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EEG Findings May Serve as a Potential Biomarker for Anti–NMDA Receptor Encephalitis

Erin Pennock Foff[1], David Taplinger[1], Joanna Suski[2], M. Beatriz S. Lopes[3], and Mark Quigg[1]

Abstract

Objective. To determine if an electroencephalographic (EEG) characteristic, beta:delta power ratio (BDPR), is significantly higher for *N*-methyl-D-aspartate receptor encephalitis (NMDARE) patients than for non-NMDARE patients on presenting EEG. Identification of an additional EEG biomarker with significant specificity for NMDARE (in the absence of frank delta brush) could potentially allow for early identification of at-risk patients. *Methods*. Single center retrospective comparison of NMDARE and non-NMDARE consecutive cases of encephalitis, collated over a 6-year period (from 2008 to 2014). *Results*. None of the 10 NMDARE patients displayed the extreme delta brush pattern on EEG previously described, but the ratio of BDPR was significantly higher for NMDARE patients ($P < .005$). There was no significant relationship between BDPR and the time of recording from symptom onset. Additional analysis of clinical characteristics also indicated that the patients with NMDARE (median age 19.5 years) were younger than the 5 patients with non-NMDARE (median age 36 years). Encephalopathy, seizure, and psychiatric complaints were the most common diagnoses at time of first health care presentation and did not favor a single etiology, though the latter was present only in the NMDARE population (50% at T_0). Prodromal illness featuring headache was more common in the non-NMDARE population. Outcomes, as measured by the Modified Rankin Scale, were globally better in the NMDARE group. *Conclusions*. Patients with NMDARE had a significantly higher BDPR on EEG when compared with non-NMDARE patients even in the absence of extreme delta brush. This suggests that early EEG characteristics may be helpful in distinguishing NMDARE from non-NMDARE.

Keywords

encephalitis, anti–NMDA receptor encephalitis, encephalopathy

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Introduction

Attention to noninfectious causes of encephalitis has grown over the past decade, with the recognition that previous cases of presumptive viral encephalitis may have been due to potentially treatable autoimmune etiologies. The most recognized form of autoimmune encephalitis is anti–NMDA receptor encephalitis (NMDARE),[1,2] representing ~1% of all admissions of young adults to the intensive care unit in one series.[3] NMDARE often presents with encephalopathy, behavioral or psychiatric disturbances, or seizures. Other associated clinical features include dysautonomia, movement disorders, and insomnia.[4] A specific EEG finding, extreme delta brushes, is seen in only ~30% of NMDARE patients.[5] The evolving experience with NMDARE has occurred in the setting of appreciation of other noninfectious, presumptive channelopathies or autoimmune epileptic encephalopathies variously termed acute encephalitis with refractory repetitive partial seizures (AERRPS) [6], fever-induced refractory epileptic encephalopathy syndrome (FIRES),[7,8] seronegative autoimmune limbic encephalitis (SNALE),[9] and new-onset refractory status epilepticus (NORSE).[10,11]

Early identification and treatment of NMDARE is associated with improved outcomes.[12] Because of the delta brush finding, we specifically hypothesized that the beta:delta power ratio (BDPR) would be altered in NMDARE patients when compared with their non-NMDARE counterparts, and that such a finding may precede extreme delta brush appearance. To determine if there were additional early electrographic findings (besides delta brush) that were associated with the presence of

[1]Department of Neurology, University of Virginia, Charlottesville, VA, USA
[2]Sidney Kimmel Medical College at Thomas Jefferson University, Philadelphia, PA, USA
[3]Department of Pathology, University of Virginia, Charlottesville, VA, USA

Corresponding Author:
Erin Pennock Foff, Department of Neurology, University of Virginia, PO Box 800394, Charlottesville, VA 22903, USA.
Email: epf4b@virginia.edu

NMDAR antibodies, we retrospectively analyzed our center's consecutive experience of patients with non-infectious encephalitis and compared the features of NMDARE to antibody-negative acute encephalitis (non-NMDARE). As an additional component, we compared clinical characteristics of these patients to determine if specific clinical features were predictive of NMDARE in our single-center cohort.

