Original article

Epileptic Disord 2020; 22 (6): 739-51

Clinical and electrographic features of persistent seizures and status epilepticus associated with anti-NMDA receptor encephalitis (anti-NMDARE)

Jacqueline S. Gofshteyn [1,a], Anusha K. Yeshokumar [2,a], Nathalie Jette [2], Kiran T. Thakur [3], Nicole Luche [1], Elissa Yozawitz [4], Shelley Varnado [5], Britany Klenofsky [2], Mary Claire Tuohy [3], Jyoti Ankam [3], Sarah Torres [3], Dale Hesdorffer [3], Aaron Nelson [5], Steven Wolf [6], Patricia McGoldrick [6], Helena Yan [1], Natasha Basma [1], Zachary Grinspan [1]

[1] WeillCornell Medical Center, New York, NY, USA
[2] Icahn School of Medicine at Mount Sinai, New York, NY, USA
[3] Columbia University Medical Center, New York, NY, USA
[4] Montefiore Medical Center, New York, NY, USA
[5] NYU Langone, New York, NY, USA
[6] Boston Children's Health Physicians and Maria Fareri Children's Hospital, New York Medical College, Valhalla, NY 10595, USA
[a] Authors contributed equally

Received June 11, 2020; Accepted August 20, 2020

ABSTRACT – *Aims*. Based on a multicenter cohort of people with anti-NMDA receptor encephalitis (anti-NMDARE), we describe seizure phenotypes, electroencephalographic (EEG) findings, and anti-seizure treatment strategies. We also investigated whether specific electrographic features are associated with persistent seizures or status epilepticus after acute presentation.

Methods. In this retrospective cohort study, we reviewed records of children and adults with anti-NMDARE between 2010 and 2014 who were included in the Rare Epilepsy of New York City database, which included the text of physician notes from five academic medical centers. Clinical history (*e.g.*, seizure semiology) and EEG features (*e.g.*, background organization, slowing, epileptiform activity, seizures, sleep architecture, extreme delta brush) were abstracted. We compared clinical features associated with persistent seizures (ongoing seizures after one month from presentation) and status epilepticus, using bivariate and multivariable analyses.

Results. Among the 38 individuals with definite anti-NMDARE, 32 (84%) had seizures and 29 (76%) had seizures captured on EEG. Electrographic-only

Correspondence:
Jacqueline S. Gofshteyn
Weill Cornell Medical College,
1320 York Avenue, Suite 611,
New York, NY 10021, USA
<Jag9194@med.cornell.edu>

doi:10.1684/epd.2020.1218

seizures were identified in five (13%) individuals. Seizures started at a median of four days after initial symptoms (IQR: 3-6 days). Frontal lobe-onset focal seizures were most common (n=12; 32%). Most individuals (31/38; 82%) were refractory to anti-seizure medications. Status epilepticus was associated with younger age (15 years [9-20] vs. 23 years [18-27]; p=0.04) and Hispanic ethnicity (30 [80%] vs. 8 [36%]; p=0.04). Persistent seizures (ongoing seizures after one month from presentation) were associated with younger age (nine years [3-14] vs. 22 years [15-28]; $p<0.01$). Measured electrographic features were not associated with persistent seizures.
Conclusions. Seizures associated with anti-NMDARE are primarily focal seizures originating in the frontal lobes. Younger patients may be at increased risk of epileptogenesis and status epilepticus. Continuous EEG monitoring helps identify subclinical seizures, but specific EEG findings may not predict the severity or persistence of seizures during hospitalization.

Key words: anti-NMDA receptor encephalitis, autoimmune encephalitis, seizure risk factors

Anti-N-methyl-D-aspartate receptor encephalitis (NMDARE) is the prototype of an expanding number of autoantibody-mediated encephalidies (Dalmau *et al*., 2007). The disease progresses from a constellation of psychiatric features, seizures, and language and memory involvement to disturbances of consciousness, dyskinesias, and autonomic instability (Dalmau *et al*., 2011). Seizures are well-established (Dalmau *et al*., 2007) and typically an early feature of the disease; however, in a subset of individuals, status epilepticus and persistent seizures (after the initial acute presentation) may occur. Yet it is unclear who is at high risk for these more severe seizure presentations.

Current literature highlights a possible age effect on seizure presentations in anti-NMDARE. Prior series have found that seizures occur in 70-80% of cases of anti-NMDARE (Leypoldt and Wandinger, 2014; Sonderen *et al*., 2018; Gillinder *et al*., 2019a). Status epilepticus (SE) is common, occurring in as many as half of affected individuals (Liu *et al*., 2017). Young age at onset is a postulated risk factor, though there are limited comparisons of seizures or EEG findings in pediatric versus adult populations (Titulaer *et al*., 2013; Veciana *et al*., 2015; Foff *et al*., 2017; Zhang *et al*., 2017; Sonderen *et al*., 2018; Gillinder *et al*., 2019a; Jeannin-Mayer *et al*., 2019). Seizures and movement disorders may be a more common initial presenting symptom in children (less than 12 years of age) than adults (over age 18) (Liu *et al*., 2017).

There is growing interest to use EEG as a biomarker for disease progression (Baysal-Kirac *et al*., 2016; Foff *et al*., 2017; Haberlandt *et al*., 2017; Zhang *et al*., 2017; Gillinder *et al*., 2019a; Jeannin-Mayer *et al*., 2019). The EEG is rarely normal in anti-NMDARE (only 10% of cases) (Gillinder *et al*., 2019a), suggesting its features may yield valuable prognostic information. However, the sensitivity and specificity of these EEG abnormalities to predict outcomes are not sufficient to serve as a reliable clinical biomarker (Schmitt *et al*., 2012; Veciana *et al*., 2015; Sonderen *et al*., 2018; Yildirim *et al*., 2018; Jeannin-Mayer *et al*., 2019), in part, due to limited outcomes studies (Gordon-Lipkin *et al*., 2017; Yeshokumar *et al*., 2017). One specific EEG pattern described in anti-NMDARE is the extreme delta brush (EDB), though this has been reported in a wide range (0-58%) of studied anti-NMDARE patients (Gillinder *et al*., 2019b), and therefore may not be a sufficiently sensitive or reliable biomarker for clinical use. More recently, severe, diffuse background slowing has been posited as a risk for poor neurologic outcome in a small pediatric cohort (Yildirim *et al*., 2018).

