Catatonia in Anti-N-Methyl-D-Aspartate (NMDA) Receptor Encephalitis Misdiagnosed as Schizophrenia

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ABSTRACT
Anti-N-Methyl-D-aspartate receptor encephalitis is an autoimmune disease of the central nervous system with prominent neurologic and psychiatric features. Symptoms appear progressively and sometimes with an exclusively psychiatric initial presentation. The patient’s evaluation should be meticulous, and we should use all the diagnostic tests required for the exclusion of entities that can mimic this disease. We report the diagnostic investigation of a case of anti-N-methyl-D-aspartate receptor encephalitis in a patient with a previous diagnosis of schizophrenia with poor response to antipsychotics. The aim of this case report is to highlight the importance of close surveillance for neuropsychiatric symptoms, especially catatonia, and to recognize autoimmune encephalitis in the differential diagnosis of psychotic disorders with neurological symptoms and resistance or intolerance to antipsychotics. A prompt diagnosis will contribute to a faster onset of therapy and an overall improvement in prognosis.

Keywords: Anti-N-Methyl-D-Aspartate Receptor Encephalitis; Catatonia; Psychosis; Schizophrenia

INTRODUCTION
Anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is a treatable autoimmune disease of the central nervous system with prominent neuropsychiatric features.1 Patients develop progressive symptoms ranging from memory deficits, seizures and psychosis, to autonomic and breathing instability and potentially lethal catatonia.2 As patients with anti-NMDAR encephalitis are often initially evaluated by psychiatrists, it is very important that all clinicians are aware of this clinical entity when attending to patients with psychotic disorders. We report the diagnostic investigation of a case of anti-NMDAR encephalitis in a catatonic patient with poor response to antipsychotics and benzodiazepines and a previous diagnosis of schizophrenia.

CASE REPORT
A 27-year-old white male was diagnosed with schizophrenia after a clinical presentation of loosely structured persecutory delusions and auditory hallucinations. One year later, he was lost to follow-up, but was apparently asymptomatic and was not taking any medication.

Six years later, the patient made three visits to the Emergency department in a single week with persistent headaches, nausea and vomiting. Two brain computed tomography (CT) scans showed no changes and he was discharged with symptomatic treatment. Three days later, he presented auditory hallucinations, persecutory delusions, insomnia and psychomotor agitation. His urine toxicology was positive for cannabinoids, without other relevant laboratory findings. He had a background of drug abuse but there was no other personal or family history.

He was admitted to our psychiatric ward with the diagnostic hypothesis of substance-induced psychosis versus schizophrenia. He started treatment with haloperidol and began to manifest fluctuating catatonic symptoms with periods of adequate behavior alternating with mutism, negativism and rigidity with waxy flexibility (the patient’s limbs retained their position for a sustained period after the examiner moved them, even in strange uncomfortable positions). The neurologic examination revealed reduction in speech volume and slowness of speech, generalized rigidity with dorsal and cervical dystonia (in sustained flexion) and limb waxy flexibility. Neuroleptics were discontinued to...
avoid neuroleptic malignant syndrome, and lorazepam was introduced, without success. There was a clinical deterioration with dysautonomic features, respiratory instability and generalized tonic-clonic seizure (Fig. 1). Post-ictal observation revealed bilateral eye and limb myoclonus. Repeated electroencephalography (EEG) revealed diffuse theta-delta slowing (Fig. 2) and a brief electrographic seizure (Fig. 3). Cerebrospinal fluid (CSF) showed only mild lymphocytic pleocytosis.