Methods

The institutional review board approved this retrospective case control study at the University of Virginia. Cases from July 2000 through June 2014 were identified via billing code and database interrogation. Records were then examined for inclusion criteria of acute or subacute encephalitis or behavioral changes with or without seizures. All included subjects had infectious etiologies evaluated via routine laboratory methodology, including polymerase chain reaction for herpes simplex virus, cytomeglaovirus, and vericella-zoster, enterovirus, human herpes virus–6 and Epstein-Barr virus, cerebrospinal fluid (CSF) and serum fungal, bacterial, and viral cultures and Gram stains. Extensive serologic and CSF studies were undertaken, including HIV, antinuclear antibodies, and other rheumatologic markers. Arbovirus and tick-borne serologies done when indicated. Exclusions were (1) identifiable bacterial or viral infections, toxic-metabolic, or structural etiologies, (2) previous diagnosis of epilepsy, and (3) autoimmune encephalitis etiologies other than NMDARE.

We were primarily interested in interrogation of the EEGs in these patients, but we extracted additional clinical information including demographics, presenting neurologic symptoms, nonneurologic prodromal symptoms, presence and time to first clinical seizure, magnetic resonance imaging (MRI), treatment, and outcomes. We did not routinely note whether patients had autonomic symptoms at presentation, and thus this was excluded from the analysis. To facilitate comparisons across cases (and to help account for initial presentations skewed by transfer from other institutions), we defined "T_0" as the earliest time at which neurologic symptoms of encephalopathy, psychiatric disturbance, and/or seizure were first noted by the patient, family, or health care provider.

The initial University of Virginia EEG recording of the patient was designated as the index recording. Medication administration during the EEG recording was noted. All recordings were performed with a multichannel EEG machine (Grass Technologies, Warwick, RI) sampling at a rate of 200 Hz obtained by certified technologists. Scalp recordings were obtained with silver–silver chloride cup electrodes placed according to the 10-20 system and glued with collodion. Impedances were maintained <10 kohm. A 1.0-Hz low- and 70-Hz high-frequency filter was used for all clinical recordings. Ten 13-second artifact- and seizure-free samples from each recording were selected blinded to group for digital analysis. Total and frequency band powers were calculated from channels C3-C4 via fast Fourier transform (FFT) analysis with the use of 6.5-second nonoverlapping Hanning bins. Beta frequency power was defined as >12 to 22 Hz, and delta 1.6 to 4 Hz. The log10 BDPR was then calculated.

NMDAR antibody status was determined by serological and/or CSF assays performed by Mayo Medical Laboratories (or, in two cases, by sending the samples to the Dalmau Laboratory prior to availability of commercial testing). Two patients had documentation of positive NMDAR antibodies in the medical record with no mention of whether these studies were performed from CSF or serum or at which laboratory they were performed.

Outcomes were scored at discharge/death or immediate follow-up using the established modified Rankin Scale (mRS) score. Because of the limited number of patients in this study, we chose to simply describe group medians and ranges rather than to conduct statistical hypothesis testing. An exception was for quantitative EEG data for which used the Mann-Whitney *U* test to compare BDPR between groups and receiver operating characteristic (ROC) curve analysis to determine specificity and sensitivity of an appropriate threshold value.

Results

Fifteen patients met criteria, 10 with NMDA receptor antibodies (NMDARE, 71.4%), and 5 with no evidence for NMDA receptor antibodies or any other identifiable seropositive causes (non-NMDARE, 33.3%; Table 1). Whereas NMDARE patients were female and young (median age 19.5 years, range 10-39 years), non-NMDARE patients were of both sexes and were older (median age 36 years, range 25-60 years; Table 2). Of the 8 NMDARE patients who eventually had seizures, those events emerged in the majority (6/8, 75%) of those patients only after presentation with other neurologic symptoms at T_0 (median time to first seizure day 6). In contrast, 3/5 (60%) of non-NMDARE had electrographic seizures or status epilepticus at presentation, and all developed seizures or status epilepticus during their illness (mean/median time to first seizure 2.8/0 days, respectively). All patients were on ongoing intravenous and/or oral antiseizure treatment at the time of the index EEG, with the exception of patient 10 (NMDARE) and patient C (non-NMDARE). Half or more of the patients in each group were receiving benzodiazepines (5/10 in NMDARE, 3/5 non-NMDARE) or were intubated/sedated with propofol or fentanyl/versed (2/10 NMDARE and 3/5 non-NMDARE) within the 24 hours preceding EEG. The median time of the initial EEG recording from T_0 was 13 days for NMDARE patients and 8 days for non-NMDARE patients, likely reflecting the higher prevalence of seizure in the non-NMDARE cohort.

