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Review article

A review of EEG in anti-NMDA receptor encephalitis

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ABSTRACT

Anti-*N*-methyl-D-aspartate receptor encephalitis (anti-NMDARE) is common among autoimmune encephalitides (AE) and can present with protean features and nonspecific laboratory and neuroimaging results. Antibody testing is specific, but results are often delayed, and prompt diagnosis and treatment is vital given associated morbidity and mortality. Electroencephalography (EEG) may be a useful tool given ease of performance and short turn-around time for results. As such, we performed a systematic review of the literature on anti-NMDARE and EEG characteristics. We found that EEG is often pathologic in anti-NMDAR encephalitis, though at times nonspecific. A stronger focus on common EEG features in patient with this type of encephalitis and an effort to identify when these features are present in the course of the disease may allow for improved diagnosis, description and differentiation of anti-NMDARE.

1. Introduction

Autoimmune encephalitis is a serious disorder which is becoming more commonly diagnosed and described in the literature. In particular, anti-*N*-methyl-D-aspartate receptor encephalitis (anti-NMDARE) has been noted as the most common form of autoimmune encephalitis (Dalmau et al., 2007; Prüss et al., 2010). Patients with anti-NMDARE can present with a wide array of symptoms and signs (Linnoila et al., 2014), which may be protean and make diagnosis difficult. Objective testing in anti-NMDARE, including magnetic resonance imaging (MRI) and cerebrospinal fluid (CSF) studies, can be nonspecific or normal (Dalmau et al., 2008; Wang et al., 2015). Antibodies in both the serum and CSF are sensitive and specific (Armangue et al., 2013) but results are often delayed. This is vital considering that early diagnosis and treatment of anti-NMDARE is associated with improved outcomes (Titulaer et al., 2013). Also, a specific antibody-associated diagnosis is necessary to guide screening for neoplasia associated with this condition (Dalmau et al., 2007). Therefore, it is imperative to use other objective tests to make a quick diagnosis and determine as well as potentially monitor treatment course.

Seizures are common in cases of anti-NMDARE (Dalmau et al., 2007; Schmitt et al., 2012) but can be confused clinically with the movement disorders these patients may also develop (Dericioglu et al., 2013). Given the importance of early diagnosis of autoimmune encephalitis and detection of seizures, electroencephalography (EEG) has been suggested as a corollary objective test (Albert et al., 2016; Mendoza et al., 2015) and is incorporated into diagnostic evaluations. Some have described what appears to be a specific EEG finding in anti-NMDARE, known as extreme delta brush (EDB), defined as rhythmic delta activity at 1–3 Hz with bursts of rhythmic beta activity superimposed onto each delta wave, resembling delta brush on premature infant EEG studies (Schmitt et al., 2012). The exact sensitivity, specificity, and prognostic utility of EDB is unknown. Others have also described other EEG characteristics in pediatric and adult patients with anti-NMDARE (Dalmau et al., 2008; Wang et al., 2015; Armangue et al., 2013; Schmitt et al., 2012; Dericioglu et al., 2013; Florance et al., 2009; Kataoka et al., 2012; Gitiaux et al., 2013; Tan et al., 2013; de Silva-Junior et al., 2014; Abdullah et al., 2011; Veciana et al., 2015; Sands et al., 2015; Nosadini et al., 2015; Nagappa et al., 2016; Huang et al., 2016; Suthar et al., 2016; Miao and Wang, 2017; Wanga et al., 2017; Foff et al., 2017; Zhang et al., 2017; Konuskan et al., 2018; Ho et al., 2018; Mohammad et al., 2016; Wang et al., 2017; Goenka et al., 2017; Haberlandt et al., 2017; Liu et al., 2015; Wang et al., 2016; Matoq et al., 2015; Chakrabarty et al., 2014; Lin et al., 2016; Pinho et al., 2012; Baysal-Kirac et al., 2015; Holzer et al., 2012). Given multiple recent papers on EEG in anti-NMDARE, an all-encompassing review of EEG in anti-NMDARE is warranted.

In this study, we set out to present a systematic review of the literature detailing EEG in cases of anti-NMDARE, while at the same time acknowledging the limitations intrinsic to a body of literature where different studies often focus on different aspects of EEG analysis and descriptors. Our goal is to better define EEG characteristics found specifically in anti-NMDARE, as well as to help guide future studies on this topic.

