Screening Autoimmune Anti-neuronal Antibodies in Pediatric Patients with Suspected Autoimmune Encephalitis

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Background and Purpose: The aim of this study was to identify and describe the pediatric autoimmune encephalitis cases positive for anti-neuronal antibody tests.

Methods: Screening of six anti-neuronal antibodies in 23 children with suspected autoimmune encephalitis was performed by cell-based indirect immunofluorescence test with patients' serum or cerebrospinal fluid.

Results: Among the 23 cases enrolled here, eight patients (35%) were positive for the anti-N-methyl-d-aspartate (NMDA) receptor antibody and one patient (4%) was positive for the anti-contactin-associated protein-like 2 (CASPR2) antibody. In the anti-NMDA receptor antibody-positive group, seizure and movement disorders were the most prominent features and were present in all patients. A tumor was present in only one patient. Three patients with infant- and toddler-onset disease did not exhibit a classic multistage illness. In addition to seizure and dyskinesia, aphasia or mutism without severe consciousness impairment was present in all three patients. These atypical clinical presentations may suggest different pathomechanism of anti-NMDA receptor encephalitis among these age groups. The patient who was positive for the anti-CASPR2 antibody was an 8-year-old girl who presented with fever, encephalopathy, and seizure. Neuromyotonia or other dyskinesia was not present.

Conclusions: Eight anti-NMDA receptor antibody positive patients and one CASPR2 positive patient were identified from the screening of six anti-neuronal antibodies in pediatric patients suspected with autoimmune encephalitis. Developmental regression specifically for language skills was suggested as one of the atypical clinical features in infants and toddler onset anti-NMDA receptor antibody positive patients. **(2014;4:55-61)**

Key words: Autoimmune encephalitis, Anti-neuronal antibody, N-methyl-d-aspartate receptor, Contactin-associated protein-like 2, Pediatric

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Introduction

Since its initial description in 2007,[1] anti-N-methyl-d-aspartate (NMDA) receptor encephalitis has become one of the leading causes of autoimmune encephalitis. Since then, anti-neuronal antibodies, such as those against the alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor,[2] gamma-aminobutyric acid (GABA) receptor,[3] leucine-rich, glioma-inactivated 1 (LGI1),[4] and contactin-associated protein-like 2 (CASPR2),[5] have been identified as causing autoimmune forms of encephalitis. Although most of these antibodies were originally identified in the context of paraneoplastic syndrome, recent studies suggest that these antibodies are al-

so present in a group of patients with no detectable tumors.[6]

Currently, the incidence of anti-neuronal antibody-mediated autoimmune encephalitis is considered to be higher than that of encephalitis with other single viral causes. In the case of anti-NMDA receptor encephalitis, a multicenter study performed in the United Kingdom demonstrated that 4% of patients with encephalitis had anti-NMDA receptor antibodies.[7] Moreover, the frequency of anti-NMDA receptor encephalitis surpassed that of any viral encephalitis, according to the California Encephalitis Project.[8] The resulting syndromes vary according to the antibody and patients, and include diverse symptoms, such as behavioral changes, psychosis, seizures, memory deficit, dyskinesia, speech problems, autonomic dysregulation, and tumors.[9]

In the pediatric population, reports of anti-neuronal antibody-mediated autoimmune encephalitis have also been rapidly increasing, thus leading to an expansion of the clinical spectrum of this type of encephalitis. However, most of the reports were restricted to anti-NMDA receptor encephalitis or anti-voltage-gated potassium channel (VGKC) complex encephalitis. Very few studies have tested a series of anti-neuronal antibodies in a group of pediatric patients in whom autoimmune causes were suspected.[7,10] Thus, we simultaneously screened six anti-neuronal antibodies in patients with encephalitis without a proven infectious etiology, to evaluate the diagnostic yield of this strategy, and describe the clinical characteristics of these pediatric patients.

