First Bahraini adolescent with anti-NMDAR-Ab encephalitis
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ABSTRACT
Anti-N-methyl-D-aspartate-receptor (NMDA-R) encephalitis is a new autoimmune, often paraneoplastic disorder that presents with complex neuropsychiatric symptoms. It was first described in 2007 by Dalmau et al. Our patient presented with headache, behavioral changes and then seizures with hallucinations. She was initially misdiagnosed to have schizophrenia and was prescribed antipsychotics. She deteriorated and developed further seizures with hypoventilation and choreoathetosis. Her blood investigations were positive for mycoplasma IGM. Her CSF studies showed high white cell counts, predominantly lymphocytes, and high anti-NMDA-R titre. Her brain MRI scans showed high T2 and FLAIR intensities in the grey and white matter of the left cerebellar hemisphere suggestive of acute disseminated encephalomyelitis. She responded to treatment with antibiotics, multiple antiepileptics, steroids and needed five sessions of plasmapheresis. There was no underlying malignancy on repeated scanning of the abdomen. She needed around one year for full recovery with intensive rehabilitation. The objective of this paper was to highlight the occurrence of this fairly new, challenging, easily missed, not-so-rare form of encephalitis often occurring in the absence of fever.

Keywords: anti-N-methyl-D-aspartate receptor antibody (anti-NMDAR-Ab), encephalitis, central nervous system (CNS), acute disseminated encephalomyelitis (ADEM)

INTRODUCTION
Autoimmune encephalitis is an exciting group of disorders that is eminently treatable and should be considered in the differential diagnosis of any child presenting with a picture of encephalitis with no other
explanation. Encephalitis with anti-\(N\)-methyl-D-aspartate receptor antibody (anti-NMDAR-Ab) has been recognized as the most frequent autoimmune encephalitis in children after acute disseminated encephalomyelitis (ADEM).\(^1\) It was first described in 2007 by Dalmau and colleagues\(^2\) and since then, hundreds of cases have been reported worldwide. It is often a paraneoplastic disorder that presents with neurological, psychological and autonomic nervous system disturbances. Through an illustrative case example, we report an initially missed classic case of anti-NMDAR-Ab encephalitis. This is the first adolescent to be described in Bahrain and the Arabian Gulf region.

**CASE PRESENTATION**

A 13-year-old Bahraini girl initially presented to a private hospital with a two day history of agitation and new onset of severe continuous bitemporal headache associated with slurring of speech. She had no history of fever, trauma, drug intake or migraine. She had no other past medical history of significance. Her birth and developmental histories were normal. She always performed well in school. Her mother had a long history of a generalized seizure disorder, which was controlled with medication. Her other family members were healthy. She was investigated for a possible cranial lesion and/or seizure, with a brain CT scan and an electroencephalogram (EEG) performed, both of which were normal. The following day she reported both vague auditory and visual hallucinations as well as fatigue. She was seen by a psychiatrist and prescribed antipsychotics for psychosis. Over the following few days, her condition worsened with a new onset of generalized tonic clonic seizures lasting for two minutes. She then presented to the emergency department at our hospital and required pediatric intensive care unit admission for monitoring and further work up. Upon examination, she was afebrile. Her blood pressure, heart rate and saturation were within normal limits. She was opening her eyes spontaneously and obeying simple commands with occasional inappropriate speech. Her Glasgow Coma Scale was 13. Her pupils were constricted bilaterally with sluggish reaction to light. Fundoscopy was normal. Her muscle tone was decreased with generalized diminished deep tendon reflexes. Her plantar responses were equivocal. Her gait was normal. She had no signs of incoordination.

