A case series of critically ill patients with anti-N-methyl-D-aspartate receptor encephalitis

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ABSTRACT

Anti-N-methyl-D-aspartate (NMDA) receptor encephalitis causes autonomic disturbances, behavioural changes and abnormal movements. It is often a paraneoplastic phenomenon that occurs in association with ovarian teratomas and is the most common paraneoplastic encephalitis.

We report nine cases of critically ill patients with anti-NMDA receptor encephalitis from Australia and New Zealand. One patient died and one had a poor neurological recovery. The remaining patients made substantial or complete neurological recoveries. This case series highlights that patients with anti-NMDA receptor encephalitis:

- often require long periods of support in an intensive care unit;
- may develop tracheostomy complications related to hypersalivation;
- may develop life-threatening hyperthermia;
- can have ovarian teratomas despite normal investigations; and
- often have very abnormal movements that are difficult to control and make ongoing care difficult.

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Antibodies against N-methyl-D-aspartate (NMDA) receptors have been shown to be associated with a characteristic form of encephalitis that presents with psychosis and abnormal movements.[1,2] Anti-NMDA receptor encephalitis is often a paraneoplastic phenomenon that occurs in patients with ovarian teratomas. The largest published series of patients with this disorder included 100 subjects, of whom 75 recovered or were left with mild disability and 25 died or were left with severe disability.[1] On the basis of available data from 360 patients with more than 6 months of clinical follow-up, the estimated mortality of anti-NMDA receptor encephalitis is 4%.[3] The recovery of patients with this disorder is often prolonged, and many patients require support in an intensive care unit during their illness.[1] Despite this, the previous intensive care literature is limited to a six-patient case series from a single neurological ICU.[4] To identify cases of anti-NMDA receptor encephalitis from Australia and New Zealand, we contacted members of the Australian and New Zealand Intensive Care Society Clinical Trials Group (ANZICS CTG) via the ANZICS CTG email list. Twenty-four cases of patients with anti-NMDA receptor encephalitis were identified from Australia and New Zealand, of which clinical details were provided for this case series for nine patients from six hospitals. The ethics committee at each institution granted approval for the use of clinical data, waiving the requirement for informed consent.

Clinical records

Demographics and clinical symptoms

The mean age of patients at the time of admission to hospital was 18 years (SD, 11 years), ranging from 1 to 38 years. Patients were most commonly of Asian or Pacific Islander descent with only one-third being of European descent (Table 1).

There was a range of presenting symptoms (Table 1). Two patients presented to hospital with predominantly psychiatric symptoms and were initially evaluated by a psychiatrist; the remainder were initially evaluated by a paediatrician, physician or a neurologist. Patients presented with various combinations of fever, headache and changes in behaviour. In some patients, abnormal movements or seizures were present at admission but, in most, abnormal movements developed after a few days of hospitalisation. The abnormal movements observed included extensor posturing, choreoathetoid movements and orofacial twitching, as well as a range of eye signs (Table 2). In four of the nine patients, focal or generalised seizures were clinically suspected and treated. Although some patients were admitted to the ICU with significant reductions in Glasgow Coma Scale score, airway patency was initially maintained in most cases. Rather than being truly comatose, several patients exhibited a dissociative state similar to that seen after administration of ketamine, where they had no response to pain but resisted movement and maintained airway patency.

Table 1. Background and presenting symptoms for nine patients with anti-N-methyl-D-aspartate receptor encephalitis