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2. Methods and materials

2.1. Search strategy and study selection

This systematic review was performed by both authors. Authors maintained adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009). Both authors agreed upon the search and exclusion/inclusion criteria, and any disagreements regarding which studies were included or excluded were resolved together and agreed upon after discussion. Literature search was performed in September 2017 and again in September 2018, using EMBASE, the Cochrane Library, and PUBMED databases. Separate searches were performed in each database using "EEG "AND "NMDA encephalitis, ""electroencephalography "AND "NMDA encephalitis," "EEG" and "NMDA," "electroencephalography" and "NMDA," "EEG" AND "NMDAR encephalitis," "electroencephalography" AND "NMDAR encephalitis," "EEG" AND "anti-*n*-methyl-D-aspartate encephalitis," and "electroencephalography" AND "anti-*n*-methyl-D-aspartate encephalitis." Eligibility criteria, which were defined prior to performing the literature search, included case series (including at least 2 cases), with EEG results being clearly and descriptively reported on patients with anti-NMDA encephalitis. Both adult and pediatric cases were included. Exclusion criteria included single case reports, publication in any language other than English, non-human studies, lack of full text availability for review, and abstracts presented without a published, comprehensive analysis reported.

Using the above criteria, titles were reviewed in all resulted publications, looking for duplicate studies. If the title described a study that would clearly be excluded based on our predefined criteria, they were removed. In all other studies, abstracts were then analyzed to determine what type of investigation was performed (case report, case series, abstract presentation, review, etc.). Full text of the papers remaining were then reviewed for specific data on EEG. If the data published in the body of the paper did not include descriptive EEG results, these studies were excluded.

Given the lack of comprehensive reviews on the topic of EEG in NMDA encephalitis, we reviewed the reference sections of all of the studies that were read in full after exclusion and inclusion criteria were adhered to, in order to capture any other reports that may have been missed.

2.2. Data extraction and assessment of quality of studies

Data was extracted from the text of the articles thus identified, relating to EEG, clinical information, and neuroimaging. As themes arose, data was then categorized and presented in this fashion in the results section. All studies were retrospective and as such a quality assessment was not pursued. Given the variability in EEG results available, statistical analyses of bias and any specific EEG characteristics were unable to be performed.

3. Results

The initial literature search yielded 5715 studies, however many of these were duplicates. Ultimately the search yielded a total of 2991 unique studies, after removing duplicates, which were reviewed for containing EEG data in a format that could be extracted for a meaningful report. Ultimately, 35 studies were included in our review (Fig. 1). These studies included a total of 684 subjects. Supplemental Table 1 summarizes the results of EEG, clinical, and neuroimaging data in these studies. These studies were retrospective in nature. There was no uniform method of EEG interpretation, nor were there consistent EEG characteristics being documented across the studies. Seven studies included both adults and children, none of which formally compared them. 16 reports evaluated pediatric patients alone and 10 only analyzed adults. The average sample size was 19.5, with a median of 11 patients included in each study and a range of 2–100 cases per report. Normal EEGs were recorded in 11 studies (Armangue et al., 2013; Schmitt et al., 2012; Veciana et al., 2015; Sands et al., 2015; Nosadini et al., 2015; Zhang et al., 2017; Konuskan et al., 2018; Ho et al., 2018; Haberlandt et al., 2017; Wang et al., 2016; Lin et al., 2016). Only some studies documented the timing of EEG vis-à-vis the patient's clinical course. Further, not all studies commented on the incidence of normal EEGs, however when they did (Armangue et al., 2013; Sands et al., 2015; Zhang et al., 2017; Haberlandt et al., 2017) most of the normal EEGs were seen in the early stage of disease or later in the recovery phase. Normal EEG were described in 7–14% of cases with the caveat that the state of the disease may not have been clearly identified (Armangue et al., 2013; Schmitt et al., 2012; Veciana et al., 2015; Konuskan et al., 2018; Ho et al., 2018; Wang et al., 2016; Lin et al., 2016).

