Biological Psychiatry

Seronegative Anti–*N*-Methyl-D-Aspartate Receptor Encephalitis

To the Editor:

We describe a case of a young woman who was admitted to a psychiatric ward with labile mood and psychosis. She developed autonomic instability and profound catatonia that was treated partially with electroconvulsive therapy (ECT). Magnetic resonance imaging (MRI) of the brain was normal, and electroencephalography (EEG) showed nonspecific findings. Her serum was negative for anti-*N*-methyl-D-aspartate (anti-NMDA) receptor antibodies, and her condition remained untreated. She remained symptomatic for several months and repeat serum samples were taken, paired with cerebrospinal fluid (CSF) samples. These were positive and the diagnosis of anti-NMDA encephalitis was made.

Anti-NMDAR encephalitis is an autoimmune disorder of uncertain incidence with a mortality rate of up to 25% (1). In 2005, Vitaliani *et al.* (2) described four young women with ovarian teratomas with a syndrome of neurologic symptoms, acute psychiatric disturbance, and autonomic instability. It has since been recognized that such presentations can be attributed to anti-NMDAR encephalitis. It is seen predominantly, but not exclusively, in young women (1); it also has been described in pediatric patients (3). A tumor is present in 59% of patients, most commonly an ovarian teratoma (1).

Most patients have a prodromal illness that progresses to an acute psychiatric presentation, ranging from anxiety to manic psychosis (1). Short-term memory impairment and language abnormalities also have been reported (4). Altered responsiveness ranging from agitation to catatonia follows. Abnormal movements, central hypoventilation, and seizures are common (4). Autonomic instability, often in the form of cardiac dysrhythmias, is frequent.

Diagnosis is by NMDAR antibody studies in the serum or CSF. Higher titers are associated with poorer outcome and the presence of a tumor. The sensitivity of testing is greater in CSF compared with serum (5). Treatment includes immunotherapy and tumor removal if indicated (6). Partial recovery has been noted with ECT. The varied presentation of anti-NMDAR encephalitis means that patients can present to different medical professionals, including general practitioners, psychiatrists, medical physicians, and neurologists.

Patient consent was obtained to report this case. A 17-year-old woman presented to her general practitioner with low mood; 6 weeks later, she was noted to be behaving bizarrely, with emotional lability and a greatly increased volume of speech. She was admitted to a psychiatric hospital. Physical examination and blood tests showed no abnormalities. Her mood was labile, with prominent restlessness and racing thoughts. She described persecutory delusions and auditory hallucinations.

She had no significant past medical or psychiatric history and no preceding viral symptoms. She had been working in a day care center. She reported occasional smoking and alcohol drinking. She achieved all of her developmental milestones in a timely fashion. However, there was a family history of affective psychosis. A diagnosis of mixed affective state was made.

She was started on quetiapine but continued to present with perseveration, persecutory delusions, and increased speech. Periods of lucidity were interspersed with marked fluctuations in mood and significant disorientation and confusion. This presentation continued for 3 weeks, when she developed intermittent catatonia, which was partially responsive to lorazepam. She then had episodes of tachycardia and hyperthermia as well as hypoventilation and dysphagia. Because of ongoing catatonia, antipsychotic medications were stopped. Neurologic examination revealed occasional myoclonic jerks.

Neurologic advice was sought. Serum antibody tests against NMDARs and voltage-gated potassium channels, MRI brain scan, and EEG were performed. Blood test results and MRI brain scan were normal. The EEG showed nonspecific bilateral slow-wave activity prominent in frontal areas. Her catatonia worsened, with verbal reduction and lack of spontaneous blinking. She was poorly orientated and lacked insight. She began a course of ECT, which partially reduced her catatonia, paranoia, and lability. However, there was persistent disorientation and confusion. Her presentation continued and her case was discussed with neurologists, who obtained paired serum and CSF samples. Both were positive for anti-NMDA receptor antibodies. She underwent a computed tomography scan which excluded a tumour.

She was started on immunoglobulin therapy, with neuropsychology input indicating improvement in her presenting symptoms. She continues on treatment and has returned to part-time work.

This case raises the question of diagnostic testing. Initial serum antibodies were negative and her condition remained untreated. Repeat serum testing, paired with CSF samples, were positive for anti-NMDA receptor antibodies. In a recent report in *The British Journal of Psychiatry*, Beck *et al.* (7) hypothesized, with reference to Steiner *et al.* (8), that seropositivity occurs in the acute stage of illness, and it is possible that seronegativity is related to the timing of the blood test. Although this hypothesis is in reference to chronic psychotic illness, the present case illustrates seronegativity in the acute stage of illness. This case highlights that seronegativity in the acute phase does not exclude a diagnosis of anti-NMDAR encephalitis.

A recent review article in *The British Journal of Psychiatry Bulletin* suggests controversy over whether serum or CSF should be tested (9). The most consistent findings are of CSF testing having higher sensitivity compared with serum testing (5). This case illustrates an example of a false negative blood result in an unwell patient resulting in delayed diagnosis and treatment. Therefore, paired serum and CSF sampling should be considered in cases of sufficient clinical suspicion regardless of initial blood results. This case supports the view held by Barry *et al.* (9) that MRI is often normal and EEG findings are nonspecific.

This patient achieved partial improvement in symptoms of catatonia, paranoia, and lability with ECT. Such partial improvement has been previously noted with ECT, related to modulation of NMDARs (10,11). Despite this result with ECT, the treatment of choice is immunotherapy and tumor removal.

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Partial improvement with ECT does not preclude a diagnosis of anti-NMDAR encephalitis or any organic illness and should be evaluated in the context of the clinical picture.

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