Anti-N-methyl-D-aspartate receptor antibodies: A potentially treatable cause of encephalitis in the intensive care unit

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Objective: **To report the occurrence of an unusual neurologic disorder requiring admission to the intensive care unit.**

Design: **Analysis of an observational cohort study of 31 patients with encephalitis admitted over a 4-yr period.**

Setting: **Neurologic intensive care unit in a tertiary referral center.**

Patients: **We identified N-methyl-D-aspartate receptor antibodies in six patients (two male and four female). All seropositive patients presented with a psychiatric prodrome, before developing seizures and obtundation requiring intensive care unit admission. They exhibited limb and truncal stereotypies and orofacial dyskinesias upon weaning sedation. Two patients had ovarian tumors.**

Interventions: **Patients were treated with sedation, antiepileptic drugs, and immunotherapy. One patient received a magnesium infusion and ketamine.**

Measurements and Main Results: **N-methyl-D-aspartate receptor antibodies were identified in serum samples by an immunofluorescent cell-based assay. Three patients made a good but slow recovery; two were left with severe neurologic deficits; and one died after return to the referring hospital. These patients accounted for approximately 20% of all patients admitted with encephalitis to this referral center.**

Conclusions: **N-methyl-D-aspartate receptor antibodies should be tested in patients with hyperkinetic encephalitis and neuropsychiatric prodrome admitted to the intensive care unit. The disorder is probably not rare and is potentially treatable. (Crit Care Med 2010; 38:679–682)**

KEY WORDS: NMDA receptor; encephalitis; ovarian teratoma; neurological intensive care; hyperkinetic

Antibodies against the N-methyl-D-aspartate subtype of glutamate (NMDA) receptors have recently been demonstrated in patients with encephalitis (1–3). Many cases are associated with ovarian teratomas, although male cases have also been described, and tumors are not always identified. Patients have improved, in some instances, achieving full recovery, after tumor removal and/or immunosuppression (2).

Patients with anti-NMDA receptor encephalitis may present with psychiatric disturbance, amnesia, seizures, autonomic features, obtundation, orofacial dyskinesias, and intermittent jerking of the limbs and trunk (2, 4). The full clinical spectrum of this disorder remains to be determined, as does its frequency relative to other causes of encephalitis. We report an unexpectedly high frequency of anti-NMDAR encephalitis in the intensive care unit (ICU).

PATIENTS AND METHODS

Requirement for prior approval for this study was waived by the local Ethics Committee. The six patients described here were cared for in the ICU at the National Hospital for Neurology and Neurosurgery between 2004 and 2008, having been referred from other hospitals. During this period, 31 patients with encephalitis, defined as acute or subacute onset of encephalopathy or seizures accompanied by cerebrospinal fluid (CSF) pleocytosis, were admitted. Patients with the following diagnoses were excluded from this cohort: bacterial meningitis, status epilepticus with an alternative etiology, and chronic paraneoplastic encephalitis.

Anti-NMDAR encephalitis was diagnosed prospectively in patients 1 to 3, and retrospectively in patients 4 to 6 from stored serum samples. These patients had previously been diagnosed with encephalitis with a possible autoimmune basis. Investigations, treatment, and outcome are summarized in Tables 1 and 2. Of the other 25 patients, nine had herpes simplex encephalitis. Enterovirus, cytomegalovirus, Q fever, Sjögren syndrome, and limbic encephalitis with voltage-gated potassium channel antibodies, each accounted for one case. Ten other cases were given a diagnosis of probable viral encephalitis. One final case resembled the six positive cases but serum was not available for retrospective antibody screening.

NMDA Receptor Antibody Cell-Based Assay

The assay was similar to that described in the work of Dalmau et al (1), but cells were not permeabilized. Furthermore, sera were tested at 1:20 dilution because this was found to yield almost exact concordance with CSF results in a larger series (Irani et al, in preparation). Human embryonic kidney (293T) cells were transfected with cDNA encoding NR1 and NR2B subunits in a 1:1 ratio. Ketamine (500 μM) was added 12 hrs later. Staining was

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Table 1. Investigation results

