

## Repetitive Transcranial Magnetic Stimulation (rTMS)-Induced Trigeminal Autonomic Cephalgia

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### ABSTRACT

Repetitive transcranial magnetic stimulation (rTMS) is an effective and novel treatment method that has been approved for the treatment of refractory depression by the U.S. Food and Drug Administration. The most common side effects of rTMS are a transient headache that usually responds to simple analgesics, local discomfort in the stimulation area, dizziness, ipsilateral lacrimation and, very rarely, generalized seizure. TMS is also regarded as a beneficial tool for investigating mechanisms underlying headache. Although rTMS has considerable benefits in terms of headache, there is the potential for rare side effects. In this report, we

present the case of a patient with no history of autonomic headache who underwent a course of rTMS for refractory unipolar depression caused by an inadequate response to pharmacotherapy. After his fourth rTMS session, the patient developed sudden headaches with characteristics of trigeminal autonomic cephalgia on the stimulated side, representing a noteworthy example of the potential side effects of rTMS.

**Keywords:** Repetitive transcranial magnetic stimulation, headache, trigeminal autonomic cephalgia

### INTRODUCTION

Repetitive transcranial magnetic stimulation (rTMS) is an effective and novel method for the treatment of refractory depression that has been approved by the U.S. Food and Drug Administration (1). This method of stimulation exhibits a superior side effect profile and requires no anesthesia compared with electroconvulsive therapy (ECT) (2). The most common side effects of rTMS treatment are a transient headache that usually responds to simple analgesics, local discomfort in the stimulation area, dizziness, ipsilateral lacrimation and, very rarely, generalized seizure (3). While rTMS has been approved for the treatment of refractory depression, the method is also used to treat auditory hallucinations and negative symptoms of schizophrenia, pain disorders, tinnitus and migraine (3,4,5,6). In addition, TMS is regarded as a beneficial tool for investigating the underlying mechanisms of headache (7). In this report, we present the case of a patient who developed trigeminal autonomic cephalgia (TAC) after the administration of rTMS for refractory depression.

### CASE

Our patient, a 35-year-old male diagnosed with major depressive disorder 1.5 years previously, was admitted to our outpatient clinic because of complaints of boredom, anxiety and sleeplessness. He had been taking duloxetine 60 mg/day for 7 months, but pharmacological treatment had not resolved his depressive symptoms. rTMS augmentation treatment was planned because of the inadequate response to the medication. The patient had no history of ECT or rTMS treatment. Informed consent was obtained prior to treatment. The rTMS protocol we chose was similar to those administered in recent rTMS studies of depression (8,9). Stimulations were applied to the left dorsolateral prefrontal cortex (DLPFC) at 110% of the motor threshold. DLPFC was considered to be located 5 cm anterior to the motor cortex in a parasagittal line, as determined by observing five consecutive contralateral hand muscle (abductor pollicis brevis) contractions. This placement method is known as the "5 cm method" and has been used in several rTMS studies of depression (8,9). Each session included 20 trains at 20 Hz for 2.5 s, with 17-s intertrain intervals, representing 1,000 pulses daily. The rTMS course comprised 15 daily sessions, for a total of 15,000 magnetic pulses. However, 1 h after the fourth session, the patient complained of sudden and severe pain, with characteristics similar to autonomic headache, in the supra-retroorbital area of the stimulated side. He described the pain as squeezing and burning behind the eye.

The patient was agitated and asked for acute treatment to relieve the pain. An examination revealed ipsilateral lacrimation, conjunctival hyperemia, eyelid edema and ptosis. Diclofenac was administered at 75 mg i.m. because of the patient's severe pain, but this medica-



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tion did not alleviate the symptoms. The pain he experienced lasted for approximately 2 h at the same level of severity. No pathological sign was observed on ophthalmological examination and a neurological evaluation also showed normal results. There was no specific finding on cranial computed tomography (CT) or magnetic resonance imaging. Oxygen inhalation was administered to alleviate the patient's severe headache during the neurology consultation, but no improvement in his symptoms was apparent. Indomethacin 50 mg p.o. was administered for the ongoing headache after oxygen inhalation and the patient's pain was partially reduced after this intervention. His headache and autonomic symptoms relapsed the next day, but they were milder than they were initially. He had no diagnosis of headache in the past. The patient was diagnosed with TAC and indomethacin 50 mg/day was prescribed for treatment. The rTMS sessions were discontinued immediately after the headache first developed. Although headache symptoms with autonomic features recurred after indomethacin treatment in the following days, the patient did not experience another headache as severe as the first attack; he continued his ongoing medication for approximately 3 months. In addition, psychiatric treatment for depression was maintained by pharmacological intervention.

## DISCUSSION

rTMS is accepted as an effective and safe stimulation technique and is increasingly being used for some neuropsychiatric disorders, most notably in major depressive disorder. Some studies have shown that it is effective even in drug-resistant and psychotic subtype depression (10). Although the therapeutic mechanism of rTMS has not been well established, it is known that rTMS results in a modulation of cortical excitability as an activating or inhibitory effect stemming from high- or low-frequency stimulation. However, in contrast to healthy people, cortical excitability has been found to be decreased in depressed patients (11). This finding can be associated with the pathway underlying the efficacy of high-frequency (HF) rTMS in depression. High-frequency rTMS, the most studied rTMS method in treating depression, can induce epileptic seizures by its activating effect; this is known to be the most serious side effect of rTMS applications. The efficacy of rTMS in treating headache has not yet been well researched. Recent studies have suggested that different stimulation protocols such as sTMS and rTMS can be effective in acute migraine treatment and migraine prophylaxis (5,12). Some studies have also indicated that HF rTMS applied to the left DLPFC can ameliorate chronic migraine (13). It has been suggested that intracortical inhibition is reduced in migraineurs and that HF rTMS can potentiate this, thereby modulating intracortical excitability via a paradoxical effect in patients suffering from migraine (14).

Some data have also supported an unexpected reduction in headache in conjunction with that of depressive symptoms following rTMS treatment (15). There is increasing evidence to suggest that neurostimulation techniques, including hypothalamic deep brain stimulation, TMS, transcranial direct current stimulation and occipital nerve stimulation, can be considered promising tools in the management of primary headache disorders such as cluster headache (16). In these stimulation methods, the stimulation region and other parameters such as intensity and frequency are considered to be important factors. However, muscular headache, which is considered to result from a different mechanism than TACs, has been reported to be the most common adverse effect of TMS. This type of headache has particularly emerged in HF and high-intensity protocols but usually responds to analgesic medication or resolves spontaneously (3). In our case, the patient had no complaints of headache in prior sessions and

perceived by the patient occurred rapidly and with autonomic symptoms in the fourth session. These findings support the diagnosis of TAC.

Although stimulation techniques are usually reported as beneficial tools in the treatment of pain syndromes and headaches, in this case, HF rTMS seemed to provoke TAC. While the pathophysiology of TAC syndrome is not well understood, it involves the activation of the trigeminal-autonomic reflex; therefore, HF rTMS application may have facilitated this pathway via its activating effect. The intensity of rTMS application in our patient was higher than that of most similar studies, which may have induced the trigeminal-autonomic reflex. To our knowledge, this is the first report of TAC emerging as a result of rTMS. Despite the favorable side effect profile of this stimulation method, we conclude that close monitoring is still crucial for the prevention of or intervention in severe adverse effects during TMS applications.

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