Anti-*N*-methyl-D-aspartate receptor encephalitis in Māori and Pacific Island children in New Zealand

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ABBREVIATIONS

HLA	Human leukocyte antigen
IVIg	Intravenous immunoglobulin
mRS	Modified Rankin Scale
anti-NMDA	Anti-*N*-methyl-D-aspartate

AIM To investigate the incidence and severity of anti-*N*-methyl-D-aspartate (anti-NMDA) receptor encephalitis in children from New Zealand.
METHOD A retrospective case series was undertaken of all children (≤18y) diagnosed with anti-NMDA receptor encephalitis from January 2008 to October 2015.
RESULTS Sixteen patients were identified with anti-NMDA receptor antibodies in the cerebrospinal fluid, three of whom had an associated teratoma. Fifteen children had Māori and/or Pacific Island ancestry. The incidence of anti-NMDA receptor encephalitis in Māori children was 3.4 per million children per year (95% confidence interval [CI] 1.4–7.0) and the incidence in Pacific children was 10.0 per million children per year (95% CI 4.3–19.8) compared with 0.2 per million children per year (95% CI 0.0–1.0) in children without Māori or Pacific Island ancestry. Sixty-seven per cent of children had a good outcome (modified Rankin Score ≤2) at 2 years' follow-up. This compares unfavourably with other cohorts despite a shorter median time to first-line immunotherapy (13d; range 4–89) and a higher proportion of children being treated with second-line therapy (50%).
INTERPRETATION Māori and Pacific Island children have a higher incidence of anti-NMDA receptor encephalitis and possibly a more severe phenotype. These data suggest a genetic predisposition to anti-NMDA receptor encephalitis in these populations.

Since anti-*N*-methyl-D-asparatate (anti-NMDA) receptor encephalitis was described in 2007, the over-representation of this disease in children of non-white ethnicities has been noted in various studies.[1–3] In adults, Asian and African-American females are more likely to have an associated teratoma, but this does not explain the ethnic disparity in children as most do not have an associated tumour.[4]

Clusters of anti-NMDA receptor encephalitis among specific ethnic groups are most likely explained by a genetic predisposition; however, potential confounders, such as socioeconomic status, must also be taken into account. The role of genetic factors in the pathogenicity of anti-NMDA receptor encephalitis has not been well explored, but several authors have recommended human leukocyte antigen (HLA) profiling.[3,5,6] Apart from the disparate representation of different ethnicities, the literature to date supporting a genetic predisposition consist of a report of anti-NMDA receptor encephalitis in 27-year-old monozygotic Filipina American twins, neither of whom had an associated ovarian teratoma.[7] There is also an isolated case of a 3-year-old child with a microdeletion involving *HLA-DPB1* and *HLA-DPB2*, which was hypothesized to contribute to the autoimmune response.[5]

Much of the pathogenesis of anti-NMDA receptor encephalitis remains to be elucidated, particularly in children, when cases are rarely associated with an ovarian teratoma.[4] The breakdown in immune tolerance giving rise to NMDA receptor antibodies most likely takes place in the systemic circulation and in 60% of cases relates to an ovarian teratoma with expression of NMDA receptors in the neural tissue.[8] A prodromal viral-like illness within 2 weeks of the onset of the neuropsychiatric symptoms may represent the activation of the immune system or be a viral infection that triggers the aberrant autoimmune response.[8] Few patients have positive serology results and the viruses detected vary.[9]

This study of patients from New Zealand with anti-NMDA receptor encephalitis was initiated to investigate the incidence of anti-NMDA receptor encephalitis in Māori and Pacific Island children, and to find out whether or not the disease is more severe in children of these

ethnicities. The predominance of Māori and Pacific Islanders in our cohort has been published previously.[10]

METHOD

This retrospective case series included all patients aged 0 to 18 years diagnosed with anti-NMDA receptor encephalitis in New Zealand from January 2008 to October 2015. Patients from New Zealand were identified by contacting adult and paediatric neurologists nationwide and searching the databases of all referral tertiary hospital laboratories for cerebrospinal fluid (CSF) samples positive for NMDA receptor antibodies. Full case ascertainment was expected on the basis that patients with anti-NMDA receptor encephalitis require specialist neurology care, and antibody testing is only arranged through tertiary laboratories.