Although there has been much attention on the electrographic background in anti-NMDARE, there are only a few descriptions of clinical seizures captured on EEG. In a large systematic review of the literature, 446 cases of NMDARE were identified with available EEG information, of which only 39 (8.7%) had seizures that were electrographically captured (Gillinder *et al*., 2019a). Oftentimes, prior studies were limited by the duration of the EEG recording, thus here we examined a cohort that often underwent long-term video-EEG monitoring, capturing data for both wakefulness and sleep. This cohort was also unique in that patients were seen by an epileptologist, which may provide deeper insight into the clinical seizure and EEG characteristics.

Here, we review patients with a diagnosis of anti-NMDARE treated at major NYC medical centers between 2010 and 2014. Our primary aims were two-fold: 1) to identify clinical and electrographic predictors of SE or persistent seizures in individuals with anti-NMDARE; and 2) to better characterize the clinical seizure subtypes seen with ant-NMDARE. We hypothesized that while seizures would be an early feature of anti-NMDARE, younger aged patients would be at risk of persistence of seizures after the initial month of presentation. In addition, our *a priori hypothesis*

regarding electroclinical seizures was that seizures would be more often focal than generalized at onset, and typically refractory to treatment and requiring multiple antiseizure medications (ASMs). The findings from this study, specifically examining risk factors for persistent and severe seizures, will add to the current body of literature regarding seizures associated with anti-NMDARE, thereby providing guidance for seizure treatment.

Methods

Study design

This was a retrospective cohort study of individuals with anti-NMDARE. Individuals were identified from the Rare Epilepsy of New York City (RENYC) database, which includes clinical information and the text of physician notes and EEG reports from five tertiary medical centers in New York City (NYC) (Weill Cornell Medicine, Mount Sinai School of Medicine, Montefiore Medicine, Columbia University Medical Center, and New York University Medical Center). The study was approved by the institutional review board at the five participating centers, facilitated by a central IRB (Biomedical Research Alliance of New York; BRANY).
The RENYC database includes the text of 650,000 clinical notes for 78,000 patients from 2010 - 2014. The data were obtained by asking each site to identify all patients with a visit associated with an ICD9 code of 345.x (epilepsy), 779.0 (neonatal convulsions), or 780.39 (convulsions). The notes included inpatient and outpatient encounters by neurologists, EEG reports, and discharge summaries. To find individuals with anti-NMDARE, we performed a text search for the string "NMDA". Clinical notes for adult and pediatric patients were then reviewed by two reviewers (JG and AY).

Inclusion and exclusion criteria

All individuals included in this study were diagnosed with definite anti-NMDRE, which was defined as per the guidelines outlined by Graus *et al*. (Graus *et al*., 2016; Panel 4). Namely, the patient was required to have IgG anti-GluN1 antibodies and a clinical presentation consistent with anti-NMDARE. Key clinical features included rapid onset of:
– decreased level of consciousness;
– psychiatric symptoms and/or cognitive dysfunction;
– seizures without a prior known seizure disorder;
– movement disorder;
– speech dysfunction;
– and autonomic dysfunction and exclusion of alternative causes (Graus *et al*., 2016).

The full evaluation for each patient was reviewed to ensure alternative diagnoses were excluded. Patients were excluded if their primary evaluation was performed at an external institution due to concern for incomplete records, or if there were insufficient clinical data or EEG reports available. When an individual visited multiple NYC medical centers within our network, records were consolidated into a single subject record.

Data abstraction

Co-investigators at each study site reviewed EEG reports and clinical notes for each included case, extracting information regarding clinical seizures and electrographic features. Clinical seizure information included timing and frequency of clinical seizures, subtype of clinical seizures (generalized vs. focal; motor vs. non-motor), and presence of clinical SE. Demographic features (age, race, ethnicity, zip code, insurance type), relevant personal and family medical history (history of psychiatric disease, history of autoimmune disease, history of seizures), hospital course information (length of stay, need for ICU care), and treatment history (immunomodulatory therapies used, anti-epileptic therapy used) were also abstracted. Time to ASM treatment or immunotherapy was documented in days from first reported clinical symptom.

EEG review

EEG reports were reviewed for five features (background organization, slowing, epileptiform features, seizures, and sleep architecture) by fellowship trained epileptologists (JG, EY, SV). It was not feasible to examine the full EEG files because most files had either been clipped or were not available, therefore, reports were used for review. All EEG reports were written by the fellowship-trained epileptologist on service at the time the patient was admitted. Ordinal scales were developed for each of the five features, based on the International League Against Epilepsy (ILAE) 2017 classification standards (Fisher *et al*., 2018a, 2018b) (*table 1*).
We grouped EEG findings into two time points:
– the first EEG, which was the first available EEG report after presentation with NMDARE symptoms;
– and all subsequent EEG findings from the initial hospitalization, to indicate the range of abnormalities present after the initial study.
We also recorded the number and timing of routine, long-term video and ambulatory EEG studies. SE was classified according to the ILAE definition and classification (Trinka *et al*., 2015).

Table 1. EEG features evaluated.

