

MANAGING ATYPICAL AND TYPICAL HERPETIC CENTRAL NERVOUS SYSTEM INFECTIONS: RESULTS OF A MULTINATIONAL STUDY

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Key words: Herpes Simplex virus; meningitis; encephalitis; atypical presentation; managing

Running Head: Herpetic meningoencephalitis

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MANAGING ATYPICAL AND TYPICAL HERPETIC CENTRAL NERVOUS SYSTEM INFECTIONS: RESULTS OF A MULTINATIONAL STUDY

Abstract

There have been many studies pertaining to the management of herpetic meningoencephalitis (HME), but the majority of them have focused on virologically unconfirmed cases or included only small sample sizes. We have conducted a multicentre study aimed at providing management strategies for HME. Overall, 501 adult patients with PCR-proven HME were included retrospectively from 35 referral centres in 10 countries; 496 patients were found to be eligible for the analysis. Cerebrospinal fluid (CSF) analysis using a PCR assay yielded herpes simplex virus (HSV)-1 DNA in 351 patients (70.8%), HSV-2 DNA in 83 patients (16.7%) and undefined HSV-DNA type in 62 patients (12.5%). A total of 379 patients (76.4%) had at least one of the specified characteristics of encephalitis, and we placed these patients into the encephalitis presentation group. The remaining 117 patients (23.6%) had none of these findings, and these patients were placed in the non-encephalitis presentation group. Abnormalities suggestive of encephalitis were detected in magnetic resonance imaging (MRI) in 83.9% of the patients and in electroencephalography (EEG) in 91.0% of patients in the encephalitis presentation group. In the non-encephalitis presentation group, MRI and EEG data were suggestive of encephalitis in 33.3% and 61.9% of patients, respectively. However, the concomitant use of MRI and EEG indicated encephalitis in 96.3% and 87.5% of the cases with and without encephalitic clinical presentation, respectively. CSF HSV-PCR, EEG and MRI data should be collected for all patients with a central nervous system infection considering the subtle nature of HME.

Keywords: Herpes simplex virus; meningitis; encephalitis; atypical presentation; managing

Introduction

Herpetic meningoencephalitis (HME) is a rare but devastating infectious disease with a mortality rate of up to 70% in the absence of appropriate treatment [1]. Despite rapid diagnostic tests and antiviral therapies, HME is still associated with high rates of mortality and serious sequelae [2-6]. The most important parameters influencing a favourable clinical course are rapid diagnosis and early antiviral therapy initiated within two days of the onset of symptoms [6]. Current guidelines recommend the use of aciclovir in proven or suspected cases of encephalitis [7]. However, the question of what constitutes suspected encephalitis is unclear for the majority of cases in routine practice because the symptoms of meningitis and encephalitis generally overlap at the initial stages of both diseases [8, 9]. As a result, a significant fraction of patients cannot be classified as suspected meningitis or suspected encephalitis by the examining clinician. Accordingly, the clinician may not predict a herpetic central nervous system (CNS) infection and may delay antiviral therapy. There are a large number of studies devoted to the management of HME, but most of them involve virologically unconfirmed cases, a small sample size or are literature reviews [4, 10-17]. The goals of this retrospective, multicentre, multinational study included identifying the characteristic features of HME, determining the performance of diagnostic tests for the disease, and developing an algorithm for an optimal clinical approach to reach the diagnosis of HME.

Materials and Methods

Study design: Retrospective multicentre study. The study was approved by the Review Board of the Dr. Lütfi Kırdar Training and Research Hospital in Istanbul, Turkey.

The predictors of unfavourable outcome in HME cases have been previously published elsewhere [6].

Setting: 35 referral centres in 10 countries including Croatia, The Czech Republic, Denmark, Egypt, France, Iraq, Italy, Lebanon, Slovenia and Turkey.

Participants: This study included all consecutive hospitalised patients with HME between 2000 and 2013. The inclusion criteria comprised the presence of all of the following:

1. Only adult patients (>15 years of age);
2. Patients with positive cerebrospinal fluid (CSF)-polymerase chain reaction (PCR) for herpes simplex virus (HSV)-1 or HSV-2 or for both in a patient with a CNS infection;
3. The unlikely presence of any other infectious disease of the brain or any neurological disorder other than HSV infection.

The exclusion criteria comprised the presence of all of the following:

1. Pediatric patients;
2. The presence of any other infectious or non-infectious disease of the brain.

The definitions used in this study according to hospital admission clinical data were as follows:

1. ***Encephalitis presentation:*** Patients with at least one clinical finding compatible with encephalitis upon hospital admission such as changes in conscious, disorientation, convulsions, amnesia, personality changes, speech disorders, hallucinations, abulia, history of unconsciousness or syncope, hemiparesis, dizziness, facial and hypoglossal cranial nerve palsies were classified in this category.
2. ***Non-encephalitis presentation:*** Patients without one of the clinical findings compatible with encephalitis upon hospital admission noted above were classified in this category.
3. ***Unfavorable outcome:*** It was defined as patients who died of HME or survived with sequelae [6].

