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Predictive values and specificity of electroencephalographic findings in autoimmune encephalitis diagnosis

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ABSTRACT

Objective: Early diagnosis of autoimmune encephalitis (AE) to not delay treatment is challenging but needed in practice. Most previous evidences of electroencephalographic (EEG) findings in AE were derived from descriptive studies. Given paucity of evidence of specific EEG findings to help with early diagnosis of AE, this study aimed to ascertain specific EEG findings and assess their predictive values in diagnosis of AE.
Methods: We included all cases with AE in our institution from January 2013 to June 2017. Cases were matched with controls by age and level of consciousness (1:2 ratio). Potential confounders for EEG findings collected as baseline characteristics were compared. Two epileptologists independently reviewed EEGs. Standardized terminology, definitions, and scoring system of EEG findings were employed. Logistic regression analysis was performed, and diagnostic performance of significant EEG features was assessed.
Results: Twenty cases and 40 controls were included in this study. Poorly sustained posterior dominant rhythm (PDR) was significantly associated with AE ($p = 0.007$) and even more predictive in anti-*N*-methyl-D-aspartate (NMDA) encephalitis. Inter-rater agreement (kappa) was 0.714. None of the cases had normal EEG nor Grand Total EEG (GTE) score < 4 (negative predictive value (NPV) of 100%). Specificity of well sustained PDR to exclude the diagnosis of anti-NMDA encephalitis was high (91.67%).
Conclusions: Simple EEG assessment can be used to help exclude AE. When AE is suspected, careful assessment of the sustainment of the PDR is warranted. The NPV of GTE score < 4 and specificity of well sustained PDR can be simply used to differentiate many conditions from AE.

1. Introduction

Autoimmune encephalitis (AE) has been well-recognized by neurologists for years. Most initial reports were cases of paraneoplastic encephalitides associated with malignant tumor. Subsequently, a number of case reports or case series of nonparaneoplastic encephalitis, i.e., anti-*N*-methyl-D-aspartate receptor (NMDAR) [1,2], antivoltage-gated potassium complex of channels (VGKC), anti-leucine-rich glioma-inactivated protein 1 (LGI1), and antiglutamic acid decarboxylase-65 (GAD-65) [3], have been reported. Early diagnosis leading to early immunotherapy treatment for AE has been advocated by researchers so that better clinical outcome and fewer neurological relapses can be achieved [2]. Electroencephalography is one promising tool to help diagnose early or distinguish other conditions from AE [4]. Until now, there have been neither established EEG features nor a developed scoring system of EEG assessment for the diagnosis of AE. Most EEG features of AE reported in the literature were accompanied with case reports or case series. These features may not be useful in clinical practice given that they are not specific for AE, but they can also be seen in other conditions. This is also true for "extreme delta brush (EDB)", which was previously-known as a unique EEG pattern in anti-NMDA encephalitis [5]. Recently, this pattern has been reported in other conditions including mesial temporal lobe epilepsy, hypoxic encephalopathy, brain tumor, stroke, metabolic derangements [6], and methotrexate neurotoxicity [7]. Sensitivity of presence of EDB to help diagnose the condition is also low since prevalence of EDB in anti-NMDA encephalitis varied from none to 30.1% [5,8,9]. To the best of our knowledge, there has been only one study until now that compared EEG findings between patients with seropositive AE and controls with seronegative AE [10]. However, this study did not find significant EEG features. Given paucity of evidence of specific EEG findings to help with early diagnosis of AE,

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this study aimed to ascertain specific EEG findings associated with AE and to assess their predictive values in helping with diagnosis.

2. Materials and methods

This is a cross-sectional study. We retrospectively recruited adult patients with AE verified by antibody testing at King Chulalongkorn Memorial Hospital (KCMH), The Thai Red Cross Society from January 1, 2013 to June 30, 2017. All patients performed EEG testing at the Chulalongkorn Comprehensive Epilepsy Center of Excellence (CCEC), KCMH. The study was approved by the local ethics committee.

2.1. Patients

We included all patients with AE who had at least one EEG performed as cases. Matched control patients with a ratio of 1:2 (case:control) were selected from our EEG database. We matched case with control by age ± 5 years and level of consciousness (LOC) (i.e., alert, lethargic, stuporous, comatose). Most selected controls underwent EEG testing within 1–3 months after each case. Cases were all positive for antibody testing in blood serum, cerebrospinal fluid (CSF), or both. All controls did not meet clinical criteria for diagnosis of possible AE, definite AE, or probable anti-NMDA encephalitis [11]. These criteria were proposed by a team of experts who reviewed the literature and gathered their experience in order to develop a practical, syndrome-based diagnostic approach to AE. These criteria were externally validated in two recent studies. One concluded that specificity of clinical criteria for diagnosis of possible AE and definite AE was 94% and 96%, respectively [12]. Both studies showed that specificity of clinical criteria for diagnosis of probable anti-NMDA encephalitis was 98% [12] and 96.7% [13], respectively. Moreover, the specificities of the definite AE and probable anti-NMDA encephalitis remained relatively high in different disease stages. All of our controls who had epilepsy had long-standing history of epilepsy (>10 years) without other neurological signs. Controls who had imaging abnormalities had intracranial lesions corresponding with neurological deficits (e.g., brain tumor, stroke). Three controls had antibody testing, and the results were all negative for AE antibodies.

