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Anti-N-Methyl-D-Aspartate Receptor Encephalitis in Korea: Clinical Features, Treatment, and Outcome

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Background and Purpose Anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is the most common type of autoimmune synaptic encephalitis and it often responds to treatment. We analyzed the clinical characteristics of anti-NMDAR encephalitis in Korea.

Methods Serum and/or cerebrospinal fluid (CSF) of adult patients (aged ≥18 years) with encephalitis of undetermined cause were screened for anti-NMDAR antibodies using a cell-based indirect immunofluorescence assay. The patients came from 41 university hospitals.

Results Of the 721 patients screened, 40 were identified with anti-NMDAR antibodies and clinical details of 32 patients were obtained (median age, 41.5 years; 15 females). Twenty-two patients (68.8%) presented with psychiatric symptoms, 16 (50%) with seizures, 13 (40.6%) with movement disorders, 15 (46.9%) with dysautonomia, 11 (34.4%) with memory disturbance, and 11 (34.4%) with speech disturbance. Magnetic resonance imaging, electroencephalography, and CSF examinations yielded nonspecific findings. Tumor information was only available for 22 patients: 5 patients had tumors, and 2 of these patients had ovarian teratomas. Twenty-two patients received immunotherapy and/or surgery, and therapeutic responses were analyzed in 21 patients, of which 14 (66.7%) achieved favorable functional outcomes (score on the modified Rankin Scale of 0–2).

Conclusions This study investigated the clinical characteristics of adult anti-NMDAR encephalitis in Korea. Currently, elderly patients who do not have tumors are commonly diagnosed with this condition. Understanding the detailed clinical characteristics of this disease will improve the early detection of anti-NMDAR encephalitis in patients both young and old.

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Introduction

Anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis belongs to a new category of immune-mediated disorders that are often paraneoplastic, treatable, and can be diagnosed serologically.[1-4] In 2005, high levels of antibodies were detected against an antigen in the hippocampus of four women with ovarian teratomas who presented with prominent psychiatric symptoms, memory loss, and a decreased level of consciousness.[1] The target antigen was identified as NMDAR in 2007,[2] since when research into this disease has expanded rapidly.

Alongside the increasing attention paid to this disease and the development of the anti-NMDAR antibody assay, the frequency of diagnoses of anti-NMDAR encephalitis has sur-

passed that of any individual viral etiology;[5] moreover, the spectrum of manifestations of anti-NMDAR encephalitis has expanded. Patients with isolated psychiatric symptoms[6] and exclusive or predominant seizure presentations[7] have been identified. In addition, children and elderly patients have been diagnosed with this disease despite their lower incidence of tumor as a presenting symptom.[4] Some patients with herpes simplex encephalitis have also developed anti-NMDAR encephalitis.[8] Finally, microdeletion in the chromosome involving the human leukocyte antigen cluster was detected in a 3-year-old boy who presented with anti-NMDAR encephalitis at 1 month after a respiratory infection,[9] suggesting that genetic factors predispose individuals to this variant of autoimmunity.

There have been a few reports of patients with anti-NMDAR encephalitis in Korea;[10,11] however, none of these have described a large series of patients. The aim of the current study was to characterize the clinical presentation, spectrum of symptoms, laboratory findings, responses to immunotherapy, and functional outcomes in encephalitis patients harboring anti-NMDAR antibodies.

Methods

This study included as subjects 721 adult patients (aged 18 years or older) who were suspected of having encephalitis of undetermined cause. Patients were either treated at the Seoul National University Hospital (SNUH) or, if they were treated at one of 40 other university hospitals in South Korea, had their samples sent to SNUH between June 2012 and July 2013. human embryonic kidney 293 cells expressing the NR1 subunit of NMDARs were used for the indirect immunostaining of patients' serum and/or cerebrospinal fluid (CSF) (Euroimmun, Lübeck, Germany). The kit used in this study was designed to detect an IgG antibody against NMDAR. The assay was performed in the Department of Neurology, SNUH.

Symptoms were categorized into the following eight groups: psychiatric symptoms, memory deficits, speech disturbances, seizures, movement disorders, loss of consciousness, autonomic instability, and central hypoventilation.[4] Brain magnetic resonance imaging (MRI), CSF examinations, electroencephalography (EEG), and radiologic screening for a systemic neoplasm were reviewed. Individual or combined use of corticosteroids, intravenous immunoglobulins, or plasmapheresis was defined as first-line immunotherapy, while administration of rituximab and cyclophosphamide was defined as second-line immunotherapy.[4] The treatment effect and outcome were assessed using the modified Rankin Scale (mRS) at 4 weeks after the initiation of immunotherapy. Favorable and poor functional outcomes were defined as mRS scores of 0−2 and 3−6, respectively. This study was approved by the institutional review board of SNUH.