Methods

Patients

From July 2011 to June 2014, we selected 23 patients who were suspected to have acute encephalopathy in two institutes: Seoul National University Children's Hospital and Seoul National University Bundang Hospital. All patients were required to be immunocompetent, younger than 18 years, and present with acute encephalopathy plus one or more of the following features: seizure, dyskinesia, psychiatric symptom, and behavioral symptom. Among them, patients with a proven viral or bacterial etiology in the early stage of disease by culture, or with a strong suspicion of other central nervous system (CNS) inflammatory disease by imaging studies, such as acute disseminated encephalomyelitis, were excluded from the study. The patients who were enrolled here received a test for six anti-neuronal antibodies, simultaneously: anti-NMDA, anti-LGI1, anti-CASPR2, anti-AMPA1/AMPA2, and anti-GABA-B. Finally, 23 patients were enrolled. Five patients underwent the tests retrospectively with samples stored in advance, after recovery from the disease. Another 18 patients received a test prospectively. All patients were examined by pediatric neurology specialists and underwent electroencephalogram (EEG), magnetic resonance imaging (MRI), CSF analysis, and extensive bacterial and viral studies. Pelvis MRI or computed tomography (CT) was performed for tumor screening. Treatment decision was determined at the physician's discretion. The neurological status at the point of last follow-up was assessed with the modified Rankin scale (mRS), to evaluate treatment outcome.[11] Patients' clinical and laboratory information were recorded by physicians responsible for medical care, and were later reviewed by one of the authors. This study was approved by the Institutional Review Board of the Seoul National University Hospital (IRB No. 1402-016-553). Samples for antibody tests and all other medical information were collected after receiving written informed consent by each patient or their legal representatives.

Anti-neuronal antibody test

A cell-based indirect immunofluorescence test was used to detect the autoantibodies (anti-NMDA receptor, anti-LGI1, anti-CASPR2, anti-AMPA1 receptor, anti-AMPA2 receptor, and anti-GABA-b receptor). In brief, diluted patient's serum or CSF (1:10) was reacted with HEK293 cells transfected with plasmids containing human target gene sequences (Euroimmun AG, Lübeck, Germany), and fluorescein isothicyanate-labeled anti-human immunoglobulin G was used as the secondary antibody. A positive reaction was defined as the presence of cytoplasmic immunofluorescence.

Results

Among the 23 patients enrolled in the study, eight patients (35%, 8/23) were positive for the anti-NMDA receptor antibody and one patient (4%, 1/23) was positive for the anti-CASPR2 antibody.

Anti-NMDA receptor antibody-positive patients

These patients showed multistage or acute onset of neurological symptoms. Their clinical features, laboratory evaluation, treatment, and clinical outcomes are shown in Table 1 and 2. The mean age was nine years (range, 0-16 years) and six patients (75%, 6/8) were female. Among these eight anti-NMDA receptor antibody-positive patients, three (38%, 3/8) had experienced prodromal symptoms such as fever, headache, or a respiratory symptom prior to disease.

Table 1. Clinical features of eight patients with anti-NMDA receptor encephalitis

	Sex	Onset age (years)	Prodromal symptoms	Presenting symptoms	Seizure	Fever duration (days)	Behavioral / Psychiatric symptoms	Movement disorder	Autonomic symptoms	Aphasia / Mutism
Patient 1	F	0.6	–	Developmental regression	+	–	Irritability	Myoclonus, dystonic spasms	–	Possible
Patient 2	F	2.0	–	Seizure	+	13	–	Myoclonus (mild)	–	+
Patient 3	F	4.3	General malaise, sleep disturbance	Seizure	+	–	Irritability, aggressiveness	Myoclonus (frequent)	–	+
Patient 4	M	8.8	Headache	Behavioral / Psychiatric symptoms	+	18	Bizarre behavior, sleep disturbance, catatonia	Orofacial dyskinesia, myoclonus, chorea, dystonia,	–	–
Patient 5	F	12.5	–	Behavioral / Psychiatric symptoms	+	44	Bizarre behavior, hallucination, catatonia	Orofacial dyskinesia, chorea, dystonia	Hypertension, breathing abnormality	–
Patient 6	F	12.8	Fever, headache	Behavioral / Psychiatric symptoms	+	47	Bizarre behavior, hallucination	Orofacial dyskinesia, dystonia, chorea	Hypertension, breathing abnormality, bradycardia	–
Patient 7	M	13.9	–	Seizure	+	3	Bizarre behavior, catatonia	Orofacial dyskinesia, dystonia	–	+
Patient 8	F	16.8	–	Behavioral / Psychiatric symptoms	+	31	Bizarre behavior, agitation, violent behavior, catatonia	Orofacial dyskinesia, dystonia	Hypertension, breathing abnormality	–

NMDA, anti-N-methyl-d-aspartate.

