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Differential Diagnosis of Encephalitis due to Anti-NMDA Receptor Antibodies

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KEYWORDS
Encephalitis;
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Abstract
Introduction: Anti-NMDA receptor (NMDAR) encephalitis usually develops as a multistage syndrome with a broad differential diagnosis.
Patients: We report 2 patients with anti-NMDAR encephalitis and a clinical picture typical of this disorder but whose initial evaluation suggested other aetiologies.
Discussion: The frequent development of this disorder in young individuals presenting with psychiatric manifestations often suggests other diagnostic possibilities, most commonly viral encephalitis, psychiatric disorders, and neuroleptic malignant syndrome. In addition, several less clearly defined syndromes or descriptively reported disorders in adult and paediatric patients were likely cases of anti-NMDAR encephalitis.
Conclusions: Anti-NMDAR encephalitis should be considered in young individuals with subacute presentation of psychiatric symptoms, abnormal movements, and autonomic dysfunction. The clinical and immunological characterization of this disorder has lead to the identification of new antibodies that affect memory, learning, behaviour and psychosis.

PALABRAS CLAVE
Encefalitis;
Anticuerpos;
Receptor NMDA;
Diagnóstico diferencial

Diagnóstico diferencial en la encefalitis por anticuerpos contra el receptor NMDA

Resumen
Introducción: La encefalitis por anticuerpos contra el receptor de NMDA (NMDAR) suele desarrollarse como un síndrome característico de evolución multifásica y diagnóstico diferencial amplio.
Pacientes: Presentamos a 2 pacientes diagnosticadas de encefalitis por anticuerpos NMDAR con un cuadro clínico típico, pero que inicialmente señaló otras etiologías.
Discusión: La afectación frecuente de pacientes jóvenes con manifestaciones psiquiátricas prominentes indica frecuentemente otras consideraciones diagnósticas; las más fre-

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cuentes son las encefalitis virales, los procesos psiquiátricos y el síndrome neuroléptico maligno. Varios síndromes previamente definidos de manera parcial o descriptiva en adultos y pacientes pediátricos probablemente eran casos de encefalitis anti-NMDAR.
Conclusiones: La encefalitis anti-NMDAR debe considerarse en pacientes jóvenes con manifestaciones psiquiátricas subagudas, movimientos anormales y alteraciones autonómicas. La caracterización clínica e inmunológica de esta enfermedad ha llevado a la identificación de nuevos anticuerpos que afectan a procesos de memoria, aprendizaje, conducta y psicosis.

Introduction

In 2007, a type of encephalitis associated with antibodies against the NMDA receptor (NMDAR) was discovered.[1] This is a cell membrane receptor with critical roles in synaptic transmission and neuronal plasticity.[2] Immune attack against this receptor produces characteristic clinical symptoms that affect multiple systems and develop in predictable stages. After prodromal symptoms that may include headache, fever and respiratory or digestive tract symptoms, patients develop prominent psychiatric symptoms (agitation, mania, hallucinations, paranoia). These psychiatric symptoms usually precede convulsive seizures and patients progress towards a rapid deterioration of consciousness, mutism, catatonia, abnormal facial, body or limb movements and autonomic dysfunctions.[3] The syndrome usually affects young patients. Its association with tumours depends on age and gender, and is most common in women over 18, who present ovarian teratoma in 56% of cases.[4] This syndrome, despite the severity of the condition and the significant neurological impairment, are potentially reversible, with symptom improvement in reverse chronological presentation phases. The symptoms respond well to both tumour treatment, if present, and to immunotherapy.[3] However, diagnosis is still very often delayed in most cases. Relative ignorance of the disease is only one cause. The clinical features of its presentation and the poor specificity of the usual analytical and radiological tests are often misleading. Various infectious diseases, as well as toxic-metabolic, psychiatric and autoimmune diseases tend to be considered at the beginning and as the symptoms develop.[5] This article reviews the differential diagnoses of this disease in 2 cases of patients with anti-NMDAR encephalitis.

