Case report

Clinical approach to the diagnosis and successful management of anti-NMDA receptor encephalitis when antibody testing is not possible

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SUMMARY

Anti-N-methyl-D-aspartate (NMDA) receptor encephalitis is a multistage illness that progresses from psychosis, memory deficits, seizures and language disintegration to a state of unresponsiveness with catatonic features often associated with abnormal movements, and autonomic and breathing instability. While the disorder predominantly affects children and young adults, and occurs with or without tumour association, the presence of a tumour (usually an ovarian teratoma) is dependent on the age, sex and ethnicity. Teratomas present more frequently in women older than 18 years, and are more predominant in black women than Caucasians. Here we present the case of a patient with probable anti-NMDA receptor encephalitis. She was subsequently found to have a mature teratoma of the ovary (dermoid cyst). Despite immune-modulated therapy, surgery was eventually performed to remove the cyst. This was met with a good clinical recovery.

grimacing, making snarl-like and grumbling sounds. It was not possible to have a conversation with her.

A provisional diagnosis of neuroleptic malignant syndrome was initially made. Anti-N-methyl-D-aspartate (NMDA) receptor encephalitis was also put forward as a possible diagnosis. Antibody testing was however unavailable in the admitting hospital. Support for this differential diagnosis was however made by trying to identify an underlying ovarian lesion (teratoma).

Her condition however continued to deteriorate, with her developing periods of agitation with opisthotonic posturing, purposeless opening of the mouth and choreic movements of her hands. Her speech was incomprehensible but she continued screaming and shouting. Episodes of agitation would last for hours followed by brief periods of stupor.

While awaiting imaging of the abdomen and pelvis, aciclovir was started along with phenytoin for potential seizure activity. These did not result in any clinical improvement.

BACKGROUND

This case is an example of why it is important to remain suspicious of anti-NMDA encephalitis. This is important even when diagnostic testing is not available as lack of appropriate management is often met with poor outcomes. Equally important, early treatment is paramount to ensuring maximal recovery.

CASE PRESENTATION

This is a case of a 19-year-old woman with no previous comorbidities. Symptoms started a day before presentation. She was found pacing about in the streets outside her workplace. She began making cat-like purring sounds when brought to the hospital. Her behaviour continued to deteriorate with episodes of aggressive shouting. It is of note that there was a maternal history of schizophrenia. She was, however, quite well adjusted in society. There was no history of alcohol abuse, smoking or illicit drug use. She worked as a cashier in a fast food restaurant.

On examination she was dehydrated and tachycardic. Cardiovascular, respiratory and abdominal examinations were otherwise normal. She resisted any passive movement of the limbs but did not have any neck stiffness. She had almost continuous facial

INVESTIGATIONS

Initial blood investigations were unremarkable with an acceptable full blood count (it showed mild microcytic anaemia only) and normal renal and liver function test (see [table 1](#)). An autoimmune screen, serology for common infections and tumour markers were also normal.

A non-contrast CT head was reported as normal.

A lumbar puncture was performed (see [table 2](#)) with normal cerebrospinal fluid biochemistry analysis, normal microscopy and no growth on culture.

Electroencephalography was abnormal with persistent delta indicative of disturbance of cerebral function which was thought to be likely metabolic, autoimmune or medication related.

MRI brain demonstrated three areas of high signal on T2, FLAIR and DWI sequences. These lesions were found in the pontine area. These areas were not typical of demyelination or acute disseminated encephalomyelitis (see [figure 1](#)). See [table 3](#) for a summary of her cerebral imaging findings.

Pelvic ultrasound suggested a left ovarian cyst with a normal right ovary. CT abdomen/pelvis, however, suggested that the lesion identified on the pelvic ultrasound scan was a left dermoid cyst. Again the right ovary was reported as normal (see [figure 2](#)).

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Table 1 Sample haematological and serum biochemical investigations. Normal ranges are given below in brackets. These results remained essentially normal and were unlikely to contribute to the clinical scenario. Importantly, dramatic changes in serum sodium were not seen

Serum sodium	142 mmol/L (137–144)
Serum potassium	4.3 mmol/L (3.5–4.9)
Serum urea	13 mmol/L (2.5–7.5)
Haemoglobin	119 g/L (130–180)
White cell count	$11.8 \times 10^9/L$ (4–11)
Serum creatinine	0.66 mg/dL (0.5–0.9)
Chloride	102 mmol/L (97–110)
Platelets	$572 \times 10^9/L$ (150–400)
Mean corpuscular volume	74.6 fL (80–96)

DIFFERENTIAL DIAGNOSIS

An initial diagnosis of neuroleptic malignant syndrome was made. Viral encephalitis was also entertained but she had no improvement with treatment. However, anti-NMDA receptor encephalitis was always considered as a possible diagnosis.

TREATMENT

She was initially started on diazepam and haloperidol for neuroleptic malignant syndrome. Aciclovir and phenytoin were also started on the day of admission (1 day after onset of symptoms). None of these treatments were, however, useful.

With the discovery of a potential ovarian lesion, a working diagnosis of paraneoplastic anti-NMDA receptor encephalitis was made. Thus from day 5 of admission (6 days after onset of symptoms), she was given methylprednisolone 1 g intravenously for 5 days, followed by intravenous immunoglobulin at a dose 40 mg/kg for a further 5 days. No improvement was however noted. She underwent a left oophorectomy on day 20 of admission. Histological findings confirmed a mature teratoma of the ovary.