EEG	Feature	Specific aspect of feature	Possible responses				
First EEG features (first 48 hours of monitoring: routine +/- LTM)	Background	Symmetric	Yes	No	Unclear		
		Normal frequency-amplitude gradient	Yes	No	Unclear		
		Normal anterior-posterior gradient	Yes	No	Unclear		
		Reactivity	Yes	No	Unclear		
	Slowing		None	Unifocal	Multifocal	Generalized	Unclear
	Epileptiform activity / periodic discharges	How often	None	Rare	Occasional	Frequent	Abundant-continuous
		Where	None	Unifocal	Multifocal	Generalized	Unclear
		What type	None	Periodic discharges	Rhythmic delta activity	Spike-wave	Unclear
	Seizures		None	Electro-graphic only	Electro-clinical	Both electrographic and electroclinical	
	Sleep features	Stage II sleep transients	Yes	No, sleep captured	No, no sleep captured		
		SWS	Yes	No, sleep captured	No, no sleep captured		
	Delta brush		Yes	No	Unclear		

Data analysis

We compared individuals with persistent seizures (ongoing seizures after one month from presentation) and those with acute seizures only (*i.e.* seizures ceased within one month of presentation), and identified EEG characteristics associated with the persistence of seizures. The five EEG features on the first EEG were compared between those with and without persistent seizures, and between those with and without SE. Bivariate analysis was performed using Wilcoxon rank-sum tests for continuous variables and Pearson's chi-squared testing for binary variables. Clinical and EEG factors were analyzed using Pearson's chi-squared testing and Wilcoxon rank-sum testing for categorical and continuous variables to identify factors associated with the development of SE. Time to treatments (both ASMs and immunotherapy) were operationalized as continuous variables. Survival analysis for time from first seizure to seizure cessation was performed using Kaplan-Meier survival analysis. Age was examined both as a continuous variable and as a binary variable (age at symptom onset ≤18 vs 19+). Data were analyzed using StataIC (STATACorp; College Station, TX) and R statistical package (RStudio v1.3.959).

Results

Demographics of the patient cohort

The text search identified 174 patients with the term "NMDA" in the clinical notes. After chart review, we identified 38 individuals (21% male) with definite NMDARE across all five centers (*supplementary table 1*). The median age at symptom onset was 21 years (IQR: 11-27 years; range: 2-41). Few patients had a personal history of autoimmune (AI) disease (*n*=3; 8%); all thyroid disease. None had a personal history of seizures, though three (8%) reported a family history of seizures (*table 2*).

Disease treatment/management

Five patients (13%) were seen at multiple institutions within the RENYC network. An additional 17 (50%) patients were seen at one institution within RENYC and another outside hospital. Overall, patients in this cohort were admitted to a median of two different hospitals (IQR: 1-2) and one rehabilitation facility during their acute presentation. Presentation to one of the RENYC hospitals occurred a median of eight days after symptom onset (IQR: 6-66 days; range: 0 - 7 years).

Immunotherapy, including corticosteroids (81% of subjects), plasmapheresis (59%), IVIG (100%), cyclophosphamide (16%), or rituximab (59%) was given to all patients in this cohort. Immunotherapy was initiated a median of 5.5 days after presentation to a hospital (IQR: 1-19 days; maximum: 721 days) and 29 days after clinical symptom onset (IQR: 17-80 days; maximum: 2,813 days). Intensive care was required in 25/38 (66%) for a median of 18 days (IQR: 6-38 days; maximum: 148 days). Hospitalizations were lengthy in this cohort, with total length of inpatient hospitalization lasting a median of 31 days (IQR: 22-58 days; range: 3-200 days). Ovarian teratoma was removed in 13 (34%) patients of this cohort.

Table 2. Demographic characteristics of individuals with anti-NMDARE in the RENYC network (*n* = 38) and EEG use.

Demographics	***n* (%) or Median (IQR)**
Age	21 (11-27)
Sex (male)	8 (21)
Race	
Unknown	4 (10.5)
White	15 (39.5)
African American	7 (18.5)
Asian	4(10.5)
Other	8 (21)
Ethnicity	
Unknown	10 (26)
Hispanic	14 (37)
Non-Hispanic	14 (37)
Site for treatment	
CUIMC	21 (55)
Montefiore	2 (5)
NYU	5 (13)
NYP-Cornell	5 (13)
MSHS	4 (10)
EEG use and findings	
EEG obtained	37 (97)
Days of EEG monitoring	9 (5-22.5)
Number of routine EEGs	1 (0-1.5)
Days after hospital presentation to first EEG	9 (5-22.5)
Seizures captured on EEG	24 (63)
Days from hospital presentation to clinical seizure	4(3-6)
Days from hospital presentation to last known seizure	9 (1.5-51.5)
Days to hospital presentation from symptom onset	18 (6-66)
Other	
Ovarian teratoma identified	13(34)

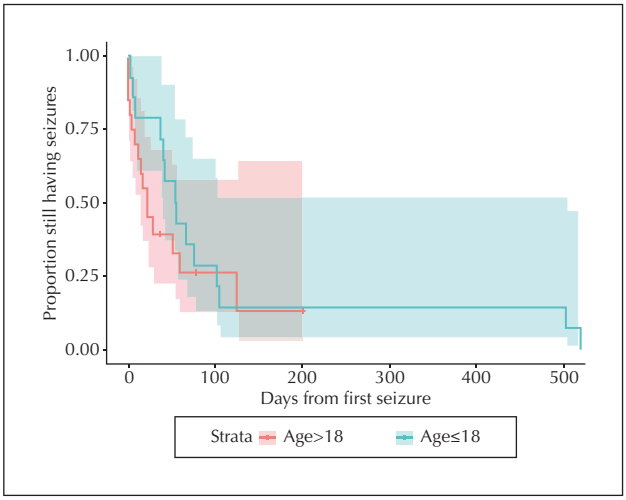

Figure 1. Time from first seizure to seizure cessation in pediatric *vs.* adult patients (median 55 days [95% CI: 40-503] for children <18 years *vs.* 22 [95% CI: 13- 45] for adults >18, p=0.4).

