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Clinical heterogeneity in patients with idiopathic blepharospasm: A cluster analysis

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ABSTRACT

Background: Idiopathic blepharospasm is a clinically heterogeneous condition. It is not known whether the various manifestations become manifest sequentially during the course of the disease or aggregate in separate clusters identifying subpopulations of patients.
Methods: Eighty-nine patients with idiopathic blepharospasm were assessed using k-means cluster analysis to identify relatively homogeneous groups on the basis of low-intragroup/high-intergroup differences across a set of selected variables.
Results: The results suggest that there may be three groups of patients. Group 1 included patients who had prolonged muscle spasms leading to complete rim closure associated with brief and/or prolonged spasms with incomplete rim closure, the most severe blepharospasm, and a greater tendency to spread to adjacent segments. Group 2 included patients characterized by prolonged spasms with partial rim closure, either alone or associated with brief spasms whereas Group 3 included patients with brief spasms with complete rim closure, the least severe blepharospasm, and the lowest tendency to spread. The severity of Group 2 blepharospasm was between that observed in Group 1 and Group 3, while the tendency to spread was similar to Group 3. The three groups did not differ for disease duration, age of onset, sex and other clinical features. The observation that inhibition of the R2 component of the blink reflex recovery cycle was more abnormal in Groups 1/2 2 than in Group 3 at least in part validates our classification.
Conclusions: The present study suggests that blepharospasm patients may be classified in different subtypes according to the type of spasms, severity of the condition and tendency to spread.

1. Introduction

Idiopathic blepharospasm (BSP) is an adult-onset focal dystonia that manifests itself more frequently in women and has a peak age at onset in the fifth-sixth decade [1]. It is commonly characterized by dystonic orbicularis oculi muscle spasms that are usually bilateral, synchronous and symmetric [2,3]. Dystonic spasms may, however, be phenomenologically heterogeneous, with either brief or prolonged spasms and narrowing or closure of the eyelids [4]. In addition to spasms, BSP patients may have a spectrum of additional signs/symptoms, including sensory symptoms in the eyes that indicate ocular diseases (e.g. dry eye syndrome) [5], an increased spontaneous blink rate [6], the presence of sensory tricks (stretching, massaging or touching the eyebrow, the eyelid or the forehead) transiently improving eyelid spasm [7], apraxia of eyelid opening [8] and dystonia in other body parts [9].

This clinical variability in patients with BSP is such that the level of heterogeneity in the disease is relatively high. However, the issue of whether heterogeneity of BSP subtypes reflect differences in the clinical phenotype has never been explored. It is not known whether the various clinical manifestations become manifest sequentially during the course of the disease or aggregate in separate clusters that may be used to identify subpopulations of patients with different natural history and disease progression. Here we used cluster analysis, a data-driven classification method

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[10,11], to identify relatively homogeneous groups of cases on the basis of low-intragroup but high-intergroup differences across a set of selected clinical variables. This approach obviates the need for the arbitrary division of patients according to given criteria and may be used to assess variables in conjunction, rather than independently. To further assess the validity of the resulting cluster classification, we investigated whether the abnormal blink reflex recovery cycle, one of the most consistent neurophysiological abnormalities in BSP [12,13] also differed in the subgroups we identified.

1.1. Patients and methods

Eighty-nine patients with idiopathic BSP were included in this study. Patients were assessed consecutively in the movement disorder centers of the Department of Neurology and Psychiatry of the Sapienza University of Rome, Italy, (n. 44), and the Department of Basic Medical Sciences, Neurosciences and Sense organs of the Aldo Moro University of Bari, Italy (n. 45), between January and May 2016. Patients were assessed by neurologists experienced in dystonia, and BSP was diagnosed according to validated diagnostic criteria [14]. All the patients had undergone a computed tomography scan or magnetic resonance imaging of the brain, with no significant pathology being found in any of the cases investigated. Permission for the study was obtained from the local ethics committee and all the patients consented to participation. Details of age at BSP onset, disease duration, eye diseases at BSP onset detected through a validated questionnaire [5], and sensory trick (ST) were recorded. The severity of BSP was assessed according to a recently validated blepharospasm severity rating scale (BSRS) that takes into account several motor manifestations and provides a composite score based on their presence, frequency and duration [4]. Brief spasms (lasting<3 s) with complete rim closure and prolonged spasms (lasting $\geq$3 s) leading to complete or incomplete rim closure were taken into consideration in both the scale and the present study, whereas brief spasms with incomplete rim closure were not because they were proven to be unreliable [4]. Apraxia of eyelid opening (AEO) was defined as a failure to voluntarily open the eyes without an apparent spasm of the orbicularis oculi muscle, despite sustained frontalis muscle contraction [8]. The scale yielded moderate to almost perfect reliability and acceptable clinimetric properties [4].