Clinical records for every patient were reviewed for demographic data, clinical features, investigation results, treatments given, and outcome details. All patients able to be contacted were invited to complete a questionnaire requesting detailed ancestry data (to the second generation), family history of autoimmune disease, and socioeconomic information from the time of illness. Questionnaires were completed by telephone, e-mail, or post. These participants gave informed consent to be included in the study.

Patients with any New Zealand Māori ancestry were classified as New Zealand Māori, including patients with equal proportions of New Zealand Māori and Pacific Island ancestry. Tongan, Samoan, and Cook Island Māori were grouped together into the Pacific Islander category. No other ethnicities were represented other than New Zealand European/white.

The Modified Rankin Scale (mRS) was used to grade disease severity at the peak of the illness, at discharge, and at follow-up. The mRS is a measure of disability with scores ranging from 0 (no symptoms) to 6 (dead). First-line immunotherapy consisted of corticosteroids, intravenous immunoglobulin, and plasmapheresis (Appendix S1, online supporting information). Second-line immunotherapy consisted of rituximab, cyclophosphamide, and any other immunosuppressants. Failure of first-line immunotherapy was defined as no sustained improvement within 4 weeks of initiation of immunotherapy or tumor removal and if the mRS score remained greater than or equal to 4. Relapse was defined as the new onset or worsening of symptoms occurring after at least 2 months of improvement or stabilization.[4]

Ethical approval was granted from the New Zealand Health and Disability Ethics Committee (14/STH/170) and local authorizations were granted by the relevant District Health Boards and Māori Research Committees.

Statistical analysis

Descriptive statistics were obtained using JMP v.10 software (SAS Inc., Cary, NC, USA). Incidence confidence intervals were calculated by the Poisson method using the StatsDirect V3.0 software (StatsDirect Ltd., Altrincham, UK). Population counts for incidence calculations were derived from the New Zealand census 2013 data (www.stats.govt.nz), specifically the 'Ethnic group (detailed single and combination) by age group and sex, for the census usually resident population count, 2013 (RC, TA)' data set. Socioeconomic status was based on the patient's residential address and determined using the census 2013 based New Zealand Deprivation Index.[11]

The population ethnic distribution of deprivation was derived by mapping 'census area units' from the New Zealand Deprivation Index to the census 2013 'Ethnic group (grouped total responses) by age group and sex, for the census usually resident population count, 2001, 2006, and 2013 (RC, TA, AU)' data set.

What this paper adds

- Māori and Pacific Island children are at increased risk of anti-*N*-methyl-D-aspartate (NMDA) receptor encephalitis (3.4 and 10.0 per million children per year respectively).
- One third of Māori and Pacific Island children with anti-NMDA receptor encephalitis have a poor outcome.

RESULTS

Sixteen patients were identified with a diagnosis of anti-NMDA receptor encephalitis between January 2008 and October 2015. All patients had at least one CSF sample positive for anti-NMDA receptor antibodies. There were no cases identified with positive serum antibodies only. Fourteen patients consented to participate in the study and completed study questionnaires. Two patients had emigrated from New Zealand and were lost to follow-up. For these two patients, hospital ethnicity data corroborated with the clinical records were used. Ten children in this case series were included in Titulaer et al.'s cohort, published in 2013.[4]

Demographic data

The age of onset ranged from 1 year 4 months to 18 years 10 months in a bimodal distribution with a younger group aged 1 to 7 years and the older postpubertal group aged 14 to 18 years (Fig. 1). The male to female ratio in children under 12 years was 0.8:1, but eight of the nine children over the age of 12 years were female. Only one patient was of full New Zealand European descent; all other patients had at least one-eighth New Zealand Māori or Pacific Island ancestry. Of the remaining four Māori patients, three did not have any Pacific ancestry. Fifty per cent of the children lived in the most deprived socioeconomic areas (New Zealand Deprivation Index 8–10), 44% lived in medium-deprived areas (New Zealand Deprivation Index 4–7), and one lived in a least deprived area (New Zealand Deprivation Index 1–3).

