THE NEW ZEALAND MEDICAL JOURNAL
Journal of the New Zealand Medical Association

Anti-NMDA-receptor autoimmune encephalitis without neoplasm: a rare condition?

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Anti-N-methyl-D-aspartic (NMDA)-receptor encephalitis is an acute and potentially lethal encephalitis. It was first described as a distinct disease by Dalmau et al in 2006,[1] with subsequent case reports from around the world.[2–7] Patients typically present with prominent psychiatric symptoms followed by progressive neurological dysfunctions and more than half of reported cases have occurred as a paraneoplastic phenomenon in association with tumours, especially ovarian teratoma.[2]

Here we present two patients seen in a secondary care hospital that presented in quick succession and were not associated with a tumour. To the best of our knowledge these are the first non-paraneoplastic anti-NMDA-receptor encephalitides reported in New Zealand.

Case report 1

A previously healthy 17-year-old girl presented with an 8-day history of agitation, anxiety, poor oral intake, sleep deprivation, and decreased communication. Symptoms were attributed to a traumatic break up with her boyfriend. Apart from an elevated white blood count initial diagnostics were normal and she was admitted to psychiatry.

Over week 1 of hospitalisation symptoms continued to fluctuate and an electroencephalogram (EEG) on hospital day 5 suggested organic delirium. Brain magnetic resonance imaging (MRI) was normal, but cerebrospinal fluid (CSF) analysis supported CNS inflammation (see Table 1). IV aciclovir, antibiotics and a three-day course of methylprednisolone (1gm/day) were started empirically without major benefit. Further extensive laboratory testing was unrevealing (see table), and a non-organic cause remained a consideration.

During week 2 she developed increasingly autonomic symptoms of intermittent tachycardia, hypertension, pupillary dilatation, and low grade fevers progressing to generalised tonic-clonic seizures, decreased level of consciousness and profound generalised dystonia requiring intubation on day 10.

At this point a diagnosis of autoimmune/paraneoplastic encephalitis was suspected, but a systemic tumour screen was negative. Despite the lack of identified tumour the patient was empirically restarted on IV steroids (dexamethasone 10mg/day) with the addition of IV immunoglobulins (0.4g/kg/day for 5 days) followed by plasmapheresis (five exchanges). Symptomatically her dysautonomia responded to clonidine, but her profound muscle rigidity was refractory to trials with benztropine, baclofen and benzodiazepines.

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Table 1. Test results

	TEST	CASE 1	CASE 2
Blood and urine	Full blood count	WBC 11.3 x 10^9/L (70% neutrophils)*	Normal
	Renal function test, Ammonia	Normal	Normal
	Liver function test	Transient mild derangement	Transient mild
	CRP	23 mg/L**	17 mg/L**
	Copper/ceruloplasm	Normal	Normal
	Beta-HCG, TSH, Catecholamines	Normal	Normal
	ANA	Negative	>1:100, diffuse***
	ENA	Positive SSA and RO52***	Negative
	ds-DNA, ANCA, Thyroglobulin, Cardiolipin, Microsome antibodies	Negative	Negative
	Pophyrins	Negative	Negative
	Anti-NMDA receptor antibodies	Positive	Positive
	Infective screen (bartonella, toxoplasma, herpes viruses, measles, mumps, tuberculosis, HIV)	Negative	Negative
	Tumour markers (CEA, Ca-125, 5HIAA)	Normal	Normal
CSF	White blood cells	27x 10^6/L (100% monocytes)	1 x 10^6/L
	Red blood cells	19 x 10^6/L	400 x 10^6/L
	Protein, Glucose, Cytology	Normal	Normal
	Electrophoresis	Normal	Oligoclonal bands
	Anti-NMDA receptor antibodies	Positive	Positive
	Cryptococcal antigen	Normal	Normal
	Viral PCR (herpes, CMV, EBV, entero-)	Normal	Normal
Imaging and Physiology	Brain	Normal (CT, MRI, MRA, MRV)	Normal (CT, MRI)
	EEG	Diffuse delta rhythm	Diffuse delta rhythm
	Pelvis ultrasound	Normal	Normal
	Full body	Normal (CT)	Normal (PET/CT)

* Fluctuated between 9.4 and 33.2 x 10^9/L during the course of admission; ** Fluctuated and normalised during course of admission; *** Not clinically significant as isolated finding and low titre

During week 3 serum and CSF were sent for NMDA-receptor antibody titres and she demonstrated first signs of recovery early during week 4 with continued gradual improvement over the next weeks. She was discharged home on a gradual oral steroid taper after 7 weeks of hospitalisation.

Ten days after discharge positive results of NMDA receptor antibody titres became available confirming the diagnosis of anti-NMDA receptor encephalitis. Three weeks after discharge she had nearly returned to baseline and was off all medications.

At six-month follow-up she had resumed her normal life without any residual symptoms except for persisting amnesia of her illness. Follow-up pelvic ultrasound remained free from evidence of neoplasm.

