The Characteristics of Autonomic Nervous System Disorders in Burning Mouth Syndrome and Parkinson Disease

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Aims: *To conduct a clinical electrophysiologic evaluation of autonomic nervous system functions in patients with burning mouth syndrome and Parkinson disease and estimate the type and intensity of the autonomic dysfunction.* ***Methods:*** *The study involved 83 subjects—33 with burning mouth syndrome, 20 with Parkinson disease, and 30 controls. The BMS group included 27 women and 6 men (median age, 60.0 years), and the Parkinson disease group included 15 women and 5 men (median age, 66.5 years). In the control group, there were 20 women and 10 men (median age, 59.0 years). All patients were subjected to autonomic nervous system testing. In addition to the Low autonomic disorder questionnaire, heart rate variability (HRV), deep breathing (exhalation/inspiration [E/I] ratio), and sympathetic skin response (SSR) tests were performed in all cases. Parametric and nonparametric tests (ANOVA, Kruskal-Wallis, and Scheffe tests) were used in the statistical analysis.* ***Results:*** *The mean values for HRV and E/I ratios were significantly lower in the burning mouth syndrome and Parkinson disease groups. Significant prolongation of SSR latency in the foot was revealed in both burning mouth syndrome and Parkinson disease patients, and lowering of the SSR amplitude occurred in only the Parkinson disease group. The autonomic questionnaire score was significantly higher in burning mouth syndrome and Parkinson disease patients than in the control subjects, with the Parkinson disease group having the highest scores.* ***Conclusion:*** *In patients with burning mouth syndrome, a significant impairment of both the sympathetic and parasympathetic nervous systems was found but sympathetic/parasympathetic balance was preserved. The incidence and intensity of autonomic nervous system dysfunction was similar in patients with burning mouth syndrome and Parkinson disease, which may suggest some similarity in their pathogeneses.* J OROFAC PAIN 2012;26:315–320

Key words: autonomic nervous system, burning mouth syndrome, Parkinson disease

Burning mouth syndrome is defined as the occurrence of pain characterized by a burning sensation with a simultaneous lack of clinically evident changes in the oral mucosa, even at the site in which the patient reports pain. In some patients, this burning sensation is accompanied by dysgeusia and xerostomia, which can also be clinical signs of dysautonomia.[1,2] The site most often affected is the tongue, usually the tip or anterior two-thirds, followed by the sides and dorsal surface. Other commonly reported sites, in order of their frequency, are the lips, palate, buccal mucosa, upper and lower alveolar ridges, pharynx, and oral cavity floor.[3,4]

In population-based studies, the incidence of burning mouth syndrome ranges from 0.7% to 14.8% or even higher. The high frequency of reported cases of burning mouth syndrome might be explained by the use of a distant (telephone-contact) standardized questionnaire.[5–7] The etiopathogenesis of the syndrome is multifactorial, and both local and systemic factors can be involved.[1,3–5,8–10] The pathophysiology of burning mouth syndrome is usually thought to be linked to disturbances in the processing of sensory information at various levels of the nervous system.[11–13] The impairment of the peripheral nervous system has been demonstrated in invasive immunohistochemical studies on patients with burning mouth syndrome[14] that have the presence of sensory neuropathy of small fibers within fungiform lingual papilla innervated by cranial nerves. Some other authors explained burning mouth syndrome ethiopathogenesis as resulting from disturbances in the central nervous system. In burning mouth syndrome, the dysfunction of the nigrostriatal pathway may be involved, since the syndrome is allegedly similar to the dysfunctions that occur in cerebral degenerative diseases associated with disturbances of the dopaminergic system, such as Parkinson disease.[15–18] Parkinson disease is a progressive neurodegenerative disorder pathologically characterized by the loss of pigmented dopaminergic neurons in the substantia nigra in the midbrain. Clinical consequences of dopaminergic disturbances are resting tremor, hypokinesis and bradykinesis, rigidity, gait disturbances, inappropriate posture, and postural instability.[19] Nigrostriatal dysfunction causes insufficient central dopamine-dependent control of pain sensations. Studies have demonstrated that 40% of patients with Parkinson disease have various sensory complaints, including pain and a burning sensation in the oral cavity.[20] A burning mouth is more frequent in patients with Parkinson disease than in the general population and affects 24% of Parkinson disease patients.[21]

Parkinson disease patients also present autonomic symptoms, including orthostatic hypotension, dysuria, swallowing difficulty, and peristalsis and sexual dysfunction. These symptoms are difficult to treat and respond poorly to dopaminergic medication. Autonomic nervous system disorders can occur in the preclinical stage of Parkinson disease, before typical motor symptoms.[22]

The aim of this study was to conduct a clinical electrophysiologic evaluation of autonomic nervous system functions in patients with burning mouth syndrome and Parkinson disease and estimate the type and intensity of autonomic dysfunction.

