Epilepsy & Behavior 49 (2015) 280–285

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

EEG extreme delta brush: An ictal pattern in patients with anti-NMDA receptor encephalitis

M. Veciana [a], J.L. Becerra [b], P. Fossas [c], D. Muriana [c], G. Sansa [d], E. Santamarina [e], C. Gaig [f], M. Carreño [f], A. Molins [g], C. Escofet [d], M. Ley [h], R. Vivanco [h], J. Pedro [a], J. Miró [a], M. Falip [a,*], In behalf of the Epilepsy Group of the SCN

[a] Servei de Neurologia, Hospital Universitari de Bellvitge, Hospitalet de Llobregat, Spain
[b] Servei de Neurologia, Hospital Germans Trias i Pujol, Badalona, Spain
[c] Servei de Neurologia, Hospital de Mataró, Spain
[d] Servei de Neurologia, Hospital Parc Taulí, Sabadell, Spain
[e] Servei de Neurologia, Hospital Vall d´Hebrón, Barcelona, Spain
[f] Servei de Neurologia, Hospital Clínic i Provincial, Barcelona, Spain
[g] Servei de Neurologia, Hospital Universitari Josep Trueta, Girona, Spain
[h] Servei de Neurologia, Hospital del Mar, Barcelona, Spain

ARTICLE INFO

Article history:
Accepted 17 April 2015
Available online 10 June 2015

Keywords:
Encephalitis
NMDAr antibodies
Autoimmune
Seizure
Ictal pattern
Status epilepticus

ABSTRACT

Introduction: The 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 still not been well documented. We reviewed electroclinical data of patients with NMDAr encephalitis to characterize their EEG and its clinical correlation.
Material and methods: We retrospectively identified 16 patients with NMDAr encephalitis from 8 Spanish medical centers, 15 of whom underwent video-EEG in the acute phase.
Results: In 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%). Magnetic resonance imaging (MRI) 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 herpes simple virus (1/15). An ovarian teratoma was found in 1 patient and other malignancies (small cell lung carcinoma) in 1 patient. The EEG was abnormal in the acute phase in 14/15 (93.3%). Extreme delta brush (EDB) was observed in 5 (33.3%), and the presence of EDB was associated with SE in all cases. Rhythmic delta activity without EDB was observed in 5 (33.3%), while excessive beta activity was present in 4 (26.6%). Extreme delta brush can follow a pattern of well-characterized electroclinical seizures.
Conclusions: Almost invariably, patients with NMDAr encephalitis had abnormal EEG. The presence of EDB, which can follow a pattern of well-characterized electroclinical seizures, in our patients was associated with seizures and SE. These findings suggest that EDB could be an evolutive pattern of an SE in NMDAr encephalitis.

This article is part of a Special Issue entitled "Status Epilepticus".

1. Introduction

Anti-N-methyl-D-aspartate receptor (NMDAr) encephalitis is an increasingly recognized etiology of previously unexplained encephalopathy and encephalitis [1]. The initial symptoms are usually psychiatric, and during the course of the syndrome, seizures, dystonia, autonomic instability, 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]. Electroencephalogram (EEG) monitoring in anti-NMDAR encephalitis typically shows diffuse background slowing or focal slow waves mostly in the frontotemporal regions [4]. Ikeda et al. [5] were the first to suggest that NMDAr encephalitis could have a specific EEG pattern that they termed burst and slow complexes. This specific EEG pattern, later termed by Schmitt et al. [6] as the extreme delta brush (EDB) pattern, has been described in up to 30% of patients with anti-NMDAr encephalitis [6]. Currently, the origin of not only the EDB pattern but also its ictal or interictal nature remains unclear.

The aim of our study was two-fold: to determine the frequency of the EDB pattern in our series of patients and to assess its relation to seizures or even to status epilepticus.

Abbreviations: NMDAr, 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.