Slow activity was noted in a number of cases (Dalmau et al., 2008; Armangue et al., 2013; Schmitt et al., 2012; Dericioglu et al., 2013; Gitiaux et al., 2013; Tan et al., 2013; de Silva-Junior et al., 2014; Abdullah et al., 2011; Veciana et al., 2015; Sands et al., 2015; Nosadini et al., 2015; Suthar et al., 2016; Wanga et al., 2017; Foff et al., 2017; Zhang et al., 2017; Konuskan et al., 2018; Ho et al., 2018; Wang et al., 2017; Goenka et al., 2017; Haberlandt et al., 2017; Liu et al., 2015; Wang et al., 2016; Chakrabarty et al., 2014; Lin et al., 2016; Baysal-Kirac et al., 2015; Holzer et al., 2012). Generalized slowing was described in almost all cases in one study (Schmitt et al., 2012), and in others ranged from 35 to 71% of cases (Armangue et al., 2013; Veciana et al., 2015; Sands et al., 2015; Wanga et al., 2017; Konuskan et al., 2018; Ho et al., 2018; Haberlandt et al., 2017; Chakrabarty et al., 2014; Lin et al., 2016; Baysal-Kirac et al., 2015; Holzer et al., 2012). Generalized slowing was found in certain stages of disease, with higher incidence in the peak illness period (Zhang et al., 2017), psychotic stage (Abdullah S, et al., 2011), and during the acute hospitalization (Sands et al., 2015). Focal slowing was seen relatively equally in the early and late stages of disease in one study (Zhang et al., 2017) and ranged from 13 to 67% of cases that reported these results specifically (Armangue et al., 2013; Gitiaux et al., 2013; Veciana et al., 2015; Konuskan et al., 2018; Ho et al., 2018; Haberlandt et al., 2017) and in most cases in another report (Foff et al., 2017). Slowing localized to the fronto-temporal regions was noted (Dalmau et al., 2008; Nosadini et al., 2015; Wanga et al., 2017; Wang et al., 2017) as well as in the temporal region (Chakrabarty et al., 2014).

Generalized Rhythmic Delta Activity (GRDA) was described in at least half of cases of those reporting this result (Schmitt et al., 2012; Dericioglu et al., 2013; Tan et al., 2013; Suthar et al., 2016), in all cases in two studies (de Silva-Junior et al., 2014; Nagappa et al., 2016), and in a few cases in two others (Konuskan et al., 2018; Liu et al., 2015). Occipital Intermittent Rhythmic Delta Activity (OIRDA) was described in 2 cases in one series (Konuskan et al., 2018), while Frontal Intermittent Rhythmic Delta (FIRDA) was also seen (Baysal-Kirac et al., 2015). Rhythmic Delta Activity (RDA) was noted in specific clinical circumstances such as in the florid stage of disease, as well as in those who were comatose (Tan et al., 2013; Nosadini et al., 2015). Focal unilateral RDA in the frontotemporal regions was noted in 8 patients at follow up, after they had demonstrated clinical improvement (Nagappa et al., 2016).

Excessive or diffuse beta activity was noted in 25–50% of cases in three studies (Schmitt et al., 2012; Veciana et al., 2015; Konuskan et al., 2018) though may have been related to sedative use (Schmitt et al., 2012). In another report, 4/62 patients in the peak stage of disease developed excessive beta activity on EEG but this was not reported at any other point during the course of illness (Zhang et al., 2017).

EDB was described in 10 analyses with varying incidence. Zhang, et al., noted a higher incidence in the peak stage of disease (Zhang et al., 2017). The incidence of EDB was described in 5–33% of cases in some reports (Armangue et al., 2013; Schmitt et al., 2012; Tan et al.,

