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Assessment of Prognostic Factors and Validity of Scoring Models in Childhood Autoimmune Encephalitis

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What is already known on this topic?

- *Autoimmune encephalitis (AIE) in children has a favorable prognosis with early immunotherapy and disease-modifying treatments. The anti-N-methyl-D-aspartate receptor Encephalitis 1-Year Functional Status (NEOS) score was designed to predict disease severity and prognosis at the first year of AIE onset, particularly in patients of anti-N-methyl-D-aspartate receptor encephalitis.*

What this study adds on this topic?

- *The presence of status epilepticus at the time of AIE diagnosis is significantly associated with prognosis and the development of autoimmune-related epilepsy. Scoring models for the outcome of AIE (NEOS) and for identifying AIE (Antibody Prevalence in Epilepsy and Response to Immunotherapy in Epilepsy) are easily applicable to the pediatric age group.*

ABSTRACT

Objective: The aim of this study is to evaluate the prognostic factors in a single-center pediatric cohort with autoimmune encephalitis.

Materials and Methods: The study group consisted of 23 pediatric autoimmune encephalitis patients (seropositive autoimmune encephalitis: 15, seronegative autoimmune encephalitis: 8). Five group prognostic parameters were evaluated: clinical manifestations, electroenc ephalography features, magnetic resonance imaging characteristics, biomarkers, and treatment modalities. Three scoring models were applied: the Antibody Prevalence in Epilepsy and Response to Immunotherapy in Epilepsy for predicting autoimmune-related epilepsy in the whole cohort and the anti-N-methyl-D-aspartate receptor Encephalitis 1-Year Functional Status score for overall outcome in patients with anti-N-methyl-D-aspartate receptor encephalitis.

Results: The initial clinical spectrum of the disease was similar in the seronegative and seropositive groups. Almost half of the patients (48%) recovered without any complications with first-line immunotherapy. The patients with movement disorders in the acute phase of the disease needed more likely second-line immunotherapy ($P = .039$). The presence of status epilepticus at admission was significantly associated with adverse outcomes and the development of autoimmune-related epilepsy ($P = .019$). Autoimmune-related epilepsy was defined in an equal proportion of patients (91.5%) with 2 immune epilepsy scores (Antibody Prevalence in Epilepsy and Response to Immunotherapy in Epilepsy). The N-methyl-D-aspartate receptor Encephalitis 1-Year Functional Status score and the modified Rankin score assessed for the first-year prognosis were strongly correlated among the patients with anti-N-methyl-D-aspartate receptor encephalitis ($P = .03$, Spearmen's rho = 0.751).

Conclusions: The presence of status epilepticus was the most important prognostic factor in the patients with the adverse outcome. The studied scoring models (Anti-N-methyl-D-aspartate receptor Encephalitis 1-Year Functional Status, Antibody Prevalence in Epilepsy, and Response to Immunotherapy in Epilepsy) have also been proven to be applicable to the pediatric age group for predicting overall outcome and autoimmune-related epilepsy.

Keywords: Anti-NMDAR encephalitis, autoimmune encephalitis, immune epilepsy, outcome, prognostic factors

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INTRODUCTION

Encephalitis is a clinical condition that arises from inflammation in the brain tissue that is characterized by impaired consciousness, focal neurological deficits, or seizures.[1] Encephalitis could develop as a result of an infection or an autoimmune disorder. Antibodies affecting the central nervous system were first identified in 1965, and the discovery of the N-methyl-D-aspartate receptor (NMDAR) antibody in 2007 expanded research into autoimmune

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encephalitis (AIE).[2,3] The management and outcome of children with AIE have altered dramatically with disease-modifying drugs in the last 15 years.[4]

In recent years, certain scoring systems have also been proposed for the definition of autoimmune epilepsy and the overall outcome of AIEs. Two scoring models (the Antibody Prevalence in Epilepsy (APE) and Response to Immunotherapy in Epilepsy (RITE)) are suggested for predicting autoimmune-related epilepsy.[5] The anti-NMDAR Encephalitis 1-Year Functional Status (NEOS) score was also designed to predict disease severity and prognosis at 1 year of AIE onset, particularly in patients with anti-NMDAR antibodies.[6-8]

In this study, we evaluated retrospectively the clinical prognostic factors for the overall outcome and presence of autoimmune-related epilepsy in a pediatric AIE cohort using the proposed scoring models (APE, RITE, and NEOS).

MATERIALS AND METHODS

The study was approved by the Ege University Medical Research Ethics Committee (Project no: 22-6.1T/71).

Study Group

The study group consisted of 23 patients diagnosed with AIE at Ege University Pediatric Neurology Clinic between January 2013 and March 2022. The patients were assessed using the AIE diagnostic criteria presented in 2016 and 2020.[9,10] According to these criteria, the identification of antibodies against neuronal membrane or synaptic proteins in the cerebrospinal fluid (CSF) and/or serum is the diagnostic criteria for the "definite AIE," for which the term "seropositive AIE" was used throughout the article. Those same criteria accept patients who are not serologically proven but meet other diagnostic criteria as "probable AIE," which was replaced in the article with the term "seronegative AIE."

Biomarkers

All patients underwent serum or CSF antibody tests, brain magnetic resonance imaging (MRI), and biochemical analyses for the differential diagnosis. The antibody screening panel included the following antibodies: NMDAR, voltage-gated potassium channels, selective glutamate receptor 1 (AMPA1), AMPA2, anti-contactin-associated protein-like 2, anti-leucine-rich glioma inactivated-1, anti-γ-aminobutyric acid-B receptor, and anti-glutamic acid decarboxylase. The isoelectric focusing method was used for the oligoclonal band test. The immunoglobulin G index is considered as high when it was greater than 0.8.