* Corresponding author at: Neurology Service, Hospital Universitari de Bellvitge, Feixa Llarga S/N, Hospitalet de Llobregat, 08907, Spain. Tel.: 34 932607711.
E-mail address: mfalip@bellvitgehospital.cat (M. Falip).

http://dx.doi.org/10.1016/j.yebeh.2015.04.032
1525-5050/

2. Methods

2.1. Study design

This was a retrospective, multicentric, observational study.

2.2. 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'Hebrón (1), Hospital del Mar (1), and Hospital de Mataró (1).

All patients had confirmed serum or CSF (cerebrospinal fluid) NMDAr antibodies. All determinations of NMDAr ab were done in the Neuroimmunology Unit of Hospital Clinic i Provincial de Barcelona following the methodology reported elsewhere [2].

2.3. Patient data

The following data on patients were collected: age; gender; presence or absence of 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, and SPECT (single-photon emission computed tomography) scan); CSF findings; PCR (polymerase chain reaction) for viruses and bacteria; antiepileptic drug treatment; sedative treatment; immunosuppressive treatment; and relapses and outcome at 6 months.

2.4. EEG data

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

2.5. Statistics

Fisher's exact test was used to perform comparisons of categorical variables between patients with and without EDB; for continuous variables, a Mann–Whitney U-test was performed.

2.6. Ethical approval

Informed consent of the patients was not required because it was a retrospective and noninterventional study. The confidential information on patients was handled following national data protection regulations. 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 remaining one was excluded because video-EEG was performed outside the acute phase.

In total, 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 had NMDAr encephalitis with an associated optical neuritis and the other one had encephalitis with behavioral symptoms. Another patient still had NMDAr antibodies after one year, while the rest (13/15) had a monophasic disease. Almost all patients (14/15) had a history of behavioral or personality changes before admission to the neurological department. Among them, in 4/15 (26%) patients, behavioral changes and psychotic ideation were the only symptoms (without seizures, altered consciousness, or other neurological abnormalities). Seizures occurred in 9 (60%) and status epilepticus (SE) in 5 (33%).

An ovarian teratoma was found in 1 patient and other malignancies (small cell lung carcinoma) in 1 patient. On MRI, T2/fluid-attenuated inversion recovery hyperintensities involving the temporal archicortex or neocortex were observed in 7 (46%), and two of them also had extratemporal hyperintensities. Hyperintensities of the extratemporal neocortex were observed in 3 patients and without temporal involvement in only one (Figs. 1 and 2). Normal MRI was found in 6 (40%) patients. Cerebrospinal fluid analysis was performed in all patients, being abnormal in 11 patients (73%). Median CSF white blood cell counts were 70 (range: 0–512) per mm^3, and CSF protein levels were elevated in 6 patients (40%). Positive PCR for herpes simplex virus and positive serology for *Mycoplasma pneumoniae* were observed in 2/15 patients. In 4 patients, SPECT/PET studies were performed in the acute phase. Interestingly in 2 patients, PET studies were abnormal while MRI was normal. Single-photon emission computed tomography performed in one patient showed extensive cortical hyperperfusion of one hemisphere (Fig. 1).