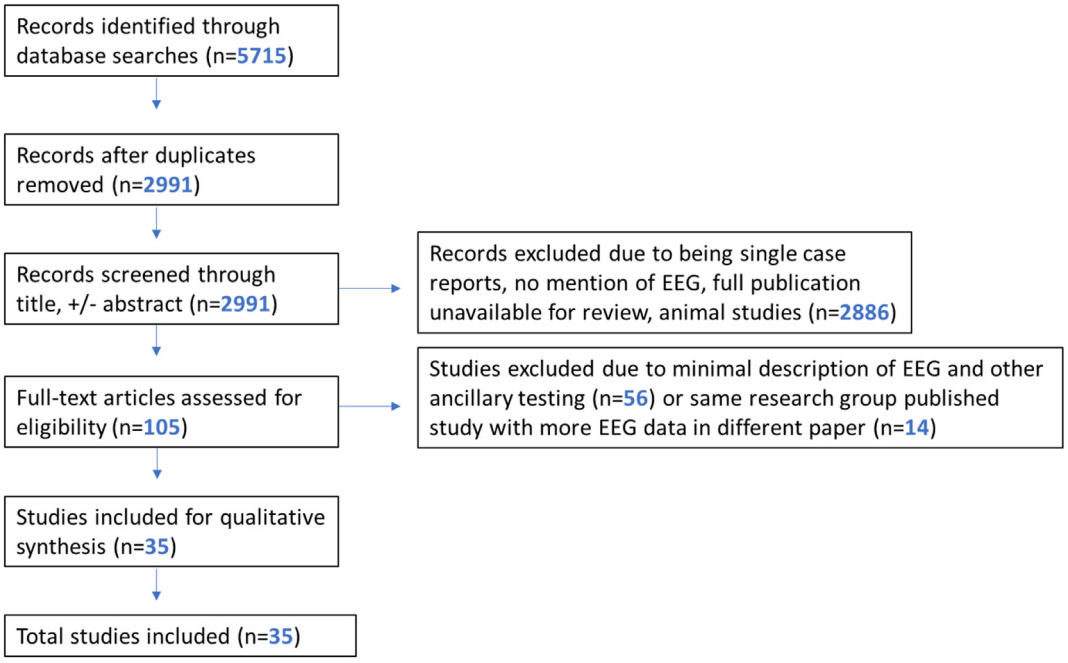

Fig. 1. Systematic review of the literature.

2013; Veciana et al., 2015; Nagappa et al., 2016; Konuskan et al., 2018; Goenka et al., 2017), in 2/3 patients in one study (Miao and Wang, 2017) and in both cases in a smaller case series (Wang et al., 2015). One study comparing pediatric and adult patients noted 50% of adults and 33% of children demonstrated EDB (Huang et al., 2016). However, other reports either did not specifically mention EDB or noted no cases with EDB in their cohorts. In response to variability in the reported detection of EDB, a recent study described calculating the beta:delta ratio (BDR) as a possible specific finding in anti-NMDA encephalitis. They noted that BDR was higher in anti-NMDA encephalitis than other cases of encephalitis (Foff et al., 2017).

Epileptiform activity as captured electrographically (with or without clinical correlate) was noted in 16–63% of cases (Dalmau et al., 2008; Armangue et al., 2013; Schmitt et al., 2012; Florance et al., 2009; Tan et al., 2013; Abdullah et al., 2011; Veciana et al., 2015; Sands et al., 2015; Suthar et al., 2016; Wanga et al., 2017; Zhang et al., 2017; Ho et al., 2018; Goenka et al., 2017; Haberlandt et al., 2017; Wang et al., 2016; Chakrabarty et al., 2014; Lin et al., 2016). Seizure incidence was highest at the peak of illness (Zhang et al., 2017), and was relatively equal between pediatric and adult patients in one study (Huang et al., 2016. Focal seizures were described in 30% in one series (Armangue et al., 2013), in 4/5 patients with seizures in another study (Sands et al., 2015), and in most patients with seizures in one study cohort (Foff et al., 2017). The incidence of generalized versus unilateral/focal seizures was relatively similar in incidence in one study (Schmitt et al., 2012). Status epilepticus was seen in both subjects in one series (Sands et al., 2015), and in 6% and 30% of the cases reported in two other larger studies, respectively (Dalmau et al., 2008; Abdullah et al., 2011). Some reported the location of focal seizures, which included frontal, bifrontal, frontocentral, frontotemporal, centrotemporal, temporal, and parietal regions (Sands et al., 2015; Suthar et al., 2016; Matoq et al., 2015; Chakrabarty et al., 2014). Ictal EEG activity, aside from spike-waves or sharp activity, was described in detail in some of the reports (Tan et al., 2013; de Silva-Junior et al., 2014; Veciana et al., 2015; Sands et al., 2015; Miao and Wang, 2017; Holzer et al., 2012). This included rhythmic diffuse monomorphic delta or rhythmic anterior delta (Holzer et al., 2012). Ictal alpha activity was described in three studies, with one noting sinusoidal alpha activity as an ictal phenomenon (Miao and Wang, 2017), and the others describing paroxysmal unilateral temporal (Veciana et al., 2015) or frontal (Tan et al., 2013) alpha activity, with secondary generalization (Veciana et al., 2015). One analysis described focal rhythmic activity without clear spikes or sharp waves which generalized at 6–12 Hz (Sands et al., 2015). Another study also reported ictal EEG as unilateral 3 Hz sharp waves that propagated posteriorly then generalized with coincident increase in beta activity (Veciana et al., 2015). Unilateral rhythmic theta followed by generalized rhythmic slowing was also noted as a seizure correlate in another study (de Silva-Junior et al., 2014). In general, an increased amount of rhythmicity was often found in patients with NMDAR encephalitis whether within or outside of the context of seizures.