Patient	MRI	CSF	EEG	Other Results
1 (F)	Four brain scans (three with Gd) were normal	74 lymphocytes, 6 polymorphs. Intrathecal synthesis of OCB. HSV PCR negative	Initially electrographic seizures; subsequently generalized slowing	Right ovarian teratoma removed after body CT
2 (M)	Three Gd-enhanced brain scans were normal	Normal cell count on 1st LP but 40 WBC (95% lymphocytes) on 2nd LP. Intrathecal synthesis of OCB. HSV PCR negative	Two electrographic seizures; subsequently generalized slowing	CT chest/abdomen/pelvis, whole-body PET, Ultrasound testes, bone marrow all normal. Serum EBV IgM positive
3 (M)	Three brain scans with and without Gd were normal	12 WBC. Positive HSV1 PCR initially[a] (negative subsequently). Intrathecal synthesis of OCB	Generalized slowing, no electrographic seizures	CT chest/abdomen/pelvis and USS testes negative
4 (F)	Brain scan initially normal; subsequently small nonenhancing cerebellar and cerebral white matter lesions	60 lymphocytes. Intrathecal synthesis of OCB. HSV PCR negative	Encephalopathic, electrographic seizure on one occasion	Not screened for a teratoma
5 (F)	Three brain scans were normal	114 WBC. Intrathecal synthesis of OCB. HSV PCR negative	Encephalopathic with occasional electrographic seizures	Normal pelvic ultrasound performed 9 mos before illness, but no screening for tumors performed
6 (F)	Two brain scans were normal	8 lymphocytes. Intrathecal synthesis of OCB. HSV PCR negative	Encephalopathic without electrographic seizures	Bilateral ovarian dermoid cysts shown on CT and removed

MRI, magnetic resonance imaging; CSF, cerebrospinal fluid; EEG, electroencephalography; Gd, gadolinium enhancement; OCB, oligoclonal bands; HSV, herpes simplex virus; PCR, polymerase chain reaction; CT, computed tomography; LP, lumbar puncture; WBC, white blood cell; PET, positive emission tomography; EBV, Epstein-Barr virus; IgM, immunoglobulin M; USS, ultrasound scan.

Extensive serum and CSF investigations excluded many alternative infectious, metabolic, autoimmune, and paraneoplastic conditions.

[a]Patient 3 was found to have positive HSV1 PCR, but HSV-specific CSF immunoglobulin and repeat HSV PCR were negative, strongly suggesting that the first PCR was spurious.

Table 2. NMDA receptor antibody score, treatment, and clinical outcome

Patient	NMDA Receptor Antibody Score	Treatment	Outcome (Time From Presentation)
1 (F)	3	Acyclovir, anticonvulsants, steroids, teratoma removal followed by plasma exchange	Full recovery, with return to higher education (10 mos)
2 (M)	4	Acyclovir, anticonvulsants, pulsed methylprednisolone, two courses of IVIG, plasma exchange	No recovery at 6 mos; died
3 (M)	3	Acyclovir (4-wk course), anticonvulsants, pulsed methylprednisolone with oral taper, plasma exchange	Improved movement disorder, fixating (5 mos)
4 (F)	2	Acyclovir, anticonvulsants, pulsed methylprednisolone with oral taper	Good recovery; mild cognitive dysfunction (3 yrs)
5 (F)	2	Acyclovir, anticonvulsants, pulsed methylprednisolone, IVIG, ketamine	Good recovery; mild cognitive dysfunction (2 yrs)
6 (F)	2	Acyclovir, anticonvulsants, pulsed methylprednisolone with oral taper, IV cyclophosphamide, Rituximab, removal of bilateral ovarian dermoid cysts	Improved movement disorder; moderate cognitive impairment (2 yrs)

NMDA, N-methyl-D-aspartate; IVIG, intravenous immunoglobulin.

Sera from ten healthy controls and 26 patients with other autoimmune neurologic disorders scored 0 on the staining scale (0–4).

scored, blind to the clinical diagnosis, on a scale of 0 to 4 (Fig. 1.) Positive sera were retested against cells transfected with another membrane protein to confirm absence of nonspecific binding. The assay was negative in 26 cases with an alternative autoimmune neurologic disorder where it was tested as well as in healthy controls.

