Encefalitis anti-receptor NMDA: un diagnóstico a considerar

Anti-NMDA receptor encephalitis: a diagnosis to consider

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Abstract

Encephalitis are inflammatory brain disorders that are secondary to different pathological processes that include infectious and autoimmune causes. In recent years, the autoimmune processes involved have been studied with an increasing identification of cases that present a wide variety of neurological and psychiatric symptoms, which often make their timely diagnosis difficult. This is a narrative review that describes the main aspects of encephalitis caused by antibodies against the N-methyl-D-aspartate receptor (NMDAR), its pathogenesis (mechanism shared with psychotic disorders), diagnosis, and clinical presentation; these are aspects that highlight the importance of a thorough evaluation of psychiatric manifestations in the clinical setting.

Key Words: Anti-N-Methyl-D-Aspartate Receptor Encephalitis; Encephalitis; Psychosis; Autoimmune Diseases

Resumen

Las encefalitis son trastornos inflamatorios cerebrales, secundarias a diferentes procesos patológicos que incluyen causas infecciosas y autoinmunes. En los últimos años se han estudiado los procesos autoinmunes involucrados, con una creciente identificación de casos donde presenta una amplia variedad de síntomas neurológicos y psiquiátricos que suelen dificultar el diagnóstico oportuno. Por tanto, esta es una revisión narrativa que describe los principales aspectos de la encefalitis por anticuerpos contra el receptor de N-

metil-D-aspartato (NMDAR), su patogénesis (mecanismo que comparte con los trastornos psicóticos), diagnóstico y presentación clínica; aspectos que destacan la importancia de una evaluación exhaustiva de las manifestaciones psiquiátricas en el ámbito clínico.

Palabras clave: Encefalitis Antirreceptor N-Metil-D-Aspartato; Encefalitis; Psicosis; Enfermedades Autoinmunes.

Introduction

The inflammation of the parenchyma of the encephalon associated with neurological dysfunction is known as encephalitis, which can be secondary to infectious, toxic, and autoimmune processes (1, 2). In recent years an increasing number of cases of encephalitis mediated by immune mechanisms have been reported, characterized by the presence of antibodies against the neuronal cell surface or synaptic proteins, which will be classified according to the type of immunity and antigen in question (1, 2).

The first record of a possible paraneoplastic autoimmune encephalitis was made in 1888 by the neurologist Oppenheim, who described in a patient with gastric cancer, symptomatology of neuropsychiatric characteristics in addition to other brain dysfunctions such as aphasia and agnosia (3). Anti-N-Methyl-D-Aspartate Receptor (NMDAR) encephalitis is a common cause of this type of pathology. This condition was described by Dalmau et al. in 2007 in a cohort of 12 women with ovarian teratomas who developed psychiatric symptoms, memory deficits, seizures, dyskinesias and autonomic instability associated with impaired consciousness (2, 4, 5).

The following is a description of the most important aspects of anti-NMDAR encephalitis since in most cases the systemic or structural causes of psychiatric manifestations are not studied (6), delaying their diagnosis and treatment, making them potentially lethal; for this reason, special emphasis is placed on their pathogenesis, as a common mechanism with psychotic conditions.

Definition

Anti-N-methyl-D-aspartate receptor encephalitis (NMDAR) is the inflammation of the cerebral parenchyma, resulting from the presence of antibodies against the NMDA glutamate receptor at neuronal synapses, which eventually manifests as neurological dysfunction (1, 4, 7).

Epidemiology

The exact incidence of this syndrome is unknown. An incidence of 5-10

per 100,000 inhabitants per year of autoimmune encephalitis is reported in high-income countries (1); at the moment there are no epidemiological data available in Latin America or Colombia. Anti-NMDAR encephalitis is among the most common encephalitis, after demyelinating encephalitis, and most frequently affects the middle-aged population (4, 5, 8). Although the disorder has been described in both genders, women represent 80% of the reported cases, with ovarian teratoma and herpes simplex virus (HSV) infection being the most frequent triggers (4, 5, 9). Other tumors associated with this condition are extra ovarian teratomas, testicular tumors, Hodgkin's lymphoma and neuroblastoma, and infections such as mycoplasma, Epstein Barr virus, Varicella Zoster and Influenza (5, 10).

