ELSEVIER

Anti-NMDA Receptor Encephalitis With Atypical Brain Changes on MRI

Sophelia H. S. Chan, MD*, Virginia C. N. Wong, MD*, Cheuk-wing Fung, MD*, Russell C. Dale, PhD†, and Angela Vincent, PhD‡

A young girl with antibodies to the *N*-methyl-D-aspartate receptor presented with a clinical syndrome suggestive of dyskinetic encephalitis lethargica with neuropsychiatric features at presentation, movement disorder, mutism, sleep disorder, and seizures. Persistent lesions in the white matter and pons were observed in magnetic resonance imaging of the brain, findings that have not been described previously in *N*-methyl-D-aspartate receptor antibody encephalitis.

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Introduction

Anti-*N*-methyl-D-aspartate (NMDA) receptor encephalitis is a newly identified category of treatment-responsive encephalitis associated with anti-NMDA receptor antibodies, which bind to extracellular epitopes in the NR1 and NR2 heteromers of the NMDA receptor. The antibodies are usually detected in the cerebrospinal fluid and sera of young women with ovarian teratomas, but can also be found in the absence of any evident tumor [1]. Anti-NMDA receptor encephalitis has recently been described also in young children [2]. *Encephalitis lethargica* is a historical term that describes an encephalopathy with psychiatric, sleep, and extrapyramidal movement disorders; both dyskinetic and parkinsonian forms have been described [3]. Encephalitis lethargica shares clinical features with the anti-NMDA receptor encephalitis, and recently NMDA receptor antibodies were reported in children as young as 15 months old with the dyskinetic form of encephalitis lethargica [4]. Described here is the case of a child with anti-NMDA receptor encephalitis presenting as the dyskinetic form of encephalitis lethargica and with atypical findings on cranial magnetic resonance imaging (MRI).

Case Report

A girl aged 3 years 9 months with a 3-day history of fever and upper respiratory tract infection was admitted, presenting with a brief generalized tonic-clonic convulsion and behavioral disturbance including agitation, screaming, and talking nonsense. For the first week, she was lethargic with fluctuating consciousness and excessive sleepiness and mutism during the day but poor sleep at night. Evaluation for acute encephalopathy including extensive autoimmune, infective, toxicologic, metabolic, and vasculitic screening yielded negative findings (Table 1). The erythrocyte sedimentation rate was mildly elevated (25 mm/hour) and cerebrospinal fluid exhibited positive oligoclonal bands with normal protein and glucose and no pleocytosis.

Urgent cranial MRI on day 3 revealed bilateral periventricular, multifocal hyperintense lesions on T_2-weighted and fluid-attenuated inversion recovery images over the frontal, parietal, and occipital regions without enhancement. Urgent electroencephalography indicated generalized slowing compatible with an encephalopathic picture. Acute disseminated encephalomyelitis was initially suspected, and she was given intravenous pulse methylprednisolone at 30 mg/kg per day for 5 days; there was minimal evident response, and so intravenous immunoglobulin at 1g/kg per day was given for 2 days.

After this first course of treatment, there was some improvement in consciousness level, but the child remained mute. Repeated electroencephalography indicated improved slowing and new presence of sleep changes. In the second week, she developed dyskinesia with mouth chewing, tongue thrusting, and finger rolling. Episodes of generalized rigidity and dystonia with oculogyric crises were seen. The dystonia resulted in rhabdomyolysis, with elevated creatine kinase level up to 2774 U/L (normal range: 60-365 U/L). The syndrome of encephalitis lethargica was initially suspected, and