Clinical correlation with the electrographic findings on EEG was not always clearly described in the literature. However, nonconvulsive events were seen in 8/23 patients although all had at least one electroclinical seizure during prolonged EEG monitoring (Schmitt et al., 2012).

Periodic discharges, which are also on the ictal-interictal continuum, were seen as bilateral independent (BIPDs) in one case (Baysal-Kirac et al., 2015), and lateralized (LPDs) in another (Konuskan et al., 2018).

One study found excessive spindles outside of sleep on EEGs in 4/11 pediatric patients (Mohammad et al., 2016). This appeared to differentiate NMDAR encephalitis from other cases of pediatric encephalitis in this analysis.

Outcome measures were described in a few studies. Those with polymorphic delta, diffuse beta, epileptiform activity, or normal EEG at peak stage had better outcome (Zhang et al., 2017). Regarding EDB, two studies found no statistically significant impact (Veciana et al., 2015; Zhang et al., 2017) while another found both prolonged hospitalization and longer EEG monitoring in those with EDB though no significant association with survival or functional outcomes (Schmitt et al., 2012). Seizures correlated with worse outcomes in one study (Foff et al., 2017) and had no effect on outcomes in another (Wanga et al., 2017).

4. Discussion

In this review, we describe EEG characteristics in patients with anti-NMDARE, which may have utility in diagnosis and prognosis. In most

cases, generalized slowing was the most common feature, which is a nonspecific finding (Gitiaux et al., 2013). EDB, which is thought to be a specific and useful finding on EEG in anti-NMDARE, had variable sensitivity in our study. BDR, a newer EEG phenomenon that has been described, may be a valuable marker in the assessment of anti-NMDARE, as it may have more utility in differentiating anti-NMDARE from other forms of encephalitis given that it is an EEG feature that can be calculated in any case (Foff et al., 2017). Rhythmic activity is seen in many cases and may correlate with clinical stage and examination. Seizures are common, and ictal EEG correlates may be of value in differentiating anti-NMDARE. In particular, sinusoidal alpha as an ictal phenomenon (Miao and Wang, 2017) is an intriguing finding not previously described by other analyses and warrants further study.

EDB may be a specific feature of anti-NMDARE, though its incidence is variable as demonstrated in this study. The results from our review may be biased due to inconsistent reporting of the presence or the absence of EDB. The variability in reports of EDB may be due to the failure of some investigators to specifically review the EEG for this feature despite the fact that only 2 studies in this review were published before or during 2012, the same year of the seminal study describing EDB in detail was published (Schmitt et al., 2012). No consistent finding was seen regarding outcomes in those with EDB. However, in one of the smaller studies, the presence of beta activity on the trough or peak of the delta waves in EDB was thought to be useful in prognostication (Wang et al., 2017). Others have noted EDB being more common in those who are comatose (Foff et al., 2017) as well as in patients with more prolonged or severe disease and EDB may therefore portend a worse prognosis (Schmitt et al., 2012; VanHaerents et al., 2014). Based on our review, further study is needed to determine the true incidence of EDB and its prognostic utility.

The effects of sedative use on beta activity/EDB has been described (Schmitt et al., 2012; Zhang et al., 2017). One must cautiously interpret excessive slowing or beta activity in the setting of sedative use, as pharmacological intervention may alter the EEG appearance iatrogenically. On the other hand, EDB has not been found to be affected by or occur in response to sedative use (Shi, 2017) and so it appears less likely that this needs to be considered when evaluating for EDB specifically.

Some studies tried to tie EEG findings to the clinical phase of disease. One noted that EEG abnormalities were more sensitive than MRI (Zhang et al., 2017) in the peak stage of the illness. Delineating EEG correlates at different stages of NMDARE may not only help to understand the clinical course of the illness, but also would allow for better utilizing EEG in making the diagnosis and assessing clinical improvement.