Age	Sex	Ethnicity	Presenting symptoms
6 years	Male	Asian	Fever and headache. Subsequently developed lip smacking and abnormal limb movements
19 years	Female	Pacific Islander	Confusion, disorientation and behavioural problems. Subsequently developed eye and mouth twitching which progressed to a severe, treatment-refractory movement disorder characterised by bruxism and severe hypertonia associated with a depressed conscious state
28 years	Female	Australian European	Auditory and visual hallucinations in association with agitation and unusual behaviour. Subsequently developed fevers and abnormal movements with orofacial twitching and episodes of truncal extension
38 years	Female	Australian European	Occipital headache and neck pain followed by fevers, mild photophobia and generalised myalgia. Developed changes in behaviour with paranoia and a generally withdrawn state but with episodes of shrieking laughter. Progressed to have increased rigidity and involuntary jerky movements of the face and arms which were most evident around the mouth. Conscious state became increasingly depressed
23 years	Female	Asian	Headache and confusion. After 48 hours in hospital had a generalised tonic–clonic seizure which progressed to status epilepticus. Developed generalised abnormal movements which were most evident in the upper limbs and perioral regions
12 years	Male	Asian	Lethargy, agitation, unusual posturing of the left upper limb and altered sensation in the left leg and foot. Developed fevers and increased tone
14 years	Male	Pacific Islander	Fevers and headache in association with erratic behaviour and visual hallucations. Developed abnormal movements soon after hospital admission in association with a fluctuating conscious state ranging from agitation to coma. Abnormal movements progressed to severe choreoathetoid movements involving the limbs and orofacial twitching
22 years	Female	Pacific Islander	Insomnia, mood swings, and hallucinations in association with periods of violent behaviour alternating with periods of catatonia and crying. Subsequently developed fevers and a depressed conscious level. Had a period of severe bradycardia and episodes of ventricular standstill requiring cardiopulmonary resuscitation. Developed abnormal facial movements with lip smacking and arm jerking. Had persistently elevated body temperature and, on Day 22 in the intensive care unit, developed severe hyperthermia with a core body temperature reaching 43.4°C shortly before suffering cardiac arrest and dying
1 year	Female	Australian European	A focal seizure affecting the right side of the body. Had ongoing problems with abnormal movements with development of severe choreoathetoid movements. Developed a depressed conscious state

Indications for ICU admission, and ICU course

Indications for ICU admission included reduced conscious state, respiratory failure, abnormal movements, and seizures (Table 3).

The predominant ICU support required was mechanical ventilation (seven patients). Only one patient required vasopressor support, and no patient required renal replacement therapy. With the exception of the 1-year-old and the 6-year-old, all patients who were ventilated received a tracheostomy and, among those ventilated, the mean (SD) duration of mechanical ventilation was 38 (30) days (range, 3–82 days). The ICU length of stay ranged from 10 to 82 days (mean [SD], 40 [26] days).

Investigations

A summary of investigations is provided in Table 4. The diagnosis of anti-NMDA receptor encephalitis was confirmed for all patients by detection of antibodies in their cerebrospinal fluid and/or their plasma. A range of investigations for teratoma resulted in histological confirmation of ovarian teratoma in four of the nine patients. Investigations performed included computed tomography (CT) of the chest, abdomen and pelvis; transabdominal and transvaginal pelvic ultrasound; testicular ultrasound; pelvic magnetic resonance imaging (MRI); and diagnostic laparoscopy. One patient had a normal pelvic ultrasound, but a pelvic MRI suggested a possible tumour on the right ovary. The tumour was removed laparoscopically and was histopathologically confirmed as a mature cystic teratoma. Pelvic ultrasound on two patients showed an ovarian teratoma, which was surgically removed, and confirmed in each case by histopathological examination. A fourth patient had a normal CT, MRI and pelvic ultrasound followed by a laparoscopy with findings of macroscopically normal ovaries. Despite this, the patient underwent a bilateral oophorectomy, and a 7 mm unilateral mature teratoma was shown on histopathological examination.

Neuroimaging results were generally normal or showed only subtle abnormalities. All patients with findings consistent with encephalopathy underwent electroencephalography (EEG). Despite clinical suspicion of seizure activity in a number of patients, no patients had EEGs showing epileptiform activity.

