CASE REPORT

UDC: 616.895.4-08-036
DOI: 10.2298/VSP1402207K

Switch to hypomania induced by repetitive transcranial magnetic stimulation and partial sleep deprivation added to antidepressant: A case report

Hipomanija indukovana primenom repetitivne transkranijalne magnetne stimulacije i parcijalne deprivacije spavanja kod bolesnika na terapiji antidepresivima

Jelena Krstić[*†], Tihomir V. Ilić[‡§]

[*]Psychiatric Hospital, Clinical Hospital Center "Dr Dragiša Mišović"-Dedinje, Belgrade, Serbia; [†]Faculty of Biology, University of Belgrade, Belgrade, Serbia; [‡]Department of Clinical Neurophysiology, Clinic of Neurology, Military Medical Academy, Belgrade, Serbia; [§]Faculty of Medicine, Military Medical Academy, University of Defence, Belgrade, Serbia

Abstract

Introduction. Bipolar depression is often unrecognized and difficult to treat because of two opposite problems: treatment resistance and risk of manic switch. **Case report.** A 53-year-old female was suffering from unipolar depressive disorder since the age of 36. During a recent major depressive episode pervasive feelings of sadness, lost of interest in activities, severe insomnia and highly expressed somatic anxiety dominated 7 months. After unsuccessful tries with two different antidepressants of adequate doses and duration, slow rate repetitive trascranial magnetic stimulation (rTMS) was started, but the patient stayed at the fixed dose of antidepressant. Partial sleep deprivation (PSD) was additionaly applied twice during these 2 weeks with the idea to boost up, or enhance rTMS treatment response. At the last two rTMS sessions depression obviously meliorated, but the patient also expressed symptoms of hypomania. The therapy of rTMS was stopped, hypomanic symptoms gradually vanished and two weeks after the rTMS treatment the patient was euthymic. Antidepressant was kept on. In a follow-up period of 2 years the diagnose of bipolar affective disorder was definitely established. **Conclusion.** This case report shows that a combination of slow rate rTMS and partial sleep deprivation in the patient at the fixed dose of antidepressants, have strong synergistic effect even with potential to induce hypomanic switch, that is the first description in the literature to our knowledge.

Key words:
bipolar disorder; diagnosis, differential; depression; antidepressive agents; sleep deprivation; transcranial magnetic stimulation.

Apstrakt

Uvod. Bipolarna depresija često se ne prepoznaje, a teškoće u njenom lečenju odnose se na dva suprotna problema: terapijsku rezistenciju i rizik od manič nog preokreta. **Prikaz bolesnika.** Bolesnica stara 53 godine, lečena je od unipolarnog depresivnog poremećaja od svoje 36. godine. Tokom nedavne epizode velike depresije tokom sedam meseci dominirala su stalna osećanja potišenosti, gubitak interesovanja za uobičajene aktivnosti, teška nesanica i izrazita somatska anksioznost. Posle dva neuspela terapijska pokušaja sa različitim antidepresivima primenjenim u odgovarajućim dozama i dovoljno dugo, započeta je terapija niskofrekventnom repetitivnom transkranijalnom magnetnom stimulacijom (rTMS). Tokom rTMS terapije bolesnica je nastavila da prima nepromenjenu dozu antidepresiva. Parcijalna deprivacija spavanja (PSD) dodatno je primenjena u dva navrata tokom ove dve nedelje sa idejom da će potencirati ili pospešiti terapijski odgovor. Tokom poslednje dve rTMS sesije, simptomi depresije bili su značajno smanjeni, ali je bolesnica ispoljavala i simptome hipomanije. Terapija rTMS je prekinuta i hipomanični simptomi su postepeno prestali. U roku od dve nedelje posle rTMS terapije bolesnica je bila eutimična. Terapija antidepersivom je nastavljena. U periodu praćenja u naredne dve godine definitivno je postavljena dijagnoza bipolarnog afektivnog poremećaja. **Zaključak.** U ovom prikazu bolesnice, pokazalo se da istovremena primena rTMS i deprivacije spavanja kod bolesnika sa nepromenjenom dozom antidepresiva ima snažan sinergistički efekat, čak sa mogućnošću da izazove manični preokret, što je ujedno, prema našim saznanjima, prvi do sada objavljeni slučaj hipomanije indukovane ovom kombinacijom antidepresivnih terapija.

