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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.
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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.

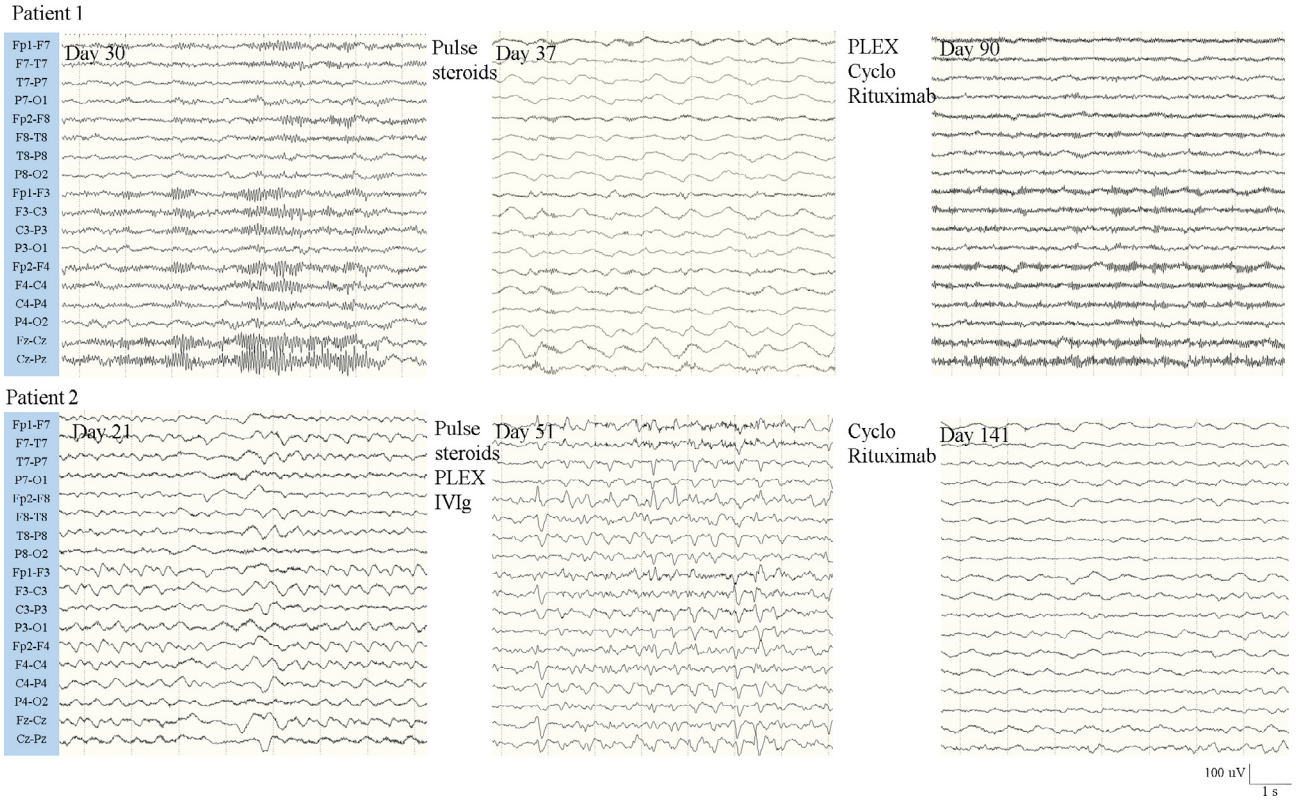

Fig. 1. EEG findings in patients 1 and 2. Patient 1 evolved from intermittent generalized polymorphic delta slow, with superimposed excessive fast activity (first EEG), to intermittent generalized rhythmic slow, progressively occupying a larger proportion of the record (second EEG), which after institution 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.

3. Results

3.1. Clinical

The four patients presented with a similar clinical picture, consisting of viral prodrome, psychiatric disturbance followed by progressive encephalopathy, dysautonomia and orofacial dyskinesias. An index generalized tonic clonic seizure was seen in one patient (patient number 1) and no clinical seizures were noted in the other patients. At the time of cEEG monitoring, all patients were stuporous and were mechanically ventilated.

