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Original article

Anti-*N*-methyl-D-aspartate receptor encephalitis in children: Incidence and experience in Hong Kong

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Abstract

Aim: The study aims to analyze the incidence, clinical features, investigation findings and treatment outcomes of anti-*N*-methyl-D-aspartate receptor encephalitis in children from Hong Kong.

Method: A retrospective study was carried out on paediatric patients diagnosed with anti-NMDAR encephalitis in Hong Kong from January 2009 to December 2015.

Results: Fifteen patients (67% female, 93% Chinese) were identified over seven years and the estimated incidence in Hong Kong was 2.2/million children per year (95% CI 1.2–3.6). The median age of presentation was 12 years (range 1–17 years). The most common symptom groups observed were abnormal psychiatric behavior or cognitive dysfunction (14/15, 93%) and seizures (14/15, 93%), followed by speech dysfunction (13/15, 87%), movement disorders (12/15, 80%), decreased level of consciousness (10/15, 67%) and autonomic dysfunction or central hypoventilation (5/15, 33%). The median number of symptom groups developed in each patient was 5 (range 3–6). All patients were treated with intravenous immunoglobulin and/or steroids. Three patients (20%) with more severe presentation required additional plasmapheresis and rituximab. Outcome was assessable in 14 patients. Among those eleven patients who had only received intravenous immunoglobulin and/or steroids, nine patients (82%) achieved full recovery. One patient (9%) had residual behavioral problem, while another one (9%) who developed anti-NMDAR encephalitis after herpes simplex virus encephalitis was complicated with dyskinetic cerebral palsy and epilepsy. Among those three patients who required plasmapheresis and rituximab, one (33%) had full recovery and two (66%) had substantial recovery. The median duration of follow up was 20.5 months (range 3–84 months).

Conclusion: Anti-NMDAR encephalitis is an acquired, severe, but potentially treatable disorder. Ethnicity may play a role in the incidence of anti-NMDAR encephalitis and we have provided a local incidence with the majority of patients being Chinese. The diagnosis of anti-NMDAR encephalitis should be considered in children presenting with a constellation of symptoms including psy-

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chiatric and neurological manifestations. Patients may respond to first line immunotherapy. For those who do not, second line therapy is indicated in order to achieve a better outcome.

Keywords: Anti-NMDAR encephalitis; NMDAR antibody; Autoimmune encephalitis; Encephalitis; Neuroimmunology

1. Introduction

Anti-*N*-methyl-D-aspartate receptor (NMDAR) encephalitis was first described in 2007, and the syndrome was fully delineated in 2008 [1,2]. It is a severe, but potentially treatable disorder associated with cerebrospinal fluid (CSF) IgG antibodies against the GluN1 subunit of the NMDAR [3]. This condition is increasingly recognized in young individuals. According to the cohort published by the California Encephalitis Project in 2012, the frequency of anti-NMDAR encephalitis has surpassed that of individual viral etiologies in patients ≤30 years and 65% of anti-NMDAR encephalitis occurred in patients ≤18 years [4]. A large-scale study of paediatric anti-NMDAR encephalitis was published by Titulaer et al. in 2013, which described 211 patients with disease onset younger than 18 years together with 366 adult patients [5]. Otherwise, literature concerning paediatric anti-NMDAR encephalitis was mainly contributed by small to medium sized case series. Regional studies of anti-NMDAR encephalitis were particularly limited and of small-scale until the study published by Wang et al, which described the clinical characteristics and treatment outcome of 51 children with anti-NMDAR encephalitis in Central South China [6]. However, the data concerning ethnicity or region-specific incidence of anti-NMDAR encephalitis is still considered limited. In order to have a better understanding of the local disease spectrum, we studied the incidence, clinical features, investigation findings and treatment outcomes of anti-NMDAR encephalitis in children in Hong Kong.

2. Material and methods

This is a retrospective study of children diagnosed with anti-NMDAR encephalitis from January 2009 to December 2015 (seven years) in the paediatric neurology units of six Hospital Authority clusters (Hong Kong East, Hong Kong West, Kowloon East, Kowloon Central, Kowloon West, New Territories East) in Hong Kong. Hospital Authority is the only local public hospital service provider. The estimated paediatric population covered by the aforementioned six clusters was 982,000 in 2011 [7].

