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Case report

Transcranial magnetic stimulation induces 'pseudoabsence seizure'

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Objective: Several studies support the hypothesis of an antidepressive or mood-enhancing effect of repetitive transcranial magnetic stimulation (rTMS) on depressive patients. The most acute concern regarding rTMS is possible seizure induction; therefore, reports on seizure during rTMS are of special significance.
Method: We describe a case in which high frequency rTMS over the left dorsolatero-prefrontal cortex (DLPC) applied as an add-on antidepressive strategy may have induced a frontal lobe complex partial seizure in a female patient affected by drug-resistant depression.
Results: The epileptic seizure was self-limited, and the patient did not report any physical sequelae. The psychopathological improvement, observed immediately after the incident in question, did not last.
Conclusion: In this case train duration in rTMS, combined with drugs modulating the norepinephrine turnover, may have contributed to the occurrence of this complex partial seizure, which neuroanatomically seems to be localized in the DLPC.

Key words: transcranial magnetic stimulation; depression therapy; side effect; seizure

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Introduction

The most acute concern regarding repetitive transcranial magnetic stimulation (rTMS) is possible seizure induction. The exact number of probands and patients who have received TMS or rTMS is unknown, but worldwide is likely to be several thousand. To date only eight cases of seizures during rTMS have been reported, including six normal volunteers (1, 13). The TMS-induced seizures were self-limited and did not seem to have permanent sequelae. The risk of seizure induction is related to the combination of various rTMS-parameters (magnetic intensity, pulse frequency, train duration and intertrain interval) which contribute to the spreading of neuronal excitation (2, 3). Psychoactive drugs *per se* are also able to induce seizures by lowering the seizure threshold (e.g. for maprotiline the incidence level is up to 12.2%) (4). We describe a case in which high-frequency rTMS induced a complex partial seizure in a medicated, depressed female patient. The origin of this seizure with its specific clinical characteristics, the sudden onset and ending with little or no postictal confusion, acute mood changes, mild oral automatisms and the impairment of consciousness (lasting less than 10 s) as well as the few interictal EEG abnormalities can be attributed to the dorsolatero-prefrontal or cingulate regions (5). Stefan classifies this frontal lobe seizure type as 'Pseudoabsence' (6).

Case report

Mrs P., a 36-year-old, right-handed, Caucasian, divorced woman, was in our psychiatric department. This was her third admission. She suffered from a mixed depressive–anxious state; codiagnosed were a dependent personality and hypothyroidism. In her case history a single, maprotiline-induced generalized seizure during her second admission in 1996 is noteworthy; the EEG then showed mild generalized slowing and the cCT did not indicate any signs of serious brain pathology. During that admission, the patient's depression was considered drug-resistant; thus, she underwent combined trazodone and electroconvulsive therapy (ECT)

resulting in good remission (7). During her later admission, the patient was medicated with trazodone 500 mg/day, citalopram 30 mg/day, lorazepam 3 mg/day and thyroxin 100 μg/day for more than 2 weeks with no psychopathological improvement. After giving her written informed consent she was recruited for antidepressive augmentation therapy with rTMS. As a first step, the patient underwent bilateral rTMS treatment without any change of medication.

rTMS protocol (bilateral, combined with 1 and 20Hz)

Using the figure-8 coil, rTMS was delivered with a Cadwell stimulator on 5 consecutive days, 1 session/day. Over the left dorsolateral prefrontal cortex (DLPC) we chose a stimulus intensity of 110% of the motor threshold (MT) of abductor digiti minimi muscle, 20 Hz frequency, 5 s duration, 10 trains and an intertrain interval lasting at least 45 s; over the right DLPC 110% of MT, 1 Hz, 300 s and 1 train, for the total dose of 6500 stimuli. In each session the left DLPC was stimulated first, followed by stimulation of the right DLPC. After each rTMS session Mrs P. experienced a general well-being, but for a maximum of 3 h only. Subsequently citalopram was replaced by venlafaxin 112.5 mg/day. Five days later we restarted with rTMS, choosing new parameters (3).

rTMS protocol (unilateral with 20 Hz)

Over the left DLPC rTMS was delivered at 110% of MT with 20 Hz, 10 s duration and 10 trains with an intertrain interval of $\geqslant 60$ s. The study protocol was designed for 5 consecutive days, 1 session/day.