A questionnaire and a complementary Microsoft for Windows Excel file were distributed to the participant centres. Data on demographics, clinical and routine laboratory parameters, cranial radiological imaging findings including magnetic resonance imaging (MRI), computerised tomography (CT), brain electroencephalography (EEG), routine CSF analysis, CSF-PCR for HSV, CSF serological analysis for HSV, length of hospital stay (LOS), treatment and outcomes were collected. At the end of the study period, the centres submitted their data as an Excel document. These data were then merged to form the final database.

Statistical methods: All the patients diagnosed as HME were classified into two groups: those encephalitis presentation group and those non-encephalitis presentation group. The data analysis was conducted SPSS (SPSS, Windows V.16.0). We present descriptive statistics as frequencies, percentages for categorical variables and as mean \pm standard deviation (SD) and median [interquartile range (IQR)] for continuous variables according to the results of a normality test (the one-sample Kolmogorov-Smirnov test). For group comparisons, we used the chi-square and Fisher's exact tests for the categorical variables, and for numerical variables, Student's *t*-test for the parametric data and the Mann-Whitney *U*-test for the non-parametric data. All of the tests were two-tailed, and we assigned statistical significance to *P* values less than 0.05.

Results

A total of 501 HME patients were included retrospectively. Of these patients, five patients were excluded due to missing CSF-PCR data and 496 patients were enrolled. The median (IQR) age of the patients was 50.5 (33.3–63.0) years. Of the study group, 266 patients (53.6%) were female. The patients were initially admitted to the departments of infectious diseases (n=326, 65.7%), neurology (n=80, 16.1%), internal medicine (n=62, 12.5%), intensive care unit (n=24, 4.8%) and other departments (n=4, 0.8%).

Clinical presentation

A total of 379 patients (76.4%) presented at least one of the symptoms associated with an initial diagnosis of encephalitis presentation (Table 1). The remaining 117 patients (23.6%) exhibited none of these findings. The primary symptoms that led the clinician to perform lumbar puncture (LP) in these 117 patients are presented in Table 1. In this subgroup of cases, headache, neck stiffness, Kernig's and Brudzinski's signs were significantly more frequent than the encephalitis presentation group ($P < 0.05$ for all comparisons). In contrast, fever was significantly less frequent compared with the number observed into the encephalitis presentation group of patients ($P < 0.0001$; Table 1). Only 2 out of the 117 patients had immunosuppressive conditions, which can explain the absence of encephalitis findings (data not shown).

The comparisons of initial abnormal radiological imaging and EEG findings between the two groups are presented in Table 1. The number of abnormal findings on MRI, EEG, CT, and one of MRI or EEG were found to be statistically more common in the encephalitis presentation group of patients than those of the non-encephalitis presentation group ($P < 0.05$ for all comparisons). However, the number of abnormal findings on the concomitant use of EEG and MRI was found to be the identical between the two groups ($P = 0.149$).

LP, CSF and routine laboratory analyses

The median time to performing an initial LP after hospitalisation was 6.0 (2.0–24.0) hours for 440 patients. The results of initial CSF analyses at various times after hospitalisation are presented in Table 2. The comparisons of routine laboratory characteristics at admission between the groups are presented in Table 3. In the encephalitis presentation group, the median percent of blood neutrophils, blood CRP level, ESR, serum AST level, BUN and creatinine levels were found to be significantly higher than the non-encephalitis presentation

group ($P < 0.05$ for all comparisons). In contrast, both the median serum sodium concentration and the number of patients with hypernatremia were significantly lower in this group of the patients ($P < 0.0001$ and $P = 0.009$, respectively). The mean \pm SD serum albumin concentration was also found to be significantly lower in this group of the patients (3.7 ± 0.8 vs 4.1 ± 0.6 g/dL; $P = 0.001$).