All the patients were video-recorded according to a standardized protocol that has been described in detail elsewhere [4,14]. For the purposes of the present study, two trained movement disorders experts performed an independent evaluation of the video-recordings, which yielded a satisfactory BSRS score agreement (Intra class correlation coefficient = 0.81, $p < 0.0001$).

1.2. Blink reflex recovery cycle

Neurophysiological testing was performed on a random subsample of 33 BSP patients and on 29 healthy control subjects. The blink reflex recovery cycle was studied according to the experimental procedure described in previous studies [12,13]. Paired square-wave pulses (pulse width of 200 μs) were delivered to the supraorbital nerve through silver chloride disc surface electrodes. The cathode was placed over the supraorbital foramen and the anode 2 cm above. The R2 threshold was determined as the minimum intensity required to evoke a reliable R2 response with an amplitude of at least 50 μV. Stimulus intensity was set at twice the threshold to evoke a consistent R2 response (2 TR2). Paired electrical stimuli were delivered at interstimulus intervals (ISIs) of 250, 500 and 1000 ms. EMG responses were recorded with pairs of silver chloride disc surface electrodes placed over both orbicularis oculi muscles. Trials with movement artifacts were rejected. Twenty trials for single- and paired-pulse stimulation were performed with an inter-trial interval of about 40–60 s. The EMG signal was amplified and band-pass filtered (20 Hz–3 kHz). The R2 response area was calculated for each block using Signal software (Cambridge Electronic Design Limited). The onset and offset for the R2 response were estimated visually from averaged rectified EMG measures. As measure of the blink reflex recovery cycle we considered the ratio between the area of the R2 response evoked by the second stimulus ("conditioned" response) and the area of the R2 response evoked by the first stimulus ("conditioning" response). Mean percentage variations of R2 was thus obtained at 250 ms, 500 ms and 1000 ms ISIs in each participant and entered in data analysis.

1.3. Statistical analysis

Statistical analysis was performed using the Stata 11.0 package (Stata Corporation, College Station, TX, USA). Clinical data were expressed as a percentage or mean ± SD and groups were compared by means of the χ^2 test and *t*-test, as well as one-way analysis of variance (ANOVA) and post hoc test, as appropriate. Non-hierarchical (k-means) cluster analysis using the Jaccard method for categorical data was performed on the 89 patients for two-, three- and four-cluster solutions [10,11]. The variables considered for the cluster analysis were selected from a range of phenotypic features that have previously been reported to be relevant to disease phenomenology and reliable. These comprised three different types of spasm (brief spasms with complete rim closure and prolonged spasms leading to complete or incomplete rim closure), sensory trick, apraxia of eyelid opening and an overall measure of BSP severity derived from the BSRS. The Calinski/Harabasz pseudo-F index stopping rule [11] was estimated to determine the optimal number of clusters: the higher the Calinski/Harabasz pseudo-F index value, the more distinct the clustering. To test the usefulness of the sub-group classification, we investigated any associations between the clusters with variables not included within the cluster analysis, such as age, sex, age of disease onset and disease duration, and the presence of eye diseases preceding BSP. Between-group repeated measures ANOVA was used to compare the blink reflex recovery cycle between BSP patients (whole group) and healthy subjects. Post hoc comparisons on the subgroups generated by the cluster analysis were then performed using either a between group ANOVA or unpaired t tests for continuous variables. The Spearman r was used to assess correlations between variables. Statistical significance was set at the 0.05 level. Data were expressed as mean ± SD.