From the *Division of Child Neurology/Developmental Paediatrics/Neurohabilitation, Department of Paediatrics and Adolescent Medicine, Queen Mary Hospital, The University of Hong Kong, Hong Kong SAR, China; †Institute for Neuroscience and Muscle Research, the Kids Research Institute at the Children's Hospital at Westmead, University of Sydney, Westmead, Australia; and ‡Neuroimmunology Group, John Radcliffe Hospital; Department of Clinical Neurology, University of Oxford, Oxford, United Kingdom.
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Communications should be addressed to:
Dr. Wong; Queen Mary Hospital, New Clinical Building Room 115, 1/Floor, 102 Pokfulam Road, Hong Kong SAR, China.
E-mail: vcnwong@hku.hk
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Table 1. Summary of investigations for underlying causes in a case of anti-NMDA receptor encephalitis with atypical brain changes revealed on magnetic resonance imaging

Investigation
Infective evaluation (all findings negative)
CSF: Gram stain and smear; bacterial, viral, fungal, tuberculosis culture; polymerase chain reaction for herpes simplex virus, enterovirus; cryptococcal antigens
Blood, urine, throat swab: bacterial cultures
Nasal, rectal, throat swabs and nasopharyngeal aspirate: viral cultures
Anti-streptolysin-O titer
Serological paired titers for influenza A, influenza B, adenovirus, parainfluenza 1/2, respiratory syncytial virus, mumps virus, measles virus, rubella virus, varicella zoster virus, enterovirus, herpes simplex virus, parvovirus, cytomegalovirus, Epstein–Barr virus (VCA-IgM and polyvalent), Japanese encephalitis virus, chlamydia, *Mycoplasma pneumoniae*, spotted fever group *Rickettsia* spp., typhus group *Rickettsia* spp.
Hepatitis B antibodies and surface antigens
Metabolic evaluation (all findings normal)
CSF: Lactate and pyruvate
Blood: Ammonia, lactate, pyruvate, ceruloplasmin, copper
Plasma: Amino acid pattern and concentration, plasma phytanic acid, very long chain fatty acid (C22:0, C24:0, C26:0, C24:0/C22:0, C26:0/C22:0)
Urine: Organic acid pattern
Spotted urine: Porphobilinogen
Autoimmune evaluation (all findings normal or negative)
C3 and C4 complement, antinuclear antibody, anti-dsDNA, rheumatoid factor, Ig pattern; anti-cardiolipin IgG
NMDA receptor antibodies*
Day 45: Serum 100; CSF 2
4 months: Serum 200; CSF 4
1 year: Serum 30; CSF 0
CSF findings
Day 1: Oligoclonal band positive; serum IgG 668 mg/dL (normal range 617-1349); protein 0.28 g/L (normal range 0.12-0.6); glucose 4.6 mmol/L (blood glucose 6.3 mmol/L); total cell count, 8×10^6/ L, with occasional red blood cells
Day 45: Oligoclonal band negative; CSF IgG 1.5 mg/dL (normal range <5.5); serum IgG 1740 mg/dL (normal range 617-1349)
4 months: Oligoclonal band negative; CSF IgG 1.8 mg/dL (normal range <5.5); serum IgG 820 mg/dL (normal range 617-1349).
1 year: Oligoclonal band not done because CSF IgG was at <0.9 mg/dL (normal range <5.5) and serum IgG was at 774 mg/dL (normal range 617-1445)

* Values represent the lowest serum dilution that was positive in each case (the dilution at which binding is just visible).

Abbreviations:

anti-dsDNA	=	Double-stranded DNA virus antibody
CSF	=	Cerebrospinal fluid
Ig	=	Immunoglobulin
NMDA	=	*N*-methyl-D-aspartate
VCA	=	Viral capsid antigen

treatment was started with 25 mg carbidopa and 100 mg levodopa. She responded well to a daily levodopa dose of 1.5 mg/kg/dose four times a day, with improvement of dystonia and rigidity.

At the third week, she developed recurrent generalized tonic-clonic convulsions. Video electroencephalography confirmed ictal epileptiform discharges with spike and wave complexes. She was initially treated with phenytoin for rapid seizure control but this therapy was intended only for short term use. Sodium valproate was added for better acute seizure control and to continue as a maintenance treatment to tide the patient over the acute and subacute phases of disease. Repeated cranial MRI on day 22 confirmed increased hyperintensity and size of the previously demonstrated lesions (T_2-weighted and fluid-attenuated inversion recovery images), with additional pons involvement and evidence of cerebral atrophy. The erythrocyte sedimentation rate was markedly elevated, at 91 mm/hour.