Molecular analysis

Real-time PCR was performed in 365 patients (73.6%), and 2 patients underwent nested PCR. All of the PCR data derived from the initial LPs as the inclusion criterion in this study. We were unable to retrieve the PCR method used from the files of 129 patients. The median (IQR) duration between admission and obtaining a positive CSF-PCR result for HSV was 72.0 (42.0–136.5) hours. In 112 patients (12.5%), CSF-PCR for HSV of an undefined type was positive; 50 of these patients were later found to be positive for HSV-1. Therefore, 351 patients (70.8%) were positive for HSV-1, and 83 patients (16.7%) were positive for HSV-2; positivity with CSF-PCR for HSV of an undefined type was established in 62 cases. Further, the number of patients with positive CSF-PCR results for HSV-1 was significantly higher in the encephalitis presentation group than the non-encephalitis presentation group [298 (78.6%) vs 53 (45.3%); $P < 0.0001$]. Conversely, the number of patients with positive CSF-PCR results for HSV-2 was significantly lower in this group of patients than the non-encephalitis presentation group [32 (8.5%) vs 51 (43.6%); $P < 0.0001$] (data not shown). A quantitative analysis of HSV-DNA in CSF was available for 41 patients (8.3%). The median (IQR) HSV-DNA load in those CSF samples was 1.8×10^4 (1.9×10^3 – 1.2×10^5) copies/ml (data not shown). A follow-up LP was performed in 167 patients after the initial LP a median (IQR) of 7.0 (3.0–14.0) days later. Of the 167 patients with a follow-up LP, HSV-DNA was repeated in 108 of them and it was found to be as positive in 57 (52.7%). When we considered the second LP, we had treatment data for 54 out of 57 PCR positive cases and 49 out of 51 PCR

negative cases. The aciclovir treatment duration did not differ between these two groups [PCR positives (n=54), median (IQR) 21.0 (19.5–21.5) days; PCR negatives (n=49), median (IQR) 21.0 (14.0–21.0) days; $P = 0.255$] (data not shown).

Serology

Blood HSV-IgM was positive in 76.5% of the patients tested (52/68), and blood HSV-IgG was positive in 13.2% of the patients tested (7/53). For the CSF analysis, HSV-IgM was positive in 39.6% of patients tested (19/48), and HSV-IgG was positive in 57.4% of patients tested (27/47). A primary CNS HSV infection (negative CSF-IgG and positive CSF-IgM) was not observed in any of the 20 out of the 48 (41.7%) CSF-IgG negative patients (data not shown).

Cranial MRI and CT

MRI was performed in 331 out of 496 (66.7%) patients. The median (IQR) time between performing MRI and hospital admission was 65.0 (24.0–96.0) hours. Parenchymal involvement was reported in a cohort of 202 patients in 42 (20.1%) of patients with cortical changes, 36 (17.8%) of patients with white matter changes, and involvement of both areas in 124 patients (61.4%). Seventy-two patients had repeated MRI scans after a median (IQR) of 16.0 (10.0–30.8) days following the first scan and we could provide radiological review reports in 57 cases with repeated MRI. Repeated MRI scans revealed regression in 56.1% (32/57) of patients and progression in 44.0% (25/57) of patients. The sites of involvement in the MRI are presented in Table 4. Cranial CT was performed in 393 patients. The median (IQR) time between CT and admission was 25.0 (9.0–72.0) hours. The abnormal findings that we detected in the CT and MRI data are presented in Table 5.

EEG testing

EEG was performed in 266 patients (53.6%) after a median (IQR) of 3.0 (1.5–5.5) days of hospitalisation. EEG abnormalities related to encephalitis were detected in 236 patients (88.7%). The MRI and EEG findings of the patients are presented in Table 6. These findings included nonspecific, diffuse, high-amplitude slow waves in 106/236 patients (44.9%), lateralised/localised slow-waves in 65/236 patients (27.5%), temporal lobe spike-and-wave activity in 64/236 patients (27.1%), PLED in 55/236 patients (23.3%) [right PLED in 27/55 patients (49.1%), left PLED in 17/55 patients (30.1%) and bilateral PLED in 11/55 patients (20.0%)] and other abnormalities in 40/236 patients (16.9%) (data not shown).

Follow-up EEG was obtained in 80/266 patients (30.0%) after a median (IQR) of 10.5 (2.8–21.0) days of hospitalisation. EEG abnormalities persisted in 62/80 patients (77.5%). These abnormalities included nonspecific, diffuse, high-amplitude slow waves in 26/62 patients (41.9%), lateralised/localised slow-waves in 21/62 patients (33.9%), temporal lobe spike-and-wave activity in 14/62 patients (22.6%), PLED in 9/62 patients (14.5%) [right PLED, left PLED and bilateral PLED in 2/9 (22.2%), 4/9 (44.4%) and 3/9 (33.3%) patients, respectively], and other abnormalities in 17/62 patients (27.4%) (data not shown).

Outcome analysis and management algorithm

The median (IQR) LOS was 19 (11.5–26.0) days among the patients and the median (IQR) LOS among the encephalitis presentation group was significantly longer than that of the non-encephalitis group [21.0 (15.0–30.0) vs 10.0 (5.0–15.0) days; $P < 0.0001$]. Furthermore, in this group of patients, the number of experienced unfavourable outcomes (deaths and surviving with sequelae) were significantly more frequent than that of the non-encephalitis presentation group at the end of the antiviral treatment [41 (10.8) vs 3 (2.6); $P = 0.003$ and 182 (48.0) vs 25 (21.4) $P < 0.0001$, respectively) (data not shown). Considering these findings, an algorithmic flowchart is presented in Figure 1 to aid clinicians in deciding when to consider encephalitis or what kind of algorithm should be followed at the start of antiviral

therapy targeting HME. We note that the contraindications of LP should be taken into consideration according to the general concepts reported elsewhere [5].