Immunotherapy Protocol

First-line therapy is initiated in all patients with pulse methylprednisolone therapy (MPT, 30 mg/kg/day, maximum 1 g/day, 5 days) and/or intravenous immunoglobulin (IVIG, 0.4 g/kg/day, 5 days, total 2 g/kg). The second-line therapy was decided based on the patient's clinical responses to the first-line therapy.[11] Since there is no globally accepted treatment protocol for maintenance therapy, the medications administered in long-term treatment and their duration are determined by the clinical condition of the patients.

Prognostic Factors

The following prognostic clinical factors were evaluated: clinical features in the acute phase of the disease (behavioral changes, speech problems, memory problems, altered level of consciousness, movement disorders, sleep disorders, autonomic instability, seizures, and status epilepticus (SE)), treatment modalities (first and second line therapies), treatment initiation and response times, the need for an intensive care unit (ICU), MRI findings, electroencephalography (EEG) features, CSF findings, age, and gender.

Autoimmune-Related Epilepsy

Autoimmunity-related seizures and autoimmune-related epilepsy were defined in proposals of the International League Against Epilepsy Autoimmunity and Inflammation Taskforce.[12] In this context, seizures in the active phase of AIE were referred to as "acute symptomatic seizures secondary to autoimmune encephalitis." The terminology of "autoimmune-related epilepsy" was also used for chronic seizures caused by ongoing brain autoimmunity and/or structural brain abnormalities. All patients had 1-hour EEG recording, which included a full wake and sleep cycle, according to the international 10-20 standard electrode placement system. In addition, the patients with refractory seizures to anti-seizure medication were evaluated with long-term video-EEG monitoring.

The Scoring Models for Autoimmune-Related Epilepsy

The APE score was designed to indicate immune etiology in anti-seizure medication (ASM)-resistant epilepsies, whereas the RITE score helps to predict the effectiveness of immunotherapy.[5] In the APE score, the total score is 15, and the parameters were subacute mental status and neuropsychiatric changes, autonomic dysfunction, viral prodrome, dyskinesia, drug-refractory seizures, CSF findings consistent with inflammation, MRI findings consistent with limbic encephalitis, and presence of underlying malignancy. For the RITE score, in addition to all the parameters used in the APE score, initiation of immunotherapy within 6 months of symptom onset and the detected neural plasma membrane autoantibody were used. The sensitivity and specificity of APE score $\geq$4 to predict neural-specific antibody positivity were 97.7% and 77.9%, respectively. The RITE score $\geq$7 has a very high sensitivity of 87.5% and high specificity of 83.8% to predict favorable seizure outcomes following immunotherapy.[5]

The Scoring Model of Autoimmune Encephalitis for the Overall Outcome

The NEOS score can accurately predict 1-year functional status in patients with anti-NMDAR encephalitis.[6] The need for an ICU, a 4-week delay in treatment initiation, a lack of clinical improvement within 4 weeks, an abnormal MRI, and a white blood cell count in CSF (>20 cells) were all employed as prognostic indicators in this scoring model. These 5 variables were assigned 1 point each to develop the NEOS score. In the original paper, the likelihood of having a low functional status at 1 year was significantly correlated with the NEOS score (3% for 0 or 1 point to 69% for 4 or 5 points, $P = .001$).[6]

Long-Term Outcome Assessment and Relationship with Scoring Models

A long-term prognosis evaluation was performed on patients who had been followed for at least 1 year. Motor function

was assessed using the modified Rankin scale (mRS). The NEOS score was evaluated in AIE patients with anti-NMDAR antibody positivity, as well as the correlation between the NEOS score and mRS. The existence of autoimmune-related epilepsy in the long term was identified by the presence of seizures, EEG abnormalities, and anti-seizure medication requirements after the third month of follow-up in patients who presented with seizures in the acute period. A standard psychometric test was not employed for the patients' neurocognitive assessments, but it was noted in their files whether they had received special education services. The presence of autoimmune-related epilepsy, an mRS score other than 0, or any special education requirement at the end of the first year was considered an "adverse outcome," whereas the lack of any was considered a "favorable outcome" (recovery without sequelae). The entire study group and the seropositive/seronegative groups were examined separately for prognostic purposes.

Statistical Analysis

Descriptive statistics stated as mean (+ standard deviation) and median (minimum-maximum) for continuous variables, and number (%) for categorical variables. Shapiro–Wilk and Kolmogorov–Smirnov tests were used for the analysis of data normality. An independent *t*-test was used for parametric data, and the results were given as mean ± standard deviation. Mann–Whitney *U*-test was used for nonparametric data, and the results were given as median (minimum, maximum). The categorical variables were tested using Pearson's chi-square or Fisher's exact chi-square, and the findings were presented as frequency and percentage. The Spearman and Pearson correlation tests were used to examine the relationship between the 2 scores. Results were considered statistically significant when $P < .05$.

RESULTS

Demographic and Clinical Prognostic Parameters

The study included 23 patients, of which 14 (60.9%) were girls (Tables 1 and 2). The mean age of diagnosis of the patients was 93.7 ±60.9 (18-204) months and the mean follow-up period of the patients was 31.3 ±33.2 (6-156) months. The most common clinical features at admission were seizures (18/23, 78.3%), altered level of consciousness (17/23, 73.9%), sleep disorders (16/23, 69.6%), and movement disorders (15/23, 65.2%). Fourteen patients (60.9%) required follow-up in the ICU. There was a statistically significant difference between the seropositive and seronegative AIE groups regarding initial clinical features. In addition, there was no significant difference for other clinical characteristics (biomarkers, MRI, EEG, treatment modalities, need for ICU, and favorable outcome) (Table 3).