Table 2. Observed abnormal movements among nine patients with anti-N-methyl-D-aspartate receptor encephalitis

Patient	Orofacial movements	Choreoathetoid movements	Extensor posturing	Rigidity	Eye deviation	Nystagmus	Ocular dipping	Focal seizures	Generalised seizures
1	✓	✓	✓	×	×	×	×	×	×
2	✓	✓	✓	✓	✓	✓	✓	✓	✓
3	✓	×	✓	✓	×	×	×	×	✓
4	✓	✓	✓	✓	✓	✓	✓	×	×
5	✓	×	✓	✓	✓	×	×	×	✓
6	×	×	✓	✓	×	×	×	×	×
7	✓	✓	✓	✓	✓		✓	×	×
8	✓	✓	✓	×	✓	✓	✓	×	×
9	✓	✓	✓	×	✓	✓	×	✓	✓

Treatments and complications

The patients' abnormal movements were particularly problematic and difficult to control. In several cases, abnormal movements led to difficulties with mechanical ventilation and maintaining lines and tubes. Remarkably, 26 different medicines were used in the nine patients in the series (mean, eight per patient) to attempt to limit abnormal movements or seizures (Table 5). None of these medicines were noted to be particularly effective. One patient developed a life-threatening toxic epidermal necrolysis that was thought to be attributable to sodium valproate. This involved 90% of her skin and precipitated a second admission to the ICU lasting 26 days.

Autonomic dysfunction was commonly reported. Clinically significant bradycardia was seen in two patients and tachycardia was seen in four. In one patient, episodes of extreme bradycardia and asystole necessitated repeated periods of cardiopulmonary resuscitation.

Fever was a universal feature. The mean peak temperature recorded in the ICU was 39.9°C (SD, 1.4°C). Two-thirds of the patients had a fever of more than 38.3°C for 5 consecutive days, and two of these had a tempera-

Table 3. Indications for admission to the intensive care unit; ICU course; and hospital length of stay

Patient	Indication(s) for ICU admission	Complications	Duration of mechanical ventilation (days)	ICU length of stay (days)	Hospital length of stay (days)
1	Depressed conscious state	Treatment-refractory movement disorder	26	28	120
2	Depressed conscious state, abnormal movements	Ventilator-associated pneumonia, toxic epidermal necrolysis (?secondary to sodium valproate). Treatment-refractory movement disorder	30	45	145
3	Depressed conscious state, seizures	Nil of note	0	35	58
4	Depressed conscious state	Treatment-refractory movement disorder, deep vein thrombosis	79	79	110
5	Depressed conscious state, seizures, and respiratory failure	Treatment-refractory movement disorder, marked autonomic instability, hypersalivation	82	82	Remains in hospital after 2 years
6	Respiratory failure	Nil of note	0	14	114
7	Depressed conscious state	Treatment-refractory movement disorder	23	45	145
8	Depressed conscious state	Bradyarrhythmia requiring cardiopulmonary resuscitation, severe hypersalivation complicating tracheostomy management, treatment-refractory movement disorder, severe hyperthermia, death	22	22 (died in ICU)	25
9	Seizures, abnormal movements	Treatment-refractory movement disorder	3	10	200

Table 4. Investigations and results among nine patients with anti-N-methyl-D-aspartate (NMDA) receptor encephalitis