Clinical seizure findings

Thirty-four patients (89% of the cohort) were treated for clinical seizures at some time during their hospitalization. Of the patients who had seizures, a third (11 of 34) did not have seizures until after the initial hospital presentation. Clinical seizures occurred at a median of three days after hospital presentation (IQR: 3-6 days; range: 0-9 days). The most common initial clinical seizure subtype was focal motor onset with impaired awareness (*n*=15; 44%). Nine (24%) were initially treated for seizures, but after capturing events on scalp EEG, the paroxysmal events were favored instead to represent abnormal movements. Among the 20 individuals with a known last day of seizures, seizures persisted for a median of 22 days (IQR: 4-83; range: 0-518 days). The remaining 14 either still had seizures at last follow-up visit or did not have an outpatient follow-up at a RENYC site. Kaplan-Meier survival analysis was performed to compare adult and pediatric patients; individuals ≤18 did not have a significantly increased duration of seizures (median of 55 days [95% CI: 40-503] for children ≤18 years vs. 22 [95% CI: 13-45] for adults >18; *p*=0.4) (*figure 1*).

Status epilepticus (SE)

Fourteen of the cohort (37%) had episodes of SE during hospitalization, 10 of which were captured on EEG. For seven individuals (18%), SE was one of the presenting symptoms upon admission to the hospital. SE began a median of two days after presentation (IQR: 0-3 days; range: 0-7 days). Four had convulsive SE, three non-convulsive SE with coma, three focal motor SE, two myoclonic SE, and two not classifiable based upon the available information.

Use of EEG

All 38 individuals with anti-NMDARE had at least one EEG. The EEG reports were available for all except one patient. Thirty-five patients had long-term video-EEG monitoring performed during their initial hospitalization, beginning a median of eight days after presentation. Video-EEG was continued for a median of nine days (IQR: 5-17 days; range: 0-118 days).

Seizure management

An ASM was first administered at a median of 13.5 days after onset of clinical symptoms (IQR: 8-73 days). Levetiracetam was the most commonly used anti-seizure medication (22/38) (*figure 2*). Most patients received three or more ASMs during hospitalization (*n*=31; 82%). Anesthetics were commonly needed (15/38 patients) including ketamine (3), propofol (9), midazolam (11), and pentobarbital (4). Twenty-three (61%) were still on ASM therapy at the last known follow-up visit. Four patients were lost to follow-up or had an unclear ASM treatment course. Of those patients whose last ASM treatment was known, ASM therapy was continued for a median of 194 days (IQR: 56-295; range: 0-2,015 days).

EEG findings

Electrographic background features were assessed for 35/38 (92%) of the patients. For the remaining patients, the EEG report did not provide sufficiently detailed information. In the initial EEG, 30 (86%) individuals had symmetric and reactive EEGs, though only 37% maintained a normal waking background (normal anterior posterior gradient [APG] and frequency amplitude gradient) throughout the hospitalization (*table 3*). Slowing was seen in most patients; 80% in the first EEG and 89% at some time during the hospitalization (*table 3*). Thirty (86%) had epileptiform or periodic discharges on subsequent EEGs, which most commonly consisted of unifocal rhythmic delta activity or sharp waves, though only 18 (51%) patients had these discharges captured on the initial EEG. Sleep was often abnormal with only 40% of patients ever having normal sleep transients or slow-wave sleep captured on EEG during their hospitalization. EEG reports described EDB in two patients. When we compared the first EEG to subsequent EEGs during the hospitalization, there were significant differences found with regards to frequency amplitude gradient, epileptiform activity (morphology, location and frequency), sleep transients, and seizures. Over the course of hospitalization, a majority of patients

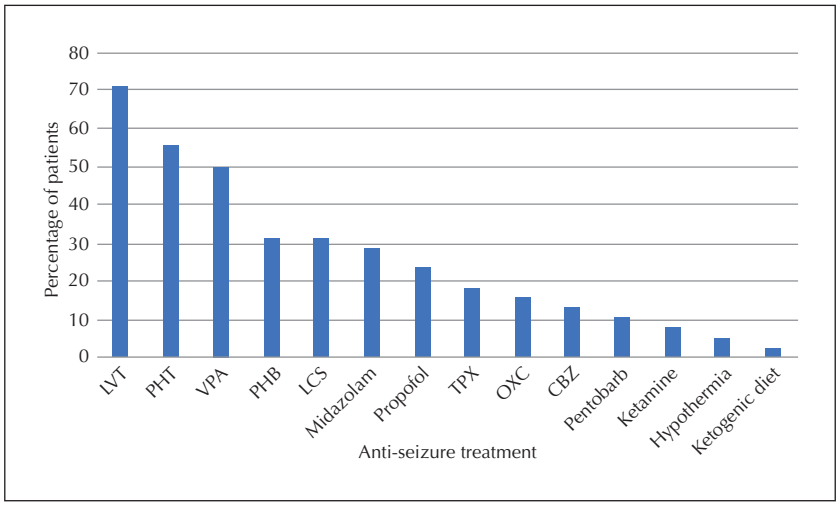

Figure 2. Antiseizure and anesthetic treatments for seizures throughout hospitalization.

with normal anterior posterior gradient (APG) (*n*=21) or preserved sleep architecture (*n*=17) on their initial EEG showed subsequent loss of these normal features (loss of APG: *n*=13 [62%]; loss of normal sleep transients: *n*=15 [71%]). Although changes in slowing patterns from the first to subsequent EEGs were not statistically significant, there were some potentially clinically important effect sizes. For example, the percentage of individuals with multifocal slowing increased from 3 to 14 and the percentage of individuals with diffuse and unifocal slowing doubled (*table 3*). Additionally, several patients (*n*=12) developed epileptiform activity or periodic discharges who did not have these findings initially. There were also seven patients who had increased epileptiform activity on subsequent EEGs. More seizures were likewise captured on subsequent EEGs compared with the initial EEG (*n*=3 vs. n=22; *p*=0.01) (*table 3*).

Twenty-four (63%) patients had seizures captured on EEG. Twelve (32%) had predominately frontal onset seizures and nine (24%) predominantly temporal onset seizures. Importantly, five (13%) patients had electrographic-only seizures, and 11 (29%) had both electrographic and electroclinical seizures. Status epilepticus was captured on EEG in 10 (26%) individuals although none had SE on the initial EEG.