Four NMDAR antibody-positive cases were triggered after herpes simplex virus (HSV) encephalitis (cases 18-21). Herpes simplex virus CSF polymerase chain reaction test was positive in all cases with HSV encephalitis. Three of the cases had been diagnosed with NMDAR encephalitis recently in the acute phase of HSV encephalitis. The remaining patient (case 19) had a diagnosis of NMDAR antibody-positive AIE with the follow-up CSF analysis around 10 months of HSV encephalitis with drug-refractory epileptic spasms. The patient (case 17) had a problematic differential diagnosis of Guillain-Barré syndrome with acute flask paralysis in the acute phase of the disease. An 8-year-old boy developed rapidly progressive muscle weakness and dysesthesia in the extremities after a flu-like episode. Nerve conduction studies showed reduced motor nerve conduction velocities, and sensory nerve action potentials could not be evoked. Magnetic resonance imaging performed before lumber puncture showed contrast enhancement on the caudal fibers and filum terminale. Then behavioral changes, speech problems, movement disorders, and sleep disorders were seen on the fifth day of the follow-up, and the NMDAR antibody was detected in the CSF. The patient with anti-Hu antibody positivity was diagnosed with neuroblastoma concurrently with encephalitis (case 23).

Biomarkers

The AIE panel was screened in 11 (47.8%) patients only in CSF, 5 (21.7%) patients only in serum, and 7 (27.4%) patients in both serum and CSF. Fifteen out of 23 patients (56.2%) were seropositive for AIE; an anti-NMDAR antibody was detected in 13 patients, an anti-GAD antibody in 1, and an anti-Hu antibody in another individual (Tables 2 and 3). In 2 patients, the NMDAR antibody result was documented as only positive, and the patients for whom the antibody titers were reported had titers ranging from 1/10 to 1/1000. The NMDAR antibody concentration in the CSF was either the same as in the serum or had lower titers. The anti-GAD antibody titers in serum showed 33.8 IU/mL, while the anti-Hu levels in serum and CSF were both +++.

Magnetic Resonance Imaging

Thirteen (56.5%) patients' cranial MRI scans were normal. Autoimmune encephalitis-related MRI findings were seen in 10 (43.5%) patients (Tables 1 and 2). One patient had a normal initial MRI. However, the second MRI revealed a reversible spinal lesion syndrome (RESLES), which was performed due to poor response to first-line therapy with unresolved encephalopathy.

Electroencephalography

All patient's EEG recordings were present. Three (%13) patients had normal EEG findings, whereas 20 (86.9%) patients' EEG findings were abnormal. At initial diagnosis, 8 (34.8%) patients had normal EEG backgrounds, 11 patients had focal, and 4 (17.4%) had generalized slow waves. There were focal epileptiform discharges in 69.6% (16/23) of the patients and generalized epileptiform discharges in 8.7% (2/23).

TREATMENT MODALITIES

In 18 patients, the duration between the first symptoms to treatment was fewer than 4 weeks. Pulse methylprednisolone therapy was given to all patients as first-line therapy. Only MPT was adequate in 5 (21.7%) patients, while additional IVIG was added to treatment in 18 (78.3%) patients. Twelve (52.2%) patients needed second-line therapy. Eleven of them received second-line therapy as rituximab; moreover, 4 of them had been treated with cyclophosphamide. In another patient, only cyclophosphamide was administered (Tables 1 and 2). Clinical conditions such as ongoing seizures and movement disorders, as well as non-recovery of mental functions, influenced the decision to switch to second-line therapy in all the patients.

Table 1. Clinical Characteristics of Patients with Seronegative Autoimmune Encephalitis

Case No:	Diagnosis Age (Months)	Clinical Presentation	MRI Findings	CSF pro/ OCB/IgG Index	First-Line Therapy	Second-Line Therapy	Maintenance Therapy	Maintenance Therapy Duration (Months)	Follow-Up Duration (Months)	Follow-Up mRS	Follow-Up Epilepsy
1	84	Behavioral changes, memory problems, altered level of consciousness, movement disorders, autonomic instability, seizures	Hippocampal involvement, contrast enhancement Ø	- - -	MPT, IVIG	RTX	Oral steroid, monthly IVIG	3	156	3	Drug refractory epilepsy
2	156	Altered level of consciousness, movement disorders, sleep disorders, status epilepticus	Normal	High Type 1 Normal	MPT	-	Oral steroid	3	48	0	-
3	72	Memory problems, altered level of consciousness, movement disorders, seizures	Normal	Normal - -	MPT	-	Oral steroid	3	15	0	-
4	72	Behavioral changes, speech problems, memory problems, altered level of consciousness, sleep disorders, seizures	Normal	Normal Type 1 Normal	MPT, IVIG	-	Oral steroid	3	6	0	-
5	42	Speech problems, altered level of consciousness, sleep disorders, status epilepticus	Bilateral occipital hyperintensity, contrast enhancement Ø	Normal - -	MPT, IVIG	RTX, CYC	Monthly MPT, monthly IVIG	12	48	0	Epilepsy
6	72	Behavioral changes, altered level of consciousness, sleep disorders, status epilepticus	Normal	Normal - -	MPT, IVIG	-	Monthly MPT, monthly IVIG	3	30	0	Drug refractory epilepsy
7	36	Behavioral changes, speech problems, altered level of consciousness, sleep disorders,	Normal	Normal Type 1 Normal	MPT, IVIG	RTX	Monthly MPT, monthly IVIG	6	18	0	-
8	66	Behavioral changes, altered level of consciousness, sleep disorders, status epilepticus	Normal	Normal - Normal	MPT, IVIG	-	Oral steroid	3	6	0	Epilepsy

