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Original Article

Anti-*N*-Methyl-D-Aspartate Receptor Encephalitis in Taiwan—A Comparison Between Children and Adults

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ABSTRACT

BACKGROUND: Since the discovery of antibodies against the *N*-methyl-D-aspartate receptor in 2007, anti-*N*-methyl-D-aspartate receptor encephalitis is increasingly recognized worldwide. We compare the clinical features of adults and children with this disorder in Taiwan. **METHODS:** Patients admitted to Chang Gung Memorial Hospital and Chang Gung Children's Hospital and those who were referred from other institutions because of unknown encephalitis from 2009 to 2013 were enrolled, and their clinical features were analyzed. Data on cases from a review of the literature were also included in the analysis. **RESULTS:** Twelve patients (10 females) aged between 7 years and 28 years with anti-*N*-methyl-D-aspartate receptor encephalitis were identified. Six patients (50%) were <18 years old, one of whom was male and three of whom had an underlying tumor. Overall, 91.6% of the patients presented with mood, behavioral, or personality changes; 91.6% developed seizures; 100% had stereotyped movements; 83.3% had autonomic instability; and 66.7% had hypoventilation. Responses to immunotherapy were slow and variable. Overall, 63.6% of the patients had a substantial recovery after immunotherapy or removal of the tumor, and one patient experienced neurological relapses. There were no significant differences in clinical manifestations between children and adults. **CONCLUSIONS:** Anti-*N*-methyl-D-aspartate receptor encephalitis is increasingly recognized in Taiwan. It is characterized by its clinical features, predominantly affects females with and/or without an ovarian tumor, and it is a potentially treatable disorder. It is important for neurologists to be familiar with the clinical presentations of the disease in children and young adults.

Keywords: anti-*N*-methyl-D-aspartate receptor, encephalitis, Taiwan, children

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Introduction

Anti-*N*-methyl-D-aspartate receptor (NMDAR) encephalitis is a recently described disorder with characteristic clinical features that is predominantly seen in young adults and children with or without teratomas.[1,2] Most patients evolve in five stages: the prodromal phase, psychotic and/or seizure phase, unresponsive and/or catatonic phase,

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hyperkinetic phase, and gradual recovery phase.[3,4] The clinical course usually begins with viral infection-like symptoms that last for up to 2 weeks (prodromal phase), followed by the rapid development of schizophrenia-like psychiatric symptoms and seizures (psychotic and seizure phase). Subsequently, in the unresponsive and/or catatonic phase, the patients become mute and unresponsive but awake during the akinetic status. They may have a decreased level of consciousness with central hypoventilation, frequently requiring mechanical ventilation. In the following hyperkinetic phase, they present with orofacial-limb dyskinesia and autonomic instability. Finally, the patients enter into a gradual recovery phase, but in some there is a possibility of relapse.[1-4]

Despite the rapid progression of the clinical course and the severity of the disorder, patients often improve with immunotherapy in autoimmune anti-NMDAR encephalitis and removal of the teratoma in paraneoplastic anti-NMDAR encephalitis.[5] An accurate and timely diagnosis is critical for the selection and implementation of treatment strategies and optimal patient outcomes. However, recovery is slow, may take ≥18 months, and a relapse can occur.[4,5] Therefore, this disorder is an important, but likely underrecognized condition because it is newly described. To facilitate the recognition of this disorder in Taiwan, we present our clinical experience in the diagnosis and management of patients with anti-NMDAR encephalitis and also review the English literature with regard to anti-NMDAR encephalitis in Taiwan since 2007.[6-9] We discuss the clinical presentations, frequency of tumor association, laboratory examinations, and outcomes and compare these findings between children and adults.

Methods

Patients and methods

Patients admitted to Chang Gung Memorial Hospital and Chang Gung Children's Hospital, and those who were referred from other institutions because of unknown encephalitis between January 1, 2009, and July 31, 2013, were enrolled. This study was approved by the Chang Gung Memorial Hospital Institutional Review Board.

