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Case Report
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Daily left prefrontal repetitive transcranial magnetic stimulation for medication-resistant burning mouth syndrome

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Abstract. Burning mouth syndrome (BMS) is a persistent and chronic burning sensation in the mouth in the absence of any abnormal organic findings. The pathophysiology of BMS is unclear and its treatment is not fully established. Although antidepressant medication is commonly used for treatment, there are some medication-resistant patients, and a new treatment for medication-resistant BMS is needed. Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive brain stimulation technology approved by the US Food and Drug Administration (FDA) for the treatment of depression. Recent studies have found beneficial effects of TMS for the treatment of pain. A case of BMS treated successfully with daily left prefrontal rTMS over a 2-week period is reported here. Based on this patient's clinical course and a recent pain study, the mechanism by which TMS may act to decrease the burning pain is discussed.

Key words: burning mouth syndrome; transcranial magnetic stimulation; chronic pain; left dorsolateral prefrontal cortex.

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Burning mouth syndrome (BMS) is a persistent burning sensation in the mouth in the absence of any abnormal organic findings.[1] The burning sensation occurs mainly in the tongue and sometimes extends to the lips, the gums, or the palate. Nearly 60% of patients with BMS complain of a dry mouth or taste disturbance (bitter/metallic taste). Some have estimated that 1.3 million Americans suffer from this condition.[1] Although the pathophysiology of BMS has not been fully elucidated, recent studies indicate that BMS is caused by some kind of dysfunction in the peripheral and/or central nervous system, and not the oral cavity.

While some researchers categorize BMS as neuropathic pain, there are studies that indicate the aetiology of BMS to be multifactorial, involving the interaction between neurophysiological mechanisms and psychological factors.[2] Furthermore, many features of BMS pain (unspecific, bilateral, migration over several nerve

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regions, alleviation with eating, and progressive increments during the day) differ from typical neuropathic pain such as trigeminal neuropathic pain, glossopharyngeal neuralgia, and post-stroke pain.

The treatment is not fully established, but the most popular treatment is antidepressant medications. Studies evaluating the efficacy and tolerance of antidepressants in the treatment of BMS have shown a reasonably high efficacy.[1] However there are some medication-resistant patients and a new treatment for medication-resistant BMS is needed.

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive brain stimulation technology that can stimulate the cortex focally and relatively painlessly by creating a time-varying magnetic field.[3] This technology has been approved by the US Food and Drug Administration (FDA) for the treatment of depression. Recent studies have found beneficial effects of TMS for acute and chronic pain.[4,5] In terms of chronic orofacial pain, there are many subtypes, and some argue that the subtypes differ substantially.[6] Although some studies have shown the efficacy of daily fast rTMS for orofacial pain including atypical facial pain, dental pain, and neuralgia,[4,5] there appear to be no reports on the efficacy of rTMS for BMS.

The authors considered that the daily use of rTMS to the left dorsolateral prefrontal cortex (DLPFC), which is used for depression, would be as effective for BMS as antidepressant medication. A case of BMS treated successfully with daily rTMS over the left DLPFC is reported below.

Case report

Patient presentation

A 64-year-old Caucasian female hairdresser, who had been divorced for several years, had a 10-year history of a burning sensation in her tongue and lower lip. This burning pain had started spontaneously. The only possible event that she could remember was accidentally sucking her lower lip with food before the BMS pain started. At the same time, she experienced a metallic taste and mouth dryness. At first, she went to her family physician and was examined by screening laboratory tests. All blood tests including haemoglobin level, platelet count, white blood cell count, red blood cell count, blood urea nitrogen, creatinine, glucose, albumin, total protein, total bilirubin, liver function (alanine transaminase, aspartate transaminase), thyroid function (thyroxine, thyroid-stimulating hormone), electrolytes (Na^+, Cl^-, HCO_3^-, Ca^{++}), serum ferritin levels, cholesterol, and triglycerides were within the normal limits. She underwent an X-ray examination and a biopsy of her lower lip submucosal and salivary glands in a dental clinic, but there were no abnormal findings. Although opioids, antibiotics, and topical dexamethasone were administered, the burning sensation did not ameliorate. Six months after the burning sensation had started, the patient attended a pain clinic. To treat the chronic pain, several antidepressants, including a tricyclic antidepressant (TCA), serotonin and norepinephrine reuptake inhibitor (SNRI), and selective serotonin reuptake inhibitor (SSRI), were prescribed. However the TCA was discontinued due to drowsiness and the SNRI and SSRI were discontinued due to nausea. The patient found these side effects intolerable, hence these medications were continued for only 2 or 3 days. Gabapentin was also prescribed for a month, but there was no effect on the BMS pain. Alpha-lipoic acid was not prescribed because the patient refused to take medication at that time. After these medications, the patient did not have any treatment for over 8 years.

