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Clinical Features and Treatment Outcomes of Seronegative Pediatric Autoimmune Encephalitis

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Background and Purpose New diagnostic criteria for pediatric autoimmune encephalitis (AIE) have been introduced recently. A substantial proportion of cases of pediatric AIE are diagnosed as seronegative based on these criteria, and so the clinical characteristics of this group remain to be investigated.

Methods This study included 46 pediatric patients younger than 18 years with suspected AIE. Clinical features, laboratory or radiological findings, and treatment outcomes were compared between seronegative and seropositive patients.

Results Nine (19.6%) of the 46 patients were diagnosed as seropositive AIE. All of the patients with seropositive AIE had anti-*N*-methyl-D-aspartate receptor antibodies. Commonly identified neuropsychiatric symptoms were altered mental status, cognitive dysfunction, seizure, speech dysfunction, and psychotic disorder in both the seronegative and seropositive groups. Immunotherapy produced favorable treatment outcomes in both the seropositive (n=7, 77.8%) and seronegative (n=35, 94.6%) AIE patients. Treatment outcomes for first-line immunotherapy were better in seronegative AIE than seropositive AIE patients (p=0.003), and hence a smaller proportion of seronegative patients required second-line treatment (p=0.015).

Conclusions Pediatric seronegative AIE patients showed clinical presentations similar to those of seropositive AIE patients, with favorable treatment outcomes after immunotherapy.

Key Words encephalitis, autoimmune encephalitis, seronegative encephalitis.

INTRODUCTION

Autoimmune encephalitis (AIE) is a neuroinflammatory disorder characterized by diverse neuropsychiatric symptoms and autoantibodies targeting neuronal antigens.[1-4] After the initial discovery of antibodies against the *N*-methyl-D-aspartate receptor (NMDAR) in 2007,[5] several more antibodies against neuronal cell surface or synaptic antigens, intracellular antigens, or onconeuronal antigens have been identified.[6] However, most AIE cases remain seronegative, with precise mechanisms still being investigated.[7-9]

Differentiating pediatric from adult cohorts has recently been emphasized when identifying clinical features and treatment outcomes. Therefore, a diagnostic approach to AIE has been proposed specifically for pediatric cohorts.[10,11] Clinical presentations of AIE in pediatric patients differ in several ways from those in adult-onset AIE patients: 1) seropositive patients present with a narrower range of autoantibodies targeting mostly anti-NMDAR, anti-GABA-A receptor, and anti-GAD65; 2) most patients present as clinically ill-defined seronegative syndromes; and 3) numerous differential diagnoses are present according to the developmental status.[12-14] However, few studies have exclusively investigated pediatric cohorts, and most of the studies conducted in pediatric patients have focused on patients

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who were diagnosed as anti-NMDAR encephalitis.[15,16] More data are therefore needed on seronegative AIE in children.

This study identified cases of seronegative AIE and compared their clinical features, disease severity, and treatment outcomes with those for seropositive AIE. The findings of this study will provide an outline for clinicians to use when diagnosing and maintaining treatment in pediatric AIE patients.

METHODS

Patient selection

We selected patients who were initially diagnosed with suspected encephalitis, tested for an autoantibody panel of AIE, and confirmed with AIE at a single center, Severance Hospital, from June 2016 to June 2020. We only included pediatric patients younger than 18 years with suspected AIE who were followed up for at least 1 year. Seropositive and seronegative AIE were clinically diagnosed based on the recent report of Cellucci et al.[11] Both seronegative-possible and seronegative-probable AIE were defined as seronegative AIE when alternative diagnoses were excluded. We excluded patients who were diagnosed with any of the following conditions: 1) infectious encephalitis with laboratory evidence of central nervous system infection; 2) various neuroinflammatory disorders, such as acute disseminated encephalomyelitis or febrile illness-related epilepsy syndrome; 3) primary psychiatric disorders; or 4) previous primary neurological disorder that might have been the cause of the clinical presentation. This study was approved by the institutional review boards of Severance Hospital (4-2020-0687).