Based on a population of 262 000 Māori and 102 000 Pacific children aged 0 to 18 years in New Zealand (24% and 9% respectively, of all New Zealand children), the incidence in Māori was 3.4 per million children per year (95% confidence interval [CI] 1.4–7.0) and the incidence in Pacific was 10.0 per million children per year (95% CI

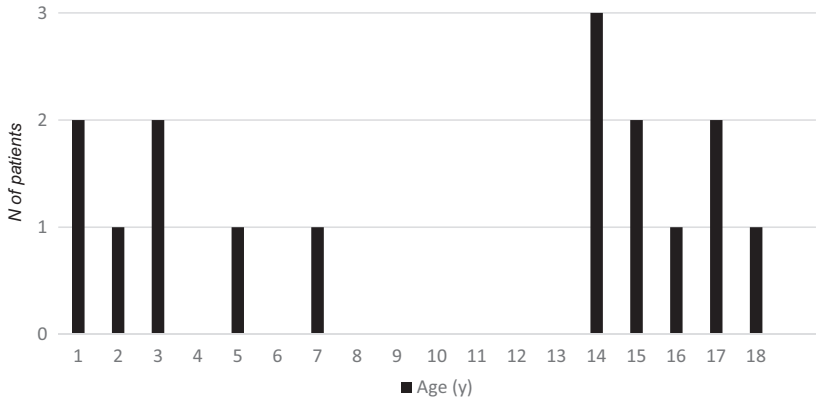

Figure 1: Bimodal distribution of age of onset in children with anti-*N*-methyl-D-aspartate receptor encephalitis.

4.3–19.8). The incidence in patients without Māori or Pacific ancestry was 0.2 per million children per year (95% CI 0.0–1.0), based on a population of 739 000 children in New Zealand with neither ancestry.

Thirty per cent of New Zealand's most deprived population (New Zealand Deprivation Index 8–10) are of Māori ethnicity and 19% of this population are of Pacific Island origin. The proportion of cases from the most deprived socioeconomic areas that are Māori (25%, 95% CI 3–65) is similar to that of the general population, whereas the proportion of cases from the most deprived socioeconomic areas that are Pacific (75%, 95% confidence interval 35–97) is considerably greater than the general population. Non-Māori and non-Pacific cases are under-represented in the most deprived areas (0% vs 51%).

Clinical and diagnostic features

Three children had premorbid developmental delay (expressive language or socialization domains), one adolescent had a 6-year history of bipolar affective disorder, and another had a 1-year history of panic attacks. The only patient with a history of autoimmune disease was of New Zealand European origin and had guttate psoriasis 3 years prior to diagnosis. The only family history of autoimmunity was rheumatic heart disease in the father of one participant. One participant had a family history of mental illness (depression not further specified). Immunizations were up to date in the 11 participants for whom immunization status was reported.

Five children had an infectious prodrome (Table I). These were described as fever, upper respiratory tract infection, or headache, and there was one case of Staphylococcus aureus and Streptococcus pyogenes impetigo. Except for the patient with impetigo, an infectious pathogen was not detected in any of these patients. In the children without prodromal symptoms, one had an elevated mycoplasma immunoglobulin M titre, one patient had chronic hepatitis C infection, one patient had a high rhinovirus viral load on nasopharyngeal aspirate, and one patient had mildly raised titres for Bartonella species and Chlamydophila pneumoniae, and legionella of uncertain significance.

Seizure was the most common presenting symptom, particularly in the younger age group (Table I). Five of the seven children under 12 years of age presented with a seizure (all afebrile, four focal, and one generalized at onset), one presented with asymmetric generalized choreoathetoid movements, and the other with right hemiparesis associated with myoclonic jerks and speech regression. The most common presenting symptom in the older age group was behavioural disturbance or personality change (decline in executive functioning, agitation, confusion, elevated or depressed mood, sleep disturbance, and auditory/visual hallucinations) frequently associated with speech disturbance. One adolescent presented with right hemiparaesthesia followed by speech disturbance and a generalized tonic–clonic seizure.