Table 2. Clinical Characteristics of Patients with Seropositive Autoimmune Encephalitis

Case No:	Diagnosis Age (Months)	Antibody	Clinical Presentation	MRI Findings	CSF pro/ OCB / IgG Index	First-Line Therapy	Second-Line Therapy	Maintenance Therapy	Maintenance Therapy Duration (Months)	Follow-Up Duration (Months)	Follow-Up mRS	Follow-Up Epilepsy
9	60	Anti-NMDA	Speech problems, movement disorders, sleep disorders, autonomic instability, seizures	Cortical, hippocampal involvement, contrast enhancement Ø	Normal - -	MPT, IVIG	-	Oral steroid, monthly IVIG	3	76	3	Drug refractory epilepsy
10	63	Anti-NMDA	Behavioral changes, memory problems, altered level of consciousness, movement disorders, sleep disorders	Normal	Normal - High	MPT, IVIG	RTX	Monthly MPT, monthly IVIG	12	30	0	-
11	156	Anti-NMDA	Behavioral changes, speech problems, memory problems, movement disorders, sleep disorders, status epilepticus	Normal	Normal - Normal	MPT, IVIG	RTX, CYC	Monthly MPT, monthly IVIG	24	36	0	Epilepsy
12	36	Anti-NMDA	Behavioral changes, speech problems, memory problems, altered level of consciousness, movement disorders, sleep disorders	Normal	Normal - -	MPT, IVIG	RTX	Monthly MPT	6	24	0	-
13	180	Anti-NMDA	Memory problems, altered level of consciousness, seizures	Normal	Normal Type 1 Normal	MPT	-	Oral steroid	3	15	0	-
14	192	Anti-NMDA	Behavioral changes, speech problems, memory problems, altered level of consciousness, movement disorders, sleep disorders, autonomic instability, seizures	First MRI: normal, at the second week follow-up: RESLES	Normal Type 2 Normal	MPT, IVIG	RTX	Monthly MPT, monthly IVIG	6	15	0	-
15	204	Anti-NMDA	Behavioral changes, speech problems, memory problems, altered level of consciousness, movement disorders, sleep disorders, seizures	Normal	Normal - -	MPT	RTX	Oral steroid	3	6	0	-
16+	144	Anti-NMDA	Memory problems, seizures	Normal	Normal Type 2 Normal	MPT	- Relapse: RTX	Oral steroid	3	12	0	Epilepsy
17◆	96	Anti-NMDA	Behavioral changes, speech problems, movement disorders, sleep disorders	Caudal fibers and filum terminale contrast enhancement +	High - Normal	MPT, IVIG	-	Oral steroid	3	36	0	-

(*Continued*)

Table 2. Clinical Characteristics of Patients with Seropositive Autoimmune Encephalitis (*Continued*)

Case No:	Diagnosis Age (Months)	Antibody	Clinical Presentation	MRI Findings	CSF pro/ OCB / IgG Index	First-Line Therapy	Second-Line Therapy	Maintenance Therapy	Maintenance Therapy Duration (Months)	Follow-Up Duration (Months)	Follow-Up mRS	Follow-Up Epilepsy
18*	24	Anti-NMDAR: 21 days**	Behavioral changes, memory problems, altered level of consciousness, movement disorders, sleep disorders, autonomic instability	Temporal lobe involvement, contrast enhancement +	High - -	MPT, IVIG	RTX, CYC	Monthly MPT, monthly IVIG	12	64	2	Drug refractory epilepsy
19*	18	Anti-NMDAR: 10 months**	Seizures	Cortical, hippocampal involvement, contrast enhancement Ø	Normal - High	MPT IVIG	-	ACTH		24	2	Drug refractory epilepsy
20*	96	Anti-NMDAR: 2 months**	Behavioral changes, speech problems, memory problems, altered level of consciousness, movement disorders, sleep disorders, status epilepticus	Cortical, basal ganglion, hippocampal involvement, contrast enhancement +	High Type 1 High	MPT, IVIG	RTX	Monthly MPT, monthly IVIG	6	36	5	Drug refractory epilepsy
21*	204	Anti-NMDAR: 1 month**	Behavioral changes, speech problems, memory problems, altered level of consciousness, movement disorders, sleep disorders, seizures	Cortical, hippocampal involvement, contrast enhancement +	High Type 2 Normal	MPT, IVIG	-	Oral steroid	3	6	1	Epilepsy
22	53	Anti-GAD	Behavioral changes, memory problems, altered level of consciousness, seizures	Basal ganglion involvement, contrast enhancement Ø	Normal - -	MPT	-	Oral steroid	3	36	0	-
23λ	30	Anti-Hu	Behavioral changes, speech problems, memory problems, altered level of consciousness, movement disorders, sleep disorders, seizures	Cortical involvement, contrast enhancement Ø	Normal Type 2 High	MPT, IVIG	RTX, CYC	Monthly MPT, monthly IVIG	Continuous	9	3	Drug refractory epilepsy

ACTH, adrenocorticotropic hormone; CSF, cerebrospinal fluid; CYC, cyclophosphamide; GAD, glutamic acid decarboxylase; IVIG, intravenous immunoglobulin; MPT, pulse methylprednisolone therapy; MRI, magnetic resonance imaging; mRS, modified Rankin scale; NMDAR, N-methyl-D-aspartate receptor; OCB, oligoclonal band; RTX, rituximab.