Patient	NMDA receptor antibodies	CT chest/ abdomen/ pelvis	Ultrasound ovaries/testes	MRI pelvis	Laparoscopic oophorectomy; result of histological examination	CT brain	MRI brain	EEG
1	Detected in CSF; not measured in plasma	nd	Testicular ultrasound, nd	nd	na	nd	nd	Encephalopathy
2	Detected in CSF and plasma	Normal	Transabdominal pelvic ultrasound, normal	Right ovarian tumour	Unilateral (right) oophorectomy; right ovarian teratoma	Subtle signs of cerebral oedema	nd	Encephalopathy
3	Detected in CSF and plasma	nd	Transvaginal ultrasound showed right adnexal mass consistent with teratoma	nd	Bilateral partial oophorectomies; right ovarian teratoma	Normal	Hyperdensity within white matter of right frontal lobe	Encephalopathy
4	Detected in plasma; not measured in CSF	Normal	Transabdominal pelvic ultrasound, normal	Normal	Bilateral oophorectomy; unilateral teratoma	Normal	nd	Encephalopathy
5	Detected in plasma; not measured in CSF	Right adnexal mass consistent with teratoma	Transabdominal pelvic ultrasound showed bilateral adnexal masses consistent with bilateral ovarian teratomas	nd	Bilateral oophorectomy performed; bilateral ovarian teratomas	Normal	nd	Encephalopathy
6	Detected in plasma; not measured in CSF	nd	Testicular ultrasound, nd	nd	na	Normal	nd	Encephalopathy
7	Detected in CSF and plasma	Normal	Testicular ultrasound, normal	nd	na	Normal	Normal	Encephalopathy
8	Detected in CSF and plasma	Normal	Transabdominal and transvaginal ultrasounds, normal	nd	nd	Normal	nd	Encephalopathy
9	Detected in CSF; not measured in plasma	nd	Pelvic ultrasound, nd	nd	nd	Normal	Meningeal enhancement	Encephalopathy

CT = computed tomography scan. CSF = cerebrospinal fluid. EEG = electroencephalography. MRI = magnetic resonanance imaging. na = not applicable. nd = not done.

ture of more than 39.5°C for 5 consecutive days. One patient developed a progressive fever despite the use of physical cooling measures and had a peak core temperature of 43.4°C recorded shortly before dying from complications of hyperthermia. This patient had received neuroleptic medications including haloperidol, and it is possible that the severe hyperthermia seen in this case was an iatrogenic complication of treatment rather than a manifestation of the anti-NMDA receptor encephalitis itself.

Four of the nine patients had marked hypersalivation. In these patients, problems with salivary contamination of tracheostomy wounds complicated management, and treatment of hypersalivation was often difficult because complicating rhythm disturbances limited the use of medicines to control hypersalivation.

In addition to supportive therapies, all patients received specific immunomodulatory therapies (Table 6). The most common of these therapies was high-dose methylprednisolone. In some cases the use of these therapies was

associated with dramatic improvement in abnormal movements, but most commonly any improvements in overall neurological condition occurred slowly over a time course of weeks rather than hours or days.

Outcomes

One of the patients died in the ICU and another remains hospitalised with severe neurological disability more than 2 years after the onset of her symptoms. All of the other patients in this series have made a substantial or complete neurological recovery. Excluding the patient who remained hospitalised at the time of this report, of the patients who survived, the mean hospital length of stay was 127 ± 43 days (range, 25–200 days).

Table 5. Medicines used to treat movement disorders among nine patients with anti-N-methyl-D-aspartate receptor encephalitis

Medicine	No. of patients
baclofen	4
benztropine	3
clonazepam	3
clonidine	3
dantrolene	1
dexmedetomidine	1
diazepam	5
droperidol	4
fentanyl	3
haloperidol	4
ketamine	1
L-dopa	1
levetiracetam	2
lorazepam	1
midazolam	9
morphine	2
nitrazepam	1
olanzapine	2
paraldehyde	2
phenobarbitone	2
phenytoin	6
propofol	4
risperidone	2
temazepam	1
tetrabenazine	1
thiopentone	1
valproate	4

Discussion

Summary of principal findings

Our case series of nine patients from six hospitals across Australia and New Zealand serves to highlight many aspects of anti-NMDA receptor encephalitis that are relevant for the management of patients in the ICU (Table 7). The primary indication for ICU admission in our patients was decreased level of consciousness, and the major requirement for ICU-level support was airway management and mechanical ventilation. In addition to potential airway compromise, potentially life-threatening complications directly attributable to anti-NMDA receptor encephalitis were hyperthermia, which led to the death of one patient, and arrhythmia.

