



## Case report

# Autoimmune encephalitis due to anti-NMDAR antibodies following dog bite and dT vaccination

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## Abstract

**Case presentation.** A 17-year-old male patient, following a dog bite and vaccination against diphtheria and tetanus, presented neuropsychiatric symptoms characterized by seizures, altered state of consciousness, right fasciobrachiorural hemiparesis, dyskinesias, myoclonus, irritability, echolalia, euphoria, sialorrhea, progressive loss of speech, and dysautonomic syndrome. **Treatment.** We ruled out metabolic, toxicological, infectious, ischemic, hemorrhagic, and traumatic disorders. The electroencephalogram reported a generalized delta rhythm, and we determined the presence of pleocytosis and antibodies against the anti-N-methyl-D-aspartate receptor in the cerebrospinal fluid. We ruled out a paraneoplastic syndrome, and considered a possible adverse event related to vaccination against diphtheria and tetanus. We initiated specific treatment in the following consecutive order: immunoglobulin, methylprednisolone pulses, and plasmapheresis. Levetiracetam and phenytoin were administered as anticonvulsants; quetiapine and haloperidol were prescribed for the psychotic symptoms. The dysautonomic syndrome was treated with propranolol. **Outcome.** After the third plasma exchange session, the patient's alertness and level of attention improved, and the dyskinesias resolved. Psychiatric symptoms disappeared three days after the end of the plasma exchange sessions. Four months after hospital discharge, the patient had recovered all higher mental functions and was walking adequately; however, dysarthria persisted.

## Keywords

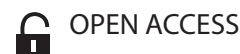
Autoimmune Diseases of the Nervous System, Receptors, N-Methyl-D-Aspartate, Seizures.

## Resumen

**Presentación del caso.** Paciente masculino de 17 años, que posterior a la mordedura de un perro y vacunación contra la difteria y tétanos, presentó síntomas neuropsiquiátricos caracterizados por convulsiones, alteración del estado de conciencia, hemiparesia fasciobraquiocrural derecha, discinesias, mioclonías, irritabilidad, ecolalia, euforia, sialorrea, pérdida progresiva del lenguaje y síndrome disautonómico. **Intervención terapéutica.** Se excluyeron alteraciones metabólicas, toxicológicas, infecciosas, isquémicas, hemorrágicas y traumáticas. El electroencefalograma reportó ritmo delta generalizado y se determinó pleocitosis y anticuerpos contra receptor N-metil-D-aspartato en el líquido cefalorraquídeo. Se descartó un síndrome paraneoplásico y se consideró un posible evento adverso a la vacunación contra la difteria y tétanos. Se instauró tratamiento específico en el siguiente orden consecutivo: inmunoglobulina, pulsos de metilprednisolona y plasmaféresis. Se administró levetiracetam y fenitoína como anticonvulsivos y quetiapina con haloperidol para el estado psicótico. El síndrome disautonómico fue tratado con propranolol. **Evolución clínica.** A partir de la tercera sesión de plasmaféresis, mejoraron el estado de vigilia, el nivel de atención y cesaron las discinesias. A los tres días de finalizar las sesiones de recambio plasmático se ausentaron los síntomas psiquiátricos. A los cuatro meses del egreso hospitalario había recuperado todas sus funciones mentales superiores y ejecutaba adecuadamente la marcha; sin embargo, persistía la disartria.

## Palabras clave

Encefalitis Autoinmune, Receptores de N-Metil-D-Aspartato, Crisis Convulsivas.



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**Encefalitis autoinmune por anticuerpos anti-NMDAR posterior a mordedura de perro y vacunación con dT**

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No conflicts of interest.

