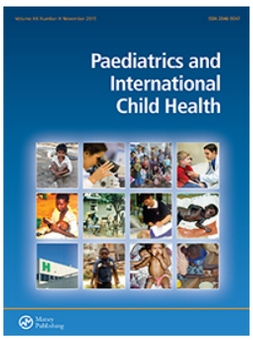

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Auto-immune anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis: three case reports

Fahad A. Bashiri[1], Abdulrahman A. Al-Rasheed[2], Saeed M. Hassan[1], Muddathir H. A. Hamad[1], Heba Y. El Khashab[1], Amal Y. Kentab[1], Fahad B. AlBadr[3], Mustafa A. Salih[1]

[1]Division of Pediatric Neurology, [2]Pediatric Rheumatology, Department of Pediatrics, [3]Division of Neuroradiology, Department of Radiology, College of Medicine and King Khalid University Hospital, King Saud University, Riyadh, Saudi Arabia

Anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is a recently identified auto-immune disorder characterised by severe memory deficit, a decreased level of consciousness, seizures, autonomic dysfunction and movement disorders. Three girls with the disorder are reported; they were aged 4 years, 5 years and 10 months. The 10-month-old infant who is one of the youngest patients reported with anti-NMDAR encephalitis worldwide, had MRI features suggestive of herpes simplex encephalitis (known to trigger anti-NMDAR encephalitis), but CSF PCR for herpes simplex was negative. All the patients presented with seizures, behavioural change, regression of speech, dystonia and choreo-athetosis. Anti-NMDAR antibodies were detected in all patients' sera and cerebrospinal fluid (CSF). Intravenous immunoglobulin, corticosteroids and rituximab were administered at different intervals. Cases 1 and 2 made a full recovery, but case 3 has mild motor and speech delay. Patients who present with encephalopathy, seizures and movement disorders should be tested for anti-NMDAR antibodies in serum and CSF in addition to being screened for herpes simplex encephalitis.

Keywords: Anti-NMDAR encephalitis, Children, Auto-antibodies, Movement disorder, Immunomodulation therapy

Introduction

Anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is a potentially reversible auto-immune disorder characterised by severe memory deficit, impaired consciousness, autonomic dysfunction and movement disorders. It was first reported in 2007 by Dalmau[1] in association with an ovarian tumour. The exact prevalence in children is unknown. It is more common in females. Anti-NMDA receptor encephalitis was initially described in young women with a strong association with tumours.[1] However, this is not the case in children.[2,3] Clinical presentation is variable; behavioural changes, cognitive deficit and aphasia invariably predominate, followed by seizures and movement disorders. Specific auto-antibodies directed against the neurotransmitter receptor 1 (NR1) sub-unit of the NMDA receptor are detected in the serum and cerebrospinal fluid.[2]

Case Reports

Case 1

A previously healthy 4-year-old Sudanese girl presented to King Khalid University Hospital (KKUH), Riyadh with sudden onset of focal seizures, gait unsteadiness and behavioural changes in the form of uncontrolled laughter for 10 days before admission. There was no history of fever, vomiting, diarrhoea or preceding trauma. Two days after admission, her mental status deteriorated and she became more agitated, mute and unresponsive to verbal commands. This was followed by orofacial dyskinesia and choreo-athetotic movements. On clinical examination there was poor social interaction but vital signs were normal. She had dystonic posturing of the right leg with hyperreflexia, yet she could walk with unsteadiness. Initial treatment included intravenous (IV) acyclovir, IV antibiotics, anti-epileptic medication (carbamazepine) and haloperidol. Brain magnetic resonance imaging (MRI) was unremarkable. Electro-encephalography (EEG) showed diffuse delta slowing with no epileptiform activity. Anti-NMDAR antibodies were positive in both serum and CSF. She was given methylprednisolone pulse therapy (30 mg/kg) for 3 days and intravenous immunoglobulin (IVIG) (1 g/kg/day for 2 days). Improvement in cognition and behaviour was evident only on initiation of rituximab (500 mg/m^2 in two divided doses 2 weeks apart) which was commenced 3 months after the onset of symptoms. There was gradual improvement and 14 months after admission

Correspondence to: F. A. Bashiri, Department of Pediatrics (39), College of Medicine & King Khalid University Hospital, King Saud University, P.O. Box 2925, Riyadh 11461, Saudi Arabia. Email: fbashiri@ksu.edu.sa

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she had normal intellectual capacity with no residual neurological deficit.