All participants had behavioural disturbance and movement disorder. The majority of patients also had clinical seizures, speech disturbance, autonomic dysfunction, sleep disturbance, and altered level of consciousness (Table I). Sixty-three per cent of patients had a mRS greater than or equal to 5 and half of patients required admission to intensive care. Medical complications included sepsis (n=9), tracheostomy insertion (n=7), anaemia requiring transfusion (n=4), contractures (n=2), dental extraction for severe mucosa trauma (n=2), severe extravasation injury (n=1), pathological femur fracture (n=1), neutropenia secondary to cyclophosphamide (n=1), anaphylaxis secondary to cryoprecipitate (n=1), and self-limited ventricular tachycardia (n=1).

Three postpubertal females had an associated ovarian teratoma. All children had tumour surveillance with either ultrasound or magnetic resonance imaging (MRI). Thirteen children (81%) had a lymphocytic pleocytosis ($>5\times10^6$/L) and no children had elevated CSF protein. Two of the five children tested (40%) had oligoclonal bands present in the CSF. Systemically, three children

Table I: Clinical features of disease (infectious prodrome, presenting symptoms, symptoms during illness, length of hospital admission, maximum modified Rankin Scale [mRS] score, and length of intensive care unit [ICU] admission) according to age at onset of disease

Age (y)	<12 (*n*=7)	12–18 (*n*=9)	All patients (*n*=16)
Infectious prodrome	1 (14)	4 (44)	5 (31)
Presenting symptom			
Seizure	5 (71)	2 (22)	7 (44)
Behavioural disturbance	0 (0)	6 (67)	6 (38)
Movement disorder	1 (14)	0 (0)	1 (6)
Other	1 (14)	1 (11)	2 (13)
Symptoms during illness			
Seizure	6 (86)	8 (89)	14 (88)
Behavioural disturbance	7 (100)	9 (100)	16 (100)
Movement disorder	7 (100)	9 (100)	16 (100)
Speech disturbance	6 (86)	8 (89)	14 (88)
Autonomic dysfunction	4 (57)	7 (78)	11 (69)
Sleep disturbance	4 (57)	6 (67)	10 (63)
Altered level of consciousness	3 (43)	6 (67)	9 (56)
Central hypoventilation	2 (29)	5 (56)	7 (44)
Cerebellar ataxia	1 (14)	1 (11)	2 (13)
Hemiparesis	1 (14)	0 (0)	1 (6)
Median (IQR) length of hospitalization (wks)	4.9 (3.4–16.1)	13.3 (5.6–18.3)	8.3 (4.7–22.0)
Mean (range) length of hospitalization (wks)	13.3 (0.6–45)	18.6 (1.4–57.4)	16.3 (0.6–57.4)
Length of hospital admission <4wks	2 (29)	1 (11)	3 (19)
Maximum mRS ≥5	5 (71)	5 (56)	10 (63)
Intensive care admission	3 (43)	5 (56)	8 (50)
Mean (range) length of ICU admission (d)	24.3 (2–48)	154.2 (20–380)	105.5 (2–380)
Length of ICU admission >1mo	1 (14)	4 (44)	5 (31)

Data are *n* (%) unless otherwise specified. IQR, interquartile range.

(19%) had leukocytosis (>11×10^9/L) and one out of 10 children tested had an elevated erythrocyte sedimentation rate. Fifteen children had a least one electroencephalogram (EEG), and 87% of these were abnormal. Three EEGs captured electrographic seizures; otherwise abnormal EEGs showed diffuse slowing with or without interictal epileptiform discharges. An extreme delta brush pattern was not reported in any case. The one patient who did not have an EEG during the acute phase of the illness was from a small secondary centre where EEGs are not readily available, but a follow-up EEG was normal. Five children (31%) had abnormalities on MRI, which included superior sulcal T2 fluid-attenuated inversion recovery hyperintensity, T2 signal hyperintensity in the hippocampi and amygdala, and small, discrete hyperintense foci in the frontal lobe white matter.