Discussion

Changes in consciousness, disorientation, language and behavioral abnormalities, cognition and memory impairment, focal neurological signs and seizures have thus far been the primary clinical indicators of HSV encephalitis. However, in addition to the encephalitic component, many cases may exhibit meningeal inflammation. As a result, meningoencephalitis is a frequently used term for the coexistence of two conditions [6]. In our study, three-fourths of patients exhibited at least one of the specified characteristics of encephalitis. However, none of these manifestations were reported or noted in one quarter of our patients. The patients in the non-encephalitis presentation group were evaluated for headache, fever and neck stiffness indicating the potential presence of dominating meningitis. Accordingly, one-third of the cases in the non-encephalitis presentation group were categorised as meningitis; 17.5% of these patients were shown to be infected with HSV-2, while HSV-1 dominated. Atypical presentation of herpetic encephalitis has been reported in mild cases and immunocompromised patients including cases of pregnancy [18-20]. However, only two patients without signs of encephalitis demonstrated potential causes of immunosuppression in this study. Because of the encephalitis patients may present either in early clinical stages or silent nature of HME, clinicians must not be overlooked to this tricky clinical presentation at diagnose [21].

In HME, xanthochromia caused by red blood cell breakdown, pleocytosis, mildly or moderately increased protein levels, normal or slightly altered glucose or lactate concentrations have been reported in CSF analyses [7, 22]. Our data revealed similar findings as previous studies. However, the confirmation of the disease relies on molecular studies in which HSV-1 has been reported to account for 90% of HME cases [5]. Although HSV-2 has

been reported to cause meningeal infections, many studies have suggested that HSV-2 is not only a major cause of aseptic meningitis but that it can also cause encephalitis [5, 23]. Along these lines, we found that CSF-PCR results were positive for HSV-2 in 32 patients (8.4%) in the encephalitis presentation group. The detection of HSV-DNA in CSF has a sensitivity of >95% and a specificity of >99% [7, 22, 24, 25]. Predictors resulting in false negativity such as analyzing CSF samples obtained early in the progression of the disease or bloody specimens have been known to exist. Hence, PCR reanalysis is recommended from CSF samples obtained after 3–7 days in probable cases [7, 26]. On the other hand, our data revealed that HSV-DNA analysed in the follow-up CSF samples obtained a median of 7 days after the initial LP was undetectable in about half of the cases and seemingly cleared from the CSF with treatment. We were unable to detect a difference in the duration of therapy between PCR positives and negatives according to our analysis of CSF samples obtained from the second LP. Therefore, the initiation of empirical antivirals may obscure a molecular diagnosis when LP is delayed. Although the detection of specific IgG antibodies in the CSF has a diagnostic value similar to positive PCR, these antibodies may be unavailable in the first CSF sample and typically show enhancement after 10–12 days. HSV-specific IgM antibody detection is typically reported less often in HSV encephalitis [22]. According to the data obtained from the entire study, 40% and 57% of the cases were positive for IgM and IgG from the CSF, respectively which indicates serology as a non-negligible diagnostic modality. Serology can accordingly be used as a complement to molecular testing. In addition, blood HSV-IgM, which was positive in three quarters of our cases, may be a surrogate marker in the diagnosis of a CNS infection due to HSV.

Magnetic resonance imaging is the most valuable radiological technique for encephalitis since it enables earlier detection of the disease [7, 27]. Two previous study suggested that MRI scan revealed brain involvement in 90% and 95% of HSV encephalitis

patients diagnosed with CSF-PCR, respectively [28, 29]. In this study, MRI data indicated encephalitis in three-quarters of all patients; signal changes and edema were the most frequent findings. Magnetic resonance imaging obtained within two days of hospital admission was reported to be abnormal in approximately 90% of patients in previous studies [30-32]; the median time until the first MRI scan was 65 hours in our cohort of patients. In the initial MRI testing, temporal lobe involvement was observed in 70% of cases; frontal lesions were document in 20% of cases. Parietal, occipital and cerebellar involvements were infrequently seen in our patients. The extent of MRI abnormality in HSV encephalitis is not correlated with the course of the disease [5]; repeat MRI testing may not be trustworthy for evaluating therapeutic efficacy. According to results of this study, 25 out of 57 patients (4%) with follow-up MRI scans obtained after a median of 16 days of treatment showed progression. However, one limitation of this study is that we do not know exactly whether this progression was due to clinical deterioration or the lack of a correlation between the neuroimaging and the clinical presentation. Furthermore, since the study period spanned a 14-year period over which the infrastructure at the participating hospitals improved significantly, some of the centres experienced temporary problems in MRI or EEG collection, particularly in the early stages of the study period. As a result, these centres were unable to provide these data. CT is another radiodiagnostic procedure that is inferior to MRI; it can be used when MRI testing is unavailable. In relatively small case series, initial testing with CT was reported to be normal in 21–33% of HSV encephalitis patients [28, 33]. However, we found that 60% of our patients had normal CT findings.

