-D (4.2±3.5 vs. 3.2±2.7,p=0.004), and LSAS (27.9±27.1 vs. 17.1±22.2,p=0.0002) but not on OCI-R (6.2±7.9 vs. 5.9±7.8,p=0.38). According to standard scale cut-offs,a greater percentage of BSP patients than controls met criteria for depression, (32/188 vs. 10/120,p=0.03), anxiety (52/188 vs 20/120,p=0.03), and social anxiety (69/188 vs. 28/120,p=0.014), while no significant different frequency of obsessive–compulsive disorder was observed (11/188 vs. 8/120,p=0.77). There was no significant correlation between BSP duration and score on OCI-R (r=0.08,p=0.24), HADS-A (r=0.02,p=0.68), HADS-D (r=−0.05,p=0.5), LSAS (r=0.11,p=0.09), and BSRS (r=−0.002,p=0.9). Likewise, there was no significant correlation between BSRS score and score on OCI-R (r=0.08,p=0.26), HADS-A (r=−0.08,p=0.27), HADS-D (r=−0.06,p=0.43), and LSAS (r=0.12,p =0.1). Correlation analysis among the four psychiatric scales yielded partial but significant Pearson’s coefficient ranging between 0,51 (p<0.0001) and 0.77 (p<0.0001) with no evidence of collinearity.

Cluster analysis

The Calinski/Harabaszpseudo-F index favoured a three cluster solution (Calinski/Harabaszpseudo-F index: two-cluster solution, 63; three-cluster solution, 69; four-cluster solution, 47). Groups 1, 2, and 3 contained 68, 49,and 71 patients,respectively (Table 1). In Group 1, 50% of patients suffered from prolonged spasms with complete rim closure, 88% suffered from prolonged spasms with partial rim closure and 84% suffered from brief spasms. In Group 2, prolonged spasms with complete or partial rim closure were present in 34% and 37% of patients, while brief spasms were present in 91% of patients. Finally, Group 3 contained patients who only suffered from brief spasms. According to standard cut off scores from HADS-A,HADS-D,and LSAS, patients meeting criteria for psychiatric disorders were significantly more frequent in Group 2 (Table 1). Using only motor features as clustering variables yielded three motor groups that were quite similar to those resulting when psychiatric features were added to the clustering (data not shown).

Table 2 showed the distribution of the variables not included in generating the cluster solution. The severity of BSP was significantly greater in Group 1 while the mean severity scores from psychiatric scales were significantly greater in Group 2. The three groups did not differ for age, sex, age at BSP onset, BSP duration, frequency of sensory trick, AEO, spread of dystonia, and eye symptoms.

Discussion

On neuropsychiatric assessment BSP patients reached higher scores on scales assessing depression and anxiety than healthy/disease controls. By contrast, obsessive compulsive disturbances were similarly represented in the two groups and, therefore, were not considered among clustering variables. Cluster analysis yielded three BSP groups that differed for type of spasms, presence/severity of psychiatric problems, and motor severity.

With regard to motor symptoms, Group 1 and Group 2 included patients who had similar high frequency of brief spasms but differed for frequency of prolonged spasms with incomplete/complete rim closure that predominated in group 1. By contrast, Group 3 included patients with only brief spasms, the least severe muscle spasms. Accordingly, the greater severity of motor symptoms as assessed by the BSRS was observed in Group 1, the least severity in Group 3. These findings agree with the results of a previous cluster analysis performed in a smaller BSP sample from two italian movement disorder centers.[3] Obtaining similar results in different BSP samples and by means of different sets of clustering variables (the previous study relied only on motor variables while the present study considered both motor and psychiatric disturbances) supports the validity of the identified BSP subtypes and added more information on the multifaceted phenomenology of blepharospasm.

Our main novel finding is that BSP motor subtypes also differed for psychiatric features. In particular, the highest psychiatric severity scores were observed in group 2 that carried intermediate motor severity rather than in the group with more severe motor symptoms (group 1). The lack of association between the groups we identified and age, sex, and disease duration indicated that none of these variables could explain differences across groups. Overall, these findings as well as the lack of correlation between BSP duration or severity and scores from the psychiatric scales support psychiatric features as part of the full clinical spectrum of BSP rather than secondary sequelae to a chronic disorder.[1,3] Given the possible coexistence of psychiatric symptoms, there was significant but partial correlation between scores from psychiatric scales. The cross-sectional design limits interpretation of the subtypes we identified. Previous observations showed that BSP motor phenomenology may progress from earlier brief spasms to later appearance/worsening of prolonged spasms.[10] Thus, the BSP subtypes identified by cluster analysis might reflect variable rates of progression of motor and psychiatric disturbances over the disease course, even though the cross sectional approach would suggest caution. Alternatively, the varying BSP phenomenology may result from aggregation of motor and psychiatric symptoms in separate clusters in different disease courses. Regardless of the explanation, early and follow-up assesment of psychiatric symptoms would be valuable to better define and treat the whole phenomenology of the disease.

