patients with catatonia associated with mood disorders has remained stable.[3] This may, in part, be due to use of antipsychotics and involvement of a GABAergic mechanism (animal studies have shown GABA modulation of GABA receptors in animals treated on antipsychotics for a period of time).[5] This may support a greater preponderance for GABAergic deficit in mood disorder patients then in schizophrenia patients. The mechanism is not clear on how valproic acid works, but it is clear that it increases CNS GABA. Studies have shown that valproic acid enhances GABA level and neuronal GABA responsiveness. The use of valproic acid should be considered an option for treatment of catatonic patients, particularly those with mood disorders.

Richard Bowers, D.O.
Sarbjot Singh Ajit, M.D
Department of Psychiatry, University of Missouri, Columbia, Mo.

References

1. Northoff G: What catatonia can tell us about "top-down modulation": a neuropsychiatric hypothesis. Behav Brain Sci 2002; 25:555–604
2. Brambilla P, Perez J, Barale F, et al: Gabaergic dysfunction in mood disorders. Mol Psychiatry 2003; 8:721–737
3. Reddick B, Stern TA: Catatonia, neuroleptic malignant syndrome, and serotonin syndrome, in Massachusettes General Hospital Psychiatry Update and Board Preparation, 2nd ed. Edited by Stern TA, Herman JB. New York, McGraw-Hill, 2000, pp 219–226
4. Petty F, Sherman AD: Plasma GABA levels in psychiatric illness. J Affect Disord 1984; 6:131–138
5. Wassel A, Baker J, Kochan LD: GABA and schizophrenia: a review of basic science and clinical studies. J Clin Psychopharmacol 2003; 23:601–640
6. Kruger S , Braunig P: Intravenous valproic acid in treatment of severe catatonia. J Neuropsychiatry Clin Neurosci 2001; 13:303–304

Stimulating Research: A Prospective, Randomized, Double-Blind, Sham-Controlled Study of Slow Transcranial Magnetic Stimulation in Depressed Bipolar Patients

SIR: Patients with bipolar disorder may spend more than half of their lives experiencing depression.[1] Unfortunately, antidepressant treatment may adversely affect the overall course of bipolar illness, increasing the rates of rapid cycling and inducing chronic depressive states.[2] Menkes et al.[3] showed that slow (F≤1 Hz) repetitive transcranial magnetic stimulation (rTMS) applied to the right dorsolateral prefrontal cortex (DLPFC) proved to be safe and effective in the treatment of unipolar depression. This exploratory study explores safety and efficacy, in bipolar depression.

Case Report

We studied five type I bipolar disorder depressed patients on a stable mood stabilizer regimen without antidepressant treatment. Four subjects were randomly assigned to receive active rTMS, and one was assigned to sham rTMS. Patients were maintained on their medications: lithium (N = 2), risperidone (N = 1), quetiapine (N = 1), divalproex (N = 1), and lamotrigine (N = 1). One patient was on two medications. Treatments were performed using a 9 cm circular coil connected to a Cadwell MES-10 stimulator (Cadwell Laborties, Kennewick, Wash). The coil was placed over the right DLPFC, and 100 consecutive stimuli of slow (1 Hz) rTMS were delivered at 95% of motor threshold. The treatments were scheduled twice a week for four consecutive weeks. Subjects were blind to treatment assignment. The 21-item Hamilton Depression Rating Scale (HAM-D) and Young Mania Rating Scale (YMRS) assessed clinical response weekly for 4 weeks and again 2 weeks after termination of treatment. The rating investigator was blind to treatment assignments.

The active group had three women and one man (average age = 44 years); the placebo subject was a man (45 years old). At the end of the study, subjects receiving rTMS showed greater improvement than the placebo-treated subject. However, throughout the first 4 weeks there was no difference between the groups. One of the subjects did not complete the study. The unequal randomization precluded statistical analysis. There was no evidence of any manic induction as all patients maintained a YMRS = 3. Side effects included unusual feeling, fatigue, memory problems, facial myoclonus, peripheral illusions, flu symptoms, sleep disturbance, dizziness, sore throat, headache, and balance disturbance. The placebo subject reported confusion, dry mouth, and myoclonus.

Comment

This exploratory study suggests that slow right DLPFC rTMS may be beneficial in depressed bipolar patients. The continued improvement from Week 4 to Week 6 suggests this treatment has effects that persist after treatment cessation and that larger future studies of slow rTMS should be extended to 6 weeks' duration, with an increased frequency of administration.

Rebecca L. Tamas, M.D.
Mood Disorders Research Program, University of Louisville School of Medicine, Louisville, Ky.
Daniel Menkes, M.D.
Rif S. El-Mallakh, M.D.
Department of Psychiatry and Behavioral Sciences, University

of Louisville School of Medicine, Louisville, Ky.

