EJCRIM
European Journal
of Case Reports
in Internal Medicine

ANTI-N-METHYL-D-ASPARTATE RECEPTOR ENCEPHALITIS PRESENTING AS ISOLATED FIRST-EPISODE PSYCHOSIS IN A 16-YEAR-OLD GIRL, COMPLICATED BY NEUROLEPTIC MALIGNANT SYNDROME

Ghizlane Khaloui[1,2], Amal Mabkhout[1,2], Linda Rachidi[1,2], Ghizlane Benjelloun[1,2]

[1] Child and Adolescent Psychiatry Department, Abderrahim Harouchi Mother-Child Hospital, Ibn Rochd University Hospital Center, Casablanca, Morocco
[2] Laboratory of Clinical Neurosciences and Mental Health, Faculty of Medicine and Pharmacy, Hassan II University, Casablanca, Morocco

Corresponding author's e-mail: drghyzlane@gmail.com

Received: 07/07/2025
Accepted: 07/07/2025
Published: 16/07/2025

Conflicts of Interests: The Authors declare that there are no competing interests.
Patient Consent: Written informed consent was obtained from the patient and her parents for the publication of her clinical history.
This article is licensed under a Commons Attribution Non-Commercial 4.0 License

How to cite this article: Khaloui G, Mabkhout A, Rachidi L, Benjelloun. Anti-N-methyl-D-aspartate receptor encephalitis presenting as isolated first-episode psychosis in a 16-year-old girl, complicated by neuroleptic malignant syndrome. *EJCRIM* 2025;**12**:doi:10.12890/2025_005679

ABSTRACT

Anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is a rare but increasingly recognized autoimmune disorder that predominantly affects adolescents and young adults. It often presents with prominent psychiatric symptoms at onset, leading to frequent misdiagnosis as a primary psychiatric disorder.

We report the case of a 16-year-old girl who presented with acute psychiatric symptoms, including mood lability, hallucinations, and aggression, initially diagnosed as first-episode psychosis. Her condition rapidly deteriorated under antipsychotic treatment, progressing to neuroleptic malignant syndrome, followed by the emergence of cerebellar ataxia, which raised strong suspicion of an underlying organic aetiology. Subsequent investigations confirmed the diagnosis of anti-NMDAR encephalitis. The patient was successfully treated with intravenous immunoglobulin, achieving complete recovery.

This case underscores the diagnostic challenges posed by isolated psychiatric presentations of anti-NMDAR encephalitis in adolescents. Early recognition and prompt initiation of immunotherapy are crucial for favourable outcomes, particularly in cases presenting with antipsychotic intolerance or atypical clinical progression.

KEYWORDS

Anti-N-methyl-D-aspartate receptor encephalitis, first-episode psychosis, neuroleptic malignant syndrome, adolescent

LEARNING POINTS

- Anti-N-methyl-D-aspartate receptor encephalitis can initially present as an isolated psychiatric syndrome mimicking primary psychosis, particularly in adolescents, often leading to misdiagnosis.
- The development of neuroleptic malignant syndrome during a first-episode psychosis, occurring rapidly and at low antipsychotic doses, should raise suspicion of an organic aetiology, notably autoimmune encephalitis.
- Magnetic resonance imaging, electroencephalogram, and cerebrospinal fluid analysis are essential to distinguish autoimmune encephalitis from primary psychiatric disorders.

EFIM
European Federation of Internal Medicine

Publisher
smc media srl

INTRODUCTION/BACKGROUND

Anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is a rare autoimmune encephalitis first described in 2007[1]. Although initially described in adults, it is now increasingly recognized in children and adolescents, where it may present with isolated psychiatric symptoms, often leading to an initial misdiagnosis as a primary psychiatric disorder[2].

Despite growing awareness, recent studies highlight that diagnostic delays remain common, especially in cases presenting solely with psychiatric manifestations. Moreover, complications such as neuroleptic malignant syndrome (NMS) following antipsychotic administration may serve as critical red flags for underlying autoimmune encephalitis[3,4].