We included patients with anti-NMDAR encephalitis younger than 18 years at disease onset. Diagnoses of anti-NMDAR encephalitis were made by pediatric neurologists in each hospital based on clinical findings and the presence of anti-NMDAR antibody in serum or CSF. Demographic data, clinical symptoms, investigation findings, treatment details and outcomes were obtained from the medical records using a standardized questionnaire. Subjects younger than 12 years at disease onset were categorized into the pre-pubertal group, while those aged 12–17 years were categorized into the post-pubertal group. The presenting symptom was defined as the first symptom observed at the disease onset. Clinical symptoms were classified into six groups according to the diagnostic criteria for anti-NMDAR encephalitis proposed by Graus et al in 2016: (1) Abnormal (psychiatric) behavior or cognitive dysfunction, (2) speech dysfunction (pressured speech, verbal reduction, mutism), (3) seizures, (4) movement disorders, dyskinesia, or rigidity/abnormal postures, (5) decreased level of consciousness and (6) autonomic dysfunction or central hypoventilation [8]. CSF pleocytosis was defined as white cell count >5/mm^3.

This study was approved by the Institutional Review Board of the University of Hong Kong and Hospital Authority Hong Kong West Cluster (UW 15-639).

3. Results

3.1. Incidence

Fifteen patients (CSF anti-NMDAR antibody positive = 13, serum anti-NMDAR antibody positive (CSF not available for testing) = 2) diagnosed with anti-NMDAR encephalitis were identified from the paediatric neurology units of six Hospital Authority clusters (seven cases from Hong Kong West (HKW) cluster, three cases from Kowloon East (KE) cluster, two cases from Kowloon Central (KC) cluster, two cases from New Territories East cluster and one case from Kowloon West (KW) cluster). Two cases have been reported previously [9,10]. The estimated incidence of anti-NMDAR encephalitis was 2.2/million children per year (95% confidence interval 1.2–3.6) (For details of individual cases, please refer to Supplementary Table 1).

3.2. Demographics and clinical characteristics

Majority of patients (14 patients, 93%) were Chinese. The only non-Chinese was a Caucasian girl. Ten patients (67%) were female. The median age of presentation was 12 years (range 1–17 years). Seven patients (47%) belonged to the pre-pubertal group (range 1–9 years), while eight (53%) belonged to the post-pubertal group (range 12–17 years). Twelve patients (80%) had antecedent infections. Eight of them had upper respiratory tract infection, while three had non-specific febrile illnesses. Only one patient (Patient 7) had microbiological proof of infection ((i.e. herpes simplex virus (HSV) polymerase chain reaction (PCR) positive in CSF)).

Nine patients (60%, pre-pubertal group = 4, post-pubertal group = 5) presented with psychiatric or behavioral symptoms, while six patients (40%, pre-pubertal group = 3, post-pubertal group = 3) presented with neurological symptoms including seizures, speech dysfunction and decreased level of consciousness. All of the patients developed a constellation of symptoms with time. The most common symptoms were abnormal (psychiatric) behavior or cognitive dysfunction (14 patients, 93%) and seizures (14 patients, 93%), followed by speech dysfunction (13 patients, 87%), movement disorders (12 patients, 80%), decreased level of consciousness (10 patients, 67%) and autonomic dysfunction or central hypoventilation (5 patients, 33%). The median number of symptom groups developed by each patient with time was five (range 3–6). There were five patients (33%) who had all six symptom groups manifested. Three patients (20%) developed five, and three patients (20%) developed four symptom groups with time. The remaining four patients (27%) had three symptom groups appeared during the disease course. Besides the six major symptom groups, eight patients (8/15, 53%) had sleep disturbance during illness (For details of demographics and clinical characteristics, please refer to Table 1a).

