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BRIEF REPORT

Neuropsychiatric outcomes of patients with encephalitis: A case series with long-term follow-up

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ABSTRACT

Objective: The long-term course of neuropsychiatric, cognitive, and behavioral symptoms that develop after encephalitis has not been studied adequately. We aimed to investigate the progression of these symptoms in a case series of patients followed up after encephalitis.

Method: Patients were evaluated through neurological and psychiatric assessments, as well as cranial magnetic resonance imaging and electroencephalography recordings at the baseline. Neuropsychiatric outcomes were assessed using the Mini-Mental State Examination (MMSE), Frontal Behavior Inventory (FBI), Hamilton Depression Rating Scale (HDRS), Neuropsychiatric Inventory (NPI), Katz Activities of Daily Living (Katz ADL) Index Scale, and Lawton Instrumental Activities of Daily Living (IADL) Scale.

Results: A total of 15 patients were evaluated at the baseline and 10 of them had a follow-up assessment after a median of 60 months. The patients with active epilepsy had worse Katz ADL scores than those with complete seizure control. MMSE scores were negatively correlated with FBI and ADL + IADL scores. While MMSE scores did not change significantly in the follow-up assessment, there was a decrease in FBI, HDRS, and NPI scores, as well as an improvement in ADL + IADL scores.

Conclusion: Our case series suggest that complete seizure control, high MMSE scores, and absence of frontal behavioral symptoms are associated with less dependence on others in activities of daily living after encephalitis. The overall cognitive status of patients who recovered from encephalitis was unchanged in the long term. However, patients demonstrated improvements in neuropsychiatric and behavioral symptoms, such as disinhibition, and better daily functioning with time.

Keywords: Encephalitis, epilepsy, neuropsychiatry, behavioral symptoms, functional status

INTRODUCTION

Encephalitis is inflammation of the brain tissue that is caused mostly by viral infections or autoimmune causes. Despite intensive investigations, the etiology remains unidentified in 30%–50% of the cases, while the most common etiology is viral infections in identifiable cases (1). Although encephalitis is an acute condition that might present with a wide range of neurological and psychiatric symptoms, it can also cause long-term disability. The focus of encephalitis diagnosis has traditionally been on neurological symptoms (2). However, early psychiatric findings may also be helpful. Glaser et al. (1) described that more than one-third of encephalitis cases in which the temporal lobe was affected presented with new-onset psychosis. A higher rate of psychosis was detected in the patient

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group due to noninfective causes (i.e., autoimmune causes) compared to infective causes in the same study. Affected individuals may experience delusions, hallucinations, agitation, and depression as a result of encephalitis (3).

Epilepsy, which can be a neurological manifestation of encephalitis, and antiseizure drugs used in the treatment of epilepsy, or status epilepticus may contribute to neuropsychiatric sequelae in patients with encephalitis. Population-based studies show that depression, psychosis, and anxiety disorders are more common in epilepsy patients than in the general population (4).

There are few studies about long-term neuropsychiatric outcomes in encephalitis in the literature. Prior to the identification of autoimmune antibodies, many studies focused on neuropsychiatric sequelae in patients recovering from infective etiology, most of them herpes simplex virus (HSV). According to a study comparing neuropsychological parameters in patients with HSV encephalitis with those without, executive function was significantly impaired in patients with HSV encephalitis (5).

Literature regarding the persistence of cognitive, neuropsychiatric, or behavioral symptoms after encephalitis is limited. Therefore, defining the course of these constructs may offer insights into the prognosis of patients recovering from encephalitis. In this study, we aimed to determine the relationship between neuropsychiatric symptoms, cognitive functions, and daily functioning and the course of these entities. Our secondary aim was to compare these outcomes based on encephalitis etiology, sociodemographic factors, and the presence of epilepsy.

