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Anti-N-Methyl-D-Aspartate Receptor Encephalitis: A Potentially Treatable Cause of Neuropsychiatric Syndrome

KKH ***Ho,*** EKC ***Yau,*** WL ***Yiu,*** NC ***Fong***

Abstract A young adolescent girl with no history of psychiatric illness presented with acute onset of delusional ideas and behavioural changes that were followed by recurrent seizures, involuntary movement and oromotor dyskinesia. Anti-N-methyl-D-aspartate receptor (NMDAR) antibodies were present in the serum and she was successfully treated with immunotherapy. The presence of neurological features including convulsions, movement disorder and autonomic disturbance are important clues to the diagnosis of anti-NMDAR encephalitis in patients who initially present with acute psychiatric symptoms. Early diagnosis and treatment is warranted as aggressive immunotherapy improves clinical outcome.

Key words Autoimmune; Encephalitis; Movement disorder; N-methyl-D-aspartate receptor

Introduction

Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis was first described as a syndrome of neuropsychiatric symptoms in young women with ovarian teratoma. Since the discovery of the pathogenic anti-NMDAR antibodies in 2007,[1] increasingly more children and adults with or without underlying tumour were identified with this syndrome, bringing to light a new association between neuronal autoantibodies and psychosis. Recent studies suggest that anti-NMDAR encephalitis is not as uncommon as previously thought.[2] Yet, anti-NMDAR encephalitis is not widely reported in our local population. We here describe a Chinese adolescent girl with antibodies to the NMDAR who presented with neuropsychiatric symptoms, seizures and movement disorder.

Department of Paediatrics & Adolescent Medicine, Princess Margaret Hospital, 2-10 Princess Margaret Hospital Road, Lai Chi Kok, Kowloon, Hong Kong

KKH **Ho**（何嘉萱） *MBChB, MRCPCH*
EKC **Yau**（丘健昌） *MRCP(UK), FHKCPaed, FHKAM(Paed)*
WL **Yiu**（姚偉廉） *MRCP(UK), FHKCPaed, FHKAM(Paed)*
NC **Fong**（方乃聰） *MRCP(UK), FHKCPaed, FHKAM(Paed)*

Correspondence to: Dr KKH **Ho**

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Case Report

A 13-year-old girl with good past health was admitted for confusion and seizure. She had a two-week history of bizarre behaviour and personality change. Mother reported that the girl was out of herself, being easily agitated with labile emotion. She had delusional ideas of secretion coming out of her mouth and not having her fringe grow back after a haircut. One week later she had a generalised tonic clonic convulsion followed by two episodes of complex partial seizure. There was no history of preceding viral illness. On admission, the girl was afebrile. She wandered around with fluctuating conscious state and incoherent speech. At one time she was orientated and responded to questioning. At another time she turned aggressive and yelled in foul language. The girl developed a cluster of seizures within the same day, some being focal seizures with left facial and limb twitching, others being generalised tonic clonic convulsion. Seizures were aborted with midazolam and phenobarbitone.

In view of a clinical picture of encephalitis, the girl was treated with ceftriaxone, clarithromycin and acyclovir and was transferred to paediatric intensive care unit (ICU).

Extensive blood tests, urine toxicology and metabolic screening were normal (Table 1). Erythrocyte sedimentation rate was mildly elevated at 23 mm/hour. Urgent computed tomography of the brain was normal. Cerebrospinal fluid

(CSF) showed pleocytosis (white blood cell 58/mm^3), of which 90% were lymphocytes. CSF viral culture, polymerase chain reaction (PCR) for herpes simplex virus and enterovirus were negative. Electroencephalogram (EEG) performed on day 4 was normal. Repeated EEG on day 35 showed no increased slow waves or epileptiform discharge. Magnetic resonance imaging (MRI) of the brain showed no intracranial pathology.