Clinical characteristics upon presentation and over the course of treatment was initially indistinguishable across patients despite variability in EEG features described below. None of the patients showed response to first line immunotherapy. One patient (patient 4) was found to have an ovarian teratoma and underwent an oophorectomy.

Salient EEG findings are illustrated in Figs. 1 and 2.

3.2. Initial EEG

Initially, all patients exhibited nonspecific generalized polymorphic delta slow intermixed with generalized rhythmic delta slow. Over time, generalized rhythmic delta occupied a greater portion of the recordings. Continuous or near-continuous generalized rhythmic delta is referred to as "extreme delta" in the remainder of the manuscript.

In addition, generalized excessive fast activity was seen, consistent with the use of benzodiazepines and propofol in all patients for management of agitation and to facilitate ventilation in the setting of dysautonomia (e.g. Fig. 1, patient 1, first EEG).

3.3. Evolution of EEG

Brief bursts of fast activity were superimposed on the crest or trough of generalized rhythmic slow, akin to the described pattern of "extreme delta brush" (e.g. Fig. 1 patient 1, second EEG, Fig. 2 patient 3, first and third EEG), distinct from delta brushes described in neonatal EEG due to its distribution, maximal in the frontal regions. These bursts (or "brushes") occurred at various stages of the disease course, and had fluctuating characteristics across patients and within the same patient: amplitude (low or high), morphology (polyspike-like, sinusoidal), duration (0.25–0.75 s). Polyspike morphology was seen most abundantly in patient 4, who exhibited the most pervasive extreme delta (Fig. 2, patient 4, third EEG). These brief bursts of fast activity ("brushes") (Fig. 1 patient 1 second EEG) were distinguished from generalized excessive fast activity (Fig. 1 patient 1 first EEG) by their short duration. In all patients, superimposed fast activity was infrequently seen, while extreme delta was continuous or near continuous.

In patients 2–4, periods of "extreme delta" occasionally evolved in frequency, distribution and morphology. Extreme delta patterns could waxe and wane (e.g. Fig. 1, patient 2, first EEG), and in patients 3 and 4, become monomorphic for prolonged periods of time (hours). Faster frequencies in the occipital regions, with occasional evolution in frequency, amplitude and morphology (acquiring sharp features), were noted in patient 3 and 4 (e.g. Fig. 2, patients 3 and 4, second EEG). This evolution was best appreciated over minutes and with slow paperspeed (30 or 60 s/page).

In patient 4, superimposed rhythmic bioccipital sharp waves became more prominent over time, while rhythmic delta progressively disappeared, and polyspike-like frontal beta persisted (Fig. 2, patient 4, third EEG).