Table 2. Laboratory evaluation, treatment, and outcome of eight patients with anti-NMDA receptor encephalitis

	Follow-up duration (months)	Tumor	CSF study		Other autoantibodies	Brain MRI	EEG	Onset to treatment (days)	Treatment	Final mRS
			WBC (/mm^3)	Protein (g/L)						
Patient 1	11	–	4	25	–	Negative except mild amount of bilateral subdural fluid collection	Bilateral temporo-occipital slowing with IEDs	54	IVIg, steroid	4
Patient 2	34	–	91	46	–	Negative	Generalized slowing with multifocal IEDs	14	IVIg	3
Patient 3	14	–	0	21	–	Negative	Normal	11	IVIg, steroid	0
Patient 4	17	–	8	25	FANA (+)	Negative	Generalized slowing	6	IVIg, steroid	0
Patient 5	11	–	16	30	–	Subtle gyral swelling at the temporal lobe	Generalized slowing, left temporal IEDs	16	IVIg, steroid, rituximab	0
Patient 6	6	–	514	63	–	Negative	Generalized slowing	4	IVIg, steroid, rituximab	5
Patient 7	18	–	0	93	–	Left precentral T2HSI	Generalized slowing	41	IVIg, steroid	0
Patient 8	24	Right ovary teratoma	2	19	–	Negative	Generalized slowing	31	IVIg, steroid, rituximab, tumor removal	1

NMDA, anti-N-methyl-d-aspartate; CSF, cerebrospinal fluid; MRI, magnetic resonance imaging; EEG, electroencephalogram; mRS, modified Rankin Scale; IED, interictal epileptiform discharge; IVIg, intravenous immunoglobulin; FANA, fluorescent antinuclear antibody; T2HSI, T2 high signal intensity.

Seizure was the initial manifestation in three patients (38%, 3/8). Behavioral or psychiatric symptoms were the first symptoms in four (50%, 4/8) patients. One 7-month-old girl (Patient 1) presented with developmental regression accompanied by loss of expressive language skills, including babbling or cooing. As the disease progressed, various types of seizure and movement disorders appeared in all patients (100%, 8/8) at the acute stage of the disease. Psychosis (defined by the presence of one or more symptoms, including bizarre behavior, hallucination, and catatonia) was present in five patients (63%, 5/8). Autonomic symptoms were present in three patients (38%, 3/8). Only one patient (Patient 8) had a tumor, right ovarian teratoma, which was removed for disease control. Three patients (Patients 1-3) showed selective aphasia or mutism without definite decrease in consciousness. One patient (Patient 7) who had underlying insulin-dependent diabetes mellitus and autism showed bizarre, violent behavior and loss of communication skills in his clinical course without decreased mentality. CSF analysis revealed pleocytosis in four patients (50%, 4/8) and elevated protein level in three patients (38%, 3/8). EEG showed generalized slowing of background activity in six patients (75%, 6/8). Focal epileptiform discharges were present in three patients (38%, 3/8). Brain MRI findings were mostly nonspecific, with the exception of subtle focal signal changes in two patients. All patients received both steroid and intravenous immunoglobulin (IVIg), and three patients received adjuvant rituximab. Seven patients were discharged to their homes and received regular outpatient checkups, whereas one patient remained under hospital treatment. The mean follow-up period in all patients was 16.8 months (range, 6-34 months). Five patients (63%, 5/8) had an mRS score of 0-1, which means that patients recovered to their premorbid state without any neurological sequelae or with minimal symptoms that did not cause any disabilities. Of the remaining three patients who had an mRS score of 2-6, two patients with developmental regression are recovering slowly, and one patient remains under hospital treatment.

Table 3. Clinical features and outcome of antibody-screening negative patients

Total number of patients	14
Sex (male:female)	8:6
Mean age of onset (years)	8.9 (range, 2-16)
Prodromal symptoms, n (%)	13 (93)
Presenting symptoms, n (%)	
Seizure	8 (57)
Movement disorder	0 (0)
Behavioral/Psychological symptoms	4 (29)
Others	2 (14)
Other manifestation in total hospital course, n (%)	
Seizure	10 (71)
Movement disorder	12 (86)
Behavioral/Psychological symptoms	8 (57)
Autonomic symptoms	7 (50)
Other autoantibodies, n (%)*	11 (79)
Anti-GAD antibody	5 (36)
Anti-La antibody	5 (36)
Anti-microsomal antibody	3 (21)
FANA	2 (14)
Anti-thyroglobulin antibody	2 (14)
Anti-GD1b antibody	1 (7)
Anti-ds DNA antibody	1 (7)
Anti-cardiolipin antibody	1 (7)
Anti-b2 glycoprotein antibody	1 (7)
Anti-Ro antibody	1 (7)
CSF analysis	
CSF pleocytosis, n (%)	5 (36)
Increased CSF protein, n (%)	5 (36)
Treatment modality, n (%)†	
Steroid	9 (64)
IVIg	11 (79)
Rituximab	1 (7)
Plasma exchange	2 (14)
None of the above	2 (14)
mRS, n (%)	
0	7 (50)
1	5 (35)
2	1 (7)
3	0 (0)
4	1 (7)
5	0 (0)
6	0 (0)

*Some patients showed positive results for several autoimmune-antibodies; †Some patients were treated with two or more modalities.
GAD, glutamic acid decarboxylase; FANA, fluorescent antinuclear antbody; CSF, cerebrospinal fluid; IVIg, intravenous immunoglobulin; mRS, modified Rankin scale.

