EEG extreme delta brush; could be an ictal pattern in patients with anti-NMDA receptor encephalitis.

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Abbreviations: NMDAr: Anti-N-methyl-D-aspartate receptor, EEG: Electroencephalogram, SE: status epilepticus, PCR: polymerase chain reaction , EDB extreme delta brush, MRI: Magnetic resonance imaging , CSF: Cerebrospinal fluid , PET: Positron Emission Tomography , SPECT: Single-photon emission computed tomography , BZD: benzodiazepine , AED: antiepileptic drugs, HSV: Herpes simplex virus.

Highlights

- The presence of EDB is associated with seizures and SE in our patients.
- EDB pattern can follow a pattern of well characterized electroclinical seizures.
- Patients without EDB were more likely to have an abnormal MRI than those with EDB.

Abstract

INTRODUCTION: Anti-NMDA receptor (NMDAr) encephalitis associated syndrome includes neuropsychiatric symptoms, impaired consciousness, seizures, autonomic instability, and hypoventilation. The electroencephalographic (EEG) activity throughout the course of the disease has not been documented enough. We reviewed electroclinical data of patients with NMDAr encephalitis contributing to characterize their EEG and its clinical correlation.

MATERIAL AND METHODS: We retrospectively identified 16 patients with NMDAr encephalitis. 15 of them underwent video-EEG in the acute phase in 8 Spanish Medical centres. The other was excluded because video EEG was performed outside the acute phase.

RESULTS: 15 patients (11 females). Median age 37.4 (range 14-87) years. Seizures occurred in 9 (60%), and status epilepticus (SE) in 5 (33.3%);, MRI (Magnetic resonance imaging) was abnormal in 10 (66.6%), and CSF (Cerebrospinal fluid) was normal in 3 and abnormal in 12 with positive PCR (polymerase chain reaction) for mycoplasma pneumoniae (1/15) and virus herpes simple (1/15). Ovarian teratoma was found in 1 patient, other malignancies (small cell lung carcinoma) in 1 patient. EEG was abnormal in acute phase in 14/15 (93.3%). Extreme delta brush (EDB) was observed in 5 (33.3%), the presence of EDB was associated with SE in all cases (3 subtle SE and 2 non convulsive SE). Rhythmic delta activity without EDB 5 (33.3%). Excessive beta was present in 8 (53%). EDB can follow a pattern of well characterized electroclinical seizures.

CONCLUSIONS: Almost invariably, patients with NMDAr encephalitis had abnormal EEG. The presence of EDB in our patients is associated with seizures, SE and can follow electroclinical seizures. These findings suggest that EDB could be an evolutive pattern of an SE in NMDAr encephalitis.

1.Introduction

Anti-N-methyl-D-aspartate receptor (NMDAr) encephalitis is an increasingly recognized aetiology of previously unexplained encephalopathy and encephalitis [1]. The initial symptoms are usually psychiatric and during the course of the syndrome seizures, dystonia, autonomic instability and hypoventilation and finally impaired consciousness evolving to coma can also occur [2]. Epileptic seizures have been reported in 76% of adults [2] and 77% of children [3]. EEG (Electroencephalogram) monitoring in anti-NMDAr encephalitis typically shows diffuse background slowing or focal slow waves mostly in the frontotemporal regions [4]. Ikeda et al [5] was the first to suggest that NMDAr encephalitis could have a specific EEG pattern that they denominated burst and slow complexes. This specific EEG pattern later on denominated by Schmuth et al [6]: the extreme delta brush (EDB) pattern, have been described in up to 30% of patients with anti NMDAr encephalitis [6]. Nowadays the origin of the EDB pattern remains unclear and also its ictal and interictal nature.

The aim of our study was to determine the frequency of EDB pattern in our series and to determine its relation to seizures or even to status epilepticus.

2.Methods

Study design: This is a retrospective, multicentric and observational study.