Clinical information was obtained by the authors or provided by the referring physicians at the acute stage of the disease. On the basis of the reported manifestations of this disorder, we categorized the symptoms into five categories: prodromal symptoms, psychiatric symptoms, neurological symptoms, movement abnormalities, and others, including autonomic dysfunction and hypoventilation.[3,4] Most patients underwent extensive diagnostic studies, including magnetic resonance imaging of the brain, electroencephalography, serum and cerebrospinal fluid viral studies, and testing for autoimmune and metabolic disorders. We assessed the results from only the first magnetic resonance imaging, electroencephalography, and cerebrospinal fluid examinations. All patients were also screened for tumors.

First-line immunotherapy was defined as the use of corticosteroids, immunoglobulins, or plasma exchange, alone or in combination. Second-line immunotherapy included rituximab or cyclophosphamide, alone or in combination.[5] The patients were considered to have a "full neurological recovery" if they were able to return to all their daily activities, a "substantial improvement" if they returned to their homes with mild deficits and they were improving, and a "limited improvement" if they were at home, in the hospital, or rehabilitation center with minimal changes in neurological status after at least 3 months of follow-up.[3]

During the same period, reported cases of anti-NMDAR encephalitis in Taiwan were reviewed through a PubMed search using key words of anti-NMDAR encephalitis, paraneoplastic syndrome, and Taiwan. Five patients were identified,[6-9] and their clinical data, including sex, prodromal symptoms, clinical presentation, cerebrospinal fluid findings, brain magnetic resonance imaging, electroencephalography, treatment, and outcomes were reviewed. We divided the patients into two groups according to age: children (age ≤18 years old) and adults (age >18 years old).

Detection of anti-NMDAR antibodies

NMDAR receptor antibodies were studied by immunofluorescence on human embryonic kidney 293 cells transfected with the NR1 subunit (glutamate [NMDA] recptor subunit zeta 1) of the NMDAR complex and immobilized on BIOCHIPs (Euroimmun Diagnosika, Lübeck, Germany). The "BIOCHIP" mosaic also included nontransfected human embryonic kidney 293 cells as negative controls and frozen sections of rat cerebellum and rat hippocampus sections as substrates for indirect immunofluorescence.[10,11] We tested for the presence of NMDAR antibodies in serum and/or cerebrospinal fluid samples and defined a positive result if the following immunohistochemical criteria were fulfilled: (1) characteristic immunohistochemical reactivity with the neuropil in the rat hippocampus and (2) a cell-based assay of human embryonic kidney 293 cells expressing the NR1 subunit of NMDAR.

Statistical analysis

Descriptive statistics were used to determine the characteristics of the clinical manifestations, and their respective frequencies were expressed as percentages. Fisher exact test for categorical variables was used to compare groups. *P* values of <0.05 were considered to indicate statistical significance, but we acknowledge the unlikelihood of positive *P* values with a small sample size. All statistical analyses were performed using SPSS version 12.0 (SPSS Inc, Chicago, IL).

Results

From January 1, 2009, to July 31, 2013, 188 cases of encephalitis of uncertain etiology were referred to our institutions. All of the patients were tested for anti-NMDAR encephalitis, seven (3.7%) of whom were positive. From the literature review, four reports on five cases of anti-NMDAR encephalitis in Taiwan were identified, resulting in a total of 12 patients. The clinical features of these 12 patients are summarized in Table 1. There were 10 (83.3%) female and two (6.7%) male patients. One (8.3%) patient was <12 years old, five patients (41.7%) were 12-18 years old, and six (50%) patients were >18 years.