Patients

Case 1

Female, 34 years old with polycystic ovary syndrome, who was found at her home suffering a case of confusion. Upon arrival at the hospital, she presented a generalised tonic-clonic seizure that resolved after administration of 4mg of lorazepam and 1g of phenytoin. She required tracheal intubation and sedation was maintained until she was admitted. She referred a case with one week evolution of general malaise, fever and headache. On admission, she had fever of 38.7°C, with no other abnormalities upon examination. Symptomatology did not point towards any other infectious foci, neck stiffness or signs of meningeal irritation. Lumbar puncture revealed a pleocytosis of 26 cells/ml, predominantly lymphocytic, with protein at 0.55 g/l and glucose at 77 mg/dl. Blood tests, urine toxics and computed tomography (CT) showed no relevant findings. Empirical treatment with 10 mg/kg of intravenous (IV) acyclovir every 8h was initiated. Sedation was removed without complications. Cranial magnetic resonance imaging (MRI) showed a bilateral signal increase in the medial and frontobasal temporal regions in fluid attenuation sequences (FLAIR). The electroencephalogram (EEG) showed no epileptic activity. Polymerase chain reaction (PCR) for herpes simplex virus (HSV) was negative, so the acyclovir treatment was stopped. The patient showed a good evolution and was discharged asymptomatic with 500 mg levetiracetam every 12h as the only treatment.

The day after discharge, the patient applied for readmission to the hospital. She had suffered episodes of agitation with significant aggression towards close relatives. She reported having had visions of assaulting her son. She did not present fever and showed no other symptoms. She was readmitted with a diagnosis of psychotic episode. Levetiracetam was replaced by valproic acid, at IV dose of 1,500 mg and a maintenance dose of 500 mg/8h, and treatment with acyclovir was resumed. A new lumbar puncture showed cerebrospinal fluid (CSF) with 30 cells/ml, protein content of 0.58 g/l and normal glucose. Oligoclonal bands were detected in fluid, with an intrathecal immunoglobulin synthesis pattern.

Bacteria and fungus cultures, Lyme, Epstein-Barr virus and arbovirus serologies and a new HSV PCR were all negative. This time, it was decided to maintain acyclovir. Serology for human immunodeficiency virus and the search for antinuclear, antineutrophil cytoplasm, antiperoxidase and anti-LGI1 (previously attributed to potassium channels) antibodies, as well as antibodies associated with classic paraneoplastic syndrome, were all negative. The EEG now showed a generally slower polymorphic activity. A second MRI revealed, in addition to the findings from the previous test, meningeal gadolinium enhancement. During her stay at the hospital, the neurological status of the patient

worsened progressively. She became very agitated and aggressive, so she was treated with lorazepam and olanzapine. Her level of consciousness progressed from a phase of confusion, aggression and withdrawal to a situation of dissociated response to stimuli coupled with lack of response to pain, but strong opposition to passive eye opening. During this period, the patient presented generalised muscle rigidity with normal reflexes, constant facial grimacing, kicking leg movements and right arm dystonic posture. She had a fever peak of 39°C, episodes of bradycardia with systolic pauses of up to 15s, arterial hypotension and hypoventilation, and she required reintubation. The creatine kinase (CPK) figures were always normal. No electrophysiological correlation with abnormal movements was revealed on EEG monitoring. Anti-NMDA receptor antibodies were detected both in serum and in CSF. A pelvic CT scan revealed an ovarian teratoma. The patient received 10 IV boluses of 1 g methylprednisolone and 5 sessions of plasmapheresis in 10 days, followed by 5 days of IV immunoglobulin (Ig), and finally one bolus of cyclophosphamide 750 mg/m2 body surface area. A salpingo-oophorectomy was also performed. The abnormal movements improved first, then the autonomic phenomena and, finally, the level of alertness. The patient was discharged with affectation of frontal functions including initiative, planning and memory, from which she recovered completely within 3 months.

Case 2

Female, 15 years old, who was diagnosed with encephalopathy of unknown aetiology in 2005. In that episode, she presented visual hallucinations, paranoid ideas, aggressiveness, tachycardia and hypertension. The clinical manifestations were blamed on clinical seizures due to an EEG with spike-wave activity in the left temporal region, but the symptoms did not improve after oxcarbazepine treatment and EEG normalisation. After receiving haloperidol for the episodes of aggression, she presented a decreased level of consciousness associated to dystonic positions of the upper extremities. She was prescribed benztropine and haloperidol was replaced by quetiapine, with partial improvement of symptoms. The CSF and MRI were normal. After receiving 5 boluses of 1 g methylprednisolone, the patient recovered completely from her symptoms. She returned to her normal life, and showed good performance at school.