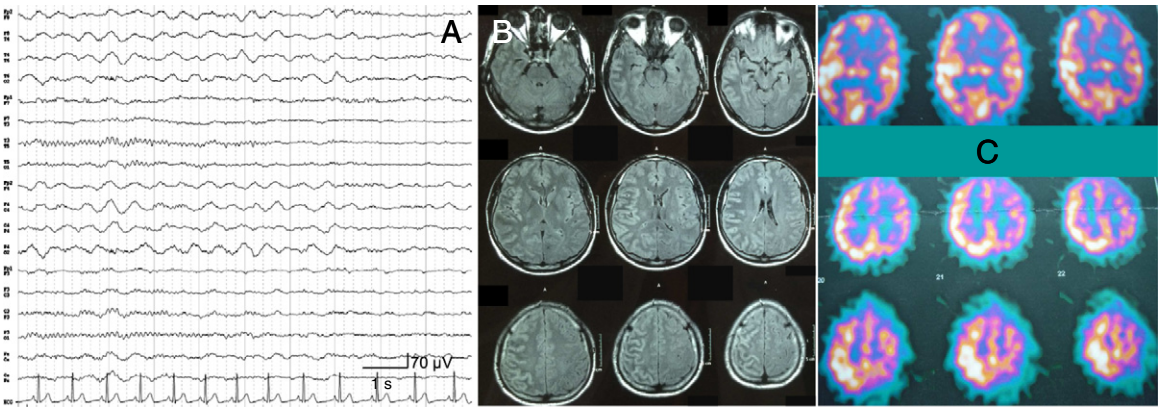

Fig. 1. Neuroradiological findings and EEG correlations. EEG of a 36-year-old man showing nearly continuous right hemisphere delta slowing. He had headache, left hemiparesis, and speech disturbances. MRI showed extensive right hemisphere cortical hyperintensities and SPECT revealed right hemispheric hyperperfusion. High pass filter: 0.5 Hz; low pass filter: 70 Hz.

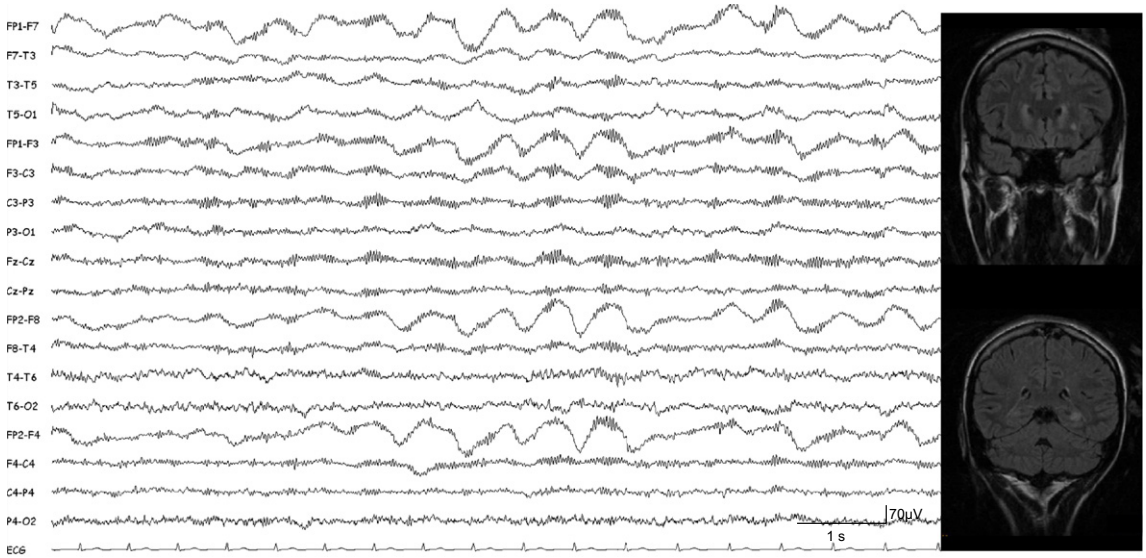

Fig. 2. Extreme delta brush. EEG of the same patient as in Figs. 3 and 4 the day after the EDB pattern without electroencephalographic seizures appeared. MRI showed left hippocampal hyperintensity and left frontosubcortical hyperintensity. High pass filter: 0.5 Hz; low pass filter: 70 Hz.

3.1. Treatment

Eleven patients (73%) received benzodiazepines (BZDs), 9 patients (60%) received various antiepileptic drugs (AEDs), and 5/15 (33%) patients received sedative drugs, 2 of which were used to induce pharmacologic coma. All patients received immunotherapy: first-line immunotherapy (corticoids, plasmapheresis, or immunoglobulins) in 5 patients (33%) and second-line immunotherapy (rituximab, cyclophosphamide) in 10 patients (66%).

