Neuroendocrinology Letters No.4 August Vol.26, 2005

CASE REPORT

Repetitive transcranial magnetic stimulation in a patient suffering from depression and rheumatoid arthritis: Evidence for immunmodulatory effects

Berthold Langguth*, Susanne Braun*, Josef M Aigner, Michael Landgrebe*, Jutta Weinerth, Göran Hajak* & Peter Eichhammer***

* Department of Psychiatry, Psychosomatics and Psychotherapy, University of Regensburg, Germany,
** Department of Rheumatology, Hospital of Barmherzige Brüder, Regensburg, Germany

Correspondence to: Berthold Langguth, MD
Department of Psychiatry, Psychosomatics and Psychotherapy
University of Regensburg
Universitaetsstraße 84, 93053 Regensburg – Germany
PHONE: +49-941-941 2099 FAX: +49-941-941 2075
EMAIL: Berthold.Langguth@medbo.de

Submitted: May 13, 2005 *Accepted: June 21, 2005*

Key words: **Transcranial magnetic stimulation, depression, immunmodulation**

Neuroendocrinol Lett 2005; **26**(4):314–316 **PMID:** 16136019 NEL260405C02 ©Neuroendocrinology Letters **www.nel.edu**

Abstract

Repetitive transcranial magnetic stimulation (rTMS) has been suggested as antidepressive treatment strategy [1]. The mechanism of action by which the antidepressive effect is brought about remains unclear at present. Here, we report findings in a patient suffering from recurrent major depression and rheumatoid arthritis. Improvement of depressive symptoms during 20 Hz rTMS of the left dorsolateral prefrontal cortex was repeatedly associated with a systemic inflammatory reaction, suggesting that rTMS induced an immunmodulatory effect.

Case report

A 70-year-old woman has been suffering from recurrent major depressive disorder with psychotic symptoms since she had given birth to her first child 36 years ago. One year later a seronegative rheumatoid arthritis (RA) was diagnosed. Without any specific drug treatment there was no relapse of the RA during the last two years prior to admission.

The current severe depressive episode started 12 months prior to admission after a stable interval of ten years. Three adequate antidepressant trials did not result in clinical improvement and over the last six months depressive and psychotic symptoms gradually increased. The medication (maprotiline 150 mg, lithium carbonate 400 mg, olanzapine 5 mg) was stable for 4 weeks before rTMS. The patient underwent 11 rTMS sessions within two weeks at the following stimulation parameters: left dorsolateral prefrontal cortex, 20 Hz, 90% of motor threshold intensity, 2000 stimuli/day. During the second week of rTMS treatment the patient improved rapidly and at the end of rTMS treatment depressive and psychotic symptoms almost completely disappeared (Hamilton Rating Scale for Depression (HAM-D) pre-rTMS: 29, HAM-D post-rTMS: 2). Simultaneous with the improvement of depressive symptoms the patient reported a relapse of her rheumatoid arthritis with generalized joint pain. After oral treatment with valdecoxib she recovered and was discharged from the hospital. At that time she was free from depressive symptoms. However, her condition remained only stable for several days, before she developed again a severe depressive episode with psychotic symptoms. She was hospitalized again and antidepressant treatment was changed to 75 mg of

imipramine (a higher dosage was not tolerated by the patient due to orthostatic side effects), 3 mg of haloperidol and 3 mg of lorazepam with only slight clinical improvement. Two weeks after admission the patient was referred again to rTMS treatment. 16 sessions with identical stimulation parameters were applied. During this second course of rTMS, immune activity was monitored by measuring serum concentrations of inflammatory parameters (C-reactive proteine (CRP), soluble interleukin-2-receptor (sIL-2R), Interleukin 6 (IL6), Interleukin 10 (IL10) and tumor necrosis factor alpha (TNF alpha)). During the second week of rTMS there was again a rapid improvement of depressive symptoms as well as an acute relapse of the RA (Hamilton Rating Scale for Depression (HAM-D) pre-rTMS: 32, HAM-D after 8 sessions rTMS: 2, HAM-D after 16 sessions rTMS: 6). An acute symmetrical inflammation of both knees and of the small joints of both hands was verified by a certified rheumatologist. Laboratory tests demonstrated an increase of CRP, IL6 and sIL2R, thus pointing to a generalized inflammatory reaction. Table 1 summarizes clinical and laboratory parameters during rTMS treatment. During the third week of rTMS lorazepam was discontinued and haloperidol was reduced to 1 mg/day. Apart from slight sleeping disturbances the condition of the patient remained stable and she was discharged from the hospital with complete remission of her depressive episode. During a follow-up period of two months the patient remained free of any depressive or psychotic symptoms, but reported lasting arthritic pain in her knees.