METHOD

Participants

Patients followed up in Istanbul University Istanbul Medical Faculty, Neurology Department, Epilepsy Unit following encephalitis between 2015 and 2020 were included consecutively in this study. Exclusion criteria were being younger than 18 years of age, illiteracy, having any psychiatric disorder diagnosis prior to encephalitis, a history of a head trauma or brain surgery, inability to understand or cooperate due to severe cognitive impairment, mental retardation, or aphasia. The study protocol was approved by the ethics committee of Istanbul University Istanbul Medical Faculty (IRB: 10/09/2021 – 2021/1493) and written informed consent was obtained from all patients. When applicable, their legal representatives or guardians after the study process had been fully explained. The study was conducted in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the World Medical Association Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects revised in 2013.

Procedure and Evaluation Instruments

Sociodemographic and clinical data of the patients were collected with a preprepared form specifically designed for this study. The etiology of patients' diagnosis of encephalitis was based on health records. The baseline and follow-up neurological examinations, as well as the Electroencephalogram (EEG) and magnetic resonance imaging (MRI) evaluations, were conducted by a neurologist, whereas patients' psychiatric examinations and neuropsychiatric assessments were carried out by a psychiatrist. The baseline evaluations were conducted at least 6 months after the encephalitis onset, and no upper time limit criterion was implemented. Patients were followed for at least 1 year, or if possible, for 5 years for the follow-up assessment. Patients lost to follow up before 1 year were excluded from the follow-up analysis.

All assessments were conducted in one session, which took approximately 1 hour. Psychiatric examinations and neuropsychiatric assessments did not need to be conducted by the same psychiatrist at baseline and follow-up. Patients' neuropsychiatric outcomes were evaluated with the Mini-Mental State Examination (MMSE), Frontal Behavior Inventory (FBI), Hamilton Depression Rating Scale (HDRS), Neuropsychiatric Inventory (NPI), Katz Activities of Daily Living (Katz ADL) Index Scale, and Lawton Instrumental Activities of Daily Living (IADL) Scale, both in the baseline and follow-up assessments.

Mini-Mental State Examination

MMSE is a well-known brief screening scale for global cognitive status that is extensively used worldwide (6,7).

Frontal Behavior Inventory

FBI was developed specifically for the assessment of behavioral symptoms of patients with frontal lobe dementia. It contains two subscales for negative and disinhibition behaviors (8,9).

Hamilton Depression Rating Scale

This scale measures the severity of depression and contains a total of 17 questions (10,11).

Neuropsychiatric Inventory

NPI assesses the presence of 12 neuropsychiatric symptoms: delusions, hallucinations, agitation/aggression, dysphoria, anxiety, euphoria, apathy, disinhibition, irritability/lability, aberrant motor activity, nighttime behavioral disturbances and appetite, and eating abnormalities (12,13).

Katz Activities of Daily Living Index Scale

Katz ADL is one of the most commonly used tools to assess basic activities of daily living: bathing, dressing, toileting, transferring, continence, and feeding (14). The Turkish version of the Katz ADL has been assessed for validity (15). We used a modified scoring where the clinician rates individuals between 0 and 2 for all six areas as either fully independent (no supervision, direction, or personal assistance needed), receiving partial assistance, or receiving total help where a higher score indicates more dependence on other people.

Lawton Instrumental Activities of Daily Living Scale

IADL assesses a person's ability to use instruments in daily living and measures eight domains: using the telephone, shopping, preparing food, housekeeping, doing laundry, using transportation, handling medication, and handling finances (16). IADL's Turkish version has been evaluated for reliability and validity (17). We used a modified scoring where each activity is scored between 0 and 2. A higher score indicates the patient is unable to perform the activity or is dependent on others, while a lower score means the patient is independent in that area.