Persistent seizures

In 10 (50%) patients, seizures stopped within the first month, and 10 (50%) had seizures persisting for longer than one month. A definite seizure cessation date was not known (due to being lost to follow-up or lack of clarity on the chart) for the remaining 18. Those who had seizures lasting longer than one month were younger than those whose seizures remitted (nine years [3-14] vs. 22 years [15-28]; $p<0.01$). Persistent seizures were not associated with type or timing of immunotherapy, EEG factors, or ASM treatment (*table 4*). Similarly, persistent seizures were not associated with teratoma removal (chi-squared= 0.23; *p*=0.64). Individuals with SE during hospitalization were more likely to have persistent seizures, though the association was not statistically significant (OR: 2.25 [0.27 – 12.47]; $p = 0.37$).

Status epilepticus

Individuals with status epilepticus were more likely to be younger (15 years [9-20] vs. 23 years [18-27]; *p*=0.04). Additionally, being of Hispanic ethnicity was associated with SE (30 [80%] for Hispanic vs 8 [36%] for non-Hispanic individuals; *p*=0.04). Teratoma removal was not associated with SE (chi-squared=2.45; *p*=0.12). None of the five measured features in the first EEG was associated with increased odds of SE. Normal EEG findings in subsequent EEGs were associated with a lower risk of SE, such as presence of reactivity (OR: 0.10 for SE [95% CI: 0.01-0.93]; *p*=0.05) and normal APG (OR: 0.20 for SE [0.03-0.90]; *p*=0.04). In 7/10 patients with SE captured on EEG, lack of a normal posterior dominant rhythm preceded the onset of SE during hospitalization. Individuals with SE had more frequent interictal epileptiform activity during hospitalization SE (OR: 2.43 [95% CI: 1.12-5.26], *p*=0.02), however, epileptiform activity was only seen in two patients prior to onset of SE. Patients with SE were more likely to have multifocal or diffuse epileptiform abnormalities whereas those without SE more frequently had unifocal epileptiform abnormalities (OR: 1.87 [95% CI: 1.01-3.50]; $p = 0.04$). SE was not associated with the presence of slow-wave sleep, sleep transients, type and timing of immunotherapy, nor ASM treatment.

Table 3. EEG features and differences between initial EEG and subsequent EEGs (*n*=35).

EEG features	First EEG *n* (%) (median: 2 days from hospitalization)	Subsequent EEGs *n* (%)	*p* value
Background			
Symmetric	29 (82.9)	28 (80)	0.69
Normal frequency-amplitude gradient	21 (60)	13 (37.1)	**0.01**
Normal posterior dominant rhythm	16 (45.7)	13(37.1)	0.34
Reactivity	29 (82.9)	31 (88.6)	1.0
Slowing			0.65
None	7 (20.0)	4 (11.4)	
Unifocal	4 (11.4)	3 (8.5)	
Multifocal	1 (2.9)	5 (14.2)	
Diffuse and unifocal	7 (20.0)	14 (40.0)	
Diffuse	15 (42.8)	11 (31.4)	
Epileptiform activity			
Frequency			**0.02**
None	20 (57.1)	8 (22.8)	
Rare	0 (0)	4 (11.4)	
Occasional	5 (14.2)	15 (42.8)	
Frequent	8 (22.8)	7 (20.0)	
Abundant-continuous	0 (0)	2 (5.7)	
Location			**0.01**
None	20 (57.1)	8 (22.8)	
Unifocal	8 (22.8)	12 (34.2)	
Multifocal	4 (11.4)	7 (20.6)	
Diffuse and unifocal	2 (5.7)	5 (14.2)	
Diffuse	1 (2.9)	3 (8.5)	
Morphology			<**0.01**
None	20 (57.1)	8 (22.8)	
Periodic discharges	1 (2.9)	0(0)	
Rhythmic delta activity	6 (17.1)	7 (20.6)	
Spike-wave	5 (14.2)	4 (11.4)	
Sharp waves	2 (5.7)	6 (17.1)	
Rhythmic delta activity+ sharp waves	1 (2.9)	11 (31.4)	
Sleep features			
Stage II transients	17 (48.5)	15 (42.8)	<**0.01**
SWS	14(40.0)	15 (42.9)	0.62
Delta brush	1 (2.9)	2 (5.7)	1.0
EEG seizures			**0.01**
None	26 (74.2)	14 (40)	
Electrographic	3 (8.6)	5 (14.2)	
Electroclinical	3 (8.6)	6 (17.1)	
Both electrographic and electroclinical	1 (2.9)	11 (31.4)	
Clinical only	2 (5.7)	0 (0)	
Status epilepticus on EEG	0 (0)	10 (28.6)	<**0.01**

Table 4. Variables associated with persistent seizures (seizures lasting longer than one month).

Factor	OR	CI	*p* value
Age<18 years	0.84	0.72-0.98	**0.02**
Male (*vs.* female)	0.56	0.44-0.73	0.48
Timing of immunotherapy	1.00	0.99-1.01	0.35
Teratoma removal	0.64	0.10-4.09	0.64
Timing of ASM treatment from first clinical symptom	0.99	0.99-1.01	0.98
Status epilepticus during admission	2.25	0.38-13.47	0.37
First EEG			
Background symmetric	1.75	0.22-14.22	0.59
Normal frequency-amplitude gradient	0.63	0.10-4.22	0.63
Reactivity present	0.99	0.87-3.45	0.15
Normal anterior-posterior gradient	1.0	0.14-7.09	1.0
Slowing	1.32	0.69-2.50	0.39
Epileptiform discharge: subtype	1.13	0.57-2.27	0.57
Epileptiform discharge: frequency	1.13	0.56-2.27	0.72
Epileptiform discharge: location	1.24	0.58-2.64	0.57
Epileptiform discharge: morphology	1.19	0.66-2.17	0.56
Sleep transients	1.27	0.34-4.77	0.72
Presence of slow-wave sleep	0.84	0.26-2.77	0.78
Subsequent EEGs			
Symmetric background	2.0	0.25-16.00	0.51
Normal frequency-amplitude gradient	0.31	0.04-2.38	0.25
Reactivity present	2.57	0.19-34.47	0.46
Normal anterior-posterior gradient	0.31	0.04-2.38	0.25
Slowing	0.69	0.28-1.67	0.40
Epileptiform discharge: subtype	0.98	0.50-1.90	0.94
Epileptiform discharge: frequency	0.79	0.30-2.03	0.61
Epileptiform discharge: location	1.0	0.42-2.40	1.0
Epileptiform discharge: morphology	0.98	0.50-1.90	0.94
Sleep transients	2.68	0.49-14.67	0.23
Presence of slow-wave sleep	2.68	0.49-14.67	0.23