Patients: Adult and child patients from the following centers were included: Hospital Universitari de Bellvitge (3), Hospital Clinic I Provincial (3), Hospital Germans Trias I Pujol (3), Hospital Parc Taulí (3), Hospital Vall d'Hebron (1), Hospital del Mar (1), Hospital de Mataro (1).

All patients had confirmed serum or CSF (Cerebrospinal fluid) NMDAr antibodies. All determination of NMDAr antibodies were done in the Neuroimmunology Unit of Hospital Clinic i Provincial de Barcelona. Methodology done as previously described [2].

Patients data: The following patients data variables were collected: age, gender, presence or absence malignancies (teratomas and others), neurological symptoms including seizures, seizure type, psychiatric symptoms, autonomic symptoms, neuroimaging findings (including MRI (Magnetic resonance imaging), PET (Positron Emission Tomography) scan, SPECT (Single-photon emission computed tomography) scan), CSF findings, PCR (polymerase chain reaction) for viruses and bacteria, antiepileptic drug treatment, sedative treatment, immunosuppressive treatment, relapses and outcome at 6 months.

EEG data: Short video-EEG monitoring (1-2 hours per day) was done in all patients. Continuous video-EEG monitoring was done whenever possible. EEG recordings and EEG reports were analysed independently by MV and CG. The following variables of the EEG characteristics were collected: presence or absence of electrographic seizures, clinical or subclinical seizures, diffuse slowing, focal slowing, rhythmic delta activity, excessive beta activity, presence or absence of extreme delta brush.

Statistics: Fisher exact test allowed comparisons of categorical variables between patients with EDB and without, for continuous variables a Mann-Whitney U test was performed.

Ethical approval: Informed consent of the patients was not required because it was a retrospective and non-interventional study. The confidential information of the patients was protected according national normative. This manuscript has been revised for its publication by the Clinical Research Ethics Committee of Bellvitge University Hospital (PR 120/15).

3.Results

We retrospectively identified 16 patients with NMDAr encephalitis. Fifteen of them underwent video-EEG in the acute phase. The other was excluded because video EEG was performed outside the acute phase.

Finally 15 patients were included, 11 females (73%), mean age 37.4 (range 14-87) years. During the follow up 2 patients had suffered a relapse one of them NMDAr encephalitis with and associated optical neuritis and the other encephalitis with behavioural symptoms. Another patient continued with NMDAr antibodies after one year, the rest 13/15 had a monophasic disease. Almost all patients (14/15) had history of behavioural or personality changes before admittance in the neurological department. Among them, in 4/15 (26%) patients behavioural changes and psychotic ideation was the only symptom without seizures, altered consciousness and other neurological abnormalities. Seizures occurred in 9 (60%), and status epilepticus (SE) in 5 (33%).

Ovarian teratoma was found in 1 patient, other malignancies (small cell lung carcinoma) in 1 patient. MRI t2/fluid–attenuated inversion recovery hyperintensities involving temporal archicortex or neocortex were observed in 7 (46%), two of them also have extratemporal hyperintensities. Hyperintensities of extratemporal neocortex were observed in 3 patients and only in one without temporal involvement (figure 1 and 2). Normal MRI was found in 6 (40%) patients. CSF analysis was performed in all patients being abnormal in 11 patients (73%). Median CSF white blood cell counts were 70 (range 0-512) per mm³ and CSF protein levels were elevated in 6 patients (40%). Positive PCR for virus herpes simplex and serology for mycoplasma pneumoniae was observed in 2/15 patients. SPECT/PET studies were realized in the acute phase in 4 patients. Interestingly in 2 patients PET studies were abnormal while MRI was normal. SPECT performed in one patient showed extensive cortical hyperperfusion of one hemisphere (figure 1).