Ključne reči:
psihoze, manično-depresione; dijagnoza, diferencijalna; depresioni poremećaji; antidepresivi; spavanje, deprivacija; transkranijalna magnetna stimulacija.

Correspondence to: Tihomir V. Ilić, Department of Clinical Neurophysiology, Clinic of Neurology, Military Medicine Academy, Crnotravska 17, 11 000 Belgrade, Serbia. Phone: +381 11 3609 064. Fax: +381 11 3608 745. E-mail: tihoilic@gmail.com

Introduction

Bipolar depression is a common and severe psychiatric disorder with high risk of suicide, but after many high quality surveys and expert consensus in practical guidelines, it is still often unrecognized and mismanaged. The main difficulties in therapy of bipolar depression regard two opposite issues: treatment resistance and risk of hypomanic/manic switch.

Antidepressant-associated manic switch was reported to be higher in bipolar type I disorder than unipolar depression [1] or bipolar type II, and antidepressant induced hypomania/mania during the treatment of unipolar depression is considered as a sign of latent bipolar disorder [2].

Transcranial magnetic stimulation (TMS) is relatively novel method of non-invasive stimulation of brain cortex and has been explored in neurology, psychiatry and neuroscince.

A number of randomized controlled trials have demonstrated effecacy and safety of rTMS in major depression [3–5], but there are only a few rTMS trials in bipolar depression where its efficacy and saftey has not yet been established. Available data, until now, are controversial.

In most rTMS studies on major depression high frequencies of stimulation (≥ 5 Hz) of the left dorso-lateral prefrontal cortex (DLPFC) and only a few trials used low frequent (≤ 1 Hz) rTMS of the right DLPFC [4, 5] suggesting its efficacy and even better safety, compared to high frequence rTMS.

Swich to hypomania/mania may occur also with therapeutic sleep deprivation [6]. A recently published review [7] including 53 rTMS randomized controlled trials in unipolar and bipolar depression found that switching occurance is similar as with antidepressant pharmacotherapy.

Several positron-emission tomography (PET) and single-photon emission computed tomography (SPECT) studies already found changes in cerebral blood flow and glucosa metabolism in prefrontal regions [8, 9] after sleep deprivation, similar to changes observed after rTMS treatment in depressive patients [10], that means possible synergistic effect of this two antidepressant treatments.

Case report

A 53-year-old female was suffering from major depressive disorder, according to the Diagnostic and Statistic Manuel of Mental Disorders – IV Edition, Text Revision (DSM- IV-TR) [11] criteria. The patient was highly educated, employed, married, had two adult children, and no history of other psychiatric or somatic disorder. In family history for psychiatric disorders data were not completely reliable, because her father had a long period of alchohol abuse and aggressive behavior, but denied psychiatric treatment. First major depressive episode was diagnosed when the patient was 36 and after short antidepressant treatment she remitted and had not been regularly monitored by the psychiatrist until the age of 48. In the next 5-year period the patient had 3 major depressive episodes. The major depressive episode (before rTMS treatment was used) started 7 months ago with pervasive feelings of sadness, lost of interest in family and activities, severe insomnia and highly expressed somatic anxiety. During that episode the patient was treated as outpatient.

Baseline Hamilton Depresssion Rating Scale -17 items (HDRS-17) score was 27. Antidepressant treatment started with sertraline (gradually titrated to the dose of 200 mg/day) for about 8 weeks. Because of poor antidepressant response with 25 points at HDRS-17, sertraline was tapered off and the patients was treated with venlafaxine (up to 225 mg/day) without significant improvement and after additional 9 weeks the patients had quite severe depressive symptoms with 28 points at HDRS-17.

With the written informed consent we started rTMS treatment. The institutional review board, following the Declaration of Helsinki (1975), approved the experimental procedures.