Symptoms were analyzed with the Fisher exact test by directly comparing patients with poor and favorable outcomes. Factors affecting outcome were assessed using univariate binary logistic regression analysis. Variables that were associated with outcome included age, symptoms (psychiatric symptoms, memory deficits, speech disturbances, seizures, movement disorders, loss of consciousness, autonomic instability, and central hypoventilation), the presence of a tumor, time from symptom onset to initiation of immunotherapy, and maximum mRS score before immunotherapy. Kendall's tau-b was used in correlation analyses. SPSS 18.0 (SPSS Inc., Chicago, IL, USA) was used for all analyses, and $p<0.05$ was considered to be indicative of statistical significance.

Results

Forty patients (20 patients from SNUH and 20 patients from other university hospitals) tested positive for antibodies against NMDAR. Antibodies were tested both in serum and CSF in 17 patients and only in serum in 13 patients, and no information on the remaining 10 patients. Clinical details of 8 patients were not obtained; 15 of the remaining 32 patients were females (46%), and their ages ranging from 19 to 80 years (median, 41.5 years). Table 1 summarizes the clinical characteristics of this group. The most common clinical features during the first 3 weeks of symptom presentation were psychiatric symptoms (n=22, 68.8%). Nine patients (40.9%) had auditory or visual hallucinations, five (22.7%) exhibited aggressive behavior, and three (13.5%) had delusional thinking. Three patients had a documented mood disorder, four patients showed bizarre behavior, and one patient had anxiety. Seizure was experienced by 16 patients (50%), among which 6 presented with nonconvulsive status epilepticus. Thirteen

Table 1. Characteristics and clinical symptoms of patients

Characteristic/symptoms	
Number	32
Age, years, median (range)	41.5, 19–80
Females, number (%)	15 (46.0)
Cumulative symptoms during first 3 weeks, number (median day of onset)	
Psychiatric symptoms	22 (0)
Memory deficit	11 (7)
Speech disorder	11 (1)
Seizure	16 (1.5)
Movement disorder	13 (11)
Loss of consciousness	9 (4)
Autonomic instability	15 (5)
Central hypoventilation	3 (6)

patients (40.6%) developed dyskinesia and movement disorders, 15 (46.9%) exhibited autonomic instability, 11 (34.4%) demonstrated memory disturbance, 11 (34.4%) displayed speech disturbance, 9 (28.1%) demonstrated a decreased level of consciousness, and 3 (9.4%) presented with hypoventilation. Psychiatric disorders, speech disturbances, and seizures appeared within the first few days, whereas movement disorders and autonomic instabilities developed later. Atypical features such as dizziness (n=1), brainstem sign (n=1), and weakness of lower extremities (n=1) were also noted. Twenty patients (62.5%) developed at least three of the eight categories of symptoms.

Table 2 presents the brain MRI, EEG, and CSF findings. No abnormality was detected in 16 of the 31 patients (51.6%) who underwent brain MRI. An increased signal on MRI fluid-attenuated inversion recovery or T2-weighted sequences was evident in 10 patients (43.5%). One patient had abnormalities in the medial temporal lobes and cerebral cortex, two in the medial temporal lobe, five in the cerebral cortex, two in the periventricular or subcortical white matter, one in the cerebellum, and one in the basal ganglia. Three patients showed MRI contrast enhancement of the cerebral cortex and meninges. EEG findings were abnormal in 22 out of 29 patients whose EEG data was available for review: 10 (34.5%) had generalized or predominantly frontotemporal slow or disorganized activity, and 12 (41.4%) had epileptiform discharges. The results of CSF examinations were obtained from 26 patients. Five patients had CSF pleocytosis only, three had increased protein concentration only, and ten patients had both pleocytosis and increased protein concentration. CSF samples from nine patients were analyzed for viral polymerase chain reaction (PCR) and antibodies, which revealed that four were positive for the Epstein-Barr virus.

