pediatric anti-NMDA receptor encephalitis strikes us as fashion driven, but it highlights the fact that catatonia is common yet often unacknowledged in children and adolescents (4, 5).

Pediatric patients who meet the criteria for anti-NMDA receptor encephalitis are better served with a diagnosis of catatonia, for which benzodiazepines and ECT are well-established first-line treatments that resolve symptoms quickly and safely. Studies comparing benzodiazepines or ECT with immune therapies in children, adolescents, and adults who meet criteria for catatonia and who test positive for the anti-NMDA receptor antibody are urgently needed (4, 6).

References

1. Chapman MR, Vause HE: Anti-NMDA receptor encephalitis: diagnosis, psychiatric presentation, and treatment. Am J Psychiatry 2011; 168:245–251
2. Wachtel LF, Kahng SW, Dhossche DM, Cascella N, Reti IM: ECT for catatonia in an autistic girl. Am J Psychiatry 2008; 165:329–333
3. Dhossche DM, Shettar SM, Kumar T, Burt L: Electroconvulsive therapy for malignant catatonia in adolescence. South Med J 2009; 102:1170–1172
4. Fink M, Taylor MA: Catatonia: A Clinician's Guide to Diagnosis and Treatment. Cambridge, UK, Cambridge University Press, 2003
5. Dhossche D, Wachtel LE: Catatonia is hidden in plain sight among different pediatric disorders: a review article. Pediatr Neurol 2010; 43:307–315
6. Braakman HM, Moers-Hornikx VM, Arts BM, Hupperts RM, Nicolai J: Pearls & oysters: electroconvulsive therapy in anti-NMDA receptor encephalitis. Neurology 2010; 75:e44–e46

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Response to Dhossche et al. Letter

TO THE EDITOR: Drs. Dhossche, Fink, Shorter, and Wachtel question whether the case of a 16-year-old boy with acute neuropsychiatric disintegration represents anti-NMDA receptor encephalitis or pediatric catatonia. A more appropriate formulation might be that of anti-NMDA receptor encephalitis and pediatric catatonia.

In the case presented, anti-NMDA receptor encephalitis was confirmed with the identification of antibodies to the NR_1/NR_2 subunits of the NMDA receptor in the patient's serum and CSF. As such, the available literature indicated response to a number of immunotherapies, and these were subsequently introduced in the management of this case. While the patient did not respond to corticosteroids, he did experience symptom amelioration first with intravenous immunoglobulin and later rituximab.

Clinical symptoms of catatonia, including excessive motor activity, agitation, aggression, negativism, and mutism, presented at various times for various durations throughout the illness course. A "benzodiazepine challenge test," proposed as a diagnostic assessment tool and a known beneficial treatment in catatonia, resulted in decreased irritability and marginally improved sleep but did not have the immediate and marked effect that would have warranted continued administration at higher doses and more frequent intervals. Because the patient did experience some benefit, 1 mg of lorazepam every 8 hours was continued for a brief period. Much remains to be learned about the symptomatic management of catatonia and other psychiatric manifestations associated with autoimmune encephalitis. Cases such as the one presented here are often protracted, with a number of interventions during the treatment course, making it difficult to establish the effectiveness of any one treatment. Other contributing factors may include the natural course of the illness, the potential for relapse, and evidence that suggests that complete recovery is achieved only with resolution of the underlying immune-mediated process.

ECT has been used on a limited basis in the management of patients with autoimmune encephalitis. As with other therapeutic modalities, direct causality between this treatment intervention and recovery has yet to be established. A majority of the cases in which ECT was used document full recovery only after the underlying disease process was ameliorated, often through tumor removal (1–3). In the case presented here, ECT was not considered as part of the overall management plan for a number of reasons that were both practical and preferential. Colorado, like many other states, has very specific laws regarding the use of ECT, particularly in patients under 18 years old. Colorado Revised Statute 13-20-403 states that under no circumstances shall electroconvulsive treatment be performed on a minor under 16 years old, and while ECT may be performed on adolescents 16–18 years old, two licensed psychiatrists must agree with the treatment plan and a parent or guardian must provide consent. Regardless, most facilities that perform ECT in Colorado elect not to perform this procedure on minors. In this case, the patient's parents were focused on the underlying medical diagnosis; they resented somewhat the fact that their son was being treated on a psychiatric unit; and they hesitated to provide consent for psychotropic medication interventions, preferring first to pursue immune therapies that had demonstrated effectiveness in other cases.

This young man presented with a catatonic disorder as a result of anti-NMDA receptor encephalitis. Aggressive management of the observable symptoms of catatonia due to a general medical condition does not preclude appropriate treatment of the underlying disease process, particularly when, as is the case with the autoimmune encephalitides, the most profound improvements in psychiatric and behavioral symptoms occur when the antibody response is suppressed or reversed.

Studies comparing the impact of immune therapies with symptomatic treatments including psychotropic medications and ECT in anti-NMDA receptor encephalitis are needed to inform the best possible management of these patients.