Other systems examination were unremarkable. She developed further seizures with shallow breathing, for which she was intubated and started on midazolam infusion, intravenous phenytoin and phenobarbitone. Her EEG showed generalized delta rhythm with sharply contoured waves over the left frontotemporal region. Valproic acid, levetiracetam and clonazepam were all needed for seizure control. She was worked up for causes of neuropsychiatric diseases such as infectious and autoimmune encephalitis with extensive laboratory investigations including complete blood counts, ANA, anti-dsDNA, C3, C4, serum copper, ceruloplasmin, urine porphobilinogen and all were normal pending the result of anti-NMDAR-Ab. Her serological tests for herpes, influenza, EBV, CMV and RSV were negative except for mycoplasma IgM. She was started empirically on IV acyclovir and ceftriaxone along with oral clarithromycin. She received 1 g/kg/dose of intravenous immunoglobulins (IVIG) once daily for two days. Cerebrospinal fluid (CSF) analysis showed pleocytosis with WBC count of 60 cells/high power field (normal 0–5 cells/high power field) and 96% lymphocytes (normal 60–70% lymphocytes) with normal glucose and protein concentrations. CSF oligoclonal bands were negative. Polymerase chain reaction (PCR) analysis of the CSF for enterovirus, CMV, herpes, EBV and mycoplasma was negative. The antibiotics were discontinued when her blood and CSF cultures returned negative. Acyclovir was then discontinued upon obtaining negative PCR viral study of her CSF. Her brain and entire spine magnetic resonance imaging (MRI) scans showed a non-sectoral lesion that was of a high signal intensity in both T2 and FLAIR involving the grey and white matter of the left cerebellar hemisphere with no spinal involvement, suggestive of ADEM and less likely of an infectious process (Fig. 1). Having excluded infection and presuming "autoimmune etiology" we proceeded with an empiric trial of steroids and intravenous pulse methyl prednisolone 30 mg/kg dose every six hours for five days which was given followed by maintenance with oral prednisolone. Anti-NMDAR-Ab assay from CSF, IgG isotype result was 1:16 (reference value 1:1). It was obtained by qualitative indirect immunofluorescence testing done at Bioscientia Institut für Medizinische Diagnostik (Ingelheim am Rhein, Germany). The result was obtained three weeks after admission. Anti-NMDAR-Ab were not identified in her serum. High anti-NMDAR-Ab confirmed our suspicion of First Bahraini adolescent with anti-NMDAR-Ab encephalitis Almuslamani and Mahmood
anti-NMDAR-Ab encephalitis. She was extubated around that time and noted to be in a catatonic state; mute, with reduced level of communication and poor appetite for food with periods of occasional agitation. She was responsive to pain, turning in bed with dystonic posturing, some choreoathetoid movements of the limbs and facial grimacing. She was accordingly started on trihexyphenidyl for dystonia and haloperidol for chorea and periodic agitation. Despite ongoing physiotherapy over a period of four weeks, she developed spasticity in her lower limbs for which baclofen was added. Her dystonia and choreoathetosis did not improve; accordingly she was given five sessions of plasmapheresis over ten days. A repeat MRI scan of her brain and entire spine showed complete resolution of the signal abnormality in the left cerebellar hemisphere with no spinal involvement (Fig. 2). She developed paralytic ileus with abdominal distension and was investigated with repeated ultrasound and CT scans of her abdomen, but neither showed any evidence of a tumor. Her family refused a follow up CSF study for anti-NMDAR-Abs.

A multidisciplinary team approach was needed. During the acute stage of the disease, the intensivists’ role was focusing on patient stabilization and intubation together with the neurologists for seizure control. Other specialist roles were involved in managing complications and rehabilitation including psychiatrists, physiotherapists, occupational therapists, speech therapists and nutritionists. Each specialists’ individualized evaluation and recommendations were obtained regularly as well as a general consensus on patient care. Over the following two months, she showed signs of improvement with seizure control, decreased spasticity and improved speech. She continued to have occasional choreoathetoid movements. Her Modified Rankin Scale scored 4 (moderately severe disability, unable to attend to own bodily needs without assistance, and unable to walk unassisted). Anticonvulsants were weaned off over the following six months. She was followed up in the outpatient clinic and noted to improve remarkably with disappearance of the extrapyramidal symptoms, regaining normal functional mobility with good recall and fluent speech. Her Modified Rankin score reduced to stage 1 (no significant disability, able to carry out all usual activities, despite some symptoms) in one year and reached stage 0 (no symptoms) in

![Figure 1. MRI brain scan T2 images showing areas of high intensities in the grey and white matter of the left cerebellar hemisphere suggestive of acute disseminated encephalomyelitis (ADEM).](image-url)
two years time. She continued to have no evidence of malignancies.