Case Histories

Patient 1. A 20-yr-old woman became irritable and forgetful. Over the subsequent 10 days, she developed headaches and malaise before becoming overtly febrile and confused on the day of her admission. She had generalized tonic-clonic seizures and a reduction in conscious level requiring ICU admission, where she was sedated, ventilated, and treated with antiepileptic medication. Upon weaning sedation, she had intermittent orofacial dyskinesias, with stereotypic pouting and grimacing, and symmetrical upper limb movements, without electroencephalography correlate. There was spontaneous eye opening and, at times, she was able to obey simple commands. After 3 months, an ovarian teratoma was identified and removed. (A contralateral teratoma had been removed 18 months earlier.) She underwent plasma exchange and the movement disorder abated. By month 4, she was able to answer questions appropriately. By month 10, she had recovered fully and resumed a university course.

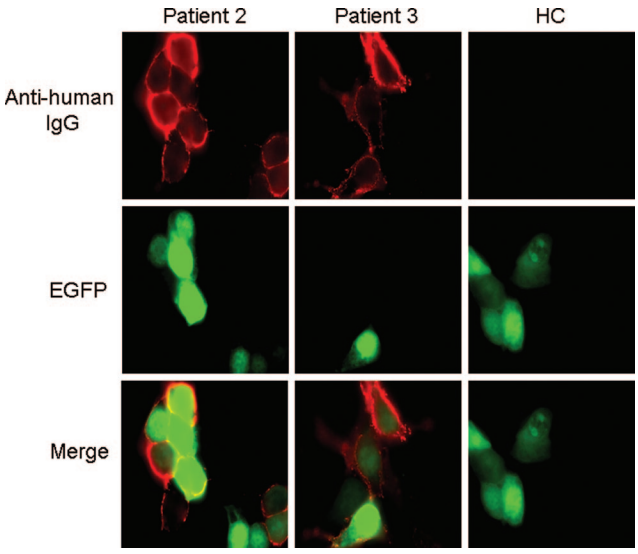

Figure 1. Human embryonic kidney cells were co-transfected with cDNA encoding NR1, NR2B, and enhanced green fluorescent proteins (*EGFP*). EGFP fluorescence was used to visualize cells expressing N-methyl-D-aspartate subtype of glutamate (*NMDA*) receptors (*green*). Cells were subsequently incubated with sera (1:20), fixed in 4% formaldehyde and incubated with AlexoFluor 568 nm antihuman immunoglobin G (*IgG,* red) (1:750, Invitrogen-Molecular probes, Paisley, UK). Coverslips were mounted, stained with 4′,6-diamidino-2-phenylindole and binding to the cell surface visualized, using a fluorescence microscope with a MacProbe v4.3 digital imaging system. Anti-NMDA receptor staining patterns are shown for patient 2, patient 3, and a representative healthy control (*HC*).

Patient 2. A 41-yr-old man presented with a 3-wk history of obsessional ideation, auditory hallucinations, and agitation. Post admission, he became febrile, less responsive, and he developed abnormal movements, including tongue biting, sudden abduction of his limbs, and episodes of apnea. He was transferred to the ICU where he had four generalized seizures, and required sedation and artificial ventilation. Upon weaning sedation, he had spontaneous eye opening but no clear response to painful stimulus or command. He continued to have symmetrical stereotypical limb movements, together with orofacial dyskinesias consisting of blinking, pouting, and tongue protrusion, without electroencephalography correlate. There was central hyperthermia. Extensive investigation failed to reveal a tumor. Despite immunotherapy, there was no neurologic recovery and the patient succumbed to pneumonia 6 months after presentation.

Patient 3. A 29-yr-old man presented with a 2-day history of increasing headache followed by two generalized seizures. He subsequently developed auditory hallucinations and delusions, and became increasingly obtunded. He was transferred to the ICU where orofacial dyskinesias (blinking, pouting, and tongue biting) and symmetrical limb and truncal jerks were noted upon decreasing intravenous sedation. There were no electrographic seizures during the jerks. He opened his eyes spontaneously but did not respond to stimuli or commands. CSF polymerase chain reaction for herpes simplex virus 1 was positive and he was treated with acyclovir, but subsequent polymerase chain reaction and serology for herpes simplex virus 1 were negative. He was also treated with immunotherapy. He gradually began to improve and, when assessed 5 months into his illness, the dyskinesias had abated and he fixated on and visually tracked faces.