In June 2008, she was hospitalised again with symptoms of aggression, impulsive behaviour, suicide threats, coprolalia, insomnia and complex visual hallucinations. She saw "white-bearded men on all fours". Various antipsychotic drugs failed to control the symptoms. She was diagnosed with a psychotic episode; the case was referred to a psychiatric facility and there she was treated with lithium and olanzapine. One week later, an episode of seizures motivated performing a lumbar puncture. The result was CSF with 7 cells/ml, protein content of 0.65 g/l and normal glucose. Oxcarbazepine and antibiotic therapy were prescribed. During this new admission, she presented fever of 38°C, muscle stiffness and episodes of confusion, agitation and auditory hallucinations. The figures for CPK reached 18,000 IU/l. She required treatment with high doses of labetalol to control blood pressure. Toxins in urine were negative, as was the search for infectious agents and metabolic disorders, including porphyrins. EEG monitoring revealed no seizure activity coinciding with agitation or autonomic episodes or with abnormal movements. The MRI was normal. A screening for tumours using thoracic-abdominal-pelvic CT was negative. The patient returned to the psychiatric centre with a diagnosis of refractory psychosis. She received 12 sessions of electroconvulsive therapy. Weeks later, anti-NMDAR antibodies were discovered in a CSF sample that had been filed during the 2005 episode. The clinical case remitted substantially upon reduction of antipsychotic medication, and it was decided not to use immunosuppressive agents.

In December 2008, the patient suffered a new relapse, with episodes of agitation and aggressiveness. She was prescribed treatment with 5 boluses of 1 g methylprednisolone and 5 sessions of IV Ig, with limited improvement of symptoms. The patient was discharged with significant sequelae. Personality disorder with bizarre behaviour, attention deficit, impulsiveness, and occasional episodes of agitation and aggressiveness persisted. She also presented mnemonic difficulties, hallucinations, insomnia and poor bowel control. She received outpatient treatment with rituximab, which was not effective. For the last 3 months, she has followed treatment with cyclophosphamide at a dose of 50 mg per day. Relatives report that, since then, the patient has shown a gradual improvement. She is oriented, has regained bowel and bladder control, achieved a normalization of sleep and a decrease in hallucinations and episodes of aggression.

Discussion

These 2 cases illustrate the main diseases commonly mistaken initially for cases of anti-NMDAR encephalitis. The presentation of the first case with fever, headache and altered level of consciousness, accompanied by generalised tonic-clonic seizure and CSF with inflammatory characteristics, requires ruling out a viral process in the first place. Of particular relevance among these is herpetic meningoencephalitis (HE), and in some cases, rabies, given that the broad clinical spectrum may overlap with anti-NMDAR encephalitis.[5] Herpes simplex virus has a high morbidity-mortality and a curative antiviral treatment. It is characterised by rapid presentation with focal symptoms and decreased level of consciousness. Due to the affinity of the virus for the limbic system, it is accompanied by memory and behaviour alterations.[6] The diagnosis is based on neuroradiological and CSF findings that indicate haemorrhagic encephalitis and is confirmed by virus PCR, a test with 94% sensitivity and 98% specificity.[7] Rabies causes prominent psychiatric disorders, altered level of consciousness, abnormal movements, hypersalivation and other autonomic alterations reminiscent of the acute phase of NMDAR antibody syndrome. There is no treatment, and its mortality is of 100%. The diagnosis is confirmed by cell culture or virus PCR. Anti-NMDAR encephalitis may have a prodromic phase similar to that of a viral infection.

However, there are clinical differences that may lead to the diagnosis. Psychiatric manifestations are far more frequent, appear in almost all patients and often represent the first manifestation.[4,5] Typical movement disorders such as orofacial grimacing, choreiform movements, kicking or limb dystonia point to the diagnosis of anti-NMDAR encephalitis.

The 2 cases presented showed prominent psychiatric symptoms. In the second, episodes of aggressiveness and impulsiveness, as well as the manifestation of suicidal ideas and hallucinations, initially pointed to psychosis. Psychosis is an alteration in the perception of reality with hallucinations, disorganised thinking and a behavioural disorder marked by impulsiveness and aggressiveness. It is part of numerous psychiatric disorders, including schizophrenia, bipolar disorder or depression. The consumption of drugs for recreation or with therapeutic purposes, as well as various neurological diseases, can produce psychotic symptoms. Ruling out an organic origin in cases of psychosis is typically a point of conflict between psychiatrists and neurologists. Some aspects may help to differentiate between them. Auditory hallucinations are traditionally considered as features of psychiatric cases. However, their presence is not pathognomonic nor do other types of hallucinations rule out purely psychiatric causes. It is important to identify possible psychotic features in the previous personality of the patient. The presence of other symptoms or focal signs point to an organic origin. Up to 77% of patients with anti-NMDAR encephalitis begin with psychiatric symptoms, and these appear in the course of the disease in all patients.[3] Family members often report changes in behaviour or personality, aggressiveness, visual or auditory hallucinations and delusions, sometimes with a mystical or religious content. In the recovery phase, many patients develop apathy and withdrawal, with a tendency towards echolalia and echopraxia. In general, these symptoms respond poorly to standard antipsychotic treatment.

