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SHORT COMMUNICATION

Focal seizures in children with anti-NMDA receptor antibody encephalitis

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Summary
Objective: We investigated the electroclinical features of seizures occurring in children with anti-NMDA receptor antibody encephalitis.
Methods: Clinical features and video EEG recordings were analyzed from pediatric patients with anti-NMDA receptor antibody encephalitis at our center over a six year period.
Results: We identified eight pediatric patients with anti-NMDA receptor antibody encephalitis. Video EEG captured multiple focal seizures in four patients. Ictal onset in all four patients consisted of a focal rhythmic sharpened 6—12 Hz activity that subsequently spread to one or both hemispheres. When there was a clinical correlate, seizure semiology was limb posturing with or without dyscognitive features. While background abnormalities were noted at presentation in three cases, the initial EEG background was normal in five, including three patients presenting with seizures. The EEG background deteriorated with clinical progression.
Conclusions: Focal seizures are common in pediatric patients with anti-NMDA receptor antibody encephalitis and have a characteristic ictal onset pattern. Anti-NMDA receptor antibody encephalitis should be considered in the differential diagnosis of a child presenting with new onset focal seizures, irrespective of the EEG background, especially if accompanied by dyskinesia, psychiatric symptoms or impaired cognition.
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Introduction

Anti-NMDA receptor antibody encephalitis is a neuroinflammatory condition characterized by psychiatric symptoms, seizures, dyskinesia, autonomic instability and impairment of cognition, memory and language (Dalmau et al., 2007). It is a relatively common cause of encephalitis in children (Gable et al., 2012) and optimal management requires

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prompt recognition and immunotherapy (Titulaer et al., 2013).

Seizures occur in over 70% of patients and are often the presenting symptom in children (Armangue et al., 2013; Florance et al., 2009). Previous studies have reported abnormal EEG backgrounds in patients with anti-NMDA receptor antibody encephalitis with findings ranging from focal or generalized slowing to the characteristic ''extreme delta brush'' (da Silva-Junior et al., 2014; Gitiaux et al., 2013; Schmitt et al., 2012). Ictal patterns have not been reported.

Here we provide the first video EEG characterization of seizures in a small cohort of pediatric patients with anti-NMDA receptor antibody encephalitis.

Methods

With approval from the UCSF Institutional Review Board for Human Research, data pertaining to clinical presentation, seizure semiology and electrographic findings were retrospectively obtained from medical records and direct review of EEG recordings of pediatric patients diagnosed with anti-NMDA receptor antibody encephalitis at the University of California, San Francisco between April 2008 and October 2014. Diagnosis was based on detection of CSF anti-NMDA receptor antibody. EEG recordings were obtained using a standard international 10—20 electrode placement in an 18-channel standard recording supplemented with a single electrocardiogram chest electrode and were reformatted digitally into sequential bipolar and referential montages for review. Concurrent continuous video recording was utilized.

Results

Clinical presentation

Eight pediatric cases of anti-NMDA receptor antibody encephalitis were identified. Patient ranged in age from two to seventeen years and included two males (Table 1). Involuntary movements, behavioral disturbances and new onset seizures were common early symptoms. Paroxysmal attacks of unclear etiology were the symptom that first led to contact with providers in five of the patients (patients 2, 3, 5, 6 and 7) with behavioral changes accounting for the other three. There was a wide spectrum of disease severity with four patients having uncomplicated courses not requiring intensive care, two with brief ICU admissions (patients 5 and 7) and two requiring prolonged ICU admissions (patients 3 and 8). All patients received first line immunotherapy with corticosteroids and IV immunoglobulin and patients 2, 3 and 4 also underwent plasma exchange. Second line therapy with Rituximab was given to patients 2, 3, 6 and 8. Patient 8 died during her ICU admission. All other patients for whom follow-up information was available had excellent to full recovery. Of note, children with seizures as part of their clinical course (patients 2, 3, 5, 6 and 7), have remained seizure free at follow-up, including patients 3 and 5, who presented in status epilepticus.

All patients tested positive for anti-NMDA receptor antibodies in the CSF. Other CSF findings are shown in Table 1. Similar to the clinical courses, there was a wide variability in CSF results and no particular study was consistently abnormal with the exception of oligoclonal bands. Imaging was normal or non-specific. Recurrent focal seizures and corresponding left hemispheric enhancement on MRI raised concerns for Rasmussen encephalitis in patient 6 (Fig. 1), echoing the experience of others (Greiner et al., 2011).

EEG background and electroclinical seizures

The EEG background was normal in initial recordings from five patients (Table 1). Background abnormalities noted in the remaining patients consisted of focal or diffuse slowing. Four patients had normal EEG backgrounds at presentation that became increasingly abnormal in correlation with their clinical progression (Table 1: patients 3, 5, 6 and 7; Fig. 2). The extreme delta brush pattern was noted in two of the most severely affected cases (patients 3 and 8).