Within 3 days postoperatively, opisthotonos resolved but she continued to have purposeless posturing of the mouth and chiroform movements. As she still remained impaired, a single dose of

Table 2 Results from cerebrospinal fluid assessment. Normal ranges are given below in brackets. There was no pleocytosis, and protein and glucose levels were both normal despite cognitive changes. Similar results have been seen in N-methyl-D-aspartate encephalitis

Protein	0.14 g/L (0.15–0.45)
White cell count	0 cells per μL (<5)
Glucose	0.59 g/L (0.5–0.7)
Red cell count	0 cells per mL (<5)

Figure 1 MRI scan of the head demonstrating hyper-intense signal changes in the pons. (A) T2 weighted transverse image, (B) fluid-attenuated inversion recovery (FLAIR) transverse image and (C) diffusion-weighted imaging (DWI) transverse image. These changes are considered non-specific.

intravenous 500 mg rituximab was given 7 days after the surgery (28 days after onset of symptoms).

OUTCOME AND FOLLOW-UP

Three days following the rituximab infusion, she was able to sit on a chair, hold a cup and drink small sips of juice. Her speech and interaction improved and she was able to walk to the bathroom with assistance and feed herself. Cognitive functions improved and she was eventually discharged from the hospital. When seen in the neurology outpatient's department, within 6 months of her initial presentation, her cognitive functions had returned to normal. She had returned to work as a restaurant cashier and reported that she had no difficulties with the management of money and doing calculations while at work. Socially also she has returned to normal with no further psychiatric concerns or unusual behaviour. This information was corroborated by her family who accompanied her to the clinic.

Her clinical course and management have been summarised as a timeline in [figure 3](#).

DISCUSSION

This case illustrates the importance of suspecting a diagnosis of anti-NMDA receptor encephalitis even in a setting where antibody testing is not possible. This patient's clinical presentation did suggest anti-NMDA receptor encephalitis as a differential diagnosis. In this scenario, an underlying ovarian lesion should be sought as a potential target for treatment.^{1–7} The necessary imaging investigations should be performed in a timely manner as recovery can be prolonged if the disease proceeds unchecked.³ In our patient's case, immunotherapy in the form of methylprednisolone was started 6 days after the onset of symptoms. Treatment was escalated based on a lack of response until she eventually had surgery 21 days after the onset of symptoms. This

Table 3 Summary of cerebral imaging findings. As noted, despite cognitive impairment CT scanning showed no changes. MRI head did show hyper intense signal changes in the pons. There were, however, no risk factors for pontine myelinosis

Type	Result
CT Non- contrast	Unremarkable
CT Contrast	Unremarkable
MRI	There are three lesions that demonstrate high signal on T2 and FLAIR within the pons. These areas demonstrate restricted diffusion with some reversal. No other lesions are noted.

Figure 2 CT of the abdomen and pelvis. This demonstrated a lesion (highlighted by the green crosshairs) behind the uterus thought to be a dermoid cyst.

delay in surgery may have contributed to persistence of symptoms for several weeks postoperatively.⁴

MRI performed on this patient illustrated changes in the brainstem in the form of high signal lesions on T2, FLAIR and DWI sequences in the pons. A differential of pontine myelinosis was made but it was noteworthy that she never experienced the electrolyte changes that would provoke pontine myelinosis. These changes may have been immune-driven demyelination although we have no evidence to prove this.

Anti-NMDA receptor encephalitis more commonly results in changes localised to the medial temporal lobes.⁵ It is here that NMDA receptor concentrations are the highest in the brain. The

absence of these typical MRI changes on our patient's MRI did not, however, discourage us from the diagnosis as many times MRI changes may be non-specific or even absent.^{5,6}

It is noteworthy that a definite diagnosis of anti-NMDA receptor encephalitis was not made in this case. The presence of rapidly evolving changes in neurology (particularly the difficulty with speech and refractory seizures), the presence of EEG abnormalities and the absence of any other probable cause made the diagnosis of probable anti-NMDA receptor encephalitis possible.²

With the lack of response to other therapies, it was thought appropriate to pursue surgery to remove the abnormal ovarian

Figure 3 A timeline of the patient's clinical course and management. Important steps of management have been highlighted. IVMP – intravenous methylprednisolone.

lesion with a working diagnosis of probable anti-NMDA receptor encephalitis.

This case also illustrates the importance of surgery for the treatment of this condition. Rapidly progressive cases have been suggested as secondary to high antibody titres, for example in cases of bilateral ovarian teratomas. When removed, clinical improvement is the norm as titre levels presumably drop.³ While continued immune modulatory treatment can be helpful in the autoimmune forms of the condition, it is significant that the paraneoplastic anti-NMDA receptor encephalitis tends to be a monophasic condition that resolves with the removal of the offending tumour.

Learning points

- ▶ The case illustrates the importance of remaining vigilant to the possibility of autoimmune encephalitis.
- ▶ A delay in diagnosis leads to poorer outcomes and rapid action is required for favourable results.^{3,4}
- ▶ Diagnosis should still be considered even if the treating hospital does not have the facility for diagnostic testing. This is especially true in the case for rare diseases presenting to hospitals in the developing world.

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