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Case report/ Kazuistyka

Repetitive transcranial magnetic stimulation for persistent auditory hallucination: Initial worsening of hallucination may not be a predictor of poor outcome

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ABSTRACT

Persistent auditory hallucination (PAH) in schizophrenia is not an uncommon phenomenon. Inhibitory repetitive transcranial magnetic stimulation over the left temporo-parietal cortex is found to be effective in the management of PAH in schizophrenia and have a better efficacy than placebo and bilateral stimulation. We highlight here a case of schizophrenia with PAH, where the patient responded well following initial worsening of auditory hallucination. The symptoms were well controlled with maintenance sessions of transcranial magnetic stimulation.

Introduction

Schizophrenia is a severe mental disorder with a prevalence of approximately 1% world-wide [1]. Patients suffering from this disorder may experience persistent auditory hallucination (PAH) despite adequate pharmacological treatment. Low-frequency (1 Hz) repetitive transcranial magnetic stimulation (rTMS) over the left temporo-parietal junction is effective in the treatment of PAH [2]. The effectiveness of low-frequency rTMS (inhibitory) in treating PAH is achieved through the suppression of the over-activated left superior temporal gyrus [3]. A recent systematic review and meta-analysis of randomized control trials (RCTs) conducted between 1999 and 2013 concluded favourably regarding the effectiveness of low frequency rTMS in PAH [4].

rTMS has been used as an adjunctive treatment to ongoing antipsychotic treatment in most of the clinical studies on schizophrenia [5]. The evidence regarding the effectiveness of TMS in the management of PAH is of level C, as concluded in existing standard guideline [6].

An earlier study by Slotema et al. revealed that priming with high-frequency rTMS, prior to giving low-frequency rTMS, is not effective in the treatment of auditory hallucination [7]. However, recent research suggests a possible role of priming by high-frequency rTMS prior to sessions of low-frequency rTMS in early reduction of the loudness of auditory hallucination [8]. Hoffman et al. concluded in their

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study that attentional salience may be a predictor of the best side (right or left) for stimulation with rTMS [9]. In their study, they gave five sessions each to right and left sides of the temporo-parietal junction consecutively. The subsequent sessions of TMS were completed on the side (right or left) which had shown better response [9]. Patients with high salience auditory hallucination had shown a better response to rTMS at the right temporo-parietal junction (right homologue of Wernicke's area) and those with low salience auditory hallucination respond to stimulation of the left temporo-parietal junction (Wernicke's area) [9].

Case history

A 30 year old, unmarried, right-handed male, a shopkeeper by occupation, suffering from schizophrenia from the age of 22 years, presented with persistent auditory hallucinations, despite receiving adequate doses of Quetiapine (up to 600 mg/day), Aripiprazole (up to 30 mg/day), Risperidone (up to 8 mg/day), Olanzapine (up to 20 mg/day) and Trifluperazine (up to 20 mg/day) in the past. He had received these antipsychotics for an adequate period of time as single drugs as well as in combinations. Due to intolerable side effects, he could not continue clozapine. During the course of his illness the patient had third-person auditory hallucination of derogatory content. He also had delusions of persecution, fearfulness, anxiety, disturbed sleep, withdrawn behaviour and poor self-care. The symptoms had persisted continuously over the previous 8 years with fluctuating severity. The patient's past and family history was insignificant. There was no history of substance abuse (current or past). His medical history was also uneventful. All possible treatment options had been discussed with the patient and his caregivers. Taking previous treatment response and available treatment options into consideration, TMS was mutually agreed upon and planned. As the patient had to receive daily sessions of TMS, he preferred to stay in hospital.

At the time of hospitalization, the patient was on ziprasidone 120 mg/day for more than six weeks with adequate compliance (which was checked from the caregiver). After hospitalization the dose of ziprasidone was increased to 160 mg/day. With ziprasidone (160 mg/day) all symptoms were well controlled except for the auditory hallucination. The baseline hallucination score on the Psychotic Symptom Rating Scale (PSYRATS) was 38 at the time of admission. PSYRATS was used, as it had a detailed elaboration of auditory hallucination in 11 domains, through a Likert scale of 0–4 [10].

It was planned to start the patient on TMS due to the persistence of auditory hallucination despite treatment optimization (two weeks after increasing the dose of ziprasidone to 160 mg/day). Complete blood counts, a Liver function test, a Renal function test, an Electrocardiogram and CT scan of the patient's head were within normal limits. Possible contraindications to rTMS were ruled out. The resting motor threshold (RMT) was determined by using a figure-8 angular coil using the magnetic stimulator of the MedStim (MS-30) TMS Therapy System (Medicaid systems). The standard visual method was used for identification of RMT (5 cm laterally from the vertex) [11]. After informed consent had been obtained, rTMS was administered to the patient in a lateral recumbent posture at 100% RMT at 1 Hz frequency, 80 pulses/train with 10 s inter-train interval in 20 trains (i.e. 1600 pulses/session). The patient received daily sessions of rTMS for 20 sessions over the course of four weeks. We used this protocol as most earlier studies used 1 Hz frequency at 80% to 115% RMT and $\geq$1000 pulses per session [6]. The patient reported no side effects and tolerated the TMS treatment. Cotton ear plugs were used for protection against noise. We adopted the technique of Hoffman et al., as described above (five consecutive sessions over the left temporo-parietal junction followed by five sessions over the right temporo-parietal junction, thereafter delivering subsequent sessions to the side having the better response).

The initial five sessions of TMS were delivered over the left temporo-parietal junction (T3-P3 junction as per 10–20 system for placement of electrodes in the electroencephalogram). The patient reported a worsening of hallucination (increased loudness and distress) lasting for around 30 min following the first rTMS session (scored at 4 each on the loudness and distress items of PSYRATS, resulting in a transient increase of total hallucination score to 41), which became normalized to the pre-rTMS level of severity (i.e. a hallucination score of 38 on PSYRATS) during the next four sessions over T3-P3 junction (Fig. 1). As there was no change in the severity of auditory hallucination, the right temporo-parietal junction (T4-P4 junction) was targeted using the same protocol in the five subsequent sessions. Again, the patient reported, a worsening of hallucination (after the first session over the T4-P4 junction), which was normalized over next four TMS sessions to the pre-rTMS level of severity (Fig. 1). A total of five sessions of TMS were given over the T4-P4 junction. Due to non-response, the subsequent sessions were delivered on the left-side (T3-P3 junction), using the same protocol. The patient's auditory hallucination had stopped completely after 12 sessions. A total of 20 sessions of TMS (the first five sessions at the T3-P3 junction, the next five sessions at T4-P4 junction and the last 10 sessions at T3-P3 junction) was given to the patient. The patient received five tapering-off sessions (after one week, 4weeks, 8 weeks, 16 weeks and 32 weeks from the last TMS session) over the T3-P3 junction using the same protocol (1600 pulses at 100% of resting motor threshold). At the 6-month follow up the patient was well maintained and there was no auditory hallucination.

Discussion

In our patient, a worsening of auditory hallucination occurred, in terms of its loudness, producing significant distress following first session of TMS in the left temporo-parietal junction. A similar worsening of auditory hallucination also occurred after the first session over right temporo-parietal junction. After giving five sessions each of TMS on left and right sides, there was no significant change in auditory hallucination. Subsequent sessions (10 in total) were delivered over the left temporo-parietal junction, and after two sessions (the 12th session of TMS), there was