Clinical evaluation

Demographic characteristics of the patients were collected through a review of electronic medical records. Clinical evidence of neuropsychiatric dysfunction included 1) altered mental status, 2) focal neurological deficit, 3) cognitive dysfunction, 4) acute developmental regression, 5) movement disorder, 6) seizure, 7) speech dysfunction, 8) psychotic symptoms, 9) sleep disorder, or 10) autonomic dysfunction. Furthermore, information was obtained on the presence of prodromal symptoms, a vaccination history, age at onset, sex, initial disease severity, and treatment outcomes. Disease severity and treatment outcomes were determined by obtaining modified Rankin Scale (mRS) scores at the onset of symptoms, before and after each immunomodulatory treatment, and at the final end point (1 year after clinical onset).[17-19] The presence of tumor (e.g., ovarian teratoma) was investigated using abdominal pelvic computed tomography (CT) or sonography. The duration of stay in the intensive care unit was also reviewed. Electroencephalographic findings were further reviewed for epileptiform discharges and encephalopathic background, such as diffuse or focal slowing.

Laboratory test results were also collected. The findings of blood tests, urine analysis, and initial cerebrospinal fluid (CSF) analysis with CSF culture and polymerase chain reaction analysis for infectious encephalitis (HSV-1, HSV-2, EBV, CMV, VZV, enterovirus, and panel for bacterial encephalitis) were obtained in order to identify and exclude other possible etiologies of encephalopathy. CSF inflammatory change was defined as leukocytosis >5 cells/mm^3, elevated protein levels, and/or oligoclonal banding.

Radiological findings were acquired, and a diagnosis was made based on magnetic resonance imaging (MRI) of the brain. Features of encephalitis according to brain MRI (e.g., increased T2/FLAIR signal intensity in the mesial temporal lobes) were identified as paraclinical evidence of neuroinflammation. In some patients with normal brain MRI findings, positron-emission tomography/CT (PET-CT) of the brain was conducted to identify brain dysfunction and neuroinflammation.

Immunomodulatory therapy

Since the early initiation of primary immunotherapy enhances treatment outcomes in AIE, our patients received immunomodulatory agents as soon as AIE was diagnosed.[20] For first-line immunotherapy, separate or combined use of high-dose dexamethasone (0.6−0.8 mg/kg/day), pulsed intravenous methylprednisolone (20−30 mg/kg/day for 3−5 days), intravenous immunoglobulin (2 g/kg over 2−5 days), or therapeutic plasma exchange (5−10 exchanges every other day) was initiated in our center. If the symptoms were not relieved within 2 weeks, second-line immunotherapy was initiated with rituximab (375 mg/m^2 weekly for 4 weeks) or cyclophosphamide (750 mg/m^2 monthly). When the patients did not improve, tocilizumab (4−8 mg/kg monthly) was tried as third-line immunotherapy. Finally, for those with prolonged symptoms or frequent relapses, chronic immunosuppression with monthly administration of methylprednisolone or immunoglobulins, oral prednisone (1 mg/kg/day), mycophenolate mofetil, or azathioprine was considered as maintenance treatment.

Antibody screening

Patient sera and CSF specimens were initially collected and sent to a laboratory at Seoul National University for the detection of autoantibodies.[21,22] A cell-based indirect immunofluorescence test was used to detect autoantibodies to anti-NMDAR, anti-LGI1, anti-CASPR2, anti-AMPA1 receptor, anti-AMPA2 receptor, and anti-GABA-B receptor. In brief, diluted patient sera and CSF (1:10) were reacted with HEK293 cells transfected with plasmids containing human target gene

sequences (Euroimmun, Lübeck, Germany), and fluorescein-isothiocyanate-labeled antihuman immunoglobulin G was used as the secondary antibody. A positive reaction was defined as the presence of cytoplasmic immunofluorescence.