Table II: Treatment and outcome by age group including length of follow-up and number of cases of relapse

Age (y)	<12 (*n*=7)	12–18 (*n*=9)	All patients (*n*=16)
Median (range) time to first-line therapy (d)	19 (4–89)	9 (8–31)	13 (4–89)
Patients given first-line immunotherapy (*n*)	7	9	16 (100)
First-line immunotherapy			
Corticosteroids	5	7	12 (75)
Immunoglobulin	7	8	15 (94)
Plasmapheresis	3	7	10 (63)
Failure of first-line therapy	4	4	8 (50)
Median (range) time to second-line therapy (d)	178 (58–952)	50 (26–56)	55 (26–952)
Patients given second-line immunotherapy (*n*)	3	5	8 (50)
Second-line immunotherapy			
Rituximab	2	4	6/8 (75)
Cyclosphosphamide	2	3	5/8 (63)
Other	0	3	3/8 (38)
Median (range) length of follow-up (mo)[a]	46 (17–82)	30 (6–72)	38 (6–82)
Relapse	1	1	2 (13)
Reached mRS 0–2 within 24mo	4	7	11 (69)
mRS score >2 at 24mo	3	2	5 (31)

[a]Excludes one patient who died. mRS, modified Rankin Score.

Treatments and outcome

All patients received first-line immunotherapy within 31 days of symptom onset except for one patient presenting with hemiplegia, who was treated on day 89 (Table II). Of the four children not treated with steroids, three were treated with intravenous immunoglobulin (IVIg) and one was treated with tumour removal, IVIg, and plasmapheresis. All of the children not treated with steroids achieved a mRS score of 0 to 2 within 24 months. The time to tumour removal ranged from 9 to 18 days from symptom onset. The one patient not treated with IVIg was given both steroids and plasmapheresis, and also had an MRS score of 0 to 2 within 24 months. Eight patients failed first-line immunotherapy. Of these, six patients were treated with second-line immunotherapy. The other two were diagnosed prior to the treatment recommendations published in 2011,[5] but despite their less aggressive treatment they achieved a mRS score of 0 to 2 within 24 months. Second-line immunotherapy was given to eight patients for their initial presentation at a median of 55 days from symptom onset (range 26–952d). Second-line immunotherapy agents other than rituximab and cyclophosphamide were intravenous methotrexate (*n*=1), intrathecal

methotrexate (n=1), alemtuzumab (n=1), and azathioprine (n=1).

The small number of patients with associated tumour precluded separate analysis of this subgroup. Two of these three patients had moderate-to-severe outcomes at 24 months (mRS score ≥3).

Two patients experienced a relapse, both of whom had been treated with steroids, IVIg, and plasmapheresis within 1 month of the onset of their initial episode. One patient had been treated with rituximab on day 58 from symptom onset. Neither patient had an associated tumour. The first was a 17-year-old female who improved without second-line immunotherapy after her initial illness but relapsed 14 months after discharge. Her relapse was managed with steroid, IVIg, and maintenance mycophenolate mofetil. She had a good final outcome with a mRS score of 0 at the 24-month follow-up. The second patient was a 2-year-old male who, despite first-line immunotherapy and rituximab, relapsed 3 months after discharge. His relapse was treated with steroids, plasmapheresis, and a repeat course of rituximab. He had a poorer outcome (mRS score of 4 at 24mo follow-up).

The length of follow-up ranged from 6 to 82 months. All children with a follow-up period of less than 24 months (n=5) achieved a mRS score of 0 to 1 at the most recent follow-up (range 6–20mo) and four of these five patients were over 12 years of age. Of those children with an mRS score greater than 2 at the 24-month follow-up, three continued to show improvement after 24 months. Two non-ambulatory patients started walking independently, demonstrated improved language skills, went into seizure remission, and one's movement disorder has completely resolved. The third patient is now physically independent but needs prompting to complete activities of daily living and supervision for aggressive behaviour. The 1-year-old male who had the longest period between first- and second-line therapy has profound global developmental delay, persistent seizures, and movement disorder at 8 years of age. Subsequent CSF analysis demonstrated clearance of anti-NMDA receptor antibodies. One patient died after ventilator support was withdrawn 12 months after symptom onset. This patient had multiple medical complications and did not respond to treatment with plasmapheresis, steroids, IVIg, rituximab, cyclophosphamide, intrathecal methotrexate, or bilateral oophorectomy (no tumour identified on histopathology).

