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## rTMS for Treatment of Depression in a Patient With Cerebral Amyloid Angiopathy: A Case Report on Safety and Efficacy

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### Dear Editor

We report on the safety and efficacy of low frequency repetitive transcranial magnetic stimulation (rTMS) on a patient presenting with a long history of medication-resistant depression and known co-morbid cerebral amyloid angiopathy (CAA). rTMS is effective in treating medication-resistant depression and its use is quickly growing [1]. Its broader use, however, raises concerns about the safety of TMS particularly in patient populations where there may either be a higher risk for side-effects or a lower likelihood of showing a positive response to treatment. There are currently two forms of rTMS with substantial evidence for efficacy in the treatment of depression, high-frequency rTMS (5–20 Hz) to the left dorsolateral prefrontal cortex (DLPFC) and low-frequency rTMS (1 Hz) to the right DLPFC [2]. While low frequency rTMS to right DLPFC has not been tested in large multicenter trials, a meta-analysis of smaller trials lends evidence for its efficacy [3]. To date, there have been no seizures reported from low frequency right DLPFC protocols and 1 Hz rTMS is being used as a treatment for epilepsy [4].

CAA is a neurovascular disease characterized by  $\beta$ -amyloid fibrils deposited in the walls of cerebral blood vessels [5]. These deposits weaken the vessel walls and predispose patients to complications such as intracerebral hemorrhage, microbleeds, and cognitive impairment. CAA microbleeds are believed to occur in greater than 30% of adults over the age of 70, and are potentially even more prevalent given the amount of asymptomatic individuals with microbleeds [6].

Currently, there is no evidence reported in the literature regarding the safety of brain stimulation techniques such as rTMS in patients with CAA. Given the seizure risk of rTMS

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and the treatment's unknown effects on weakened cerebrovasculature, it is unclear whether patients with CAA who could benefit from rTMS treatment should be subjected to an induction and maintenance course of stimulation.

## Patient presentation

This 73 year-old male retired physician, who is married without children, has a long history of chronic medication resistant depression dating back to adolescence. He had a strong maternal family history of depression. Around age 50 he was initiated on therapy with paroxetine, which was discontinued a couple of months later due to side effects. Over the course of the next few years he attempted trials of medications from several classes of anti-depressant medications including bupropion, venlafaxine, St. John's Wart, nefazodone, remeron, risperidone, and mirtazapine. Venlafaxine was the only agent to show minor improvement in mood, but was ultimately discontinued due to intolerable side effects. The rest were either not beneficial, not tolerable, or both.

In the late 1990s the patient was hospitalized and received over twenty sessions of electroconvulsive therapy. These also had no positive effect on his depression and caused severe memory loss, including some degree of retrograde amnesia that did not fully resolve. Since then he has continued to try various combinations of anti-depressant medications with little to no success.

The patient recently experienced episodes of acute vertigo for which he received an MRI to investigate. The MRI unexpectedly showed approximately 40 microbleeds (Fig. 1A), leading to a diagnosis of probable CAA [7]. No parenchymal hemorrhages have occurred and he has been followed with serial imaging for a number of years. During his course, he participated in a CAA research study that included amyloid imaging with Pittsburgh Compound B (PiB). This study (obtained as described with the patient's informed consent) demonstrated increased cortical PiB retention (Fig. 1B) in a pattern consistent with CAA [8].

## Treatment plan

The patient was referred to our clinic by his psychiatrist for possible treatment with TMS given the refractory nature of his symptoms. There were no focal findings on his neurological exam and no signs of any cognitive symptoms. One concern that arose in the evaluation was whether the combination of rTMS and CAA might increase the risk of a seizure. After explaining the potential risks of the treatment and with his consent, therapy was started with 1hz to the right DLPFC as defined by 5.5 cm anterior to motor threshold site. Motor threshold was defined as the intensity over the motor hotspot at which 50% of pulses produced a discernable visual motor response in the patients' hand. Stimulation intensity was set to 110% of the resting motor threshold, and rTMS was applied at 1 Hz for 1600 pulses per day for 3 weeks. A Magstim Super Rapid2 repetitive stimulator (Magstim Company Ltd., Whitland, Carmarthenshire, UK) was used to conduct all rTMS sessions.

## Patient response

The patient tolerated the treatments well and showed an excellent response with a decrease in his Beck Depression Inventory II (BDI-II) from a baseline of 21 to 1 at the end of the initial course. His Hamilton Rating Scale for Depression (HAM-D) dropped from a 10 at initial evaluation to a 1 at the end of his induction course.

His observed affect (assessed by clinicians involved in his treatment) was reported to be noticeably improved – he was said to be more engaged and alert, and was able to both enjoy and deliver humor. There was no exacerbation of microbleeds due to CAA on visual inspection of a follow-up MRI.

## Discussion

The patient's treatment was completed successfully and without complication. He received a total of 15 daily sessions over three weeks, during which he entered full remission. Since completion of induction, this patient has continued maintenance sessions of rTMS due to episodic and mild recurrence of decreased mood. He continues to show a good response.

Low frequency rTMS was performed without complications in a patient with CAA and medication-resistant depression. Whether risks could emerge with additional patients and whether high frequency left DLPFC treatments can be performed safely remains unanswered. At least initially, low frequency right DLPFC treatment should incur a lower risk of complications, particularly seizures, in patients with CAA and for whom rTMS is medically indicated.

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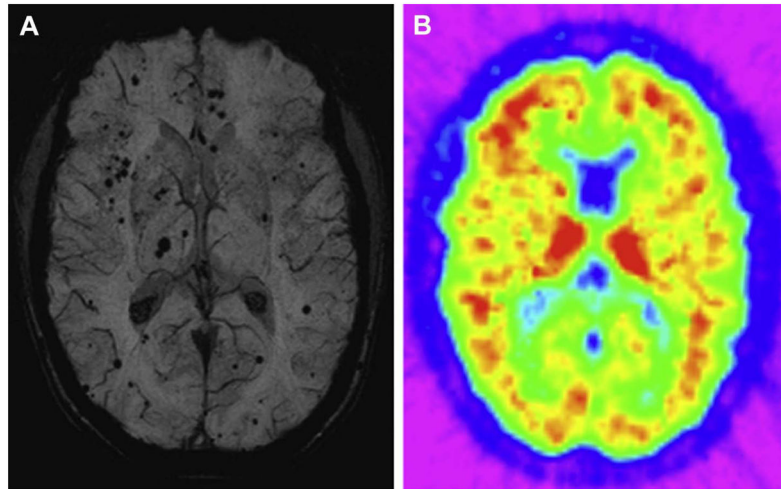
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**Figure 1.** The left-hand image (A) shows a susceptibility weighted MRI sequence revealing numerous micro hemorrhages in the patient. The right-hand image (B) shows PiB-PET imaging, showing high levels of cortical uptake indicating amyloid deposition.