Statistical analysis

The clinical features of patients according to serological status were compared in order to identify the associated factors. Numerical and categorical data were compared between two groups using Student's *t*-test, Mann-Whitney test, chi-square test, or Fisher's exact test, as appropriate. A linear mixed model was used to identify the factors associated with treatment outcomes in seronegative AIE. Treatment outcomes of seropositive AIE patients and seronegative AIE patients after the second-line or maintenance treatment were not included in the model due to the small cohort.

The Statistical Package for the Social Sciences (version 23.0, IBM Corp., Armonk, NY, USA) was used for all statistical analyses, and p values <0.05 were considered statistically significant. Data are presented as number and percentage, mean±standard deviation, or median and interquartile range (IQR) values.

RESULTS

Patient demographics

This study reviewed 92 patients who were diagnosed with suspected encephalitis. Upon applying the diagnostic criteria recently proposed by Cellucci et al.[11] and excluding patients with alternative diagnoses, 46 patients were finally diagnosed as AIE. Nine (19.6%) patients tested positive for antibodies, all of which were anti-NMDAR encephalitis. The remaining 37 (80.4%) seronegative AIE patients comprised 10 (21.7%) diagnosed as possible AIE and 27 (58.7%) diagnosed as seronegative-probable AIE.

The 46 AIE patients included 22 (47.8%) males. The age at disease onset was 9.6±4.6 years. Twenty-nine patients were evaluated for a possible tumor, and two (6.9%) seropositive AIE patients were diagnosed with ovarian teratoma, which was treated by surgical removal. Prodromal symptoms and a vaccination history before the clinical onset of AIE were noted in 36 (78.3%) patients, with the most common symptom being fever (*n*=30, 65.2%). The most frequent neuropsychiatric symptom at the initial admission was seizure (*n*=28, 60.1%). Inflammatory changes in the CSF were diagnosed in 26 (56.5%) patients, and abnormal MRI findings suggestive of AIE were noted in 21 (45.7%) patients. Brain biopsy was not performed in our cohort. Electroencephalographic signals exhibited slow and disorganized backgrounds in all of the patients, and focal epileptic discharges or slowing was diagnosed in 20 (43.5%) patients.

The most common clinical feature of neuropsychiatric dysfunction in our cohort during the follow-up period was psychiatric symptoms (*n*=40, 85.1%), followed by speech dysfunction (*n*=38, 82.6%), seizure (*n*=37, 80.4%), altered mental status (*n*=36, 78.3%), cognitive dysfunction (*n*=36, 78.3%), movement disorder (*n*=28, 60.9%), acute developmental regression (*n*=27, 58.7%), sleep disorder (*n*=22, 47.8%), autonomic dysfunction (*n*=17, 37.0%), and focal neurological deficit (*n*=4, 8.7%). Forty-two (91.3%) patients had at least four neuropsychiatric features.

Clinical characteristics and treatment outcomes

The sex ratio did not differ significantly with the serological status, with 3 of 9 (33.3%) male patients diagnosed as seropositive AIE and 19 of 37 (51.4%) male patients diagnosed as seronegative AIE (p=0.464). The age at disease onset was 11.4±5.6 years in seropositive AIE patients and 9.2±4.3 years in seronegative AIE patients (p=0.196). Tumor (ovarian teratoma) was diagnosed in only two of the nine (22.2%) patients with seropositive AIE (anti-NMDAR encephalitis) (p=0.089). Prodromal symptoms or a vaccination history were initially present in 5 of the 9 (55.6%) seropositive AIE patients and 31 of the 37 (83.8%) seronegative AIE patients (p=0.087). Patients diagnosed with seropositive AIE tended to present with more-diverse clinical features of neuropsychiatric dysfunction compared with seronegative AIE patients (p=0.038; mRS score=7.4±1.3 vs. 5.9±2.1). Neurological dysfunction such as seizure or speech dysfunction was more common in seropositive patients during the overall follow-up period, while psychological dysfunction was more common in seronegative patients. However, both seropositive and seronegative AIE patients more commonly presented with neurological symptoms than psychotics disorders at admission (Table 1).