DISCUSSION

Anti-NMDAR-Ab encephalitis is a new autoimmune, often paraneoplastic disorder, in which patients have CSF and serum antibodies to a restricted epitope region of the NR1 subunit of the NMDA receptor. In a series of over 400 patients, it was found that at least 80% of sufferers were females, with a preceding paper finding 20% of sufferers under the age of 19 and a smaller series finding the mean age of presentation at 18.5 years.

Anti-NMDAR-Ab encephalitis is noted to evolve over five phases. In the initial "prodromal phase," the patient suffers from a "flulike" illness. In the second "psychiatric phase," behavioral disturbances, psychosis, hallucinations, anxiety, agitation and paranoia supervene; temper tantrums or hyperactivity dominate in children. Usually, most patients are evaluated by psychiatrists at this stage. By stage three, the neurological nature of the illness is evident. Patients develop altered sensorium (88%) and seizures (76%). Frank dysautonomia (70%), including cardiac arrhythmias, hypo- or hyperthermia, central hypoventilation (66%), unexplained pyrexia, apneic spells and blood pressure fluctuations complicate this phase, and admission into intensive care is necessary. By phase four (hyperkinetic phase), movement disorders such as orofacial dyskinesias, bruxism, lip and tongue biting, dystonia, complex stereotyped movements, opisthotonus, oculogyric crises and choreic movements are observed in around 86% of patients. Phases four and five are usually combined and during these phases, patients are often unresponsive for long periods of time and lie with eyes open, mute or mumbling incoherently in a state resembling catatonia (wakeful unresponsiveness).

The presentation of anti-NMDAR-Ab encephalitis in children can be different from that reported in adults. Armangue et al., found that 60% of children presented with seizures, abnormal movements, and focal neurological deficits. They noted that children older than 12 presented more often with psychiatric symptoms (45%) compared to those younger than 12 (33%). Previous experiences with large series of predominantly young adults demonstrated that 70% presented with psychosis and other psychiatric symptoms.
Differential diagnosis of patients who present with an encephalitis picture include herpes simplex encephalitis, non–paraneoplastic autoimmune limbic encephalopathy, and other causes of autoimmune–related encephalopathies, including systemic lupus erythematosus cerebritis, antiphospholipid antibody syndrome, Sjögren’s syndrome, and Hashimoto’s encephalopathy, as well as primary central nervous system and systemic angiitis. Our patient was misdiagnosed to have primary psychosis when she was in phase two and was started on antipsychotics. She then deteriorated and was admitted to hospital. Her findings of unilateral epileptiform discharges in the EEG and lymphocytic pleocytosis in the CSF were suggestive of viral encephalitis. At this stage, anti–NMDAR–Ab encephalitis was a more likely diagnosis since the patient did not respond to treatment and her illness was complicated by a movement disorder. Her diagnosis was only confirmed after receiving the high titres of anti–NMDAR–Ab in the CSF. Serum NMDA receptor antibody titres are of a lesser value compared to CSF antibody titres as the sensitivity of NMDA receptor antibody testing was found to be higher in CSF than in serum. She developed paralytic ileus with abdominal distension, which could be due to autonomic disturbances related to her primary disease. The use of antipsychotics or the autonomic disturbances could explain her constricted pupils. We unfortunately were unable to do serial anti–NMDAR–Ab levels; these have been reported to correlate with clinical severity over time in patients.

In our search for a pathogen, there was evidence of a mycoplasma infection. It has been reported that in about 50% of patients, mycoplasma pneumonia serum IgM is positive. Although the significance of this is unknown, infections may trigger an autoimmune encephalitic process akin to PANDAS (pediatric autoimmune neuropsychiatric illness associated with streptococcal infections) mediated by antistreptococcal–antineuronal antibodies. A possible seasonal trigger was hypothesized for non–tumor NMDAR encephalitis, as a subset of studied patients without tumors had their onset of symptoms primarily in warm months. The pathophysiology behind the anti–NMDAR–Ab encephalitis can help us better understand our patient symptoms. NMDA receptors are widely distributed across the brain and their blockade produces different effects. Anti–NMDAR–Abs predominantly block the GABAergic neurons, leading to a disinhibition of the excitatory pathways and increased extracellular glutamate. The resulting frontostriatal syndrome is characterized by psychosis, catatonia, mutism and dystonia. The brainstem central pattern generator, which is normally inhibited by the GABAergic systems, is disinhibited, leading to the orofacial dyskinesias and the involuntary movements of the limbs and trunk. The ubiquitous presence of NMDAR in the dopaminergic, cholinergic and noradrenergic systems and the resultant hypofunction may explain the dysautonomia. Finally, a direct effect of the antibodies on the nucleus of the Kölliker–Fuse or the pontomedullary respiratory network could explain the respiratory dysfunction.

