ACCSCIENCE PUBLISHING

Brain & Heart

LETTER TO EDITOR

QTc interval and sympathetic tone in burning mouth syndrome

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Dear Editor,

The autonomic nervous system is closely related to the central nervous system and controls a variety of physiological functions. Increasing focus is being paid to the functionality of the neurocardiac axis and the crosstalk between brain and cardiac function. Brain function is enabled by the functional connectivity between different neural regions, which is referred to as a large-scale brain network. The functional brain networks consist of at least seven major networks: Sensorimotor system, visual system, limbic system, dorsal attention network, central executive network, default mode network, and salience network.[1] Alterations in brain network connectivity have been observed in a variety of diseases, and exploring therapies that modulate large-scale brain networks have been gaining traction in recent years. In this letter, I would like to share my perspectives regarding a paper on neural networks surgery by Yu *et al.*, which is an interesting read.[2] They described the application of brain network knowledge to the surgical treatment of cerebrovascular disorders from a neurosurgical perspective, and indicated that the treatment could protect the hubs that connect the nerves, and protect the connections between the hubs. The perspective of this paper can also be applied to our research area of chronic orofacial pain disorders of unknown origin. Therefore, we considered the aforementioned hubs play a pivotal role in patients with burning mouth syndrome (BMS), one of unexplained orofacial pain disorders, based on the measurement of QTc intervals as a marker related to the neurocardiac axis.

BMS is an intractable chronic pain disorder of unknown cause characterized by burning sensation without any organic abnormality in the oral mucosa. According to the International Classification of Headache Disorders, Third Edition (ICHD-3), BMS is defined as an oral burning sensation or dysesthesia that recurs daily for more than 2 h, without a clinically evident causative lesion, lasting more than 3 months.[3] In psychopharmacotherapy for BMS, low-dose amitriptyline is the first-line drug, which modulates serotonergic neurotransmission and stimulates the descending pain inhibitory pathway and the parasympathetic tone. In view of the recent findings by Yu *et al.*,[2] we undertook a study to investigate the autonomic nervous system of BMS patients, who were not instructed to take any pharmacotherapy to avoid the influence of psychotropic agents. During the first consultation, we obtained information such as the degree of pain as well as emotions associated with pain, and performed an electrocardiogram on the patients. This study was a single-center cohort study of consecutive patients who visited our hospital from April 2018 to March 2019. These patients were diagnosed with BMS according to ICHD-3 criteria, and consented to participating in the study. Exclusion criteria of this study are as follows: (i) Patients with obvious cardiac disease, (ii) patients

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Citation: Nagamine T, Watanabe T. QTc interval and sympathetic tone in burning mouth syndrome. *Brain & Heart*. 2024;2(1):2016. https://doi.org/10.36922/bh.2016

Received: October 11, 2023

Accepted: September 19, 2023

Published Online: February 13, 2024

taking medications that affect the QTc interval, and (iii) patients with comorbid psychiatric disorders or taking psychotropic medications. The degree of pain was examined using a visual analog scale (VAS), with 0 representing no pain and 100 representing the worst pain ever. The pain catastrophizing scale (PCS) was used to assess negative feelings associated with pain.[4] The QTc interval according to Bazett's formula was used as a measure of autonomic tone. Correlations between variables were examined using Spearman's rank correlation coefficient. All patients provided written informed consent for participating in this study. The personally identifiable information was not disclosed throughout the study to ensure anonymity and privacy. We were able to accumulate data from a total of 51 BMS patients: 11 males (21.5%) and 40 females (78.5%) with a mean age of 61.2 ± 1.6 years (mean ± SE). The VAS, PCS, and QTc at the first visit were 55.2 ± 3.2, 30.6 ± 4.1, and 417.8 ± 6.9 msec, respectively. The subjective degree of pain as measured by the VAS and destructive thoughts of pain as measured by the PCS were mildly correlated with a Spearman's correlation coefficient of 0.357 (P = 0.011; Figure 1). Interestingly, the VAS and QTc interval did not correlate (r = 0.087, P = 0.540; Figure 2), but the PCS and QTc interval showed a statistically significant correlation with a Spearman's correlation coefficient of −0.404 (P = 0.003; Figure 3).

