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ข้อมูลทางอาการ อาการแสดง และผลของการรักษาในผู้ป่วยเด็กโรคสมองอักเสบจากแอนติบอดีต่อตัวรับเอ็นเอ็มดีเอ(NMDAR) ในโรงพยาบาลศรีนครินทร์

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Clinical Manifestations and Outcomes of Pediatric Anti-N-methyl-D-aspartate Receptor (NMDAR) Encephalitis in Srinagarind Hospital

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บทคัดย่อ

หลักการและวัตถุประสงค์: โรคสมองอักเสบจากแอนติบอดีต่อตัวรับเอ็นเอ็มดีเอ (Anti-N-methyl-D-aspartate receptor, NMDAR) เป็นโรคสมองอักเสบจากภาวะแพ้ภูมิต้านทานที่พบได้บ่อยในเด็กแต่สามารถรักษาหายได้ การศึกษานี้มีวัตถุประสงค์เพื่อศึกษาอาการ อาการแสดง การตรวจวินิจฉัย การรักษา ผลการรักษา และปัจจัยที่อาจทำให้เกิดโรคซ้ำในผู้ป่วยเด็ก

วิธีการศึกษา: การศึกษาย้อนหลังในเด็กโรคสมองอักเสบจากแอนติบอดีต่อตัวรับเอ็นเอ็มดีเอที่เข้ารับการรักษาในโรงพยาบาลศรีนครินทร์ ระหว่างเดือนมกราคม พ.ศ. 2559 – มีนาคม พ.ศ. 2563 จำนวน 10 ราย

ผลการศึกษา: อายุเฉลี่ย 9.5 ปี (1-16 ปี) และร้อยละ 90 เป็นเพศหญิง อาการแสดงที่พบมากที่สุดในเด็กก่อนวัยรุ่นคือชัก ส่วนในวัยรุ่นพบมีปัญหาพฤติกรรม ผู้ป่วยทั้งหมดพบแอนติบอดีต่อตัวรับเอ็นเอ็มดีเอในน้ำไขสันหลังและเลือด แต่ไม่พบเนื้องอกในร่างกาย มี 3 ราย เป็นโรคสมองอักเสบจากเชื้อไวรัสมาก่อน เชื้อไวรัสที่พบได้แก่ Herpes simplex ในผู้ป่วย 2 รายและ Varicella zoster 1 ราย ผู้ป่วยทุกรายได้รับการรักษาด้วยยากดภูมิคุ้มกันขั้นแรก ร้อยละ 60 อาการดีขึ้นหลังได้รับยาและจากการติดตาม ร้อยละ 50 หายเป็นปกติ มี 4 รายที่ ได้รับยากดภูมิคุ้มกันขั้นที่สอง และ 2 รายเกิดโรคซ้ำ เมื่อเปรียบเทียบทางสถิติพบว่าระยะเวลาตั้งแต่มีอาการจนได้รับการรักษาของกลุ่มที่เป็นโรคซ้ำ (78.5 days, IQR 74-83) นานกว่ากลุ่มที่ไม่เป็นซ้ำ (19 days, IQR 13.5-28.5) อย่างมีนัยสำคัญทางสถิติ (p = 0.036)

สรุป: อาการในผู้ป่วยเด็กโรคสมองอักเสบจากแอนติบอดีต่อตัวรับเอ็นเอ็มดีเอมีความแตกต่างกันตามช่วงวัย การติดเชื้อไวรัสนำมาก่อนอาจส่งผลให้ผลการรักษาไม่ดีและการรักษาล่าช้าอาจเป็นปัจจัยเกี่ยวข้องที่ทำให้เกิดโรคซ้ำได้

คำสำคัญ: โรคสมองอักเสบจากแอนติบอดีต่อตัวรับเอ็นเอ็มดีเอ, เด็ก, อาการ, ผลการรักษา, การเกิดโรคซ้ำ

Abstract

Background and Objective: Anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is common and treatable autoimmune encephalitis in children. This study aimed to describe clinical manifestation, investigation, treatment, outcome, and possible factors associated with relapse in pediatric anti-NMDAR encephalitis in Srinagarind Hospital.

Methods: The medical records of 10 children diagnosed with anti-NMDAR encephalitis at Srinagarind Hospital during January 2016-March 2020 were retrospectively reviewed.

