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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

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