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Extreme delta – With or without brushes: A potential surrogate marker of disease activity in anti-NMDA-receptor encephalitis

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HIGHLIGHTS

- Rhythmic delta is increasingly seen in anti-NMDA receptor encephalitis (NMDARE) refractory to first line immunotherapy.
- Rhythmic delta decreases after second line immunotherapy and predates clinical improvement.
- Rhythmic delta is not seen in other autoimmune encephalitides and is likely specific to NMDARE.

ABSTRACT

Objective: Anti-NMDA receptor encephalitis (NMDARE) may not respond to first line immunotherapy. Biomarkers to track disease course and guide escalation of immunotherapy are needed. We describe the evolution of EEG in four patients with NMDARE requiring prolonged intensive care.
Methods: Within a database of 121 patients with immune-mediated neurological disorders, ten with NMDARE were retrospectively identified. Four patients did not respond to first line immunotherapy. Continuous EEG was reviewed and correlated with clinical status and treatment.
Results: Intermittent polymorphic delta slowing was present in all patients. Generalized rhythmic delta occupied increasing proportion of the EEG as disease progressed, at times with superimposed beta. The institution of second line immunotherapy was followed by progressive decrease in rhythmic delta, predating clinical improvement. In one patient who did not respond to second line immunotherapy, rhythmic delta continued to occupy a majority of the recording. The extreme delta pattern was not seen in a comparison cohort of patients with autoimmune encephalitis without anti-NMDA-R antibodies.
Conclusions: Extreme delta, with or without brushes, increases with progression of NMDARE, responds to escalation of immunotherapy, predating clinical improvement, and is likely specific to NMDA-R antibodies.
Significance: Extreme delta may be a surrogate marker of disease activity in NMDARE refractory to first line immunotherapy.

1. Introduction

NMDARE is a treatable antibody-mediated neurological syndrome resulting in neuropsychiatric disturbances and seizures, which may evolve to severe encephalopathy, autonomic disturbance and orofacial dyskinesias (Dalmau et al., 2011). Clinical seizures are seen in 80% of cases (Dalmau et al., 2011) and EEG abnormalities in 90% (Titulaer et al., 2013), of which the potentially specific EEG pattern of "extreme delta brush" may carry worse prognosis (Schmitt et al., 2012) and may be associated with electrographic seizures (Veciana et al., 2015). While there have been attempts at defining EEG patterns in terms of phase of disease (Gitiaux et al., 2013; Nosadini et al., 2015), detailed descriptions of electrographic patterns over the course of the critical illness and in relationship with immunotherapy are still incomplete. While antibody titres have been shown to parallel disease activity

Abbreviations: AEDs, antiepileptic drugs; cEEG, continuous EEG; GAD65, glutamic acid decarboxylase 65; IVIg, intravenous immunoglobulin; LGI1, leucine-rich glioma inactivated 1; NMDARE, anti-NMDA-R receptor encephalitis; NORSE, new onset refractory status epilepticus; PLEX, plasma exchange; VGKC, voltage-gated potassium channel.

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(Gresa-Arribas et al., 2014), there is a need for additional biomarkers which may guide escalation of immunotherapy.

We explored the potential role of EEG as a biomarker of disease activity in NMDARE by examining the relationship between EEG findings, clinical status, and immunotherapy in a selected group of patients with NMDARE who did not respond to first line immunotherapy and who underwent cEEG recordings throughout their illness. We then present a summary of the available literature on electrographic features of NMDARE and propose a continuum of EEG findings, across which critically ill NMDARE patients may lie and oscillate over the course of their disease, potentially reflecting disease activity.

2. Methods

2.1. Patient inclusion

Amongst a Mellen Center database of 121 patients with autoimmune-mediated neurological disorders, 10 patients with NMDARE were identified on the basis of a consistent clinical syndrome and positive NMDA-R antibodies through cell-based assays (serum in 9/10 with titres ranging from 1:20 to 1:640 and/or CSF in 7/10 with titres ranging from 1:5 to 1:320).

Of these 10 patients, 4 patients had prolonged critical illness, failed to respond to first line immunotherapy (at least two of: steroids, IVIg and PLEX) and underwent cEEG recordings spanning the majority of the illness (mean 50.5 days, range 20–109). The remainder 6 patients, not included in this study, did not require critical care and underwent cEEG for a mean of 3.3 days (range 2–5) with findings ranging from normal, intermittent generalized slowing to continuous generalized slowing. Clinically, they were distinguished by lack of progression to dysautonomia, severe encephalopathy and orofacial dyskinesias, and by response to first line immunotherapy (steroids, IVIg or PLEX) although three patients also received second line immunotherapy (cyclophosphamide and/or rituximab) in the setting of pediatric age in one patient (in whom the treatment protocol at our institution includes concurrent first and second line immunotherapy) and a delayed relapse for the other two adult patients.