3.2. Evolution

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

3.3. EEG findings

The 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%), and increased beta activity in 8 (53%) patients. Seizures were reported in 9 (60%) patients, mostly focal with motor signs and with secondary generalization. Ictal EEG recordings were obtained in 5/9 patients: showing a pattern of electroencephalographic seizures in 3 patients and generalized rhythmic evolving to delta activity in two patients.

Extreme delta brush was observed in 5 patients (33%) (Fig. 2). In some of our patients, the delta brush pattern was not present during the first few days. Three of the patients had similarities in the clinical presentation: 1- to 2-week history of behavioral changes and psychotic symptoms and seizures (versive seizures evolving to a generalized tonic–clonic seizure) followed by a progressive stupor with brief episodes of eye and head turning with or without other subtle movements (atypical oromandibular automatism resembling oromandibular dyskinesias, dystonic postures, palpebral myoclonia, or finger and toe myoclonia). Fig. 3 shows a representative seizure pattern of one of the patients. These seizures start with alpha-like activity arising in the left temporal region and propagating to both hemispheres, and some hours later, the seizure pattern changes (Fig. 4) to sharp waves at 3 Hz arising from temporal regions and propagating to parietooccipital regions and evolving in frequency together with excessive beta activity; an EDB pattern (Fig. 2) without electroencephalographic seizures appeared the following day. In another patient (a 26-year-old woman in anesthetic coma who was transferred from another hospital), after tapering sedative treatment, a continuous and evolving delta activity was observed. This pattern was recorded mixed with the EDB pattern. Lastly, a woman with an EDB pattern was admitted due to behavioral changes, generalized convulsive seizures, and a stupor evolving to coma. Anesthetic coma was induced. Electrical seizures induced by stimuli were recorded while tapering anesthetic drugs, and the EDB pattern was observed some days later.

3.4. Patients with EDB compared to patients without EDB (Table 1)

No differences in age and sex were observed when comparing patients with and without EDB, but interestingly, all the men in the series (4/15) had an EEG without EDB. All patients with EDB reported seizures in comparison to only 4 (40%) patients without EDB ($p = 0.015$). Moreover, all patients with EDB suffered recurrent seizures without recovering consciousness, being diagnosed with status epilepticus, and none of the patients without an 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 months. The modified Rankin Scale score was slightly higher in EDB patients compared with non-EDB patients (1.20 vs 0.8), but no statistically significant differences were found and no differences in terms of 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