2. Results

2.1. Study population

The final group of 89 patients included 30 men and 59 women aged 70.9 years (SD, 9; range 44–90) The mean age at disease onset was 58.1 years (SD, 10; range 30–78) and mean disease duration was 12.9 years (SD, 8.2; range 1–33). At the time of the study, brief spasms were present in 83/89 patients, prolonged spasms with partial rim closure were present in 47/89 patients, and prolonged spasms with complete rim closure in 24/89 patients. Thirty-seven patients had only one type of spasm (brief spasms in 32, prolonged spasms with incomplete rim closure in 4, and prolonged spasms with complete rim closure in 1), while the remaining 52 patients manifested more than one type of spasm. The additional signs and symptoms included eye symptoms in 63/89 patients, sensory trick in 36/89 patients, apraxia of eyelid opening in 18/89

Table 1
Association of clusters with variables included in the cluster analysis.

Variable	Cluster 1 (n. 24)	Cluster 2 (n. 33)	Cluster 3 (n. 32)	P
Number of patients with brief spasms with complete rim closure (%)	22 (92%)	29 (88%)	32 (100%)	0.14
Number of patients with prolonged spasm with incomplete rim closure (%)	14 (58%)	33 (100%)	0	<0.0001
Number of patients with prolonged spasm with complete rim closure (%)	24 (100%)	0	0	<0.0001
Blepharospasm severity score (mean + SD)	11.2 + 3*	6.1 + 1.3*	3.8 + 1.3*	F = 105.2 <0.0001
Number of patients with apraxia of lid opening (%)	13 (54%)	12 (36%)	11 (34%)	0.3
Number of patients with spread of dystonia (%)	16 (67%)	11 (33%)	11 (34%)	0.02
Number of patients with sensory trick (%)	8 (33%)	5 (15%)	5 (15%)	0.2

*ANOVA post hoc test: each group different from all other groups, $p < 0.05$.

patients, and spread of dystonia to other parts of the body in 38/89 patients. In particular, dystonia was observed to have spread to the oromandibular region in 32 patients, to the larynx in 2 patients, to the neck in 14 patients, and to the upper limb in 7 patients. The spread of dystonia occurred 1–5 years (mean ± SD, 1.9 ± 1.4) after the onset of BSP.

2.2. Cluster analysis

We considered models with 2–4 clusters. The Calinski/Harabasz pseudo-F index favoured a three-cluster solution (Calinski/Harabasz pseudo-F index: two-cluster solution, 1.35; three-cluster solution, 88.73; four-cluster solution, 47.37). When we carried out the k-means cluster analysis using the optimum number of clusters previously determined, the resulting three groups contained 24 patients (Group 1), 33 patients (Group 2) and 32 patients (Group 3), respectively.

With regard to the variables included in generating the cluster solution (Table 1), all 24 patients in Group 1 suffered from prolonged spasms with complete rim closure; these patients also suffered from spasms with partial rim closure (58%) and/or brief spasms with complete rim closure (92%). In Group 2, prolonged spasms with partial rim closure were present in all 33 patients, brief spasms with complete rim closure were present in 88% of patients, while no subject in this group suffered from prolonged spasms with complete rim closure. Finally, Group 3 only contained patients who suffered from brief spasms with complete rim closure. The severity of BSP was significantly greater in Group 1 than in the other two groups. Likewise, the spread of dystonia was significantly more frequent in Group 1 than in the other two groups. By contrast, no significant difference was observed between the three groups in the frequency of ST and AEO.

With regard to variables not included in the cluster analysis (Table 2), no difference was observed between the three groups in age, sex, age at BSP onset, disease duration or frequency of eye symptoms.

2.3. Blink reflex recovery cycle

The blink reflex cycle was tested in a random subsample of 33 BSP patients and 29 healthy control subjects. The demographic/clinical characteristics of these BSP patients were similar to those of the overall group of 89 patients (data not shown). After a blind neurophysiological assessment, BSP patients were stratified in the three groups resulting from the cluster analysis. There were no differences in age, sex or disease duration between the patients who underwent the neurophysiological assessment in Groups 1, 2, and 3 (data not shown).