The complex partial seizure reported occurred during the first session. The patient, on being submitted to the third rTMS train corresponding to 600 stimuli, reported a sensation of nausea which we interpreted as gastral aura; immediately afterwards she lost consciousness and showed mild oral automatism. We observed no twitching of limb-muscles, nor focal or generalized motor activities and no eye deviation. The ispilateral evoked motor potential of the target muscle, recorded simultaneously, revealed neither spreading nor after-discharge phenomena. After 8 s the patient was awake again, alert with no postictal confusion; she had no memory of what had happened. The patient felt euphoric for almost 18 h and did not complain of any side effects, but then became depressed. The EEG recorded bifrontopolar paroxysmal delta activities during hyperventilation immediately after the seizure. Despite the low specificity and paucity of ictal and postictal EEG changes in frontal lobe seizures (5) these findings indicate at least an involvement of the frontal lobe. Two days after this event the SPECT scan, with simultaneous measurements of ^{18}FDG and ^{99m}Tc HMPAO, showed hyperperfusion in the hippocampal regions bilaterally and left-sided hypoperfusion in the DLPC, indirectly supporting that an ictal discharge may have remained restricted to the DLPC (5, 8). Hypometabolism in both basal ganglia regions was also diagnosed. Eventually, the patient underwent successful ECT augmentation treatment in combination with trazadone and venlafaxine. No side effects, especially of cardiovascular type, were observed (7).

Discussion

There is no doubt that the increase of rTMS train duration contributed to the occurrence of this complex partial seizure, which might be localized neuroanatomically in the DLPC (5, 6, 8). This type of seizure contrasts to other rTMS-related seizures described previously, because no motor activities were observed. The comedication and its selective influence on specific neurotransmitters must not be disregarded; the severely depressed female patient, as reported by Pascual-Leone, was taking amitriptyline and haloperidol as she experienced a seizure with secondary generalization, although she had received rTMS at this area several times before without incidents. Both drugs have no direct effect

Table 1. Seizures induced by rTMS: overview over cases in literature

Source/subject/seizure type	SI (% MT)	f (Hz)	Dur (s)	Intertrain (s)
Dhuna (12)/epileptic/generalized/$n=1$/F/32y	2.2 T	16	10	After 2 train
Pascual-Leone (13, 14)/volunteers/generalized/$n=2$/F/35y	200	10	10	300–600
	250	25	10	'long'
Wassermann (15)/volunteers/generalized/$n=2$/F/27y/39y	105	15	0.75	0.25
	110	25	0.80	1.0
NINDS (16)/volunteer/generalized/$n=1$/F	120	15	2.5	120
Mercuri (1)/volunteer/partial-motor/$n=1$/M	130	3	7	'long'
Pascual-Leone (1)/medicated, depressed/generalized/$n=1$/F	90	10	10	60
Conca/medicated/depressed/pseudoabsence/$n=1$/F/36y	110	20	10	60

F = female; M = male; y = age; SI = stimulus intensity; MT = motor threshold; f = frequency; dur = duration.

on MT, but induce a reduction in the threshold for spread (1). Thus, the importance of the prescription of the combined noradrenaline and serotonin re-uptake inhibitor in our patient should be discussed, based on the knowledge that maprotiline, a potent noradrenaline re-uptake inhibitor, is prone to induce generalized cerebral seizures (4). Noradrenaline could cause an enhancement of excitatory neurotransmitter responses, either by specific interaction with the glutamate neurotransmisson pathway or more generally by modulating neuronal physiology, providing a sensitization for excitatory stimuli (9). The transient euphoric reaction observed, which may be assumed to be modulated by noradrenaline (10) following the partial complex seizure, supports the hypothesis of noradrenergic involvement. The age and sex of our patient are in accordance with the mean age (so far reported) of 33.5 years and the predominance of females (6/1) in the cases listed in Table 1. Whether there is an influence of age and gender on MT, similar to the impact on the seizure threshold during electroconvulsive therapy (11), will be a topic for further investigations. Finally, there is no evidence to suggest that a single provoked seizure or even a series of induced seizures, as in electroconvulsive therapy, makes another seizure more likely in an otherwise healthy individual.