No clear qualitative differences between groups were seen on review of EEG recordings. Most patients had either evidence of a focal epileptic lesion (temporal slowing, spikes, or seizures) or reactive diffuse slowing (Figure 1A). None of the patients from either group had visible "extreme delta brushes" during the index recordings or later on. The median log BDPR was significantly higher for NMDARE patients (median −0.94,

Table 1. Demographic and Clinical Characteristics of Encephalitis Patients.

Patient	Age (Years)/Sex	Presenting Symptom at T_0	Time From T_0 to Hospital	Prodrome	Seizure (Time From T_0)	MRI (Days From T_0)	EEG (Time From T_0)	Treatment (Time From T_0)	Outcome (mRS)
NMDARE									
1	17/female	Enceph	7	Gastrointestinal illness, fever	Day 10	Nl (10)	RDS, temporal slowing, seizures (10)[a]	PLEX (25), then steroid, R/C	1
2	35/female	Psych	4	Insomnia	N/A	Nl (11)	RDS (10)[a]	IVIg (24) then teratoma resection, PLEX, R/C	1
3	10/female	Seizure	0	N/A	Day 0	Nl (3)	RDS (4)	Steroids (17), then PLEX	2
4	21/female	Psych	20	N/A	Day 20	Nl (29)	RDS bitemporal slowing (20)	IVIG (day 24), then PLEX, teratoma resection	0
5	17/female	Enceph	2	Upper respiratory infection	2	Abnl (8)	Left temporal irritability (19)[a]	IVIg (44), then C, R, M[a]	0
6	24/female	Psych	41	N/A	Day 41	Nl (71)	RDS, temporal seizures (60)[a]	IVIg (109) then M	2
7	17/female	Seizure	0	HA, malaise	Day 0	Abnl (5)	UDS (16)[a]	Steroids (14) IVIG, R/C, teratoma resection (106)	2
8	39/female	Psych	8	Tinnitus	Day 12	Abnl (10)	UDS (10)[a,b]	IVIg (32), then R/C	1
9	18/female	Enceph and Psych	2	N/A	Day 2	Nl (3)	RDS, temporal spikes and seizures (2)[b]	IVIG (7) then then R/C, teratoma resection	2
10	22/female	Enceph and Psych	14	N/A	N/A	Nl (19)	RDS (19)	IVIg (27) then R/C	3
Non-NMDARE									
A	36/female	Seizure	0	Fever, chills, HA × 5 days	Day 0	Nl (0)	RDS, bitemporal spikes and seizures(0)[a,b]	IVIg (8)	6
B	57/male	Enceph	3	HA, malaise	Day 8	Nl (5)	RDS, temporal spikes (8)[a,b]	IVIg (10), then R/C, M	1
C	60/female	Enceph	5	Malaise, sore throat, HA	Day 6	Nl (22)	RDS (13)	IVIg (26), then Steroids	0
D	29/female	Seizure	0	HA, fever × 5 days	Day 0	Abnl (11)	RDS, bifrontal spikes(1)[a]	None	6
E	25/male	Seizure	0	Fever, neck stiff	0	Abnl (2) (bilat ext capsule FLAIR)	RDS, focal right temp spikes, + seizure (9)[a,b]	PLEX (11)	4

Abbreviations: NMDARE, *N*-methyl-D-aspartate receptor encephalitis; Enceph, encephalitis; Psych, psychiatric complaints; HA, headache; Nl, normal; Abnl, abnormal; N/A, not applicable; RDS/UDS, reactive and unreactive diffuse slowing; T_0, estimated date of onset of presenting neurologic symptom. mRS, Modified Rankin Scale; R, rituximab; C, cyclophosphamide; M, methotrexate; PLEX, plasma exchange; IVIg, intravenous immunoglobulin.
[a]Benzodiazepines within 24 hours.
[b]Intubated/sedated.

range −2.20 to 0.95) compared with non-NMDARE patients (median −1.27, range −2.15 to 0.33; $P < .004$ Mann-Whitney U test) (Figure 1B). No significant relationship between BDPR and the duration of each recording from T_0 was present (tested with simple regressions, not shown). The ROC curve area was 0.60 (95% CI 0.53-0.68). A log BDPR cutoff value of −1.19 yielded a specificity of 60% and sensitivity of 71% indicating NMDARE.