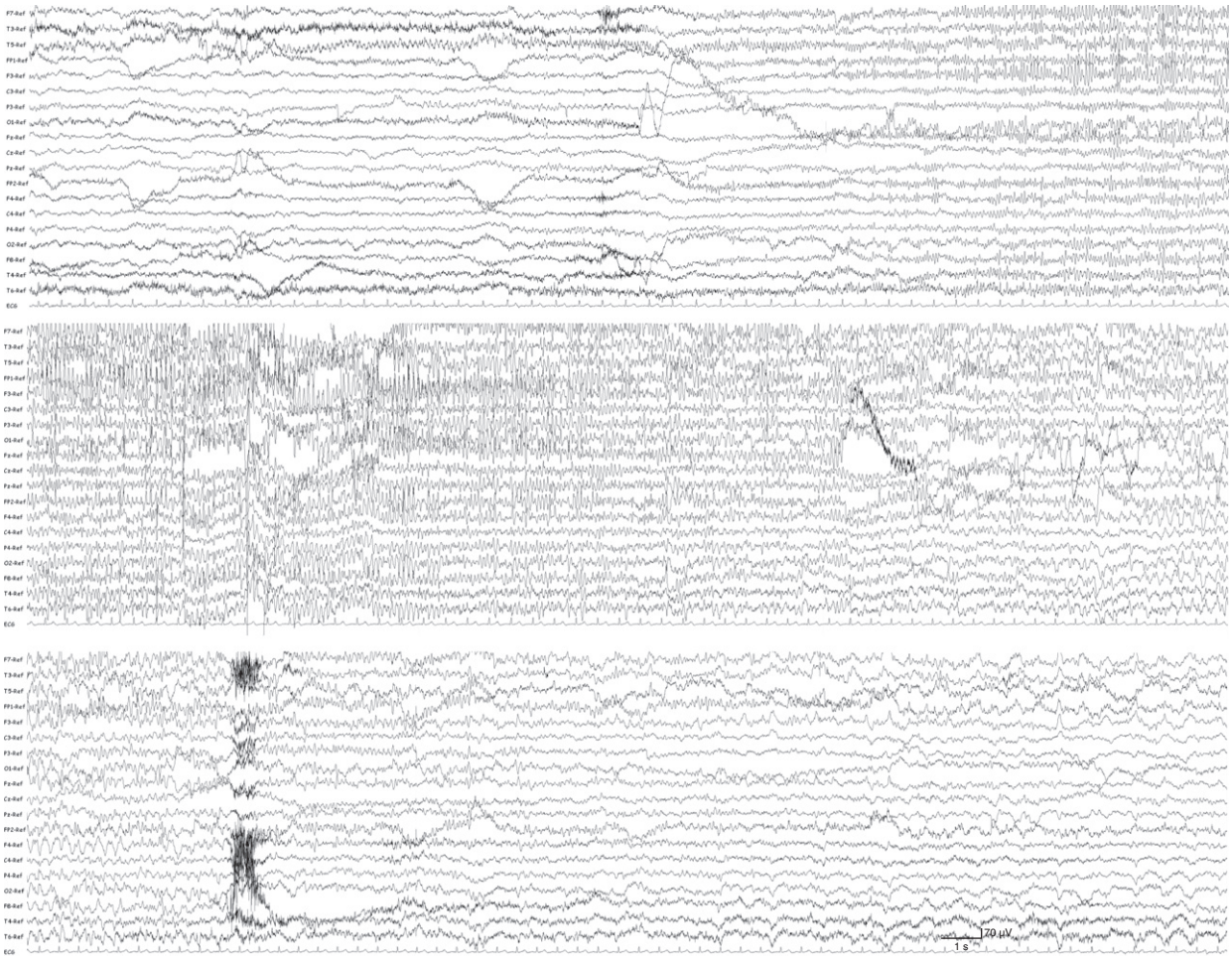

Fig. 3. Ictal EEG in a patient suffering status epilepticus due to NMDAr encephalitis. EEG of a 25-year-old woman. She was admitted to a psychiatric hospital because of episodes of behavioral disturbances for 2 weeks and was treated with antipsychotics and benzodiazepines. She was transferred to a general hospital because of a right versive seizure which evolved to a generalized tonic–clonic seizure. Later on, the patient was unresponsive with movements like automatism in both hands. The EEG shows alpha-like activity arising in the left temporal region and propagating to both hemispheres. High pass filter: 0.5 Hz; low pass filter: 70 Hz.

suffered only behavioral abnormalities and psychiatric symptoms without seizures recorded using scalp electrodes 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 the prognosis of anti-NMDAr encephalitis depends on early recognition and prompt immunomodulatory therapy. The second group of patients suffered behavioral abnormalities, psychiatric symptoms, seizures, autonomic dysfunction, and some obnubilation progressing to coma. In addition, all patients in this group suffered SE. An EDB pattern was only observed among these patients in the last group.

Patients who suffered status epilepticus and had EDB on EEG tended to have less abnormal findings on MRI than patients without EDB, our findings in this respect were similar to those observed by Schmitt et al. [6].