Different studies have reported prevalence of 20-59% of the coexistence of anti-NMDAR encephalitis and tumors (10). However, the presence of a paraneoplastic syndrome is not essential and can occur in the absence of tumors; monosymptomatic syndromes are rare, representing less than 5% of the affected population (5, 6). The limited knowledge about anti-NMDAR encephalitis makes data on its prevalence inaccurate because it is possible that more cases exist yet have not been identified (6).

Pathogenesis

The anti-N-methyl-D-aspartate receptor is a tetrameric glutamatergic and inotropic complex, composed of two GluN1 subunits and a combination of two GluN2 or GluN3 subunits; with a localization in the forebrain, hippocampus, and limbic system (4, 11). Its functions include pre and post synaptic regulation, neuronal maturation, and brain plasticity (6). It's up-regulation and hyperfunctionality is associated with ictal states and its inhibition is anticonvulsant but is associated with psychosis. Anti-NMDA antibodies inhibit GABAergic interneurons, leading to dopaminergic hyperactivity and presentation of psychotic symptoms (6).

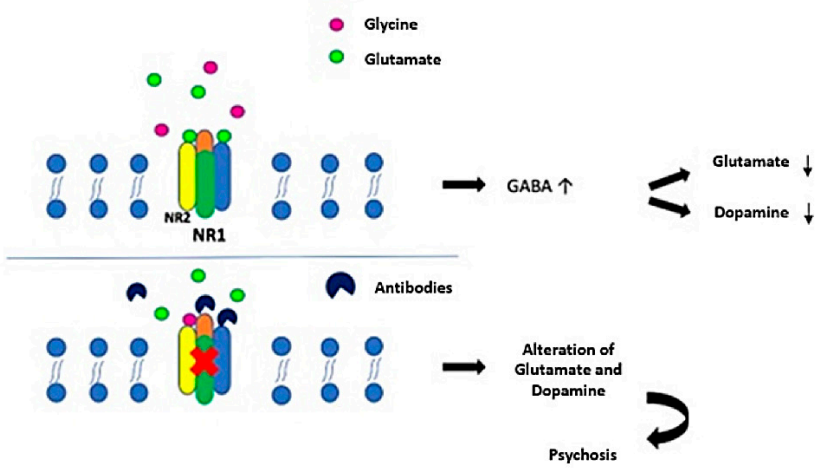
Anti-NMDA receptor encephalitis is recognized by immunoreactivity of IgG antibodies in CSF against the GluN1 subunit of the NMDA receptor. These highly specific antibodies have demonstrated their pathogenicity at the neuronal level (1, 10). When antigens are generated by the secondary apoptosis to tumor or infectious processes, these are captured by the antigen presenting cells and subsequently taken to the plasma cells whose function is the production of antibodies which cross-react with the NMDA receptors (10). The antibodies bind to the receptor, produce internalization of the receptor and its hypofunction (7, 9). Two additional mechanisms have been

described in the literature, which are blockade of ion entry by antibodies and complement-mediated cell lysis (10). Synaptic effects and symptom severity are described to be reversible with antibody removal. It should be noted that other proteins and synaptic structures are not affected in the pathogenesis of this syndrome (7).

a. Psychotic manifestations hypothesis

There is evidence that NMDA receptor blocks by autoantibodies can cause psychosis. For example, experimental blockade of NMDA receptors by ketamine in most healthy volunteer subjects causes acute paranoid psychosis (12). The mechanism associated with this process is understood as follows: the glutamate is an excitatory neurotransmitter released by pyramidal cells, its action at the interneuronal level on the NMDA receptor, allows the release of the inhibitory neurotransmitter GABA (12), when the effects of glutamate on the NMDA receptor of the interneurons are blocked, the inhibitory neurons are deactivated. This leads to reduced GABA release and subsequent disinhibition/activation of cortical circuits, with subsequent dopaminergic hyperactivity, which is responsible for psychotic phenomena (6, 12). (Figure 1)

Figure 1. Diagram of NMDA receptor hypofunction or blockade by antibodies. Figure modified from Maneta et al. 2013 (6).