Clinical features

A summary of the clinical features is shown in Table 2. In the prodromal phase, symptoms including fever, headache, or a nonspecific viral-like illness (upper respiratory symptoms, vomiting, and/or nausea) within 2 weeks before admission to the hospital were noted in eight (66.7%) of the 12 patients. In the psychotic and seizure phase, all the patients had psychiatric symptoms, including 11 (91.6%) with mood, behavioral, or personality changes, including agitation, mood lability, and bizarre behavior, and eight (66.7%) patients had visual or auditory hallucinations. In addition to psychiatric symptoms, 11 (91.6%) patients had seizures during this phase, which were mostly generalized tonic–clonic seizures. However, two patients had seizures as the initial presenting symptom followed by aggressive behavior (case 6 and case 11). In the unresponsive and/or

TABLE 1.
Clinical Features of the 12 Patients With Anti-NMDA-Receptor Encephalitis in Taiwan

Author, yr	Sex/Age, yr	Tumor	Prodromal Symptoms	Neuropsychiatric Symptoms	Movement Abnormalities	Autonomic Dysfunction and Hypoventilation
Children (age ≤18 yr)						
Hung et al (2011)[6]	F/14	No	Headache, dizziness, and no fever	Mood lability, hallucination, mute, memory deficit, OCD, decreased consciousness, and seizure (GTC)	Orofacial dyskinesia	Insomnia, hypotension, and excessive sweating
Kuo et al (2012)[7]	F/16	No	Fever, cough, and rhinorrhea	Inappropriate laughing and sang loudly, agitation, bizarre behavior, hallucination, change in consciousness, and seizure (clonic)	Orofacial dyskinesia	Difficulty sleeping, hyperthermia, tachycardia, and hypoventilation*
Hsu et al (2013)[9]	F/7	Ovarian tumor	–	Intractable seizure, aggressive behaviors, talkative, and mutism	Orofacial dyskinesia	Hypoventilation‡
Hsu et al (2013)[9]	F/14	Ovarian tumor	–	Hallucination, depression, and mutism	Orofacial dyskinesia	Hypoventilation† and hypersalivation
Present study (2013)	M/15	No	Fever, cough, and rhinorrhea	Decreased consciousness, agitation, seizure, mood lability, and disorientation	Orofacial dyskinesia and dystonia	Hypoventilation*, hyperthermia, and bradycardia
Present study (2013)	F/15	No	Anorexia and nausea	Seizure (GTC), agitation, mood lability, decreased consciousness, and hallucination	Orofacial dyskinesia and dystonia	Hyperthermia, difficulty sleeping, hypertension, and urine retention
Adults (age >18 yr)						
Dou et al (2012)[8]	F/26	No	Fever and headache	Hallucination, seizure (GTC), and decreased consciousness	Orofacial dyskinesia and dystonia	Hyperthermia and hypoventilation‡
Present study (2013)	F/20	No	No	Decreased consciousness, agitation, seizure (focal), mood lability, disorientation, hallucination, and aphasia	Orofacial dyskinesia and dystonia	Insomnia, hyperthermia, sweating, dilated pupils, and hypoventilation†
Present study (2013)	F/23	No	No	Agitation, mood lability, hallucination, seizure (GTC), decreased consciousness, impaired speech, and memory deficit	Orofacial dyskinesia and dystonia	Insomnia, hyperthermia, tachycardia, urine frequency, and difficulty sleeping
Present study (2013)	F/24	No	Fever, nausea, and headache	Mood lability, disorientation, impaired speech, and seizure (focal)	Orofacial dyskinesia and dystonia	Urine retention, hypoventilation*, and tachycardia
Present study (2013)	M/20	No	Fever	Decreased consciousness, behavioral changes, visual abnormal, seizure, memory deficit, mood lability, and disorientation	Orofacial dyskinesia	Hypertension, tachycardia, and sleep dysfunction
Present study (2013)	F/28	Ovarian tumor	Cough, rhinorrhea, and no fever	Decreased consciousness, mood lability, hallucination, impaired speech, disorientation, and seizure (GTC)	Orofacial dyskinesia and dystonia	Hypertension, tachycardia and/or bradycardia, urine retention, ileus, hypothermia, and hypoventilation*

Abbreviations:
BiPAP = Biphasic positive airway pressure
GTC = Generalized tonic-clonic
NMDA = *N*-methyl-D-aspartate
OCD = Obsessive compulsive disorder
* Hypoventilation with intubation.
† Hypoventilation with BiPAP use.
‡ No mention of treatment.

catatonic phase, eight (66.7%) patients developed decreased consciousness, which progressed to a catatonic-like state, and seven (58.3%) patients had severe speech problems including speech reduction, aphasia, or mutism.