Case report 2

A 23-year-old New Zealand woman presented to a British hospital with acute psychiatric symptoms. She had no history of medical, psychiatric or personality disorders. Five weeks before admission she became unduly anxious about a potential unwanted pregnancy (repeated negative tests), apathetic and ate poorly losing about 10Kg.

Admitted to a psychiatry unit she displayed mutism, dystonic postures, psychomotor retardation and agitation treated with haloperidol. Over week 1 of admission she developed fever, tachycardia, tremor and drowsiness, for which she was transferred to a medical unit. During week 2 she had two convulsive seizures requiring temporary intensive care, and received aciclovir and phenytoin.

At this stage brain imaging and serum laboratory investigations were unremarkable, including a non-specific low ANA titre (see table). Extensive CSF tests (see table) were also normal apart from oligoclonal bands (suggesting CSF inflammation, but not deemed specific for multiple sclerosis as not consistent with clinical picture and MRI findings). An EEG showed generalised rhythmic delta activity without epileptiform features.

During week 3 episodic dysautonomia (midriasis, fever, hyperhydrosis) was noted together with posturing, catatonic episodes, repetitive buccal movements and hyperreflexia. A working diagnosis of autoimmune encephalopathy was made and serum sample for anti-NMDA receptor antibodies sent. Pelvic MRI and full body PET/CT were unremarkable. She received plasma exchange over 5 days and IV methylprednisolone 0.5g daily for 5 more days followed by oral prednisone. Her psychiatric symptoms were managed with olanzepine and benzodiazepines.

From week 5 alertness, behaviour and appetite gradually improved; impaired cognition, mild tremor, stuttering, and hyperreflexia persisted. On day 40 NMDA receptor antibodies resulted positive. She then was transferred to Palmerston North Hospital and received intravenous immunoglobulins 0.4g/Kg/day for 5 days.

Upon arrival she was noted to exhibit disinhibited behaviour, anxiety, insomnia and amnesia but these gradually resolved over the following weeks. She was discharged on day 94 with residual mild impairment of strategic function and memory. At a 4-month outpatient follow-up all medications had been stopped and the only residual deficits were mild ongoing anterograde amnesia and subtotal amnesia to her medical illness. A 6-month pelvic ultrasound follow-up did not show any evidence of neoplasm.

Discussion

Anti-NMDA receptor encephalitis has only recently been described as a discrete entity that appears to be mediated by antibodies targeted mainly at the extracellular N-terminal domain of the NR1 subunit of NMDA receptors. These antibodies reversibly decrease the number of cell-surface NMDA receptors.[1,2]

The typically, but not exclusively, young female patients initially present with a characteristic neuropsychiatric syndrome with change of personality and behaviour, paranoia, and memory disturbances. This is accompanied or rapidly followed by multiple neurological deficits, predominantly dystonia, dyskinesia, seizures, autonomic instability, and decreased level of consciousness.[1,2]

The diagnosis depends on recognising the characteristic clinical picture usually associated with CSF pleocytosis or other raised CSF inflammatory markers and abnormal EEG findings. MRI studies are often unrevealing although some patients will have increased FLAIR or T2 signal in the medial temporal lobes.[2]

The majority of patients have evidence of a systemic tumour, most commonly ovarian teratoma. The definitive diagnosis is based on NMDA-receptor antibodies identified in serum or CSF. Treatment includes corticosteroids, plasma exchange, intravenous immunoglobulins, rituximab, cyclophosphamide, and azathioprine as well as tumour resection if detected.[8]

Whilst the incidence of anti-NMDA-receptor encephalitis has not been established, publications on this condition are limited to case reports and case series and amongst these cases the majority were associated with systemic neoplasm suggesting that the non-paraneoplastic variety is a rather rare condition. However, the presentation of these two cases within only weeks of one another raises the question whether this could be a more common disorder than previously thought and may currently be underdiagnosed.

The two cases presented here were diagnosed and treated more rapidly than many other reported cases in the literature and enjoyed a very favourable outcome. The lack of identified tumour, even months after initial presentations in our patients, highlights the importance to initiate aggressive immune modulatory therapy even without evidence of a tumour and strongly argues against empiric ovarian resections which has been suggested by some. Early recognition and treatment appears to be critical to achieve a favourable outcome and cannot await positive NMDA receptor antibody results, which can take up to several weeks to be processed as is demonstrated in these two cases.

In summary, particularly young women initially presenting with prominent psychiatric symptoms followed by seizures, movement disorder, and dysautonomia should prompt this diagnostic consideration and if an alternative cause is not readily found treated aggressively even without evidence of systemic tumour or the reassurance of confirmatory antibody tests.

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Acknowledgements: We acknowledge and thank Drs Richard Frith, Ted Burns, Nina Solenski, David Abernathy, Neil Anderson, Josep Dalmau, and the staff at Palmerston North Hospital who assisted with patient management.

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