Patient 4. A 28-yr-old woman presented with headache, fever, and neck stiffness. This improved but 2 wks later she re-presented with agitation, confusion, visual and auditory hallucinations, disinhibition, and perseveration. Over the next 10 days, she had two generalized seizures, became obtunded, and developed repetitive orofacial movements with blinking, tongue protrusion, and rhythmical palatal movements. There were repetitive flailing and gripping movements of the upper limbs and unexplained hyperthermia. She was treated with corticosteroids. Three months after presentation, the involuntary movements had ceased and she only showed evidence of mild frontal lobe dysfunction. Three years after presentation, she was working as a dressmaker, having previously worked as a paralegal.

Patient 5. A 26-yr-old woman presented with headache and acute confusion. She had become forgetful and exhibited impaired verbal fluency and speech comprehension. A week later, she re-presented with worsening word-finding difficulties and increasing memory impairment. Her conscious level began to fluctuate and she developed involuntary movements described as "athetoid" at the referring hospital. She required tracheal intubation and was transferred to the ICU. She was subsequently noted to have bilateral facial twitching and grimacing together with bilateral rhythmic movements of her upper limbs and involuntary movements of the trunk. She was treated with corticosteroids, and subsequently with intravenous immunoglobulin, magnesium infusion, and ketamine. Seven months after presentation, she had improved to the point that she was able to sit up in bed and copy some visual cues. She eventually made a good recovery and was left with mild cognitive deficits only.

Patient 6. A 21-yr-old woman presented with headache, fever, agitation, visual hallucinations, and acute confusion. She had a generalized seizure, and developed facial twitching, repetitive eye rolling, and jerky movements of the limbs. Five months after presentation, in spite of immunomodulatory treatment, she continued to have involuntary movements requiring ICU care, but had begun to track family members visually. Subsequently, bilateral ovarian dermoid cysts were removed laparoscopically. Two years after presentation, she had recovered the ability to speak and write a few words, but exhibited perseveration and disorientation. Motor examination revealed unilateral cog-wheeling but no involuntary movements.

DISCUSSION

The six patients described here all presented with psychosis and/or amnesia, followed by seizures, obtundation, symmetrical limb stereotypies, and orofacial dyskinesias. All required ICU admission for management of seizures, a decreased level of consciousness, or a prominent hyperkinetic movement disorder. Limb, trunk, and orofacial jerking occurred without electroencephalography correlate, and was the primary indication for protracted sedation in five patients. A re-

cent large case series reports on the occurrence of catatonia and other hypokinetic manifestations in anti-NMDA receptor encephalitis (2). Although some of our patients exhibited mutism after successful weaning from sedation, this was not prominent at the onset.

All patients had evidence of intrathecal immunoglobulin G synthesis and a CSF pleocytosis, supporting the view that cerebral inflammation is a consistent feature in anti-NMDA receptor encephalitis. However, five of the patients had normal cerebral magnetic resonance imagings. Although tumors were only identified in two patients, several patients made a moderate or good recovery after immunomodulatory therapy and/or tumor removal. The NMDA blockers magnesium and ketamine were used in one patient, with no worsening, and possibly a mild improvement, in her condition. A pathogenic role of the antibodies is supported by evidence that, as also shown here by binding unpermeabilized, the epitope is extracellular (5) and that patients can improve with plasma exchange. Furthermore, there is similarity between the pattern of immunoglobulin G deposition within a patient's hippocampus at autopsy and the pattern of immunolabeling upon incubating rodent brain slices with the antibodies (1).

It is difficult to extrapolate the frequency of anti-NMDA receptor and other causes of encephalitis from the present study because patients with diagnostic and/or management difficulties were more likely to be referred to our unit. Nevertheless, the finding that anti-NMDA receptor encephalitis accounts for approximately 20% of patients with encephalitis requiring ICU admission in this tertiary center implies that the condition is not rare.

Anti-NMDA receptor antibodies should be screened for in any patient presenting with neuropsychiatric prodromal symptoms and a prominent movement disorder. Anti-NMDA receptor encephalitis can have a good outcome (2, 6), underlining the importance of obtaining the diagnosis. The precise epidemiology and optimal immunomodulatory treatment remain to be established.

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