As noted in our results, EEG features that may prove useful as prognostic indicators were described in a few studies (Schmitt et al., 2012; Zhang et al., 2017). However, these findings were not reported consistently, and future analyses should focus on EEG in prognosis in cases of NMDARE.

The length of EEG monitoring was reported in only few of the studies. One paper concluded that EEG findings may have eluded detection without continuous monitoring (de Silva-Junior et al., 2014). Continuous EEG monitoring (CEEG) offers certain advantages over brief spot EEG studies such as the ability to assess waking, drowsiness and sleep in detail. CEEG also allows a comprehensive evaluation of epileptiform features characteristics, including the diagnosis of subclinical seizures and the differentiation of movement disorder from epileptic seizure. Therefore, CEEG should be utilized preferentially in future analyses.

Overall, the incidence of seizures in these studies varied. There was no consensus that the presence of seizures portended a worse outcome. One might assume that limbic encephalitis subtypes should be characterized by seizures localizing to the limbic system, yet seizures arising from other locations were reported also. Further evaluation of the predictive value of epileptiform discharges and seizures in anti-NMDARE is therefore necessary, particularly when taken in the context of the stage of the disease.

While we found studies that included either pediatric or adult patient populations or both, only one study truly attempted to differentiate EEG as a whole in these populations (Lin et al., 2016), while another did compare EDB in pediatric and adult patients, noting lower rates of incidence in pediatric patients (Zhang et al., 2017). Patients diagnosed with anti-NMDARE range from infant age to the elderly (Dalmau et al., 2007; Goldberg et al., 2014) and therefore reporting of results should be clearer regarding age and EEG features, given that even normal subjects vary in their EEG characteristics at different ages. Future analyses should better define EEG in adult and pediatric cases.

Another demographic that may need further attention is gender. The association of NMDARE with ovarian teratoma has been well described (Dalmau et al., 2007). One study found in our review, which did not meet inclusion criteria due to the absence of EEG data, notes clinical differences in cases of NMDARE in men and women (Viaccoz et al., 2014). This has implications for further studies on anti-NMDARE.

The ultimate goal of better defining EEG is to help delineate anti-NMDARE in cases of autoimmune encephalitis. This was attempted (Konuskan et al., 2018; Mohammad et al., 2016; Baysal-Kirac et al., 2015; Holzer et al., 2012), though sample sizes and depth of EEG interpretation do not suffice to make any definitive conclusions. Therefore, directly comparing NMDARE to other forms of encephalitis would be an appropriate endeavor.

These studies overall demonstrated significant variability in outcome measures. As noted in our results, EEG characteristics were not consistently addressed, making it difficult to draw fundamental conclusions regarding EEG in NMDARE. Correlating clinical indicators of anti-NMDARE with EEG features would have utility in diagnosis/prognosis but this was not well-described in these studies other than that which we noted above. The presence of psychiatric symptoms, dysautonomia, movement disorders, and relapses and their coincident EEG features were not well reported and should be collected systematically in the future. Based on the current literature our review was therefore often largely narrative.

5. Conclusions

In this systematic review, we describe EEG features in anti-NMDARE. Our review uncovered a number of analyses but we are limited by the retrospective nature of these studies as well as the lack of a standardized approach. We found EEG features that may be useful in diagnosis and prognosis in anti-NMDARE. We also described a number of shortcomings in the reports available in the current literature that need to be addressed in future study. These include the systematic analysis of relevant EEG features, evaluation of EEG features in the context of disease stage and determining prognostic features, the use of CEEG particularly in the assessment of epileptiform burden, and the comparison of EEG findings in pediatric and adult patients as well as among men and women, and among different subtypes of autoimmune encephalitis. There is some promise in evaluating BDR, as well as ictal sinusoidal alpha activity, both of which may hold promise as specific markers of anti-NMDARE, though more studies specifically focusing on these EEG patterns are needed. Though EDB may be a relatively specific finding in anti-NMDARE, its low sensitivity and unclear specificity may limit its utility. Further studies are needed to specifically address EEG characteristics in anti-NMDARE given the possible utility of EEG in earlier diagnosis and institution of treatment, as well as more targeted evaluations to uncover the possible onconeuronal origin of the illness.

Author contributions

BF and EKR both contributed to drafting and revisions of manuscript, study concept and design, and data acquisition, analysis and interpretation.

Disclosure

We declare no competing interests or funding.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jneuroim.2019.03.010.

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