Inflammatory changes in CSF were noted in 6 of the 9 (66.7%) patients with seropositive AIE and 20 of the 37 (54.1%) patients with seronegative AIE (p=0.711), while encephalitic features in radiological findings were detected in 2 (22.2%) and 19 (51.4%) patients, respectively (p=0.151). PET-CT was conducted in only four (10.8%) seronegative AIE patients, and they exhibited with hyper- or hypometabolism of the brain, suggestive of an encephalitic feature (Table 1).

Since the initial disease severity as assessed using mRS scores showed severe disability in both seropositive (median=5, IQR=0) and seronegative (median=4, IQR=2) encephalitis (p=0.086), first-line treatment was initiated in all patients regardless of their serological status. However, outcomes after the initiation of first-line treatment were better in seronegative AIE patients (median=1, IQR=2) than in seropositive AIE patients (median=4, IQR=2) (p=0.003). Therefore, second-line treatment

Table 1. Baseline demographics of the study participants (*n*=46)

	Seronegative AIE (*n*=37)	Seropositive AIE (*n*=9)	*p*
Sex			0.464
Male	19 (51.4)	3 (33.3)	-
Female	18 (48.6)	6 (66.7)	-
Age at onset, years	9.2±4.3	11.4±5.6	0.196
Tumor	0	2 (22.2)	0.089
Prodromal symptoms	31 (83.8)	5 (55.6)	0.087
Fever	27 (73.0)	3 (33.3)	-
Headache	10 (27.0)	3 (33.3)	-
Gastrointestinal symptom	10 (27.0)	3 (33.3)	-
Respiratory symptom	7 (18.9)	0	-
Vaccination history	1 (2.7)	0	-
Neuropsychiatric features, mRS score	5.9±2.1	7.4±1.3	0.038*
Altered mental status	29 (78.4)	7 (77.8)	>0.999
Focal neurological deficit	2 (5.4)	2 (22.2)	0.167
Cognitive dysfunction	29 (78.4)	7 (77.8)	>0.999
Acute developmental regression	20 (54.1)	7 (77.8)	0.270
Movement disorder	20 (54.1)	8 (88.9)	0.069
Seizure	28 (75.7)	9 (100.0)	0.171
Speech dysfunction	29 (78.4)	9 (100.0)	0.324
Psychotic disorder	32 (86.5)	8 (88.9)	>0.999
Sleep disorder	16 (43.2)	6 (66.7)	0.276
Autonomic dysfunction	13 (35.1)	4 (44.4)	0.707
CSF inflammation	20 (54.1)	6 (66.7)	0.711
MRI abnormality	19 (51.4)	2 (22.2)	0.151
PET-CT abnormality	4 (10.8)	0	-
ICU stay	7 (18.9)	4 (44.4)	-

Data are *n* (%) or mean±standard deviation values.
*$p<0.05$.
AIE: autoimmune encephalitis, CSF: cerebrospinal fluid, ICU: intensive care unit, MRI: magnetic resonance imaging, mRS: modified Rankin Scale, PET-CT: positron-emission tomography/computed tomography.

(p=0.015) was applied more frequently in seropositive AIE (5/9, 55.6%). Maintenance treatment (p=0.092) was also applied more frequently in seropositive AIE (5/9, 55.6%), although the difference was not statistically significant. Only one patient diagnosed as seropositive AIE received third-line treatment (p=0.196). Furthermore, although not statistically significant, disease relapse was more frequent in seronegative AIE (13/37, 35.1%) than in seropositive AIE (2/9, 22.2%) (p=0.696), but was not related to grave disease severity. Final treatment outcomes after 1 year from disease onset showed the same mild severity in seropositive (median=1, IQR=2) and seronegative (median=1, IQR=2) groups (p=0.703) (Table 2).