Results: The median age of patients was 9.5 years (1-16 years), 90% were female. The most common presentation in pre-puberty was seizure, post-puberty was behavioral symptoms. CSF and serum NMDAR antibodies were identified in all patients. Three patients had evidence of previous viral encephalitis (2 Herpes simplex encephalitis (HSE),1 Varicella zoster encephalitis). Electroencephalography revealed focal epileptiform discharge (60%), extreme delta brush (40%), generalized slow activity (30%). Neuroimaging of previous HSE showed temporal lobe abnormalities (20%), the rest of patients showed non-specific disease finding. Neoplasms were not detected. All received first-line and maintenance immunotherapy. Second-line immunotherapy was given to 4 patients. Six patients (60%) improved after first-line immunotherapy, 2/6 patients developed relapse. Five patients (50%) had complete recovery, Pediatric cerebral performance category (PCPC) score of 1 at last follow-up. The median interval between symptom onset and initiation of immunotherapy was significantly longer in relapse group (78.5 days, IQR 74-83) than non-relapse group (19 days, IQR 13.5-28.5) (p = 0.036).

Conclusions: Seizure was predominated in young children while behavior change typically presented in adolescents. Preceding viral infection may be a trigger and associated with unfavorable outcome. Prolonged interval between symptom onset and first-line immunotherapy was one of possible associated factor of relapse.

Keywords: Anti-N-methyl-D-aspartate receptor encephalitis, children, clinical manifestation, outcome, relapse

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Introduction

Anti-N-methyl-D-aspartate receptor encephalitis (anti-NMDAR encephalitis) is a most common cause of autoimmune encephalitis in children and adolescents. This disorder has been described since 2007[1] and increasingly diagnosed.

The common presentations in children are seizures, abnormal behavior, and movement disorder.[2] The etiology is unclear. Although, it has been shown as associated with tumor[3,4], the presence of underlying tumor in children is uncommon. The outcome of children with anti-NMDAR encephalitis after immunotherapy is favorable.[5]

This study aimed to assess demographic characteristics, clinical manifestations, ancillary examination results, treatments, and outcomes and factors associated with relapse in anti-NMDAR encephalitis in children.

Methods

This study was a retrospective descriptive study. The population was all patients aged 1-18 years diagnosed with anti-NMDAR encephalitis between January 1, 2016 and March 31, 2020 at the department of Pediatrics, Srinagarind Hospital, Faculty of Medicine, Khon Kaen University, Thailand. The study was approved by Khon Kean University Ethics Committee for Human Research.

The diagnosis of anti-NMDAR encephalitis was based on clinical symptoms and confirmed by presence of NMDAR antibodies in cerebrospinal fluid (CSF) by both immunohistochemistry assay and cell-based assay. Medical information was collected from medical records. The demographic data, clinical manifestation, investigation, treatment, and outcome after treatment were reviewed. Outcome was assessed by using the pediatric cerebral performance category (PCPC).[6]

Statistical analysis was performed using SPSS software version 20.0 Continuous data were assessed by mean, median, standard deviation, and range while categorical data were presented as number and percentage. We compared the characteristics between non-relapse and relapse groups by using Fisher's exact test for categorical variables and Mann-Whitney U test for continuous variables. P-value less than 0.05 was considered to indicate statistical significance.

Results

Ten patients diagnosed with anti-NMDAR encephalitis during the study period. The median age was 9.5 years (1-16 years), and nine patients (90%) were female. The nationality were Thai (nine patients) and Lao (one patient). Ten patients were divided into two groups by age; six patients were younger than 12 years of age (pre-pubertal group) and four patients aged 12-18 years (post-pubertal group). Five patients had prodromal symptoms, including headache, fever, and symptoms of upper urinary tract infection within two weeks before the symptom onset. Three patients had evidence of previous viral infection before the symptom onset of anti-NMDAR encephalitis; two patients aged 1 year with Herpes simplex virus type 1 (HSV-1) encephalitis, they had positive polymerase chain reaction (PCR) for HSV-1 in the first CSF evaluation then after a month treatment with acyclovir the result was found negative PCR for HSV-1 and positive NMDAR antibodies in CSF. A patient aged four years with Varicella zoster virus (VZV) infection, she had evidence of infection for ten days before the symptom onset. Initial symptoms were fever and rash that was compatible with chickenpox and CSF varicella zoster IgG and IgM were positive, titers 3,215 IU/L (0-100 IU/L) and 1.8 IU/L (0-0.8 IU/L) respectively but PCR for VZV in CSF showed negative.

The clinical manifestations of anti-NMDAR encephalitis are shown in Table 1. All patients developed at least two symptoms over the course of their disease. The median number of symptoms was 3.5 (range 2-5). The most common presenting symptoms were seizures (80%) and behavioral symptoms (70%), including confusion, irritability, agitation, and echolalia. All patients in the pre-pubertal group (six patients) had seizures, while all patients in post-pubertal group (four patients) presented with behavioral change.