TMS was delivered by a Magstim Magnetic Stimulator with a figure 8-shaped coil.

rTMS was then delivered at 110% rot test motor treshold (RMT) intensity on the frontal scalp area overlying the right dorsolateral prefrontal cortex (DLPFC), localized according to previous reports 5 cm in front of the best spot for inducing MEPs from the abductor policis brevis (APB) muscle [12].

The patient received 10 sessions of 1 Hz right prefrontal rTMS at 110% of RMT intensity, over a 2-week period (5 days/week). Each daily session of rTMS consisted of 5 trains 60 stimuli (300 stimuli/daily), with inter-train pauses of 3 minutes, lasted approximately 20 min. The total number of stimuli the patient received during a 2-week treatment was 3,000.

Twice during a 2-week period late partial sleep deprivation (PSD) was applied; the patient went to bed as usual, woked-up at 01.30 h and stayed awake approximately the next 20 h. We chose late PSD instead of total sleep deprivation (TSD) because its proven efficacy similar to TSD (13) and abbreviated procedure seemed more likely acceptable for patients compliance. The patient was naive to sleep deprrination as well as rTMS. A family member was monitored the patient`s complience.

During the rTMS treatment the patient stayed at fixed dose of venlafaxine (225 mg/day).

At the last two rTMS sessions depression obviously meliorated (11 points at HDRS), but the patient also expressed symptoms of hypomania – became talkative, cheerful, optimistic, self-confident, and hyperactive at times and had a quite unrealistic plans. Young Mania Rating Scale (YMRS) score was 13 (symptoms adequate to meet DSM-IV-TR mild hypomania criteria).

rTMS was stopped after 10 sessions, as it was scheduled, because hypomania started at the end of treatment, and patient was carefully monitored. One week after the rTMS treatment the patient came to outpatient clinic with milder hypomania symptoms, not so hyperactive anymore, but still euphoric and at moments showed inappropriate friendly attitude toward doctor and nurses (8 points at YMRS). Two weeks after rTMS treatment patient was

definitely euthimic (4 points at YMRS, 8 points at HDRS-17) and then was decided to keep on with antidepressant treatment (225 mg venlafaxine/day), and be careful in monitoring a possible bipolar affective disorder. Remission was sustained in the next 8 months, when the patient was admitted to the hospital with severe depressive symptoms. Fifty mg/day of amytriptiline was added to venlafaxine 225 mg/day, without significant response. When amytriptiline dose was increased to 75 mg/day, the patient switched to mania, first time in her life. Antidepressants were stopped and the treatment with mood stabilizer started (lithium carbonatis 900 mg/day). After a 2-year follow-up, the patient stayed euthimic.

Discussion

This case report shows that a combination of slow rate rTMS boosted with partial sleep deprivation has strong, possibly synergistic antidepressant effect, with the potential to induce hypomanic switch in the patient at the fixed dose of antidepressants.

Our patient previously did not respond to high doses of sertraline and venlafaxine that justified the diagnose of treatment resistant depression. During the rTMS treatment the patient stayed at the fixed dose of medication, but it was not likely that venlafaxine caused switch to hypomania (although switch might be attributed to a long-term use of antidepressants, which may destabilize the illness). It is also not likely that after 9 weeks at the fixed dose of venlafaxine without mood improvement, venlafaxine caused manic switch; moreover, the patient became euthimic when rTMS was stopped, but venlafaxine was kept on, during the observation period. Thus, it is more likely that the low-frequent rTMS and partial sleep deprivation had strong synergistic antidepressant effect that result in hypomania in misdiagnosed bipolar spectrum disorder patient treated all the time with antidepressant monotherapy.

Interestingly, during the first major depressive episode in her life the patient was also treated with amytriptiline monotherapy and with 125 mg/day had a significant improvement, without switch to hypomania/mania. Hypomanic switch during rTMS combined with SD and followed by manic switch that occurred in a follow-up period, after the last major depressive episode, could be similar to reports of new onset of bipolar disorder during rTMS in patients previosely thought to have unipolar illness [14].

