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EEG and Magnetic Resonance Imaging Abnormalities in Patients with Acute Limbic Encephalitis

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ABSTRACT

Objective: To describe the characteristics of electroencephalography (EEG) and MRI in patients with acute limbic encephalitis (LE). Patients and Methods: We retrospectively reviewed medical records of 57 patients with diagnosis of LE from May 1994 to April 2010 and selected those with available EEG and MRI records. We analyzed EEG characteristics (type of abnormality, location and periodicity), reviewed MRIs and compared both. Results: We included 22 patients, age ranging from 3 months to 71 years. EEG was abnormal in 21 patients (95.5%): Periodic lateralized epileptiform discharges (PLEDs) in 9 patients (40.9%), epileptiform discharges and/or temporal slow waves in 7 (31.8%) and 5 (22.7%) with only background slowing. MRI showed abnormalities in temporal lobes of 19 patients (86.4%). The presence of PLEDs was strongly associated with hyperintense MRI-FLAIR signal involving hippocampus and temporal lobe cortex. Bilateral periodic lateralized epileptiform discharges (Bi-PLEDs) seen in two patients were related to extensive symmetrical bitemporal hyperintense MRI-FLAIR signal. Three patients with PLEDs had only mild ipsilateral FLAIR-hyperintense abnormalities, while contralateral temporal areas were moderate to severely affected on MRI. In four patients with smaller asymmetric bilateral lesions we observed PLEDs in the most affected side. Diffuse slow waves were observed in three patients with discrete hyperintense signal on MRI. Conclusion: PLEDs are a typical EEG finding in LE, but not present in all cases. However EEG may predict the extension of MRI abnormalities: slow, mild and nonspecific EEG abnormalities may be related to discrete MRI lesions, while PLEDs to extensive lesions. Moreover, in bilateral, asymmetrical and widespread lesions PLEDS may be contralateral to the most affected ("burned-out") area on MRI.

Keywords: acute limbic encephalitis; PLEDs; magnetic resonance imaging.

RESUMO

Anormalidades de EEG e ressonância magnética em pacientes com encefalite límbica aguda

Objetivo: descrever as características de EEG e ressonância magnética em pacientes com encefalite límbica aguda (EL). **Pacientes e Métodos:** Foram analisados retrospectivamente os prontuários de 57 pacientes com diagnóstico de EL de maio de 1994 a abril de 2010 e selecionados aqueles com registros disponíveis de eletroencefalograma e ressonância magnética. Analisamos as características do EEG (tipo de anormalidade, a localização e periodicidade) e ressonância magnética e comparamos os resultados dos dois exames. **Resultados:** Foram incluídos 22 pacientes, com idade variando de 3 meses a 71 anos. O EEG foi anormal em 21 pacientes (95,5%): Descargas periódicas epileptiformes lateralizadas (PLEDs) em 9 pacientes (40,9%), descargas epileptiformes e /ou ondas lentas temporais em 7 (31,8%) e 5 (22,7%) com apenas lentificação da atividade de base. A ressonância magnética mostrou anormalidades nos lobos temporais de 19 pacientes (86,4%). A presença de PLEDs foi fortemente associada com o sinal FLAIR-RM hiperintenso envolvendo hipocampo e córtex do lobo temporal. Bi-PLEDs (descargas periódicas epileptiformes bilaterais) visto em dois pacientes estavam relacionados com extensa alteração de sinal FLAIR-RM bitemporal simétrica. Três pacientes com PLEDs apresentaram apenas anormalidades leves ipsilaterais nas imagens FLAIR, enquanto que a ressonância

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magnética mostrou áreas em lobo temporal contralateral com alterações de sinal moderadas a intensa. Em quatro pacientes com pequenas lesões bilaterais assimétricas na RM observamos PLEDs no lado mais afetado. Ondas lentas difusas foram observadas em três pacientes com hipersinal discreto na ressonância magnética. **Conclusão:** PLEDs são achados típicos de EEG na LE, mas não estão presentes em todos os casos. No entanto o EEG pode prever a extensão de alterações à RM: Anormalidades EEG leves do tipo ondas lentas podem estar relacionada a lesões discretas de ressonância magnética, enquanto PLEDs estão relacionados à lesões extensas. Além disso, em lesões bilaterais, assimétricas e difusas nas imagens FLAIR os PLEDs podem estar localizados no lobo temporal contralateral à zona mais afetada na ressonância magnética.

