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Double cone coil repetitive transcranial magnetic stimulation for severe obsessive-compulsive disorder after reversible cerebral vasoconstriction syndrome with intracerebral hemorrhage: a case report

Braz J Psychiatry. 2022 xxx-xxx;00(00):000-000
doi:10.47626/1516-4446-2022-2556



Obsessive-compulsive disorder (OCD) is characterized by obsessions and/or compulsions that cause clinically significant distress or impaired functioning.¹ The first-line pharmacological treatment for OCD is selective serotonin reuptake inhibitors (SSRI), usually requiring high doses to reach clinical remission. Although the safety profile of this drug class is good, it can have severe and undesirable side effects, usually unknown by the majority of clinicians, such as reversible cerebral vasoconstriction syndrome (RCVS).² RCVS is a clinical condition characterized by temporary diffuse vasoconstriction of cerebral artery segments. Its clinical presentation includes recurrent thunderclap headaches that may be associated with seizures and transient or permanent focal neurological deficits.² Although its precise incidence is unknown, estimated hospitalizations in United States due to RCVS have been calculated at approximately 3 per million per year.³ Some triggering behaviors and/or conditions (bathing, stressful situations, orgasms, postpartum state), specific medications (such as SSRI, triptans, oral contraceptives, nasal decongestants) and illicit drugs, may be associated with 50-60% of RCVS cases.^{2,4} This syndrome can have serious complications, such as hemorrhagic or ischemic brain lesions, which occur in one-third to one-half of cases.² Considering the growing evidence that SSRI is associated with hemorrhagic risk, especially gastrointestinal and intracranial, it is important to consider the potential severity of this complication and the risk of bleeding recurrence, which has already been demonstrated in the literature.⁵

There is still uncertainty about psychiatric treatment for affected patients, i.e., whether to reintroduce serotonergic agents or not, especially if RCVS was associated with a hemorrhagic complication. In such cases, it might be important to consider first-line non-drug therapies, such

as cognitive behavioral therapy. Nevertheless, when there is no satisfactory response to cognitive behavioral therapy, the options become restricted. In this context, more experimental treatments, such as repetitive transcranial magnetic stimulation (rTMS) emerge as relevant alternatives.⁶

We report the case of a 29-year-old female patient with no family history of psychiatric disorders, except for a sister with early-onset (10 y/o) OCD. At 20 years old, she gradually began developing mild OCD symptoms of the cleaning/contamination and checking dimensions, although at that time the symptoms were not very prominent. She spent more than 8 hours daily dealing with these intrusive symptoms, resulting in severe disruption of social functioning. At this time, she was treated with fluvoxamine, which was increased to 350 mg/day. She had marked improvement after a few weeks, reducing the time spent on obsessions and compulsions to 1 hour per day, which positively affected her social functioning. She was kept on fluvoxamine for the following five years, and an oral contraceptive was the only other medication she used (and had been on continuously for 10 years).

In 2017, she had an abrupt episode of fever, headache, and cervical pain, prompting admission to a tertiary hospital with suspected meningitis, but no supporting evidence was found on cerebrospinal fluid analysis, and a head computed tomography scan was normal. Extensive blood testing discarded other types of infection or conditions, with the only abnormal result being a C-reactive protein level of 155 mg/L. On the third day of hospitalization, she suddenly complained of severe headache, described as the worst of her life, followed by loss of consciousness and arterial hypertension. A new head computed tomography scan showed an intracerebral hemorrhagic lesion in the left frontal lobe and computed tomography-angiography showed vasoconstriction of the left anterior cerebral artery and an active "spot sign" within the lesion.

After excluding other etiologies, fluvoxamine and/or the oral contraceptive were suspected of triggering RCVS and both were suspended. After hospital discharge, she underwent a trial with clomipramine, which resulted in localized skin rash and was immediately withdrawn. Over the next few weeks, she experienced a gradual improvement in OCS and ultimately reached clinical remission of her main symptoms. The patient remained symptom-free for 2 years, with no OCD medication or psychotherapeutic treatment, except quetiapine 25 mg for sleep management and levetiracetam for seizure prevention, as recommended by her neurologist.