During the course of the disease, a large proportion of the patients developed the hyperkinetic phase, including 100% with orofacial dyskinesia and 58.3% with dystonic postures. In addition, most of the patients also developed autonomic

TABLE 2.
Summary of the Clinical Features of the 12 Patients With Anti-NMDA-Receptor Encephalitis in Taiwan

Characteristic	Children (n = 6)	Adults (n = 6)	Total (n = 12) (%)	*P* Value
Prodromal symptoms			7 (58.3)	
Fever	2	3	5 (41.7)	NS
Headache and/or dizziness	1	2	3 (25)	NS
Upper respiratory symptoms	2	1	3 (25)	NS
Nausea and/or vomiting	1	1	2 (16.6)	NS
Initial symptoms				
Psychiatric symptoms	4	6	10 (83.3)	NS
Neurological symptoms	2	0	2 (16.6)	
Symptom presentation				
Psychiatric symptoms				
Mood, behavior, or personality changes	6	5	11 (91.6)	NS
Hallucination (visual or auditory)	4	4	8 (66.7)	NS
Neurological symptoms				
Seizures	5	6	11 (91.6)	NS
Decreased consciousness	4	4	8 (66.7)	NS
Speech reduction or mutism	3	4	7 (58.3)	NS
Movement abnormalities				
Orofacial dyskinesia	6	6	12 (100)	NS
Dystonic postures	2	5	7 (58.3)	NS
Autonomic dysfunction and hypoventilation				
Cardiac dysrhythmias, unstable blood pressure, and hyperthermia and/or hypothermia	4	6	10 (83.3)	NS
Central hypoventilation	4	4	8 (66.7)	NS
Sleep dysfunction	3	3	6 (50)	NS

Abbreviations:
NMDA = *N*-methyl-D-aspartate
NS = Not significant

instability, including 10 (83.38%) with cardiac dysrhythmias, unstable blood pressure, and hyperthermia and/or hypothermia, and eight (66.7%) with central hypoventilation. Four patients required intubation for central hypoventilation, and one patient required bilevel positive airway pressure for airway protection. Six (50%) patients were also noted to have sleep dysfunction. However, there were no differences in the clinical manifestations between children and adults (Table 2).

Regarding the clinical manifestation of the disease, eight patients had prodrome phase. In children group, all patients developed the four-phase paradigm. However, in adult group, only one patient developed the typical four-phase paradigm. Three patients developed psychotic and/or seizure phase and unresponsive and/or catatonic phase at the same times, and one patient developed unresponsive and/or catatonic phase followed by psychotic and/or seizure phase. These four patients developed hyperkinetic phase and gradual recovery phase later. The other one patient developed psychotic and/or seizure phase followed by hyperkinetic phase, unresponsive and/or catatonic phase, and gradual recovery phase, respectively.

Ancillary tests

All the patients received magnetic resonance imaging, electroencephalography, and cerebrospinal fluid examinations. Nine patients had negative finding in magnetic resonance imaging and six patients had generalized or focal epileptic discharges. In case 11, brain magnetic resonance imaging revealed hyperintensity lesions in the bilateral occipital white matter on T2-weighted image and fluid-attenuated inversion recovery sequence (Figure A,B), but no significant abnormality on T1-weighted and gadolinium-enhanced T1-weighted images (Figure C,D). Cerebrospinal fluid studies revealed leukocyte counts of 0-123 cells/μL, 2-100% lymphocytes, and total protein levels of 21.1-280.51 mg/dL (Table 3). All had negative results for viral assays.

Three patients had an ovarian tumor identified by computed tomography or ultrasonography, two (66.6%) of whom were <18 years old. All of these patients developed neurological symptoms before the tumor diagnosis (2 months, 3 weeks, and 1 month, respectively, in case 3, 4, and 12). The pathology showed that two of the tumors were ovarian teratomas (case 3 and 4), and one was ovarian fibroma (case 12).