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Invited comment

Repetitive transcranial magnetic stimulation (rTMS) exerts antidepressant effects. Its advantage over other treatments is that it is free from side effects and can be administered without anaesthetic intervention. The case reported in this issue (1), however, illustrates seizure risk. The young female had a history of generalized seizure with maprotiline. The resting EEG was also abnormal, showing diffuse slowing. The effect of activation procedures (e.g. hyperventilation and photic stimulation) on EEG may have exposed underlying seizure proneness before rTMS. It is of interest to note that most subjects who developed seizures with rTMS were young, which is in keeping with the lower seizure threshold as well as risk for prolonged seizures in ECT (2, 3). Female preponderance could well reflect the population referred to rTMS. However, seizure threshold in ECT is also lower in females (4). This case highlights that female sex, younger age, history of adult onset seizures and an abnormal EEG are high-risk factors for seizures during rTMS. It maybe noted that a seizure, even if unwanted, was benign.

Essentially, rTMS stimulates certain brain structures but at a clinically subconvulsive level; the stimulus level is set either at or above motor threshold. However, seizure-like physiological response has not been seen on surface EEG recording (5). Other indirect indices of central seizure are negative; prolactin elevation occurs with ECT (6) but not with rTMS (5). However, rTMS has some similarities with ECT. The motor threshold to transcranial magnetic stimulation increases with age (7), as does seizure threshold in ECT (2). Hyperventilation, which

lengthens seizures in ECT (8), also increases amplitude of motor potential with transcranial magnetic stimulation (9). Anticonvulsants also increase threshold to transcranial magnetic stimulation (10). Occasional seizures under rTMS procedure, as in this case, also point to the potential epileptogenic effects of rTMS. In the treatment of depression, rTMS therapy yields response rates of just 50% (11), unlike nearly 90% with true ECT (12). This lends support to the classical findings of Ottosson et al. (13) that a cerebral seizure is necessary for potent antidepressant effects. Interestingly, the response rates with rTMS were twice as high in younger depressives than older depressives (14). This may suggest that the former, by virtue of age, manifested more seizure-like physiology with rTMS and hence a better outcome. It is likely that a subconvulsive seizure response with rTMS may cause an antidepressant effect and perhaps it is necessary for the same.

In this context an alternative non-pharmacological treatment in depression merits mention. Janakiramaiah et al. (15) demonstrated antidepressant effects of Sudarshana Kriya Yoga (SKY) in an open trial. SKY also produced a significant 'improvement' in P300 amplitude along with antidepressant effect both in dysthymic and melancholic patients (16). Interestingly, the antidepressant potency of SKY was equivalent to drugs but inferior to ECT in melancholic patients (17). In male dysthymic patients SKY produced significant elevations in prolactin, suggesting effects similar to ECT (15). The SKY procedure involves different rates of breathing, one of which involves hyperventilation. The latter is an accepted 'activation' procedure used during EEG investigation of epileptic patients and is known to produce seizures in those susceptible, e.g. absence seizure patients (18). It is likely that SKY also brings about antidepressant effects by eliciting an autogenous, subconvulsive seizure response.

In summary, antidepressant effects may be mediated by seizures. Some antidepressant drugs predispose individuals to risk of seizures. Similarly, rTMS can also occasionally induce seizures. Another potent antidepressant therapy, SKY, also has some biological effects related to seizure. Lastly, the most potent antidepressant therapy, ECT, needs a seizure for it to be effective. Advancing our understanding of antidepressant mechanisms may be aided by the knowledge of the electrical and molecular mechanisms of seizure.

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