The girl became increasingly stuporous in the following week. From time to time she had self muttering and incongruent smile. She also had facial grimacing, stereotypic oromotor movement, dystonic posturing and involuntary movement. Autonomic disturbance was present with sinus tachycardia up to 150/min at rest. She was treated for suspected autoimmune encephalitis with intravenous immunoglobulin (IVIg) at 1 g/kg/day for two days on day

Table 1 Summary of investigations for the underlying cause of encephalitis in a girl presented with confusion and convulsion

Investigation	Result
Infection	
Complete blood picture	WBC 5.6 x10^9/L; Hb 10.2 g/dL; Platelet 330x10^9/L
C-reactive protein	6.5 mg/L
Blood culture	Negative
Viral titre	Rising second antibody titres (post IVIg treatment)
Throat swab/rectal swab for viral culture	Negative
Nasopharyngeal aspirate for viral culture	Negative
Cold agglutinin	<64
Mycoplasma IgM	Negative
EBV VCA IgM	Negative
Anti-streptolysin O titre	<200 IU/mL
Rickettsial antibody titre	Negative
Japanese B encephalitis antibody	Negative
CSF cell count	WBC 58/mm^3 (90% lymphocyte); RBC 131/mm^3
CSF protein; glucose	0.29 g/L; 2.8 mmol/L (serum glucose 4.3 mmol/L)
CSF culture	Negative
CSF viral study	Negative
CSF enterovirus/herpes simplex virus PCR	Negative
CSF herpes simplex virus/varicella antibody	Negative
CSF AFB culture	Negative
Autoimmune	
Erythrocyte sedimentation rate	23 mm/hour
C3, C4	Negative
Antinuclear antibodies	Negative
Rheumatoid factor	32.3 mg/L (4.8-59 mg/L)
CSF IgG	Quantity insufficient
CSF oligoclonal band	Quantity insufficient
Metabolic	
Thyroid function	fT4 17.8 pmol/L (7.2-17.7 pmol/L) TSH 0.43 mIU/L (0.44-4.24 mIU/L) (repeated thyroid function was normal)
Ceruloplasmin	0.3 g/L (0.19-0.67 g/L)
Serum copper	14.3 umol/L (12-25 umol/L)
Ammonia	54 umol/L
Glucose	4.3 mmol/L
Blood gas	Normal
Urine for amino acids/organic acids	Negative
Toxicology	
Urine toxicology	Negative

WBC: white blood cell; Hb: hemoglobin Concentration; IVIg: intravenous immunoglobulin; IgM: immunoglobulin M; EBV: Epstein-Barr virus; VCA: viral capsid antigens; CSF: cerebrospinal fluid; RBC: red blood cell; IgG: immunoglobulin G; PCR: polymerase chain reaction; AFB: acid fast bacilli; TSH: Thyroid-stimulating hormone

6-7 and high dose corticosteroids (methylprednisolone 30 mg/kg/day) for three days from day 10-12. Her conscious state, however, remained fluctuating in the first month. Most often she was confused and mute. At times she lapsed into agitation with forceful kicking, struggling and utterance of incomprehensible sounds. Creatine kinase was raised up to 4121 U/L. She had difficulty falling asleep and required chloral hydrate. The girl had one more episode of generalised convulsion four weeks after admission before she became seizure-free. Her serum was sent for anti-NMDAR antibody testing and it was positive. Yet, there was insufficient CSF for the test. As the patient had persistent fluctuating conscious state, she was given another course of methylprednisolone 30 mg/kg/day from day 28-30. She was continued on a 4-week course of oral prednisolone 1 mg/kg/day.

Starting from the fifth week of admission she showed signs of recovery. There were progressively longer periods of lucidity when she became orientated, though slow in response. Ultrasound abdomen and pelvis did not identify any ovarian teratoma. The girl was discharged on day 49. Upon discharge, she scored 28 out of 30 in the Mini-Mental State Examination, with one score being deducted from the category of orientation and one from attention and calculation. She was followed up at three months after onset of symptoms and there was no recurrence of neuropsychiatric symptoms and no sequelae except for a subjective feeling of mild forgetfulness as reported by the patient and her parents.