Unitermos: encefalite límbica aguda; PLEDs; ressonância magnética; EEG.

INTRODUCTION

Encephalitis is the presence of inflammation in the brain parenchyma associated with clinical evidence of brain dysfunction. It can be due to a noninfective condition such as in acute disseminated encephalomyelitis (ADEM) or to an infection, which is diffuse and usually of viral origin. Herpes simplex virus type 1 (HSV-1), varicella-zoster virus (VZV), Epstein-Barr virus (EBV), mumps, measles and entero-viruses are responsible for most cases of viral encephalitis in immune competent individuals.¹ Herpes simplex is the most common cause of viral encephalitis. The adult form of herpes simplex encephalitis is known as herpetic limbic encephalitis due to the virus predilection for the limbic system.² Acute limbic encephalitis (LE) typically affects the mesial temporal lobe and limbic mesial cortical structures (cingulate gyrus, orbito-frontal cortex, and mamillary bodies).³ It usually involves one or both temporal lobes, in particular the hippocampus, amygdala, insular and parahipocampal gyrus. Spread may occur to the frontal and parietal lobes and it may lead to prominent memory and personality disturbances and seizures as sequelae (Fig. 1).^{2,3}



Figure 1. T1 weighted – IR (inversion recovery) coronal MRI. The structures most commonly involved of the limbic system in herpes encephalitis are identified (Yellow: cingulate gyrus; red: hippocampus; green: temporal lobe neocortex; blue: insula, pink: uncus; P: parahippocampal gyrus).

A thorough diagnostic evaluation typically includes cranial magnetic resonance imaging (MRI), electroencephalography (EEG), and cerebrospinal fluid (CSF) examination, but abnormalities may be nonspecific. This study was undertaken to define the spectrum of abnormalities found in the investigation of LE and to identify and compare any findings that may be specific to LE.³

PATIENTS AND METHODS

Clinical Material

Cases in which another neurological disorder was identified were excluded. Data from CT, MRI and CSF tests were considered to exclude other non-infective causes.

We retrospectively reviewed medical records of 57 patients with diagnosis of acute limbic encephalitis in the context of a febrile disease accompanied by headache, altered level of consciousness, and symptoms and signs of cerebral dysfunction (cognitive dysfunction, behavioural changes and seizures) with less than 7-day duration, from May 1994 to April 2010 and selected those with available EEG and MRI. We analyzed EEG characteristics (type of abnormality, location and periodicity), reviewed MRIs and compared both.

Laboratory Data

Electroencephalography was performed using analog and digital 16-channel and 21-channel instruments; scalp electrodes were placed according to the standard 10-20 International System. All EEGs were reviewed independently. Magnetic resonance imaging was performed according to standard clinical protocols. Sagittal and axial T1-weighted and T2-weighted images and thin-section coronal fluid-attenuated inversion recovery (FLAIR) sequences were obtained for all patients. Additionally CT was performed on the first day of admission. MRI abnormalities were evaluated qualitatively for each patient and compared with EEG results.

RESULTS

Clinical Features

We identified 22 patients with LE (Table 1). The median age was 32.9 years (range 3 months to 71 years). Signs or symptoms of cognitive dysfunction were the most common complaints (54.5%); these included memory impairment and confusion. Eleven patients (50%) had prominent psychiatric symptoms, most frequently irritability, anxiety, and hallucinations. In 3 patients (13.6%), behavioral disturbances were the initial manifestation of LE. One or more seizures occurred in 13 patients (59%) and these had clinical features of a focal onset: 7 patients had seizure semiology suggestive of temporal origin.