Treatment and outcomes

At the time of initial assessment, nine patients without tumors had been treated with first-line immunotherapy that consisted of a combination of corticosteroids, immunoglobulins, or plasma exchange. However, one patient who was resistant to these treatments received rituximab (case 5). Three patients with tumors underwent tumor resection, one of who did not receive immunotherapy (case 3), whereas the other two patients received immunotherapy (case 4 and case 12; Table 3).

One patient without a tumor was lost follow-up. The follow-up period ranged from 3 months to 4 years. In the patients without tumors, two had limited improvements, and the other six patients had substantial improvements at follow-up. In those with tumors, one patient had a substantial clinical improvement, and two patients had limited improvements. In case 12, the clinical condition was exacerbated after removal of the tumor. She was resistant to the combination of corticosteroids, immunoglobulins, and

plasma exchange, and she had a limited improvement after cyclophosphamide treatment. Overall, seven (63.6%) of 11 patients had a substantial recovery after immunotherapy or removal of the tumor.

Neurological relapses

One (9.1%) of the 11 patients had a neurological relapse (case 4) at follow-up. She had severe encephalitis-like and psychiatric symptoms before the diagnosis of ovarian teratoma, and the symptoms remitted 2 months after removal of the tumor. She relapsed into oromotor dyskinesia 2 years later, which subsided soon after the recurrent ovarian tumor was removed. The pathology demonstrated neuronal components in her teratoma.[9]

Discussion

Anti-NMDAR encephalitis is a severe but a potentially treatable disorder. The exact incidence is unknown; however, various studies have established the frequency of NMDAR antibodies in different populations. In one retrospective analysis of encephalitis of unknown origin, NMDAR antibodies were identified in 1% of the patients (aged 18-35 years) admitted to an intensive care unit.[12] In a multicenter, population-based prospective study on the causes of encephalitis in England, anti-NMDAR encephalitis was found in 4% of patients, and it was reported to be the second most common cause of immune-mediated encephalitis after acute demyelinating encephalomyelitis.[13] In the California Encephalitis Project, anti-NMDAR encephalitis was found in 4.2% of patients, which surpassed that of any specific viral cause in young patients.[14] In the current study, anti-NMDAR encephalitis was found in 3.7% of the patients with encephalitis of unknown etiology.

Approximately 80% of patients with anti-NMDAR encephalitis are female. It can occur in patients of all ages; however, it predominantly affects young adults and children.[1,2] In a case series of 400 patients, an underlying teratoma was detected more often in female patients >18 years.[14] These findings suggest that female patients with anti-NMDAR encephalitis should be screened for ovarian tumors, and periodic screening for ovarian teratomas for at least 2 years has been recommended even if the patients have recovered from encephalitis.[3] In the present study, 10 (83.3%) patients were female. All the patients were