Case 2

A 6-year-old Saudi girl presented with confusion, agitation, episodes of fearfulness and insomnia for 5 days prior to admission.This was associated with a fluctuating level of consciousness and focal seizures and involuntary movements involving the left side of the body with orofacial dyskinesia. She had poor interaction with abnormal speech, was unable to stand and showed hyperreflexia in the lower more than the upper limbs. Primary treatment included IV acyclovir and IV antibiotics, carbamazepine and haloperidol. Her condition deteriorated a week after admission; she became agitated with fluctuation in the level of consciousness and involuntary choreo-athetotic movements involving all extremities. This was associated with autonomic dysfunction in the form of unexplained tachycardia and persistent hypertension requiring a short period of anti-hypertensive therapy. A brain MRI was unremarkable, and the EEG showed diffuse delta slowing with no epileptiform activity. Anti-NMDAR antibodies were positive in both serum and CSF. Initially, IVIG did not provide symptomatic relief. However, marked improvement was seen after treatment with intravenous methylprednisolone followed by two doses of rituximab. Ten months after the onset of symptoms she had returned gradually to her normal baseline activity with no neurological deficit.

Case 3

A 10-month-old previously healthy Saudi girl presented to a local hospital with a history of fever, vomiting and seizures. She was treated empirically with IV antibiotics and IV acyclovir for possible herpetic encephalitis despite a negative result of PCR for herpes simplex virus (HSV) in CSF. Three weeks later, she developed excessive irritability, involuntary movements and fluctuation in the level of consciousness associated with high-grade fever. On presentation to KKUH, clinical examination demonstrated an obtunded infant with orofacial dyskinesia, generalised choreo-athetotic movements involving the trunk and extremities, associated with increased tone and exaggerated reflexes in all extremities. Initially, she was kept on IV antibiotics, IV acyclovir, anti-epileptic medication (phenobarbitone and clonazepam) and haloperidol. Brain MRI (Fig. 1) showed features suggestive of herpes simplex encephalitis. EEG showed diffuse delta slowing with no epileptiform discharges. Anti-NMDAR antibodies were positive in both serum and CSF. The patient showed marked improvement in her movement disorder following treatment with IVIG and methylprednisolone pulse therapy. She became less agitated and more interactive after administration of two doses of rituximab, but she continued to have mild spasticity and mild motor delay. At the last clinic visit at the age of 30months, she was able to walk without support, could feed herself, was interactive socially, could say ‘baba’ and ‘mama’ and recognised her parents and siblings. Nevertheless, she manifested a mild behavioural disorder in the form of hyperactivity.

Screening for underlying malignancy for all patients by computed tomography of the chest, abdomen and pelvis was negative. Other investigations,including complete blood count, liver function tests, serum antiviral antibodies (screening for mycoplasma IgM, cytomegalovirus, Epstein–Barr virus, herpes simplex virus (HSV) type I and varicella zoster virus) were negative. Auto-immune markers [anti-nuclear antibody (ANA) and anti-double-stranded DNA (dsDNA)], serum lactate, ammonia, toxicology screen, plasma amino acids and urine for organic acids were also negative. CSF PCR for HSV was negative, and CSF culture and chemistry were normal in all three patients. A summary of the clinical course, diagnostic tests, therapy and outcome is given in Tables 1and 2.

