Clinical Case Report

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# Anti-*N*-methyl-D-aspartate receptor encephalitis associated with acute *Toxoplasma gondii* infection

## A case report

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**Abstract**

**Rationale:** Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis has been recognized as the most frequent autoimmune encephalitis in children. Several infectious agents have been implicated in anti-NMDA encephalitis.

**Patient concerns:** A previously healthy immunocompetent 9-year-old girl first presented with seizures, headaches and vomiting. Cerebrospinal fluid and brain magnetic resonance imaging were normal. After one week onset, the patient gradually developed unexplained personality and behavior changes, accompanied by fever and seizures again. Repeated CSF analysis revealed a slightly lymphocytic predominant pleocytosis and positive anti-NMDAR antibody. A variety of pathogenic examinations were negative, except for positive toxoplasma IgM and IgG.

**Diagnoses:** The patient was diagnoses for anti-NMDA encephalitis associated with acute acquired toxoplasma gondii infection.

**Interventions:** The patient received 10 days azithromycin for treatment of acquired toxoplasma infection. The parents refuse immunotherapy because substantial recovery from clinical symptoms.

**Outcomes:** The patient was substantially recovered with residual mild agitation after therapy for acquired toxoplasma gondii infection. Two months later, the patient was completely devoid of symptoms, and the levels of serum IgM and IgG of toxoplasma gondii were decreased.

**Lessons:** Acquired toxoplasma gondii infection may trigger anti-NMDAR encephalitis in children, which has not been reported previously. Clinicians should assess the possibility of toxoplasma gondii infection when evaluating a patient with anti-NMDA encephalitis.

**Abbreviations:** CSF = cerebrospinal fluid, CT = computerized tomography, EEG = electroencephalography, HIV = human immunodeficiency virus, MRI = magnetic resonance imaging, NMDAR = *N*-methyl-D-aspartate receptor, PCR = polymerase chain reaction.

**Keywords:** anti-NMDA receptor encephalitis, children, *Toxoplasma gondii* infection

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## 1. Introduction

Since its first description in 2007, anti-NMDAR (anti-*N*-methyl-D-aspartate) receptor encephalitis has been recognized as autoimmune encephalitis that is mediated by antibodies recognizing the NR1 subunit of NMDAR and attenuating NMDAR function. This form of encephalitis is characterized by various symptoms, such as memory loss, confusion, emotional disturbances, psychosis, dyskinesis, decrease in speech intelligibility, and seizure.[1–4] Florance et al[5] reported the first pediatric patient (age <18 years) with anti-NMDA receptor encephalitis. Although the clinical manifestation of anti-NMDAR encephalitis in children and adults was similar, most children did not have underlying tumors.[5–7] This autoimmune response to the NR1 subunit of the NMDA receptor is possibly triggered by various infectious agents. Previous reports have suggested that anti-NMDAR encephalitis may be associated with the herpes simplex virus, mycoplasma pneumoniae, measles virus, mumps, and group A hemolytic streptococcus.[6,7]

Although *Toxoplasma gondii* infects a large proportion of the human population, acute acquired *T gondii* infection is usually asymptomatic or accompanied by lymphadenopathy in immunocompetent children. In rare cases it can cause severe neurological disease.[8] To date, anti-NMDAR encephalitis associated with acute acquired *T gondii* infection has not been

reported. In this report, we present the case of an immunocompetent girl who was diagnosed with anti-NMDAR encephalitis associated with acute *T gondii* infection.

## 2. Case report

A 9-year-old previously healthy girl was admitted following 5 seizures accompanied by vomiting and headache in 1 day. There was no history of fever, trauma, infection, vaccination, or drug usage. The neurological examination was normal. Laboratory testing revealed normal erythrocyte sedimentation rate, complete blood count, and biochemistry (blood gas analysis, blood electrolyte, blood ammonia, and blood lactic acid). Chest radiography and ophthalmological examination results were normal. Brain computerized tomography (CT) and magnetic resonance imaging (MRI) were normal. Virus serologic test results for hepatitis A, B, and C; herpes simplex, Epstein–Barr virus, cytomegalovirus, varicella, measles, rubella, mumps, and human immunodeficiency virus (HIV) were negative. Blood culture and tuberculin skin test results were negative. Blood cellular and humoral immunity were normal. Cerebrospinal fluid (CSF) analysis and bacterial culture were negative. Electroencephalography (EEG) was normal. She had complete recovery and was discharged 3 days later.