Between-group repeated measure ANOVA performed to compare the blink reflex recovery cycle between BSP patients (the whole group of 33 patients) and healthy control subjects yielded a significant factor GROUP ($F_{(1,60)} = 179.5$; $p < 0.00001$), factor ISI ($F_{(2,120)} = 119.7$; $p < 0.0001$) and a significant ISI × group interaction ($F_{(2,120)} = 15.5$; $p < 0.0001$). The R2 component of the blink reflex was less inhibited in BSP patients than in healthy control subjects at all ISIs (between group ANOVA: 250 ms ISI $F_{(1,60)} = 123.8$; $p < 0.000005$; 500 ms ISI $F_{(1,60)} = 201.7$; $p < 0.000001$; 1000 ms ISI $F_{(1,60)} = 34.6$; $p < 0.0001$).

Between group ANOVA performed to compare the blink reflex recovery cycle at the various ISIs tested in the 3 groups of BSP patients identified by the cluster analysis showed that the inhibition of the R2 component of the blink reflex in the three subgroups differed significantly at 250 ms ISI ($F_{(2,30)} = 4.7$, $p = 0.02$; post hoc test: Group 3 vs. other groups, $p < 0.05$) and 500 ms ISIs ($F_{(2,30)} = 12.9$, $p < 0.001$; post hoc test: Group 3 vs. other groups, $p < 0.01$) but was comparable at 1000 ms ($F_{(2,30)} = 1.8$, $p = 0.18$). The R2 component of Groups 1 and 2 was less inhibited than that of Group 3 (Fig. 1).

When the relationships between changes in the blink reflex recovery cycle and the severity scores yielded by the BSRS were assessed, a significant positive relationship between these two parameters was observed at 500 ms ISI (Spearman r, 0.52; $p = 0.002$) and 1000 ms ISI (Spearman r, 0.50; $p = 0.003$), though not at 250 ms ISI (Spearman r, 0.20; $p = 0.11$).

3. Discussion

This study explored the presence among BSP patients of distinct groups that may be recognized by variables related to the clinical phenomenology of the condition. The results of the cluster analysis suggest that there may be three groups of BSP patients that can be distinguished on the basis of the type of spasms, the severity of their condition, and the tendency to spread. Group 1 included patients who had prolonged spasms leading to complete rim closure

Table 2
Association of clusters with variables not included in the cluster analysis.

Variable	Cluster 1 (n. 24)	Cluster 2 (n. 33)	Cluster 3 (n. 32)	P
Age (mean years + SD)	71.4 ± 12.3	69.3 ± 9.7	72.3 ± 8.5	F = 0.75, p = 0.5
Women sex (%)	15 (62%)	25 (76%)	19 (59%)	0.3
Age at blepharospasm onset (mean years + SD)	57.3 ± 10.4	57.9 ± 10.4	. 58.8 ± 9.5	F = 0.16, p = 0.8
Disease duration (mean years + SD)	13.9 ± 9.7	11.4 ± 7.1	13.5 ± 8.2	F = 0.81, p = 0.4
Number of patients with eye symptoms (%)	17 (71%)	24 (73%)	22 (69%)	0.9

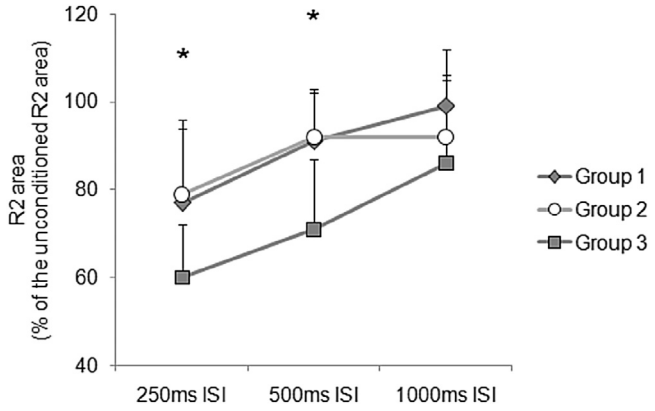

Fig. 1. Blink reflex recovery cycle (expressed as mean percentage variation ± SD) of the R2 component of the blink reflex at 250 ms, 500 ms and 1000 ms interstimulus interval (ISI) in the three clusters of patients with blepharospasm (BSP). Asterisks indicate statistical significance.

associated with brief and/or prolonged spasm with incomplete rim closure, the most severe muscle spasms as assessed by the BSRS, and a greater tendency to spread. By contrast, Group 3 included patients with brief spasms with complete rim closure, the least severe muscle spasms, and the lowest tendency to spread. Group 2 included patients characterized by prolonged spasms with partial rim closure, which were present in all the patients, either alone or associated with brief spasms; the severity of BSP in this group was between that observed in Groups 1 and 3, while the tendency to spread was similar to that in Group 3. The frequency of other clinical features included in generating the clustering solution was comparable in all three groups.