In view of both clinical and radiologic evidences of an active ongoing encephalitic process, on day 22 a second course of treatment was started. Intravenous immunoglobulin (1 g/kg per day) was given for 3 days followed by methylprednisolone (30 mg/kg per day) for 3 days. In contrast to the first course, the child responded well to this second course of treatment; she gradually regained consciousness and became seizure free 3 days after the start of treatment. After completion of the intravenous course, oral prednisolone was begun. Phenytoin was stopped after 2 weeks and the sodium valproate was continued.

Repeated cranial MRI on day 32 again revealed increased hyperintensity, predominantly in the subcortical white matter of both frontal and parietal regions and extending to the occipital lobes. There was also an increase in extent of the lesion in the midline of the pons. Ventricles were slightly enlarged (Fig 1). Single voxel magnetic resonance spectroscopy placed in the left frontal and right parieto-occipital white matter, as in the previous MRI, demonstrated normal *N*-acetylaspartate, choline, and total creatine peaks. The NMDA receptor antibodies, measured by a cell-based assay scored visually on a scale from 0 to 4 (normal value < 1) [6], first measured at day 45, were positive in both serum and cerebrospinal fluid. Ultrasonography of the pelvis was unremarkable.

After rehabilitation, the patient could walk on her own, resumed full oral feeding, and demonstrated normal verbal understanding at 6 weeks after onset of illness; however, she remained mute. She still had sleep problems, with sleep inversion, and easy irritability and fragmented sleep during the daytime. Melatonin treatment was started to improve the nocturnal sleep pattern.

She initially had verbal dyspraxia with difficulty in initiation of tongue and lip movement for making sounds at 2 months after onset of illness. Her speech gradually improved and at 4 months was back to normal. The multidisciplinary team assessment at 4 months indicated normal intelligence, age-appropriate gross and fine motor skills, and normal verbal understanding and expression. Vision and hearing were normal. Notably, despite clinical ongoing improvement, a repeated evaluation indicated higher levels of serum and cerebrospinal fluid NMDA receptor antibodies at 4 months. Oral prednisolone was gradually withdrawn and was ended completely at 3 months after the onset of illness. Because her sleep pattern had improved, melatonin was withdrawn at 5 months. Sodium valproate was withdrawn at 6 months after the onset of illness (Fig 2).

At the 1-year follow-up examination, the child remained well and had no relapse of seizures. She enjoyed school, had no learning difficulties, and was able to fully participate in all her previous extracurricular activities. Repeated cranial MRI still revealed multifocal hyperintensity, but the pons lesion had resolved. Her serum NMDA receptor antibody levels had dropped considerably, and cerebrospinal fluid had become negative for the antibodies. Evaluation for NMDA receptor antibodies was repeated in serially diluted paired serum and cerebrospinal fluid samples (Table 1). Electroencephalography indicated improvement in the background slowing, with the posterior dominant rhythm in the theta range and normal sleep changes.

Discussion

The patient, a young girl (3 years 9 months of age) of French ethnic origin, had a presentation typical of NMDA receptor antibody encephalitis, with initial neuropsychiatric presentation and brief seizures followed by prominent sleep disorder, mutism, and gradual development of orofacial-limb dyskinesia and dystonia in the second week with further deterioration and recurrent seizures by the third week. This case would originally have been diagnosed as dyskinetic encephalitis lethargica [4,5]. The upper respiratory tract infection preceding