3.3. Investigations

Serum anti-NMDAR antibody of all 15 patients (100%) was assessed and 10 (67%) were observed positive. While CSF anti-NMDAR antibody of 13 patients (87%) was tested, all patients (100%) were found positive. For patient 7, anti-NMDAR antibody was not checked upon onset of HSV encephalitis. It was only checked on Day 26 since onset of second phase of disease. All patients underwent lumbar puncture and 11 patients (73%) were found to have CSF pleocytosis (range 6/mm^3–107/mm^3). Thirteen patients had CSF oligoclonal band assessed and only two (15%) were positive. CSF neopterin was not checked in any patient.

All patients underwent brain Magnetic Resonance Imaging (MRI) performed during illness. Twelve patients (80%) were reported as normal by radiologists, while two (13%) were found to have non-specific T2 hyperintensities. The patient who developed anti-NMDAR encephalitis after HSV encephalitis was found to have encephalomalacic change involving the whole brain. Electroencephalography (EEG) was performed

Table 1a
Demographics and clinical features of 15 children with anti-NMDAR encephalitis.

Demographics and clinical characteristics	<12 years (n = 7)	12–17 years (n = 8)	Total (n = 15)
Female sex	4 (57%)	6 (75%)	10 (67%)
Chinese ethnicity	6 (86%)	8 (100%)	14 (93%)
Age of presentation (mean, median, range)	4.3, 4, 1–9 years	13.3, 13, 12–17 years	9, 12, 1–17 years
Antecedent infections	7 (100%)	5 (63%)	12 (80%)
First presenting symptom			
• Psychiatric / behavioral	4 (57%)	5 (63%)	9 (60%)
• Neurological	3 (43%)	3 (38%)	6 (40%)
Symptom groups developed with time			
• Abnormal (psychiatric) behavior or cognitive dysfunction	6 (86%)	8 (100%)	14 (93%)
• Seizures	6 (86%)	8 (100%)	14 (93%)
• Speech dysfunction	6 (86%)	7 (88%)	13 (87%)
• Movement disorders	7 (100%)	5 (63%)	12 (80%)
• Decreased level of consciousness	5 (71%)	5 (63%)	10 (67%)
• Autonomic dysfunction or central hypoventilation	1 (14%)	4 (50%)	5 (33%)
Number of symptom groups developed with time			
• 1	0 (0%)	0 (0%)	0 (0%)
• 2	0 (0%)	0 (0%)	0 (0%)
• 3	2 (29%)	2 (25%)	4 (27%)
• 4	1 (14%)	2 (25%)	3 (20%)
• 5	3 (43%)	0 (0%)	3 (20%)
• 6	1 (14%)	4 (50%)	5 (33%)

in all patients and 13 patients (87%) had abnormal findings (electrographical seizure = 3(20%), generalized slowing = 7(47%), focal slowing = 2(13%), epileptiform discharge = 1(6.7%)). None was identified to have the EEG feature of extreme delta brush. Imaging was performed on all patients (Ultrasound scan in 14 patients and PET scan in one patient) at the time of disease onset to detect pelvic tumor and all patients had negative findings (For details of investigations, please refer to Table 1b).

3.4. Treatment and outcomes

All of the patients received immunotherapy. Thirteen patients (87%) were treated with the combination of intravenous immunoglobulin (IVIG) and steroids, while one (6.7%) was treated with IVIG alone and one (6.7%) was treated with steroids only. Twelve patients received IVIG 1 g/kg/day for 2 days, while two patients received IVIG 1 g/kg/day for a total of 5 days. For steroid therapy, six patients received pulse methylprednisolone 30 mg/kg/day (maximum 1 g per day) for 5 days, while five patients and two patients received the same dose of methylprednisolone for a total of 3 days and 6 days respectively. The patient (Patient 7) who developed anti-NMDAR encephalitis after HSV encephalitis received methylprednisolone 15 mg/kg/day for 3 days. Pulse methylprednisolone was followed by oral prednisolone tailed off over months. The median time of initiating IVIG therapy was 2 weeks from symptom onset (range 1–4 weeks), while that of initiating steroid therapy was 2.5 weeks from symptom onset (range 1–8 weeks).