We report a case of anti-NMDAR encephalitis in a 16-year-old girl whose initial presentation was exclusively psychiatric and later complicated by NMS, underscoring the diagnostic challenges and the importance of early recognition.

CASE DESCRIPTION

A 16-year-old female was referred for sudden-onset behavioural changes and sleep disturbances. She had no personal or family psychiatric history and was performing well academically in her first year of high school.

Psychiatric symptoms began 1 week prior to referral, including irritability, mood lability, alternating episodes of psychomotor agitation and social withdrawal with psychomotor slowing, insomnia, and significant difficulties with concentration—despite her previously excellent academic performance.

The clinical course progressed rapidly, marked by the onset of psychotic features, including auditory and visual hallucinations and persecutory delusions. By day 10 after symptom onset, her condition worsened, with increased agitation, verbal and physical aggression towards family members, transient manic-like episodes with euphoria and disinhibition, impulsivity, and multiple suicide attempts by self-inflicted wrist cutting and attempted strangulation, which were prevented by her family.

Initial psychiatric evaluation revealed a tense, irritable, and non-cooperative patient with both verbal and physical aggression. Her speech was intermittently disorganized. She reported auditory and visual hallucinations and expressed persecutory delusions ("Everyone is trying to harm me… they are going to kill me…") accompanied by intense anxiety and emotional distress. A diagnosis of first-episode psychosis was initially suspected based on Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition criteria. Hospital admission was recommended but initially refused by her family.

A comprehensive medical workup showed no abnormalities. Results of complete blood count, liver and renal function tests, serum electrolytes, and toxicology screening (blood and urine) were normal. Screening serologies for human immunodeficiency virus, viral hepatitis, and syphilis were negative. Electrocardiography was also normal, as part of the pre-treatment evaluation.

Low-dose risperidone was initiated at 0.25 mg/day, with gradual titration by 0.25 mg every 24 hours under close outpatient monitoring. However, her symptoms fluctuated daily with no significant improvement. On day 9 of treatment, after reaching 2 mg/day of risperidone, the patient developed a high-grade fever (39 °C), profuse sweating, generalized muscular rigidity, and a shuffling gait. NMS was suspected. Creatine kinase (CK) was elevated at 1,482 IU/l. Risperidone was immediately discontinued, and the patient was admitted to intensive care for hydration and close monitoring of mental status and haemodynamics. Lorazepam was initiated at 2 mg/day. NMS symptoms resolved progressively within 24 hours, with full somatic recovery within 72 hours, although psychiatric symptoms persisted.

Two days later (day 24 of illness), she developed ataxia, with an unsteady, staggering gait and impaired coordination. Further history revealed a flu-like syndrome one week prior to psychiatric symptom onset. Given the atypical psychiatric presentation, resistance to antipsychotics, rapid onset of NMS, and emergence of neurological signs, an organic aetiology was strongly suspected.

Urgent brain magnetic resonance imaging (MRI) revealed cerebellar hyperintensities *(Fig. 1)*. Cerebrospinal fluid (CSF) analysis was positive for anti-NMDAR antibodies. Electroencephalogram (EEG) showed diffuse background slowing, predominantly in the frontotemporal regions, with intermittent generalized delta waves and no epileptiform activity. Based on the clinical presentation, MRI, CSF findings, and the preceding viral prodrome, a diagnosis of anti-