An EDB pattern, in our series, was clearly related to seizures as well as to SE. Ikeda et al. [5] were the first to describe this EEG pattern in a patient suffering a convulsive SE due to NMDAr encephalitis. Moreover, they report that the EDB pattern was not present from the beginning of the disease but rather was seen when the patient's initial convulsive seizures evolved to a subtle status epilepticus (fragmented multifocal myoclonus of the whole body) and disappeared later on. Like other authors [8], we have also observed that an EDB pattern can either follow a pattern of well-characterized electroclinical seizures or be mixed with them. Other case reports also focusing on ictal EEG patterns in patients with NMDAr encephalitis suffering SE have reported other patterns such as high-voltage generalized sharp rhythms cyclically evolving with favorable response to AEDs [9], evolving rhythmic delta activity [10], or focal rhythmic delta activity that improves with AEDs [11]. Generalized rhythmic delta activity without evolution is an uncertain pattern. Some authors using depth electrode recordings have confirmed their ictal nature in some patients [12]. Other authors rule out their ictal nature on the basis of an absence of voltage or field evolution or nonresponse to BZDs [13–15]. Also, depth electrode recordings have determined their nonictal nature in one patient with anti-NMDAr encephalitis [16].

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

5. Conclusions

The presence of EDB was associated with seizures and SE in our patients. We also observed that the EDB pattern can follow a pattern of