Attempting to control abnormal movements was the major therapeutic challenge. A mean of eight medicines per patient were administered to attempt to control abnormal

Table 6. Immunomodulatory therapies used in nine patients with anti-N-methyl-D-aspartate receptor encephalitis

Medicine	No. of patients
Corticosteroids	9
Immunoglobulins	5
Plasma exchange	5
Rituximab	5
Cyclophosphamide	2

Table 7. Key learning points supported by this case series

- Anti-N-methyl-D-aspartate (NMDA) receptor encephalitis is a rare autoimmune encephalitis characterised by fevers and psychiatric symptoms as well as abnormal movements which are often most evident around the mouth
- The most common indication for intensive care unit admission in patients with anti-NMDA receptor encephalitis is a depressed conscious state
- Anti-NDMA receptor encephalitis commonly occurs in association with ovarian teratoma and normal investigation does not exclude the presence of an ovarian teratoma; excision of a teratoma appears to be associated with improved prognosis
- Hypersalivation may complicate tracheostomy management
- Abnormal movements are often refractory to simple medical treatment and the use of multiple medications can lead to iatrogenic complications
- Autonomic dysfunction including cardiac arrhythmia and hyperthermia can be life threatening
- Recovery from anti-NMDA receptor autoimmune encephalitis is extremely slow, often taking months or even years, but most patients recover well

movements, and one patient developed a life-threatening drug reaction. Four of the nine patients were found to have ovarian teratomas — and in one, this diagnosis was only confirmed after laparascopic removal of macroscopically normal ovaries subsequent to a series of investigations that included an MRI of the pelvis. Most patients had prolonged ICU requirements and needed long periods of hospitalisation. However, the patients in this series usually recovered gradually over a period of several months.

Comparison with previous studies

The exact incidence of anti-NDMA receptor encephalitis is unknown; however, available evidence indicates it is probably the most common paraneoplastic encephalitis.[3] The proliferation of cases described in the literature suggests that this is not a very rare disorder.[3] In one study, anti-NMDA receptor encephalitis accounted for about 20% of all patients admitted to a tertiary neuro-ICU with non-bacterial meningoencephalitis.[4] Given that anti-NMDA receptor encephalitis was not described until 2005[5] and was not well known until more recently,[1] our identification of 24 recent cases from Australian and New Zealand ICUs suggests that this is a disorder with which ICU specialists should be familiar.

In line with previous studies, our patients were most often female.[3] Our patients were all children or young adults. While anti-NMDA receptor encephalitis is predominantly a disease affecting younger people,[3] this disorder has also been described in the elderly.[5] In our study, most patients were of non-European descent, with Pacific Islanders being disproportionately represented, raising the possibility that among our population there may be an ethnic predisposition to the disease.

The clinical features of the patients in our case series are similar to those described previously.[1] In anti-NMDA receptor encephalitis it appears that antibodies against the NMDA receptor preferentially affect the hippocampus, forebrain, basal ganglia, spinal cord, and cerebellum.[6] This may account for the unique combination of personality change, cognitive impairment, bradycardia, and abnormal movements associated with the syndrome. Cerebellar manifestations are less common[7] and were not prominent in any of our patients. It seems likely that the dissociative state observed in our patients is akin to that produced by NMDA receptor antagonists like ketamine.

The autonomic disturbances associated with the disorder have been described in detail[3] and the occurrence of hypersalivation in association with this syndrome has been recognised.[8] Four of our patients had problems with tracheostomy management that were attributable to salivary contamination of tracheostomy wounds. This issue has not been highlighted previously. One of our patients had life-threatening bradycardia. Although pacing was not used in our patient, a requirement for temporary cardiac pacing has been described previously.[9] While fever is often seen in this disorder, we are not aware of any reports of patients in whom severe hyperthermia potentially contributed to death.