## Introduction

Anti-N-methyl-D-aspartate receptor antibody (anti-NMDAR) encephalitis is a rare autoimmune disease that is often under-diagnosed. The pathophysiology is due to the binding of autoantibodies that cause

neuronal dysfunction.<sup>i</sup> The mortality rate of autoimmune encephalitis is around eight to 18.5 %<sup>ii</sup> and approximately 20 % of survivors have sequelae.<sup>iii</sup> The clinical presentation includes psychiatric disturbances, cognitive impairment, seizures, focal neurological deficits, movement disorders, loss of conscious-

ness and dysautonomia.<sup>iii,iv</sup> Early diagnosis and targeted treatment can lead to better outcomes in most patients.<sup>iv</sup> First-line treatment is based on the administration of immunoglobulin, corticosteroids and/or plasmapheresis.<sup>iii,iv</sup> The aetiology of autoimmune encephalitis is largely unknown, but it is often associated with a tumour or a previous infectious nexus (post-infectious encephalitis).<sup>v,vi</sup> Isolated cases have been reported in which vaccination has been implicated as the triggering event for anti-NMDAR encephalitis.<sup>vi</sup>

The differential diagnosis of autoimmune encephalitis includes primary psychiatric disorders, drug abuse, infectious encephalitis and even rabies.<sup>vii</sup> In this study, we report a case of anti-NMDAR autoimmune encephalitis with an aetiological and differential diagnostic challenge due to a history of dog bite and vaccination against diphtheria and tetanus. The aim of this work was to describe the therapeutic and multidisciplinary approach to make timely decisions that affected the patient's prognosis.

Case presentation

Seventeen-year-old male patient with no relevant medical history who received dT vaccine (diphtheria and tetanus) four days after being bitten by a dog on the right foot. Three hours after vaccination, he presented with generalised tonic-clonic seizures with posictal phase, somnolence and right fasio-brachio-crural hemiparesis. He was admitted to a second-level hospital for seven days, where serology (HIV, VDRL, hepatitis B and C, febrile agglutination tests) and drug toxicology (marijuana, cocaine, barbiturates, opioids, amphetamines, methamphetamines) were negative. No conclusive diagnosis was made and he was discharged with home treatment of carbamazepine 400 mg every 12 hours. However, the patient did not recover his baseline neurological status, and also presented psychiatric changes (irritability, echolalia, inattention, abulia, euphoria), abnormal orofacial movements, limb dystonia and progressive loss of speech.

Fourteen days after vaccination, the patient again presented with generalized tonic-clonic seizures that did not resolve with diazepam and did not respond to a loading dose of phenytoin, requiring additional levetiracetam impregnation and induction. He was admitted to intensive care for deterioration of consciousness, seizures and dysautonomic syndrome (fever, tachycardia, tachypnea, profuse diaphoresis and hypotension). Physical examination revealed horizontal nystagmus, sialorrhea, hyperreflexia, myoclonus of the right upper

and lower limbs, and dyskinetic movements of the mouth and extremities.

Complementary tests were ordered, including haemogram, renal and liver profile, ionogram, thyroid hormones and vitamin B12 levels, which were normal. Cerebrospinal fluid (CSF) analysis, meningitis-encephalitis panel, imaging studies and electroencephalogram were also performed. CSF polymerase chain reactions for bacteria, viruses and fungi were negative. CSF cytochemistry at 14 and 19 days after symptom onset showed pleocytosis, adequate CSF albumin/serum ratio, protein, glucose and lactate dehydrogenase (LDH) within normal limits (Table 1), and culture without bacterial growth.

Table 1. Cytochemical study of cerebrospinal fluid

Date: 06/07/2024: (14th day following the initial onset of the clinical condition)	Date: 10/07/2024: (19th day following the initial onset of the clinical condition)
pH: 8	pH: 8
WBC: 32 000	WBC: 14 000
Neutrophils: 9 %	Neutrophils: 14 %
Lymphocytes: 91 %	Lymphocytes: 86 %
Protein: 16.7 mg/dL	Protein: 29.8 mg/dL
Albumin: 10.9 mg/dL	Albumin: 18.8 mg/dL
Glucose: 70.9 mg/dL	Glucose: 79.3 mg/dL
LDH: 11.8 u/L	LDH: 9.78 u/L
RBC: ++	RBC: abundant

WBC: White blood cells  
LDH: Lactate dehydrogenase  
RBC: Red blood cells

We did not identified alterations on cranial tomography and magnetic resonance imaging of the brain, both simple and contrasted. The 15-minute electroencephalogram (performed 48 hours after admission for logistical reasons), with the patient in a waking state and with anti-commitment treatment in place, reported a generalized delta rhythm of greater amplitude in the left hemisphere and bilateral frontal regions.