One week after being discharged home, the girl developed unexplained personality and behavior changes including agitation, amnesia, periods of hyperexcitability, and intolerable paroxysmal skin itching. The patient was readmitted to the pediatric neurological unit, and her medical history was updated with information that the girl had played with neighbor's dog in the previous 6 months. The neurological examination was normal and the skin was free of rash. CSF analysis revealed a lymphocytic pleocytosis ($18 \times 10^6$/L) with 87% lymphocytes and normal glucose and protein levels. CSF polymerase chain reaction test for HSV was negative. Toxicological screening was negative. Testing for antibodies to cell surface or synaptic proteins and oligoclonal bands of immunoglobulin (Ig)G was conducted by Peking Union Medical College Hospital. A repeat brain MRI was normal. The EEG demonstrated 14 Hz sporadic positive spikes without diffuse slow activity, and epileptiform discharges. Serum serologic tests for adenovirus, Epstein–Barr virus, Coxsackie virus, rubella virus, cytomegalovirus, and enterovirus were negative. Mycoplasma antibody was negative. A *T gondii* serologic test result was positive (Table 1). Humoral and cellular immunity tests were normal. After the third day of her readmittance, the patient developed high fever and experienced generalized convulsions for 1 minutes. The patient then began a 10-day course of oral azithromycin. Two weeks after admission, the patient had substantially recovered with residual mild agitation remaining. Subsequently, a positive result for NMDA receptor antibodies was received (positive antibody reactivity in CSF (Fig. 1), weak positive antibody reactivity in serum, other paraneoplastic antibodies, and oligoclonal bands of IgG were negative). Because of her substantial recovery from clinical symptoms, the patient's parents refused immunotherapy including gamma globulin and methyl prednisone. After completing tumor screening via chest and abdomen contrast-enhanced CT and pelvic ultrasound, for which the results were normal, the patient was discharged. She received follow-up 2 months later, and presented with complete resolution of symptoms. *Toxoplasma gondii* serologic test results were rechecked and the levels of serum IgM and IgG had declined notably at this 2-month follow-up (Table 1).

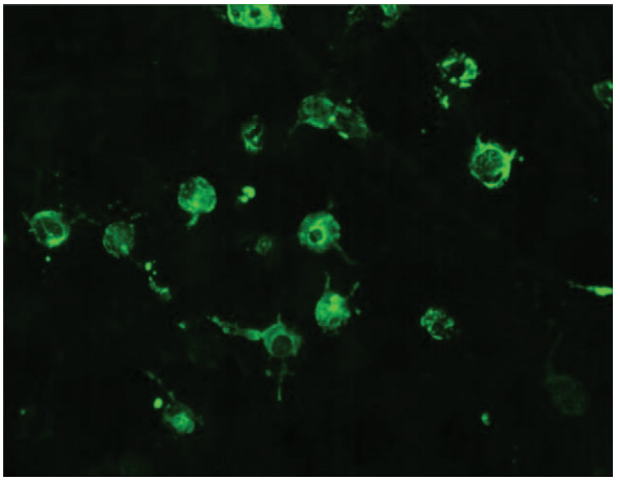

**Figure 1.** Using indirect immunofluorescence method, an anti-NMDA receptor IgG antibody was detected to be positive in the patient's CSF. CSF = cerebrospinal fluid, Ig = immunoglobulin, NMDA = *N*-methyl-D-aspartate receptor.

**Table 1**

***Toxoplasma gondii* serologic test results.**

| Date of testing | IgM, AU/mL | IgG, IU/mL |
|---|---|---|
| Initial | 11.2 | >400 |
| 2 months later | 6.3 | 181 |

*Toxoplasma gondii* serologic IgM: Negative <6.0 suspicious 6.0–8.0 positive >8.0.
*Toxoplasma gondii* serologic IgG: Negative <7.2 suspicious 6.0–8.8 positive >8.8.
Ig = immunoglobulin.

## 3. Discussion

In this patient, the clinical presence of psychiatric symptoms, seizure, and paresthesia, accompanied by positive NMDA receptor antibodies in CSF and serum, led to consideration of a diagnosis of anti-NMDAR encephalitis.[1–4] Anti-NMDAR encephalitis was first described in a young woman with ovarian teratoma and initially found in association with thymomas and other tumors. However, an increasing number of cases have been reported in children without tumors.[5–7] The NMDA receptor is found in dense concentrations in the hippocampus, which is involved in spatial learning and long-term potentiation, both of which are key features of memory formation.[1,9–11] The clinical finding that patients with anti-NMDAR encephalitis experience persistent amnesia is consistent with the NMDA receptor's role in learning and memory.[12] It has been hypothesized that sustained hypoactivity of the NMDAR receptor is thought to underlie the pathogenesis of schizophrenia and hyperactivity linked to psychosis, Alzheimer's disease, and now autoimmune encephalitis.[1,10,11] The mechanism that begins the autoimmune process is currently unclear.

Approximately 50% of these patients have a tumor that was suspected to have triggered the syndrome (most frequently an ovarian teratoma)[12]; in contrast, in the pediatric population, the condition is most commonly diagnosed in the absence of tumors.[5] Although the phenotype in children has the same characteristic as that of adults, there are significant differences with respect to the association with tumor.[5,13] The mechanism

that triggers the autoimmune process may differ between adults and children.