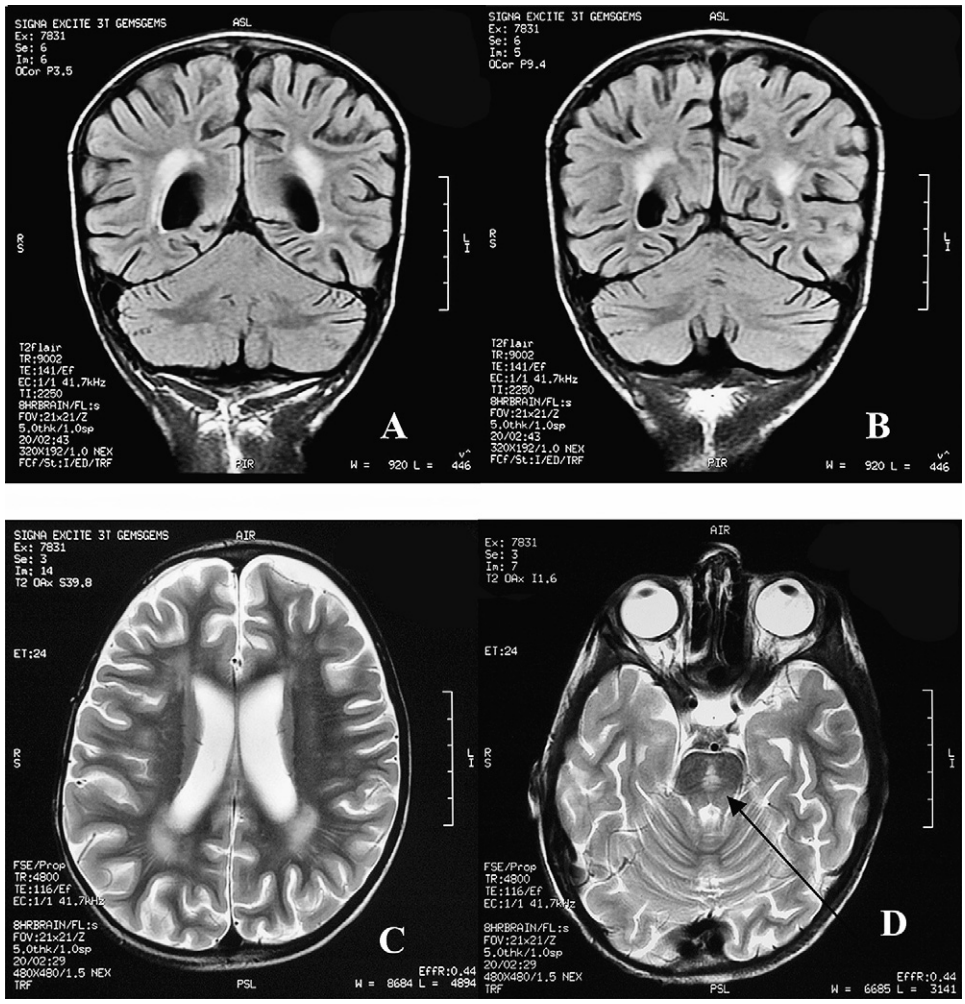

Figure 1. Four cranial magnetic resonance images taken on day 32. Note multiple areas of hyperintensity evident on T_2-weighted fluid-attenuated inversion recovery imaging (A,B) and fast spin echo imaging (C,D), predominantly in the subcortical white matter of both frontal and parietal regions and extending to the occipital lobes. Note also lesion in the midline of the pons (D, thin arrow). Ventricles are slightly enlarged.

the illness and the positive response to immunomodulating therapies all point to an underlying autoimmune mediated process causing inflammatory changes of the central nervous system. The positive response to levodopa also suggested an underlying pathogenesis that perturbs dopaminergic transmission, possibly related to alteration in NMDA receptors.

The present case is noteworthy because of the atypical MRI changes. The cranial MRI findings of bilateral white matter changes are similar to those described in acute disseminated encephalomyelitis. In most cases, MRI findings in NMDA receptor encephalitis are normal, or indicate nonspecific cortical changes. In a large study of 100 patients by Dalmau et al. [1], 45% had normal findings and 55% had increased signal on fluid-attenuated inversion recovery or T_2 MRI sequences; changes included faint or transient contrast enhancement of the cerebral cortex, overlaying meninges, or basal ganglia, or involvement of a single area of the brain. There were abnormalities in the medial temporal lobes, corpus callosum, and in one case in the brainstem. Follow-up studies indicated that many of those who recovered or were left with mild deficits had improved or normalized MRI findings.

