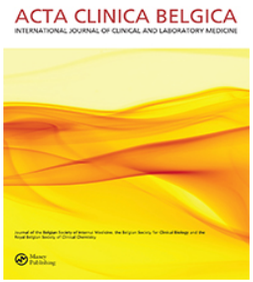

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Case Report

# AN UNUSUAL CASE OF ACUTE PSYCHOSIS IN AN ADOLESCENT

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## ABSTRACT

Anti-N-methyl-D-aspartate receptor (NMDA-R) encephalitis is a severe form of encephalitis that has been identified within the context of acute neuropsychiatric manifestations. We report the case of an 18-year-old adolescent referred for a first episode of acute psychosis. The clinical picture rapidly deteriorated to a state of catatonia, decreased consciousness and autonomic instability. Detection of highly positive anti-NMDA-R antibodies confirmed the diagnosis of anti-NMDA-R encephalitis. Immunosuppressive treatment and repeated plasma exchange resulted in slow recovery. The literature on diagnosis and treatment of this specific type of encephalitis is reviewed.

**Key words:** anti-NMDAR-encephalitis, psychosis, immunosuppressive therapy

## INTRODUCTION

A paraneoplastic encephalopathy associated with ovarian teratoma was first described in 2005 (1) and shortly thereafter immunologically identified as anti-NMDA-R encephalitis (2). Many cases, including a series of more than 400 patients of anti-NMDA-R encephalitis have been published since then (3). The exact incidence of anti-NMDA-R encephalitis is unknown. Children and young adults are most at risk. About 80% of the patients are females. Association with a tumour (usually an ovarian teratoma) is more often seen in women older than 18 years and affects more black than white females (3).

## CASE REPORT

An 18-year-old previously healthy female was hospitalised in the psychiatry ward with signs of acute psychosis. Despite treatment, she clinically deteriorated presenting decreased responsiveness, episodes of catatonia and agitation, oro-facial dyskinesia, and dystonic posturing with head deviation. Increasing haemodynamic instability necessitated transfer to the ICU. During her ICU stay, she developed severe respiratory and circulatory failure and had several consecutive septic episodes. Weaning was complicated by neurological "dissonance" characterised by hyperthermia, blood pressure swings and sustained tachy-arrhythmia. She also experienced two episodes of bradycardia followed by transient asystole responding to atropine. Cardiac electrophysiological assessment could not reveal any underlying heart disease. Laboratory tests, including a complete hormonal and tumour biomarker panel, were normal. Infectious screening only showed a positive Mycoplasma pneumoniae serology. Porphyria and other metabolic diseases were excluded. Autoimmune screening was unremarkable except for highly positive anti-NMDA-R antibodies. Brain and full spine magnetic resonance imaging (MRI) were normal. EEGs repeatedly showed a continuous slow wave pattern without epileptic activity. No pleocytosis or abnormal levels of protein and glucose were detected in the cerebrospinal fluid (CSF). However, oligoclonal banding was present in the CSF, but not in serum, compatible with any acute or chronic inflammatory central nervous system disease. Based on the above findings, the diagnosis of anti-NMDA-R encephalitis was put forward. Subsequent extensive, in particular ovarian, cancer screening remained negative.

Treatment was initiated with methylprednisolone 1 g bolus/day for 5 days followed by 10 plasmafiltration sessions and 60 mg methylprednisolone daily. Because of insufficient clinical response, 700 mg/m$^2$ cyclophosphamide was added on a once-monthly basis. After the first bolus, a slow but consistent recovery was observed. The autonomic symptoms were first to disappear, followed by progressive regain of consciousness. Immunosuppressive therapy was continued and after 2 months the patient was discharged from the ICU. Another 2 months later, she left the hospital presenting only discrete frontal signs.

## DISCUSSION

Anti-NMDA-R encephalitis is a multifaceted disease. Atypical prodromal symptoms (headache, fever, nausea, vomiting, and diarrhea) occur in 70% of patients. Within a few days, psychiatric symptoms (anxiety, delusions, paranoia …) arise. Such behavioural changes are difficult to detect in young children. Therefore, initial symptoms in this population are often non-psychiatric (seizures, dystonia, mutism, ...). The primary encephalopathy phase is then followed by a state of disturbed responsiveness with alternating episodes of agitation and catatonia. Motor symptoms such as oro-lingua-facial dyskinaesia, dystonia, oculogyric deviation and opisthotonus are common. Another characteristic feature is autonomic instability which may cause extremely variable and unpredictable swings of blood pressure and heart rate, often necessitating catecholamine treatment or pacemaker insertion. Central hypoventilation, requiring respiratory support, usually occurs as the patient becomes comatose but occasionally develops at an earlier stage of the disease process (3, 4).