Anti-CASPR2 antibody-positive patient

The patient with anti-CASPR2 antibodies was an 8-year-old girl. She exhibited fever as the first manifestation, followed by seizure, psychosis, and later, memory deficit. Fever was sustained for 10 days without definite signs of infection. Her brain MRI showed meningeal enhancement only, and EEG revealed a generalized slowing of background activity. The patient received both steroid and IVIg. She recovered slowly and was discharged to her home. Her final mRS score, which was evaluated 18 months after the disease onset, was 1. Although she suffered from intermittent seizure shortly after discharge, her seizure has become controlled with antiepileptic drugs.

Antibody-screening negative patients

Among the patients enrolled, 14 patients had a negative result in the anti-neuronal antibody screening. Clinical information, test results, and treatment outcome are shown in Table 3. Six of these patients were female. The mean age of disease onset was 8.9 years (range, 2-16 years). With the exception of one patient, all had prodromal symptoms including fever, headache, or signs of upper respiratory infection. Seizure was the initial presentation in eight patients (57%, 8/14), and behavioral or psychological symptoms were the first symptoms in four patients (29%, 4/14). None of the patients showed movement disorder as the first manifestation of the disease. Patients showed various manifestations in their entire hospital course. Specifically, seizure in 10 patients (71%, 10/14), movement disorder in 12 (86%, 12/14), behavioral or psychological symptoms in eight (57%, 8/14), and autonomic symptoms in seven (50%, 7/14) appeared. All patients underwent blood withdrawal and testing for other autoimmune antibodies. Eleven patients showed positive results for 10 kinds of other autoimmune antibodies, including anti-glutamic acid decarboxylase (GAD) antibody in five patients, anti-La antibody in five, and anti-microsomal antibody in three patients. Twelve patients received immunotherapy on the basis of clinical suspicion. Ten patients received immunotherapy with both steroids and IVIg, including one patient who received adjuvant plasma exchange, and one patient who received plasma exchange and rituximab. One patient received steroids only, and two received IVIg only. Two patients did not receive any immunotherapy. The mean follow-up period was 15.5 months (range, 2-32 months). Twelve patients (86%) who had an mRS score of 0-1 recovered to a premorbid state, whereas two patients who had an mRS score of 2-6 showed various degrees of sequeale, including frequent seizures, sustained dyskinesia, and impulse control disorder. In the two patients who did not receive immunotherapy, the mRS scores were 0 and 1, respectively.

Discussion

Although pediatric anti-neuronal antibody-mediated autoimmune encephalitis has been increasingly recognized, very few studies have screened various neuronal antibodies in a group of encephalitis patients who were suspected of having an autoimmune etiology. The present study, which tested six anti-neuronal antibodies, showed that nine out of 23 patients (45%, 9/23) had a positive result. Most of the positive test results were confined to anti-NMDA receptor antibody (eight out of nine positive patients). Finally, we report for the first time a pediatric CASPR2-positive patient who presented with encephalitis, despite the small number of patients enrolled in the study.

Although this number is small, the overall clinical features of the eight anti-NMDA receptor antibody-positive patients were consistent with those reported in previous pediatric studies.[12-14] A tumor was found in only one patient, despite of extensive tumor screening. Furthermore, seizure and dyskinesia were predominant initial clinical features, as well as during the entire disease course. Autonomic symptoms, including hypoventilation, were less prevalent compared with the results of previous adult reports.[14] However, on a closer look, an atypical presentation in infant and toddler patients could be clearly differentiated from the classic presentation of patients with older-age onset. Four patients (Patients 4-6 and Patient 8) exhibited a classic multistage illness that started as a brief period of behavioral and psychiatric symptoms and then progressed to persistent fever, severe impairment of consciousness, and severe movement disorder (including orofacial dyskinesia) that lasted from weeks to months. Three patients (Patients 1-3) with infant- and toddler-onset presented with either seizure or developmental regression. Fever either was absent or subsided within a short period. Aphasia or mutism was typically recognizable without profoundly decreased consciousness. These atypical clinical features in infants and toddlers have been increasingly reported and reviewed in the recent literatures.[15,16] Of the 10 infant- and toddler-onset patients listed in these reports, seven patients exhibited speech arrest or mutism, in addition to seizures, behavioral changes, and dyskinesia. Although the clinical features were not uniformly described in detail, most of the patients did not appear to experience typical multistage illness. Thus, aphasia or mutism needs to be carefully examined in this age group and warrants further research on the possible age-specific pathogenesis of anti-NMDA receptor encephalitis on language function and development.