Three patients (20%) (Patient 9, 10, 13) with severe conditions did not respond well to the combination of IVIG and methylprednisolone, and treatment had to be escalated to plasmapheresis and rituximab. Patient 9 and patient 13 required mechanical ventilation, which failed to be weaned off after first line therapy, while patient 10 showed persistent symptoms including seizures, dyskinesia, mutism and emotional outbursts. Plasmapheresis (5 cycles) was initiated at week 3 to week 5 from the symptom onset, while rituximab (375 mg/m^2-/dose weekly for 4–6 weeks) was started at week 4 to week 7 from the symptom onset. All three patients showed partial response to plasmapheresis, and the symptoms further improved after rituximab treatment. Rituximab was well tolerated in all three patients with no obvious adverse effect noted.

Ten patients (67%) required admission to the intensive care unit and the median length of stay was 10 days (range 4–38 days). The outcome was known in 14 patients and one was left for follow up after hospital stay for 39 days. The median duration of follow up in our cohort was 20.5 months (range 3–84 months) and there was no relapse noted during the follow-up period. Ten patients (71%) achieved full recovery after treatment with no functional deficit, including one patient who received plasmapheresis and rituximab treatment (Patient 13). He was noted to have mood and cognitive problems immediately after acute phase. However, he continued to improve till 22 months after presentation. The other two patients (Patient 9 and 10) who received second line therapy showed substantial recovery with only mild behavioral problem, which did not require any psychiatric input or treatment. Both of them became more short-tempered when compared with their premorbid state. A 13-year-old girl (Patient 5) had more behavioral problems including impulsivity and emotional outbursts required psychiatric intervention. The patient with the worst outcome was the infant who developed anti-NMDAR encephalitis after HSV-1 encephalitis (Patient 7). The beginning of anti-NMDAR encephalitis was marked by the development of confusion and choreoathetosis 26 days after the onset of HSV encephalitis, which was treated with a full

Table 1b
Investigation findings of 15 patients with anti-NMDAR encephalitis.

Investigation findings	<12 years (n = 7)	12–17 years (n = 8)	Total (n = 15)
Serum anti-NMDAR antibody	5 (71%)	5 (63%)	10 (67%)
CSF anti-NMDAR antibody (assessable in 13 patients)	6/6 (100%)	7/7 (100%)	13/13 (100%)
CSF pleocytosis	5 (71%)	6 (75%)	11 (73%)
CSF oligoclonal band (assessable in 13 patients)	2/6 (33%)	0/7 (0%)	2/13 (15%)
MRI brain with abnormal findings	2 (29%)	1 (13%)	3 (20%)
• Non-specific T2 hyperintensities	1 (14%)	1 (13%)	2 (13%)
• Generalised encephalomalacic change	1 (14%)	0 (0%)	1 (6.7%)
EEG with abnormal findings	6 (86%)	7 (88%)	13 (87%)
• Electrographical seizure	1 (14%)	2 (25%)	3 (20%)
• Generalised slowing	3 (43%)	4 (50%)	7 (47%)
• Focal slowing	2 (29%)	0 (0%)	2 (13%)
• Epileptiform discharge	0 (0%)	1 (13%)	1 (6.7%)
Pelvic tumor detected by imaging	0 (0%)	0 (0%)	0 (0%)

course of intravenous acyclovir (20 mg/kg every 8 h for 33 days). The diagnosis was supported by the presence of serum anti-NMDAR antibody, which was checked on Day 26 since onset of second phase of disease, and concurrent negative CSF HSV PCR along with viral culture. Our patient was treated with IVIG and methylprednisolone with no obvious improvement. This case presented in early 2009, when anti-NMDAR antibody testing was still in the development phase in the local laboratory and result was only available several months later. Therefore, our patient was empirically treated with IVIG and methylprednisolone and second line immunotherapy was not introduced. The child later experienced dyskinesia, epilepsy, severe global developmental delay and oromotor dysfunction required gastrostomy feeding (For details of treatment outcomes, please refer to Table 1c).