During the consultation with the neurology specialty, the possible diagnosis of autoimmune encephalitis was suggested on the basis of the following criteria: CSF pleocytosis, abnormal electroencephalogram (slow activity), altered mental status, psychiatric symptoms, cognitive alterations and exclusion of other etiologies (infectious, metabolic, traumatic, ischemic, hemorrhagic and toxicological).

In consideration of the established association between autoimmune encephalitis and preneoplastic syndromes, we conducted studies to identify extracranial neoplasms. These studies involved the utilisation of computed axial tomography of the thorax, abdomen and pelvis, in addition to the assessment of tumour markers. The results of these studies were normal. Testicular ultrasound revealed a simple cyst of the left epididymis, which was deemed to be of no clinical significance. We suspected that autoimmunity was triggered by the dT vaccine.

## Treatment

The patient was initiated on a course of specific treatment involving human immunoglobulin (20 grams daily, calculated to a body weight of 50 kg) for a duration of five days. However, this treatment did not result in any clinical improvement. Consequently, a prescription of one gram of methylprednisolone was issued for a period of three days, followed by six sessions of plasmapheresis. In response to the seizures observed during the initial admission, treatment with phenytoin and levetiracetam was initiated to address the periods of irritability and psychomotor agitation, antipsychotics such as quetiapine and haloperidol were administered. The dysautonomic syndrome was managed with the administration of propranolol.

## Outcome

During his stay in intensive care, his mental state fluctuated between hypersomnia and periods of psychomotor agitation with verbigeration and abnormal postures. Dyskinetic movements, myoclonias and oculogyric crises were frequent.

After a lack of response to immunoglobulin, corticoid pulses and plasmapheresis were indicated. From the third plasma exchange session onwards, a significant clinical progress was observed, with improvement of attention state, gradual cessation of dyskinesias and improvement of wakefulness.

At 72 hours after the end of the six plasmapheresis sessions, he showed behavioural control with no psychiatric symptoms, he interacted with the environment and carried out simple commands, but he still had gait ataxia and speech recovery was slow. Four weeks after hospitalisation, he was discharged with treatment of prednisone 50 mg daily (with gradual tapering), azathioprine 50 mg daily, quetiapine 50 mg

three times a day, risperidone 1 mg one hour before bedtime and physiotherapy.

We did outpatient monitoring, and four months after discharge from hospital, he had preserved higher mental functions and normal gait, but continued to have dysarthria.

## Clinical diagnosis

The diagnosis was confirmed by CSF antibody analysis by indirect immunofluorescence technique, which was positive with a titer greater than 1/10 for anti-NMDAR antibodies.

## Discussion

Anti-NMDAR encephalitis is the most studied form of autoimmune encephalitis, affecting one in 1.5 million people per year,<sup>iii,v</sup> tiene predilección has a female predilection with a female to male ratio of 4:1,<sup>viii</sup> and although it predominates in young people, the age of the affected population ranges from two months to 85 years.<sup>viii,ix</sup>

In its paraneoplastic aetiology it is associated with tumours such as ovarian teratoma, lung cancer, breast cancer, testicular tumours, thymic carcinoma, pancreatic cancer, prostate cancer, Hodgkin's lymphoma, pineal dysgerminoma, neuroblastoma, and other benign and precancerous lesions.<sup>x</sup> In men and young people, the tumour relationship is less frequent,<sup>x</sup> but after the diagnosis of encephalitis by anti-NMDAR, it is indicated to rule out the above neoplasms.<sup>iii</sup>