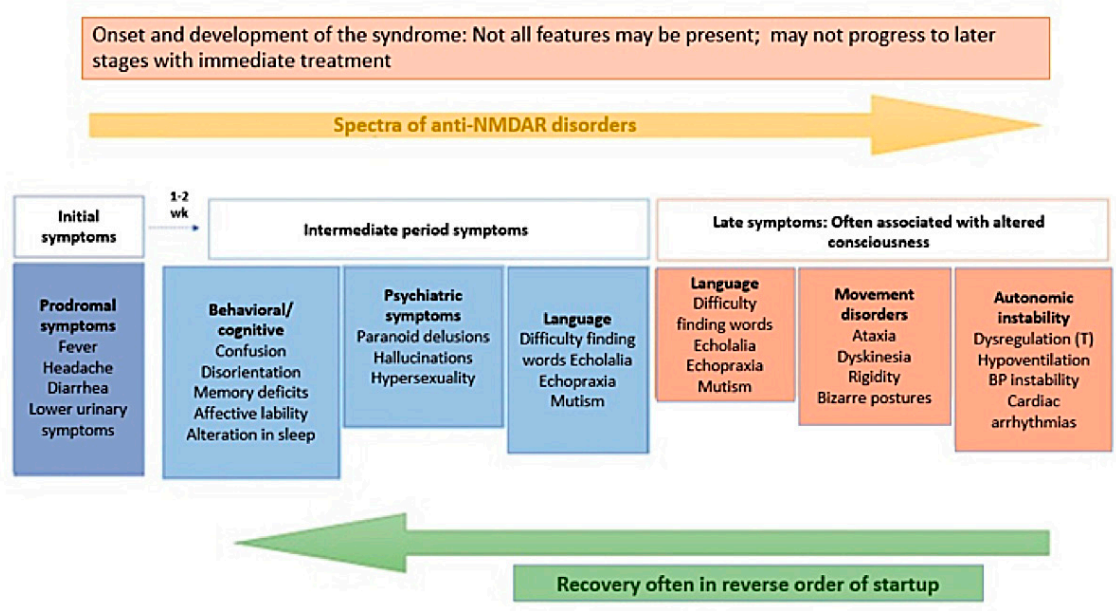
Another brain area implicated in the onset of psychiatric symptoms is the hippocampus. At this level, long-term activation of microglia could lead to a loss of hippocampal volume, documented in neuroimaging. Hippocampal hypotrophy could explain the mnestic failures reported in psychotic patients. However, this theory is controversial since such microglial activation could also be understood as a protective event that prevents brain tissue degeneration (10, 12). Therefore, neuroinflammation is considered to play an impor-

tant role in the development of autoimmune conditions and neuropsychiatric manifestations, explaining the overlap of symptoms between encephalitis and psychotic disorders (9, 13).

Clinical Presentation

Anti-NMDA receptor encephalitis can manifest with different syndromes that complicate its recognition (14). But frequently the clinical picture progresses through the following stages: 1. a prodromal period, 2. an intermediate period, 3. a phase with predominance of neurological symptoms (4, 7) (Figure 2).

Figure 2. Phases of anti-NMDAR encephalitis. Modified from Newman et al.. (5)



1. **Prodromal period:** Similar symptoms to viral infections with respiratory and gastrointestinal tropism that can last from 5 days to 2 weeks, in this period the subjects manifest: headache, febrile peaks, upper respiratory tract symptoms, fatigue, nausea, emesis and diarrheal stools. In different retrospective studies, the presence of these symptoms has been reported in up to 70% of the cases (4, 5, 7).