Materials and Methods

This nonrandomized study involved 83 subjects divided into three groups.

Group I consisted of 33 subjects with burning mouth syndrome who had sought treatment at the Department of Oral Pathologies of Wroclaw Medical University, Wroclaw, Poland. This group included 27 women and 6 men, ranging in age from 41 to 82 years (mean age, 61.5 ± 9.4 years; median age, 60.0 years). Group II included 20 Parkinson disease subjects, hospitalized in the Neurological Department of Wroclaw Medical University, Wroclaw, Poland. They included 15 women and 5 men with an age range of 51 to 81 years (mean age, 65.6 ± 8.4 years; median age, 66.5 years).

Group III (control) consisted of 30 healthy volunteers with no symptoms of burning mouth syndrome or Parkinson disease. They included 20 women and 10 men, ranging in age from 42 to 83 years (mean age, 60.5 ± 10.5 years; median age, 59.0 years). The groups were age- and sex-matched.

The exclusion criteria in the groups were as follows:

- Clinical manifestations of pathologic changes in the oral mucosa that could have caused pain
- Deficiency of platelet-producing factors (vitamin B12, iron, folic acid)
- Deficiency of B vitamins
- Diabetes or blood glucose intolerance
- Presence of a positive culture for pathogenic *Candida* in the oral cavity

The criteria outlined by Scala et al[1] were used to distinguish secondary burning mouth syndrome.

Subjects who took medication modifying the autonomic nervous system functions, such as antiepileptic drugs, beta-adrenergic blocking agents, or tricyclic antidepressants, were excluded.

All the subjects in the study provided informed consent for their inclusion. The study was approved by Wroclaw Medical University's Bioethical Committee.

All patients underwent three neurophysiologic tests of the autonomic nervous system that used Viking Select 7.1.1c., a Nicolet Biomedical device with Multi Mode Program (MMP Plus) and a Polish computer program for spectral analysis of R-R intervals based on the fast Fourier transform. These tests were as follows.

Heart rate variability (HRV). This test helps to determine the effect of particular elements of the autonomic nervous system on the sinoatrial node of the heart and provides a picture of the changes

Table 1 Intergroup Analysis of the Mean and SD of HRV Percentages and E/I Ratios

	Burning mouth syndrome			Parkinson disease			Controls			
	Mean	SD	n	Mean	SD	n	Mean	SD	n	*P*
E/I ratio	1.2**	0.1	31	1.1**	0.1	19	1.3	0.2	30	< .001
HRV %	15.2**	6.7	33	11.6**	2.8	20	24.1	6.4	30	< .001

SD, standard deviation; E/I, expiration/inspiration; HRV, heart rate variability. Nonparametric Kruskal-Wallis test). **Significant difference between burning mouth syndrome and controls or Parkinson disease and controls.

in the balance between the sympathetic and parasympathetic systems. The percentage of HRV at rest was analyzed, but for the precise study, a spectral analysis of R-R intervals (the interval between ventricular depolarizations) based on the fast Fourier transform was used.[23] Two parameters were analyzed: high-frequency (HF) (0.15 to 0.4 Hz range) and low-frequency (LF) (0.04 to 0.15 Hz range) rates. HF is a marker of parasympathetic activity, while LF reflects mainly sympathetic function. The LF/HF ratio was also estimated as an indicator of sympathetic-parasympathetic balance.[23,24]

The deep breathing test. This test assesses changes in heart rhythm during deep breathing (six breaths per minute), eg, the influence of the parasympathetic system on the rhythm. It uses physiologic reflex phenomena known as respiratory arrhythmia (ie, the slowing of the heart rate during exhalation and its acceleration during inhalation). Electrocardiogram readings are continuously monitored and the exhalation/inhalation (E/I) ratio (ie, the quotient of the longest R-R interval during exhalation to the shortest interval during inhalation) is calculated as a mean calculated from five cycles.[23,24]

Sympathetic skin response (SSR). This test allows an assessment of the sympathetic nervous system by recording the surface potential as a result of temporary changes in skin resistance in response to sudden stimuli.[25] The test was conducted using electrical stimulation of the median nerve at the wrist (unexpected square electrical impulses of 10 to 30 milliamperes), which evoked potentials in the hand and foot. The shortest latency of SSR and its amplitude were analyzed. A lack of response, or a prolonged latency above two standard deviations, was considered abnormal. Changes in the amplitude had only a secondary importance.

The Low autonomic disorder questionnaire, as modified by the Warsaw Medical University Neurology Department, was also used.[2] This questionnaire assesses both objectively and subjectively the most prevalent symptoms of autonomic dysfunction and permits a quantitative evaluation of the autonomic nervous system. The results are presented as a point score, where 1 to 3 points indicates unspecified dysautonomia, 4 to 7 points indicates mild dysautonomia, 8 to 11 points indicates moderate dysautonomia, and a score of 12 or more points indicates severe dysautonomia.

