The research project titled LONGITUDINAL ANALYSIS OF CLINICAL AND NEUROPHYSIOLOGICAL VARIABLES IN IDIOPATHIC (BENIGN ESSENTIAL) BLEPHAROSPASM funded by BEBRF in 2018 was published in the *European Journal of Neurology* in February 2019.

(Eur J Neurol. 2019 Feb;26 (2):268-273. doi: 10.1111/ene.13832. Epub 2018 Nov 12)

In the research project titled LONGITUDINAL ANALYSIS OF CLINICAL AND NEUROPHYSIOLOGICAL VARIABLES IN IDIOPATHIC (BENIGN ESSENTIAL) BLEPHAROSPASM we performed a longitudinal study to better understand the clinical heterogeneity of blepharospasm (BSP) and whether the variable phenomenology of dystonic spasms becomes manifest sequentially during the course of the disease or aggregates in separate clinical subtypes in different disease courses.

In this study, we used a standardized video protocol to evaluate the clinical features of a cohort of 60 BSP patients at baseline and after five years. To assess whether possible clinical changes were accompanied by modifications in neurophysiological parameters, we tested the blink reflex recovery cycle at enrolment and at follow-up in a subgroup of 18 patients.

In the patients enrolled, we observed changes in the clinical features of involuntary eyelid closure over the five-year period. The patients studied all had BSP for more than five years. Despite this long disease duration upon enrolment, results showed that BSP clinical features changed significantly in the subsequent five years in the majority of patients, and that BSP severity had worsened significantly by the follow-up examination. The main changes consisted of the appearance of prolonged spasms in patients who only had brief spasms at baseline evaluation and an increased duration and frequency of spasms in those who already had prolonged spasms at baseline evaluation. Moreover, we also showed that blink reflex recovery cycle abnormalities had worsened by the follow-up evaluation.

The follow-up study of these patients suggested that clinical heterogeneity in BSP was not due to different pathophysiological mechanisms. Conversely, a shared pathophysiological mechanism with different susceptibility to disease progression among the subjects may explain this clinical variability. Consistent with the hypothesis of a common pathophysiological mechanism, there is evidence that patients with various types of spasms all have the same type of R2 blink reflex abnormalities, although to a different extent.

Moreover, we hypothesize that aging plays a role in disease progression. In this regard, we speculate that aging-related mechanisms make BSP patients more susceptible to the development or worsening of prolonged OO muscle spasms (which was especially true in our BSP patients aged between 68-73 years during our follow-up study). The possible role of aging in disease progression is supported by several studies reporting that aging reduces both the intracortical inhibitory pathways at the cortical level and the excitability of the blink reflex circuit.

In conclusion, BSP is a heterogeneous condition characterized by different clinical phenotypes. Disease progression is characterized by the appearance or worsening of prolonged spasms that are accompanied by changes in the excitability of brainstem interneurons.