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Case Report

Atypical schizophrenia with anti-*N*-methyl-D-aspartate receptor antibody positivity treated with modified electroconvulsive therapy

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A 56-year-old woman who was diagnosed with schizophrenia at 30 years old presented with acute exacerbation of psychiatric symptoms. She was treated with increasing doses of antipsychotics owing to suspicion of worsening schizophrenia. Thereafter, she rapidly developed pyrexia, marked sweating, tremors, myotonia/postural abnormalities, stupor with akinesia, and decreased blood pressure, suggesting neuroleptic malignant syndrome (NMS) caused by the increased dose of antipsychotics. As a differential diagnosis, we considered malignant catatonia caused by schizophrenia. In addition, because the patient showed atypical symptoms and an atypical course of schizophrenia, we considered malignant catatonia caused by an organic disease and performed an antibody test of her cerebrospinal fluid. Modified electroconvulsive therapy was performed to treat the NMS, and the patient's psychiatric and somatic symptoms improved. During treatment, she exhibited positivity for anti-*N*-methyl-D-aspartate (NMDA) receptor antibodies. However, she did not meet the consensus criteria for anti-NMDA receptor encephalitis. Thus, as a final diagnosis, we considered NMS of atypical schizophrenia with anti-NMDA receptor antibody positivity. Anti-NMDA receptor encephalitis can be misdiagnosed as schizophrenia because of similar psychiatric symptoms. This case emphasizes the importance of testing for anti-NMDA receptor antibodies in patients with an atypical course of schizophrenia.

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Introduction

Anti-*N*-methyl-D-aspartate (NMDA) receptor encephalitis is a category of autoimmune encephalitis that causes a variety of psychiatric symptoms (e.g., anxiety, lethargy, apathy, depression, excitement, hallucinations, and delusions)[1]. The psychiatric symptoms of NMDA receptor encephalitis are similar to those of primary psychiatric disorders (e.g., schizophrenia and bipolar disorder) and are often misdiagnosed[2,3]. In misdiagnosed cases, patients may receive unnecessary antipsychotic treatment because of suspected primary psychiatric disorders. Consequently, they may suffer from serious side effects of these medications. In addition, some patients with anti-NMDA receptor encephalitis exhibit catatonia[4]. Catatonia is a syndrome characterized by akinesia, mutism, stupor, and catalepsy, which also occurs in various psychiatric disorders such as schizophrenia and mood disorders[5]. Catatonia with autonomic symptoms is malignant (malignant catatonia); therefore, delay in treatment sometimes results in a fatal outcome[6]. Neuroleptic malignant syndrome (NMS) is a life-threatening condition associated with the use of psychotropic medications. Catatonia and NMS share similar clinical features, pathology, and treatment[7]. Benzodiazepines and modified electroconvulsive therapy (mECT) are recom-

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mended as treatments for catatonia caused by primary psychiatric disorders[8, 9]. For the treatment of NMS, however, dantrolene sodium is used, but the efficacy of benzodiazepines and mECT has also been reported[10]. Here, we present a case of mECT treatment for catatonia/NMS in a patient with atypical schizophrenia with anti-NMDA receptor antibody positivity.

Case presentation

A 56-year-old woman had a medical history of schizophrenia with no relevant family history. She was the eldest daughter among three siblings. At the age of 30, after giving birth to her first child, the patient started to exhibit psychiatric symptoms such as hyperkinesia, anxiety, paranoia, insomnia, and mild hallucinations. The patient visited a psychiatric hospital and was diagnosed with schizophrenia. Her symptoms disappeared after treatment with a small dose of risperidone (2 mg/day). After her symptoms improved, continuous antipsychotic medication was discontinued. She resumed risperidone only when symptoms such as insomnia recurred. She lived a stable life for many years. At the age of 56, fatigue was abruptly observed. A few days later, auditory hallucinations, thought insertions, delusions, and intense excitement were observed. She developed rigidity, and her body movements gradually became difficult. She was treated in a psychiatric hospital, and pharmacotherapy with antipsychotics was administered on suspicion of worsening schizophrenia. The dose of antipsychotics was increased 2 months after treatment was initiated (perospirone: 8 mg/day and aripiprazole: 12 mg/day). Thereafter, the patient had pyrexia of approximately 39°C. In addition, marked excessive sweating, tachycardia, tremors, stiffness, catalepsy, waxy flexibility, dysphagia, and myotonia/postural abnormalities rapidly developed. The patient exhibited stupor with akinesia and had decreased blood pressure, leading to a state of shock. Brain magnetic resonance imaging (MRI) showed no specific results (Figure 1). Electroencephalography (EEG) showed slow waves in the frontal lobe, which was consistent with impaired consciousness. No epileptic EEG signal was observed. Serum laboratory data showed an elevated white blood cell count, C-reactive protein level, and creatine kinase level; cerebrospinal fluid (CSF) laboratory data indicated a mildly elevated lactate dehydrogenase level, but no clear specific findings were obtained. The serum and CSF laboratory data are summarized in Table 1 and Table 2. The clinical manifestations indicated NMS caused by an increased dose of antipsychotic medication. The diagnosis of NMS was made using international consensus diagnostic criteria[11, 12].