2. **Intermediate period:** May last from 1 to 3 weeks. Psychiatric symptoms predominate with wide and varied manifestations. In adults, there is a predominance of psychotic manifestations, with delusional thinking, altered sensory perception and disorganized behavior. Anxiety, psychomotor agitation, and emotional lability are present (7, 9). In a study by Kayser et al, the symptoms frequently found were: delirium in up to 74%, 70% of

mood disturbances, psychomotor agitation 57% and visual and auditory hallucinations in 43% (3).

On the other hand, in the pediatric population, it is common to find manic symptoms such as irritability, behavioral problems, sleep pattern disturbance, hyperactivity and hypersexuality (3, 7). A higher incidence of atypical symptoms such as hemiparesis or cerebellar ataxia has been described in this same population (10). In addition to the described manifestations, cognitive impairment and language disturbances (e.g., alogia, echolalia, perseveration and mutism) are frequently reported in patients of all ages, and may persist in other stages of the disease (7).

Neurological symptoms are usually absent during this phase. This results in patients often being assessed for the first time by psychiatric services in approximately 72 to 84% and misdiagnosed as a primary or substance-induced psychotic disorder (7, 9, 10). It is therefore important to consider this entity as a differential diagnosis in acute mental disorders.

3. **Period of neurological symptoms:** The first psychiatric changes are usually followed by alterations of consciousness, expressed with a decrease in responsiveness that sometimes progresses to a catatonic state. At this stage, movement disturbances such as orofacial dyskinesias, dystonic posture and choreic-like movements and even psychomotor agitation are also often found (7, 9). All this is associated with hypoventilation and autonomic instability (hyperthermia, tachycardia or bradycardia, hypo- or hypertension); a condition that therefore requires respiratory support. In relation to this aspect, reports have been made on the duration of assisted ventilation, finding that in some patients it has even been required for a period of 2 months (7, 9).

Seizures are also part of the spectrum of symptoms and occur in almost 80% of the cases, these may be motor or partial complex, and may even be present in early stages of the disease, being occasionally refractory to treatment; however, their intensity and frequency may decrease as they evolve over time (5, 7).

It is important to note that cases of anti-NMDAR encephalitis may not follow the phasic progression described and may not include all the above-mentioned symptomatology, which makes the diagnosis more complicated. Herken and Pruss proposed red and yellow flag symptoms indicative of an autoimmune process. The yellow flags include altered level of consciousness, abnormal postures/movements, autonomic instability, focal neurological deficits, aphasia/dysarthria, and rapid progression of psychosis. It should

be noted that there is no specific psychiatric symptom associated with autoimmune encephalitis, however, an association with catatonia is reported (3, 9).

Red flags correspond to generalized or faciobrachial seizures, suspicion of neuroleptic malignant syndrome (NMS) and at the paraclinical level the presence of pleocytosis and oligoclonal bands in the CSF without infectious process, abnormalities in the MRI (mesiotemporal hyperintensities, atrophy pattern) and electroencephalogram (EEG) alterations (slowing, epileptic activity or extreme delta brush) (9).

The identification of these characteristics in patients with acute psychiatric disorder is associated with a better prognosis, due to the establishment of the appropriate treatment of the immunological process; which includes the implementation of immunotherapy, thus improving patient outcomes (9).

Diagnostic criteria

The diagnosis of possible anti-NMDA receptor encephalitis (1) can be made when the three criteria presented in Table 1 are met:

Table 1. Probable anti-NMDA receptor encephalitis criteria. Taken from Graus et al. 2016 (1).