CSF findings

The results of CSF analysis were abnormal in all patients analyzed. The most common findings were

Table 1. Summary of the clinical data, surface EEG and MRI

lymphocytic pleocytosis (documented in all patients) and mildly elevated protein (>45 mg/dL).

EEG Findings

In all 22 patients (Table 1), EEG was performed and was abnormal in 21 (95.5%). Slow-wave abnormalities were documented in 12 patients; these were diffuse in 5 patients. Focal slow waves restricted to the temporal region were seen in 5 patients and, in one patient, slow waves involved the whole hemisphere, with major emphasis on the temporal lobe. Focal epileptiform discharges were observed in 3 patients, all restricted to the temporal lobe. One patient had bilateral independent temporal spikes and sharp waves and one had unilateral temporal epileptiform activity. Periodic lateralized epileptiform discharges (PLEDs) were recorded in 9 patients (40.9%); 6 of whom had eletroclinical seizures involving predominantly the frontotemporal region; 7 out of 9 were unilateral PLEDs, while 2 were bilateral independent PLEDs (Bi-PLEDs).

Patient n°	Age (years)	Sex	Seizures	Type seizures	СТ	MRI (Hypersignal Flair)	EEG
1	23	М	Yes	GTC	Normal	Severe bi-temporal cortex, hippocampus, parahippocampus	Bi-PLEDs
2	49	М	No	_	Nonspecific	Mild bi-temporal cortex, insula, hippocampus	Diffuse slow activity
3	40	F	Yes	GTC	Nonspecific	Severe bi-temporal cortex, hippocampus, parahippocampus	Bi-PLEDs
4	51	М	No	-	Normal	Severe bi-fronto-temporalT cortex, hippocampus, parahippocampus, insula > right	PLEDs left fronto-temporal
5	12	М	Yes	FC - GTC	Abnormal	Severe bi-temporal cortex, hippocampus, parahippocampus, insula, uncus > right	PLEDs right temporal
6	1	М	Yes	FC	Normal	Bi-temporal cortex, uncus, parahippocampus > left	Slow waves left temporal
7	14	М	Yes	FC	Normal	Mild bi-hippocampus, frontal cortex > right	Normal
8	41	F	No	-	Abnormal	Severe bi-temporal cortex, insula, uncus, hippocampus, parahippocampus >left	PLEDs right fronto-temporal
9	43	М	No	-	Normal	Normal	Diffuse slow activity
10	10	F	Yes	FC-GTC	Normal	Mild bi-hippocampus	Focal slow waves left fronto-temporal
11	61	F	No	FC	Normal	Bi-fronto-temporal cortex, insula, hippocampus, parahippocampus > left	Left temporal wicket spikes and slow waves
12	33	М	Yes	FC-GTC	Normal	Mild bi-temporal cortex, uncus, hippocampus, parahippocampus > left	Left fronto-temporal slow waves
13	37	М	Yes	GTC	Normal	Severe bi-fronto-temporal cortex, insula, hippocampus, parahippocampus > left	Left fronto-temporal PLEDs
14	17	М	Yes	GTC	Normal	Mild bi-hippocampus	Diffuse slow activity
15	25	М	Yes	GTC	Abnormal	Severe bi-FT cortex, insula, hippocampus, parahippocampus > left	Left temporal PLEDs
16	71	F	No	-	Abnormal	Severe bi-temporal cortex, insula, uncus, hippocampus, parahippocampus > left	Right temporal PLEDs
17	30	М	Yes	FC	Abnormal	Bi-F-T cortex, H, PH, insula > right	Right temporal wicket spikes
18	56	М	No	-	Normal	Bi-temporal cortex, insular, hippocampus, parahippocampus, frontal cortex > left	Left temporal slow waves
19	40	М	No	-	Normal	Normal	Bi-temporal slow waves
20	50	М	No	-	Nonspecific	Severe bi-temporal and frontal cortex, insula, hippocampus, parahippocampus > left	Left fronto-temporal PLEDs
21	3 months	F	Yes	GTC	Normal	Normal	Diffuse slow activity
22	20	М	No	-	Normal	Mild right temporal cortex	Diffuse slow activity