Statistical Analyses

Statistical Package for Social Sciences (SPSS) version 20 (IBM Corp.) for MS Windows was used to analyze the data. Results are given as median (interquartile range [IQR]) for continuous variables and as count and percentages (%) for categorical variables. A p-value of less than 0.05 was considered statistically significant. Categorical variables were analyzed with either the Chi-squared test or Fisher's exact test where appropriate, and continuous variables were analyzed using the Mann–Whitney U test. Pearson's correlation coefficients were calculated to explore the relationship between continuous variables. As our study was exploratory in nature, the assumptions related to sample size were not used for correlation analysis.

RESULTS

A total of 15 patients were included in our study after excluding three patients, one of whom was illiterate, one with pre-encephalitis psychotic disorder, and one younger than 18 years of age. The mean age of the included patients was 41.20±14.89 years, and 10 of the patients were females (66.7%). Five of the patients had a high school education or higher, and the mean years of education of the whole sample were 8.87±4.00. There were 4 patients who could not work and 2 patients who were retired. All of the participants lived at home with their families (12 with their partners, 1 with their children, and 2 with their parents), and no one lived in an institution. Baseline evaluations of the participants were conducted after a median of 44 (67) months of encephalitis onset. Ten of the participants had a follow-up evaluation with a median of 60 (15) months.

Each individual's clinical features, MRI, and EEG findings are presented in Appendix 1. If the patients' cerebrospinal fluid (CSF) findings were compatible with infectious etiology (i.e., positive for Herpes PCR), they were diagnosed and treated accordingly. If the patients' CSF findings were not compatible with an infectious etiology (i.e., negative for Herpes PCR) and no other cause was identifiable, they were treated with 1000 mg intravenous methylprednisolone for 5 days followed by intravenous immunoglobulin for 5 days per standard protocol in the hospital. After reviewing patients' health records, 2016 Autoimmune Encephalitis clinical criteria by Graus et al. (18) were used for reporting patients' diagnoses of autoimmune encephalitis. However, there was no information in the health records of the patients regarding a further investigation of the etiology.

The median age at encephalitis onset was 32.5 years (28), and the median time passed since encephalitis onset was 52.0 (67.5) months. One of the patients had epilepsy prior to encephalitis and 13 patients (86.7%) had epilepsy post-encephalitis. All of the participants, except for 1 patient without epilepsy, were using antiseizure medication at the initial evaluation. Six of the patients (40%) had a status epilepticus history. Nine of the patients (60.0%) had developed a psychiatric disorder that required treatment after encephalitis, and one of them had a suicide attempt and subsequent psychiatric hospitalization.

Table 1: Cognitive, neuropsychiatric, behavioral, and functional status of the patients

Case no.	Age (years)	Sex	Time between tests (months)	MMSE		FBI, negative behavior		FBI, disinhibition		FBI, total		HDRS		NPI, total		Katz ADL		IADL		ADL + IADL	
				B	F/U	B	F/U	B	F/U	B	F/U	B	F/U	B	F/U	B	F/U	B	F/U	B	F/U
1	37	F	–	28	–	14	–	6	–	20	–	15	–	19	–	2	–	6	–	8	–
2	18	F	–	28	–	8	–	7	–	15	–	7	–	15	–	1	–	3	–	4	–
3	32	M	66	30	29	8	0	1	0	9	0	9	2	17	1	0	0	0	0	0	0
4	21	F	63	28	29	7	1	9	2	16	3	24	7	63	10	1	0	3	0	4	0
5	63	M	63	22	21	16	12	7	4	23	16	16	7	43	13	1	1	5	6	6	7
6*	32	F	–	30	–	2	–	7	–	9	–	15	–	33	–	–	–	–	–	–	–
7	36	F	59	18	18	19	18	2	3	21	21	14	13	24	16	4	2	11	11	15	13
8	50	F	–	8	–	11	–	16	–	27	–	14	–	48	–	3	–	8	–	11	–
9	56	M	60	26	25	11	3	7	2	18	5	3	1	9	2	0	0	1	0	1	0
10	53	F	60	24	26	4	1	4	2	8	3	9	3	29	4	4	0	9	1	13	1
11	61	F	48	26	28	1	1	2	1	3	2	8	3	8	5	0	0	0	0	0	0
12	40	M	61	30	30	6	0	4	1	10	1	16	2	49	1	1	0	0	0	1	0
13	59	M	48	26	28	2	2	2	0	4	2	2	1	3	2	0	0	5	0	5	0
14	36	F	15	26	26	3	1	0	0	3	1	9	7	12	7	1	1	2	2	3	3
15	24	F	–	29	–	1	–	0	–	1	–	0	–	0	–	0	–	0	–	0	–