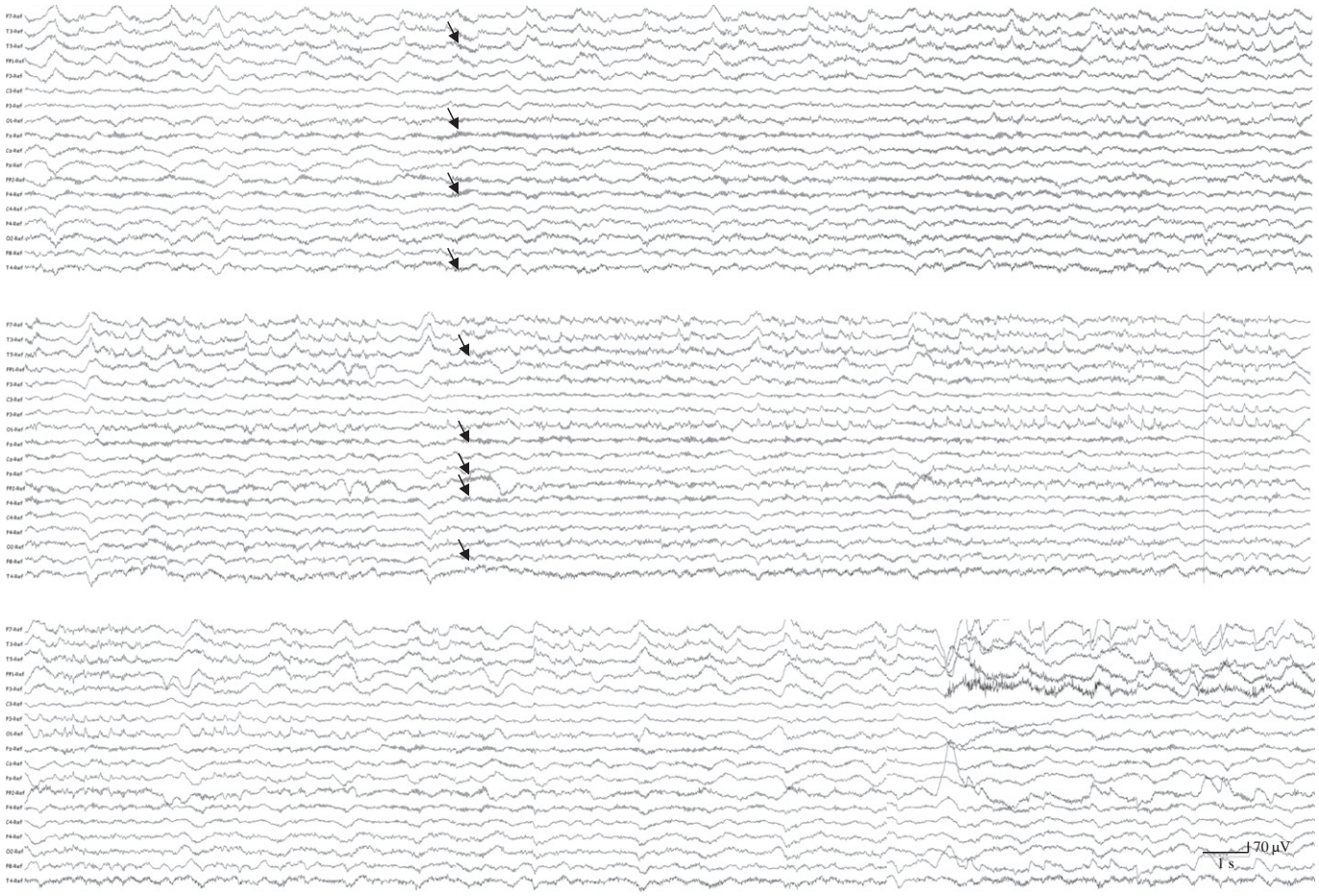

Fig. 4. Evolution of the ictal EEG in a patient suffering status epilepticus due to NMDAr encephalitis. EEG of the same patient as in Fig. 1 some hours later: the seizure pattern changes to sharp waves at 3 Hz arising from the temporal regions, propagating to parietooccipital regions, and evolving in frequency together with excessive beta activity (arrows). The patient was unresponsive with subtle movements (atypical oromandibular automatism resembling oromandibular dyskinesias, dystonic postures, palpebral myoclonia, or finger and toe myoclonia). High pass filter: 0.5 Hz; low pass filter: 70 Hz.

Table 1
Clinical characteristics comparing patients with and without EDB.

Characteristics	EDB (n = 5)	No EDB (n = 10)	p-Value
Age, median (range)	28.6 (14–44)	41.8 (17–87)	NS
Female	5/5 (100%)	6/10 (60%)	NS
Teratoma present	0 (0%)	1 (10%)	NS
Other malignancies	0 (0%)	1 (10%)	NS
Seizures: clinical	5 (100%)	4 (40%)	0.04
Status	5 (100%)	0 (0%)	<0.001
Behavioral changes	5 (100%)	9 (90%)	NS
Abnormal MRI	1/5 (20%)	8/10 (80%)	0.05
CSF abnormal	4 (80%)	7 (70%)	NS
Blood cell count (mean)	42.8	84	NS
Elevated proteins	2 (40%)	4 (40%)	NS
Other features[a]	0 (0%)	2 (20%)	NS
Immunotherapy			
First line	1 (20%)	4 (40%)	NS
Second line	4 (80%)	6 (60%)	NS
BZD	5 (100%)	6 (60%)	0.15
AED	5 (100%)	4 (40%)	0.04
Sedative drugs	4 (80%)	1 (10%)	0.02
Sedative drugs to induce coma	2 (40%)	0 (0%)	NS
Evolution			
Relapses	1 (20%)	1 (10%)	NS
Cognitive decline	2 (40%)	6 (60%)	NS
Abnormal persistent EEG	1 (20%)	0 (0%)	NS
New seizures	0 (0%)	0 (0%)	NS
Rankin Scale score at 6 months	1.20	0.8	NS
Return to baseline	2 (40%)	5 (50%)	NS

Data are given as n (%) of patients.
[a] Concomitant infection of HSV (herpes simplex virus) or *Mycoplasma pneumoniae*.

well-characterized electroclinical seizures or be mixed with them. These findings suggest that EDB could be seen in the evolution of EEG patterns in patients with SE associated with NMDAr encephalitis.

Acknowledgments

The authors thank all patients for their collaboration and Mr. Dave McFarlane for technical assistance. This study was not financially supported.

Conflict of interest statement

All authors declare not to have any conflict of interest.