References

1. Judd LL, Akiskal HS, Schletter PJ, et al: A prospective investigation ofthe natural history of the long-term weekly symptomatic status of bipolar II disorder. Arch Gen Psychiatry 2003; 60:261–269
2. El-Mallakh RS, Karippot A: Use of antidepressants to treat depression in bipolar disorder. Psychiatr Serv 2002; 53:580–584
3. Menkes DL, Bodnar P, Ballesteros RA, et al: Right frontal lobe slow frequency repetitive transcranial magnetic stimulation (SF r-TMS) is an effective treatment for depression: a case-control pilot study of safety and efficacy. J Neurol Neurosurg Psychiatry 1999; 67:113–115

Hereditary Hemorrhagic Telangiectasia and Psychopathology

SIR: Hereditary hemorrhagic telangiectasia (HHT) is an autosomal dominant vascular dysplasia that affects 1 in 5,000 to 8,000. Its clinical picture comprises nosebleeds, gastrointestinal hemorrhage, mucocutaneous telangiectasia, pulmonary and cerebral arteriovenous malformations, as well as hepatic involvement due to abnormal vascular structures. The clinical significance of this disorder has increased since asymptomatic screening programs have shown a much higher frequency of arteriovenous malformations than was initially suspected.[1] HHT can be the result of mutations in genes on at least two chromosomes. The first is in the gene encoding endoglin (chromosome 9q34; *ENG, HHT1*). The second is in the gene encoding activin A receptor type-like kinase 1 (chromosome *12q13; ALK-1, HHT2*).[2]

There is a paucity in published clinical reports of neuropsychiatric complications despite the frequent cerebral involvement. We describe two patients who were primarily referred for neuropsychiatric evaluation without a suspected association with HHT.

Case Report

A 21-year-old man was referred because of behavioral problems. At the age of 14 he underwent an embolization for a pulmonary arteriovenous malformation. Magnetic resonance imaging (MRI) and angiography of the brain as well as an echography of the liver were normal. The patient and his mother were both suffering from HHT. Genetic analysis demonstrated a mutation in the ENG gene (*HHT1*).

The patient's early development was characterized by abnormal language development and disinhibited behavior. At the age of 14, he was institutionalized because of behavioral disturbances and learning difficulties. Psychological examination (SON-R) showed a total IQ of 74. He showed repetitive and stereotyped behaviors, a qualitative impairment in communication and social interaction, and episodic impulsivity with temper tantrums. In addition, paranoid ideation and hallucinatory experiences were observed. Two years later he developed bizarre behavior and intermittent psychotic symptoms. In subsequent years, his behavior became more disinhibited and aggressive, and he was referred for a neuropsychiatric reevaluation. Somatic examination demonstrated telangiectases on the mucosa of the mouth and nose. Extensive laboratory tests did not show abnormalities except a slight elevation of the liver function tests.

A diagnosis of pervasive developmental disorder and borderline mental retardation was made. Before extensive somatic, neuroradiological, and neuropsychiatric examination could be completed, the patient died suddenly due to a massive pulmonary bleeding. An autopsy was not performed.

Case Report

A 58-year-old woman had been psychiatrically admitted for the first time at the age of 23, most probably because of a psychosis. At the age of 42 she was referred to the outpatient department because she felt overstrained and unable to cope with daily events. At that time, her mood was dysphoric and irritable, her thoughts were chaotic, and she spoke circumlocutorily. No formal psychiatric diagnosis was made. In the subsequent 16 years, no psychiatric intervention was necessary.

Recently, she was admitted because of a manic episode with prominent religious delusions, incoherence of speech, euphoric mood, disinhibited behavior, and poor social judgment. Somatic examination demonstrated multiple telangiectases in the nose and on the tongue and pinpoint telangiectases on the fingertips as well as temporary mild hematuria. Extensive laboratory tests did not show any abnormalities. Neuropsychological examination demonstrated a total IQ of 72 (WAIS-III) and slow mental processing.

MRI scanning of the brain revealed no signs of cerebral complications. A computed tomography (CT) scan of the lungs showed a small arteriovenous malformation with a diameter of 5 mm. Her somatic history mentioned recurrent epistaxis, uterus extirpation, venous varicosities and hypertension. No family history with psychiatric disorders was present. Based on the trials, epistaxis, telangiectasias, and positive family history, the diagnosis of HHT was established that was genetically confirmed as a mutation in the ALK-1 gene (HHT2).

Comment

Although HHT has a relatively high prevalence, it is remarkable that vir-