†Relapsed; ◆GBS overlap with NMDAR encephalitis; *NMDAR antibody-positive cases were triggered after herpes simplex virus encephalitis; **The interval between herpes simplex virus encephalitis and NMDAR antibody-positive autoimmune encephalitis; λneuroblastoma.

Table 3. Prognostic Factors of Pediatric Patients with Autoimmune Encephalitis (n = 23)

Prognostic Factors (I-V) for AIE	Seropositive Autoimmune Encephalitis* (n = 15) (65.2)	Seronegative Autoimmune Encephalitis (n = 8) (34.8)	*P*
Age (months), median (minimum–maximum)	96 (18-240)	72 (36-156)	.651
Gender, n (%)			.023
Girl	12 (80)	2 (25)	
Boy	3 (20)	6 (75)	
I. Clinical features, n (%)			
Behavioral changes	11 (73.3)	5 (62.5)	.657
Speech problems	9 (60)	3 (37.5)	.4
Memory problems	12 (80)	3 (37.5)	.071
Altered level of consciousness	10 (66.7)	7 (87.5)	.369
Movement disorders	11 (73.3)	4 (50)	.371
Sleep disorders	11 (73.3)	5 (62.5)	.657
Autonomic instability	3 (20)	1 (12.5)	.990
Seizure	11 (73.3)	7 (87.5)	.621
Status epilepticus	2 (13.3)	4 (50)	.131
II. Abnormal electroencephalography, n (%)	13 (86.7)	7 (87.5)	.999
Background rhythm focal slow	6 (40)	5 (62.5)	
Generalized slow	3 (20)	1 (12.5)	
Epileptic discharges focal	12 (80)	4 (50)	
Generalized	1 (6.7)	1 (12.5)	
III. Abnormal magnetic resonance imaging, n (%)	8 (53.3)	2 (25)	.379
Temporal/hippocampal involvement	6 (40)	2 (25)	
Cortical lesion	6 (40)	1 (12.5)	
Basal ganglion/thalamus involvement	3 (20)	-	
IV. Biomarkers, n (%)			
>20 Cerebrospinal fluid cell	10 (66.7)	2 (25)	.089
High cerebrospinal fluid protein	4 (26.7)	2 (25)	.332
Oligoclonal band type 2	4 (66.6)	-	-
Increased IgG index	4 (40)	-	-
Herpes simplex virus encephalitis	4 (17.7)	-	-
V. Treatment modalities, n (%)			
Initiation first-line therapy (day), median (minimum–maximum)	13 (2-90)	7 (3-60)	.145
The interval between symptoms and initiation of first-line therapy <4 weeks	11 (73.3)	7 (38.9)	.62
Duration of response to first-line therapy >4 weeks	7 (46.7)	2 (25)	.4
Need for second-line therapy	9 (60)	3 (37.5)	.4
Need for intensive care unit, n (%)	10 (66.7)	4 (50)	.657
Favorable outcome, n (%)	7 (46.7)	5 (62.5)	.667

AIE, autoimmune encephalitis; IgG, immunoglobulin G.
*Anti-NMDA Ab: 13, Anti-GAD Ab: 1, Anti-Hu: 1.

Corticosteroids were used for 3-12 months for all patients on maintenance treatment. A 2-month-tapering period was performed after the oral steroids had been delivered at 1 mg/kg for 1 month in 11 cases.

The Value of Clinical Prognostic Factors for Outcomes

Nine initial clinical features and serological biomarkers, MRI, EEG, treatment modalities, and the necessity for ICU were evaluated to define the necessity of second-line therapy in Table 4. Only the presence of movement disorder in the initial phase of the disease and duration of response to first-line therapy >4 weeks were defined as statistically significant predictors.

For long-term outcomes, 16/23 patients with at least 1-year follow-up were evaluated. Nine patients (56.2%) have recovered completely without any sequelae. When evaluating the factors influencing long-term outcomes except for the anti-NMDAR-positive AIE patients, which occurred after HSV encephalitis, the adverse outcome has been found related to the presence of SE at the time of diagnosis ($P = .019$) (Table 5).

The Value of Clinical Prognostic Factors and the Scoring Models (Antibody Prevalence in Epilepsy and Response to Immunotherapy in Epilepsy) for Autoimmune-Related Epilepsy

At the end of the 1-year follow-up, 6 patients had drug-refractory epilepsy with a seizure frequency of once a week or more. Compared with the epileptic and non-epileptic groups at the end of the 1-year follow-up, the presence of SE at the initial diagnosis was statistically more frequent in the epileptic group ($P = .019$) (Table 6).

For seizure outcome and autoimmune-related epilepsy, APE and RITE scores were evaluated with 21 patients who had seizures at admission. Only 2 (9.5%) patients had an APE score of less than 4, and 2 patients (%9.5) had a RITE score of less than 7. One of the 2 patients with an APE score < 4 was anti-NMDAR encephalitis, whereas the other was in the seronegative AIE group.