This study may have limitations. This was not a population-based study, even though it included a large and representative sample of the general BSP population. BoNT treatment may have affected the results on motor phenomenology but patients were studied at least three months after the last treatment, when its significant motor effects has worn off. The methodology we used for cluster analysis may be criticised. However, the variables included in the clustering solutions were carefully selected so as to allow exploring the clinical heterogeneity and comparing the variables not included in the cluster analysis. The similar age at BSP onset, disease duration, and frequency of eye symptoms and sensory trick in the three BSP groups supports the lack of influence of these variables on cluster analysis. Sleep and cognitive disturbances were not considered for analysis because the dystonia coalition protocol lacked such data. We also paid attention to the size of the sample to be clusterized. The rule of thumb provided by Formann[11] recommended a sample size of at least 2m, where m equals the number of clustering variables. Accordingly, including 7 clustering variables would need at least 128 patients, whereas our sample included 188 BSP patients included.

Despite the foregoing limitations, our findings add to the growing list of evidence that BSP is not a single disorder but a heterogeneous group of related disorders and support the usefulness of carrying out a careful evaluation of psychiatric symptoms along to motor signs over the disease course. This heterogeneity has profound implications for understanding the biology of the disorder and best treatment strategies. From the biological perspective, a more refined recognition of clinical subtypes may facilitate identification of responsible genes or neuroanatomical substrates. From the clinical perspective, the same treatment strategies are often offered to all patients with BSP when different strategies may be more appropriate. This may be the case of the markedly varied responses of BSP to deep brain stimulation.[12] Of course, identificaton of a subgroup with depression or anxiety may require psychiatric interventions. Further studies that more precisely delineate clinically relevant subtypes of BSP are clearly needed.

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M. Hallett is an inventor of patents held by NIH for an immunotoxin for the treatment of focal movement disorders and the H-coil for magnetic stimulation; in relation to the latter, he has received license fee payments from the NIH (from Brainsway). He is on the Medical Advisory Boards of CALA Health and Brainsway (both unpaid positions). He is on the Editorial Board of approximately 15 journals and receives royalties and/or honoraria from publishing from Cambridge University Press, Oxford University Press, Springer, Wiley, Wolters Kluwer, and Elsevier. He has research grants from Medtronic, Inc. for a study of DBS for dystonia and CALA Health for studies of a device to suppress tremor.Disclosures

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Data Availability Statement:

Due to privacy concerns, regulations, and informed consent provided by participants, this data cannot be uploaded to a freely accessible public repository.

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- psychiatric symptoms are part of the clinical spectrum of Idiopathic blepharospasm
- depression and anxiety scores were higher in patients than in controls
- Cluster analysis with motor/psychiatric resulted in three groups of patients
- lowest severity of psychiatric symptoms in the least severe motor symptoms' cluster
- highest psychiatric severity scores in the intermediate motor severity cluster

Table 1.

Clusters with variables included in generating the cluster solution.

Variables included in the cluster analysis	Group 1 (n.68)	Group 2 (n. 49)	Group 3 (n. 71)	P by Chi square test or one-way ANOVA
Motor features				
Brief spasms with complete rim closure, n. pts (%)	57 (84%)	44 (91%)	71 (100%)	0.003
Prolonged spasm with incomplete rim closure, n.pts (%)	60 (88%)	18 (37%)	0	<0.0001
Prolonged spasm with complete rim closure, n. pts (%)	34 (50%)	17 (34%)	0	<0.0001
Apraxia of lid opening, n. pts (%)	24 (35%)	17 (35%)	14 (20%)	0.08
Psychiatric diagnosis				
Anxiety (HADS-A > 7), n. pts (%)	2 (3%)	43 (88%)	7 (10%)	<0.0001
Depression (HADS-D > 7), n. pts (%)	0	30 (61%)	2 (3%)	<0.0001
Social anxiety (LSAS >30), n. pts (%)	20 (29%)	39 (80%)	10 (14%)	<0.0001

Table 2.

Clusters with variables not included in the cluster analysis

Variables not included in the cluster analysis:	Group 1 (n.68)	Group 2 (n. 49)	Group 3 (n. 71)	P by Chi square test or one-way ANOVA
Women, n. patients (%)	46 (68%)	35 (71%)	47 (66%)	0.8
Age at blepharospasm onset (mean years±SD)	52.2 ± 9.9	53.8 ± 8.6	51.8 ± 11	F=0.6, p=0.54
Disease duration (mean years±SD)	12.4 ± 10.4	13.1 ± 10.8	11.4 ± 10.5	F=0.4, p=0.67
Blepharospasm severity rating scale (mean score±SD)	9.8 ± 3.3 *	7.9 ± 3.9 *	4 ± 1.2 *	F=72, p<0.0001
Sensory trick, n. pts (%)	42 (62%)	30 (61%)	32 (45%)	0.09
Spread of dystonia, n. pts (%)	48 (71%)	33 (67%)	40 (56%)	0.2
Eye symptoms, n. pts (%)	59 (87%)	44 (90%)	63 (89%)	0.9
HADS-A score (mean ± SD)	2.8 ± 2 *	9.7 ± 3.5 *	3.7 ± 2.5 *	F=109, p<0.0001
HADS-D score (mean ± SD)	2.7 ± 2.1	8.5 ± 3.3 *	2.8 ± 2.2	F=96, p<0.0001
LSAS score (mean ± SD)	20.1 ± 20.4	53.8 ± 28.9 *	17.3 ± 15.4	F=49, p<0.0001

* Newman-Keuls post hoc test: different from other groups, $p < 0.05$