Electroencephalography has been reported to be more sensitive at the acute stage of encephalitis. Abnormalities such as unilateral or bilateral periodic sharp waves or attenuation of amplitude, focal or generalised slow waves or epileptiform discharges, or electrical seizures can be observed. Focal or lateralised EEG abnormalities are highly indicative of

herpetic encephalitis in particular, although EEG has been reported to be less specific than radiological assessments [34-36]. In this study, nonspecific, diffuse, high-amplitude and lateralised/localised slow waves were the most frequent EEG findings followed by temporal lobe slow waves and PLEDs. Further, EEG data also suggested encephalitis in 91% of all cases and 62% of non-encephalitis presentation patients. In the follow-up EEG testing obtained a median of 10 days after hospitalisation, four-fifths of patients still exhibited abnormal EEG findings related to encephalitis. Therefore, although we cannot provide specific data, EEG seems to be a valuable technique for diagnosing HSV encephalitis.

In this study, MRI and EEG data revealed the presence of encephalitis in 33% and 62% of cases without encephalitic clinical presentation, respectively. Concomitant use of MRI and EEG indicated encephalitis in the majority of cases, and there was no significant difference between the encephalitis presentation and the non-encephalitis presentation groups, which motivates the urgent use of both tests in a patient with CNS-infection. The patients without positive findings with the concomitant use of these techniques may have gone undetected due to sensitivity issues or relatively local and insignificant involvements. A delay in establishing an effective antiviral treatment more than two days significantly increases the risk of unfavorable outcome [6].

Our study is the largest case series ever reported with CSF-PCR-positive patients for HSV. Although a major limitation of this study is its retrospective design, it is very difficult to provide such a cohort prospectively. After a careful physical examination, encephalitis presentation patients with compatible findings should receive antiviral treatment in a timely manner. Lumbar puncture and molecular analysis should accordingly be performed whenever contraindications are eliminated in patient with suspected CNS infection. Considering the significantly benign nature of the clinical table for patients in the non-encephalitis presentation group and owing to the improved laboratory infrastructures of the hospitals with

easy access to these tests in many parts of the world, suspending antiviral therapy until positive radiological, electrophysiological or molecular results are obtained seems rational for this subgroup of patients. This approach will likely prevent excessive antiviral use for the entire cohort of CNS infections other than HSV disease.

In conclusion, CSF-PCR analysis for HSV should be conducted for all patients with a CNS infection considering the subtle nature of HME. Furthermore, the combined use of MRI and EEG (or CT if MRI is not feasible) appears to be advantageous. If a patient has compatible clinical, MRI and EEG findings with HME, a negative CSF-PCR test should be repeated later. In addition, a negative CSF serology alone cannot rule out HME and blood HSV-IgM may provide clues about the disease.

Acknowledgements: The present study is an ESCMID Study Group for Infectious Diseases of the Brain (ESGIB) and Infectious Diseases International Research Initiative (ID-IRI) cooperative study.

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Table 1. Initial clinical, radiological imaging and electroencephalography findings of encephalitis and non-encephalitis presentation patient groups *

Variable	Encephalitis presentation (N = 379)	Non-encephalitis presentation (N = 117)	P-value
Encephalitis symptoms		Irrelevant	
Changes in consciousness	304 (80.2)		NA
Disorientation	221 (58.3)		NA
Personality changes	123 (32.4)		NA
Speech disorders	109 (28.8)		NA
Convulsion	98 (25.9)		NA
Amnesia	98 (25.9)		NA
Hallucinations	23 (6.1)		NA
Abulia	16 (4.2)		NA
History of unconsciousness **	13 (3.4)		NA
Hemiparesis	6 (1.6)		NA
History of syncope	3 (0.8)		NA
Dizziness	1 (0.3)		NA
Facial and hypoglossal cranial nerve palsy	1 (0.3)		NA
Non-specific CNS infection symptoms and signs			
Fever ($\geq 38^{\circ}\text{C}$)	316 (83.4)	73 (62.4)	< 0.0001
Headache	227 (59.9)	109 (93.2)	< 0.0001
Neck stiffness	106 (27.9)	59 (50.4)	< 0.0001
Kernig's sign	25 (6.6)	18 (15.4)	0.003
Brudzinski's sign	20 (5.3)	12 (10.3)	0.055
Abnormal radiological imaging and EEG findings, <i>n/N</i> (%) (N = 496)			
Magnetic resonance imaging (MRI)	225 / 268 (83.9)	21 / 63 (33.3)	< 0.0001
Computerized tomography (CT)	135 / 312 (43.3)	18 / 81 (22.2)	0.0005
Electroencephalography (EEG)	223 / 245 (91.0)	13 / 21 (61.9)	0.0008
MRI or EEG ***	293 / 326 (89.9)	29 / 69 (42.0)	< 0.0001
MRI and EEG ***	182 / 189 (96.3)	14 / 16 (87.5)	0.149