Clinical manifestations of autoimmune encephalitis include neuropsychiatric signs and symptoms such as apathy, anxiety, fluctuating consciousness, bizarre behaviour, dyskinesias, aphasia, amnesia, apraxia, sleep-wake cycle disorder, irritability and delirium, focal or generalised seizures, and dysautonomic disturbances.<sup>xi</sup>

The diagnosis of anti-NMDAR autoimmune encephalitis is complex. Infectious, toxic, metabolic, psychiatric, rabies, demyelinating disorders, gliomas, lymphomas, prion illnesses and other autoimmune diseases must be excluded.<sup>xii-xiv</sup>

Proposed criteria for considering a possible autoimmune encephalitis include: rapid onset of symptoms (less than three months), psychiatric symptoms, movement disorders, decreased level of consciousness, cognitive impairment, seizures, signs of neurological focalization, speech dysfunction, dysautonomia, abnormal electroencephalogram, pleocytosis or oligoclonal bands in CSF, and exclusion of other causes.<sup>xiii-xv</sup> This patient fulfilled all of the above criteria.

IgG anti-NMDAR antibodies are detected by indirect immunofluorescence in serum and CSF,<sup>iii</sup> with analysis in CSF being more cost-effective due to its higher sensitivity. In a recent study, the sensitivity for detecting the presence of anti-NMDAR antibodies in blood was 68-73 %, whereas the sensitivity in CSF was 99 %; in both cases, the specificity is 99 %.<sup>xvi</sup> Anti-NMDAR antibody titers in CSF and blood may vary depending on the time of diagnosis (they are always present in CSF but only 13.2 % in serum);<sup>xvii</sup> association with paraneoplastic processes (high serum titers are more often associated with teratomas); finally, high antibody titers are associated with poor prognosis.<sup>xvi,xviii</sup>

The electroencephalogram may show non-specific findings such as generalised slowing with theta or delta waves, focal or generalised seizures, excessive beta activity, extreme brush delta.<sup>xiii,xviii</sup>

Regarding imaging studies, magnetic resonance imaging (MRI) shows changes in only 20-50 % of patients and is often normal or with mild changes even in comatose patients with anti-NMDAR encephalitis.<sup>xi</sup> In the early stages, MRI shows normal images; however, three to six months after clinical onset, hyperintense lesions can be observed in the temporal lobe, occipital and hippocampal areas, particularly on Fluid Attenuated Inversion Recovery (FLAIR) sequence.<sup>xix</sup>

The primary treatment for autoimmune encephalitis includes corticosteroids (1 g of methylprednisolone IV for 3-5 days), intravenous immunoglobulins (0.4 g/kg/day for five days) and plasmapheresis.<sup>iii</sup> Initial immunotherapy has been shown to produce improvement in 53 % of patients within the first four weeks, and 97 % show favourable results at 24 months.<sup>x</sup> A significant recovery (absence of sequelae or minimal disability) is observed in 75 % of patients with NMDA receptor antibody encephalitis, while the remaining 25 % may exhibit severe deficits or eventual mortality.<sup>x</sup>

In relation to long-term immunosuppressive therapies, such as rituximab, cyclophosphamide, mycophenolate mofetil and azathioprine, there is a lack of substantial data regarding their efficacy. Nonetheless, these therapies are typically recommended with the objective of attenuating disease severity, minimising chronic corticosteroid utilisation, ensuring prolonged disease management and mitigating the risk of recurrence.<sup>xx</sup>

