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Viewpoints on the Clinical Heterogeneity of Blepharospasm

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Abstract

Recent studies suggested that Blepharospasm (BSP) is phenomenologically a heterogeneous condition. Although spasms of the orbicularis oculi muscle remain the hallmark of BSP, patients may be characterized by different types of spasms and also by increased blinking. It has been currently investigated whether clinical heterogeneity of BSP implies heterogeneity in the pathophysiological mechanisms. This article will discuss how these new clinical and neurophysiological observations may provide the basis for developing new treatment strategies in BSP.

Blepharospasm (BSP) is a focal dystonia characterized by involuntary and bilateral spasms of the orbicularis oculi muscle [1-4]. Patients with BSP may also have other motor manifestations, including apraxia of eyelid opening [5] and increased blinking [6,7] as well as non-motor features [8-10].

Muscle spasms of the orbicularis oculi muscle in BSP may be prolonged (lasting more than 3 seconds) or brief (lasting less than 3 seconds) and be associated with complete or incomplete closure of the eyelids [11,12]. Recent evidence suggests that BSP patients may be classified in three groups according to the duration of orbicularis oculi muscle spasms (patients with prolonged spasms with complete or incomplete rim closure with or without brief spasms; patients with prolonged spasms with incomplete rim closure with or without brief spasms; patients with brief spasms with complete rim closure) [2]. The severity is greater and the prognosis worse in patients with prolonged muscle spasms than in patients with brief spasms, regardless of age, disease duration or sex [2]. The degree of disability in daily activities is higher in patients with prolonged spasms with complete rim closure because they are functionally blind and tend to a greater spread of dystonia to adjacent body segments [13,14].

A number of patients may also present increased blinking alone or increased blinking associated with muscle spasms. A recent follow-up study reported that patients with increased blinking alone may develop orbicularis oculi muscle spasms over the years [15]. This observation confirms that the clinical heterogeneity of BSP is found at both the inter-subject and intra-subject levels and that increased blinking alone may be considered as a form fruste of this focal dystonia [7].

Neurophysiological studies have shown that pathophysiological mechanisms in BSP as well as in other types of focal dystonia include loss of inhibition and altered sensory-motor integration [16]. One neurophysiological hallmark consistently reported in patients with BSP is the enhanced blink reflex recovery cycle [7,17-19]. The blink reflex recovery cycle is a neurophysiological technique that investigates the excitability of brainstem circuits. It is well known that the basal ganglia modulate the excitability of blink reflex pathways via substantia nigra pars reticularis inhibition of the superior colliculus [20]. Consistently previous investigations reported enhanced blink reflex recovery cycle in patients with Parkinson's disease [21,22]. Patients with BSP have an increased excitability of brainstem circuits that is believed to reflect reduced inhibitory descending control from cortical and subcortical areas on brainstem circuitry [16]. In addition, the abnormal blink recovery cycle reflects the duration of orbicularis oculi muscle spasms [2].

BSP patients, regardless of the type of spasms, and patients with increased blinking alone both have an increased Somatosensory Temporal Discrimination Threshold (STDT) [7,23-25]. The STDT is defined as the shortest interstimulus interval at which a subject recognizes two tactile stimuli as asynchronous. The STDT is integrated at the cortical and basal ganglia levels and this increase in STDT values is considered to be due to the loss of inhibitory activity in S1 and basal ganglia [26-28]. Since the STDT is abnormally increased in both affected [29, 30] and unaffected

body regions [31] in patients with dystonia as well as in the patients' unaffected relatives [29-31], it has been proposed as an endophenotypic feature of dystonia [28]. On the basis of STDT abnormalities, patients with increased blinking are considered to have a dystonic trait [7]. In conclusion, neurophysiological findings suggest that the STDT is an endophenotypic marker of dystonia whereas the enhanced blink reflex recovery cycle is a marker of disease severity.

Neuroimaging data on gray matter changes in cortical areas, in basal ganglia and other subcortical structures are controversial and different patterns of abnormalities have been described [32-38]. The lack of correlations between neuroimaging results and clinical features suggests that the reported changes represent secondary manifestations. Only one study revealed fractional anisotropy reductions in the white matter of cerebellum and parietal lobe, abnormalities which correlate with BSP disease severity and duration [38]. In conclusion, the variable results obtained with neuroimaging techniques further suggest that BSP is an heterogeneous clinical condition.

The observation that muscle spasms of the orbicularis oculi may develop during the course of the disease in patients with increased blinking alone and that the blink reflex recovery cycle concomitantly becomes altered [15] supports the hypothesis of a two-hit model of disease in BSP. Abnormalities in inhibitory mechanisms in BSP may reduce the inhibitory descending projections from cortical and subcortical structures, including the superior colliculus [39,40] to the brainstem circuits. This reduced descending inhibition facilitates the brainstem interneurons, thereby creating a permissive background. Other environmental factors, including dry eyes, greater exposure to sunlight and photophobia [41-43] may then trigger the clinical manifestations of BSP. In this regard, it has recently been suggested that greater exposure to sunlight may induce an increase in orbicularis oculi muscle drive, which is an adaptive process in healthy subjects but may turn into a maladaptive mechanism in subjects predisposed to BSP [44]. Other factors that affect blinking are the level of dopamine in the central nervous system and aging. Decreased dopamine levels increase the blink duration and trigeminal blink reflex excitability [45-47].

Since dopamine decreases dramatically with age (especially in 50- to 60-year-old, which is the typical age of BSP onset), dopamine-related pathophysiological mechanisms may contribute to the development of BSP. Aging may also act through non-dopaminergic mechanisms by altering inhibitory activity in the brain [16,48,49]. In conclusion, the development of orbicularis oculi muscle spasms may be ascribed to several concurrent processes, some of which may be modifiable (environmental factors), while others may not be (endophenotypic and age-related factors).

Research efforts should consider treatment options that can modify the pathophysiological chain of events by targeting the modifiable factors. The first-line treatment for BSP consists of Botulinum Toxin (BoNT) injections [50]. By inducing chemical denervation of injected muscles, BoNT reduces both the muscle spasms and increased blinking [51,52] with the treatment having proved to be clinically efficacious. The main limitation of symptomatic therapy with BoNT is that while it improves the clinical severity and disability, it fails to modify the natural history of BSP. Indeed, previous neurophysiological studies have shown that although BoNT does improve the clinical manifestations of dystonia, it leaves the enhanced blink reflex recovery cycle and STDT alterations unmodified [53,54]. Despite the advances made in our understanding of the pathophysiological mechanisms involved in BSP, a treatment approach that focuses on the modifiable factors underlying the development of BSP is still lacking. If the "two-hit" model applies to BSP [43] alternative therapeutic strategies should be adopted when patients are still in the prodromal phase before a maladaptive behaviour in response to environmental factors is developed. Previous investigations in patients with BSP have shown that wearing FL-41-tinted lenses to some extent reduces the severity of BSP and the mean blink rate [55,56]. Along the same vein, using FL-41 tinted lenses may provide a greater beneficial effect in patients in the prodromal phase than in those with overt clinical features.

In conclusion, new evidence pointing to a marked heterogeneity of patients with BSP and of a prodromal phase of the disease highlights the need for future investigations that should include the development of individualized treatment approaches designed to block or, idealistically, prevent the pathophysiological processes resulting in spasms.

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