Epidemiology and diagnostic challenges of anti-NMDAR encephalitis: a study from the Waikato region

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ABSTRACT

AIMS: Anti-NMDAR encephalitis is an increasingly recognised autoimmune disorder with evolving diagnostic criteria. This study aims to analyse the prevalence and diagnostic patterns of anti-NMDAR encephalitis in a New Zealand hospital setting.

METHODS: Data from Waikato Hospital's lab database, encompassing anti-NMDAR antibody requests between August 2013 and July 2023, were examined. Cases were categorised based on age, gender and diagnostic outcomes.

RESULTS: In all requests, 288/318 (91%) were processed and 10/288 (3.5%) anti-NMDAR antibodies were positive. Positive cases were equally frequent by sex, with an average age of 29.4 years. Only 6/10 were diagnosed with anti-NMDAR encephalitis, while others received alternative diagnoses. Māori ethnicity was overrepresented. This study indicates a low prevalence of anti-NMDAR encephalitis in the Waikato region, with adult predominance. Ethnic disparities were observed. The need for refining testing criteria to optimise cost-effectiveness is discussed.

CONCLUSION: Anti-NMDAR encephalitis is relatively rare in Waikato Hospital, New Zealand, with diagnostic challenges related to testing criteria and ethnic diversity. Further research and consideration of testing protocols are warranted.

Anti-NMDA receptor encephalitis is increasingly recognised, with over 100 cases reported in the literature, yet its true prevalence remains unknown.[1] The first comprehensive description of anti-NMDAR encephalitis was provided in 2007.[2] However, the criteria for diagnosing this condition were not established until 2016.[3] Over the last two decades, the aetiology of encephalitis has shifted from infections as the primary known cause to the identification of multiple autoantibodies in encephalitis patients. Liem et al. discovered that autoimmune encephalitis in New Zealand was led by anti-LGI1 antibodies, followed by anti-NMDAR antibodies, in patients aged 15 and older presenting with encephalitis.[4]

In a recent systematic review, it was described that psychiatric symptoms were reported in 1,050/1,100 (95%) anti-NMDAR encephalitis patients, but only 52/1,100 (5%) had isolated psychiatric features.[5] Further research showed that anti-NMDAR antibodies were not found in patients with a First Episode of Psychosis unless they had anti-NMDAR encephalitis. It was concluded that warning signs and criteria for autoimmune psychosis have limited utility when neurologic symptoms are absent or paraclinical tests are normal.[6]

Clinically, anti-NMDAR encephalitis presents with a prodromal phase, including fever and viral-like symptoms such as headaches. After a few days, this is followed by a multistage progression of psychiatric manifestations, abnormal movements, seizures, sleep difficulties, language dysfunction and autonomic instability. Mutism, catatonic postures and decreased levels of consciousness might follow.

Both brain MRI and lumbar puncture are usually unremarkable, especially at the onset of symptoms. EEG readings are often slow and can show a characteristic delta brush pattern. These test results can be non-specific, making antibody testing crucial for confirming the diagnosis.

While anti-NMDAR antibodies are consistently found in the CSF of patients, they are absent in approximately 20% of serum samples. Serum NMDAR-antibodies test positive in 3% of both healthy and disease controls, leading to so-called "clinically irrelevant" results. Consequently, the absence of CSF positivity in this context is considered indicative of a lack of direct autoantibody pathogenicity.[3]

A study in Japan found that among children who met the probable criteria for anti-NMDAR encephalitis, 32% (13/41) tested positive for anti-NMDAR antibodies when requested. In contrast, only 3% (3/96) of those who did not meet the criteria tested positive for these antibodies. Most

false-positive diagnoses were associated with neurologic autoimmunity.[7] In a retrospective study of 221 adult patients with clinically suspected autoimmune neurological disorders, anti-NMDAR antibodies were detected in 85% (34/40) of patients meeting the probable criteria, while they were detected in only 3% (5/180) of patients not fulfilling the criteria.[8] A prospective study with admitted patients who fulfilled criteria for possible autoimmune encephalitis and/or red flags along a time window of 7 years found a positivity rate of 65% (100/160).[9] Although psychiatric symptoms were frequent, after multivariate analysis, the clinical hallmarks of anti-NMDAR encephalitis seemed to be catatonia–delirium comorbidity, tonic-clonic seizures and orolingual dyskinesia.[9]

Method

An audit (CASU # 4471P) was conducted with retrospective data from Waikato Hospital's lab database, identifying patients with suspected encephalitis and anti-NMDAR antibody requests between August 2013 and July 2023. An Excel spreadsheet was used for data collation and analysis. Based on the HDEC screening form, the audit was out of scope and did not require HDEC approval.