4. Discussion

Data concerning ethnicity dependent incidence of anti-NMDAR encephalitis is limited. The estimated incidence in Hong Kong was 2.2/million children per year and 93% of the patients were Chinese. It was higher than 0.85/million children per year as described by Wright et al. in the United Kingdom-based surveillance study, which involved various ethnicities including 55% Caucasians and 26% Asians [11]. However, the estimated incidence of anti-NMDAR encephalitis in Hong Kong was less than those reported in Maori and Pacific children, which could be up to 3.4 and 10/million children per year respectively, as reported by Jones et al [12]. While the voluntary reporting nature of the study by Wright et al. could result in underestimation of the true incidence, it is possible that ethnicity or genetic factors may also contribute to the risk of anti-NMDAR encephalitis.

Demographic data of our patients were similar to what were described in the previous paediatric cohorts in terms of female predominance and the median age of presentation [6,11,13–20]. The proportion of our patients having symptoms of antecedent infections (80%) was higher than that reported in the previous paediatric case series, which varied from 32% to 70% [6,13,14,17–19]. Only one patient (Patient 7) was identified to have positive HSV PCR in the CSF preceding anti-NMDAR encephalitis.

Clinical symptoms were classified into six major groups according to the diagnostic criteria for anti-NMDAR encephalitis proposed by Graus et al. in 2016 [8]. All patients developed a constellation of symptoms with time and the median number of symptom groups fulfilled at any time of illness was 5 (range 3–6). The findings suggested that clinicians should review the working diagnosis regularly as symptoms emerge and the clinical diagnosis of anti-NMDAR encephalitis should be questioned in monosymptomatic cases. Literature suggested that the rate of psychiatric presentation increased with age [14], but our series failed to demonstrate a significant difference between the rate of psychiatric presentation in pre-pubertal (57%) and post-pubertal patients (63%).

Our CSF findings were compared with those reported in previous paediatric case series that included 20 or more patients. The prevalence of CSF pleocytosis in our study was 73%, while that reported in previous studies ranged from 45% to 87%. The prevalence of CSF oligoclonal band in our study was 15%, while that reported in other studies ranged from 19% to 83% [6,11,13,14,17,19]. This indicated that normal routine CSF findings do not exclude anti-NMDAR encephalitis. Although it is not included in the diagnostic criteria proposed by Graus et al. CSF neopterin may act as a non-specific biomarker of central nervous system inflammation and it may be elevated in patients with anti-NMDAR encephalitis [21]. Five of our patients (5/13, 38%) with negative anti-NMDAR antibody in serum analysis were found to be positive in CSF

Table 1c
Treatment and outcome of 15 patients with anti-NMDAR encephalitis.

Treatment and outcome	<12 years (n = 7)	12–17 years (n = 8)	Total (n = 15)
Immunotherapy	7 (100%)	8 (100%)	15 (100%)
• IVIG + steroid	6 (86%)	7 (88%)	13 (87%)
• IVIG only	0 (0%)	1 (13%)	1 (6.7%)
• Steroid only	1 (14%)	0 (0%)	1 (6.7%)
• Plasmapheresis	0 (0%)	3 (38%)	3 (20%)
• Rituximab	0 (0%)	3 (38%)	3 (20%)
ICU admission	4 (57%)	6 (75%)	10 (67%)
• Length of stay in ICU (median, range)	8.5, 6–10 days	17, 4–38 days	10, 4–38 days
Number of patients with outcome assessable	6	8	14
• Duration of follow up (median, range)	17.5, 11–84 months	27, 3–48 months	20.5, 3–84 months
• Full recovery	5 (83%)	5 (63%)	10 (71%)
• Substantial improvement	0 (0%)	2 (25%)	2 (14%)
• Limited improvement	1 (17%)	1 (13%)	2 (14%)

analysis. This was in line with what was described in the literature. A study, which included 250 patients with anti-NMDAR encephalitis, suggested that up to 14% of patients had antibodies in the CSF, but not serum [22]. CSF antibody analysis should therefore be included in the diagnostic testing in order to improve the diagnostic sensitivity.