In a cohort of 44 consecutive cases of NMDA-R encephalitis, Irani et al. (4) observed a striking dichotomy in time of onset of the clinical features. Neuropsychiatric symptoms and seizures, with a predominant cortical localisation, occurred at disease onset whereas subcortical presentations (motoric disorders, dysautonomia, decreased consciousness, and gaze deviation) appeared 10 to 20 days later (4). However, Dalmau et al. consider the classification into cortical and subcortical stages as a highly inaccurate oversimplification. They rather support the concept of a diffuse encephalopathy characterised by an intricate network of dysfunctional subcortical structures, limbic regions, amygdalae, and frontostriatal circuits (3).

Brain MRI is unremarkable in half of the patients. EEGs are abnormal, mostly showing non-specific, slow and disorganised activity and occasionally epileptic activity. Initially, lymphocytosis and sparse oligoclonal bands are present in the CSF, but with evolving disease, lymphocytosis wanes and oligoclonal bands become more prominent (5). NMDA-R antibodies can be identified both in serum and in the CSF. Ovarian teratomas are typically associated with anti-NMDA-R encephalitis (2). The ovarian teratoma has neural tissue that expresses the NR1 and NR2 subunits of the NMDA receptor which likely acts as antigenic material. Whether other tumours represent true associations or merely unrelated coincident disorders remains to be established (3). A possible role of predisposing racial or genetic factors or an auto-immune trigger effect due to non-specific systemic infections or vaccinations in non-paraneoplastic anti-NMDA-R encephalitis has not been proven. Our patient did not have an underlying malignant disease. Any contribution of the Mycoplasma pneumoniae infection to the observed encephalitis remains hypothetical.

Given its atypical presentation and evolution, anti-NMDA-R encephalitis is not easily diagnosed. Occurring at an early stage in adults, it is often mistaken for acute psychosis and antipsychotic medication is started. When dyskinaesias and autonomic instability emerge, patients are often thought to suffer from neuroleptic malignant syndrome. During the course of the disease, other differential diagnoses must be considered such as propofol infusion syndrome, viral encephalitis, rabies, encephalitis lethargica, … (3). Definite confirmation of anti-NMDA-R encephalitis is obtained by demonstrating the presence of anti-NMDA-R antibodies in serum or CSF. All assays use human embryonic kidney cells, which are transiently transfected with the complementary DNAs encoding for NR1 and NR2B subunits of the NMDA receptor, and subsequently incubated with patient sera. The NR1 subunit is now considered the target subunit and commercial assays are being developed. Clinicians need to check requirements for the antibody assay and technique with their immunology laboratory (4)

There are no established guidelines for treatment of anti-NMDA-R encephalitis. Dalmau et al. (3) propose a treatment algorithm based on own experience and literature data. Treatment should focus on removal of an eventual underlying tumour and immunosuppression. First-line immunosuppressive therapy consists of methylprednisolone 1 g/day for 5 days and concomitant intravenous immunoglobulins (0.4 g/kg/day for 5 days) or plasma exchange. If no response is obtained after 10 days, second-line therapy is started. In adults, Dalmau et al. propose rituximab (375 mg/m$^2$ /week for 4 weeks) combined with cyclophosphamide (750 mg/m$^2$ given with the first dose of rituximab), followed by monthly cycles of cyclophosphamide. This treatment is discontinued when patients have substantial clinical recovery. Paediatricians often prefer to use only one immunosuppressant (3). Irani et al (4) suggest that pulsed intravenous methylprednisolone treatment should be followed by high-dose oral prednisolone administration, which is tapered over a period of 6 to 12 months after hospital discharge.

About 75% of patients with NMDA-R encephalitis recover completely or with mild sequelae. Recovery occurs stepwise and in reverse order of symptom presentation. As autonomic functions stabilise, respiration recovers and dyskinaesias subside, patients awake from coma. Subsequently, patients regain ability to follow simple commands before recovering verbal function. Psychotic symptoms and episodes of agitation may eventually flare up but disappear at further recovery. Social and executive functioning is usually the last to improve. Recovery can take several months and may be incomplete (3,4).

The described case underscores the importance to consider anti-NMDA-R encephalitis as a possible diagnosis in any young individual, and in particular in children or teenagers, who presents a rapidly evolving neuropsychiatric disorder, characterised by severe motoric dysfunction and autonomic instability.

**CONFLICT OF INTEREST:** None.

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