Seizures are a well described feature of this disease, but difficulty in distinguishing seizures from other abnormal movements has been noted.[3] In four of our patients, seizures were clinically suspected, but none of the patients had epileptiform changes on EEG. In one previous series, epileptiform activity was seen in 21 of 92 patients.[1] The frequency of seizures tends to decrease as the illness progresses,[3] and the patients in our series may well have had true seizures that were not captured on EEG. Potentially, both "overtreatment" of movements that are not attributable to seizure activity[10] and "undertreatment" of seizures that are dismissed as non-epileptiform abnormal movements might occur.[3] It is noteworthy that non-convulsive status epilepticus has been described in these patients.[11] One case report described a patient who had non-convulsive status epilepticus and was treated with pentobarbital coma for several months before undergoing a prophylactic oophorectomy that revealed a microscopic ovarian teratoma and led to resolution of EEG changes and clinical improvement.[12] Given the difficulty of distinguishing seizures from other abnormal movements, optimal management is probably urgent investigation with video EEG before commencement of antiepileptics. The encephalopathic EEG pattern observed in our patients is the most commonly observed EEG abnormality in patients with this disorder.[1]

Our observed rate of ovarian teratoma was similar to that described previously.[1] It appears that the frequency with which ovarian teratomas are seen in association with this disorder increases with age. In one study, teratomas were seen in 56% of female patients over 18 years of age, and 31% of female patients under 18 years, but in only 9% of those under 14 years of age.[10] Non-ovarian tumours are only rarely seen in this condition. Of 400 patients, only 2% had a tumour other than an ovarian teratoma, and it is unclear whether these tumours represented true associations or unrelated coincident disorders.[3] Based on the experience described in this study, exhaustive attempts to identify ovarian teratoma appear more likely to achieve diagnostic yield than CT of the chest and abdomen.

"Surgical cure" by tumour removal may be possible.[12-14] In a series of 105 consecutive patients, 80% of patients with a tumour had substantial improvement after tumour removal and first-line immunotherapy (corticosteroids, intravenous immunoglobulin (IVIG) or plasma exchange), whereas only 48% without a tumour responded after first-

line therapy ($P < 0.001$).[3] The discovery of an ovarian teratoma in the absence of abnormal imaging findings in one of our patients highlights the potential role for prophylactic oophorectomy in patients who fail to respond to therapy. Others have suggested follow-up ultrasound and/or MRI of the pelvis in females who have initial normal findings,[10] and yearly screening for ovarian teratomas for at least 2 years has been recommended for females who recover from encephalitis.[3]

The immunomodulatory therapies used in our patients were generally consistent with currently recommended therapies. According to current recommendations,[3] treatment should begin with concurrent IVIG 0.4 g/kg per day for 5 days and methylprednisolone 1 g/day for 5 days. While plasma exchange is an alternative first-line therapy it may be difficult to perform because of a patient's abnormal movements and is more invasive. If there is no improvement after 10 days, second-line therapy with rituximab 375 mg/m^2 every week for 4 weeks combined with cyclophosphamide 750 mg/m^2 monthly should follow. These second-line therapies should be ceased when substantial clinical recovery has occurred. If the patient shows no response to second-line therapies then oral or intravenous methotrexate can be considered. Because of the risk of relapse (particularly in patients without teratoma), immunosuppression with mycophenolate or azathioprine is recommended for at least 1 year after initial immunotherapies are discontinued.

Limitations and strengths

Although we identified 24 cases of anti-NMDA receptor encephalitis, we were only able to collect case details for nine patients because clinicians who had cared for the remaining 15 were too busy to contribute. It is possible that the cases we have presented are not representative of the true spectrum of disease seen in Australian and New Zealand ICUs. Clinicians may have been less willing to contribute data for patients who had the most prolonged stays because reviewing the data of such patients would have been very time consuming. On the other hand, patients who had the shortest, least complicated ICU stays may have been less memorable.

Our study has a number of significant strengths as the largest case series of anti-NMDA receptor encephalitis published in the intensive care literature. It includes patients from six hospitals in two countries — paediatric cases managed in paediatric ICUs, a paediatric case managed in a mixed adult and paediatric ICU and a number of cases managed in adult ICUs. Together, they highlight a number of important learning points that may aid clinicians in the management of patients with anti-NMDA receptor encephalitis when they encounter them in clinical intensive care practice.

Competing interests

None declared.

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