Discussion

Anti-NMDAR encephalitis is a multi-stage disorder characterised by a prodromal period of fever, headache and viral-like illness in 70% of patients,[3] followed by the development of neuropsychiatric symptoms within days to weeks. Adult patients may present with behavioural disturbance or frank psychotic symptoms, many of whom may be treated with psychotherapy.[4] Indeed in a case series of 100 patients from the United States, 77% of them were first evaluated and managed by psychiatrists.[5] Quite often, neurologists became involved when patients developed seizures, either generalised tonic clonic convulsion or complex partial seizure, which might be resistant to anticonvulsants and evolved into status epilepticus.[6] Young children tend to present with neurological rather than psychiatric symptoms as behavioural changes such as temper tantrum and irritability are difficult to detect. As the disease progresses, both groups of patient move on to a catatonic phase with alternating periods of akinesis and agitation.[5] Sleep disturbance is often observed.[4] Speech impairment in the form of echolalia, reduced verbal response or frank mutism are also common. At the next stage, stereotypic movements become prominent. Oro-facial-lingual dyskinesias, such as lip smacking, facial grimacing, chewing and tongue thrusting, are most characteristic.[5] Many patients have limb or trunk choreoathetosis and in severe cases opisthotonus and dystonic posturing with raised muscle enzyme level. Autonomic involvement is another common manifestation, though it is less severe in children. Patients may present with tachy- or bradycardia, hyper- or hypothermia and blood pressure fluctuations. The most severe complication is central hypoventilation, which was reported in 23% in a series of children and 66% in a series composed mainly of adults.[7] In such cases, prolonged ventilatory support ensues.

CSF lymphocytic pleocytosis is common in anti-NMDAR encephalitis. There might be normal or mildly increased CSF protein. Oligoclonal bands are positive in 60%.[5] MRI brain is unremarkable in 50% while the remaining shows transient T2 or Fluid Attenuated Inversion Recovery (FLAIR) signal hyperintensity in one or more areas of the brain.[3] EEG is abnormal in most patients and may show non-specific slow activity and electrographic seizures or continuous, rhythmic activity in the delta-theta range in the catatonic stage.[5,7] Definitive diagnosis is made by detecting anti-NMDAR antibodies, which are often present in higher concentrations in CSF than in serum, or in CSF alone if patients have been given immune-modulatory treatment or become seronegative in a protracted clinical course.[2,7] It is now well demonstrated that NMDAR antibodies are pathogenic of the disease. These antibodies cause internalisation of post-synaptic surface NMDARs,[5,8] leading to neuronal dysfunction resembling the action of several NMDAR antagonists such as ketamine which also induce anti-NMDAR encephalitis-like symptoms. The CSF titre of NMDAR antibody correlates well with symptom severity and clinical outcome.[5] In patients with persistent symptoms despite treatment, CSF antibody titres often remain high. It is now recognised that detection of an underlying tumour is dependent on age, sex and ethnicity. Ovarian tumour is less prevalent in young children and more common in Black women.[3]

The mainstay of treatment for anti-NMDAR encephalitis is immunotherapy. Based on data from a review of more than 400 patients with anti-NMDAR encephalitis, Dalmau et al proposed a treatment protocol

of concurrent methylprednisolone and IVIg as first-line therapy.[3] Plasmapheresis is an alternative, although it might be difficult in young patients or patients with autonomic instability. All patients should undergo screening for an underlying tumour, especially ovarian teratoma or testicular germ-cell tumour, as tumour removal enhances immunotherapy effectiveness and leads to more complete and rapid recovery. If patient remains unresponsive after 10 days, second-line therapy such as rituximab, cyclophosphamide or both should be initiated. Overall, 75% of patients achieve improvement though it takes weeks to months before they return to their premorbid state.[5] Chronic immunosuppression with mycophenolate mofetil or azathioprine for one year was recommended in patients without an underlying tumour as they are at a higher risk for relapses.[3] Lizuka and colleagues reported spontaneous neurological recovery in four patients with anti-NMDAR encephalitis who were initially diagnosed with idiopathic encephalitis and not given immunotherapy.[9] They recovered but at the expense of prolonged hospital stay of up to 9 months and slower recovery of up to 7 years. The estimated mortality is 4%. Fourteen out of 360 patients with follow-up longer than 6 months died in ICU from various complications including sepsis, sudden cardiac arrest, acute respiratory distress, refractory status epilepticus and tumour progression.[3]

With heightened awareness of this disorder, several retrospective studies have now identified NMDAR antibodies in a substantial proportion of patients previously diagnosed with idiopathic encephalitis or dyskinetic encephalitis lethargica.[2,10] Apparently this disease entity has gone under-recognised. Since most patients have good prognostic outcomes after immunotherapy, paediatricians, neurologists and psychiatrists should be aware of this clinical syndrome for timely diagnosis and aggressive therapy. It is important to include anti-NMDAR encephalitis as a differential diagnosis in patients, particularly young females, who present with neuropsychiatric syndrome with features of seizure, movement disorder and autonomic instability.

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