References

[1] Prüss H, Dalmau J, Harms L, Höltje M, Ahnert-Hilger G, Borowski K, et al. Retrospective analysis of NMDA receptor antibodies in encephalitis of unknown origin. Neurology 2010;75(19):1735–9.
[2] Dalmau J, Gleichman AJ, Hughes EG, Rossi JE, Peng X, Lai M, et al. Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. Lancet Neurol 2008;7:1091–8.
[3] Florance NR, Davis RL, Lam C, Szperka C, Zhou L, Ahmad S, et al. Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis in children and adolescents. Ann Neurol 2009;66:11–8.
[4] Irani SR, Bera K, Waters P, Zuliani L, Maxwell S, Zandi MS, et al. N-methyl-D-aspartate antibody encephalitis: temporal progression of clinical and paraclinical observations in a predominantly non-paraneoplastic disorder of both sexes. Brain 2010;133(6):1655–67.

[5] Ikeda A, Matsui M, Hase Y, Hitomi T, Takahashi Y, Shibasaki H, et al. "Burst and slow complexes" in nonconvulsive epileptic status. Epileptic Disord 2006;8(1):61–4.
[6] Schmitt SE, Pargeon K, Frechette ES, Hirsch LJ, Dalmau J, Friedman D. Extreme delta brush: a unique EEG pattern in adults with anti-NMDA receptor encephalitis. Neurology 2012;79(11):1094–100.
[7] Titulaer MJ, McCracken L, Gabilondo I, Armangué T, Glaser C, Iizuka T, et al. Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. Lancet Neurol 2013;12(2):157–65.
[8] VanHaerents S, Stillman A, Inoa V, Searls DE, Herman ST. Early and persistent 'extreme delta brush' in a patient with anti-NMDA receptor encephalitis. Epilepsy Behav Case Rep 2014;2:67–70.
[9] Johnson N, Henry C, Fessler AJ, Dalmau J. Anti-NMDA receptor encephalitis causing prolonged nonconvulsive status epilepticus. Neurology 2010;75(16):1480–2.
[10] Kirkpatrick MP, Clarke CD, Sonmezturk HH, Abou-Khalil B. Rhythmic delta activity represents a form of nonconvulsive status epilepticus in anti-NMDA receptor antibody encephalitis. Epilepsy Behav 2011;20(2):392–4.
[11] Bayreuther C, Bourg V, Dellamonica J, Borg M, Bernardin G, Thomas P. Complex partial status epilepticus revealing anti-NMDA receptor encephalitis. Epileptic Disord 2009;11(3):261–5.
[12] Wieser HG, Hailemariam S, Regard M, Landis T. Unilateral limbic epileptic status activity: stereo EEG, behavioral, and cognitive data. Epilepsia 1985;26(1):19–29.
[13] da Silva-Júnior FP, Castro LH, Andrade JQ, Bastos CG, Moreira CH, Valério RM, et al. Serial and prolonged EEG monitoring in anti-N-methyl-D-aspartate receptor encephalitis. Clin Neurophysiol 2014;125(8):1541–4.
[14] Gitiaux C, Simonnet H, Eisermann M, Leunen D, Dulac O, Nabbout R, et al. Early electro-clinical features may contribute to diagnosis of the anti-NMDA receptor encephalitis in children. Clin Neurophysiol 2013;124(12):2354–61.
[15] Di Capua D, García-Ptacek S, García-García ME, Abarrategui B, Porta-Etessam J, García-Morales I. Extreme delta brush in a patient with anti-NMDAR encephalitis. Epileptic Disord 2013;15(4):461–4.
[16] Probasco JC, Benavides DR, Ciarallo A, Sanin BW, Wabulya A, Bergey GK, et al. Electroencephalographic fluorodeoxyglucose-positron emission tomography correlates in anti-N-methyl-D-aspartate receptor autoimmune encephalitis. Epilepsy Behav Case Rep 2014;2:174–8.