Table 4. The Impact of Clinical Factors on the Need for Second-Line Therapy

	Second-Line Therapy (–) (n = 10) (43.5)	Second-Line Therapy (+) (n = 13) (56.5)	*P*
Age (months), mean ±SD	98.9 ±60.3	89.7 ±63.5	.729
Gender, n (%)			.417
Girl	5 (50)	9 (69.2)	
Boy	5 (50)	4 (30.8)	
I. Clinical features, n (%)			
Behavioral changes	6 (60)	10 (76.9)	.650
Speech problems	3 (30)	9 (69.2)	.999
Memory problems	5 (50)	10 (76.9)	.221
Altered level of consciousness	8 (80)	9 (69.2)	.660
Movement disorders	4 (40)	11 (84.6)	.039
Sleep disorders	6 (60)	10 (76.9)	.650
Autonomic instability	-	4 (30.8)	.104
Seizure	9 (90)	9 (69.2)	.339
Status epilepticus	2 (20)	4 (30.8)	.660
II. Abnormal electroence-phalography, n (%)	9 (90)	11 (84.6)	.999
Background rhythm focal slow	5 (50)	6 (46.2)	
Generalized slow	3 (30)	1 (7.7)	
Epileptic discharges focal	6 (60)	10 (76.9)	
Generalized	1 (10)	1 (7.7)	
III. Abnormal magnetic resonance imaging, n (%)	3 (30)	7 (53.8)	.402
Temporal/hippo campal involvement	2 (20)	6 (46.2)	
Cortical lesion	2 (20)	5 (38.5)	
Basal ganglion/ thalamus involvement	1 (10)	2 (15.4)	
IV. Biomarkers, n (%)			
>20 Cerebrospinal fluid cell	3 (30)	3 (23.1)	.999
High cerebrospinal fluid protein	3 (30)	3 (25)	-
Oligoclonal band type 2	1 (25)	3 (60)	-
Increased IgG index	1 (17)	3 (42.8)	-
Herpes simplex virus encephalitis	2 (20)	2 (15.4)	.999
AIE associated antibody positive	5 (50)	10 (76.9)	.221
V. Treatment, n (%)			
Initiation first-line therapy (day), median (minimum–maximum)	7 (4-90)	13 (2-60)	.740
The interval between symptoms and initiation of first-line therapy <4 weeks	8 (80)	10 (76.9)	.999
Duration of response to first-line therapy >4 weeks	9 (90)	5 (38.5)	.029
VI. Need for intensive care unit, n (%)	6 (60)	8 (61.5)	.999
Favorable outcome, n (%)	7 (70)	5 (38.5)	.214

AIE, autoimmune encephalitis; IgG, immunoglobulin G; SD, standard deviation.

The Value of the Anti-N-Methyl-D-Aspartate Receptor Encephalitis 1-Year Functional Status for Overall Outcomes

The NEOS is used to define the functional outcome. A significant positive correlation was found between the NEOS score and the first-year outcome of the anti-NMDAR encephalitis patients. Two patients with mRS at the end of first-year follow-up equal to 5 had NEOS scores of 3 and 4, respectively, whereas 2 individuals with mRS equal to 2 had NEOS scores of 2 (Figure 1, $P = .03$, Spearmen's rho = 0.751).

DISCUSSION

Autoimmune encephalitis, a group of antibody-related diseases, is effectively treated with immunotherapy and disease-modifying drugs, if possible, tumor extraction. In the case of clinical suspicions, early initiating of immunotherapy without waiting for the results of laboratory testing improves the patient's survival and complete recovery. In this study, we evaluated to define the clinical prognostic factors for overall outcome and for defining autoimmune-related epilepsy in a single pediatric cohort with seropositive and seronegative AIEs. Almost half of the patients (48%) were successfully treated with first-line therapy with MPT and/or IVIG. The patients with movement disorders in the acute phase of the disease needed more second-line immunotherapy. The presence of SE at admission was significantly associated with adverse outcomes and the development of autoimmune-related epilepsy. Autoimmune-related epilepsy was defined in an equal proportion of patients (91.5%) with 2 immune epilepsy scores (APE and RITE).

In previous studies, including all age groups, 18% of the patients were reported to be seronegative. However, seronegative ranged from 10.7% to 64.2% in these studies which only included children.[13-16] A wide variety of clinical spectrums has been reported in studies, including adult and pediatric patients with AIE. In a recent case series, it was reported that movement disorders and CSF oligoclonal bands were more common in the seropositive group, and seizures were more frequent in the seronegative group.[15] It was revealed that male gender is common in seronegative AIE patients and more comprehensive care is essential for seizure management.[14] In our study,

Table 5. The Impact of the Prognostic Factors on Long-Term Outcome

	Favorable Outcome (n = 9) (56.2)	Adverse Outcome (n = 7) (43.8)	*P*
Age (months), mean ±SD	98.2 ±61.7	84 ±48.6	.614
Gender n (%)			.999
Girl	5 (55.6)	4 (57.1)	
Boy	4 (44.4)	3 (42.9)	
I. Clinical features, n (%)			
Behavioral changes	6 (66.7)	4 (57.1)	.999
Speech problems	4 (44.4)	4 (57.1)	.999
Memory problems	6 (66.7)	4 (57.1)	.999
Altered level of consciousness	7 (77.8)	4 (57.1)	.596
Movement disorders	6 (66.7)	5 (45.5)	.999
Sleep disorders	6 (66.7)	4 (57.1)	.999
Autonomic instability	1 (11.1)	2 (28.6)	.550
Seizure	5 (55.6)	7 (100)	.088
Status epilepticus	-	4 (57.1)	**.019**
II. Abnormal electroenc ephalography, n (%)	6 (66.7)	7 (100)	.213
Background rhythm focal slow	3 (33.3)	3 (42.9)	
Generalized slow	2 (22.2)	1 (14.3)	
Epileptic discharges focal	4 (44.4)	6 (85.7)	
Generalized	1 (11.1)	1 (14.3)	
III. Abnormal magnetic resonance imaging, n (%)	2 (22.2)	4 (57.1)	.302
Temporal/hippocampal involvement	1 (11.1)	1 (42.9)	
Cortical lesion	-	3 (42.9)	
Basal ganglion/ thalamus involvement	1 (11.1)	-	
IV. Biomarkers, n (%)			
>20 Cerebrospinal fluid cell	2 (22.2)	1 (14.3)	.999
High cerebrospinal fluid protein	2 (22.2)	1 (14.3)	
Oligoclonal band type 2	1 (11.1)	2 (28.6)	
Increased IgG index	1 (11.1)	1 (14.3)	
Herpes simplex virus encephalitis	-	2 (100)	
AIE associated antibody positive	6 (66.7)	4 (57.1)	.999
V. Treatment, n (%)			
Initiation first-line therapy (day), median (minimum–maximum)	19 (6-60)	13 (2-90)	.723
The interval between symptoms and initiation first-line therapy <4 weeks	7 (77.8)	5 (71.4)	.999
Duration of response to first-line therapy >4 weeks	2 (22.2)	4 (57.1)	.302
Need for second-line therapy	4 (44.4)	6 (85.7)	.145
VI. Need for intensive care unit, n (%)	6 (66.7)	3 (42.9)	.615