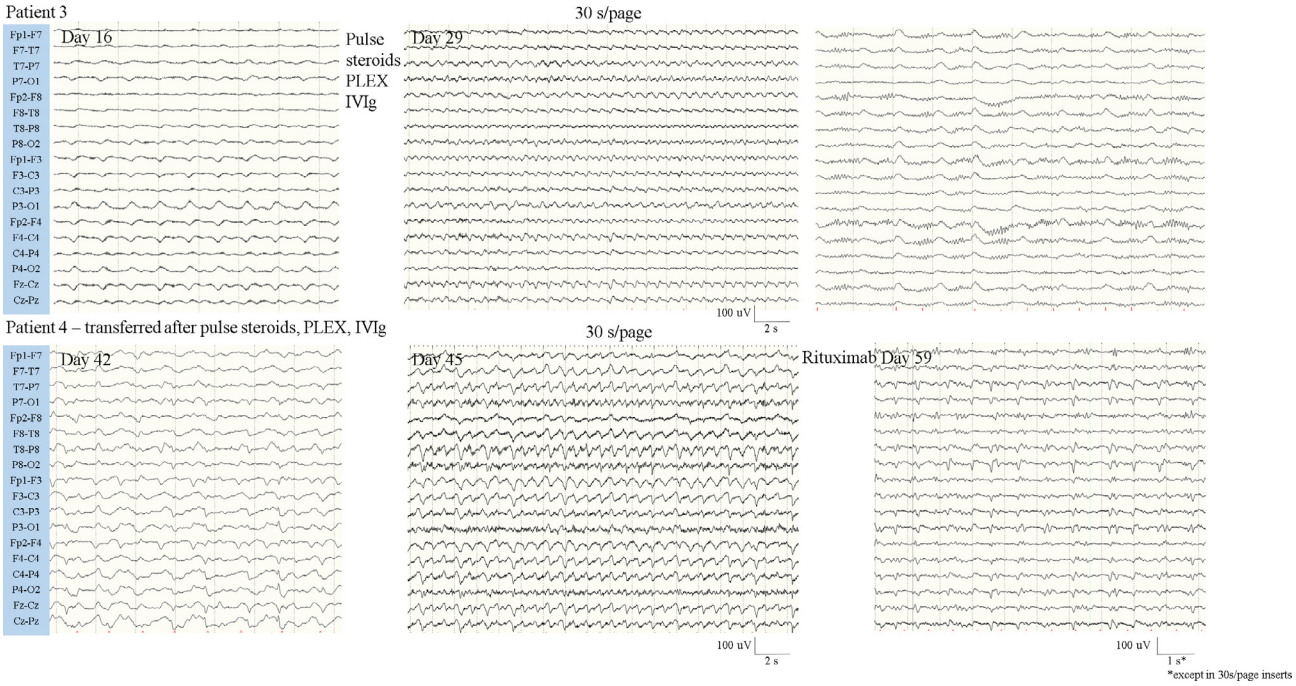

Fig. 2. EEG findings in patients 3 and 4. Patient 3 evolved from generalized rhythmic slow (first EEG) to patterns with fronto-occipital distribution and increasingly sharply contoured morphology (second EEG), best seen on compressed 30 s/page. In other patients, superimposed beta burst ("extreme delta brush") were seen on the trough of rhythmic delta (third EEG). Although not shown here, with second line immunotherapy and treatment with barbiturates, rhythmic slow decreased and was slowly replaced by polymorphic slow. D. Patient 4 had similar patterns of intermittent rhythmic delta, with or without superimposed beta bursts initially, at times sharply contoured (first EEG), which quickly evolved in a similar manner to patient 3 to rhythmic slow with fronto-occipital distribution, with faster frequencies in the occipital regions (second EEG). Rhythmic bioccipital sharp waves then became the dominant feature, with persistent bifrontal bursts of beta with polyspike morphology (third EEG). Despite second line immunotherapy, the patient continued to show pervasive generalized rhythmic slow and did not have any clinical improvement. High frequency filter 0.53 Hz, low frequency filter 70 Hz.