Headache at or prior to T_0 was more common in the non-NMDARE group (5/5) compared with only 1 (of 10) NMDARE patients. Prodromal (pre-T_0) symptoms of URI, gastrointestinal illness, malaise, fever, insomnia, and tinnitus were present in both groups (5/10 NMDARE patients and 5/5 non-NMDARE patients). Presenting neurologic complaints within the NMDARE group were encephalopathy (confusion/lethargy; 50%), psychiatric disturbances (40%), and seizures (20%). None of the non-NMDARE patients presented with psychiatric features.

Latencies from T_0 to first physician evaluations, admissions, MRI, EEG, or treatment did not differ remarkably between groups (Table 1). However, we noted that within the NMDARE group particular factors were associated with a tendency toward delayed recognition. The patients with psychiatric manifestations had the longest latency from T_0 to hospital admission (Table 1). The median time to first admission was 14 days after symptoms onset for patients with primarily psychiatric manifestations, compared with 2.0 days for those with encephalopathy or seizure as first symptom. Commensurately, the median time to treatment was 4.2 days earlier for NMDARE patients presenting with encephalopathy or seizure than for those presenting with psychiatric disturbance. Furthermore, patients evaluated more recently experienced quicker recognition of immune status (timing of NMDAR positive status from T_0, data not shown) testifying either to improving experience with NMDARE or from more rapid turnover of NMDARE laboratory results.

One confounder in the neuroimaging of encephalitis is that changes on MRI may arise from the causative lesion or from inflammatory changes secondary to ongoing seizures.[13] In our series, most patients had normal MRIs (NMDARE 70%, non-NMDARE 60%), on initial scan taken a median of 10 and 5 days after T_0 in NMDARE and non-NMDARE, respectively. For those who had abnormal imaging, there was neither correlation between neurologic symptoms at T_0 nor with times to MRI imaging from T_0.

Regarding treatment and etiology, all of the NMDARE patients were evaluated for the presence of germ cell tumors and 4 were found to have ovarian teratomas (40%) that were resected. Presence and resection of a germ cell tumor did not correlate with outcome (Table 1). We did not find clear correlations between outcomes and time to treatment, primary neurologic symptom at T_0, or BPDR. However, the presence of seizure at onset favored poorer outcome. Two of the 5 non-NMDARE patients died due to uncontrolled status epilepticus or its complications. In contrast, all NMDARE patients fared at or better than mRS score of 3.

Table 2. Comparative Features of Clinical Presentation and Characteristics.

	NMDARE (n = 10)	non-NMDARE (n = 5)
Age, years, median (range)	19.5 (10-39)	36 (25-60)
Female, n (%)	10 (100)	3 (60)
Presenting symptom (T_0)		
Encephalopathy	4/10	2/5
Psychiatric complaints	5/10	0
Seizure	2/10	3/5
Prodromal illness	5/10	5/5
Fever	1/10	3/5
Headache	1/10	5/5
Fatigue/malaise	1/10	2/5
Gastrointestinal	1 (10)	0
URI	1 (10)	0
Seizure during course	6 (60)	5 (100)
Days to first seizure, median (IQR)	6 (17.5)	0 (7)
Abnormal MRI	3/10	2/5
EEG at first recording		
Normal	0	0
Diffuse or focal slowing	8	5
Electrographic seizure	3/10	3/5
Treatment		
Teratoma excision	4/10	0
IVIg	8/10	3/5
Rituximab/ cyclophosphamide	7/10	1/5
Plasma exchange (PLEX)	4/10	1/5
Methotrexate	2/10	1/5
Intravenous steroids	3/10	1/5
None	0	1/5
Outcome: modified Rankin Scale		
0-2	9/10	2/5
3-5	1/10	1/5
6	0/10	2/5

Abbreviations: URI, upper respiratory infection; IQR, interquartile range; IVIg, intravenous immunoglobulin; NMDARE, *N*-methyl-D-aspartate receptor encephalitis.