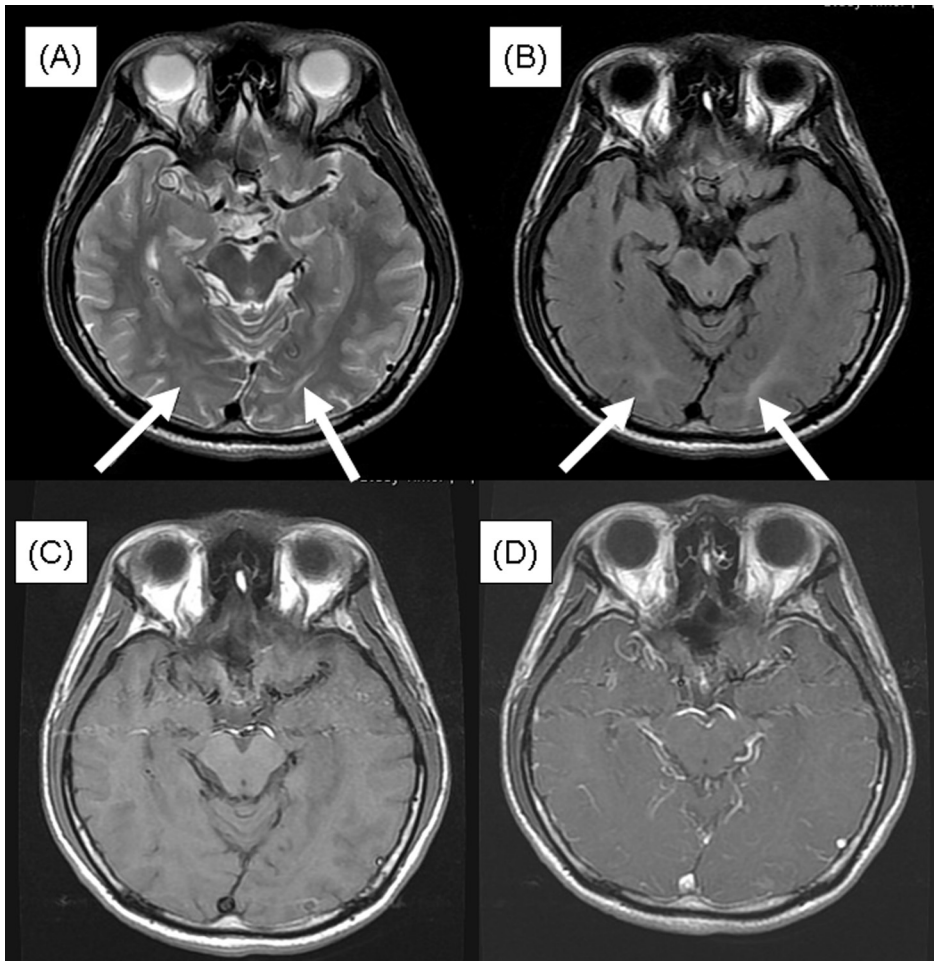

FIGURE.
In case 11, the brain magnetic resonance imaging of a 20-year-old male patient revealed hyperintensity lesions in the bilateral occipital white matter on T2-weighted image (A) (white arrow) and fluid-attenuated inversion recovery sequence (B) (white arrow), but no significant abnormality on T1-weighted and gadolinium-enhanced T1-weighted images (C and D).

TABLE 3.
Ancillary Tests, Treatment, and Outcomes of the 12 Patients With Anti-NMDA-Receptor Encephalitis in Taiwan

Author	CSF Finding			Brain MRI	EEG	Treatment	Outcome (Follow-up Time)
	Leukocytes, Cells/μL	TP, mg/dL	OCB				
Children (age ≤18 yr)							
Hung et al[6]	2	35.6	–	Negative	Slow background	MP and IVIG	Substantial improvement (mo)
Kuo et al[7]	Negative	–	–	Negative	Slow background	MP and IVIG	Loss follow-up
Hsu et al[9]	Pleocytosis	–	–	Right parietal hyperintensity	Focal ED	Tumor removal	Mutism; limited improvement (1 yr)
Hsu et al[9]	Negative	–	–	Negative	Negative	Tumor removal, IVIG, and MP	Substantial improvement* (3 yr)
Present study	123; 92% Lym	39	Negative	Effacement of the sulci	Generalized ED	MP, IVIG, and rituximab	Limited improvement (9 mo)
Present study	2; 100% Lym	21.1	Negative	Negative	Focal ED	MP and IVIG	Substantial improvement (5 mo)
Adults (age >18 yr)							
Dou et al[8]	261; 97% Lym	63	—	Negative	Slow background	MP, PE, and IVIG	Substantial improvement (mo)
Present study	74; 24% Lym	280.5	Positive	Negative	Focal ED	PE and MP	Substantial improvement (3 mo)
Present study	0	25.3	Negative	Negative	Focal with second generalized ED	Prednisolone	Limited improvement (4 yr)
Present study	58; 97% Lym	23.4	–	Negative	Slow background	PE and MP	Substantial improvement (3 mo)
Present study	5; 2% Lym	34	–	Bilateral occipital hyperintensity	Slow background	PE and MP	Substantial improvement (3 mo)
Present study	2; 55% Lym	44.1	–	Negative	Focal ED	Tumor removal, MP, PE, IVIG, and cyclophosphamide	Limited improvement (2 yr)