Table 2. Disease severity and treatment strategies according to serological status

	Seronegative AIE (*n*=37)	Seropositive AIE (*n*=9)	*p*
Initial mRS score	4 [2]	5 [0]	0.086
mRS score after first-line treatment	1 [2]	4 [2]	0.003*
Final mRS score	1 [2]	1 [2]	0.703
First-line treatment	37 (100.0)	9 (100.0)	-
Second-line treatment	5 (13.5)	5 (55.6)	0.015*
Third-line treatment	0	1 (11.1)	0.196
Maintenance treatment	8 (21.6)	5 (55.6)	0.092
Relapse	13 (35.1)	2 (22.2)	0.696

Data are median [interquartile range] or *n* (%) values. First-line treatment: high-dose dexamethasone (0.6–0.8 mg/kg/day), pulsed intravenous methylprednisolone (20–30 mg/kg/day for 3–5 days), intravenous immunoglobulin (2 g/kg over 2–5 days), or therapeutic plasma exchange (5–10 exchanges every other day). Second-line treatment: rituximab (375 mg/m^2 weekly for 4 weeks) or cyclophosphamide (750 mg/m^2 monthly). Third-line treatment: tocilizumab (4–8 mg/kg monthly). Maintenance treatment: monthly administration of methylprednisolone or immunoglobulins, oral prednisone (1 mg/kg/day), mycophenolate mofetil, or azathioprine.
*$p<0.05$.
AIE: autoimmune encephalitis, mRS: modified Rankin Scale.

Clinical features associated with treatment outcomes of seronegative AIE

First-line treatment was initiated in all 37 patients diagnosed as seronegative AIE. Second-line (n=5, 13.5%) and maintenance (n=8, 21.6%) treatments were considered only in those with poor treatment outcomes after the first-line treatment or with disease relapse. One year after disease onset, 23 (62.2%) patients achieved an mRS score of 0 or 1, thereby presenting with almost no significant disabilities. Furthermore, only two (5.4%) patients presented with an mRS score ≥3 (moderate-to-severe disability), indicating good treatment outcomes in seronegative AIE.

To exclude confounding factors, the clinical features associated with favorable treatment outcomes were further analyzed using a linear mixed model. This analysis revealed that the disease severity of seronegative AIE improved over time (p<0.001), and that the mRS score after first-line treatment was the only factor associated with treatment outcome (p=0.006) (Table 3).

DISCUSSION

This study found that clinical presentations of pediatric AIE patients did not vary markedly with the serological status, and that both seronegative and seropositive AIE patients showed favorable treatment outcomes after applying the recently proposed pediatric diagnostic criteria.[11] This demonstrates the

Table 3. Clinical features associated with treatment outcomes of seronegative AIE

	Estimate	Standard error	*p*
Sex	0.017	0.226	0.941
Diagnosis	-0.091	0.384	0.815
Prodromal symptoms	0.183	0.236	0.448
CSF inflammation	0.201	0.351	0.572
Altered mental status	-0.080	0.235	0.737
Focal neurological deficit	0.315	0.419	0.461
Cognitive dysfunction	-0.115	0.272	0.677
Acute developmental regression	-0.142	0.217	0.519
Movement disorder	0.018	0.167	0.915
Psychotic disorder	0.336	0.347	0.345
Seizure	-0.148	0.364	0.689
Speech dysfunction	-0.142	0.256	0.585
Sleep disorder	0.031	0.199	0.878
Autonomic dysfunction	-0.407	0.235	0.097
MRI abnormality	-0.048	0.208	0.821
Second-line treatment	-0.085	0.500	0.866
Maintenance treatment	0.605	0.415	0.161
Relapse	-0.121	0.318	0.708
ICU stay	0.166	0.421	0.698
Initial mRS score			0.323
2	-0.801	0.421	-
3	-0.513	0.402	-
4	-0.395	0.338	-
mRS score after first-line treatment			0.006*
0	-2.563	0.915	-
1	-2.224	0.780	-
2	-1.277	0.737	-
3	-0.925	0.510	-
4	-0.448	0.614	-
Time			<0.001*