Discussion

Quantitative EEG may provide insights on both pathophysiology and diagnosis of NMDARE. Since "extreme delta brushes" have been proposed to be a finding specific—but not especially sensitive—for NMDARE but not other causes of noninfectious encephalitis, we anticipated evidence of increased beta activity, compared with delta activity, may be analogous to extreme delta brushes and may offer more sensitivity. Our finding that beta power is elevated relative to delta power in patients with NMDARE compared with non-NMDARE patients suggests a potential biomarker between encephalitis groups. Importantly, several medications are known to induce beta activity, including benzodiazepines and phenobarbital, which could have potentially skewed our findings. However, similar ratios of patients in each group received these drugs at time of index EEG; for instance 6/10 and 2/10 NMDARE patients and 3/5 and 2/5 non-NMDARE patients had received benzodiazepine and/or phenobarbital respectively within several hours prior to index EEG. Furthermore, our EEG findings fit well with an earlier study of 23 patients with NMDARE encephalitis that 30% had visual evidence of "extreme delta brushes."[5] These

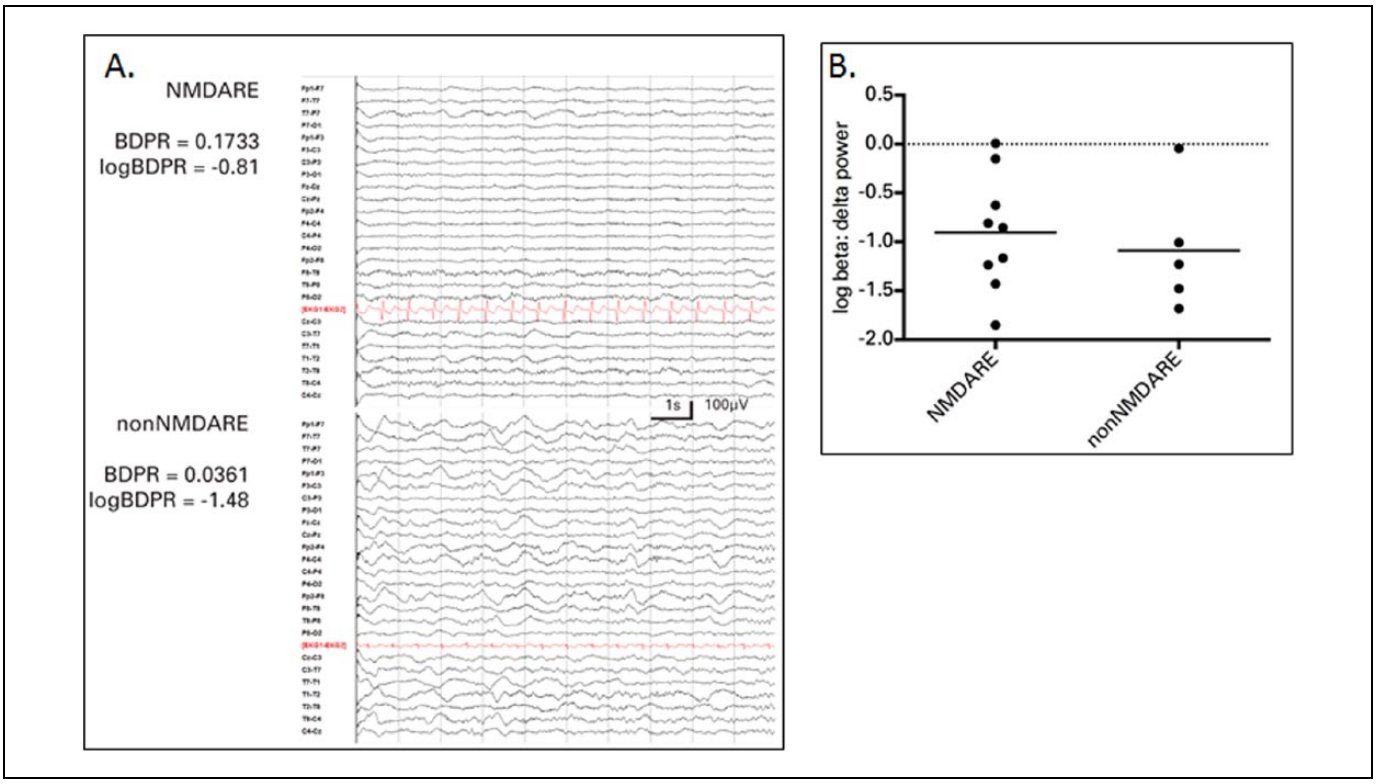

Figure 1. (A) Representative examples of continuous EEG (cEEG) tracings from index EEG of NMDARE versus non-NMDARE patients. (B) Graphical representation of the mean (horizontal line) log BDPR and range of observed values in NMDARE versus non-NMDARE patients, indicating a significantly higher value in the NMDARE population ($P < .004$). NMDARE, *N*-methyl-D-aspartate receptor encephalitis; BDPR, beta:delta power ratio.