Commonly, patients who are NMDA receptor positive receive steroids, IVIg, or plasma exchange as the first-line therapy. Moreover, if symptoms do not improve, second-line immunotherapy, such as rituximab, cyclophosphamide, or both could be added. To date, it has been believed that patients with a tumor show better treatment response, fewer relapse episodes, and need second-line immunotherapy less frequently compared with patients without a tumor, if the tumor was removed properly.[13,14] However, in this study, only three patients (38%), all aged above 12 years, received ad-

juvant rituximab, and all patients younger than 12 years showed a meaningful recovery with only steroids and IVIg. All treatment agents were administered if autoimmune encephalitis was suspected, before test results were reported. According to our data, only one patient had a tumor, one patient (Patient 8) exhibited hypoventilation requiring a mechanical ventilator, no patient passed away, and no patient had relapsed yet, although the follow-up period was rather short and variable.

Although the anti-CASPR2 antibody was reported in three pediatric patients with epilepsy of unknown cause,[17] this is the first report of a pediatric CASPR2-positive patient presenting with acute encephalitis. CASPR2 was identified as a component of the VGKC complex with LGI1 and Tag-1/contactin-2.[5] VGKC channelopathy was initially described in neuromyotonia, and subsequently Morvan's syndrome,[18] limbic encephalitis,[19] and epilepsy[20] in adults. Recently, reports of anti-VGKC complex autoantibody-positive patients have been increasing in the pediatric population.[7,10,21] However, specific anti-CASPR2 antibodies have never been identified in children presenting with acute encephalitis, even in cases of simultaneous testing in pediatric patients with anti-VGKC antibody.[10,22] Therefore, researchers considered that anti-VGKC antibodies do not work against LGI1 or CASPR2 in the pediatric population.[22,23] The anti-CASPR2-positive case presented in our study may be an index in an expanding spectrum of pediatric autoimmune encephalitis, even though anti-VGKC testing was not performed in this study.

In the antibody-screening negative group, it was remarkable that the detection rate of other autoantibodies was high. The anti-GAD and anti-La antibodies were present in five patients each, and autoantibodies against the thyroid, such as the anti-microsomal antibody or anti-thyroglobulin antibody, were detected in five patients. Among the 12 patients who received immunotherapy, 10 showed recovery to a premorbid state (mRS score, 0-1). Although they received other treatments, such as antibiotics or antiviral agents concomitantly, the high detection rate of other autoantibodies and the high response rate to immune-modulating treatment suggest the contribution of autoimmune etiology to pathogenesis and warrant further research to differentiate the known anti-neuronal antibody-mediated autoimmune encephalitis. In fact, the association between the anti-GAD antibody and nonparaneoplastic limbic encephalitis has been increasingly reported in the literature[24-26] and its pathogenesis is being investigated actively.

Autoimmune encephalitis caused by anti-neuronal antibodies represents a new category of noninfectious encephalitis that is treatable and can be diagnosed easily. Although we identified the first pediatric patient with anti-CASPR2 encephalitis, most of the screening-positive patients were restricted to anti-NMDA receptor encephalitis, warranting further search for a new CNS-specific autoantibody. When considering expanding the clinical spectrum of these diseases, especially in infant- and toddler-onset anti-NMDA receptor encephalitis, testing a broad spectrum of suspected patients is recommended.

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Author contributions

Study concept and design: Byung Chan Lim and Soo Yeon Kim, *Acquisition of clinical data*: Soo Yeon Kim, Sun Ah Choi, and Hye Won Ryu, *Drafting of manuscript:* Byung Chan Lim and Soo Yeon Kim, *Anti-neuronal antibody test*: Soon-Tae Lee, Kon Chu, and Sang Kun Lee, *Critical revision of the manuscript for important intellectual content:* Hunmin Kim, Hee Hwang, Jong-Hee Chae, Jieun Choi, Ki Joong Kim, and Yong Seung Hwang, *Obtained funding*: Ki Joong Kim.

Conflict of interest

All authors have no conflict of interest to disclose.

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Ethical approval

This study was approved by the Institutional Review Board of the Seoul National University Hospital (IRB No. 1402-016-553).

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