Treatment: 11 patients (73%) received benzodiazepines (BZD), 9 patients (60%) received several antiepileptic drugs (AED) and 5/15 (33%) patients received sedative drugs, 2 of them in order to induce pharmacologic coma. All patients received immunotherapy, first line immunotherapy (corticoids, plasmapheresis or immunoglobulins) in 5 patients (33%) and second line (rituximab, cyclophosphamide) in 10 patients (66%).

Evolution: The median modified Rankin Scale score at 6 months was 0.85 (0-3) returned to baseline 8 patients (53%) and 7 patients (46%) suffered cognitive decline being severe in 2 patients (13%): one due to severe aphasia and the other due to severe frontal lobe syndrome. Other permanent deficits were hemiparesia, psychotic ideation and memory disturbances. No patients had reported non provoked seizures in the follow up but in 1 patient (6%) a persistent abnormal EEG with focal epileptiform activity.

EEG findings.

EEG was normal in only one patient. Diffuse background slowing was seen in 7 (46%). Generalized delta activity was seen in 7 (46%), Focal delta activity in 7 (46%), increased beta activity in 8 patients (53%). Seizures were reported in 9 (60%) patients mostly of them focal with motor signs and with secondary generalization. Ictal EEG recordings were obtained in 5/9 patients showing a pattern of and electroencephalographic seizures in 3 patients, 2 generalized rhythmic evolutive delta activity.

EDB was observed in 5 patients (33%) (figure 2). In some of our patients the delta brush pattern was not present in the first days. Three of the patients had similarities in the clinical presentation: 1-2 weeks history of behavioural changes and psychotic symptoms and seizures (versive seizures evolving to a generalized tonic-clonic seizure) followed by progressive stupor with brief episodes of eyes and head turning with or without other subtle movements (atypical oromandibular automatism resembling oromandibular dyskinesias, dystonic postures, palpebral myoclonia or fingers and toes myoclonia). Figure 3 shows a representative seizure of one of them, These seizures starts with alfa like activity arising in left temporal region and propagating to both hemispheres, some hours later the seizure pattern changes (Figure 4) to sharp waves a 3Hz arising from temporal regions propagating to parietooccipital regions and evolving also in frequency together with excessive beta activity and the day after EDB (figure 2) pattern without electroencephalographic seizures appeared. Another patient, a 26 years-old woman, who was transferred in anaesthetic coma from another hospital. After tapering sedative treatment a continuous and evolving delta activity was observed. This pattern was recorded mixed with EDB pattern. Last woman with EDB pattern was admitted due to behavioural changes, generalized convulsive seizures and stupor evolving to coma. Anaesthetic coma was done. Electrical seizures induced by stimuli where recorded while tapering anaesthetic drugs and EDB pattern was observed days after.

Patients with EDB compared with patients without EDB (table 1).

No differences in age and sex were observed comparing patients with EDB and without but, interestingly all the men of the series (4/15) had and EEG without EDB. All patients with EDB referred seizures but only 4 (40%) of patients without EDB ($p=0.015$). Moreover all patients with EDB suffered recurrent seizures without recovering consciousness being diagnosed of status epilepticus and none of the patients without EDB pattern suffered a status epilepticus ($p<0.001$). Two of the patients with EDB were treated with an anesthetic coma (40%). Patients without EDB were more likely to

have an abnormal MRI than those with EDB ($p=0.05$). No differences were observed in evolution after 6 month, Rankin scale score was a little bit higher in EDB patients compared with non EDB patients (1.20 vs 0.8) but no statistical differences were found and no differences considering return to baseline or cognitive decline were observed.

4. Discussion

In our series of patients with NMDAr encephalitis we have observed different clinical evolutions. The first group of patients suffered only behavioural abnormalities and psychiatric symptoms without epileptiform activity recorded in scalp and no other neurological symptoms. All of them received immunosuppressive treatment probably earlier in the evolution of the disease. Previous studies [7] have suggested that anti-NMDAr encephalitis prognosis depends on early recognition and prompt immunomodulatory therapy. The second group of patients have suffered behavioural abnormalities, psychiatric symptoms, seizures, autonomic dysfunction and some obtundation progressing to coma and finally the last group apart of all the previously mentioned symptoms suffered SE. EDB pattern was observed in our series in last group of patients.