Discussion

Anti-NMDAR encephalitis is considered to be an auto-immune disorder with neuropsychiatric manifestations related to the presence of auto-antibodies in serum and CSF which interfere with normal neurotransmitter function.[1, 4]

The exact frequency of anti-NMDA receptor encephalitis is unknown but in some studies it is estimated to be around 4% of adults and children presenting with an encephalitis-like disorder.[2] It is more prevalent in females between the ages of 2 and 14 years, which is consistent with the present study, except that the third patient presented in infancy and is one of the youngest patients to be reported.[5] The aetiopathogenesis remains an enigma. However, the possibility of a viral or tumour-induced immune response is considered, especially when preceded by prodromal symptoms in addition to a strong association with ovarian tumours.[1]

The symptom complex described in the literature includes behavioural disturbance with mutism followed by dyskinesia and seizures. The sequence of symptoms in children can vary;[3] the predominant presentation comprises autonomic dysfunction (86%), movement disorders (84%) such as orofacial dyskinesia, choreo-athetotic movements followed by seizures (77%) and behavioural changes in the form of labile mood, anxiety and personality changes.[3] It is very difficult to connect an auto-immune reaction with the type of movement disorder. Nevertheless, children with anti-NMDAR encephalitis commonly present with orofacial dyskinesia, followed by chorea, ataxia, limb dystonia, limb myorhythmia, oromandibular dystonia, facial myorhythmia, blepharospasm, opisthotonus, athetosis and tremor.[6] Movement disorders are typical but non-specific symptoms of anti-NMDAR encephalitis.[7] More than one movement disorder may be present, which can make early diagnosis difficult and delay commencement of appropriate treatment.[8] Multiple movement disorders may be