B: Baseline; F/U: Follow-up; F: Female; M: Male; MMSE: Mini-mental status examination; FBI: Frontal Behavioral Inventory; HDRS: Hamilton Depression Rating Scale; NPI: Neuropsychiatric Inventory; Katz ADL: Katz activities of daily living; IADL: Lawton instrumental activities of daily living; ADL + IADL: Combined score of Katz ADL and IADL; *: Baseline Katz ADL, IADL, and ADL + IADL scores are missing for case 6.

Table 2: Correlation matrix of baseline neuropsychiatric test scores

Pearson's correlation	MMSE	FBI, negative behavior	FBI, disinhibition	FBI, total	HDRS	NPI, total	ADL + IADL
Age							
r	-0.375	0.080	0.070	0.091	-0.190	-0.091	0.138
p	0.168	0.778	0.805	0.746	0.497	0.746	0.638
Education level							
r	0.304	-0.387	**-0.560***	**-0.558***	-0.463	-0.371	-0.175
p	0.270	0.154	**0.030**	**0.031**	0.082	0.173	0.550
Time since encephalitis onset							
r	0.003	-0.223	-0.144	-0.229	-0.377	-0.376	0.012
p	0.993	0.424	0.610	0.411	0.166	0.167	0.967
MMSE							
r	–	-0.465	**-0.567***	**-0.616***	-0.147	-0.277	**-0.675****
p	–	0.081	**0.028**	**0.014**	0.602	0.317	**0.008**
FBI, negative Behavior							
r		–	0.348	**0.875****	0.400	0.305	**0.541***
p		–	0.204	**0.000**	0.140	0.269	**0.046**
FBI, disinhibition							
r			–	**0.758****	0.477	**0.640***	0.332
p			–	**0.001**	0.072	**0.010**	0.246
FBI, total							
r				–	**0.524***	**0.543***	**0.536***
p				–	**0.045**	**0.036**	**0.048**
HDRS							
r					–	**0.892****	0.324
p					–	**<0.001**	0.259
NPI, total							
r						–	0.299
p						–	0.298

MMSE: Mini-mental status examination; FBI: Frontal Behavioral Inventory; HDRS: Hamilton Depression Rating Scale; NPI: Neuropsychiatric Inventory; ADL + IADL: Combined score of Katz Activities of Daily Living Index Scale and Lawton Instrumental Activities of Daily Living Scale. *: Correlation is significant at the 0.05 level (two-tailed); **: Correlation is significant at the 0.01 level (two-tailed).

Each individual's neuropsychiatric assessment results are presented in Table 1. Ten patients (66.7%) were above the 8-point cutoff of HDRS. Three (20%) of the patients had a score of 1 or higher in NPI hallucinations, and the other 3 had a score of 1 or higher in the NPI delusion subscales. The baseline neuropsychiatric test (MMSE, FBI, HDRS, NPI, Katz ADL, and IADL) scores were not statistically different between males and females, early and late age of onset of encephalitis (<35 years old vs >35 years old), or patients with autoimmune encephalitis and viral encephalitis. Additionally, there was no relationship between left and right lateralization, defined according to MRI or EEG findings and baseline neuropsychiatric test scores. Similarly, the scores were not different among patients with different types of seizures or whether the patient was using antiseizure drug monotherapy or combination therapy. When the patients were divided into two groups according to whether they had epileptic seizures in the past year or not, the patients with active epilepsy had worse Katz ADL scores than those with complete seizure control (2.14±1.57 vs 0.43±0.53, p=0.027). There was no difference between IADL, combined scores of Katz ADL and IADL (ADL + IADL), and other baseline neuropsychiatric tests (all p>0.05).