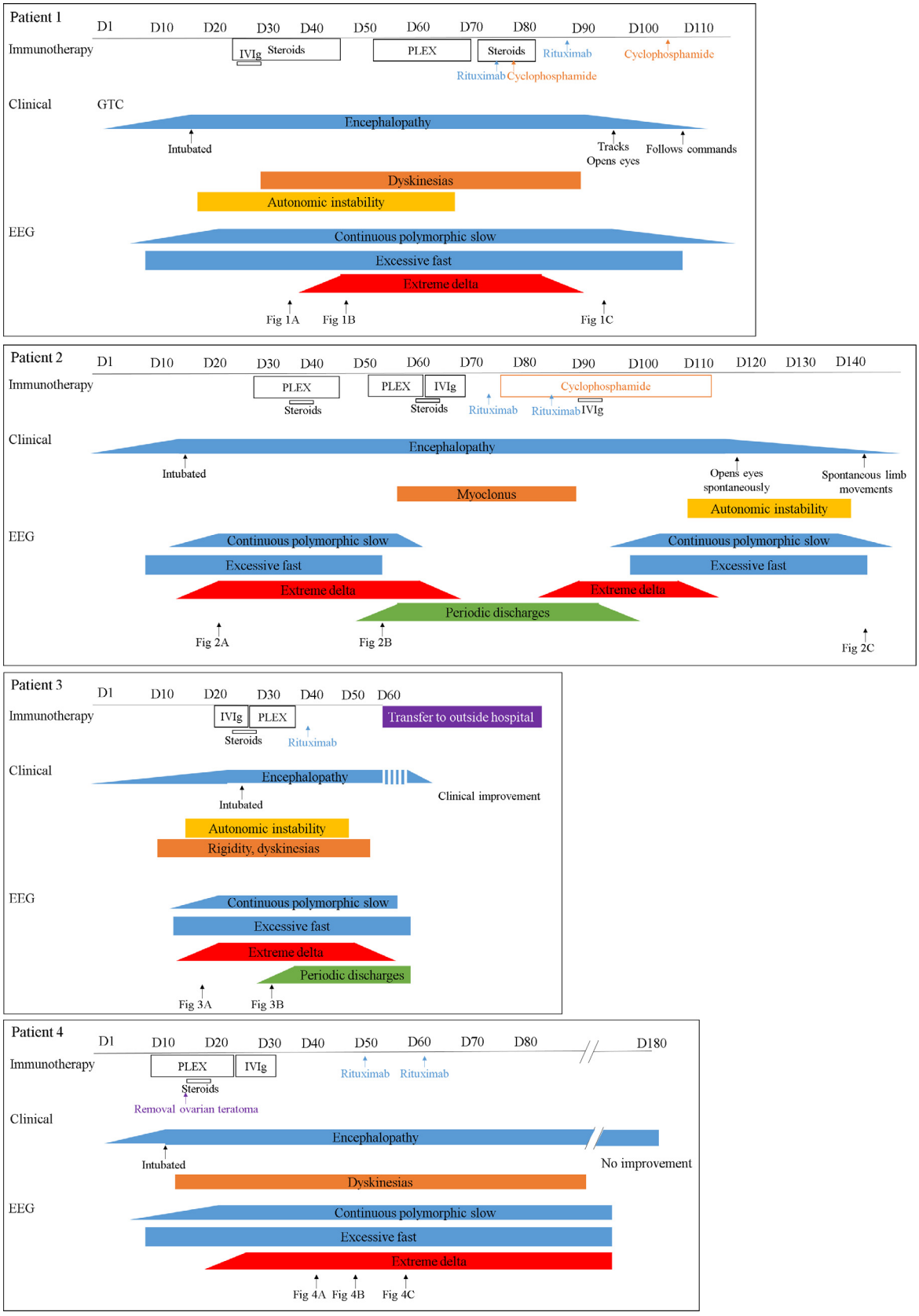

Fig. 3. Representation of each patient's clinical course, immunotherapy and EEG findings. Abbreviations: IVIG – intravenous immunoglobulin, PLEX – plasmapheresis.

All patterns were subclinical, although orofacial dyskinesias could randomly co-occur with periods displaying evolution in distribution (fronto-occipital) and frequency (monomorphic delta).

High doses of barbiturates (level range 54–64, 44–60 μg/mL) and high number of AEDs (5) together with anesthetics (midazolam, propofol) were administered to obtain burst suppression, given the concern that some of these patterns could be ictal in nature. When weaned, generalized periodic patterns with epileptiform morphology emerged, as expected (e.g. Fig. 1, patient 2, second EEG).

3.4. Relationship between EEG and clinical status and treatment

After second line immunotherapy was administered (patient 1: cyclophosphamide and rituximab 3 months from onset, patient 2: cyclophosphamide and rituximab 2 months from onset, patients 3 and 4: rituximab 1 month from onset), generalized rhythmic delta became less abundant and was progressively replaced by generalized polymorphic delta in patient 1. In patients 2–4, concurrent treatment with barbiturates and second line immunotherapy was associated with burst suppression, and as barbiturates were weaned, periodic patterns emerged then were replaced by generalized polymorphic delta, progressively increasing in frequency to theta in patients 1–3. The improvement in EEG predated clinical improvement in patients 1–3. Patient 4 continued to exhibit pervasive generalized rhythmic delta and did not show any signs of clinical improvement despite use of rituximab. Fig. 3 highlights the relationship between clinical status, immunotherapy and EEG findings.