Routine brain MRI is frequently negative and if alterations are observed, they are of limited consistency and do not correspond well to clinical symptoms, ranging from periventricular white matter changes similar to demyelination, to hyper–intensities in the white matter of the hippocampi, cerebellar or cerebral cortex, frontobasal and insular regions, basal ganglia, pons and, in rare occasions, the spinal cord on fluid–attenuated inversion recovery/T2 sequences. Interestingly, a significant reduction of hippocampal functional connectivity was observed in patients with NMDAR encephalitis. EEG is abnormal in 75% of patients, with diffuse or localized slowing in the frontal or temporal regions and a possible finding of paroxysmal sharp waves. Scmitt et al., reported extreme delta brush in one third of patients with anti–NMDA–R encephalitis. Patients with anti–NMDAR–Ab encephalitis respond to immunotherapy. First–line immunotherapy includes intravenous methylprednisolone and immunoglobulins, which aim to suppress/modulate immune response or plasma exchange and attempts to remove antibodies and other inflammatory cytokines. If there is no clinical improvement and CSF titres remain high at one month, then one can consider rituximab, cyclophosphamide or both as second–line therapies, where both aim to suppress the antibody production. Recovery can take more than 18 months.

The finding of anti–NMDAR–Ab should lead to a search for a tumor, which if present, is almost always an ovarian teratoma that contains nervous tissue and expresses NMDAR. Younger patients (< 18 years of age) are less likely to have tumors (27–31%) as
compared with older patients, where the frequency is 55–60%. Some patients (usually older than 12 years) do have a teratoma, and as occurs in young adults, the tumor may be detectable after the patient has recovered from encephalitis. An interesting correlation was found between anti-NMDA antibodies titres and teratomas wherein serial antibody titres in CSF and serum were found to be higher in patients with teratoma than in patients with no tumor. Our patient was screened almost every six months over a period of two years with abdominal ultrasound and CT scans, looking for possible hidden malignancies and all were normal.

Relapsing disease affects 20–25% of patients with anti-NMDAR-Ab encephalitis. Clinical relapses can be monosymptomatic and less severe than the initial presentation. It was found that antibody titres in CSF and serum were higher in patients with poor outcome than in those with good outcome. The same study reported that titre change in CSF was more closely related with relapse than that of serum. Titulaer et al., found that two independent predictors of good outcome included lower severity of symptoms assessed as no need for ICU support, and prompt initiation of immunotherapy and tumor removal, if appropriate. They also noted that lower frequency of neurological relapses (12% vs. 20–24% reported in previous studies) is likely due to better recognition of the disorder, earlier treatment, and increasing use of second-line immunotherapy.

CONCLUSION
General physicians, pediatricians and psychiatrists should be familiar with anti-NMDAR-Ab encephalitis as they might be the first to encounter these cases. Anti-NMDAR-Ab encephalitis requires a multidisciplinary approach to patient management. Infectious, inflammatory and other organic causes should be excluded before diagnosing a primary psychiatric disorder and in diagnosing neuropsychiatric diseases as this is an example of a classically missed case. It is feasibly diagnosable, and potentially a fatal condition if left unrecognized. Finding high CSF anti-NMDAR-Ab titres diagnose this condition and serial serum and CSF antibody titres can help in managing and understanding the prognosis, particularly in relation to tumor development. Its course can span a period of months to years from symptoms to complete recovery. An aggressive and prompt treatment renders a favorable prognosis even after prolonged hospitalization. Anti-NMDAR-Ab encephalitis should be considered in cases of encephalitis in the absence of fever and those of unclear etiology.

DISCLOSURE
The authors report no conflicts of interest in this work.

ABBREVIATIONS

- **CSF**: cerebrospinal fluid
- **EEG**: electroencephalography
- **IVIG**: intravenous immunoglobulin
- **MRI**: magnetic resonance imaging
- **NMDAR**: N-methyl-D-aspartate receptor
- **PCR**: polymerase chain reaction

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