Table 2. Results of ancillary tests

Test	Number
Brain MRI (information from 31 patients)	
Total abnormal findings	16
Medial temporal lobes	3
Cerebral cortex	7
Cerebellum	0
Basal ganglia	1
Contrast enhancement in cortex/meninges	3
Periventricular or subcortical white matter	3
EEG (information from 29 patients)	
Total abnormal findings	22
Slow activity*	10
Epileptic activity	12
CSF (information from 26 patients)	
Total abnormal findings	18
Pleocytosis	15
Increased protein concentration	13

*EEG delta or theta activity, generalized or in the frontotemporal regions.

The results of radiologic screening for a systemic neoplasm were available for 22 of these patients. Six patients (27.3%) were identified as having a neoplasm: ovarian teratoma was identified in 2 patients, breast cancer in 2 patients, and colon cancer in 1 patient. The other patient had non-small-cell lung cancer and had already received treatment.

Of the 29 out of 32 patients for whom information about immunotherapy was available, 22 were treated with immunotherapy and/or surgery. In this treated group of patients, 14 received first-line immunotherapy and 8 received both first- and second-line immunotherapies. Two patients with ovarian teratomas and one patient with colon cancer underwent both tumor resection and immunotherapy; the remaining seven patients did not undergo either immunotherapy or surgery due to patient refusal after spontaneous improvement (n=3), loss to follow-up (n=3), or death before the autoantibody results were obtained (n=1). Of the 21 patients with ≥4 weeks of follow-up after initiation of immunotherapy (median follow-up period, 4 months; range, 1−12 months), 14 (66.7%) had favorable functional outcomes and 7 (33.3%) had poor functional outcomes. The two patients with teratomas showed favorable outcomes. Loss of consciousness, dysautonomia, and central hypoventilation were more common in patients with poor outcomes than in those with favorable outcomes (62.5% vs. 11.8%, p=0.017; 87.5% vs. 41.2%, p=0.042; and 37.5% vs. 0%, p=0.024; respectively). According to our univariate analysis, the factors associated with poor outcome were decreased consciousness and dysautonomia (Table 3). Early treatment (within 1 month of symptom onset) appeared to affect the clinical outcome, but this relationship was not statistically significant (τ_b=-0.403, p=0.063).

Discussion

This is the first reported case series of Korean patients with adult-onset anti-NMDAR encephalitis. The median age was 41.5 years and no gender difference was identified in this sample. Many patients presented with psychiatric symptoms, seizures, movement disorders, memory disturbances, and/or reduced level of consciousness. Tumors were detected in 6 of

Table 3. Factors associated with poor outcome (mRS score of 0–2) by univariate analysis

	p	Odds ratio (95% confidence interval)
Loss of consciousness	0.016	12.50 (1.60–97.64)
Autonomic dysfunction	0.031	12.83 (1.26–130.51)

mRS: modified Rankin Scale.

the 22 patients, of which 2 had ovarian teratoma. Twenty-two patients received immunotherapy and 14 of the 21 patients showed favorable functional outcomes after a median follow-up period of 4 months. Patients who presented with decreased consciousness and autonomic instability had the poorest outcomes.

According to previous studies,[1-4] anti-NMDAR encephalitis is predominantly found in young females with prominent psychiatric symptoms, catatonia, agitation, seizures, decreased level of consciousness, abnormal movements, and autonomic instability. Among the large study cohort (577 cases) of anti-NMDAR encephalitis described by Titulaer et al.,[4] 38% of patients had tumors and 94% of the tumors were ovarian teratomas. Moreover, most patients with anti-NMDAR encephalitis in that study cohort responded to immunotherapy. Most of the patients in the present study initially presented with psychiatric symptoms, followed by symptoms of movement disorder and dysautonomia; additionally, most had favorable outcomes following immunotherapy, which is in agreement with previous findings.[1-4,12] However, the median age in the present study was higher than that in previous reports involving American cohorts. Furthermore, there was no predominance of female patients in the present study, and only 6 of 22 patients (27.3%) had tumors.

This study was carried out only in adult subjects, because pediatric physicians did not participate in patient referral. Thus, the exclusion of patients younger than 17 years of age might have resulted in the demographic characteristics differing between our study and previous studies.[1-4] In a recent study[13] that showed the clinical features and outcome of anti-NMDAR encephalitis in patients ≥45 years old compared with younger adults (18−44 years), the listed patient demographics (median age, 52 years; range, 45−84 years; 45% males) were similar to those of our study. Indeed, similar to our findings, the patients in that previous investigation exhibited a lower incidence of tumors (23%) with few teratomas. The patients in that study had less severe symptomatology; however, delays in diagnosis were more common and patients showed overall poorer outcomes than did the younger adults.