*$p<0.05$.
AIE: autoimmune encephalitis, CSF: cerebrospinal fluid, ICU: intensive care unit, MRI: magnetic resonance imaging, mRS: modified Rankin Scale.

validity of recent pediatric diagnostic criteria that are distinct from those for adult cohorts, and indicates that, despite a negative serological status, the autoimmune pathophysiology of seronegative AIE is similar to that of seropositive AIE.

While the clinical features and treatment outcomes of our pediatric AIE cohort mostly resembled those of adult-onset AIE, their initial presentations showed more neurological signs, such as seizure, altered mental status, and speech dysfunction, which contrast with higher prevalence rates of psychotic disorders in adult-onset AIE reported previously.[11,23,24] However, psychotic symptoms or sleep disorder were also frequently detected during the disease course, with more than 90% of patients presenting with at least four neuropsychiatric features. Furthermore, autonomic dysfunction such as urinary retention, tachycardia, bradycardia, or blood pressure fluctuation was common in both the anti-NMDAR-encephalitis-seropositive and anti-NMDAR-encephalitis-seronegative groups, which indicates the significance of the early suspicion and detection of clinical presentations in diagnosing AIE.

Childhood-onset seropositive AIE cases mostly comprise anti-NMDAR encephalitis, followed by anti-GABA-A-receptor encephalitis or anti-GAD65 encephalitis.[12] Anti-NMDAR encephalitis is the most common form of antibody-mediated encephalitis in pediatric cohorts, and is a prototypic AIE with an established clinical syndrome of neuropsychiatric dysfunction with favorable treatment outcomes in more than 80% of patients.[25,26] Tumor (ovarian teratoma) association and female predominance characterize this patient group, despite the equal sex ratio, with a rare association with tumors in pediatric patients younger than 10 years.[12,27] Consistent with this, nine of our patients diagnosed as seropositive AIE were all confirmed with anti-NMDAR encephalitis. These patients initially presented with a polysymptomatic clinical syndrome with grave disease severity, although seven (77.8%) of them showed favorable treatment outcomes after 1 year. Furthermore, two of four female patients who were older than 10 years were diagnosed with ovarian teratoma, which was immediately removed.

Gastaldi and colleagues[28,29] reported that seronegative AIE presents with clinical phenotypes and relapse occurred similarly to seropositive AIE, with more than 60% of adult patients showing favorable treatment responses. Hacohen et al.[14] also reported that clinical features (seizure predominance) and treatment outcomes of pediatric seronegative and seropositive AIE patients were similar at presentation. However, those previous studies did not apply objective diagnostic criteria, and identified patients using a blinded clinical review panel. In the present study we were able to successfully identify patients with AIE by applying a new diagnostic approach proposed by experts. The seronegative patients in our pediatric cohort showed similar clinical presentations with favorable treatment outcomes as those of the seropositive AIE patients, suggesting that this new diagnostic approach can effectively identify AIE patients regardless of their serum antibody status.

The detection of autoantibodies for diagnosing AIE is not perfect for several reasons: 1) false negatives due to methodological problems and low titers, 2) phase lag relative to clinical features, 3) possibility of unknown antibodies, and 4) unknown mechanisms not associated with antibody-mediated immunity.[14] Previous studies have found that considerable proportions of patients tested for AIE autoantibodies are seronegative with unknown etiologies.[14,28] Among our pediat-

ric AIE cohort, about only 20% of patients were diagnosed with autoantibodies against neuronal antigens, with 80% of patients diagnosed as seronegative AIE. This indicates the importance of performing a precise analysis that compares seronegative and seropositive AIE.