Based on the results, both VAS and PCS values were high and moderately correlated with each other, although some patients had PCS values higher than VAS values and had negative feelings about pain. The recent functional imaging results of the participants, interpreted alongside the VAS, PCS, and QTc results, revealed a previously unidentified finding that some BMS patients have excessive sympathetic tone. Studies using functional connectivity magnetic resonance imaging have shown that individuals with unexplained pain such as BMS, fibromyalgia, back pain, and headache have an enhanced salience network activity, decreased functional connectivity between the default mode network and the executive control network, and decreased functional connectivity between the default mode network and the descending pain inhibitory pathway.[5] The salience network is strongly functionally coupled to the dopaminergic reward system of the basal ganglia and increases sympathetic tone in the hypothalamus. In our study, PCS was negatively correlated with the QTc interval, indicating that patients with destructive feelings of pain had a shortened QTc interval. Recent studies have shown that the QTc interval is associated with autonomic imbalance and tends to shorten with sympathetic tone.[6] The QTc interval reflects the degree of sympathetic tone under certain conditions, such as the absence of cardiac disease. Therefore, the negative correlation between PCS and QTc interval suggests that pain-induced emotion increases sympathetic tone. Patients with high PCS were

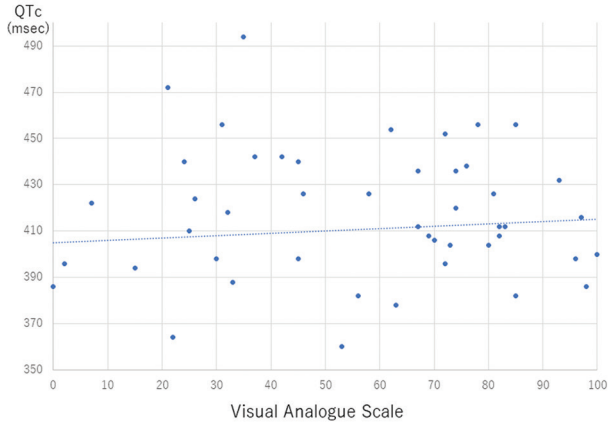

Figure 2. Correlation between QTc interval and visual analog scale.

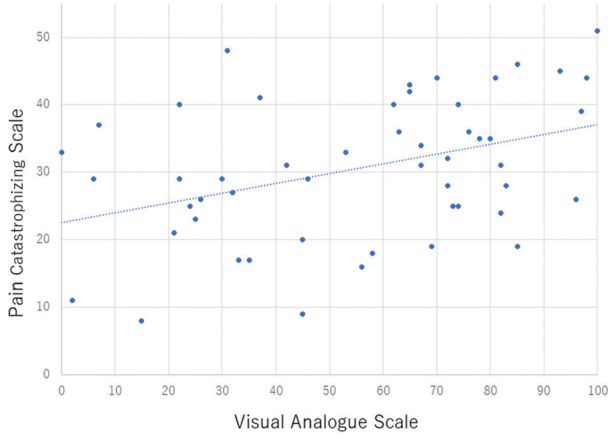

Figure 1. Correlation between visual analog scale and pain catastrophizing scale.