Statistical Analysis

The hypothesis that the mean parameters in the groups were equal was tested with the analysis of variance (ANOVA) test. In groups with heterogeneous variance, the nonparametric Kruskal-Wallis test was used (the homogeneity of variances was checked using the Bartlett test). For variables with significant differences, when the three study groups were compared, a post-hoc analysis of contrasts was run using the Scheffe test. For each test, a *P* value of ≤ .05 was regarded as statistically significant.

The n values for the three groups varied between and within the tables, because some tests were not carried out in all patients (mostly HRV tests) due to other disorders (eg, cardiac arrythmia).

Results

An intergroup analysis for the mean values of HRV percentage at rest and E/I ratio are presented in Table 1 and Figs 1 and 2. Both parameters were significantly lower in patients with burning mouth sydrome and Parkinson disease than in the controls. There were no differences between the burning mouth sydrome and Parkinson disease groups. LF, HF, and LF/HF ratios were also similar in both patient groups and the controls (Table 2).

The results of the SSR evoked in the hand and foot are presented in Table 3. Burning mouth sydrome and Parkinson disease patients showed a significantly longer SSR latency in the foot. The latency also differed between burning mouth syndrome and Parkinson disease groups. SSR amplitude in the foot was lower in the burning mouth syndrome group than the Parkinson disease and control groups.

The modified Low questionnaire score in burning mouth sydrome and Parkinson disease groups was higher than in the control group. The score was the highest for Parkinson disease patients (Tables 4 and 5).

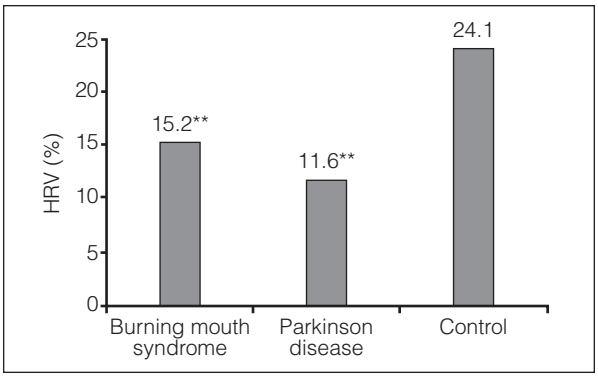

Fig 1 Intergroup analysis of the mean HRV percentage in patients with burning mouth syndrome and Parkinson disease and controls. **Significant difference between burning mouth syndrome and controls or Parkinson disease and controls.

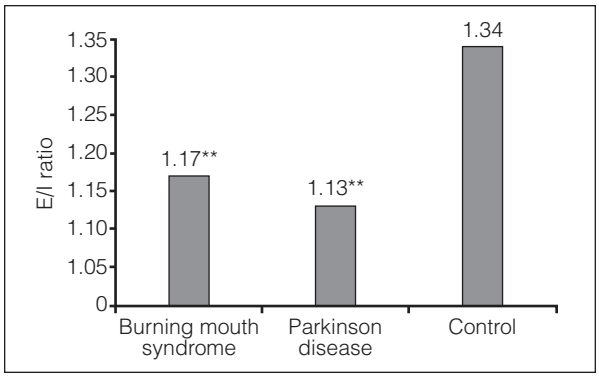

Fig 2 Intergroup analysis of the mean E/I ratio in patients with burning mouth syndrome and Parkinson disease and controls. **Significant difference between burning mouth syndrome and controls or Parkinson disease and controls.

Table 2 Intergroup Analysis of the Mean and SD of HRV in the Fast Fourier Transform

	Burning mouth syndrome (n = 33)		Parkinson disease (n = 20)		Controls (n = 30)		
	Mean	SD	Mean	SD	Mean	SD	*P*
LF $(bpm)^2$	45.3	16.9	43.3	19.8	40.9	9.2	.536
HF $(bpm)^2$	13	8.3	13.1	5.9	12.4	3.6	.895
LF/HF	3.7	0.8	3.5	0.5	3.4	0.6	.364

SD, standard deviation; LF, low frequency; HF, high frequency.