A total of 29 sessions of double cone coil rTMS was applied, targeting the anterior cingulate cortex using neuronavigation (20 Hz, 2000 pulses per session), following an adapted version of Carmi et al.'s protocol.⁶ Scores on the Y-BOCS, the Clinical Global Impressions Severity Scale, and the Clinical Global Impressions Improvement Scale were measured during hospitalization and at discharge. Severity Scale scores were 7

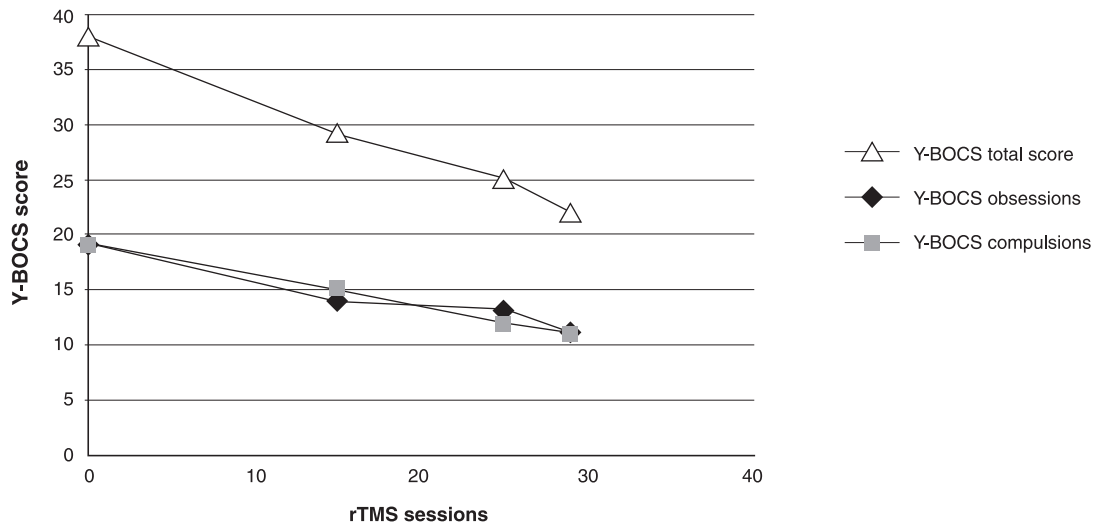


Figure 1 Evolution of Yale Brown Obsessive Compulsive Scale (Y-BOCS) scores over 29 deep repetitive transcranial magnetic stimulation (rTMS) sessions.

(extremely ill) at admission and 4 (moderately ill) at discharge. The Y-BOCS score was 38 on the first day of hospitalization, 29 at the third week, 24 at the fifth week and 22 at discharge; this progression is shown in Figure 1.

A growing body of evidence supports the efficacy of deep rTMS for OCD, and U.S. Food and Drug Administration approval of this treatment will likely lead to more widespread clinical use. In the current case report, rTMS was used because the patient had a history of RCVS with intracranial hemorrhage, probably triggered by fluvoxamine, although concomitant contraceptive use cannot be excluded as a contributing factor.

In a cohort of 210 patients who had not restarted SSRI in 6 months to 7 years follow-up, RCVS was reported to recur at a rate of 5%.^{4,7} Although we are not aware of studies reporting the recurrence risk of RCVS in patients who restarted SSRI, considering the severity of RCVS, it is crucial to study the recurrence risk in these patients and develop alternative treatments. Besides being an important trigger of RCVS, SSRI have also been associated with a slightly higher risk of intracranial hemorrhage.^{8,9} In a 2020 cohort of 1279 post-intracranial hemorrhage patients, a higher recurrence of intracranial hemorrhage was found among those using SSRI, and this association was more important among patients at higher risk of recurrent hemorrhagic stroke, such as carriers of *APOE* $\epsilon 2/\epsilon 4$ alleles, patients with lobar intracranial hemorrhage, and patients with prior intracranial hemorrhage.⁵ In this context, double cone coil rTMS may represent a safer first treatment option than attempting to reintroduce SSRI.

Further work is needed to better assess the efficacy and safety of this rTMS protocol, as well as its individualization, especially in individuals suffering from severe collateral effects, such as RCVS. A possible case of RCVS triggered by rTMS was reported in a previous article.¹⁰ These data indicate a need for further research on the side effects of rTMS; however, since it was an isolated case, a causal relationship could not be

established. Furthermore, the risk of RCVS recurrence following the reintroduction of SSRI therapy must also be assessed. Thus, rTMS may be an important alternative treatment for these individuals, as well as for individuals with other contraindications to SSRI. Finally, follow-up studies should investigate whether symptom reduction is relatively stable post-discharge and how maintenance therapy could be applied.

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Submitted Feb 27 2022, accepted May 14 2022.

Acknowledgements

ARB receives scholarships and support from Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP), Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq-1B), Escola de Medicina da Universidade de São Paulo (FMUSP), the UK Academy of Medical Sciences (Newton Advanced Fellowship), and the International Health Cohort Consortium (IHCC).

Disclosure

The authors report no conflicts of interest.

How to cite this article: Silveira JB, Damiano RF, Abelama Neto E, Gomes RNSM, Klein I, Borrione L, et al. Double cone coil repetitive transcranial magnetic stimulation for

severe obsessive-compulsive disorder after reversible cerebral vasoconstriction syndrome with intracerebral hemorrhage: a case report. *Braz J Psychiatry*. 2022;00:000-000. <http://doi.org/10.47626/1516-4446-2022-2556>

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