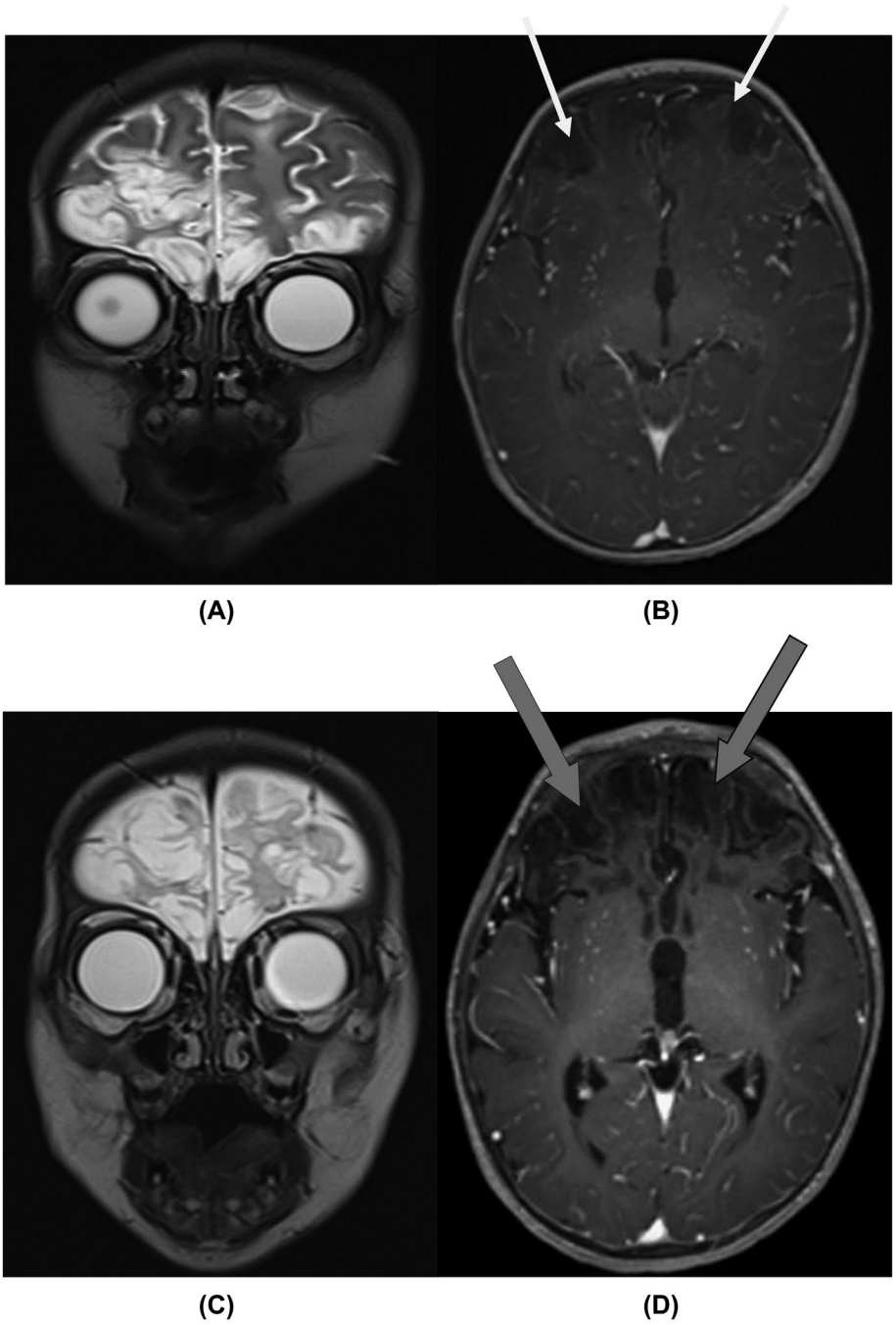

Figure 1 Case 3: Initial MR images (day 3 of admission): (A) T2-weighted SE (3000/120/1) (TR/TE/NEX), and (B) Gadolinium enhanced T1-weighted SE (400/15/2) (TR/TE/NEX) show bilateral asymmetrical cortical and sub-cortical cystic encephalomalcia in the frontal lobes (white arrows). MR after 2 weeks: (C) T2-weighted SE, and (D) Gadolinium-enhanced T1-weighted SE with same parameters demonstrate progressive bilateral frontal cystic encephalomalacia without abnormal enhancement (grey arrows).

seen in the same patient, and the movement disorder often evolves and changes with the disease course; thus, none of these movement disorders alone can be a guide to a specific auto-immune disease.[6]

Diagnosis relies on excluding other causes of encephalitis and undertaking the antibody screen for the NMDA receptor in serum as well as CSF, which is usually positive.[1, 3, 6] Neuro-imaging in children is often normal. However, diffusion tensor imaging sometimes demonstrates white matter changes which may correlate with the severity of the disease.[9] Case 3 had an abnormal MRI compatible with the findings in herpes simplex encephalitis although her CSF PCR for HSV was negative.[10] HSV has recently been recognised as a trigger of anti-NMDAR encephalitis and several cases were reported in association with HSV, whereas other reported cases manifested as clinical relapses of HSV owing to anti-NMDARencephalitis.[11] Two infants aged 8 months and 6 months with severe hyperkinetic movements owing to anti-NMDAR encephalitis associated with HSV have been reported.[5, 12]

In anti-NMDAR encephalitis, EEG abnormalities manifest as extreme delta brushes (EDB), rhythmic delta

Table 1 Characteristics of patients

	Case 1	Case 2	Case 3
Age at onset	4 yrs	5 yrs	10 mths
Gender	Female	Female	Female
Clinical presentation	Behavioural changes, seizures, movement disorders, limping (right side)	Behavioural changes, seizures, movement disorders, hypertension	Fever, vomiting, seizures, movement disorders
Neurological findings	Disoriented, agitated, orofacial dyskinesia, choreo-athetotic movements, right-sided weakness, hyperreflexia (right > left side)	Disoriented, agitated, choreo-athetotic movements, hyperreflexia (left > right side)	Irritability, disorientation, choreo-athetotic movements, hypertonia and hyperreflexia
Treatment given	Methylprednisolone pulse therapy for 3 days, IVIG followed by rituximab (500 mg/m^2 in 2 divided doses, 2 wks apart) (3 mths after admission)	Methylprednisolone pulse therapy for 3 days, IVIG followed by rituximab (500 mg/m^2 in 2 divided doses 2 wks apart) (2 wks after admission)	Methylprednisolone pulse therapy for 3 days, IVIG followed by rituximab (500 mg/m^2 in 2 divided doses 2 wks apart) (2 wks after admission)
Response to treatment	Response achieved 14 months after initial presentation	Response achieved 10 mths after initial presentation	Partial recovery achieved 20 mths after initial presentation
Outcome	Full recovery	Full recovery	Last follow-up clinic at age 30 mths showed remarkable improvement in cognition and movement disorders but there was mild motor and speech delay and hyperactivity