Discussion

In this study we found that, although seizures were a common (89%) and early (median: 3 days after symptom onset [IQR: 3-6]) presenting symptom of anti-NMDARE, as has been previously described (Graus *et al*., 2016; Viaccoz *et al*., 2014), in a subset of individuals, seizures were also prolonged, persistent, and resulted in status epilepticus. Younger individuals were indeed more likely to experience status epilepticus and persistent seizures beyond one month. However, this conclusion is tempered by our survival analysis, which failed to identify a clear difference between pediatric and adult patients. Interestingly, being Hispanic was also associated with increased risk of status epilepticus. EEG recordings, while helpful in identifying subclinical seizures, did not provide a biomarker for persistent seizures or status epilepticus despite extended use (median of nine days in this cohort).

Persistent seizures were identified in half of individuals for whom a definite seizure cessation date was known. There is an important distinction between symptomatic seizures and development of epilepsy with anti-NMDARE. Most patients with anti-NMDARE have symptomatic seizures that resolve soon after the initiation of immunotherapy (de Bruijn *et al*., 2019). Development of epilepsy after anti-NMDARE

is thought to be rare, though there is poor longitudinal data available to fully examine this (Sonderen *et al*., 2018; Spatola and Dalmau, 2017). In this study "persistent seizures" is not synonymous with having epilepsy, however, persistent seizures were still noted more frequently than hypothesized. This may be secondary to the severity of illness in this cohort. Most patients (66%) were treated in the ICU, many for >two weeks (median 18 days), and status epilepticus was common. Thus, seizures may be associated with undetected cortical injury rather than something intrinsic to the anti-NMDARE disease process. Our inability to predict who will have persistent seizures may reflect our lack of sensitive markers for cortical injury associated with anti-NMDARE.

Relatedly, electrographic features did not predict who would have persistent seizures. Although individuals in this cohort were monitored frequently with EEG (median of nine days of continuous monitoring), the extracted EEG features were not found to be valuable as a biomarker. EDB was only noted in two (5%) in this patient cohort, supporting a previously raised concern that EDB lacks the sensitivity and specificity for anti-NMDARE (Baykan *et al*., 2018; Sonderen *et al*., 2018). EDB was identified in 3% of a neurological ICU population with altered consciousness (not due to autoimmune encephalitis), and 1% of a cohort with mesial temporal lobe epilepsy with hippocampal sclerosis (Armangue *et al*., 2013; Veciana *et al*., 2015; Mohammad *et al*., 2016; Foff *et al*., 2017; Haberlandt *et al*., 2017; Zhang *et al*., 2017; Baykan *et al*., 2018; Sonderen *et al*., 2018; Gillinder *et al*., 2019a). It is important to note that our assessment of EDB was determined by review of the EEG report only, and not the EEG tracings themselves.

Our findings support extended use of continuous video-EEG for seizure detection and differentiation. Electrographic-only seizures were seen in 13% of the cohort. Additionally, nine patients had events that were initially treated as seizures but later considered non-epileptic movements. Also, frontal lobe seizures were common in this cohort (32%) and can be difficult to clinically identify. Last, the number of individuals with seizures captured on EEG increased more than sevenfold (n=3 to n=22) with continued monitoring.

We found a greater proportion of patients with focal epileptiform discharges in our cohort than in prior reports. For example, in a study of 12 pediatric patients, only one had localized epileptiform discharges on the first EEG (Yildirim *et al*., 2018) compared to 47% on initial EEG and 79% in subsequent EEGs in our cohort. Although generalized tonic-clonic seizures are described as the most common seizure type in the literature (Cooray *et al*., 2015; Dalmau *et al*., 2008), focal motor onset with impaired awareness was more frequent in our cohort, suggesting that localized cortical hyperexcitability is a component of anti-NMDARE. This supports the overall conception of anti-NMDARE as a multifocal diffuse central nervous system process.

Timing of treatment (immunomodulatory and ASM) was not associated with persistence of seizures or SE. Early immunomodulatory treatment is important for improving outcomes such as motor disability (Graus *et al*., 2016) as well as seizures (de Bruijn *et al*., 2019). Thus, we were surprised not to see an association of treatment timing with seizure outcomes. We speculate that this may be due to the delay in initiation of immunotherapy overall in the cohort (median of 28 days from clinical symptom onset), and thus the initial window for rapid seizure treatment and cessation may have passed. Future prospective studies are needed to determine if the duration of seizures is affected by timing of immunomodulatory or ASM treatment.

Many patients were seen at multiple institutions within the NYC area, highlighting the fragmented care in this population. Here, presentation to a tertiary medical center was delayed, occurring after a median of eight days- in one patient 66 days. Fragmentation of care may contribute to poorer epilepsy outcomes (for cases both associated and not associated with anti-NMDARE) due to misdiagnosis and medication errors (England *et al*., 2012; Grinspan *et al*., 2015). Seizures and status epilepticus are a large component of the need for hospitalizations. A recent study found that median hospital charges for individuals with autoimmune encephalitis were more than $70,000 and substantially higher if admitted to the ICU ($173,000 per admission) (Cohen *et al*., 2019). More effective treatments for seizures associated with anti-NMDARE are essential for cost reduction.