In a recent series of 32 children and adolescents with NMDA receptor encephalitis, 10 patients had abnormal cranial MRI findings, mainly with transient fluid-attenuated inversion recovery hyperintensity in one or more areas (medial temporal lobe, periventricular, cerebellar) or transient contrast enhancing abnormality [2]. In 10 pediatric patients with encephalitis lethargica and NMDA receptor antibodies, cranial MRI during the first weeks was normal in 7 patients, and 3 had subtle cortical gray matter enhancement, which was absent on subsequent imaging; on follow-up imaging 1 patient had clear cerebral atrophy [4]. White matter changes have been noted in a recent study, particularly during the dyskinetic stage of the disease [6]; gray matter lesions were found earlier in a few cases, although many had neither white nor gray matter changes at any stage in that study. In the present case, the patient presented with early white matter changes evident on the first cranial MRI imaging 3 days after the initial onset of illness, before the development of dyskinesia and dystonia in the second week.

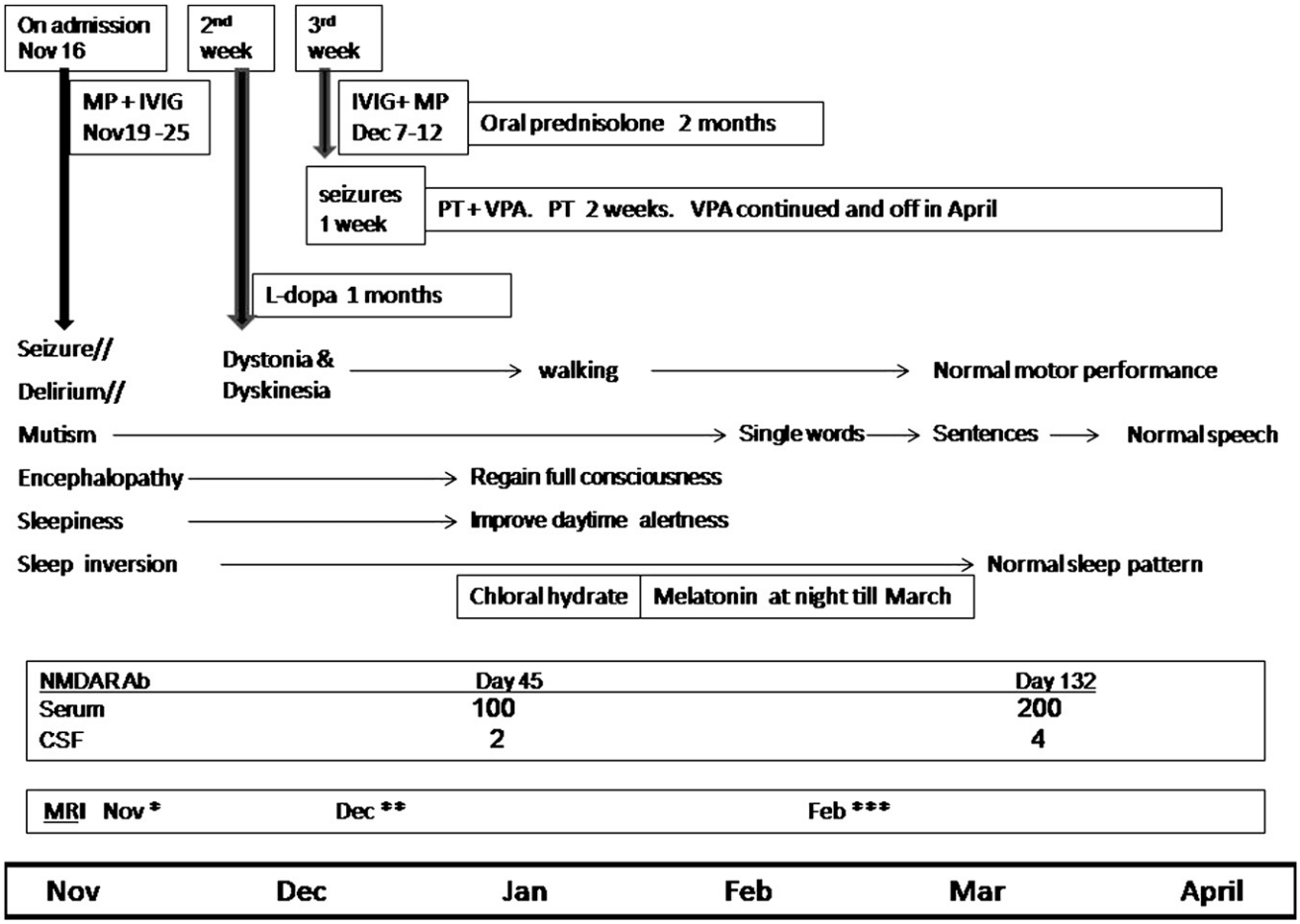

*Figure 2. Disease course and management: The patient had ongoing improvement after the second course of intravenous immunoglobulin and methylprednisolone, at approximately 1 month after onset of illness. She was fully recovered at 4 months after admission. Notably, in both serum and cerebrospinal fluid (CSF) the levels of N-methyl-D-aspartate receptor antibodies (NMDAR Ab) were still elevated when the clinical course had already improved. Cranial magnetic resonance imaging (MRI) findings after admission revealed abnormal white matter changes (November, *), with persistent abnormal findings and also pons involvement in subsequent imaging (December, **; February, ***). Abbreviations: IVIG, intravenous immunoglobulin; L-dopa, levodopa (L-3,4-dihydroxyphenylalanine); MP, methylprednisolone; PT, phenytoin; VPA, sodium valproate. Analysis performed by L. Jacobson.*