Within the same Mellen Center database of autoimmune neurological disorders, 17 cases of autoimmune epilepsy without associated NMDA-R antibodies were identified. 11 harboured another antineuronal antibody (VGKC with or without LGI1, GABA-B, GAD65, Hu) and six were antibody-negative, but met diagnostic criteria for autoimmune encephalitis (Graus et al., 2016). 12 patients underwent continuous EEG monitoring upon their initial presentation, and five had NORSE and were used as a comparison group.

2.2. Data collection

Chart review was conducted to collect information regarding clinical status (level of consciousness, need for mechanical ventilation, outcome at discharge and at last follow-up) and treatment (immunotherapy, AEDs). EEG tracings and reports were reviewed.

2.3. Standard protocol approvals, registration and patient consents

Institutional Review Boards Ethics approval was obtained. Due to the retrospective nature of the study, consent waiver was granted.

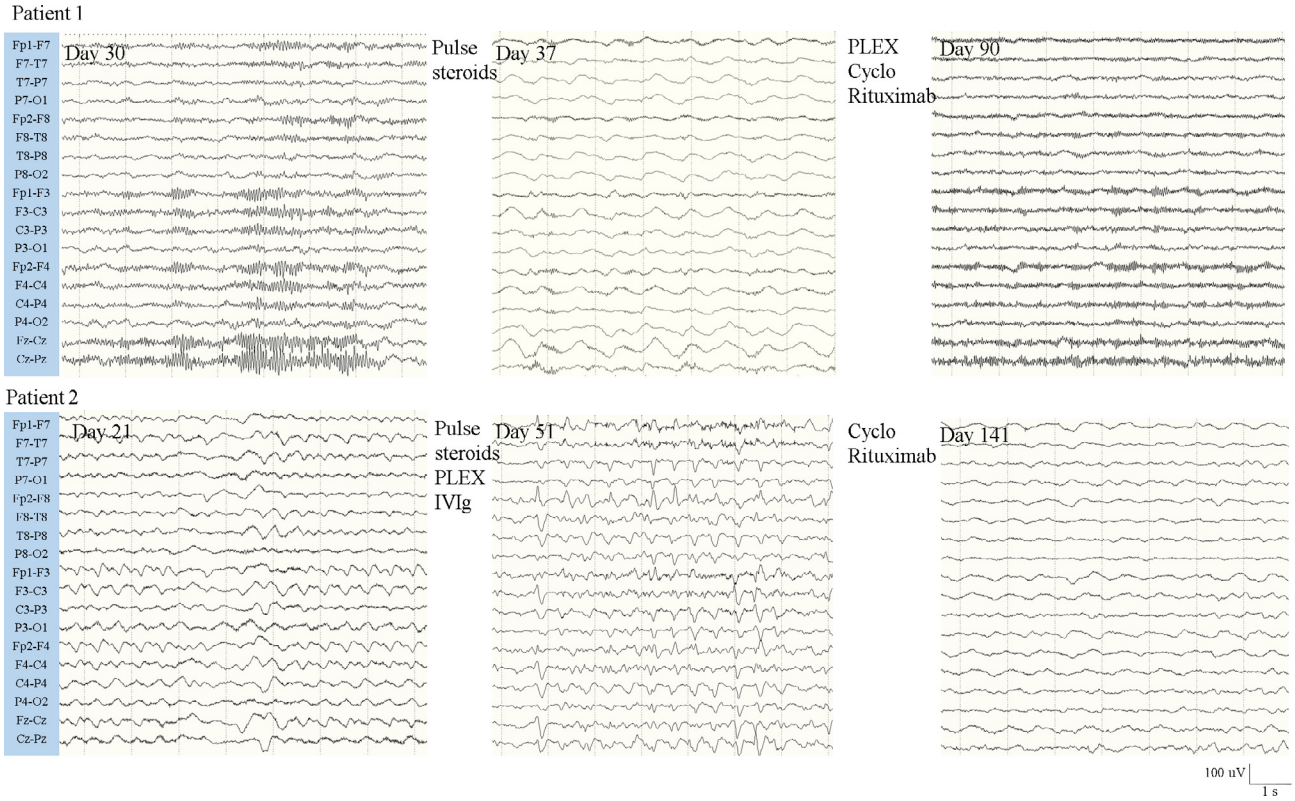

Fig. 1. EEG findings in patients 1 and 2. Patient 1 evolved from intermittent generalized polymorphic delta slow, with superimposed excessive fast activity (first EEG), to intermittent generalized rhythmic slow, progressively occupying a larger proportion of the record (second EEG), which after institution of second line immunotherapy, reverted to generalized polymorphic slow (third EEG), predating clinical improvement. Patient 2 similarly had intermittent generalized polymorphic or rhythmic slow, with superimposed beta bursts, and developed increasing periods of generalized rhythmic slow (first EEG), which was replaced by generalized periodic discharges, with frontooccipital distribution (second EEG). After institution of second line immunotherapy, these discharges disappeared and generalized polymorphic slow returned (third EEG). High frequency filter 0.53 Hz, low frequency filter 70 Hz.

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