Correlations between age, education level, time since encephalitis onset, and baseline tests are shown

Table 3: Baseline and follow-up neuropsychiatric test scores

	Baseline test (n=15)				Follow-up test (n=10)				Test statistics*	
	Mean	Median	SD	IQR	Mean	Median	SD	IQR	Z-score	p
MMSE	25.3	26	5.8	5	26.0	27	3.8	5	-1.127	0.260
FBI, negative behavior	7.5	7	5.7	9	3.9	1	6.1	4.5	-2.807	0.005
FBI, disinhibition	4.9	4	4.2	5	1.5	1.5	1.4	2.25	-2.527	0.012
FBI, total	12.5	10	8.2	16	5.4	2.5	7.1	6.75	-2.442	0.015
HDRS	10.7	9	6.4	8	4.6	3	3.8	5.25	-2.673	0.008
NPI, total	24.8	19	18.9	34	6.1	4.5	5.3	9	-2.803	0.005
Katz ADL†	1.3	1	1.4	2.25	0.4	0	0.7	1	-1.841	0.066
IADL†	3.8	3	3.7	6.5	2	0	3.7	3	-1.625	0.104
ADL + IADL†	5.1	4	5	8	2.4	0	4.4	4	-2.043	0.041

*: Wilcoxon signed-rank test: the score for MMSE is based on negative ranks; all others are based on positive ranks; †n: 14 in the baseline test; IQR: Interquartile range; MMSE: Mini-mental status examination; FBI: Frontal Behavioral Inventory; HDRS: Hamilton Depression Rating Scale; NPI: Neuropsychiatric Inventory; Katz ADL: Katz activities of daily living; IADL: Lawton instrumental activities of daily living; ADL + IADL: Combined score of Katz ADL and IADL; p<0.05 is considered significant (bold values).

in Table 2. There was no significant correlation between the neuropsychiatric test scores and age, age at encephalitis onset, and time passed since encephalitis onset. The only sociodemographic variable correlated with neuropsychiatric outcome was education level, which was negatively correlated with FBI disinhibition scores. MMSE scores were negatively correlated with FBI disinhibition and total FBI scores, as well as ADL + IADL scores. FBI-negative was correlated with ADL + IADL scores, and FBI disinhibition was correlated with NPI total scores. Correspondingly, the FBI total score was correlated with both ADL + IADL and NPI total scores, along with HDRS scores. HDRS scores were only correlated with the total NPI score.

There were no sociodemographic (sex, age, education level, and employment status) or clinical (age at onset, type of encephalitis, having epilepsy, antiseizure drug use, type of seizure, and having a psychiatric disorder history) differences among patients who attended their follow-up examinations except that the patients who were living with their partners were more likely to participate to the follow-up visit (p=0.024). Baseline neuropsychiatric test scores were not significantly different between those who did and did not attend the follow-up visit. Patients' cognitive, behavioral, and neuropsychiatric symptoms and daily functioning at baseline and follow-up tests are shown in Table 3. There was a decrease in all items of NPI in the follow-up assessment, especially in the median scores of agitation/aggression, dysphoria/depression, and apathy/indifference items, although these decreases were not statistically significant after the Bonferroni correction for multiple comparisons (Fig. 1).