Discussion

The possibility of a pure coincidence of rTMS treatment, spontaneous remission of depression and inflammatory reaction can be largely ruled out by the fact that the closed temporal link between rTMS, recovery from depression and acute inflammatory activation was reproducible. Compared to the large body of literature about complex interactions between depression and the immune system [5], the knowledge about rTMS effects on immune system activity is very limited. In rats high frequency rTMS resulted in a downregulation of hypothalamic-pituitary adrenal (HPA) axis activity [2,3,4]. In depressed patients early findings of a normalization of the dexamethason suppression test after successful rTMS treatment [7] contrast with recent data of a persisting HPA system hyperactivity after rTMS treatment independent from the clinical outcome [9]. One animal study which investigated the impact of rTMS on inflammatory mediators did not find any effect of long-term high-frequency rTMS on the mRNA expression of interleukin (IL)-1beta, IL-6 or cyclooxygenase 2 [6].

The enhanced inflammatory reactivity in our patient with RA may have been allowed to detect rTMS effects on immune system activity, which remain undetected in other patients. We are aware that we can not rule out the possibility that the inflammatory reaction in our patient is only related to the recovery from depression and not to rTMS treatment, thus representing a pure epiphenomenon of rTMS treatment. However, never before recovery from a depressive episode in this patient was related to such a simultaneous relapse of RA, how it was now observed two times during rTMS. This close temporal relation between recovery from depression and inflammatory reaction, which was exclusively observed during rTMS supports a causal role for rTMS treatment.

Puzzling is the fact that both the acute inflammatory reaction as well as the fast and complete remission in a patient with medication resistant severe psychotic depression are unusual during rTMS treatment. This may lead to speculation as to whether the extraordinary therapeutic response may be linked to the distinct activation of inflammatory mediators. Lack of a sham condition and the single patient report limit this interpretation.

Table 1 Clinical and laboratory parameters before, during and after the second course of repetitive transcranial magnetic stimulation

	Pre rTMS	After 8 sessions rTMS	After 16 sessions rTMS
HAM-D	32	2	6
Bf-S	43		2
CRP	6.7 mg/l	25 mg/l	30 mg/l
IL 6	3.4 ng/l	15 ng/l	
IL 10	3.6 pg/ml	3.0 pg/ml	
SIL-2R	1225 kU/l	1662 kU/l	
TNF alpha	9 ng/l	10 ng/l	

HAM-D: Hamilton Rating Scale for Depression; Bf-S: Befindlichkeitsskala nach Zerssen (subjective rating scale for the assessment of quality of life [8]); CRP: C-reactive proteine; sIL-2R: soluble interleukin-2-receptor, IL6: Interleukin 6; IL10: Interleukin 10; TNF alpha: tumor necrosis factor alpha.

REFERENCES

1 Gershon AA, Dannon PN, Grunhaus L. Transcranial magnetic stimulation in the treatment of depression. American Journal of Psychiatry. 2003; **160**:835-845.
2 Hedges DW, Salyer DL, Higginbotham BJ, LundTD, Hellewell JL, Ferguson D, Lephart ED. Transcranial magnetic stimulation (TMS) Effects on Testosterone, Prolactine, and Corticosterone in Adult Male Rats. Biological Psychiatry. 2002; **51**:417-421.
3 Keck ME, Engelmann E, Muller MB, Henninger MS, Hermann B, Rupprecht R, Neumann ID, Toschi N, Landgraf R, Post A. Repetitive transcranial magnetic stimulation induces active coping strategies and attenuates the neuroendocrine stress response in rats. Journal of Psychiatric Research. 2000; **34**:265-276.
4 Keck ME, Welt T, Post A, Muller MB, Toschi N, Wigger A, Landgraf R, Holsboer F, Engelmann M. Neuroendocrine and behavioural effects of repetitive transcranial magnetic stimulation in a psychopathological animal model are suggestive of antidepressant-like effects. Neuropsychopharmacology 2001; **24**:337-349.
5 Leonhard B. Stress, Depression and the Activation of the Immune System. World Journal of Biological Psychiatry. 2000; **1**:17-25.
6 Okada K, Matsunaga K, Yuhi T, Kuroda E, Yamashita U, Tsuji S. The long-term high-frequency repetitive transcranial magnetic stimulation does not induce mRNA expression of inflammatory mediators in the rat central nervous system. Brain Research. 2002; **957**:37-41.
7 Pridmore S. Rapid transcranial magnetic stimulation and normalization of the dexamethasone suppression test. Psychiatry and Clinical Neurosciences. 1999; **53**:33-37.
8 Zerssen, D.v.. Beschwerdeskalen bei Depressionen. Therapiewoche. 1973; **46**:4426-4440.
9 Zwanzger P, Baghai TC, Padberg F, Ella R, Minov C, Mikhaiel P, Schule C, Thoma H, Rupprecht R. The combined dexamethasone-CRH test before and after repetitive transcranial magnetic stimulation (rTMS) in major depression. Psychoneuroendocrinology 2003; **28**:376-385.