The patient attended the laboratory alone for possible treatment with TMS. At this first examination she was fully oriented and verbally fluent. She had no history of any psychiatric conditions. Another oral examination failed to find any cause of the BMS. The continuous pain developed as the day progressed and improved with meals. Based on clinical, laboratory, and historical data, a diagnosis of BMS was established. She had a history of migraine and menopausal syndrome and had taken medications for over 5 years (sumatriptan 10 mg/day, rizatriptan 10 mg/day, clonazepam 1 mg/day, progesterone 125 mg/day). These medications were not changed during this clinical study.

After explaining the potential risks of the treatment and with her consent, rTMS was started with 10 Hz to the left DLPFC at medial frontal 10–20 system EEG-electrode location (F3), as defined by Beam et al.[7] The intensity was set at 110% of the resting motor threshold (RMT), 5 s on and 10 s off for 15 min (3000 pulses/day) for 10 consecutive weekdays. A MagVenture MagPro $\times 100$ Stimulator (MagVenture, Inc., Denmark) with figure-of-eight coil was used for the RMT assessment and all rTMS sessions. For the RMT assessment, the TMS machine was initially set to 50% of its maximal output. Single pulses were administered near the primary motor cortex until the area that produces contraction of the abductor pollicis brevis (APB) was identified. The minimum machine output necessary for visible APB contraction 50% of the time that pulses were delivered was used to determine RMT.

A visual analogue scale (VAS) for tongue pain intensity was used as the primary outcome measure. We also recorded a VAS for the head pain under the TMS coil during each session and applied the Brief Pain Inventory (BPI) functional impairment, Short Form McGill Pain Questionnaire (SFMPQ), Patients' Global Impression of Change (PGIC), and Clinical Global Impression Global Improvement (CGI-I).

Patient response

Figure 1 shows the clinical course of this case. The solid line shows the mean pain intensity of the tongue (tongue pain) and the dotted line shows the pain intensity of the head under the TMS coil during each session (TMS device pain). Over the course of the baseline week, the pain intensity of the tongue was relatively stable (mean VAS 57.7). The mean score of BPI functional impairment was 5.44 and the SFMPQ sensory category was 1.4 and affective category was 1.5.

After 1 week of treatment, the tongue pain decreased slightly and was roughly the same as the rating of the TMS device pain. However after 2 days off for the weekend, the VAS score increased to 70. During the second week of treatment, the pain intensity decreased. Finally after 2 weeks of treatment, the VAS tongue pain score was 18. The mean BPI score was 2.6 and the SFMPQ sensory category was 0.5 and affective category was 1.3. The PGIC after 2 weeks of treatment was 5 (moderately better) and the CGI-I was 2 (much improved). After the course of treatment, the VAS score was checked for 1 week. In addition, VAS, PGIC, and CGI scores were checked at 1 month and 2 months after the treatment. Although there was a temporary aggravation of the BMS pain at 1 month after the treatment, it quickly settled down. At 2 months after the treatment, the VAS score was 17, the PGIC score was 6, and the CGI-I score was 2. When the pain intensity was checked at 4 months after the treatment, it was still stable. The TMS procedural head pain only occurred during the treatment time and did not persist after the treatment. In addition to the relief from the burning pain, the patient's taste disturbance also improved; however the mouth dryness and the migraine were unchanged.