At last follow-up, patient 1 was back at school with residual cognitive complaints (mRS 1, follow-up 5 years), patient 2 was verbal and ambulatory but had persistent severe cognitive sequelae (mRS 3, follow up 1.5 years), patient 3 showed improvement after transfer to home hospital (no further follow up), patient 4 was bedridden and was discharged to a long term care facility (mRS 5 upon discharge, no follow up).

3.5. Specificity of the "extreme delta" finding to NMDA-R encephalitis

Five patients with autoimmune encephalitis not associated with NMDA-R antibodies presented with NORSE. Of these patients, VGKC and LGI1 antibodies (3 patients), GABA-B (1 patient) or no antibodies (1 patient – meeting diagnostic criteria for autoimmune encephalitis) were identified. EEG status epilepticus was multiregional or localized to the temporal regions. Table 1 summarizes the clinical characteristics of these patients compared to that of the NMDARE patients. None of these patients exhibited extreme delta with or without brushes despite many receiving similar sedative medications. However, severity of illness was worse in the NMDARE cohort compared to the autoimmune NORSE comparison cohort, with higher rates of mechanical ventilation, anesthetic and barbiturate use and intensive care unit stay.

4. Discussion

We describe the evolution of electrographic patterns in critically ill NMDARE, across which "extreme delta", with or without brushes (superimposed fast activity), may oscillate in its predominance. Progressive reduction in periods of "extreme delta" occurred following institution of second line immunotherapy and predated clinical improvement in the three patients who showed response to institution of rituximab and/or cyclophosphamide. We propose a potential independent role for EEG as a biomarker of disease activity, which may provide indication of treatment effect before expected clinical changes are seen (in the setting of polypharmacy required in this patient population) and put forth an EEG severity scale, across which patients may fall (Fig. 4). Rather than strict definitions of ictal versus interictal patterns, leading to the controversies in interpretation highlighted by Chanson et al., 2016, it may be reasonable to propose that the "extreme delta" pattern is a neurophysiologic expression of active disease, of which slow evolution in distribution and frequency may represent a more severe form. Furthermore, the presence of "extreme delta" was not noted in a comparison cohort of autoimmune NORSE, many requiring anesthetic and barbiturate treatment, thus making this finding unlikely to be iatrogenic or linked to the severity of the encephalopathy.

Determination of clinical status and response to treatment can be challenging in patients with NMDARE receiving anesthetics and barbiturates for management of autonomic disturbance, movement disorder and nonconvulsive status epilepticus.

Table 1
Clinical characteristics of patients with NMDARE refractory to first line immunotherapy and NORSE secondary to autoimmune encephalitis but without NMDA-R antibodies.

	NMDARE refractory to first line immunotherapy (n = 4)	NORSE secondary to autoimmune encephalitis (n = 5)
Mean age (range)	26 (22–31)	57 (26–83)
Female (%)	2 (50%)	4 (80%)
Mechanical ventilation	4 (100%)	3 (60%)
Anesthetic use (propofol, midazolam) (%)	4 (100%)	3 (60%)
Barbiturate use (%)	3 (75%)	2 (40%)
Mean mRS at nadir of illness (range)	5 (5)	4.6 (3–5)
Mean length of stay of first hospitalisation (range)	110 (24–177)	30 (7–58)
Intensive care unit stay (%)	4 (100%)	4 (80%)

NMDARE – Anti-NMDA receptor encephalitis, NORSE – new onset refractory status epilepticus.

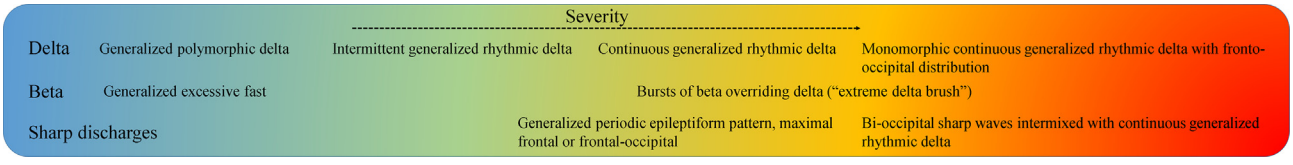

Fig. 4. Proposed continuum of EEG findings in NMDARE, ranging from least (blue) to most (red) severe. Patients may oscillate at various ends of the spectrum throughout illness, with predominance of generalized rhythmic slow increasing as disease progresses and decreasing with institution of second line immunotherapy. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 2
Review of the literature on electroencephalographic findings in relation to the clinical findings and treatment course of anti-NMDA-receptor encephalitis.