DISCUSSION

This study demonstrates that Māori and Pacific Island children are at greatly increased risk of anti-NMDA receptor encephalitis, compared with other children. The incidence in these children (3.4 and 10.0 per million per year respectively) is many times greater than children in the UK (0.9 per million per year).[1]

There is evidence this ethnicity risk is independent of socioeconomic factors. Pacific Islanders are over-represented in highly deprived areas in New Zealand, but the number of cases in our cohort was nearly four times greater than would be expected if low socioeconomic status alone mediated the increased risk.

New Zealand Māori cases more closely resemble all New Zealand Māori children in their representation in the highest deprived areas, indicating that ethnicity may not be so much an independent risk factor in those children. Conversely, there is evidence that the considerably lower risk of anti-NMDA receptor encephalitis in children of neither Māori or Pacific ancestry is largely independent of their socioeconomic status. More precisely, delineating the impact of ancestry from socioeconomic status will require future study with a larger number of cases.

These cases were treated more aggressively than most earlier cohorts with a shorter time to first-line immunotherapy and a higher percentage treated with second-line immunotherapy.[4,12,13] Our approach was similar to that described in a more recent paediatric cohort,[14] reflecting the trend towards frequent use of early and second-line immunotherapy since the description of anti-NMDA receptor encephalitis. The role of early immunotherapy in improving outcome is well supported,[4,15,16] along with the prompt use of second-line therapy in non-responders,[4,15] although the French series did not find any difference in 2-year outcome for children and adolescents treated more aggressively with second-line therapy compared with other retrospective cohorts.[14]

Despite aggressive and early treatment, this population appears to have more severe illness and poorer outcomes than described in other populations. At the peak of illness, this cohort compares with other case series, with no difference seen in number of major symptoms, number of patients with maximum mRS greater than or equal to 5, and rate of admission to intensive care units. However, the mean length of admission was longer than reported in two other cohorts.[13,17] In this cohort only 67% of patients attained a good outcome (mRS ≤2) within 2 years. This compares unfavourably from the other cohorts in which greater than 80% had only mild disability (mRS ≤2) at 24 months.[4,13] Furthermore, this difference in outcome may be underestimated because 10 children in this case series were included in Titulaer et al.'s cohort.[4]

Limitations to our study include the retrospective nature of our cohort. Also, the mRS is not validated in children; however, this was used rather than the Pediatric Cerebral Performance Category because it could be applied more accurately in retrospect with the necessary data available from the clinical records. Furthermore, the relatively small sample size, as expected for this disease in New Zealand, has limited the extent of our analysis.

We hypothesize that the increased frequency and severity of anti-NMDA receptor encephalitis in Māori and Pacific Island children may pertain to an underlying genetic predisposition for this disease. HLA polymorphisms indicate Māori and Pacific Island populations are closely related, and this would suggest an underlying genetic factor is common to both populations.[18] Māori

and Pacific Island populations are rarely affected by autoimmune diseases that typically affect white people, such as coeliac disease and ankylosing spondylitis. However, they are more susceptible to other autoimmune conditions such as juvenile systemic lupus erythematosus and rheumatic fever, and, in the case of lupus nephritis, have more severe disease.[19] Native Polynesians were significantly more likely to be affected by Guillain–Barré syndrome following Zika virus infection in the 2013 to 2014 French Polynesian outbreak.[20] Autoimmune disease in Māori and Polynesians has not been well investigated, and this study supports the need for further research in this area. The findings of this study indicate Māori and Polynesian children are at increased risk of anti-NMDA receptor encephalitis and lend support to the potential value of HLA typing and other genetic investigation into this disease.

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SUPPORTING INFORMATION

The following additional material may be found online:

Appendix S1: Medication doses.

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