Majority of our patients demonstrated EEG abnormalities including electrographical seizures, generalized slowing, focal slowing or epileptiform discharges. However, none was identified to have extreme delta brush on EEG, which is one of the abnormal investigation criteria proposed by Graus et al. and is also considered to be a characteristic EEG feature in adults with anti-NMDAR encephalitis [8,23]. This may be due to under-recognition of this EEG feature in our retrospective study or genuine difference in presentation between adult and paediatric patients. Extreme delta brush was seldom reported in previous paediatric literature except a Chinese study that reported prevalence up to 33% [24]. After the diagnosis of anti-NMDAR encephalitis has been confirmed, tumor screening should be conducted. If a tumor is present, it is almost always an ovarian teratoma. Teratomas located elsewhere and other tumors are uncommon [3]. The indication of tumor screening using abdominal imaging on male patients with anti-NMDAR encephalitis is unclear. Although it is not a routine, all of the patients including male patients underwent abdominal imaging upon presentation and none was found to have pelvic tumor. This is in line with the previous case series revealing lower risk of tumor in children than that in adults, which could vary from 0% to 25% [6,11,13–15,17–19,25]. None of our patients experienced clinical relapse during the follow up period, while the relapse rate reported from previous Western studies ranged from 8% to 25% [11,13,14,17,18]. However, a recent Chinese-based study, which involved 51 children with mean duration of follow up of 16.1 months, demonstrated that the relapse rate could be as low as 0.02% [6].

Only three patients (20%) received plasmapheresis and rituximab in our series. The rate was lower than that reported in previous studies which ranged from 23% to 81% [5,11,13,14,18]. This might be partly due to financial limitation as Rituximab is a self-financed item in Hong Kong. On the other hand, this decision was also clinically driven. Besides the patient who developed anti-NMDAR encephalitis after HSV encephalitis, 9 out of 10 patients who had only received IVIG and/or steroids achieved full recovery without the use of plasmapheresis or second line therapy. However, the positive response to plasmapheresis and rituximab in three of our patients with severe presentation still illustrated the importance of escalating immunotherapy in those who did not improve with the combination of IVIG and steroids. Titulaer et al. demonstrated that in the group of patients who did not respond to first line therapy within the first four weeks treatment, those who received rituximab, cyclophosphamide, or both, had better outcomes than those who were continued with the first line immunotherapy or who received no further immunotherapy. Among the three patients who received plasmapheresis and rituximab in our study, one achieved completed recovery with time and two had mild behavioral problems noted at the study period. However, both of them had a relatively short duration of follow up (12 months and 3 months). According to Titulaer et al. recovery could continue until 18 months of follow up, and therefore, there is a chance of ongoing improvement in the above two patients included in this study [5].

One of the patients developed anti-NMDAR encephalitis after HSV encephalitis. This entity is increasingly recognized in children and adults. Differentiating immune mediated mechanism from relapse due to new viral replication can be difficult, but clinical features may help. Nosadini et al. have performed a systematic review of literature on patients with biphasic disease with HSV encephalitis followed by anti-NMDAR encephalitis. When compared with HSV encephalitis, anti-NMDAR encephalitis was characterized by a significantly higher frequency of movement disorder (2.5% vs 75% respectively, $p < 0.001$) and a significantly lower rate of seizures (70% vs 30% respectively, $p = 0.001$) [26]. CSF anti-NMDAR antibody should therefore be checked in patients with apparent relapse after HSV encephalitis, especially in those presenting with movement disorder, as this may have treatment implication, since more aggressive immunotherapy might be able to improve the clinical outcome.

Our study was limited by its retrospective nature, small number of patients and a relatively short period of follow-up (median 20.5 months). Moreover, detailed neuropsychological assessment was not performed to identify subtle deficits. Future large-scale collaborative studies investigating ethnicity dependent incidence and outcome are worth considering.

5. Conclusion

Ethnicity may influence the incidence of anti-NMDAR encephalitis and we have provided a local incidence with majority of patients being Chinese. The diagnosis should be considered in children and adolescents presenting with a constellation of symptoms including psychiatric and neurological manifestations. Patients may respond to first line immunotherapy. For those who do not, second line therapy is needed in order to achieve better outcome. Comprehensive neuropsychological testing is needed for detailed outcome assessment. Anti-NMDAR encephalitis after HSV encephalitis has been increasingly recognized in recent

years and a high index of suspicion for anti-NMDAR encephalitis is needed in subjects with apparent clinical relapse after HSV encephalitis.

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Appendix A. Supplementary data

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