Reference	Number of patients	Interictal EEG	Ictal EEG	Correlation between clinical and EEG findings	Correlation between treatment and EEG findings	Notes
Ikeda et al. (2006)	1	Burst and slow complexes (similar to "extreme delta brush")	None	Irregular fragmented myoclonus without synchrony to EEG	Gradual disappearance of burst and slow complexes after second barbiturate coma therapy	Prior to NMDA-R antibodies characterization. Positive antiglutamate antibodies and characteristic clinical presentation.
Bayreuther et al. (2009)	1	Generalized pseudo periodic complexes 3 Hz	1 Hz rhythmic right hemispheric discharges	No correlation with orofacial dyskinesias	Not stated	Ictal patterns preceding generalized periodic complexes
Johnson et al. (2010)	1	Burst suppression	Cyclical generalized delta alternating with theta sharp activity, evolving to electrographic seizures, left and right independent.	Associated myoclonus and tonus with electrographic seizures	Improvement after immunotherapy and oophorectomy with emergence of faster frequencies without periodic features	Abortion of rhythmic EEG patterns by propofol thought to provide support for ictal nature
Kirkpatrick et al. (2011)	1	Continuous generalized rhythmic delta	Evolution of rhythmic delta to status epilepticus	Improvement of EEG followed by gradual clinical improvement	Status epilepticus refractory to barbiturates, immunotherapy and teratoma resection. Improvement after felbamate	Authors suggest using compressed pages to highlight evolution of ictal patterns
Schmitt et al. (2012)	23	Diffuse background slowing Severe diffuse slowing Generalized rhythmic delta at times with superimposed beta bursts ("extreme delta brush")	Seizures (nonconvulsive and clinical) – right or generalized/ unknown onset		Return of extreme delta brush upon barbiturate wean	Coining of term "extreme delta brush"
Da Silva-Junior et al. (2014)	3	Diffuse background slowing Bursts of theta/delta Lateralized in 1 patient Generalized rhythmic delta activity without evolution occupying 20% of recording, with superimposed bursts of beta/ alpha, rhythmic in 2/3 patients. Epileptiform discharges in 1/3 Background slowing and polymorphic slowing at follow-up	1/3 with lateralized seizure pattern	GRDA first present 2 weeks-2.5 months after onset, with shorter bursts 4–7 months after clinical onset and following clinical improvement	Not stated	Generalized rhythmic delta seen in all patients
Probasco et al. (2014)	1	High voltage rhythmic delta	None	Not stated	Not stated	Depth recordings in medial temporal structures showing rhythmic delta, no ictal patterns
Van Haerents et al. (2014)	1	Extreme delta brush	Early left and right independent	Early electrographic seizures, extreme delta brush after coma persisting for 121 days	No clinical or EEG improvement with first and second line immunotherapy, AEDs, anesthetics	Persistence of extreme delta brush in a patient refractory to first and second line immunotherapy and oophorectomy
Nosadini et al. (2015)	5	Diffuse background slowing High voltage delta rhythmic delta slowing, maximal bifrontal Preservation of sleep structures	None	Slowing more pervasive with higher severity of illness	Not stated	Paediatric cohort
Veciana et al. (2015)	15	Diffuse background slowing Generalized and focal delta Increased beta Extreme delta brush	Generalized rhythmic delta evolving to ictal pattern Focal onset ictal pattern Stimulation induced		Electrographic seizures upon anesthetic taper, then extreme delta brush	EDB pattern associated with electrographic seizures