Increased risk of SE amongst Hispanic patients may indicate disparate access to medical care (Price *et al*., 2015) and reflect socioeconomic status, language barriers, or limited access to treatment (Kelvin *et al*., 2007; England *et al*., 2012). It is unlikely that these specific care-delivery findings are unique to NYC (Burneo *et al*., 2009). Prior studies on sociodemographic disparities in delivery of epilepsy care found that differences associated with race and ethnicity persisted despite care site (Begley *et al*., 2009). An alternative explanation is that Hispanic individuals may develop a more severe autoimmune or inflammatory reaction, resulting in worsened seizure outcomes. This concern has been raised for other autoimmune diseases such as systemic lupus erythematosus (Contreras *et al*., 2006; Burgos *et al*., 2011). Differences in risk seen in other autoimmune diseases between Hispanic and non-Hispanic populations has led to examination of HLA-subtypes. Some have identified differences in risk conferred by HLA subtype based upon ethnic background, for example HLA*DRB1-positive patients of Hispanic origin may have different risk for type 1 diabetes, scleroderma,

and rheumatoid arthritis compared to non-Hispanic populations. Based on a prior genome-wide association study, HLA allele imputation identified HLA-I allele B*07:02 as a risk allele for anti-NMDARE. Further examination of immunogenetics may further delineate the relationship between ethnicity, HLA alleles, and risk of autoimmune disease.

Several limitations merit discussion. First, our analysis of EEGs was limited because the raw EEGs were unavailable for review, and thus the interpretations were not standardized. Second, we suspect we have underestimated the incidence anti-NMDARE, as there has subsequently been increased awareness of autoimmune encephalitis over the intervening years, and thus this cohort may not be representative of the full spectrum of the disease. Third, there were gaps in available data, importantly, the timing of seizure cessation, particularly if care was fragmented or clinical documentation was cursory or incomplete. This may have specifically imparted our survival analysis comparing pediatric and adult patients. Last, this study was performed at RENYC study sites which are tertiary care academic centers; thus, the cohort may be biased to contain more severe cases.

Our inability to predict persistent seizures using clinical or electrographic features underscores significant gaps in our understanding of who is at risk of epilepsy following anti-NMDARE and, more broadly, our understanding of autoimmune-associated seizures. This study supports a role for continued close monitoring of anti-NMDARE patients for seizures beyond the acute period of presentation. It further highlights the need for investigating risk factors and biomarkers for persistent seizures. Finally, the variation in current treatment practices targeting seizures associated with autoimmune encephalitis identified here provides future opportunities for research on comparative effectiveness. □

Key points

- Seizures associated with anti-NMDARE can persist after one month and can be difficult to treat.
- Seizures are typically focal and were most commonly localized to the frontal lobe in this cohort.
- Although EEG findings were not predictive of persistent seizures, EEG was useful in identifying electrographic seizures.
- Younger patients may be at increased risk of persistent seizures and status epilepticus associated with anti-NMDARE.

Supplementary data.
Summary didactic slides and supplementary table are available on the www.epilepticdisorders.com website.

Acknowledgements and disclosures.
Research Reported in this publication was supported by the Centers for Disease Control and Prevention grant number U01 DP006089; Jacqueline Gofshteyn is supported by the NIH-NINDS K12 Award Number NS066274-10; Anusha Yeshokumar receives grant funding from the American Epilepsy Society; Zachary Grinspan receives research funding from the National Center for Advancing Translational Science of the National Institute of Health Under Award Number UL1TR002384, Pediatric Epilepsy Research Consortium, the BAND foundation, Weill Cornell Medicine, the Centers for Disease Control and Prevention, the Morris and Alma Schapiro Fund, the Children's Hospital of Philadelphia Orphan Disease Center, and Clara Inspired. Nathalie Jette receives grant funding paid to her institution for grants unrelated to this work from NINDS (NIH U24NS107201, NIH IU54NS100064) and PCORI; she is the Bludhorn Professor of International Medicine., and receives an honorarium for her work as an Associate Editor of *Epilepsia*. Kiran T Thakur receives funding from NINDS-NIH K23; grant number 1K23NS105935-01.
None of the authors have any conflicts of interest to declare.

References

Armangue T, Titulaer MJ, Malaga I, *et al*. Pediatric anti-N-methyl-D-aspartate receptor encephalitis-clinical analysis and novel findings in a series of 20 patients. *J Pediatr* 2013; 162(4): 850-6.e2.

Baykan B, Gungor Tuncer O, Vanli-Yavuz EN, *et al*. Delta brush pattern is not unique to NMDAR encephalitis: evaluation of two independent long-term EEG cohorts. *Clin EEG Neurosci* 2018; 49(4): 278-84.

Baysal-Kirac L, Tuzun E, Altindag E, *et al*. Are there any specific EEG findings in autoimmune epilepsies? *Clin EEG Neurosci* 2016; 47(3): 224-34.

Begley CE, Basu R, Reynolds T, *et al*. Sociodemographic disparities in epilepsy care: results from the Houston/New York City health care use and outcomes study. *Epilepsia* 2009; 50(5): 1040-50.

Burneo JG, Jette N, Theodore W, *et al*. Disparities in epilepsy: report of a systematic review by the North American Commission of the International League Against Epilepsy. *Epilepsia* 2009; 50(10): 2285-95.

Burgos PI, McGwin GJ, Pons-Estel GJ, Reveille JD, Alarcon GS, Vila LM. US patients of Hispanic and African ancestry develop lupus nephritis early in the disease course: data from LUMINA, a multiethnic US cohort (LUMINA LXXIV). *Ann Rheum Dis* 2011; 70(2): 393-4.

Cohen J, Sotoca J, Gandhi S, *et al*. Autoimmune encephalitis: a costly condition. *Neurology* 2019; 92(9): e964-72.

Contreras G, Lenz O, Pardo V, *et al*. Outcomes in African Americans and Hispanics with lupus nephritis. *Kidney Int* 2006; 69(10): 1846-55.

Cooray GK, Sengupta B, Douglas P, Englund M, Wickstrom R, Friston K. Characterising seizures in anti-NMDA-receptor encephalitis with dynamic causal modelling. *Neuroimage* 2015; 118: 508-19.

Dalmau J, Tuzun E, Wu H, *et al*. Paraneoplastic anti-N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. *Ann Neurol* 2007; 61(1): 25-36.