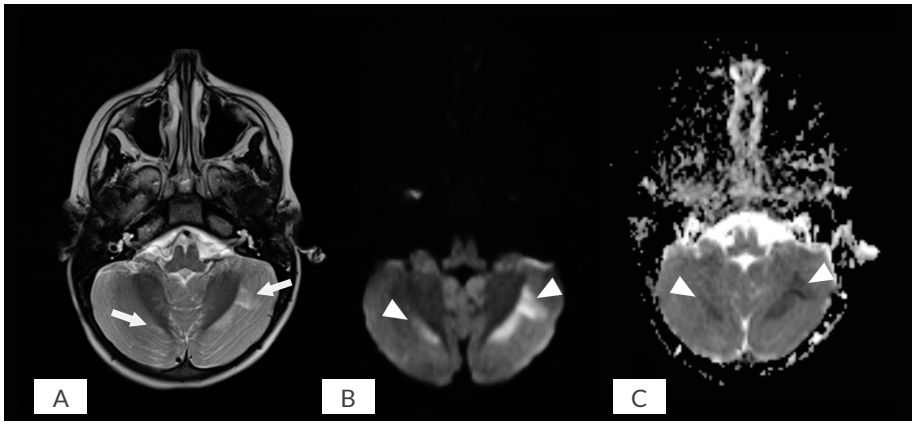


Figure 1. Brain magnetic resonance imaging T2-weighted sequence revealed A) bilateral cerebellar hyperintensity, more pronounced on the left side (arrows). The diffusion-weighted imaging sequence showed B) diffusion hyperintensity in these abnormalities, with corresponding low signal on the apparent diffusion coefficient map (C), consistent with diffusion restriction (arrowheads).

NMDA receptor encephalitis was established. Treatment was initiated in collaboration with the paediatric team, using intravenous immunoglobulins (IVIG) at a total dose of 2 g/kg administered over 5 consecutive days. The clinical course was favourable, with full resolution of psychiatric symptoms within 1 month and progressive neurological recovery, resulting in complete remission within 2 months. By the end of the fourth month, the patient had returned to her premorbid level of functioning, including full academic reintegration.

DISCUSSION

Anti-NMDAR encephalitis has emerged as a leading cause of autoimmune encephalitis in children and adolescents. Its pathogenesis involves IgG1 antibodies targeting NMDA receptors, which disrupt glutamatergic neurotransmission in cortical and subcortical regions, resulting in a wide range of neuropsychiatric symptoms[1,5].

In adolescents, the initial presentation is often dominated by psychiatric symptoms, including mood lability, agitation, psychosis, or catatonia[6]. In our patient, the initial presentation as an acute psychotic episode with no prior psychiatric history highlights the diagnostic challenge of distinguishing a primary psychiatric disorder from autoimmune encephalitis. As in this case, such presentations are frequently misdiagnosed as primary psychiatric disorders, such as schizophrenia or bipolar disorder.

Although psychiatric manifestations are common at onset (reported in up to 80% of cases), presentations completely isolated from neurological features are uncommon, with prevalence estimates of about 3–7% in paediatric series[2].

The occurrence of NMS shortly after antipsychotic exposure, particularly in patients with acute-onset psychiatric symptoms, should raise suspicion of underlying anti-NMDAR encephalitis. This association is increasingly recognized in paediatric and adolescent populations[7].

Recent studies have shown that up to 12% of patients with anti-NMDAR encephalitis treated with antipsychotics may develop NMS-like symptoms[4]. The pathophysiological link likely involves NMDA receptor hypofunction with consequent dopaminergic dysregulation[5].

Neuroimaging findings in anti-NMDAR encephalitis are often subtle or even normal but may reveal nonspecific abnormalities, such as cortical or subcortical hyperintensities, most commonly in the medial temporal lobes or cerebellum. The cerebellar hyperintensity observed in our patient, although unusual, has been described in paediatric cases, particularly those with demyelinating features[5].

EEG typically reveals nonspecific abnormalities, such as generalized or focal slowing, and can support the diagnosis in the appropriate clinical context. The extreme delta brush (EDB) pattern, considered more specific to anti-NMDAR encephalitis, was not observed in our patient. Nevertheless, its absence does not exclude the diagnosis, as EDB is detected only in a subset of patients, often those with more severe disease[8].

Our patient's CSF was positive for anti-NMDAR antibodies, confirming the autoimmune aetiology of her presentation. Notably, antibody titres in CSF have been shown to correlate better with disease activity and prognosis than serum titres, underscoring the importance of CSF testing even when serum testing is available[9].