AIE, autoimmune encephalitis; IgG, immunoglobulin G; SD, standard deviation.

Table 6. The Value of Clinical Features with Respect to Autoimmune-Related Epilepsy

	Autoimmune Epilepsy (–) (n = 9) (42.9)	Autoimmune Epilepsy (+) (n = 12) (57.1)	*P*
Age (months), mean ±SD	114.2 ±67.3	83 ±57	.268
AIE-associated antibody, n (%)			.999
Positive	6 (66.7)	8 (66.7)	
Negative	3 (33.3)	4 (33.3)	
Seizure type, n (%)			
Focal	4 (44.4)	2 (16.7)	.271
Generalized	4 (44.4)	2 (16.7)	
Multiple	-	2 (16.7)	
Spasm	-	-	
Non-convulsive status epilepticus	1 (11.1)	1 (8.3)	
Presence of status epilepticus, n (%)	-	6 (50)	**.019**
Duration of status epilepticus (day), mean ±SD	-	5.7 ±1.7	
Abnormal electroencephal ography, n (%)	8 (88.9)	12 (100)	.429
Background rhythm focal slow	5 (55.6)	6 (50)	
Generalized slow	2 (22.2)	2 (16.7)	
Epileptic discharges focal	6 (66.7)	10 (83.3)	
Generalized	1 (11.1)	1 (8.3)	
Abnormal magnetic resonance imaging, n (%)	2 (22.2)	8 (66.7)	.056
Temporal/hippocampal involvement	1 (11.1)	7 (58.3)	
Cortical lesion	-	7 (58.3	
Basal ganglion/ thalamus involvement	1 (11.1)	2 (16.7)	
Number of ASM at the acute phase of the disease	1 (0-3)	2 (1-6)	.152
Preference of ASM at the acute phase of disease, n (%)*			
Levetiracetam	6 (75)	12 (100)	
Diphenylhydantoin	3 (37.5)	5 (41.7)	
Valproic acid	1 (12.5)	7 (58.3)	
Carbamazepine	2 (25)	4 (33.3)	
Number of ASM at the 1-year follow-up	-	2.5 (1-4)	-
Antibody Prevalence in Epilepsy score	6 ±1.9	6.5 ±2.7	.638
Response to Immuno-therapy in Epilepsy score	9.1 ±1.9	9.6 ±3.17	.650

AIE, autoimmune encephalitis; ASM, anti-seizure medication; SD, standard deviation.
*Some patients had more than 1 ASM.

the male gender was more prevalent in the seronegative AIE group. However, there was no significant difference between seropositive and seronegative AIEs with respect to the studied 5 group prognostic parameters: (i) clinical manifestations,

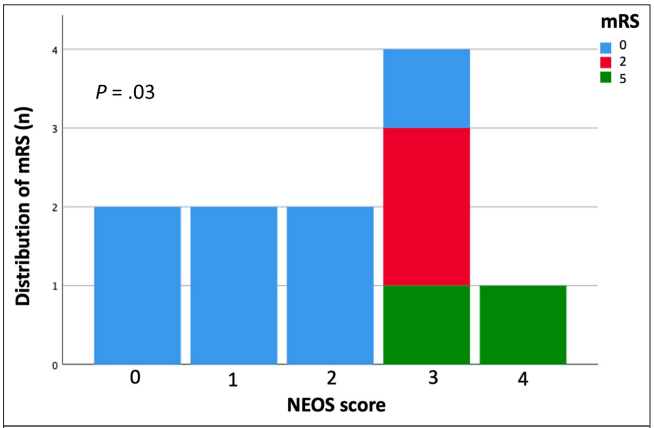

Figure 1. Distribution of the NEOS score and mRS at the first-year follow-up in anti-NMDAR encephalitis patients. mRS, modified Rankin scale, n, number of patients; NEOS, anti-N-methyl-D-aspartate receptor encephalitis 1-year functional status score.

(ii) abnormal EEG features, (iii) abnormal MRI characteristics, (iv) biomarkers, and (v) treatment modalities. A recent study also reported no difference in electrophysiological, clinical, or radiological outcomes between seronegative and anti-NMDAR encephalitis.[16]