Bipolar affective disorder symptoms onset peaks in much younger age and it happens rarely that a patient is first time diagnosed as bipolar at the age of 53. Clinicians also know this sometimes happens considering the fact that many patients use to come on treatment only during depression phase and almost never come during hypomania when their subjective feeling is `high`, insight is poor and they often deny being ill at all. Family members are also happy to see a patient cheerful and active after severe suffering during depression phase, and sometimes hypomania episodes are so long and frequent that they see a patient as sick only during depression and as `normal – that is he/she – during hypomania. Clinical experience often shows that proper diagnoses of bipolar affective disorder have long delays, sometimes more than 10 years [15].

Nedjat and Folkerts [16] reported transient hypomanic symptoms during high frequency rTMS of the left PFC in 3 of 50 healthy volunteers.

Most of rTMS studies reporting on switch to hypomania/mania used high frequencies of stimulation. Until now, to our knowledge, only a few studies using low frequencies of stimulation in depression reported switch to hypomania/mania [17–19].

Ella et al. [17] reported two cases of manic switch during slow (1 Hz) rTMS treatment of the right DLPFC in resistant major depression, but the number of stimuli *per* session they used (1,200 stimuli/day) was much higher than we used (300 stimuli/day), and was applied during 3 weeks (15 sessions); in both cases switch occurred few days after the last sessions, that was similar to our case.

One study used bilateral rTMS (high over the left DLPFC and low over the right DLPFC) to enhance antidepressant outcome but a patient switched to mania on day 7 of stimulation [18].

Fitzgerald et al. [19] in a double-blind, parallel design study reported one switch to mania with stimulation of 1Hz, 100% RMT, 300 stimuli/session (in a group stimulated with 10 Hz was no switch).

Sakkas et al. [20] in their study protocol used more aggressive stimulation with 20Hz, 110% RMT, 1600 stimuli/ session, two sessions/day and reported one case of hypomania and one case of mania (one of them was in age of 55 first time experienced manic symptoms related to rTMS, similarly to our patient). This report definitely shows that mania-induced potential of rTMS correlates with the intensity of rTMS, but our protocol with less intensive stimulation also resulted in switch to hypomania.

Conclusion

Our case report shows that a combination of rTMS and partial sleep deprivation added to antidepressant may have strong antidepressive synergistic effect even with potential to induce hypomanic switch.

In the treatment of resistant depression clinicians always should be aware of possible unrecognized bipolar disorder, or, in other words, that bipolar depression is often a treatment-resistant depression.

Further controlled studies should give more precise safety guidelines and optimal tretment strategies in cases of hypomania/mania induced by rTMS; even a bit flexible individual strategies should still be the base of treatment of every particular patient with bipolar depression.

Acknowledgment

This research was partially supported by grants from the Ministry of Education, Science and Technological Development of the Republic of Serbia (Project No. 41014) and the Ministry of Defense of the Republic of Serbia (Project MFVMA/12/13-15).