waveforms consist of bursts of beta frequency activity superimposed on delta frequency slowing. Although none of our patients had visible brushes, the higher proportion of fast frequencies relative to slowing may be a quantitative correlate. Extreme delta brush is more common in NMDARE patients who are minimally conscious with Glasgow Coma Scale (GCS) scores <8, though this is not always true. Notably, only 2 of our NMDARE patients met this GCS parameter, which may be why we did not note extreme delta brushes. One may speculate that elevations in beta activity relative to slowing form a spectrum in NMDARE encephalitis, becoming visible extreme delta brushes when elevated to larger degrees. These findings support the hypothesis that NMDARE has unique physiological effects arising from specific and pathological activation of NMDA receptors.[5]

In our cohort, NMDARE occurred mainly in younger women who presented early with psychiatric symptoms, whereas patients with non-NMDARE were older, more frequently complained of preceding headache, lacked psychiatric symptoms, and had early seizures or status epilepticus. The fact that our NMDARE cohort infrequently complained of headache is in contrast to published reports citing high headache frequency in this population, and may reflect our decision to note only whether headache was present at or prior to T0 and not whether it was present at any time during course of illness. We noted a trend toward delays in diagnosis and treatment when patients presented primarily with psychiatric disease.

In contrast to prior reports, our study found no clear relationships between diagnosis delay from NMDARE onset and outcome.[12] This may be due to the manner in which our definition of onset time may differ from earlier studies. However, our comparison indicated one of the dangers of NMDARE; recognition in those who do not present "neurologically" with status epilepticus or encephalopathy tends to be delayed. As the features of NMDARE encephalitis become more widely known and community practitioners become more familiar with the features of patient presentation, we anticipate that the latency to diagnosis will improve.

In comparison with the outcomes of NMDARE patients that had generally good outcomes (9/10 patients had mRS 0-2), those of non-NMDARE varied between good and poor (2/5 with mRS 0-2, 1/5 with mRS 3-5, and 2/5 died (mRS 6)). Though not described at the time, these patients would likely meet criteria for new-onset refractory status epilepticus (NORSE). NORSE predominantly affects women in young adulthood and has been alternately described as "status epilepticus owing to presumed encephalitis."[14] Both of our patients who died secondary to refractory status epilepticus of unknown etiology in this cohort were young women with otherwise exhaustive negative work-ups. Since the time of their

presentations to our hospital, a new entity has been described: $GABA_A$ receptor antibody mediated encephalitis, which often manifests as refractory status epilepticus.[15] Further studies on autopsy tissues in these cases would be warranted and are pending family approval.

A limitation, of course, is the small sample size of this single hospital experience. Additionally, we saw our patients at variable times after onset, blurring the longitudinal accuracy of our description. We tried to mitigate this by detailed chart examination to determine a common T_0 to refer symptoms and signs to a common reference point. One problem that we encountered, probably not unique to our institution, is that the relative rarity of these syndromes combined with a variety of presenting symptoms and signs makes tracking and accumulating patients into appropriate groups a challenge. More resources dedicated to standardized data elements and central reporting may be the only way to fully characterize the range of possible entities that comprised our non-NMDARE group. Of course, non-NMDARE patients represent a heterogeneous control group; future studies—as we improve methods of identifying specific etiologies—may well narrow candidates for comparisons.

Conclusions

In conclusion, NMDARE patients represent a group of heretofore "cryptogenic" encephalitis with an underlying autoimmune etiology with relatively homogeneous presenting symptoms, EEG findings, and, with appropriate diagnosis, better outcomes than the growing list of currently less specific encephalitides. Further studies with a combined cohort of patients may help further classify noninfectious encephalitis and potentially establish the BDPR as a valid early biomarker for NMDARE.

Author Contributions

Dr Foff contributed to initiation and conceptualization of the project, aided in the chart review and data collection, wrote the first draft and edited subsequent drafts of the manuscript and created Tables 1 and 2. Dr Taplinger aided in data collection and analysis, cowrote additional drafts, as well as analyzed the EEG data. Dr Quigg contributed to the initiation and conceptualization of the project, performed EEG analysis, edited the manuscript, and created Figure 1. Dr Suski aided in data collection. Dr Lopes provided additional patient information and aided in data collection.

Declaration of Conflicting Interests

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