Table 1 Clinical manifestations of 10 patients with anti-NMDAR encephalitis Data are n value.

Clinical manifestations	Pre-pubertal group (n=6)	Post-pubertal group (n=4)	Total (n=10)
Seizure	6	2	8
Abnormal movement			
Limb dyskinesia	3	2	5
Orofacial dyskinesia	3	1	4
Choreoathetosis	3	0	3
Dystonia	1	0	1
Behavioral change	3	4	7
Speech disorder	3	3	6

NMDAR: N-methyl-D-aspartate receptor

The first manifestation included abnormal behavior in five patients (50%), seizures in three patients (30%) and movement disorder in two patients (20%), including limb dyskinesia and choreoathetosis.

The following investigations were performed in all patients including CSF analysis, CSF and serum NMDAR antibodies, electroencephalography (EEG), neuroimaging; magnetic resonance imaging (MRI) and/or computerized tomography (CT) scan of the brain, and tumor screening with abdominal or testicular ultrasound, results as presented in Table 2. NMDAR antibodies were identified in both CSF and serum in all patients. EEG showed various findings such as generalized slow activity, focal epileptiform discharge, and extreme delta brush. Neuroimaging of two patients who were diagnosed with herpes simplex encephalitis (HSE) showed temporal lobe abnormalities. Tumor screening was performed in all patients after diagnosing and yearly follow-up. Ovarian or testicular tumor were not found. Clinical manifestations, treatments, and outcomes in each patient were summarized in Table 3. The median interval between symptom onset and immunotherapy treatment was 21.5 days, ranged from 6 to 83 days. All patients received first-line immunotherapy; five of ten patients (50%) were treated within 30 days of first symptom onset. Four patients (40%) were exclusively treated with intravenous methylprednisolone (30 mg/kg, maximum 1,000 mg daily for three to five days), five patients (50%) with both intravenous methylprednisolone and IVIG (0.4 g/kg per day for 5 days or 1 g/kg per day for two days, total 2 g/kg), and only one patient with intravenous dexamethasone (Dexamethasone 5 mg IV every 6 hours for 5 days). Six patients (60%) showed improvement after four weeks of first-line immunotherapy. Particularly in this group, four patients showed good outcome at the last follow-up (PCPC score of 1; full recovery). Among four patients who did not improve from using first-line treatment within the first four weeks, three patients were followed by the second-line immunotherapy and one patient did not receive any second-line therapy since the patient refused. Second-line immunotherapy was given to four patients; three patients with no improvement within four weeks after first-line immunotherapy; one patient received at the time of relapse (recurrence of symptoms after improvement from first-line therapy). All of them received six cycles of monthly intravenous cyclophosphamide (IVCY) (500 mg/m^2, maximum 1 g). The outcome in patients with second-line immunotherapy showed with PCPC scores at last follow-up of 1-3. Maintenance therapy was given to all patients for two years; four patients received azathioprine (1-3 mg/kg/day) and six patients received prednisolone (1 mg/kg/day). The median duration of follow-up was two years, with a range of one to four years. Until the last follow-up, five patients (50%) had complete recovery (PCPC score of 1) and the median of time to complete recovery is eight months; two patients (20%) had mood/ behavioral disorder or mild disability (PCPC score of 2); and two patients (20%) had moderate disability, sufficient cerebral function for age-appropriate independent activities of daily life (PCPC score of 3). One patient with delayed treatment and having relapse with recurrent

seizures had poor outcome (intractable epilepsy with dyskinesia); severe disability (PCPC score of 4). No deaths were reported in this study. Three patients with previous viral infection (HSV and VZV) showed unfavorable outcome (PCPC score of 2-4) However, two patients treated with the only methylprednisolone in first-line therapy developed relapse at 4 and 16 months after the first event, respectively. They had different improvements after re-initiation of treatment, PCPC score in the last follow-up showed 4 (severe disability) and 1 (complete recovery).

Table 4. shows comparisons of the relapse and non-relapse groups. The median interval between symptom onset and immunotherapy treatment was significantly longer in the relapse group (78.5 days, IQR 74-83) than in the non-relapse group (19 days, IQR 13.5-28.5) (p=0.036). Initial symptoms, co-infection, first-line immunotherapy, second-line immunotherapy and maintenance immunotherapy showed no significant between-group differences.

Table 2 Results of investigations of 10 patients with anti-NMDAR encephalitis.