Anti-N-methyl-D-aspartate receptor encephalitis has been identified only very recently and therefore is still underrecognized by clinicians. Consequently, many young female patients exhibiting psychiatric features due to anti-NMDAR encephalitis may be admitted to psychiatric wards. Movement disorders such as dyskinesia, rigidity, and hyperthermia are common symptoms of anti-NMDAR encephalitis. However, muscle rigidity is also a symptom of neuroleptic malignant syndrome, which is caused by adverse reactions to neuroleptic and antipsychotic drugs. Therefore, patients with anti-NMDAR encephalitis may be commonly misdiagnosed as having psychiatric disorders. The low rates of diagnosis of this disease in Korea might also have contributed to differences in results between this study and other studies. The possibility of bias due to misdiagnosis of this condition as a psychiatric disorder in young patients also cannot be excluded. Interestingly, a study of anti-NMDAR encephalitis that mainly involved European subjects[12] found no definite female predominance (11 of the 34 adult patients were male), and only 26% of the tumors were ovarian teratomas. Considering that most subjects in previous studies have been patients from North America, these demographic differences might indicate a genetic predisposition to this disease.

Some of our patients with anti-NMDAR encephalitis had positive PCR results for the Epstein-Barr virus in their CSF. Anti-NMDAR antibodies [immunoglobulin G (IgG), immunoglobulin A (IgA), immunoglobulin M (IgM)] were recently detected in 30% (13/44) of patients with PCR-proven herpes simplex encephalitis.[9] This finding might be due to a secondary immunological phenomenon that follows viral infection. In that study, anti-NMDAR antibodies of the IgA, IgG, and IgM classes were present in nine, five, and nine cases, respectively. In two patients, anti-NMDAR antibodies were only reactive with NR1a/NR2b subunit-transfected cells (not the NR1a subunit alone), suggesting that different antibody repertoires can exist in patients with herpes simplex encephalitis and classical anti-NMDAR encephalitis. Interestingly, the same research group has reported a case where synthesis of anti-NMDAR antibodies began subsequent to the onset of herpes simplex encephalitis.[14] More extensive studies are needed to confirm the relationship between anti-NMDAR antibodies and viral encephalitis.

The application of immunotherapy produced favorable outcomes in 66.7% of the patients in the present study. We could not compare outcomes between patients with and without immunotherapy because only seven patients did not receive immunotherapy, and three of those were lost to follow-up. The patients who received second-line treatment after failing first-line treatment had better outcomes than those who did not receive second-line treatment.[4] However, we could not evaluate the efficacy of additional second-line treatment because almost all of our patients who failed to respond to first-line immunotherapy underwent second-line treatment. Furthermore, those few patients who were in very poor condition and did not undergo immunotherapy could not be treated as control patients for comparison. Nevertheless, the prognosis in patients with an early onset of immunotherapy tended to be good, as demonstrated previously.[4]

The present study was subject to some limitations. First, we did not validate our results in a referral laboratory; we used only cell-based assays for the diagnosis of anti-NMDAR en-

cephalitis. Irani et al.[12] reported that cell-based assays were more sensitive and specific for diagnosis than were quantitative fluorescent immunoprecipitation assays. Differences in demographic findings might therefore have resulted from the high sensitivity of our diagnostic method. Second, our study had a short follow-up period. Titulaer et al.[4] followed anti-NMDAR encephalitis patients for a median duration of 24 months. Forty-five of 577 patients in that study experienced clinical relapses, new onset of symptoms, or worsening of symptoms after at least 2 months of improvement or stabilization. We could not assess the probability of relapse in the present study due to our short follow-up period. Third, we enrolled only adult patients, which might have resulted in our patients being older and more often being male compared to the patient samples of previous studies.

Elderly patients without tumors were common in our cohort of patients with anti-NMDAR encephalitis, and there was no gender difference in the diagnosis of this condition. Increasing awareness of this disorder has resulted in the expansion of the clinical spectrum of this disease. Genetic or racial predisposition, secondary autoimmune mechanisms after viral infection, and underrecognition of anti-NMDAR encephalitis in Korea are all factors that may have contributed to bias in the patients included in the current study. However, the reported results will promote an improved understanding of the clinical characteristics of this disease, which will likely aid efforts at early detection, in turn leading to improved functional outcomes following the early onset of immunotherapy.

Conflicts of Interest

The authors have no financial conflicts of interest.

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