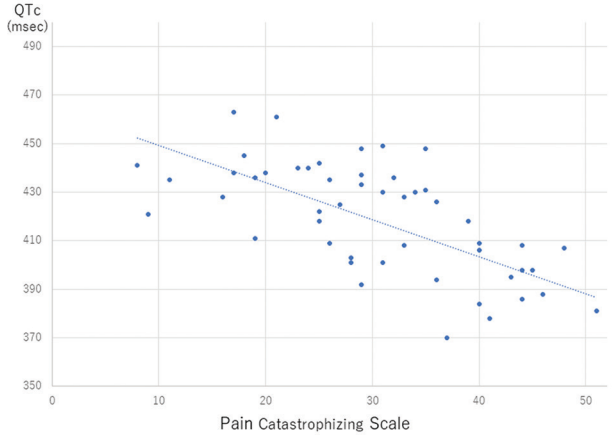

Figure 3. Correlation between QTc interval and pain catastrophizing scale.

considered to have an activated salience network and an activated anterior cingulate gyrus, which is one of the important hubs of the salience network and the center of the sympathetic nervous system. On the other hand, the VAS did not correlate with QTc interval, suggesting that pain itself does not tone the sympathetic nervous system. Energy-intensive organs such as the brain attempt to conserve energy in every way possible. Sympathetic tone with acute pain increases daily energy expenditure by 60%, while chronic pain increases energy expenditure by only 15%.[7] Chronic pain normally strengthens the functional connectivity between the somatosensory cortex and the default mode network, increasing the parasympathetic tone and decreasing energy expenditure.[8] Patients with high VAS but no shortening of QTc may have reduced energy consumption by decoupling pain from the sympathetic nervous system and connecting it to the parasympathetic nervous system. Although it is necessary to use the hub of the default mode network to link pain to the parasympathetic nervous system, the default mode network is also a network of self-recognition, which may also mean internalizing pain as one's own.

The VAS and PCS correlate only to some extent because the brain network may also be different for each individual BMS patient. The balance between the salience network and the default mode network is important for the autonomic nervous system to be stable. The salience network is controlled primarily by dopaminergic neurons, and the default mode network is regulated mainly by serotonergic neurons. Thus, pharmacotherapy such as aripiprazole (a dopamine D2 receptor partial agonist) and amitriptyline (a tricyclic antidepressant) may be effective for some BMS patients by modulating dopamine and serotonin.[9] However, a dose-response relationship is not seen with pharmacotherapy, and the therapeutic effect is only pronounced when high doses of pharmacotherapy, which are sufficient to induce antidepressant effect, are applied.[10] This indicates that drug therapies that target monoamines to alter neurotransmission may not necessarily improve the balance of the neural network because they are not site-selective and altering hub functions. As Yu *et al.* have shown, new treatments need to be considered for hub protection and network stability.[2] Network science provides theoretical and computational tools that can be used to understand simple concepts of human brain function; for instance, neuroimaging data analysis of functional networks of neurons emerges as a useful approach to enhancing our understanding of brain function.[11] New, network science-based psychopharmacological treatments that target key hub functions of pain circuits are warranted to alleviate the sufferings of BMS patients.

In conclusion, our study showed that drug-naïve BMS patients have increased sympathetic tone. The intraoral environment of BMS patients was worse than that of general dental patients.[12] Thus, it is necessary to examine whether there is a relationship between the oral condition of BMS patients and the sympathetic tone. Ultimately, treatments need to be designed, taking into account the neural networks of individual BMS patients and target key hub functions such as the basal ganglia and anterior cingulate gyrus. Further studies on brain networks and neurocardiac axis in these patients are needed.

Acknowledgments

I would like to thank everyone at the Department of Psychosomatic Dentistry, Tokyo Medical and Dental University (Prof. Toyofuku A.), for their generous cooperation in conducting this research.

Funding

None.

Conflict of interest

The authors declare that they have no competing interests.

Author contributions

Conceptualization: Takahiko Nagamine
Investigation: Takeshi Watanabe
Methodology: Takahiko Nagamine
Writing – original draft: Takahiko Nagamine
Writing – review & editing: All authors

Ethics approval and consent to participate

All patients provided written informed consent to participate in this study. The study protocol was approved by the Ethics Committee of the School of Dentistry, Tokyo Medical and Dental University. The personally identifiable information was not disclosed throughout the study.

Consent for publication

Not applicable.

Availability of data

Data are available from corresponding author on reasonable request.

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