Investigation	Median (range) or n (%) values
Cerebrospinal fluid (n=10)	
Normal finding	4 (40%)
Pleocytosis	6 (60%)
Median WBC (cell/mm^3)	8 (0-90)
Median protein (mg/dl)	52.5 (22-241)
Positive PCR for Herpes simplex virus type 1	2 (20%)
Positive varicella-zoster antibodies IgG & IgM	1 (10%)
Positive oligochonal band	1 (10%)
Electroencephalogram (n=10)	
Extreme delta brush	4 (40%)
Generalized slow activity	3 (30%)
Focal epileptiform discharge	6 (60%)
Computed tomography (n=8)	
Normal	4 (50%)
Abnormal (Any type)	4 (50%)
• Hypodensity lesion at right temporal lobe (n=1)	
• Brain atrophy at bilateral frontal and temporal lobe (n=1)	
• Diffuse brain swelling (n=1)	
• Asymmetrical narrowing temporal horn of left lateral ventricle, normal brain parenchyma (n=1)	
Magnetic resonance imaging (n=6)	
Abnormal (Any type)	6 (100%)
• Cystic encephalomalacic change at bilateral frontal and temporal lobe (n=1)	
• Non-specific hyperintensity of white matter on T2-weighted (n=3)	
• Diffuse brain atrophy (n=1)	
• Hyperintensity on T2-weighted with restriction on DWI, no gadolinium enhancement at cortical part of parasagittal of left frontal lobe and bilateral mesial temporal lobe (n=1)	
Tumor screening (n=10)	
Tumor detection	0 (0%)

DWI: *Diffusion-weighted* imaging, NMDAR: N-methyl-D-aspartate receptor, PCR: Polymerase chain reaction, WBC: White blood cell count

Table 3 Clinical presentation, treatment, and outcome of 10 patients with anti-NMDA receptor encephalitis

No.	Sex	Age (year)	Symptom	Co-infection	Time to treatment (day)	First-line therapy	Four-week outcome	Second line therapy	Relapse time (treatment)	Maintenance therapy	Follow up (year)	PCPC Score[‡] (last visit)	Complete recovery (month)
1	M	1	SZ*, OD, LD	HSV-1	11	MP+I	Not Improve	IVCY	-	Pred	2	2	-
2	F	1	SZ*, C	HSV-1	74	MP	Improve	IVCY (relapse)	4 months (MP+I+IVCY)	A	2	4	-
3	F	3	BC*, SZ, OD, SD	-	19	MP+I	Improve	-	-	Pred	3	1	6
4	F	4	C*, SZ, OD, DY	VZV	19	MP+I	Not improve	IVCY	-	Pred	1	3	-
5	F	8	LD*, SZ, BC, SD, C	-	24	MP+I	Improve	-	-	A	3	1	10
6	F	11	BC*, SZ, LD, SD	-	83	MP	Improve	-	16 months (MP)	Pred	4	1	12
7	F	13	BC*, SZ, OD, LD, SD	-	16	MP+I	Not improve	IVCY	-	Pred	1	1	7
8	F	14	BC*, LD, SD	-	33	MP	Improve	-	-	A	1	2	-
9	F	15	SZ*, BC	-	6	D	Not improve	-	-	Pred	1	3	-
10	F	16	BC*, SD	-	56	MP	Improve	-	-	A	2	1	8

***** The first symptom

‡ PCPC score; 1= normal, 2= Mild disability, 3= Moderate disability, 4= Severe disability, 5=coma or vegetative state, 6= brain death

A: azathioprine, BC: behavioural change, C: choreoathetosis, D: dexamethasone, DY: dystonia, F: female, HSV-1: Herpes simplex virus type 1, I: intravenous immunoglobulin, IVCY: intravenous cyclophosphamide, LD: limb dyskinesia, M: male, MP: methylprednisolone, OD: orofacial dyskinesia, Pred: prednisolone, SD: speech disorder, SZ: seizure, VZV: varicella-zoster virus

Table 4 Factors associated with relapse of 10 patients with anti-NMDA receptor encephalitis

	Non-relapse (n=8)	Relapse (n=2)	Total (n=10)	P-value*
Median interval between symptom onset and treatment in days (IQR)	19 (13.5-28.5)	78.5 (74-83)	21.5 (16-56)	0.036
First clinical manifestation				
• Seizures	2 (25)	1 (50)	3 (30)	1
• Behavioral change	4 (50)	1 (50)	5 (50)	1
• Limb dyskinesia	2 (25)	0 (0)	2 (20)	1
Co- infection	2 (25)	1 (50)	3 (30)	1
First-line immunotherapy				
• Steroids	3 (37.5)	2 (100)	5 (50)	0.444
• Steroid plus IVIG	5 (62.5)	0 (0)	5 (50)	0.444
Second-line immunotherapy				
• IVCY	3 (37.5)	1 (50)	4 (40)	1
Maintenance immunotherapy				
• Prednisolone	5 (62.5)	1 (50)	6 (60)	1
• Azathioprine	3 (37.5)	1 (50)	4 (40)	1

Data are median (IQR) or n (%) values.