The patient was transferred to a Neurology ward with the diagnostic hypothesis of encephalitis of unknown aetiology. A new CSF test showed normal cytology and was negative for neurotropic viruses. The brain magnetic resonance imaging (Fig. 4) scan showed a right fronto-opercular and temporal anterior lesion compatible with head trauma in probable relation with unattended epileptic seizures during hospitalization in the psychiatric ward. Infections were excluded and an autoimmune study was performed: antinuclear antibodies (ANA) and anti-ganglioside, anti-sulfatide, anti-neuronal, anti-myelin-associated glycoprotein (anti-MAG), anti-glutamic acid decarboxylase (anti-GAD), anti-contactin-associated protein-like 2 (anti-CASPR2), anti-voltage-gated potassium channel (anti-VGKC) complex and anti-NMDAR antibodies. The CT scan of the cervical spine, chest, abdomen and pelvis scan, scrotal ultrasound, dermatologic and cавum examinations were all normal so an occult neoplasm was excluded.

Treatment with valproic acid, quetiapine and lorazepam in high doses showed some clinical improvement.

One month later, positive anti-NMDAR antibodies were detected in the CSF and the diagnosis of anti-NMDAR encephalitis was confirmed. The patient was treated for five days with high-dose intravenous (IV) corticosteroids (methylprednisolone 1 g/day) followed by five more days of IV immunoglobulins (0.4 g/kg/day). He continued treatment with oral prednisolone 60 mg/day (20 days), then switched to a lower dose (50 mg/day for 36 days) and underwent monthly treatments with cyclophosphamide.

Seven months after discharge, the neurological examination revealed bilateral postural tremor with myoclonic jerks and axial and limb rigidity that was more prominent on the left side; the neuropsychological evaluation revealed severe executive and memory deficits and puerile behaviour disturbance; a new brain MRI was performed that showed a partial resolution of the previously described lesions and a new search for anti-NMDAR antibodies in serum and CSF was negative.

Three years after discharge, the patient has a normal neurological examination and showed a clear improvement in repeated neuropsychological assessment, revealing only a mild deficit in working memory and learning ability. Nowadays, he is only taking azathioprine 200 mg/day and...
Figure 3 – EEG revealing the beginning of rhythmic electrographic activity in the F7, T3 and T5 leads, interpreted as a brief electrographic seizure. Patient awake with no clinical manifestation.

Figure 4 – MRI showing right fronto-opercular lesion compatible with head trauma

**DISCUSSION**

Isolated psychiatric episodes can occur as initial onset or relapse of anti-NMDAR encephalitis in about 4% of patients and those with milder presentations do not necessarily progress to more severe multi-symptom disease, despite prolonged periods without treatment. In the present case, our patient had a psychotic episode at the age of 27 and although anti-NMDAR antibodies were not tested at the time, we propose that his earlier episode may have represented a limited presentation of the anti-NMDA receptor encephalitis, as has been previously described by other authors.4

Since evidence suggest that early treatment improves outcomes, an approach based on conventional clinical assessment would allow the initiation of preliminary treatment while other studies and comprehensive antibody tests are processed and later used to refine the diagnosis and treatment. We speculate that if we had followed this approach a better outcome could have been attained.

A pattern that may start with a flu-like prodrome, followed by psychiatric symptoms, seizures and movement disorders and autonomic instability later, along with resistance or intolerance to antipsychotics, should always raise the suspicion of autoimmune encephalitis. We hope that this case highlights the importance of close surveillance for neuropsychiatric symptoms.

On the other hand, although only a minority of patients with psychosis are anti-NMDA receptor antibody positive, it remains to be established whether this subset of patients differs from antibody-negative patients in terms of underlying disease and response to antipsychotic treatment.7 The anti-NMDA receptors are a new piece in the puzzle of schizophrenia, and more research is needed in order to clarify it.

All patients presenting with catatonic symptoms, even with a psychiatric or drug abuse history, deserve a careful examination to discard an eventual neurological cause.

**PROTECTION OF HUMANS AND ANIMALS**

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association.
DATA CONFIDENTIALITY
The authors declare having followed the protocols in use at their working center regarding patients’ data publication.

PATIENT CONSENT
Obtained.

REFERENCES

CONFLICTS OF INTEREST
All authors report no conflict of interest.

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