F: female; M: male; GTC: generalized tonic-clonic seizure; FC: focal complex seizure; PLEDs: periodic lateralized epileptiform discharges; BI-PLEDs: bilateral periodic epileptiform discharges

Imaging Findings

CT was performed in all patients, with abnormal results related to research in only 5 and 3 patients with nonspecific findings.

Brain MRI was performed in all patients (Table 1) and images from 22 patients were available for retrospective review. Of these, 19 (86.4%) showed either symmetrical or asymmetrical temporal lobe abnormalities. Fifteen scans (68.2%) showed increased T2 and FLAIR signals in the mesial temporal region, 11 (50%) of which bilateral. Extratemporal increased signal was observed in 13 individuals (59.1%), mainly in the insular region and orbitofrontal cortex and subcortex.

Relation of MRI and EEG abnormalities

EEGs from the 2 patients with normal MRI showed focal or diffuse, nonspecific slow waves. This was also

present in EEGs from patients that had asymmetrical FLAIR hyperintensities over the temporal region, hippocampus and insula (*Patient 1*). The presence of PLEDs was strongly associated with hyperintense FLAIR signal involving hippocampus and temporal lobe neocortex. BI-PLEDs (2 patients) were related to extensive symmetrical bitemporal hyperintense FLAIR signal (*Patient 2*). Three patients with PLEDs on EEG had discrete ipsilateral and severe contralateral FLAIR-hyperintense abnormalities (*Patient 3*). In 4 patients with smaller bilateral asymmetrical lesions, we observed PLEDs in the most affected side (*Patient 4*). Diffuse slow waves were observed in 3 patients with discrete hyperintense signal on MRI (*Patient 5*).



Patient 1. Male, 56 years. **A)** EEG, longitudinal bipolar mountage: continuous slow activity in the left temporal region. **B)** MRI-FLAIR, coronal image: bilateral increased signal over the insula, hippocampus and temporal basal cortex.



Patient 2. Female, 40 years. **A)** EEG, referential (average) mountage: interval of 4sec between Bi-PLEDs in the temporal regions. **B)** MRI-FLAIR, coronal view: bilateral symmetrical hyperintense signal in the hippocampi, uncus and parahippocampal gyri.



Patient 3. Male, 51 years. **A)** EEG, longitudinal mountage: PLEDs occuring every 3 sec in the left temporal region. **B)** MRI-FLAIR, coronal image: hyperintense signal over medial temporal regions, parahippocampal cortex, hippocampus and insula, with right sided predominance.



Patient 4. Male, 37 years. **A)** EEG, longitudinal mountage: PLEDs occuring every 1.5 sec in the left temporal region. **B)** MRI-FLAIR, coronal image: hyperintense signal in mesial temporal structures, insular region, as well as in the supraorbital, inferior frontal gyrus and cingulate gyrus (not shown here).



Patient 5. Male, 20 years. A) EEG, longitudinal mountage: Diffuse slow activity. B) MRI-FLAIR, coronal image: hyperintense signal in the mesial temporal regions.