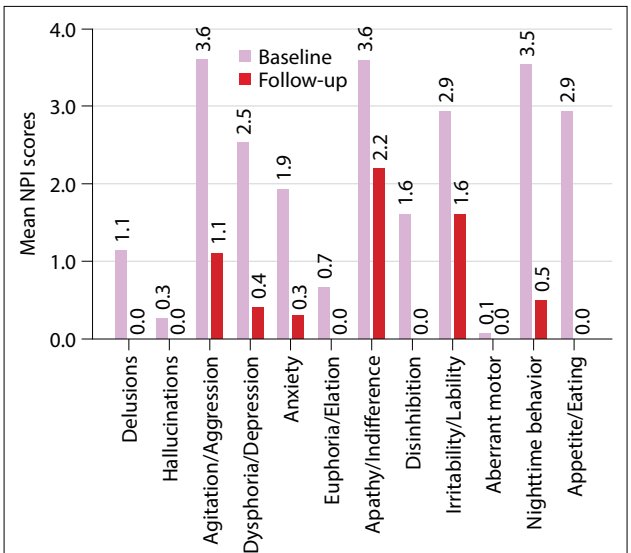

Figure 1. Change in mean scores of neuropsychiatric inventory domains at baseline and follow-up.

DISCUSSION

In this case series with a prospective design, we present a detailed neuropsychiatric evaluation of 15 patients who recovered from encephalitis. Ten of these patients had a follow-up evaluation with a median of 60 months, and they showed improvements in behavioral and neuropsychiatric symptoms and daily functioning while there was no major change in their cognitive status.

We have found that lower cognitive functioning after encephalitis was correlated with frontal behavioral symptoms. Likewise, lower cognitive status was associated with more dependence on

others in activities of daily living. Contrary to evidence from dementia research (19), we did not find an association between neuropsychiatric symptoms and ADLs in patients who recovered from encephalitis. Frontal disinhibition and apathy symptoms were other measures we used to quantify behavioral problems. Although cases of behavioral disinhibition have been reported after viral encephalitis (20), to our knowledge, there is no literature indicating the same after autoimmune etiology. This may be related to the fact that viral encephalitis affects mainly the temporal and orbitofrontal regions (21), while autoimmune encephalitis mostly affects the temporal regions solely (22). Patients' daily functioning worsened with increasing apathy, whereas disinhibition was related to neuropsychiatric symptoms.

The total HDRS score was only correlated with the total NPI score, possibly due to the same symptom domains (such as anxiety, depression, and irritability) being scored in both questionnaires. Our results suggest that depressive symptoms following encephalitis do not predict diminished cognitive status or dependence on others in activities of daily living, in contrast to previous literature from older adults (23).

Epilepsy patients' seizure type and frequency, use of multiple antiseizure drugs, and history of status epilepticus have been reported to be associated with neuropsychiatric impairment (24). In our study, we observed a deterioration in functional status measured by activities of daily living scale if patients did not have complete seizure control in the past year, pointing out the importance of meticulous treatment of epilepsy. However, we did not find a relationship between seizure type, multiple antiseizure drug use, and history of status epilepticus and patients' cognitive, neuropsychiatric, or behavioral problems, as suggested in the literature (25).

Patients' negative and disinhibition frontal behavior scores, depressive and other neuropsychiatric symptoms, and independence in daily activities had improved over the follow-up period. Contrary to this, patients' cognitive status, measured with MMSE, did not change significantly. This implies that neuropsychiatric and frontal behavioral symptoms due to encephalitis are not directly related to cognitive impairment and might improve even if there is no change in the patient's cognitive status. Also, the reduction of behavioral and neuropsychiatric symptoms may have contributed to the improvement of daily living activities.

Neuropsychiatric sequelae such as disinhibition, aggression, and irritability have been described after viral or autoimmune encephalitis. Among these symptoms, irritability was noted to be the most common and persistent (26). In a study examining the long-term course of psychiatric symptoms in patients who recovered from Japanese encephalitis, agitation, apathy, depression, and emotional instability were commonly encountered initially, but these symptoms abated over time (27). Despite the decrease in the severity of each symptom domain in the follow-up assessment in our study, scores for agitation-aggression, apathy-indifference, and irritability-lability remained elevated. On the other hand, it is promising to see that the symptoms of disinhibition decreased over time in our study, which is also closely related to caregiver burden and stress (28). Another study has also shown that patients with anti-NMDA encephalitis continue to have long-term cognitive deficits although lessening over time (29). The authors reported that the recovery was time-dependent and was more pronounced in the earlier years after encephalitis. As our first assessment of our patients was about 4 years after encephalitis onset, they might have already improved considerably, so we could not find any more improvement between the first and second assessments. A relatively high mean MMSE score of 25.8 in our initial assessment supports this view. In addition, MMSE might not be specific enough to detect changes reported in other studies, which used a more comprehensive assessment of cognition.

