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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).

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