DISCUSSION

In clinical practice, acute limbic encefalitis should be suspected in patients with nonspecific systemic symptoms (fever and headache) and acute onset of cognitive impairment, especially when associated with seizures. Although the latter is not always present, it is helpful in clinical diagnosis, specially if it has focal onset with or without secondary generalization.⁴⁻⁶ Our results are similar to those reported in previous studies on LE, but it has other important observations.^{1,3,7} The clinical characteristics mentioned above associated with abnormal EEG have contributed even more in the diagnosis of EL. EEG is considered a sensitive test (90%), but poorly specific (30-35%)⁸. This sensitivity was higher in our study, possibly due to the large participation of limbic structures. EEG characteristics vary between studies. Most commonly, studies have shown focal or diffuse slow activity in the temporal region and PLEDs in the same location. The differential diagnosis, however, requires other ancillary tests.^{6,7} PLEDs is a typical finding in acute limbic encephalitis, but it may occur in other diseases such as stroke, cancer and degenerative disorders.⁸⁻¹¹ PLEDs were associated in some cases with seizures (22,7% of all patients), suggesting that PLEDs in this situation may represent both ictal and interictal phenomenon.¹²⁻¹⁵

The most typical finding was bilateral MRI signal abnormality in mesial temporal structures, including uncus and hippocampus. It occurred often asymmetrically, and with accompanying extratemporal alterations, mainly in insula and orbitofrontal gyri.¹³ According to previous studies, a minority of patients have hyperintense T2 signal in one temporal lobe, or are normal 6,16,17 An important finding of our study was the high frequency of extratemporal MRI abnormalities, usually in the insular cortex.^{1,7} This difference is probably related to the frequent use of coronal FLAIR sequences to evaluate mesial temporal structures, as well as being a retrospective, not blinded study. The details of the mesial temporal neuroanatomical structures, including the hippocampus, are best appreciated when coronal images are acquired perpendicular to the long axis of hippocampus.^{3,18} So when LE is suspected, coronal T2-weighted and FLAIR images should be acquired. MRI is more sensitive and specific than CT for the evaluation of LE, as it is able to detect early injury in the first 48 hours. CT is recommended as a screening test, when there is low clinical suspicion of encephalitis or when MRI is unavailable.1,19,20

We found that EEG abnormalities were strongly associated with MRI hyperintense signal abnormalities; however, PLEDs although usually ipsilateral to the MRI lesion, may be contralateral to the most affected area on MRI. Epileptiform discharges that come from the less affected side has been reported in previous articles on bilateral hippocampal sclerosis and, in such cases, refered to as the "*burn-out*" phenomenon.^{16,17}

CONCLUSIONS

The evolution of acute limbic dysfunction (less than 7 days) associated with fever should suggest the possibility of LE and lead to the search for infectious causes. Laboratory investigations should be performed to confirm cerebral dysfunction and show the involvement of temporolimbic structures, as well as exclude other diagnoses such as carcinomatosis or paraneoplastic encephalitis, which may have a subacute or chronic evolution. Cerebrospinal fluid analysis (CSF) reveals abnormalities that may often be nonspecific, but it is essential to exclude other infectious or noninfectious causes. In cases with typical symptoms and subacute evolution paraneoplastic antibody detection by serological global evaluation facilitates early diagnosis of paraneoplastic LE and directs the search for malignancy. Although the gold standards for definitive diagnosis of the etiology of LE are the CSF and serological tests, imaging studies and EEG are useful to guide the diagnosis and treatment. The diagnosis of LE is very unlikely when both EEG and cranial MRI are normal. EEG, although nonspecific, is almost always abnormal in LE reflecting the presence of cerebral dysfunction with predominant involvement of the temporal regions. Neuroimaging studies, especially MRI, can show a pathological process in mesial temporal lobes and associated limbic structures such as the insular cortex. Comparing these studies we conclude that the presence of PLEDs is a typical EEG finding in LE, but it is not present in all cases. However EEG can predict the extension of MRI abnormalities: slow, mild and nonspecific EEG abnormalities are best correlated with discrete MRI lesions, while PLEDs with extensive lesions. However, in bilateral, asymmetrical and widespread lesions PLEDS may be contralateral to the most affected area ("burn-out" phenomenon).

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