References

1. Florance NR, Davis RL, Lam C, Szperka C, Zhou L, Ahmad S, Campen CJ, Moss H, Peter N, Gleichman AJ, Glaser CA, Lynch DR, Rosenfeld MR, Dalmau J: Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis in children and adolescents. Ann Neurol 2009; 66:11–18
2. Lee A, Glick DB, Dinwiddie SH: Electroconvulsive therapy in a pediatric patient with malignant catatonia and paraneoplastic limbic encephalitis. J ECT 2006; 22:267–270

3. Kaestner F, Mostert C, Behnken A, Boeckermann I, Ternes F, Diedrich M, Zavorotnyy M, Arolt V, Weckesser M, Rothermundt M: Therapeutic strategies for catatonia in paraneoplastic encephalitis. World J Biol Psychiatry 2008; 9:236–240

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Monitoring Ketamine Treatment Response in a Depressed Patient via Peripheral Mammalian Target of Rapamycin Activation

To the Editor: Most clinically used antidepressants target monoaminergic reuptake mechanisms. However, a limited efficacy and a delayed onset combined with several side effects make the currently available antidepressants less than ideal drugs. Treatment resistance occurs in approximately 15%–20% of depressed patients (1). To improve antidepressant drug efficacy, one line of research has focused on the *N*-methyl-D-aspartic acid (NMDA) receptor and its pathway in order to manipulate glutamatergic neurotransmission. One important signaling event following NMDA receptor stimulation is mammalian target of rapamycin (mTOR) activation that results in the protein's phosphorylation on serine residues 2481 and 2448. The ensuing signaling cascades are important for the induction of neuroplasticity (2).

Ketamine is a hypnotic and analgesic drug used in anesthesia. It is an NMDA receptor noncompetitive antagonist with functions in monoaminergic and cholinergic neuronal transmission. Ketamine improves depressive symptoms in patients with major depressive disorder who are resistant to conventional therapy (3).

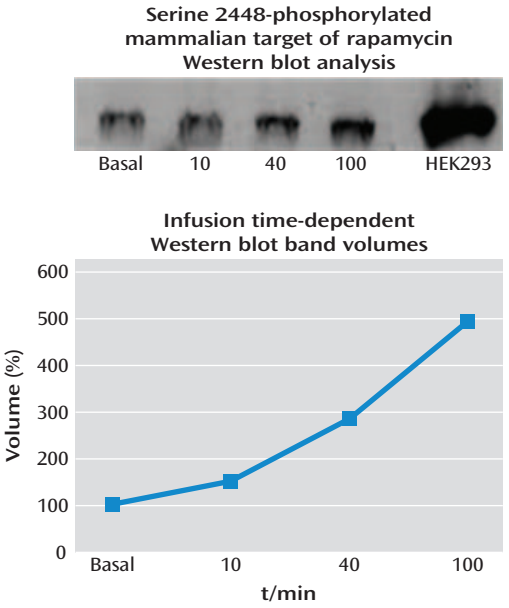
Using the Western blot test analysis of peripheral mononuclear cell protein extracts, we provide for the first time evidence of increased mTOR phosphorylation in a depressed patient after (*S*)-ketamine treatment. The patient's depressive symptoms improved rapidly after an infusion of (*S*)-ketamine and did not return for 24 hours. These results are in line with animal data reporting rapid mTOR phosphorylation on serine residue 2448 in the prefrontal cortex of a rat after ketamine treatment (4). Our data provide preliminary evidence that findings in the rat have the potential to translate to clinical studies monitoring ketamine treatment response in patients.

Case Report

A 56-year-old woman with major depressive disorder showed considerable resistance to conventional antidepressive therapy. Over the course of a 9-month period of high-dosage standard antidepressant and augmentation treatments, including a combination of antidepressant drugs (citalopram, escitalopram, amitriptyline, clomipramine, venlafaxine, and moclobemide), atypical antipsychotics, and benzodiazepines, we observed no improvement of symptoms. Based on these negative results, we decided to give 0.25 mg/kg of (*S*)-ketamine intravenously with a 40-minute injection duration (3). Written informed consent was obtained from the patient after the procedure had been fully explained. Blood was collected at baseline and 10 minutes, 40 minutes, and 100 minutes after initiating the (*S*)-ketamine infusion. Before, during, and after the infusion, the patient was evaluated for depression using the Beck Depression Inventory (BDI), the Montgomery-Åsberg Depression Rating Scale (MADRS), and the Brief Psychiatric Rating Scale. The depressive and anxiety parameter scores rapidly improved after (*S*)-ketamine infusion, and the best results were observed at the end of the treatment (baseline scores: MADRS=29/BDI=18; posttreatment scores: MADRS=4/BDI=3). Acute dissociative symptoms monitored using the Clinician-Administered Dissociative States Scale were slightly elevated during the treatment (baseline=0, posttreatment=12) and returned to basal levels immediately after the end of treatment. No psychotic or delusional symptoms were recorded during or after the (*S*)-ketamine treatment.

In a Western blot analysis of peripheral blood cells, we observed a continued increase of mTOR phosphorylation on serine 2448 starting from baseline up to 100 minutes after the start of the (*S*)-ketamine infusion (Figure 1).

FIGURE 1. Western Blot Analysis of Peripheral Blood Cells in a Study of (*S*)-Ketamine Infusion for the Treatment of Depressive Symptoms[a]



[a] Blood mononuclear cell protein extracts were analyzed at baseline and 10 minutes, 40 minutes, and 100 minutes after the 40-minute (*S*)-ketamine infusion was begun. For comparison, protein extracts from HEK293 cells were analyzed on the same gel. The protein band is detected at the expected molecular weight of 250 kDa.

References

1. Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D, Niederehe G, Thase ME, Lavori PW, Lebowitz BD, McGrath PJ, Rosenbaum JF, Sackeim HA, Kupfer DJ, Luther J, Fava M: Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. Am J Psychiatry 2006; 163:1905–1917
2. Hoeffer CA, Klann E: mTOR signaling: at the crossroads of plasticity, memory, and disease. Trends Neurosci 2009; 33:67–75
3. Zarate CA Jr, Singh JB, Carlson PJ, Brutsche NE, Ameli R, Luckenbaugh DA, Charney DS, Manji HK: A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. Arch Gen Psychiatry 2006; 63:856–864