The early diagnosis and urgent initiation of the first-line and second-line therapies with disease-modifying drugs are vital for favorable outcome.[11,17] A study that evaluated only anti-NMDAR encephalitis patients in all age groups reported that first-line therapy might be inadequate in the presence of movement disorders, impaired consciousness, central hypoventilation, hypoalbuminemia, and pulmonary infection. The necessity for an ICU, increased CSF pressure, and elevated neutrophil–lymphocyte ratio were presented as important factors affecting the response to first-line treatment.[18] In the present study, almost half of the patients were successfully treated with first-line therapy. The patients with movement disorders in the acute phase of the disease needed more second-line therapy. When the seropositive and seronegative AIE groups were evaluated separately, second-line therapy was needed for 66.6% and 37.5% of seropositive and seronegative AIE patients, retrospectively. While the first-line therapy was insufficient in those with movement and sleep disorders in the seropositive group, no significant difference was found in the parameters investigated in the seronegative AIE group. In a meta-analysis, delayed or no treatment with immunotherapy agents, change in consciousness, and the requirement of the ICU were reported to be associated with poor prognosis in cases of anti-NMDAR encephalitis. On the contrary, the same study revealed that older age, gender, SE, MRI findings, CSF abnormalities, antibody titers, autonomic dysfunction, and underlying malignancy had no prognostic significance.[19] In research that especially included anti-NMDAR encephalitis patients in childhood, MRI abnormalities and cognitive impairment were related to poor prognosis at the sixth-month follow-up. Similar to our study, this research found, the need for rituximab therapy was not associated with a poor outcome.[20] In another paper that evaluated only anti-NMDAR encephalitis patients in childhood, the presence of SE and the need for ICU were defined as parameters affecting the prognosis.[15] Another study in children with AIE without any serological distinction concluded that extremity dyskinesia was related to poor prognosis.[21] Except NMDAR antibody-positive cases were triggered after HSV encephalitis, the presence of SE was associated with adverse prognosis in our study.

Using the NEOS score to forecast 1-year outcomes may offer additional benefits during clinical practice. The first paper examined this scoring system in a pediatric cohort of 30 patients with anti-NMDAR encephalitis.[7] The reported NEOS scores were substantially correlated with functional results, with 75% of children with NEOS 0 and 0% of patients with NEOS 4 having favorable functional outcomes at 1 year. Similarly, in our study, we found a correlation between mRS and NEOS scores among anti-NMDAR encephalitis patients. While mRS was 0 in all our study groups with a NEOS score of ≤2, 80% of those with a NEOS score of >2 had an mRS >2. However, further statistical analysis could not be performed due to the limited number of cases in these 2 studies. A recent study that included 175 children with anti-NMDAR encephalitis assessed the validity of the NEOS score. They reported good discrimination and calibration power of the NEOS score in pediatric cases with an AUC of 0.86 and Spearman r = 0.3878 (95% CI: 0.2500-0.5103).[22]

Recent studies indicate a certain description of acute symptomatic seizures and autoimmune-related epilepsy.[12] Seizures are the most common clinical sign in AIE, regardless of serological status. Most of the seizures are focal, as in our study. The incidence of SE varies between 33% and 43.5%.[23,24] Electroencephalography abnormalities are crucial for differential diagnosis in anti-NMDAR-positive AIE patients, especially those with psychiatric symptoms.[25] The frequency of EEG abnormalities in this patient group is 45%, with slow posterior dominant background rhythm being the most common finding.[12,23] In a study including 2525 AIE patients, the first clinical manifestation was a seizure in 50 of the cases, and 54% of the patients achieved seizure-free status. Although levetiracetam (LEV) was the most used ASM, it was shown to be unsuccessful in seizure control. On the other hand, carbamazepine, lacosamide, phenytoin, and oxcarbazepine have been presented as effective ASMs in seizure management.[13] In our study, LEV was the most often selected ASM. It was proven to be beneficial as monotherapy when taken in combination with immunomodulatory treatment. Immune epilepsy rates in anti-NMDAR encephalitis patients ranged from 5% to 15% following the acute phase. Immune epilepsy has been reported to be more common in seronegative AIE patients.[14,16] In our study, the rate of immune epilepsy was 50.1% in the first year of follow-up, which was higher than in previous studies. Status epilepticus in the acute phase was significantly more frequent in patients that acquired immune epilepsy in the first year of follow-up ($P = .019$).

The anti-NMDAR encephalitis may also overlap with other diseases that are demyelinating disorders, such as acquired demyelination, brain stem encephalitis, leukoencephalopathy following herpes simplex encephalitis, and neuromyelitis optica spectrum disorder.[26,27] In addition to being widely dispersed in the neocortex, NMDA receptors are also found in the anterior horn cells of the spinal cord.[28] The pathogenic circulating antibodies have the potential to harm both the central nervous system and the peripheral nervous system. In the case of anti-NMDAR encephalitis, motor neurons had

suffered antibody-mediated injury during autopsy.[29] In addition, patients with anti-NMDAR encephalitis, like our case, had also been documented to anticipate Guillain-Barré syndrome.[30,31] It has been shown that 27%-30% of patients with HSV encephalitis develop AIE during the follow-up period. In addition, AIE usually occurs 2 months after HSV encephalitis, the symptoms are age-dependent, and the neurological outcome is worse in younger children.[32,33] In our study group, 30% of anti-NMDAR encephalitis patients had a history of HSV encephalitis, with antibody positivity occurring typically 25 days to 2 months following HSV encephalitis. Moreover, the patients younger than 12 years had neurologic deficits and drug-refractory epilepsy, while the patients older than 12 years had mostly favorable outcomes in the sixth month.

In conclusion, we defined a favorable outcome with a rate of 56% in a small pediatric cohort of AIE with a restricted departmental treatment protocol. The presence of SE was the most important prognostic factor in the patients with the adverse outcome as well as autoimmune-related epilepsy. The studied scoring models (NEOS, APE, and RITE) have also been proven to be applicable to the pediatric age group for predicting overall outcome and autoimmune-related epilepsy.

Ethics Committee Approval: The study was approved by the Ege University Medical Research Ethics Committee (Project no: 22-6.1T/71).

Informed Consent: Informed consent was obtained from the patient's family, who agreed to take part in the study.

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