Chanson et al. (2016)	1	High voltage and monomorphic delta with intermittent rhythmic organization	Evolution of rhythmic delta activity	No EEG change during myoclonic jerks Erratic tonic and orofacial movements during rhtyhcmi slow waves and beta rhythms	Disappearance of patterns with wean of sedation	No change in ICP during rhythmic delta with or without beta brushes
Ueda et al. (2017)	1	Excessive beta Intermittent slow Generalized rhythmic delta Extreme delta brush Arousal alpha pattern	Left parietal status epilepticus (initial EEG)	Fading of extreme delta brush then intermittent slow with clinical improvement Persistence of excessive beta after clinical improvement	Lack of response of generalized rhythmic delta to diazepam Generalized rhythmic delta and extreme delta resolution prior to completion of first line immunotherapy	Direct correlation between clinical status and EEG reported Generalized rhythmic delta and extreme delta resolution prior to completion of first line immunotherapy No second line immunotherapy administered

Therefore, establishing the role of EEG alongside other biomarkers such as antibody titers (Gresa-Arribas et al., 2014) and FDG-PET (Leypoldt et al., 2012; Novy et al., 2016) would be valuable given the practical challenges in utilizing clinical status to determine response to treatment. Correlation between EEG and clinical status has been reported in the literature previously (see Table 2) with variability in delay to clinical improvement. Here we showed that improvement in EEG predated clinical improvement, similarly to the detailed patient analysis outlined in Ueda et al. (2017). Furthermore, EEG continued to show pervasive "extreme delta" in the patient who did not show signs of improvement. Therefore, the resolution of "extreme delta" was a marker of response to second line immunotherapy and predictor of clinical improvement in this small cohort.

Other previously highlighted EEG findings were replicated in this cohort. We also noted the presence of superimposed bursts of beta (completing the features of "extreme delta brush"), albeit occupying a smaller proportion of the recordings and of potentially lower value to centers with less access to continuous EEG recordings. In addition, the presence of periodic epileptiform discharges was thought to be nonspecific and has been described in association with anesthetic and barbiturate wean (Beat et al., 2014).

Other NORSE case series, including NMDARE as an etiology, have not shown any distinguishing electrophysiological signatures between cases with and without a proven etiology (Gaspard et al., 2015). However, within the cohort of autoimmune epilepsy and encephalitis at our center, we found that the presence of "extreme delta" with or without brushes was not seen in other NORSE cases. There are two possible explanations for this finding. One may be that extreme delta is specific for NMDARE. Another is that extreme delta is reflective of worse disease severity, which may be more likely in NMDARE as reflected by more frequent need for mechanical ventilation and anesthetic use in NMDARE compared to other autoimmune NORSE cases (Table 1).

The mechanism of "extreme delta" in NMDARE may be hypothesized as follows. First, it has been demonstrated that NMDAR cluster density and NMDAR-mediated currents are decreased in NMDARE (Hughes et al., 2010; Planaguma et al., 2015). Meanwhile, injection of NMDAR antagonists in rats (Buszaki, 1991; Zhang et al., 2009) and cats (Miyasaka and Domino, 1968) is associated with high amplitude rhythmic delta bursts morphologically similar to that described in patients with NMDARE. One proposed mechanism in animal models has been that of hyperpolarization of the resting membrane potential of neurons through blockade of NR2C receptors in the nucleus reticularis of the thalamus, leading to deinactivation of T-type calcium channels and switch from tonic to burst mode (Zhang et al., 2009). One may hypothesize similar neurophysiological mechanisms in NMDARE, however noting the NR1 epitope target of NMDA-R antibodies rather than NR2C as discussed above (Kreye et al., 2016).

The main limitations of this study are the small number of patients and its retrospective nature. Patients requiring prolonged continuous EEG monitoring, owing to poor response to treatment, were selected. While this led to a small number of patients being included, it also resulted in thorough analysis of the most challenging group of patients with this disease, in whom the development of ancillary biomarkers is much needed.

5. Conclusions

High amplitude synchronous delta bursts, with or without superimposed beta, are specific to severe NMDARE refractory to first line immunotherapy and decrease with second line immunotherapy, predating clinical improvement. The frequency and abundance of this pattern appear to correlate with severity

of the disease and may serve as a potential biomarker of severity of NMDARE. The presence of extreme delta may warrant early consideration of second line immunotherapy.

Conflict of interest

Drs. Steriade, Hantus, Naduvil and Rae-Grant have no disclosures.

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