Our study has some limitations. First, our sample size was quite small, and one-third of our patients were lost at follow-up. While we could detect significant differences in daily functioning levels between patients with active epilepsy and seizure-free patients, due to the limited number of cases, our study may be underpowered to detect some weaker associations between subgroups. Other limitations of the study were the heterogeneity of encephalitis etiology, the inability to exclude medical comorbidities, and the marked difference between cases in terms of time passed after encephalitis diagnosis. Owing to the small sample size, we were not able to establish associations or make any inferences with regard to encephalitis etiology and neuropsychiatric outcomes. On the other hand, prospective follow-up of the patients for a median of 60 months is a strength of our study.

This study illustrates the relationship between cognitive, behavioral, and neuropsychiatric symptoms and daily functioning after encephalitis and the long-term course of these measures. Complete seizure control, high MMSE scores, and absence of frontal behavioral symptoms were associated with less dependence on others in activities of daily living after encephalitis. The overall cognitive status of patients who recovered from encephalitis was unchanged in the long term; however, they demonstrated improvements in neuropsychiatric symptoms and behavioral problems, especially agitation and disinhibition. Our results suggest that neuropsychiatric symptoms may persist for years after encephalitis, though their severity decreases with time and patients' dependence on others lessens. Future studies with larger sample sizes are needed to determine if the identified risk factors can predict the persistence of neuropsychiatric outcomes after encephalitis. In the meantime, treating residual behavioral symptoms and aiming for full control of epileptic seizures seems to be necessary for the effective utilization of health services and to reduce caregiver burden.

Contribution Categories		Author Initials
Category 1	Concept/Design	E.B., S.K., N.B., I.B.K.
	Literature review	E.B., S.K., M.E., F.U.D.
	Data analysis/Interpretation	M.E., F.U.D.
Category 2	Drafting manuscript	M.E., F.U.D., E.B., S.K.
	Critical revision of manuscript	N.B., I.B.K.
Category 3	Final approval and accountability	M.E., F.U.D., E.B., S.K., N.B., I.B.K.
Other	Technical or material support	N.B., I.B.K.
	Supervision	N.B., I.B.K.

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Appendix 1: Clinical features, MRI findings, and EEG characteristics of the patients

Case no.	Age (years)	Sex	Encephalitis diagnosis	Time since encephalitis (months)	Post-encephalitic psychiatric diagnosis*	Seizure frequency (in a month)	Type of seizure			Antiseizure drugs used	MRI findings	EEG findings
							FIAS	GTCS	MS			
1	37	F	Probable LE	25	–	5	(+)	(+)		LEV 2500 mg/d, VPA 1500 mg/d, CBZ 1200 mg/d	Hyperintense areas on FLAIR sections in the R mesial temporal and insular regions	Severe slowing and epileptic discharges in the R temporal region
2	18	F	VZV encephalitis	136	–	2	(+)	(+)		TPM 250 mg/d, CBZ 1200 mg/d, CLZ 0,6 mg/d	Encephalomalacia in the R occipital region	Mild slowing and epileptic discharges in the R frontotemporal region
3†	32	M	Probable LE	84	Panic disorder	–		(+)		VPA 300 mg/d	Normal	Mild generalized slowing
4†	21	F	Probable LE	41	Depressive disorder	–		(+)		LEV 750 mg/d	Hyperintense areas on FLAIR sections in the L temporoparietal region	Normal
5†	63	M	HSV encephalitis	31	Organic mental disorder	–	(+)	(+)	(+)	CBZ 1000 mg/d	Encephalomalacia in the R temporal region	Mild generalized slowing
6†	32	F	TBC encephalitis	93	–	–	(+)	(+)		LEV 1000 mg/d	Contrast-enhancing regions in bilateral insular, R cerebellum, and caudate nucleus	Normal
7	36	F	Definite LE	92	Organic mental disorder	3	(+)	(+)		LEV 2000 mg/d, CBZ 1000 mg/d, TPM 50 mg/d	Hyperintense areas on FLAIR sections in the bilateral mesial temporal region	Generalized slowing, severe in the R hemisphere and epileptic discharges in the R frontotemporal region
8	50	F	HSV encephalitis	63	Organic mental disorder	1	(+)	(+)		LEV 2000 mg/d, GPTN 800 mg/d	Hyperintense areas on FLAIR sections in the L temporoparietal region	Generalized slowing, severe in the L hemisphere