IVIG: intravenous immunoglobulin, IVCY: intravenous cyclophosphamide

*****Fisher's exact test, except for interval between symptom onset and treatment, which is Mann-Whitney U test

Discussion

In this study, it was found that clinical presentations of anti-NMDAR encephalitis in children were similar to previous report.[7] Multiple co-infections can predispose patients to autoimmune encephalitis, infective pathogens have been implicated as triggering factors for the non-tumor-related anti-NMDAR encephalitis.[8] Three cases in this study were identified with significant recent viral infection. From the observation, it can be concluded that there is a relationship between viral infections and autoimmunity of the central nervous system. In this study, both CSF and serum NMDAR antibodies were positive in all patients. This may be described by the obvious and multiple presentations of anti-NMDAR encephalitis in our patients. The neuroimaging (CT and/or MRI) of two patients with Herpes simplex encephalitis showed abnormal finding at temporal lobe that was commonly seen in Herpes simplex encephalitis[9] and non-specific white matter lesion was found in patient with previous VZV infection. Although this data cannot conclude specific finding in the neuroimaging of anti-NMDAR encephalitis but neuroimaging still important to work up in patients with suspected anti-NMDAR encephalitis because those modalities can rule out other conditions causing a similar neurologic presentation and uncover more information of neuroimaging in anti-NMDAR encephalitis.

EEG was performed in all patients before received immunotherapy. The finding showed the corresponding results reported in both children and adult with anti-NMDAR encephalitis including generalized slow activity, focal epileptiform discharge, and extreme delta brush. From the findings, it suggested that generalized slow activity support to diagnosing acute stage of anti-NMDAR encephalitis. On the other hand, extreme delta brush was detected in three patients with the varying outcomes (PCPC scores of 1-3). This finding was inconsistent with the recent study that indicated the presence of extreme delta brush patterns as marker of more severe disease among patients with anti-NMDAR encephalitis corresponding with worse outcome.[10] Similar to the previous series and case reports, there was no underlying tumor reported in most children with

anti-NMDAR encephalitis after diagnosing and yearly follow up.

Moreover, decisions of type and duration of immunotherapy in this study were made by attending physicians. Therefore, the first-line immunotherapy and maintenance therapy varied. All patients underwent first-line immunotherapy. Four patients were followed by the second-line immunotherapy with intravenous cyclophosphamide. Interestingly, 3 patients whose first-line treatment has failed received both intravenous methylprednisolone and IVIG and had short time interval to treatment (11, 19, 16 days) which is inconsistent with the knowledge that the early treatment and combination immunotherapy give better results. This may be explained by our patients had obvious and severe presentations of anti-NMDAR encephalitis that physician usually give early treatment and combination of immunotherapy, but outcome in this group is unfavorable. The outcome of using second-line immunotherapy varied (PCPC scores at last follow-up of 1-4), these different from the previous study suggesting that second-line immunotherapy significantly improve outcomes in patients who did not respond to first-line therapy.[11] This can be explained by anti-NMDAR encephalitis with CNS infection triggering had poor outcome due to sequelae of the initial infection[12,13] that our study showed 3 patients with previous viral encephalitis is poor response of treatment (2 patients had first-line immunotherapy failure and 1 patient with relapse). The outcome of the patient receiving only low dose steroids that is not standard first-line immunotherapy with no second-line immunotherapy was poor (PCPC score of 3). Therefore, the aggressive immunotherapy was suggested to the patient as it was found to be associated with greater outcome.

Withregards to risk factor of relapse, the previous study[14] reported the risk of relapse was significantly lower in patients when receiving three or more different immune therapies after the first disease diagnosed that corresponding with this study found no relapse of disease in patient who received combination of high dose corticosteroids and IVIG. In addition, factor associated with relapse was found significantly longer in patient having prolonged interval between symptom onset and first-line immunotherapy. These findings indicated that the earlier and more aggressive immunotherapy at symptom onset may reduce relapse.

Conclusion

Seizures and abnormal movement were predominated in young children while behavioral change typically presented in adolescents. Preceding viral infection may be a trigger and associated with unfavorable outcome. Prolonged interval between symptom onset and first-line immunotherapy might be one of associated factor of relapse. Therefore, early diagnosis and aggressive immunotherapy should be considered to achieve favorable outcome and to reduce risk of relapse.

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