Abbreviations:
CSF = Cerebrospinal fluid
ED = Epileptiform discharge
EEG = Electroencephalography
IVIG = Intravenous immunoglobulin
Lym = Lymphocytes
MP = Methylprednisolone
MRI = Magnetic resonance imaging
NMDA = *N*-methyl-D-aspartate
OCB = Oligoclonal band
PE = Plasma exchange
TP = Total protein
* Remitted at 2 months, recurrent dyskinesia 2 years later, and remitted 1 month after tumor removal.

screened for ovarian teratomas, and three were found to have ovarian tumors identified with computed tomography or ultrasonography. Two of three patients were <18 years old. Therefore, we suggest that screening for ovary tumors should be performed in all female patients with anti-NMDAR encephalitis, including children and adults, with the presentation of encephalopathy with unknown etiology.

Anti-NMDAR encephalitis has highly characteristic clinical manifestations.[1-4] It usually presents with a prodrome of viral infection-like symptoms, followed by psychiatric manifestations, which progress to seizures, catatonia, dyskinesia, autonomic instability, and hypoventilation. However, the initial presentations vary between children and adults. In the first case series of anti-NMDAR encephalitis, which mostly included adults, 85% of the patients initially presented with psychiatric symptoms such as anxiety, agitation, paranoia, and visual or auditory hallucinations.[1] However, in another report, which included patients of all ages, most of the adolescents had similar symptoms to the adults, whereas 50% of the children <12 years presented with seizures or movement disorders.[5] The initial presentations are more often neurological in children and more often psychiatric in adults, and in most cases, the progression of symptoms evolves toward a similar course. In young children, the behavioral changes can be difficult to detect because they often present with temper tantrums, hyperactivity, or irritability as opposed to frank psychosis.[2] Therefore, the recognition of psychotic symptoms related to encephalopathy in younger children may be a challenge for pediatric physicians. In the present study, six (50%) of the 12 patients were <18 years and most initially presented with psychiatric symptoms similar to adults. However, two patients had seizures as the initial presenting symptom followed by aggressive behavior. Therefore, the initial presentation of seizures before the onset of psychotic symptoms is mostly seen in children with anti-NMDAR encephalitis and rarely in adults.

Seizures and status epilepticus may develop at an early stage or any time during the course of the disease. In general, the frequency and intensity of the seizures decrease as the disease evolves. The overlap of abnormal movements

and epileptic seizures can lead to underrecognition of the seizures or unnecessary escalation of antiepileptic medications for dyskinesia, which is interpreted as a seizure.[4,15] Therefore, video electroencephalography should be considered for such patients to appropriately diagnose and treat seizures or dyskinesia.

The management of anti-NMDAR encephalitis should initially focus on immunotherapy and the detection and removal of ovarian tumors.[1-5] In general, corticosteroids, immunoglobulin, or plasma exchange can be used as the first-line immunotherapy. If there is no response, second-line immunotherapy (rituximab or cyclophosphamide, or both) is usually required.[1-5] The outcomes are usually good; however, the recovery is slow.[4,5] Outcomes have been reported to continue to improve for up to 18 months after the onset of symptoms.[5] In a study by Titulaer et al.,[5] 81% of the patients with anti-NMDAR encephalitis who received immunotherapy and removal of tumors had substantial neurological improvements after a median follow-up of 24 months. In the present study, three patients with tumors underwent tumor resection, 11 patients received first-line immunotherapy, and two patients received second-line immunotherapy. At the end of follow-up, seven (63.6%) of the 11 patients had achieved a substantial recovery after immunotherapy or removal of tumors.

Conclusions

Anti-NMDAR encephalitis should be suspected in any patient who develops a rapid change in behavior or psychosis, seizures, orofacial and limb dyskinesia, and hypoventilation. All patients should be examined for the presence of an underlying tumor. It is important for neurologists to be familiar with the clinical presentations of the disease in children and young adults.

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