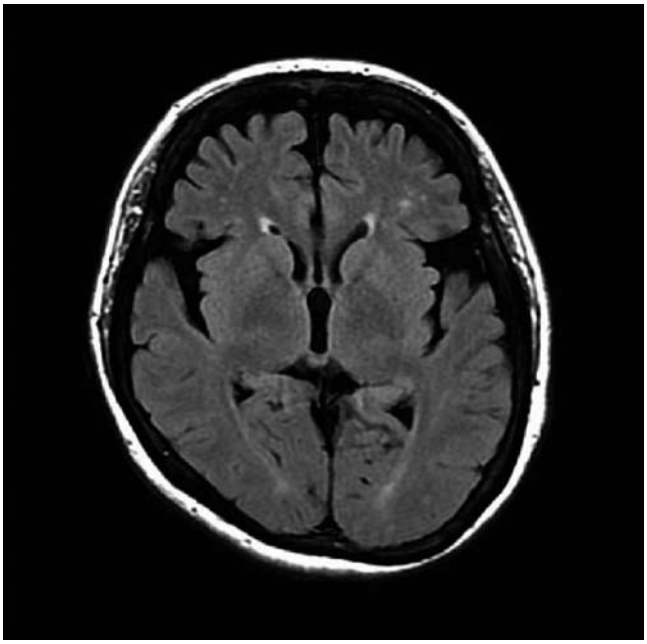

Figure 1. Brain magnetic resonance imaging (MRI)
Axial MRI. Mild atrophy was present in the frontal lobe but was not a specific finding.

Differential diagnosis

As a differential diagnosis, we considered malignant catatonia caused by schizophrenia. In addition, because the patient showed atypical symptoms and an atypical course of schizophrenia, we considered malignant catatonia caused by an organic disease and performed qualitative analysis of anti-NMDA receptor antibodies in her CSF. The diagnosis of catatonia was made using the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition[13].

Treatment

Dantrolene (40−80 mg/day) was used as a muscle relaxant for myotonia, and lorazepam (3 mg/day) was used to treat NMS/malignant catatonia. However, the effect of these treatments was limited and were therefore terminated after 1 week of administration. Next, using a Thymatron® system (Somatic LLC, Lake Bluff, IL, USA), mECT was performed 10 times for NMS/malignant catatonia (anesthetic: propofol, 30 mg; muscle relaxant: rocuronium, 30 mg; stimulus dose: 30%−100%; frequency: two times/week). No adverse events were observed in any of the 10 sessions. After the course of mECT, the patient was found to be positive for anti-NMDA receptor antibodies. Although whole-body scanning including pelvic MRI was performed to identify the source of antibody

Table 1. Serum laboratory data

Laboratory test	Value		
	Normal range	Before mECT	After mECT
WBC (10^3/μL)	3.5−9.5	37.4	7.6
Hb (g/dL)	13.0−16.5	10.6	11.7
PLT (10^4/μL))	15.0−35.0	40	309
BUN (mg/dL)	8−22	23	11
CRE (mg/dL)	0.6−1.1	1.01	0.47
T-Bil (mg/dL)	0.3−1.2	3	0.5
AST (U/L)	7−42	119	16
ALT (U/L)	10−35	41	13
LDH (U/L)	120−240	402	165
CK (U/L)	30−172	375	18
CRP (mg/dL)	<0.3	33.97	0.33

Abbreviations: mECT, modified electroconvulsive therapy; WBC, white blood cell count; Hb, hemoglobin; PLT, platelet cells; BUN, blood urea nitrogen; CRE, creatinine; T-Bil, total bilirubin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; CK, creatine kinase; CRP, C-reactive protein.