2.2. Antibody testing

All serology and CSF antibody testings were performed at the Neuroscience Center for Research and Development, KCMH, using Indirect Immunofluorescence Test (IIFT) kits from EUROIMMUN, Luebeck, Germany (In Vitro Diagnostic Devices (IVD)-validated and "Conformite Europeenne" certificate (CE Mark)-labeled). Twenty-one autoimmune and paraneoplastic neurological syndrome (PNS)-related antibodies consisting of anti-NMDA, anti-2-amino-3-(5-methyl-3-oxo-1,2-oxazol-4-yl) propanoic acid (AMPA)-1 and -2 receptors, anti-contactin-associated protein 2 (CASPR2), anti-LGI1, anti-gamma-aminobutyric acid (GABA)-A and -B receptors, anti-dipeptidyl-peptidase-like protein-6 (DPPX), anti-Hu (ANNA-1), anti-Ri (ANNA-2), anti-Yo (PCA-1), PCA-2, anti-Tr, anti-MAG, anti-myelin, anti-GAD, anti-CV2, anti-amphiphysin, anti-neuroendothelium, anti-GFAP, anti-synaptophysin, and AGNA/anti-SOX1 were determined by indirect immunofluorescence (IIF) assay in serum and CSF. Briefly, 10-fold dilution of specimen was incubated on slides containing either individual antigens expressing in HEK cells or specific tissues (cerebellum, pancreas, intestine, and nerve cell) followed by the second antibody conjugated with fit-C fluorescence. Then, the reaction slides were studied with an inverted fluorescence microscope.

2.3. EEG recordings

Electrodes were placed according to the 10–20 system of the International Federation. Electroencephalographies were recorded on a 21-channel digital machine (Stellate Systems). Oz was used as a system reference during the recording. Electrocardiogram (EKG) as well as left and right electrooculogram (LOC, ROC) channels were applied in all records. Photic stimulation and hyperventilation as activation procedures were applied in all cases unless contraindicated. Upon reviewing the EEG, a set of reformatted montages of both bipolar and reference montages were employed. The standard length of the recording was at least 20 min. All EEG tracings were independently reviewed by two certified epileptologists (C.L. and S.J.), using a unified case record form for EEG findings. The former was certified by the Canadian Society of Clinical Neurophysiologists (CSCN) and the latter by the American Board of Psychiatry and Neurology (ABPN). Inter-rater agreement (kappa) was calculated. Any disagreement was solved through discussion. Both reviewers were blinded from clinical diagnosis of the conditions of either cases or controls.

2.4. Data collection

The following data were collected in four different parts: 1) demographic data including age and gender; 2) clinical characteristics including symptom at first presentation, LOC at time of EEG, interval between the first symptom and EEG, drugs used at time of EEG, history of epilepsy, underlying diseases, and imaging findings; 3) antibody testing and laboratory results; and 4) EEG findings. All mentioned data were extracted from patient charts, EEG-requisition forms, and EEG-technician note sheets. The latter was completed on a regular basis in every case. One investigator (C.D.) was responsible for extracting all data, except for EEG findings, which were reviewed by two board-certified epileptologists. All data were recorded in EpiData version 3.1.

2.5. Assessment of EEG findings

Assessment of EEG findings was blinded from knowing clinical diagnosis of the conditions of cases or controls. Only the first routine EEG or first 20 min of the continuous-EEG recording after initial presentation was reviewed. Detailed characteristics of the EEG findings were analyzed. Features of the normal and abnormal EEG findings during wakefulness and sleep were defined according to Fisch and Spehlmann (chapters 8, 9, and 15) [14]. Given the lack of standardized definition of sustainment of the posterior dominant rhythm (PDR), we specified poorly sustained PDR if the PDR was significantly (≥50% of the recording time) intermixed with low- (<20 μV) to high (>50 μV)-amplitude theta activity (4 to <8 Hz) or delta activity (0.5 to <4 Hz) or both, noticeable in T5-O1, T6-O2. Posterior slow waves of youth patients were considered as physiologic waves. Well sustained PDR was defined when the PDR was completely absent of slow waves or minimally (<50% of the recording time) intermixed with slow waves. The frequency and amplitude of the slow waves were defined as above. Terminology and definitions regarding distribution, morphology (including rhythmic and periodic patterns), and persistence of the EEG patterns in critically ill patients were described according to standardized terminology proposed by the American Clinical Neurophysiology Society 2005 [15]. Definition of seizures was defined according to Chong and Hirsch [16]. We also assessed EEG findings with the previous EEG scoring system, namely "Grand Total EEG (GTE) score" [17]. We chose this scoring system to quantitate a degree of EEG abnormality in order to find potential predictive values of the EEG to help diagnose AE. Required EEG features to be assessed in the GTE score consist of EEG findings, which can be seen in all spectrum of patients, ranging from normal EEG findings to severe degree of encephalopathy. This was in contrast with the other previous EEG classification systems, Young et al. [18] and Synek [19], which were both constructed for assessing comatose patients. The GTE score was originally designed to help diagnose dementia in patients with Alzheimer's [20] and subsequently used for distinguishing Alzheimer's disease from dementia with Lewy bodies [17,21]. The degree of abnormalities was scored on a scale including 6 items, shown in Supplementary