The presence of seizures can be confusing. Some antiepileptic drugs such as levetiracetam, used in the first patient, have known psychiatric side effects. The development of psychosis after a seizure has been classified as postictal psychosis.[8] In these cases, psychosis can occur after the crisis has been followed by a lucid period of 1 week, may last up to 3 months and has been associated with a history of encephalitis; these facts indicate that some patients with postictal psychosis may have suffered anti-NMDAR encephalitis. However, psychiatric manifestations of anti-NMDAR encephalitis generally precede the development of epileptic seizures.

Another diagnosis to be considered is neuroleptic malignant syndrome (NMS). The 2 patients presented had developed, at some stage of the disease, fever, altered level of consciousness, muscle rigidity, and dysautonomia, and both had received neuroleptics. This syndrome may occur after the first dose of medication and is most commonly associated with a rapid escalation of the dose, high doses and classic neuroleptics. It usually presents the symptom tetrad in a rapid and sequential manner.[9] These symptoms are very common in anti-NMDAR encephalitis with or without prior neuroleptic medication.[10] Rhabdomyolysis may also occur, with elevated CPK and acute kidney injury. However, in anti-NMDAR encephalitis, symptoms resembling NMS occur in the context of a broader condition that generally includes catatonic features and abnormal movements. In patients treated with neuroleptics, the main doubt is whether the symptoms common to NMS are due to only encephalitis, to a true NMS or to the coexistence of both processes.

Table 1 Differential diagnosis of encephalitis by anti-NMDA

Most frequent diagnoses
Psychosis, schizophrenia, catatonia, malignant catatonia
Infections or post-infectious syndromes (viral, Mycoplasm, PANDAS)
Drug abuse
Malignant neuroleptic syndrome
Encephalitis lethargica
Hashimoto encephalopathy
Descriptive entities which resemble anti-NMDA encephalitis
Demonic Possession[15]
Acquired reversible autistic syndrome in acute encephalopathic illness in children[16]
Coma associated with intense bursts of abnormal movements and long-lasting cognitive disturbances[17]
Immune-mediated chorea encephalopathy syndrome in childhood[18]
Acute diffuse lymphocytic meningoencephalitis*
Acute reversible limbic encephalitis*
Acute juvenile female non-herpetic encephalitis*
Acute juvenile non-herpetic encephalitis*
Acute encephalitis with refractory partial seizures*

PANDAS: Paediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections.

*Some of these patients initially diagnosed with these descriptive terms later proved to have anti-NMDA receptor antibodies.[19]

Anti-NMDAR encephalitis has historically been mistaken for different toxic-metabolic, infectious and autoimmune diseases, as well as multiple processes defined by purely descriptive terms (table 1).[15-19] For example, encephalitis lethargica is composed of a spectrum of symptoms ranging from akinetic mutism to a hyperkinetic condition, or from insomnia to hypersomnia. This symptomatic spectrum is difficult to explain with a single pathogenic mechanism. It is likely that each variety hides within it several diseases with different pathogenic mechanisms. Consequently, it was not surprising that, when retrospectively considering the serum or CSF of patients with processes defined as "encephalitis and dyskinesia" or "dyskinetic encephalitis lethargica", approximately 50% of cases presented anti-NMDAR antibodies.[5,11] The discovery of this autoimmunity not only pathogenetically refines and unifies some of these processes, it also leads to the search for similar mechanisms to explain other diseases whose aetiology is not established. For example, some processes with purely psychiatric manifestations, memory alteration or limbic involvement

syndromes are due to anti-AMPA antibodies or GABAB receptors.[12,13]

The importance of these synaptic immunities is that the clinical course correlates with the concentration of antibodies, particularly in the CSF, and that, despite the duration or severity of symptoms, they generally respond to immunotherapy. With respect to the basic study, antibodies directly alter synaptic antigens and clinical cases are similar to animal models in which receptors have been genetically or pharmacologically altered.[14] This reveals a new category of central nervous system processes directly mediated by receptor antibodies with critical roles in processes of memory, learning, behaviour and psychosis.

Clarification

This work was carried out during the stay of Dr. Jaime González-Valcárcel at the Neuro-Oncology Division of the University of Pennsylvania. His current address is: Servicio de Neurología del Hospital Universitario Ramón y Cajal, Madrid.

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Conflict of interests

The authors declare no conflict of interests.

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