* Data are presented as *n* (%) of column, unless otherwise indicated.

** History of unconsciousness unperceivable on hospital admission.

*** Findings indicating encephalitis in one of MRI or EEG.

NA: Not applicable. CNS: Central nervous system.

Table 2. Results of cerebrospinal fluid (CSF) analyses obtained from the initial lumbar puncture after hospitalization *

Variable	0-24 hours (N = 359)	25-72 hours (N = 59)	73 hours-10 days (N = 16)	11-22 days (N = 6)
High opening pressure	65 / 228 (28.6)	3 / 19 (15.8)	2 / 6 (33.3)	0 / 3 (0)
Appearance				
• Clear	289 / 329 (87.8)	42 / 46 (91.3)	10 / 13 (76.9)	5 / 5 (100.0)
• Turbid	24 / 329 (7.3)	2 / 46 (4.3)	1 / 13 (7.7)	0
• Bloody	13 / 329 (3.9)	1 / 46 (2.2)	1 / 13 (7.7)	0
• Xanthochromia	2 / 329 (0.6)	1 / 46 (2.2)	1 / 13 (7.7)	0
Leucocyte count (1/mm³)				
• 0-4	14 / 352 (3.9)	2 / 58 (3.4)	5 / 14 (35.7)	1 / 6 (16.7)
• 5-49	66 / 352 (18.8)	19 / 58 (32.8)	2 / 14 (14.3)	2 / 6 (33.3)
• 50-99	40 / 352 (11.4)	13 / 58 (22.4)	2 / 14 (14.3)	3 / 6 (50.0)
• 100-499	176 / 352 (50.0)	17 / 58 (29.3)	5 / 14 (35.7)	0
• 500-999	31 / 352 (8.8)	5 / 58 (8.6)	0	0
• ≥ 1000	25 / 352 (7.1)	2 / 58 (3.4)	0	0
Neutrophil count (1/mm³)				
• 0-4	76 / 299 (25.4)	21 / 41 (51.1)	7 / 11 (63.6)	1 / 3 (33.3)
• 5-49	128 / 299 (42.8)	18 / 41 (43.9)	4 / 11 (36.4)	2 / 3 (66.7)
• 50-99	57 / 299 (19.1)	2 / 41 (4.9)	0	0
• 100-499	30 / 299 (10.0)	0	0	0
• 500-999	5 / 299 (1.7)	0	0	0
• ≥ 1000	3 / 299 (1.0)	0	0	0
Lymphocyte count (1/mm³)				
• 0-4	10 / 324 (3.1)	1 / 48 (2.1)	3 / 12 (25.0)	0
• 5-49	64 / 324 (19.8)	18 / 48 (37.5)	2 / 12 (16.7)	3 / 4 (75.0)
• 50-99	45 / 324 (13.9)	24 / 48 (50.0)	2 / 12 (16.7)	1 / 4 (25.0)
• 100-499	160 / 324 (49.4)	4 / 48 (8.3)	5 / 12 (41.7)	0
• 500-999	29 / 324 (8.9)	1 / 48 (2.1)	0	0
• ≥ 1000	16 / 324 (4.9)	0	0	0
Erythrocyte count (1/mm³)				
• 0-50	215 / 293 (73.4)	27 / 46 (58.7)	9 / 13 (69.2)	3 / 4 (75.0)
• 51-250	32 / 293 (10.9)	8 / 46 (17.4)	1 / 13 (7.7)	1 / 4 (25.0)
• 251-500	14 / 293 (4.8)	3 / 46 (6.5)	0	0
• >500	20 / 293 (6.8)	7 / 46 (15.2)	2 / 13 (15.4)	0
• Hemorrhagic appearance	12 / 293 (4.1)	1 / 46 (2.2)	1 / 13 (7.7)	0
Hypoglycorrhachia (CSF/blood glucose ratio < 0.60)	132 / 263 (50.2)	14 / 23 (60.9)	9 / 23 (39.1)	3 / 3 (100.0)
High protein level (> 45 mg/dL)	263 / 339 (77.6)	48 / 55 (87.3)	13 / 15 (86.7)	5 / 5 (100.0)
Lactate, median (IQR) (mmol/L)	2.8 (2.3-3.6) (n = 18)	2.7 (2.0-3.4) (n = 9)	6.3 (3.1-7.4) (n = 3)	0
LDH, median (IQR) (U/ml)	50 (24.8-59.3) (n = 10)	ND (n = 2)	0	0

* Data are present as *n/N* (%) of patients, unless otherwise indicated. Total *n* = 440.