1. Fast onset (less than 3 months) of at least four of the following six symptom clusters: a. Abnormal behavior or cognitive dysfunction b. Speech dysfunction (hurried speech, verbal reduction, mutism). c. Seizures d. Movement disorder, dyskinesias or stiffness/ abnormal postures e. Decreased consciousness level. f. Autonomic dysfunction or central hypoventilation.
2. At least one of the following laboratory study results: a. Abnormal EEG (slow or disorganized focal or diffuse activity, epileptic activity or extreme delta strain). b. CSF with pleocytosis or oligoclonal bands.
3. Reasonable exclusion of other disorders

The diagnosis can also be made in the presence of three of the above symptom clusters accompanied by a systemic teratoma (1). In relation to the confirmatory diagnostic criteria for definite anti-NMDA receptor encephalitis,

«However, in many institutions nationwide, there is limited access to antibody testing, making it imperative to properly assess and use of the diagnostic criteria.»

the presence of one or more of the six major symptom clusters and anti-GluN1 IgG antibodies in CSF is listed, after reasonable exclusion of other disorders. Consequently, to establish the precise diagnosis, cerebrospinal fluid (CSF) studies are required (1,7,9). However, in many institutions nationwide, there is limited access to antibody testing, making it imperative to properly assess and use of the diagnostic criteria (14).

a. Diagnostic tools:

- **Magnetic Resonance Imaging:** it may be normal in 50 - 70% of all cases. When it is abnormal, hyperintensities in T2 or FLAIR are frequently described in cortical, hippocampal or subcortical brain regions and spinal cord and in case of using contrast the enhancement is usually mild. Such findings are not related to the severity of symptoms and are usually transient. (7, 9, 10).
- **Electroencephalogram:** shows nonspecific abnormalities, such as slow and disorganized activity in the delta/theta range, especially the recording of an epileptic activity or extreme delta strain can be obtained (7, 9).
- **Serum anti-NMDAR antibody assay:** the test is not as sensitive as CSF antibody assay (9). However, some authors consider it necessary to test both samples to reduce the risk of false positives and false negatives (10).
- **Positron emission tomography:** has been shown to be useful in the study of patients with autoimmune encephalitis. Hypometabolism has been described at the occipital level, which has been suggested as a biomarker that distinguishes anti-NMDA encephalitis from other autoimmune encephalitis and in other states subcortical hypermetabolism (6, 10).
- **Cerebrospinal fluid (CSF):** leukocyte pleocytosis at the expense of lymphocytes has been documented in 89 - 90% of cases and specific oligoclonal bands in 60%. Antibody titers in CSF (NR1 - NR2) indicate intrathecal antibody production and correlate with disease severity (6, 8, 10).

b. Differential diagnosis:

In any patient with suspected autoimmune encephalitis, other diseases should be carefully ruled out, including infectious causes, especially viral (e.g., Epstein-Barr virus, cytomegalovirus [CMV], herpes simplex virus [HSV], varicella zoster virus [VZV], human immunodeficiency virus [HIV], human

herpes virus 6 and 7 [HHV6/ HHV7], arboviruses, and rabies virus) (1, 7, 9).

The differential diagnosis of patients with N-methyl-D-aspartate receptor (NMDAR) encephalitis is very broad given the large number of symptoms, such as neuropsychiatric lupus, Hashimoto's encephalopathy, primary central nervous system vasculitis, prion encephalopathy, primary CNS lymphomas, and temporal lobe gliomatosis, among other entities (2, 3, 7).

It has been described that 65% of patients present to the psychiatry service for psychotic and manic manifestations (7), with schizophrenia being one of the most important primary psychotic disorders to rule out, since more than one third of patients with anti-NMDAR encephalitis present similar symptoms. For this reason, it is relevant to mention the main differences in the symptoms present in these two entities: patients with schizophrenia meet the criteria established in the DSM-5 for the duration of symptomatology; the previous presence of depressive symptoms has also been documented, as well as an age range of presentation (before 30 years of age) and the long-term development of negative symptoms (9). In addition to an acute psychotic episode with schizophreniform features, anti-NMDAR encephalitis is followed by a rapid deterioration of consciousness, seizures, central hypoventilation, and autonomic instability (15). Moreover, it is frequent that after the initiation of antipsychotic management, a clinical deterioration of the patient occurs, due to the inappropriate response to psychopharmacological management, in comparison with typical patients of the psychotic spectrum (9). Therefore, it is important to consider neuroleptic malignant syndrome as a differential; characterized by altered mental status, rigidity, rhabdomyolysis, hyperthermia and hemodynamic instability (7, 16).