Table 2. Cerebrospinal fluid laboratory data

Lab test	Value	
	Normal range	Before mECT
Appearance and Color	Clear, colorless	Clear, colorless
WBC (/mm^3)	0−8	10
RBC (/mm^3)	<1	0
Mononuclear cells (%)	98−100	80
Polymorph cells (%)	0−1	20
GLU (mg/dL)	50−70	72
Cl (mEq/L)	120−125	125
TP (mg/dL)	15−45	32
LDH (U/L)	<25	37

Abbreviations: mECT, modified electroconvulsive therapy; WBC, white blood cell count; RBC, red blood cell count; GLU, glucose; Cl, chloride; TP, total protein; LDH, lactate dehydrogenase.

production, no neoplastic lesions were found. After mECT, plasmapheresis was provided two times and immunoglobulin administration provided once.

Outcome and follow-up

The patient's stuporous condition gradually improved after mECT initiation, and the psychiatric and somatic symptoms including myotonia also improved. At the end of the mECT course, her serum laboratory data improved, and conversations and activities of daily living became possible. Finally, the patient's status improved, and she was discharged from the hospital. The serum laboratory data after mECT are summarized in Table 1.

Discussion

The patient was treated for schizophrenia for more than 20 years. Although the patient was positive for anti-NMDA receptor antibodies, she did not meet the consensus criteria for autoimmune encephalitis[14] because her symptoms could be explained by schizophrenia exacerbations or antipsychotic-induced NMS. In addition, the effectiveness of mECT and her recovery without methylprednisolone pulse therapy also suggested schizophrenia. Thus, as a final diagnosis, we considered NMS with atypical schizophrenia and anti-NMDA receptor antibody positivity. Regarding the psychiatric symptoms of schizophrenia and anti-NMDA receptor antibodies, 6.5% of patients with initial schizophrenia reportedly have anti-NMDA receptor antibodies, suggesting that patients with anti-NMDA receptor encephalitis may be included among those diagnosed with schizophrenia[15]. In addition, 4% of antibody-positive patients reportedly present with only psychiatric symptoms[16]; therefore, anti-NMDA receptor encephalitis should be considered in the differential diagnosis of psychiatric symptoms that follow an atypical course. Interestingly, patients with schizophrenia and anti-NMDA receptor antibody positivity do not exhibit classical signs of encephalitis[17]. Moreover, anti-NMDA receptor antibodies from psychotic patients can alter synaptic transmission and long-term potentiation in cultured neurons and mouse brains, whereas those from healthy subjects do not, suggesting that anti-NMDA receptor antibodies from psychotic patients have a pathogenic effect[17]. Considering that glutamate receptor hypofunction has been proposed as a key factor in the pathogenesis of schizophrenia[18], we suggest that it is possible that mechanisms different from

those of encephalitis mediated by anti-NMDA receptor antibodies may have affected the psychiatric symptoms of the patient. The concept of autoimmune psychosis, a mechanism different from encephalitis, has become a compelling example of the interface between neurological disease and psychiatric disease, and the emerging field of immunopsychiatry offers a new perspective on these diseases[19].

The effectiveness of mECT for treatment of psychiatric symptoms in anti-NMDA receptor encephalitis has been reported, albeit in a small number of patients[4]. Regarding side effects, 86.7% of patients completed the treatment without safety concerns[4]. However, mECT is known to have cognitive side effects that usually involve anterograde memory, working memory, processing speed, and executive function[20]. Moreover, mECT is contraindicated for encephalitis[21]. Thus, the indication for mECT should be carefully considered in cases in which the possibility of encephalitis cannot be completely excluded. For our patient, no adverse events were observed in any of the 10 sessions, although further investigation on the safety of this treatment is required.

In summary, an atypical schizophrenia patient with anti-NMDA receptor antibody positivity who presented with NMS was treated with mECT, which resulted in favorable therapeutic effects. However, the efficacy and safety of this treatment needs to be further studied in the future. At the interface of neurological and psychiatric disorders, immune processes are a major factor in central nervous system health and disease. Additionally, further research on the relationship between immune dysregulation and psychiatric disorders is an opportunity to introduce neurologists and psychiatrists into the new field of immunopsychiatry.

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Competing financial interests statement

The authors declare no conflicts of interest associated with this article.

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