The NMDA receptor, which binds the neurotransmitter glutamate, is highly expressed by excitatory neurons throughout the brain [7]. When activated, the NMDA receptor functions as a conduit for calcium influx from the extracellular milieu, resulting in large intracellular calcium increases, which can exert excitotoxic effects. The mechanisms for NMDA receptor antibodies causing white matter changes are unknown; however, NMDA receptors are present in the white matter, so it is possible that the antibodies could also cause white matter changes as seen in the present case, although these changes are atypical.

Magnetic resonance spectroscopy in the present case indicated normal *N*-acetylaspartate levels and creatine peaks. This finding is in contrast to a recent report of a case with reduction of *N*-acetylaspartate levels in the basal ganglia and thalamus and a decrease in the *N*-acetylaspartate to creatine ratio in the frontal region during the involuntary movement phase [8].

In one study of serum antibodies at onset and follow-up, in mainly adult patients, the degree of neurologic improvement appeared to correlate well with the decrease in changes in NMDA receptor antibody levels, as measured by an enzyme-linked immunosorbent assay [1]. Notably, in the present case the patient had already improved clinically at the time of maximum serum and cerebrospinal fluid antibodies. This suggests the possibility that the underlying pathogenesis and the location of the disease process within the central nervous system differ between pediatric and adult populations. Further studies focusing on pediatric patients to explore the relationship between antibody levels in serum and cerebrospinal fluid and clinical severity, may lead to further understanding.

Many of the original patients studied were female young adults or adolescents with ovarian teratomas. These tumors are very uncommon in young children overall, but were found in 30% of the pediatric cohort with anti-NMDA receptor encephalitis [2]. Given that most pediatric patients have been diagnosed only during the last 2 years, there has not yet been sufficient follow-up time to exclude tumors in this age group, and periodic screening with either MRI or ultrasound of the abdomen and pelvis will need to be done for at least 2 years, as recommended [4].

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