Recent reports suggest that postinfectious immune-mediated etiology may be linked to anti-NMDAR encephalitis without a tumor association.[5–7,12–15] Various infectious agents can damage the blood–brain barrier and trigger a synaptic inflammatory response. Sutcu et al[16] reported 7 pediatric cases of post-herpes simplex virus encephalitis relapses associated with autoantibodies against NMDA receptors. Prüss et al[17] reported that 30% of patients with simplex herpes virus encephalitis had NMDAR antibodies detected in serum or CSF. In some patients with anti-NMDAR encephalitis, there are associations with other pathogens, including *Mycoplasma pneumoniae*[5,6,18] and influenza viruses A and B, *Chlamydophila pneumoniae*, *Bordetella pertussis*, *Bordetella parapertussis*,[19] densovirus,[20] varicella zoster virus,[21] and Epstein–Barr virus.[22]*Toxoplasma gondii* infection may trigger anti-NMDAR encephalitis; this possibility has not been reported previously.

In our case, brain viral infection seems unlikely because viral screenings were negative and cranial MRI studies were normal. Because our patient was positive for CSF *T gondii* antibodies and psychosis is an atypical symptom of toxoplasmic encephalitis,[8,23,24] we need to distinguish psychiatric disorders induced by *T gondii*. Toxoplasmic encephalitis is a common opportunistic infection in patients with acquired immunodeficiency syndrome[8,25] that is rarely observed in patients with normal immune function. A presumptive diagnosis of toxoplasmic encephalitis requires the following 3 stipulations: clinical manifestations, positive IgG for blood *T gondii*, and characteristic neuroradiological abnormalities.[25,26] Typical patients with toxoplasmic encephalitis present with fever, headache, seizures, psychosis, altered mental status, and focal neurologic symptoms. Goïta[26] reported the clinical characteristics of cerebral toxoplasmosis in patients with HIV infection as focal neurological deficits (73.07%), signs of intracranial hypertension (69.20%), meningeal syndrome (15.40%), seizures (57.69%), and consciousness disorders (30.80%). Neuroimaging studies are crucial in the diagnosis of toxoplasmosis encephalitis. *Toxoplasma gondii* cysts can invade the central nervous system, causing perivascular inflammation that gradually progresses to necrotizing encephalitis. Brain MRI reveals multiple ring-enhancing lesions surrounded by edema. Lesions are most often located in the subcortical white matter, the basal ganglia, or the brainstem.[27] In our case, the patient's innate immune state was normal, serum HIV test was negative, brain MRI images were normal, and CSF examination was nearly normal; clinical manifestations consisted of psychiatric symptoms, seizure, and paresthesia without focal neurological symptoms. Therefore, we do not believe that there was reasonable evidence by which to diagnose toxoplasmosis encephalitis.

Psychosis may occur in systemic toxoplasmic infection, but not as a major clinical manifestation.[26] At the same time, some investigations of patients with psychosis (i.e., schizophrenia, bipolar disorder, and depression) have revealed a higher prevalence of IgG antibodies to *T gondii* compared to neurotypical individuals.[28] The underlying mechanism that links *T gondii* infection and psychiatric disorders is unclear. Huber et al suggested that toxoplasmosis might induce elevated levels of dopamine in the mouse brain. Animal research shows that *T gondii* infection may trigger an inflammatory response and impair the blood–brain barrier.[29] Recently, Hayes et al[28] found increased inflammatory molecules in patients with psychiatric disorders induced by toxoplasma infection, which suggests that the immune system participates in the psychiatric disorders induced by *T gondii* infection. In our case, we found anti-NMDA receptor antibodies in CSF; as such, we speculate that anti-NMDA receptor antibodies may be one of the possible causes of psychiatric symptoms induced by toxoplasma infection. We suggest that CSF should be tested for anti-NMDA receptor antibodies in patients with acquired toxoplasma infection who present with psychiatric symptoms. This speculation needs to be validated in more patients with toxoplasma infection.

The immunoreaction of NMDAR antibodies is reversible, and the immune response is self-limiting.[30] Titular et al[3] reported 577 cases of anti-NMDAR encephalitis, 29 cases were not treated with immunotherapy or surgery, and 70% had a good outcome. Spontaneous improvement has also been described by other authors.[16,30,31] In our patient, the clinical symptoms were atypical; the level of anti-NR1 receptor antibodies was not notably high (antibody reactivity in CSF was positive, and there was weak positivity for the antibody in serum) and after anti-*T gondii* treatment by oral azithromycin, the patient recovered without immunotherapy.

Taken together, the biphasic course of symptoms of our patient, along with CSF positive for NMDAR antibodies, a positive *T gondii* serologic test, no additional changes in the brain MRI, and improved clinical symptoms after anti-*T gondii* treatment suggested that this patient with acquired *T gondii* infection may have contracted anti-NMDAR encephalitis. This possible link between both disorders also suggests a post-infectious immune-mediated etiology. Future studies should address these issues in clinical trials.

## 4. Conclusion

Anti-NMDA receptor encephalitis in children is generally associated with a postinfection state rather that the presence of tumor. Acute *T gondii* infection could trigger anti-NMDA receptor encephalitis. Appropriate treatment helps relieve symptoms and foster a good prognosis.

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