Table 3 Intergroup Analysis of the Mean and SD of the SSR Latencies and Amplitudes from Hand and Foot

	Burning mouth syndrome			Parkinson disease			Controls			
Group	Mean	SD	n	Mean	SD	n	Mean	SD	n	*P*
SSR hand latency (ms)	1,455.2	238.6	33	1,572	192	20	1,522	116.9	30	.107
SSR hand amplitude (uV)	3,061	1,913.9	33	2,373.1	1,775.2	20	3,122.1	1,812	30	.32
SSR foot latency (ms)	2,424.8***	412.9	31	2,699.1**	508.1	19	2,174.7	237.9	30	< .001
SSR foot amplitude (uV)	1,124.9***	690	31	1811.7	1,426.3	19	2,230.9	1,216.9	30	< .001

SD, standard deviation; SSR, sympathic skin response. **Significant difference between burning mouth syndrome and controls or Parkinson disease and controls. ***Significant difference between burning mouth syndrome and Parkinson disease and burning mouth syndrome and controls.

Table 4 Low Questionnaire Results: Types of Dysautonomia Presented as a Point Score in Patients with Burning Mouth Syndrome, Parkinson Disease, and Controls

Dysautonomia (points)	Burning mouth syndrome (persons)	Parkinson disease (persons)	Controls (persons)
Nonspecific (1–3)	8	1	23
Mild (4–7)	18	15	7
Moderate (8–11)	6	4	0
Severe (12 or more)	1	0	0

Table 5 Intergroup Analysis of the Mean and SD of the Points Obtained in the Low Autonomic Nervous System Disorder Questionnaire

	BMS (n = 33)		PD (n = 20)		Controls (n = 30)		
	Mean	SD	Mean	SD	Mean	SD	*P*
Low questionnaire	5.6**	2.8	6.2**	1.7	2.2	1.7	< .001

SD, standard deviation. Scheffe's analysis of contrasts. *Significant difference between burning mouth syndrome and controls or Parkinson disease and controls.

Discussion

In the literature, there are no clinical or electrophysiologic reports of autonomic nervous system function in burning mouth sydrome patients. However, Heckmann at al[26] indicated a higher vasoreactivity in burning mouth syndrome patients following the application of dry ice. The authors of the present study analyzed different autonomic nervous system functions by using subjective and objective input from the Low questionnaire and electrophysiologic tests.[2] The results were compared not only with controls, but also with Parkinson disease patients because of the presumed similarities in the pathogenesis of both clinical situations.

In the burning mouth syndrome and Parkinson disease groups, both the decreased HRV at rest and E/I ratios indicated an impairment of the parasympathetic modulation of the heart rate. The lack of differences in the LF/HF ratio between patient groups and controls suggests the maintenance of the sympathetic/parasympathetic balance. Sympathetic nervous system dysfunction was also observed in both burning mouth syndrome and Parkinson disease groups and was more pronounced in Parkinson disease patients. A prolonged latency and reduced amplitude of SSR, mostly in the lower limbs, were also observed. Distal axonopathy usually begins in the longest fibers (in the lower limbs as in the present study's groups) and then, in the course of the disease, the shorter fibers (eg, in the upper limbs) become involved. The process is known as the dying back process.[27] It probably depends on the distance from the source of materials and enzymes that are derived from the cell body, transported by the axons, and responsible for axon survival. The impairment of neuronal fibers in burning mouth syndrome and Parkinson disease groups might be due to the dying back process, but further studies are needed to address this.[14,25,27]

Analysis of the questionnaire revealed significantly higher values in the burning mouth syndrome and Parkinson disease patients than in the control group. Of the 83 participants, there was only one severe case (a burning mouth syndrome patient). This confirms that dysautonomia in burning mouth syndrome and Parkinson disease is usually mild.

The frequency and intensity of autonomic nervous system dysfunction were similar in patients with burning mouth syndrome and Parkinson disease. Of the 10 analyzed variables, the only statistically significant difference between patients with burning mouth syndrome and Parkinson disease was the longer SSR latency in the lower limbs in the Parkinson disease group.

Several studies have pointed to nigrostriatal pathway impairment as a main cause of burning mouth syndrome, and this is very similar to the dysfunctions in Parkinson disease.[15–18] On the other hand, according to the literature and the authors' previous studies, psychologic and psychiatric abnormalities may be present in the course of burning mouth syndrome and Parkinson disease, and are thought to influence autonomic regulation.[3]

This study confirmed clinical and electrophysiologic similarities between Parkinson disease, as well as noted the presence of similar autonomic dysfunction. The results are consistent with the concept of central impairment, together with small-fiber neuropathy in the pathogenesis of burning mouth syndrome.[12,14,16,17,28] If this is confirmed in subsequent studies, it could lead to the development of new diagnostic and therapeutic algorithms.

Conclusions

The following can be concluded from the results of this study:

- Significant impairment of both sympathetic and parasympathetic autonomic nervous system function was found in burning mouth syndrome patients, but functional sympathetic/parasympathetic balance was maintained.
- Patients with burning mouth syndrome usually presented mild dysautonomia.
- The incidence and intensity of autonomic nervous system dysfunction was similar in patients with burning mouth syndrome and in those with Parkinson disease, which could indicate some common features in their pathogeneses.

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