The validity of this classification is supported by the results of the analysis of the variables not included in the cluster analysis. Indeed, the lack of any association between the groups we identified and age, sex and disease duration indicates that the differences between the BSP groups cannot be explained by any of these variables. We are also confident that the differences in the tendency of dystonia to spread displayed by the three groups is not an artifact of disease duration because, in keeping with reports in the literature [9], the spread of dystonia in our sample occurred within five years of disease onset, which is a significantly shorter time interval than that observed in patients in whom dystonia did not spread.

To further assess the validity of our classification, we tested whether the clusters we identified fitted into the relevant BSP neurophysiological abnormalities. Reduced inhibition of the R2 component of the blink reflex tested with the paired-pulse technique is one of the most consistent neurophysiological abnormalities in BSP [12,15,16]. This reflects an increased excitability of the brainstem interneurons that mediate the orbicularis oculi muscles reflex, a factor likely to predispose subjects to BSP development. The observation that inhibition of the blink reflex R2 recovery cycle differed in Group 3 and Group 1 (being more abnormal in Group 1 than Group 3) suggests clinical heterogeneity among BSP patients and a relationship between prolonged OO spasms and reduced inhibition of the R2 component in the blink reflex recovery cycle.

Although patients participating in this study were all affected by idiopathic BSP it is possible that under this clinical category BSP may be due to different aetiologies. Therefore, the clinical differences between BSP patients highlighted by our cluster analysis may reflect differences in aetiology. According to this hypothesis, however, aetiological-related parameters, such as age at BSP onset, sex distribution, eye disease possibly triggering BSP in predisposed subjects [5,17], should differ across the subgroups we identified, but did not. Alternatively, the clinical differences in the phenomenology of spasms, in the severity of dystonia, and in the tendency to dystonia spread across the subgroups might reflect a varying strength of the pathophysiological changes that lead to BSP across the subgroups. The varying extent to which the blink reflex recovery cycle changed in the subgroups identified by the cluster analysis as well as the significant positive relationships between changes in the blink reflex recovery cycle and the severity of BSP, as assessed by the BSRS, appear to support this view.

We acknowledge that the possibility of generalizing our results is limited by the relatively small sample size. However, although the cohort is not population-based, our BSP patients do present the well-known phenotype [1,2] and the diagnosis was based on standardized and validated published criteria [14]. Although a longitudinal study would have been preferable to validate the identified subpopulations of patients, the validity of findings from this cross-sectional study is supported by the lack of differences in disease duration among subgroups. Whilst this study has clearly identified subgroups of patients, the methodology may be criticised, with the choice and number of variables selected for inclusion, as well as the number of clusters sought, potentially affecting the results. However, the variables included in the clustering solutions sought in this study were carefully selected so as to allow the clinical heterogeneity to be explored and to enable the variables not included in the cluster analysis to be compared, which validates the group classification. Lastly, in our cluster analysis we did not include neuropsychiatric disturbances, which are now considered to be part of the full clinical spectrum of BSP and other focal dystonias [18–20], though this investigation will be undertaken in future researches.

In conclusion, the present study identified the existence of clinical heterogeneity among BSP subjects using a data-driven approach. It suggests that BSP may be classified in different subtypes according to the type of spasms, severity of the condition and tendency to spread. Our results, which are partly validated by the neurophysiological evaluation and the assessment of variables not included in cluster analysis, indicate that subtypes generated using a three-cluster solution may have an internal cohesion and external isolation. A longitudinal assessment of these BSP patients is warranted to further check the findings from cluster analysis and the variable relationships with changes in the blink reflex recovery cycle. The results of this cluster analysis are potentially relevant for clinical trials aiming to test drugs or interventions for BSP.

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Conflict of interest

The authors declare that they have no conflict of interest.

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