In the analysis of this case, it is necessary to consider the differential diagnosis with rabies encephalitis. Firstly, rabies is known to produce significant psychiatric alterations, including extreme agitation, altered levels

of consciousness, abnormal movements, hypersalivation and other autonomic alterations that are similar to those seen in anti-NMDAR encephalitis.<sup>xxi</sup> However, rabies presents with aerophobia and hydrophobia, elevated CSF protein levels,<sup>xxii</sup> and, in contrast to anti-NMDAR encephalitis, brain MRI is frequently normal. Conversely, MRI of rabies patients often reveals symmetric grey matter involvement of the dorsal brainstem, thalamus, basal ganglia, or central region of the spinal cord.<sup>xxiii,xxiv</sup> Once symptoms have manifested, there is no treatment for rabies.<sup>xxi</sup> In this patient, the diagnosis of rabies encephalitis was excluded on the basis of a comprehensive analysis of the clinical and radiological data. This determination was made in light of the patient's history of rabies immunization, the absence of any suspicious signs exhibited by the dog, and the absence of any documented cases of rabies in humans in Ecuador over the past 14 years.<sup>xxv</sup>

Although autoimmune encephalitis can be idiopathic, the most common triggers are viral and paraneoplastic diseases.<sup>xxvi</sup> However, cases of autoimmune encephalitis have been reported in association with a history of recent vaccination. In the study on disproportionality conducted by Martin *et al.*,<sup>xvii</sup> which utilised pharmacovigilance data from the World Health Organization, 51 vaccines were identified as potentially associated with the occurrence of anti-NMDAR encephalitis, including: The following vaccines are recommended: human papillomavirus (HPV), diphtheria/pertussis/tetanus/polyomyelitis (DTP-polio), influenza, varicella-zoster, pneumococcal, *Haemophilus influenzae* type b, SARS-CoV-2, yellow fever, rabies, typhoid, hepatitis A and B. The median time to onset of illness following vaccination was found to be four days (range: 0-730). The most probable vaccines associated with anti-NMDAR encephalitis were HPV (15.7 %), DTP-polio (15.7 %), and influenza (13.7 %), with the likelihood ratio demonstrating a higher probability with DTP-polio.<sup>xviii</sup>

One hypothesis that aims to explain the pathophysiology of vaccines as triggers of anti-NMDAR autoimmune encephalitis is the molecular mimicry of the microRNA of the viral or bacterial particles used in vaccines and the proteins of the NMDA receptor.<sup>xxviii</sup> While the development of anti-NMDAR encephalitis in this patient cannot be directly attributed to vaccination, the existence of a temporal relationship, in addition to the exclusion of other potential causes, raises the possibility of a post-vaccination event. The aforementioned

fact was communicated to the National Health System of Ecuador.

Autoimmune encephalitis has been observed to result in neuropsychiatric symptoms, often accompanied by frequent and disabling sequelae that may persist for weeks or months. The early initiation of and response to first-line treatment were found to be valuable predictors of prognosis in this patient. Consequently, the implementation of meticulous monitoring post-discharge facilitates the identification of persistent cognitive, psychiatric, motor, or linguistic impairments, which necessitate rehabilitation and/or pharmacological interventions.

Differential diagnoses of autoimmune encephalitis include viral encephalitis, such as rabies, however, clinical and epidemiological knowledge guide the diagnosis.

Although autoimmune encephalitis may be idiopathic, the observed relationship between vaccination and the onset of this disease, as well as the documented case reports that link these two factors, give rise to the hypothesis of an anti-NMDAR encephalitis that manifests in the aftermath of vaccination, particularly in instances involving the dT vaccine. Nevertheless, that the causal relationship between these two factors remains unconfirmed.

Vaccines have been shown to have a significant impact on the reduction of morbidity and mortality associated with infectious diseases. However, it is important to acknowledge the minor adverse effects that have been observed. The timely identification of these effects enables the implementation of necessary measures, which can contribute to achieving optimal recovery rates. In order to improve upon and validate these findings, it is necessary to conduct large-scale, prospective, randomized, controlled studies that establish a causal relationship between autoimmune encephalitis and vaccination.

## Ethical aspects

Informed consent was obtained from the patient's legal representative (the mother) for the use of clinical data and the publication of results. It is asserted that the ethical guidelines for human research established by the Ministry of Public Health of Ecuador and the Helsinki Declaration were adhered to in their entirety throughout the course of the study..

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