R E F E R E N C E S

1. *Bond DJ, Noronha MM, Kauer-Sant'Anna M, Lam RW, Yatham LN*. Antidepressant-associated mood elevations in bipolar II disorder compared with bipolar I disorder and major depressive disorder: a systematic review and meta-analysis. J Clin Psychiatry 2008; 69(10): 1589−601.
2. *Akiskal HS, Hantouche EG, Allilaire JF, Sechter D, Bourgeois ML, Azorin JM,* et al. Validating antidepressant-associated hypomania (bipolar III): a systematic comparison with spontaneous hypomania (bipolar II). J Affect Disord 2003; 73(1−2): 65−74.
3. *Padberg F, George MS*. Repetitive transcranial magnetic stimulation of the prefrontal cortex in depression. Exp Neurol 2009; 219(1): 2−13.
4. *Fitzgerald PB, Huntsman S, Gunewardene R, Kulkarni J, Daskalakis ZJ*. A randomized trial of low-frequency right-prefrontal-cortex transcranial magnetic stimulation as augmentation in treatment-resistant major depression. Int J Neuropsychopharmacol 2006; 9(6): 655−66.
5. *Krstic J, Diligenski V, Ilic TV*. Low-frequency repetitive transcranial magnetic stimulation conjugated with partial sleep deprivation in treatment of major depression-pilot study. Clin Neurophysiology 2010; 121(4): e9−e10.
6. *Colombo C Benedetti F, Barbini B, Campori E, Smeraldi E*. Rate of switch from depression into mania after therapeutic sleep deprivation in bipolar depression. Psychiatry Res 1999; 86(3): 267−70.
7. *Xia G, Gajwani P, Muzina DJ, Kemp DE, Gao K, Ganocy SJ*, et al. Treatment emergent mania in unipolar and bipolar depression: focus on repetitive transcranial magnetic stimulation. Int J Neuropsychopharmacol 2008; 11(1): 119−30.
8. *Wu JC, Gillin JC, Buchsbaum MS, Schachat C, Darnall LA, Keator DB,* et al. Sleep deprivation PET correlations of Hamilton symptom improvement ratings with changes in relative glucose metabolism in patients with depression. J Affect Disord 2008; 107(1−3): 181−6.
9. *Smith DF, Jakobsen S*. Molecular tools for assessing human depression by positron emission tomography. Eur Neuropsychopharmacol 2009; 19(9): 611−28.
10. *Kimbrell TA, Dunn RT, George MS, Danielson AL, Willis MW, Repella JD*, et al. Left prefrontal-repetitive transcranial magnetic stimulation (rTMS) and regional cerebral glucose metabolism in normal volunteers. Psychiatry Res 2002; 115(3): 101−13.
11. *American Psychiatric Association*. Diagnostic and statistic manuel of mental disorders. 4th ed. Text revision. Washington, DC: American Psychiatric Association; 2000.
12. *Pascual-Leone A, Rubio B, Pallardo F, Catala MD*. Rapid-rate transcranial magnetic stimulation of left dorsolateral prefrontal cortex in drug-resistant depression. Lancet 1996; 348(9022): 233−7.
13. *Giedke H, Schwarzler F*. Therapeutic response of sleep deprivation in depression. Sleep Med Rew 2002; 6(5): 361−77.
14. *Rachid F, Bertschy G*. Safety and efficacy of repetitive transcranial magnetic stimulation in the treatment of depression: a critical appraisalof the last 10 years. Neurophysiol Clinique 2006; 36(3):157−83.
15. *Hirschfeld RM, Lewis L, Vornik LA*. Perceptions and impact of bipolar disorder: how far have we really come? Results of the national depressive and manic-depressive association 2000 survey of individuals with bipolar disorder. J Clin Psychiatry 2003; 64(2): 161−74.
16. *Nedjat S, Folkerts HW*. Induction of a reversible state of hypomania by rapid-rate transcranial magnetic stimulation over the left prefrontal lobe. J ECT 1999; 15(2): 166−8.
17. *Ella R, Zwanzger P, Stampfer R, Preuss UW, Muller-Siecheneder F, Moller HJ,* et al. Switch to mania after slow rTMS of the right prefrontal cortex. J Clin Psychiatry 2002; 63(3): 249.
18. *Hausmann A, Kramer-Reinstadler K, Lechner-Schoner T, Walpoth M, Rupp CI, Hinterhuber H*, et al. Can bilateral prefrontal repetitive transcranial magnetic stimulation (rTMS) induce mania? A case report. J Clin Psychiatry 2004; 65(11): 1575−6.
19. *Fitzgerald PB, Brown TL, Marston NA, Daskalakis ZJ, De CA, Kulkarni J*. Transcranial magnetic stimulation in the treatment of depression: a double-blind, placebo-controlled trial. Arch Gen Psychiatry 2003; 60(10): 1002−8.
20. *Sakkas P, Mihalopoulou P, Mourtzouhou P, Psarros C, Masdrakis V, Politis A*, et al. Induction of mania by rTMS: report of two cases. Eur Psychiatry 2003; 18(4): 196−8.

Received on July 7, 2012.
Revised on August 13, 2012.
Accepted on August 16, 2012.