Patients whom suffered seizures or even status epilepticus and with EDB on EEG tend to have less abnormal findings on MRI than patients without EDB being our findings similar as observed by Schmitt et al [6].

EDB pattern, in our series, was clearly related to seizures and even to SE. Ikeda et al [5] was the first to describe this EEG pattern in a patient suffering a convulsive SE due to NMDAr encephalitis. Moreover they report that EDB pattern was not present from the beginning of the disease. EDB pattern was seen when the patient whom suffered initially convulsive seizures evolve to a subtle status epilepticus (fragmented multifocal myoclonus of the whole body) and disappeared later on. We and other authors [8] have also observed that EDB pattern can follow a pattern of well characterized electroclinical seizures or mixed with them. Other case reports also focusing on ictal EEG pattern in patients suffering an status epilepticus in NMDAr encephalitis have reported other patterns such as high voltage generalized sharp rhythms cyclically evolving with favorable response to AED[9], evolving rhythmic delta activity [10] or focal rhythmic delta activity that improve with AED [11]. Generalized rhythmic delta activity without evolution is an uncertain pattern. In anti NMDAr encephalitis patients other authors rule out their ictal nature founded on neither voltage or field evolution or not response to BZD [12-14]. Also depth electrodes recordings have determined their no ictal nature in an antiNMDAr encephalitis patient [15]. However Some authors using depth electrodes recordings have confirm their ictal nature in some patients of other etiologies [16].

It has been suggested that EDB pattern may be a marker of more severe disease and perhaps worse outcome at discharge [6], in our series patients with EDB pattern did not have a worse long term outcome but they needed more aggressive treatment with anesthetic coma and with hospitalization in intensive care unit setting.

5.Conclusions

The presence of EDB is associated with seizures and SE in our patients. We have also observed that EDB pattern can follow a pattern of well characterized electroclinical seizures or mixed with them. These findings suggest that EDB could be an evolutive pattern of an SE in NMDAr encephalitis.

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Figure captions:

Figure 1: Neuroradiological findings and EEG correlations

A: EEG of a 36-year old man, showing nearly continuous right hemisphere delta slowing. He has headache, left hemiparesis and speech disturbances. B: MRI showed an extensive right hemisphere cortical hyperintensities, and C: SPECT right hemispheric hyperperfusion. High pass filter 0.5 Hz; low pass filter 70Hz.

Figure 2: Extreme delta brush

EEG of the same patient as in figure 3 and 4, the day after EDB pattern without electroencephalographic seizures appeared. MRI showed Left hippocampal hyperintensity and left frontosubcortical hyperintensity. High pass filter 0.5 Hz; low pass filter 70Hz.

Figure 3: Ictal EEG in a patient suffering status epilepticus due to NMDAR encephalitis

EEG of a 25-year old woman. She started with episodes of behavioral disturbances for 2 weeks, followed by right versives seizures with evolved to generalized tonic-clonic seizures. Latter on the patient was unresponsive with movements like automatism in both hands, the EEG shows alfa like activity arising in left temporal region and propagating to both hemispheres. High pass filter 0,5Hz; low pass filter 70Hz.

Figure 4: Evolution of the ictal EEG in a patient suffering status epilepticus due to NMDAr encephalitis.

EEG pattern evolution patient 1 the seizure pattern changes to sharp waves a 3Hz arising from temporal regions propagating to parietooccipital regions and evolving also in frequency together with excessive beta activity. The patient was unresponsive with subtle movements (atypical oromandibular automatism resembling oromandibular dyskinesias, dystonic postures, palpebral mioclonia or fingers and toes myoclonia). High pass filter 0,5Hz; low pass filter 70Hz.