CSF: Cerebrospinal fluid. LDH: Lactate dehydrogenase. IQR: Interquartile range. ND: Not determined.

Table 3. Comparison of admission routine laboratory characteristics for the encephalitis and non-encephalitis presentation groups

Variable	Total (N = 496)	Encephalitis presentation (N = 379)	Non-encephalitis presentation (N = 117)	P-value	Normal
Hemoglobin, mean \pm SD (mg / dL)	13.1 \pm 1.7	13.2 \pm 1.7	13.1 \pm 1.6	0.560	14–18 (male) 12–16 (female)
Leucocyte, median (IQR) ($\times 10^3$ / mm ³)	9.7 (7.5–13.0)	10.0 (7.6–13.4)	8.8 (7.1–11.3)	0.627	4–11
Neutrophil (%), median (IQR)	71 (60–82)	75 (63–83)	65 (55–75)	< 0.0001	40–75
Platelet, median (IQR) ($\times 10^3$ / mm ³)	209 (171–261)	205 (168–253)	223 (176–274)	0.067	150–450
CRP, median (IQR) (mg / L)	0.8 (0.2–2.0)	0.8 (0.3–3.0)	0.5 (0.2–1.0)	0.015	0–8.0
ESR, median (IQR) (mm/h)	19.0 (11.8–30.0)	20.0 (12.0–34.5)	16.0 (11.0–20.0)	0.014	\leq 15 (male) \leq 20 (female)
Glucose, median (IQR) (mg/dL)	105.0 (90.0–129.0)	112.5 (91.3–138.8)	95.0 (87.0–104.5)	< 0.0001	70.0–110.0
AST, median (IQR) (IU/L)	27 (19–37)	27 (19–40)	24 (17–33)	0.013	15–41
ALT, median (IQR) (IU/L)	23 (16–32)	22 (16–31)	25 (16–34)	0.404	17–63
Serum sodium (mEq/L)					
• Median (IQR) value	136 (131–139)	135 (130–138)	139 (136–141)	< 0.0001	135–150
• Hyponatremia, <i>n</i> (%)	178 (44.2)	144 (37.9)	34 (29.1)	0.078	
• Hypernatremia, <i>n</i> (%)	7 (1.7)	2 (0.5)	5 (4.3)	0.009	
BUN, median (IQR) (mg/dL)	17.0 (11.8–26.0)	19.6 (12.7–33.5)	13.0 (10.6–17.0)	< 0.0001	7.0–20.0
Creatinine, median (IQR) (mg/dL)	0.8 (0.7–1.0)	0.9 (0.7–1.0)	0.8 (0.6–0.9)	0.001	0.7–1.2
Albumin, mean \pm SD (g/dL)	3.8 \pm 0.7	3.7 \pm 0.8	4.1 \pm 0.6	0.001	3.5–5.0

CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, BUN: Blood urea nitrogen.

Table 4. The cerebral involvement sites in initial and follow-up cranial magnetic resonance imaging (MRI) scan *

	Temporal	Frontal	Parietal	Occipital	Cerebellum	Others	No involvement
Initial MRI (N = 331) **							
• Left hemisphere	82 (24.8)	26 (7.9)	17 (5.1)	6 (1.8)		29 (8.8) ***	85 (25.7)
• Right hemisphere	75 (22.7)	20 (6.0)	7 (2.1)	1 (0.3)			
• Bilateral	73 (22.1)	21 (6.3)	6 (1.8)	4 (1.2)	3 (0.9)		
Follow-up MRI (N = 64)							
• Left hemisphere	16 (25.0)	4 (6.3)	1 (1.6)		1 (1.6)	8 (12.5) ****	15 (23.4)
• Right hemisphere	19 (29.7)	7 (10.9)		1 (1.6)			
• Bilateral	18 (28.1)	4 (6.2)	2 (3.1)	1 (1.6)			

* Data are present as *n* (%) of patients.

** Number of MRI reports with comments in the hospital records.

*** Insula 6, diffuse 5, limbic system 4, basal ganglia 3, thalamus 2, hippocampus 2, pons 1, mesencephalon 1, corpus callosum 1, uncus 1, centrum semiovale 1, corona radiata 1, lacunar 1.