Other entities that should be considered in the management of the patient with suspected anti-NMDAR encephalitis include other autoimmune causes (e.g., limbic encephalitis, paraneoplastic encephalitis, systemic lupus erythematosus, antiphospholipid syndromes, Sjögren's syndrome, Graves' disease, Hashimoto's encephalitis), vasculitis, substance use disorder, and mitochondrial disorders (9).

« Moreover, it is frequent that after the initiation of antipsychotic management, a clinical deterioration of the patient occurs, due to the inappropriate response to psychopharmacological management, ...»

Treatment

The best results are associated with early identification and treatment, as this prevents damage to brain structures. When a germ cell tumor is identified, resection of the tumor produces remarkable improvement in days or weeks. However, immunotherapy is the main treatment with or without the presence of a tumor, involving corticosteroids, intravenous immunoglobulins, and plasmapheresis (9). Intravenous immunoglobulin 0.3 g/kg per day for 5 days and methylprednisolone 1 g/day for 5 days have been suggested. After minimal improvement with plasmapheresis treatment, the next line of treatment is immunosuppression, using rituximab or cyclophosphamide, for one year, generally indicated in patients without tumor pathology (9, 10). Just as response to tumor resection plus immunotherapy has been demonstrated, treatment with antiepileptics and benzodiazepines has been documented for relief of acute symptomatology (15).

Course and prognosis

Anti-NMDAR encephalitis has been associated with a longer hospitalization time, reporting cases of 3 to 4 months duration with the requirement of intensive care unit and the need for immunomodulatory therapies (14). 25% of patients may present severe deficits and die; 50% present a complete recovery and approximately 45% present a course with sequelae that may be mild or severe (7, 9). This type of encephalitis usually has a better prognosis compared to the other specified causes (10).

The recovery process is characterized by a regression of disease stages, with a recovery of autonomic and respiratory functions, followed by the resolution of movement abnormalities, some authors consider it necessary to monitor serum and CSF antibody levels, which have a better correlation with long-term prognosis and likelihood of relapse (7, 9, 10).

It should be noted that cognitive and psychiatric functions often take the longest time to improve, since recurrence of psychotic symptoms is frequent and relapse rates are between 20 and 25%; this percentage is lower compared to other synaptic encephalitis and may increase if immunotherapy treatment was not used (7, 9).

In accordance with this, it has been reported that the time required for a full recovery, taking into account their previous level of functioning, is years (9).

Late cognitive and behavioral consequences

Approximately 85% of patients take some time to return to baseline function

after discharge from the hospital. Since most of them persist with significant cognitive and behavioral abnormalities they require monitoring and guided rehabilitation by a multidisciplinary team; among the abnormalities described are alterations in executive function, impulsivity, behavioral disinhibition, and abnormal sleep patterns (7). Balu et al. designed the NEOS (anti NMDA encephalitis one-year functional status) tool, which allows estimating the clinical course after diagnosis and thus identifying the need to benefit from new management (17).

Conclusions

Anti NMDAR encephalitis represents a syndrome of great importance to be considered in clinical practice. It is a severe and potentially fatal condition that may initially be mistaken as a primary psychiatric disorder because of the association with different neuropsychiatric manifestations.

Its diagnosis and timely treatment is associated with a decrease in the morbidity and mortality rate. It is important to take a complete clinical history, adequate evaluation and differentiation of psychiatric disorders that include psychotic episodes in their symptomatology, with schizophrenia being the most common.

This complex disorder requires management and coordination of care among multiple medical specialties in order to provide adequate rehabilitation. The psychiatric physician should be familiar with this syndrome as proper diagnosis may help to anticipate the complications mentioned above.

Conflicts of interest:

The authors declare that there are no conflicts of interest.

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