Results

Over 10 years, 318 lab requests were made, of which 286 were for patients 18 years old or older. However, 30/318 (9%) of the requests were not tested or analysed (Table 1). The primary cause for this occurrence for 20/30 (60%) was the unavailability of a mandatory neurologist review. The remaining instances were not processed due to laboratory registration errors (4/30), or because an inadequate or unsuitable sample was received for the requested test (6/30).

The 10 anti-NMDAR antibodies positive cases were equally frequent by sex, with an average age of 29.4 years (range from 0 to 81). Only 6 out of 10 positive cases were diagnosed as anti-NMDAR encephalitis. The remaining cases received alternative diagnoses, such as Neuromyelitis spectrum disorder, HSV-1 encephalitis, progressive ascending lower motor neuron process of uncertain aetiology and chronic schizophrenia. While most anti-NMDAR encephalitis cases' ethnicity was identified as European, 2/6 were Māori.

The main clinical features present in the six anti-NMDAR encephalitis cases were: movement disorders, dyskinesias or rigidity/abnormal postures (5/6), abnormal behaviour or cognitive dysfunction (4/6), decreased level of consciousness (4/6), autonomic dysfunction or central hypoventilation (2/6), speech dysfunction (1/6), seizures (1/6). Additionally, 3/6 (50%) cases presented a concomitant teratoma.

Discussion

At Waikato Hospital, requests for anti-NMDAR antibody testing require review by a neurologist, but meeting the probable criteria for anti-NMDAR encephalitis is not mandatory. This is consistent with findings from other countries in the last decade for patients clinically suspected of having autoimmune encephalitis, despite not fulfilling the probable criteria.[1] Notably, in our study merely one out of 48 tested patients received a diagnosis of anti-NMDAR encephalitis. The present audit suggests that anti-NMDAR encephalitis would be likely rare in the Waikato District Health Board (DHB), occurring at a rate of 0.6 cases per year at Waikato Hospital and being more prevalent among adults. The crude incidence estimate for NMDAR encephalitis in the DHB would be 0.14 cases per 100.000 person/year. Māori ethnicity was overrepresented in our sample, but due to the small number of cases, this finding might not be conclusive.

Our findings are limited to the tests requested for inpatients at Waikato Hospital, so cases in the community or other healthcare facilities would be missing, potentially affecting the validity of our conclusions.

Given the low incidence of clinically suspected encephalitis confirmed as anti-NMDAR encephalitis, the cost-effectiveness of stricter testing approval criteria is worth considering when autoimmune psychosis is suspected.

Table 1: Anti-NMDAR antibody requests (August 2013 to July 2023).

	Total	Adults	Under 18
Requested	318/318 (100%)	286/318 (90%)	32/318 (10%)
Tested	288/318 (91%)	257/286 (90%)	31/32 (97%)
Detected	10/318 (3%)	9/286 (3%)	1/32 (3%)
Diagnosed	6/318 (2%)	6/286 (2%)	0/32 (0%)

Table 2: Probable anti-NMDAR encephalitis criteria.[3]

1. Rapid onset (less than 3 months) of at least four of the six following major groups of symptoms: a. Abnormal behaviour or cognitive dysfunction b. Speech dysfunction (pressured speech, verbal reduction, mutism) c. Seizures d. Movement disorders, dyskinesias, or rigidity/abnormal postures e. Decreased level of consciousness f. Autonomic dysfunction or central hypoventilation.
2. At least one of the following laboratory study results: a. Abnormal EEG (focal or diffuse slow or disorganised activity; epileptic activity, or extreme delta brush) b. CSF with pleocytosis or oligoclonal bands.
3. Reasonable exclusion of other disorders* a. The diagnosis of probable anti-NMDAR encephalitis can also be made in the presence of three of the above group of symptoms and identification of a teratoma. b. The diagnosis of definite anti-NMDAR encephalitis can be made in the presence of three of the above group of symptoms and IgG anti-GluN1 NMDA receptor antibodies after reasonable exclusion of other disorders.

COMPETING INTERESTS
The authors declare that there is no conflict of interest.

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URL
https://nzmj.org.nz/journal/vol-137-no-1598/epidemiology-and-diagnostic-challenges-of-anti-nmdar-encephalitis-a-study-from-the-waikato-region

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