Table 2 Investigations

	Case 1	Case 2	Case 3
CSF	WBC 3 (×10^6/L), (M 100%, PMN 0%)Protein 0.19 g/L (0.15–0.45)Glucose 3.7 mmol/L (2.5–4)Anti-NMDAR-positive	WBC 10 (×10^6/L), (M 90%, PMN 10%)Protein 0.14 g/L (0.15–0.45)Glucose 3.2 mmol/L (2.5–4)Anti-NMDAR-positive	WBC 0 (×10^6/L)Protein 0.28 g/L (0.15–0.45)Glucose 3.1 mmol/L (2.5–4)Anti-NMDAR-positive
Serum	Anti-NMDAR-positive	Anti-NMDAR-positive	Anti-NMDAR-positive
CT chest, abdomen & pelvis	Normal	Normal	Normal
Brain MRI	Normal	Normal	Abnormal
EEG	Diffuse delta activity without PD	Diffuse delta activity without PD	Diffuse delta activity without PD

Anti NMDAR, anti-N-methyl D-aspartate receptor antibody; CT, computed tomography; EEG, electro-encephalography; M, monocytes; MRI, magnetic resonance imaging; PD, paroxysmal discharge; PMN, polymorphonuclear cells

activity without EDB, generalised rhythmic delta activity and excessive beta activity.[13, 14]

As an auto-immune disorder, treatment modalities include immunoglobulin, corticosteroids and immune modulation therapies such as cyclophosphamide, methotrexate and rituximab. There is no consensus regarding the management of anti-NMDAR encephalitis. Corticosteroids and immunoglobulins are considered to be the first-line management in addition to excision of any tumour.[15] There is no clear evidence regarding when to proceed with the second line of therapy, i.e. cyclophosphamide, rituximab or methotrexate; However, early consideration of these drugs is associated with a better outcome.[15] Our patients showed remarkable improvement in behaviour and dyskinesia with the first-line treatment, but, owing to the persistence of symptoms, all required second-line therapy with rituximab. In addition to specific management of NMDAR encephalitis, patients require anti-epileptic drugs and symptomatic treatment for the movement disorder. The treatment of seizures in anti-NMDAR encephalitis is for acute symptomatic seizures, and the choices of anti-convulsants usually depend on the seizure type and EEG changes. Status epilepticus can also be a manifestation of anti-NMDAR encephalitis.[16] Symptomatic treatment of movement disorders in anti-NMDAR encephalitis is challenging; antipsychotic medications, sedatives and sleep medications have been used to treat the symptoms with variable responses. It is recommended that anti-psychotic therapy be used for a short period to avoid extrapyramidal side-effects.[17] A multidisciplinary approach including psychiatric support is very important. The recovery rate is considered to be excellent in children with anti-NMDAR encephalitis. However, the duration of symptoms varies.[7, 15] Outcome depends on early recognition and therapeutic intervention. This was evident in our patients as case 2 recovered more quickly than cases 1 and 3. Case 3 did not achieve full recovery, probably owing to being younger or the severity of the underlying illness. All patients were seen in the follow-up clinic with no evidence of recurrence, and annual ultrasound of the abdomen and pelvis is planned. Patients with relapsing HSE or prolonged atypical symptoms with negative CSF PCR for HSV should be tested routinely for anti-NMDAR antibodies in CSF and serum.[18]

Anti-NMDAR encephalitis should be considered as one of the most important differential diagnoses in all patients with non-infectious encephalitis, especially those who present with movement disorders or unexplained behavioural changes. Early diagnosis and therapeutic intervention usually achieve a favourable outcome.

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