First-line treatment consists of high-dose corticosteroids, intravenous immunoglobulins IVIG, and/or plasma exchange. Our patient was treated with IVIG at a total dose of 2 g/kg administered over 5 days, leading to complete resolution of psychiatric symptoms within 1 month and full neurological recovery within 2 months. This case highlights the importance of early recognition and prompt treatment, which are associated with a favourable prognosis, particularly in young patients[10].

CONCLUSION

Anti-NMDAR encephalitis should be considered in adolescents presenting with acute-onset, atypical psychiatric symptoms, particularly when associated with poor response to antipsychotics, neurological deterioration, or features of NMS. Early recognition and timely initiation of immunotherapy are essential to optimize outcomes and reduce the risk of acute complications as well as long-term sequelae.

REFERENCES

1. Dalmau J, Tüzün E, Wu HY, Masjuan J, Rossi JE, Voloschin A, et al. Paraneoplastic anti-N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. *Ann Neurol* 2007;**61**:25-36. doi: 10.1002/ana.21050
2. Kayser MS, Titulaer MJ, Gresa-Arribas N, Dalmau J. Frequency and characteristics of isolated psychiatric episodes in anti–N-methyl-d-aspartate receptor encephalitis. *JAMA Neurol* 2013;**70**:1133-1139. doi: 10.1001/jamaneurol.2013.3216
3. Sarmiento RJC, Diestro JDB, Antonio AKD, Prado MB, Adiao KJB, Dioquino-Maligaso CP. Neuroleptic Malignant Syndrome in a Patient With Anti-N-Methyl-D-Aspartate Receptor Encephalitis: Case Report and Review of Related Literature. *Neurohospitalist* 2022;**12**:80-85. doi: 10.1177/19418744211002978
4. Ramirez-Bermudez J, Restrepo-Martinez M, Espinola-Nadurille M, Martinez-Angeles V, Lopez-Hernandez JC, Hernandez-Vanegas LE, et al. Examining the Features of Neuroleptic Malignant Syndrome in Anti-NMDA Receptor Encephalitis: A Case-Control Study. *J Acad Consult Liaison Psychiatry* 2024;**65**:222-230. doi: 10.1016/j.jaclp.2023.12.002
5. Li Y, Luo H, Zheng Y, Zhou L, Jiang Y, Li X, Ma J, et al. Pediatric anti-NMDAR encephalitis with demyelination on brain MRI: A single center study. *Mult Scler Relat Disord* 2023;**80**:105063. doi: 10.1016/j.msard.2023.105063
6. Barry H, Hardiman O, Healy DG, Keogan M, Moroney J, Molnar PP, et al. Anti-NMDAR encephalitis: an important differential diagnosis in psychosis. *Br J Psychiatry* 2011;**199**:508-509. doi: 10.1192/bjp.bp.111.092197
7. Lejuste F, Thomas L, Picard G, Desestret V, Ducray F, Rogemond V, et al. Neuroleptic intolerance in patients with anti-NMDAR encephalitis. *Neurol Neuroimmunol Neuroinflamm* 2016;**3**:e280. doi: 10.1212/NXI.0000000000000280
8. Schmitt SE, Pargeon K, Frechette ES, Hirsch LJ, Dalmau J, Friedman D. Extreme delta brush: a unique EEG pattern in adults with anti-NMDA receptor encephalitis. *Neurology* 2012;**79**:1094-1100. doi: 10.1212/WNL.0b013e3182698cd8
9. Gresa-Arribas N, Titulaer MJ, Torrents A, Aguilar E, McCracken L, Leypoldt F, et al. Antibody titres at diagnosis and during follow-up of anti-NMDA receptor encephalitis: a retrospective study. *Lancet Neurol* 2014;**13**:167-177. doi: 10.1016/S1474-4422(13)70282-5
10. Nosadini M, Mohammad SS, Ramanathan S, Brilot F, Dale RC. Immune therapy in autoimmune encephalitis: a systematic review. *Expert Rev Neurother* 2015;**15**:1391-1419. doi: 10.1586/14737175.2015.1115720