**** Insula 2, diffuse 2, limbic system 1, basal ganglia 1, pons 1, limbic system 1.

Table 5. Abnormal findings on cranial computerized tomography (CT) and magnetic resonance imaging (MRI) scan *

Characteristic	Computerized tomography (CT) (N = 393)	Magnetic resonance imaging (MRI) (N = 331)	Concomitant use of CT and MRI (N=270)
Total abnormal findings	153 / 393 (38.9)	246 / 331 (74.3)	97 / 270 (35.9)
• Density changes	75 / 153 (49.0)	167 / 246 (67.9)	42 / 97 (43.3)
• Edema	49 / 153 (32.0)	93 / 246 (37.8)	21 / 97 (21.6)
• Hemorrhage	17 / 153 (11.1)	28 / 246 (11.4)	5 / 97 (5.2)
• Infarction	18 / 153 (11.8)	24 / 246 (9.8)	4 / 97 (4.1)
• Cerebral thrombosis	3 / 153 (1.9)	0	0
• Others **	0	2 / 246 (0.8)	0

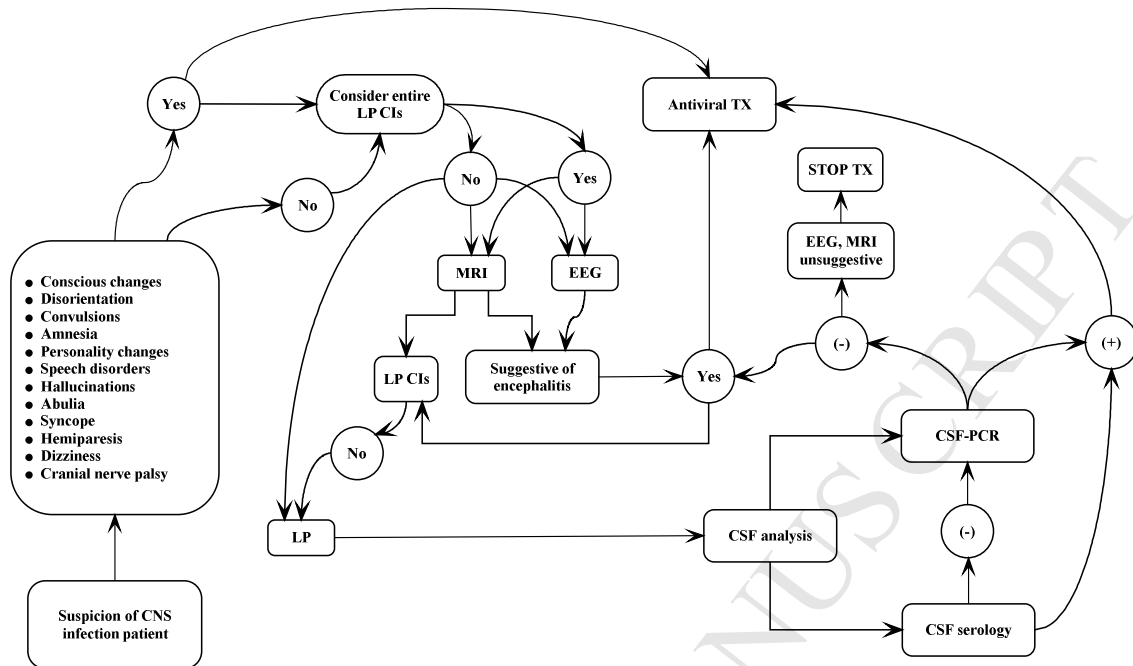
* Data are present as n/N (%) of patients.

** Right facial nerve inflammation 1, Basal ganglion infarction 1.

Table 6. The initial magnetic resonance imaging (MRI) scan and electroencephalography (EEG) findings of the patients *

	Magnetic resonance imaging		Electroencephalography	
	Normal	Abnormal	Normal	Abnormal
Magnetic resonance imaging (N = 331)				
• Normal	85 / 331 (25.7%)		9 / 26 (34.6%)	17 / 26 (65.4%)
• Abnormal		246 / 331 (74.3%)	17 / 178 (9.6%)	161 / 178 (90.4%)
Electroencephalography (N = 266)				
• Normal	16 / 25 (64.0%)	9 / 25 (36.0 %)	30 / 266 (11.3%)	
• Abnormal	18 / 179 (10.1%)	161 / 179 (89.9%)	236 / 266 (88.7%)	

* Data are presented as n/N (%) of patient.



CI: Contraindications, Tx: Treatment, CSF: Cerebrospinal fluid, PCR: Polymerase chain reaction, CNS: Central nervous system, MRI: Magnetic resonance imaging, EEG: Brain electroencephalography

Figure 1. Diagnostic algorithm