The early initiation of primary immunosuppressive strategies, such as corticosteroids, intravenous immunoglobulin, or therapeutic plasma exchange, is usually associated with favorable treatment outcomes.[30] We found that the disease severity upon admission was not significantly associated with treatment outcomes, although mild disease severity after primary immunotherapy was significantly associated with an overall favorable outcome. Other clinical features were also investigated, and they were found to have no significant associations with treatment outcomes. Moreover, as in previous studies, disease severity was milder on relapse, suggesting that the presence of relapse was not related to an unfavorable treatment outcome.[31,32] Therefore, the early initiation of primary immunotherapy and the precise identification of disease severity may be significant.

Several observational studies have demonstrated that appropriate initiation of second-line immunotherapy results in better functional outcomes and lower relapse rates.[27,33] Maintenance therapy is also recommended in a specific population of patients in order to improve functional outcomes and ensure long-term complete remission.[30] Among 16 patients in our cohort with moderate-to-severe disease severity (mRS score ≥3) after primary immunomodulatory therapies, 13 (81.3%) received either second-line or maintenance immunotherapy, which led to better functional outcomes.

Our study had some limitations. Firstly, this was a retrospective study, and our autoantibody panel comprised only six autoantibodies. A few recent studies have identified additional autoantibodies, including anti-myelin oligodendrocyte glycoprotein (anti-MOG) antibody. Future studies with a more-extensive autoantibody panel would therefore be helpful.[14,34,35] Secondly, due to the small cohort and the retrospective design of this observational study, the effectiveness of second-line, third-line, and maintenance immunotherapies could not be analyzed precisely. Further prospective studies of these advanced treatments are warranted. Finally, some patients diagnosed with possible seronegative AIE may have been misdiagnosed as autoimmune-mediated encephalitis. Nevertheless, it is important to note that these patients showed phenotypes similar to the seropositive and seronegative-probable AIE patients when careful exclusion of additional diagnoses was performed. Furthermore, the early initiation of primary immunotherapies resulted in significant improvements in the treatment course of AIE, and few severe side effects have been reported.[36] Therefore, hesitation in initiating immunotherapies in these patients must be avoided.

In conclusion, this study found that despite slight differences, the clinical characteristics of the included patients diagnosed with AIE were similar regardless of their serological status, with favorable treatment outcomes after initiating immunomodulatory agents. Moreover, the present findings indicate that treatment outcomes in patients diagnosed with seronegative AIE are significantly associated with the early initiation of primary immunotherapies, as well as the precise identification of disease severity after first-line treatment, thus suggesting autoimmune etiologies similar to those of seropositive AIE.

Author Contributions

Conceptualization: Sangbo Lee, Se Hee Kim, Hoon-Chul Kang. Data curation: Sangbo Lee, Se Hee Kim, Hoon-Chul Kang. Formal analysis: Sangbo Lee, Se Hee Kim, Hoon-Chul Kang. Funding acquisition: Se Hee Kim, Hoon-Chul Kang. Investigation: Sangbo Lee, Se Hee Kim, Hoon-Chul Kang. Methodology: all authors. Project administration: Se Hee Kim, Hoon-Chul Kang. Resources: Se Hee Kim, Hoon-Chul Kang, Heung Dong Kim, Joon Soo Lee. Supervision: Se Hee Kim, Hoon-Chul Kang. Validation: Se Hee Kim, Hoon-Chul Kang. Visualization: Sangbo Lee, Se Hee Kim, Hoon-Chul Kang. Writing—original draft: Sangbo Lee, Se Hee Kim, Hoon-Chul Kang. Writing—review & editing: Sangbo Lee, Se Hee Kim, Hoon-Chul Kang.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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