Dalmau J, Gleichman AJ, Hughes EG, *et al*. Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. *Lancet Neurol* 2008; 7(12): 1091-8.

Dalmau J, Lancaster E, Martinez-Hernandez E, Rosenfeld MR, Balice-Gordon R. Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. *Lancet Neurol* 2011; 10(1): 63-74.

de Bruijn MAAM, van Sonderen A, van Coevorden-Hameete MH, *et al*. Evaluation of seizure treatment in anti-LGI1, anti-NMDAR, and anti-GABABR encephalitis. *Neurology* 2019; 92(19): e2185-96.

England MJ, Liverman CT, Schultz AM, Strawbridge LM. Epilepsy across the spectrum: promoting health and understanding. A summary of the Institute of Medicine report. *Epilepsy Behav* 2012; 25(2): 266-76.

Fisher RS, Cross JH, D'Souza C, *et al*. Instruction manual for the ILAE 2017 operational classification of seizure types. *Epilepsia* 2017a; 31(4): 282-95.

Fisher RS, Cross JH, French JA, *et al*. Operational classification of seizure types by the International League Against Epilepsy: position paper of the ILAE Commission for Classification and Terminology. *Epilepsia* 2017b; 31(4): 272-81.

Foff EP, Taplinger D, Suski J, Lopes MBS, Quigg M. EEG findings may serve as a potential biomarker for anti-NMDA receptor encephalitis. *Clin EEG Neurosci* 2017; 48(1): 48-53.

Gillinder L, Warren N, Hartel G, Dionisio S, O'Gorman C. EEG findings in NMDA encephalitis: a systematic review. *Seizure* 2019; 65: 20-4.

Gordon-Lipkin E, Yeshokumar AK, Saylor D, Arenivas A, Probasco JC. Comparative outcomes in children and adults with anti-N-methyl-D-aspartate (anti-NMDA) receptor encephalitis. *J Child Neurol* 2017; 32(11): 930-5.

Graus F, Titulaer MJ, Balu R, *et al*. A clinical approach to diagnosis of autoimmune encephalitis. *Lancet Neurol* 2016; 15(4): 391-404.

Grinspan ZM, Shapiro JS, Abramson EL, Hooker G, Kaushal R, Kern LM. Predicting frequent ED use by people with epilepsy with health information exchange data. *Neurology* 2015; 85(12): 1031-8.

Haberlandt E, Ensslen M, Gruber-Sedlmayr U, *et al*. Epileptic phenotypes, electroclinical features and clinical characteristics in 17 children with anti-NMDAR encephalitis. *Eur J Paediatr Neurol* 2017; 21(3): 457-64.

Jeannin-Mayer S, André-Obadia N, Rosenberg S, *et al*. EEG analysis in anti-NMDA receptor encephalitis: description of typical patterns. *Clin Neurophysiol* 2019; 130(2): 289-96.

Kelvin EA, Hesdorffer DC, Bagiella E, *et al*. Prevalence of self-reported epilepsy in a multiracial and multiethnic community in New York City. *Epilepsy Res* 2007; 77(2-3): 141-50.

Leypoldt F, Wandinger K-P. Paraneoplastic neurological syndromes. *Clin Exp Immunol* 2014; 175(3): 336-48.

Liu X, Yan B, Wang R, *et al*. Seizure outcomes in patients with anti-NMDAR encephalitis: a follow-up study. *Epilepsia* 2017; 58(12): 2104-11.

Mohammad SS, Soe SM, Pillai SC, *et al*. Etiological associations and outcome predictors of acute electroencephalography in childhood encephalitis. *Clin Neurophysiol* 2016; 127(10): 3217-24.

Price P, Kobau R, Buelow J, Austin J, Lowenberg K. Improving understanding, promoting social inclusion, and fostering empowerment related to epilepsy: Epilepsy Foundation public awareness campaigns-2001 through 2013. *Epilepsy Behav* 2015; 44: 239-44.

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.

Sonderen A, van A, Arends S, Tavy DLJ, *et al*. Predictive value of electroencephalography in anti-NMDA receptor encephalitis. *J Neurol Neurosurg Psychiatry* 2018; 89(10): 1101-6.

Spatola M, Dalmau J. Seizures and risk of epilepsy in autoimmune and other inflammatory encephalitis. *Curr Opin Neurol* 2017; 30(3): 345-53.

Titulaer MJ, McCracken L, Gabilondo I, *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.

Trinka E, Cock H, Hesdorffer D, *et al*. A definition and classification of status epilepticus: report of the ILAE Task Force on Classification of Status Epilepticus. *Epilepsia* 2015; 56(10): 1515-23.

Viaccoz A, Desestret V, Ducray F, *et al*. Clinical specificities of adult male patients with NMDA receptor antibodies encephalitis. *Neurology* 2014; 82(7): 556-63.

Veciana M, Becerra JL, Fossas P, *et al*. EEG extreme delta brush: an ictal pattern in patients with anti-NMDA receptor encephalitis. *Epilepsy Behav* 2015; 49: 280-5.

Yeshokumar AK, Gordon-Lipkin E, Arenivas A, *et al*. Neurobehavioral outcomes in autoimmune encephalitis. *J Neuroimmunol* 2017; 312: 8-14.

Yildirim M, Konuskan B, Yalnizoglu D, Topaloglu H, Erol I, Anlar B. Electroencephalographic findings in anti-N-methyl-D-aspartate receptor encephalitis in children: a series of 12 patients. *Epilepsy Behav* 2018; 78: 118-23.

Zhang Y, Liu G, Jiang M, Di M, Li LP, Su YY. Analysis of electroencephalogram characteristics of anti-NMDA receptor encephalitis patients in China. *Clin Neurophysiol* 2017; 128(7): 1227-33.

TEST YOURSELF

1. In this cohort, what was a key unifying risk factor for both persistent seizures and status epilepticus?
2. Were focal or generalized seizures seen more commonly in this anti-NMDARE cohort?
3. What sociodemographic concerns were identified in the treatment of anti-NMDARE in this cohort?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".