Appendix 1 (cont): Clinical features, MRI findings, and EEG characteristics of the patients

Case no.	Age (years)	Sex	Encephalitis diagnosis	Time since encephalitis (months)	Post-encephalitic psychiatric diagnosis*	Seizure frequency (in a month)	Type of seizure			Antiseizure drugs used	MRI findings	EEG findings
							FIAS	GTCS	MS			
9¶	56	M	HSV encephalitis	39	Psychotic disorder	–	–	–	–	–	Hyperintense areas on FLAIR sections in the L mesial temporal region	Possible epileptic foci in the L frontotemporal region
10	53	F	HSV encephalitis	17	Depressive disorder	1	(+)			LEV 1250 mg/d	Encephalomalacia in the R temporal region	Generalized slowing, severe in the R frontotemporal region
11†	61	F	HSV encephalitis	80	Depressive disorder	–	(+)			CBZ 400 mg/d	Hyperintense areas on FLAIR sections in the L mesial temporal region	Periodic lateralized epileptiform discharges in the L temporal region
12†	40	M	Encephalitis of unknown origin	9	–	–	(+)	(+)		LEV 1500 mg/d, VPA 1500 mg/d, PRG 600 mg/d	Nonspecific ischemic gliotic foci in bilateral corona radiata regions	Severe generalized slowing
13†	59	M	HSV encephalitis	348	–	–	(+)	(+)		CBZ 400 mg/d, LEV 1000 mg/d	Encephalomalacia in the R anterior temporal region	Normal
14	36	F	HSV encephalitis	44	Depressive disorder	7	(+)	(+)		LCS 300 mg/d, LEV 2000 mg/d	Hyperintense areas on FLAIR sections in the L mesial temporal region	Normal
15§	24	F	HSV encephalitis	24	–	1	(+)	(+)	(+)	LEV 1000 mg/d	Normal	Normal

F: Female; M: Male; LE: Limbic encephalitis; HSV: Herpes simplex virus; VZV: Varicella zoster virus; TBC: Tuberculosis; FIAS: Focal impaired awareness seizure; GTCS: Generalized tonic-clonic seizure; MS: Myoclonic seizure; LEV: Levetiracetam; VPA: Valproate; CBZ: Carbamazepine; TPM: Topiramate; CLZ: Clonazepam; GPTN: Gabapentin; PRG: Pregabalin; LCS: Lacosamide; MRI: Magnetic resonance imaging; EEG: Electroencephalogram; FLAIR: Fluid attenuated inversion recovery; R: Right; L: left; *: Psychiatric diagnosis is based on clinical evaluation according to DSM-IV-TR; †: Cases 3, 4, 5, 6, 11, 12, and 13 had no seizure in the past year; ¶: Case 9 never had epileptic seizures; §: Case 15 also had epileptic seizures before encephalitis.