We recorded multiple focal seizures from four children with anti-NMDA receptor antibody encephalitis (patients 3, 5, 7 and 8). For three patients, there was concern for non-epileptic spells at the time of admission for video EEG monitoring, each having had normal EEGs and having failed appropriate empiric outpatient management for presumed focal seizures (patients 3, 5 and 7). Patients 5 and 7 had actually been diagnosed with psychogenic seizures by providers within the preceding two weeks. Focal seizures were captured shortly following EEG placement in patients 3 and 8, but prolonged periods were recorded without epileptiform discharges in two others (15 h in the case of patient 5 and 60 h in the case of patient 7). In patients 3, 5 and 8 seizures presented as focal status epilepticus. Limb posturing was a semiologic feature in patients 3, 5 and 7, with patients 5 and 7 demonstrating preservation of awareness during their seizures. Patients 3, 7 and 8 had subclinical events. Electrographically, we observed a characteristic ictal onset pattern, consisting of a focal rhythmic activity without clear spikes or sharp waves that subsequently spread to one or both cerebral hemispheres (Fig. 1). This was in the alpha band in patients 3, 5 and 6, but was in the theta band at 6 Hz for patient 7. The seizures emanated from one to two stable foci in individual patients, but these foci differed from patient to patient.

Discussion

We report on the electrographic features of a small cohort of children with anti-NMDA receptor antibody encephalitis. The background EEG was not a sensitive indicator of either the encephalitis or of the propensity for seizures. Many children with anti-NMDA receptor antibody encephalitis first come to medical attention for paroxysmal events concerning for seizure and under such circumstances, a normal EEG background would be falsely reassuring. In this respect, the background EEG is similar to neuroimaging and CSF profile in that normal results do not exclude the condition. The relatively high rate of normal EEG background at presentation in our patients compared to what has previously been reported likely reflects an increased suspicion for this diagnosis earlier in the clinical course owing to improved recognition of the spectrum of presenting symptoms and a lower threshold for testing patients without a full complement of

Table 1 Clinical and electrographic features of a series of pediatric patients with anti-NMDA receptor encephalitis.

Patient	Age (years)/sex	Presenting symptoms	CSF	MRI	EEG background	Seizure characteristics (seizures recorded, ictal onset, clinical features)	Treatments	Clinical course	Last follow-up and outcome
1	9/M	Behavioral, dyskinesia	23 wbc, 32 prot[b]	Diffuse atrophy	Diffusely slow (47 h)	None recorded	Steroids, IVIg	3.5 month inpatient	No information
2	2/F	Seizures, behavioral, dyskinesia	1 wbc, 25 prot[b]	Normal → diffuse atrophy	R Frontal slowing → diffuse slowing (82 h)	None recorded	Steroids, IVIg, PLEX, rituximab	2 month inpatient	1 year from discharge; full recovery
3	14/F	Seizures[a], autonomic → behavioral	9 wbc, 30 prot, IgG index 1.3, >5 OCB	R temporal T2 hyperintensity	Normal → R > L slowing, EDB (1041 h)	Multiple episodes focal status epilepticus; 12—13 Hz, F4 and Cz; L eye/head version, limb stiffening with dyscognitive features or subclinical	Steroids, PLEX, IVIg, rituximab	13 month inpatient, with significant ICU stay	> 2 years from discharge with mild residual neuropsychiatric symptoms seizure free for >2 years; remains on oxcarbazepine
4	14/F	Behavioral, insomnia → dyskinesia	2 wbc, 22 prot, IgG Index 1.6, 1 OCB	Normal	Normal (limited study at outside hospital)	None recorded	Steroids, PLEX, IVIg	1 month inpatient	4 months from discharge had ongoing improvement of oral dyskinesia and neuropsychiatric symptoms, then lost to follow up
5	10/M	Seizures[a] → dyskinesia, behavioral	1 wbc, prot 22, IgG index <0.1, 1 OCB	Normal	Normal → diffusely slow (119 h)	Episode of focal status epilepticus (~28 seizures); 10—12 Hz, C4; L eye/head version, asymmetric tonic posturing without dyscognitive features	Steroids, IVIg	2 weeks inpatient	10 months from discharge with residual psychiatric symptoms seizure free for >10 months; remains on oxcarbazepine
6	17/F	Seizures → behavioral, insomnia, autonomic	311 wbc, 21 prot[b], OP 44 cm H_2O	Meningeal enhancement	Normal → diffusely slow (14 h)	None recorded	Steroids, IVIg, rituximab	3 weeks inpatient	9 months from discharge; full recovery
7	13/F	Seizures[a], dyskinesia → behavioral	10 wbc, 18 prot, IgG index 0.5, 2 OCB	L Parietal enhancement	Normal → focal slowing at P3 (71 h)	7 Focal seizures; 10—12 Hz, P3/Pz; R arm posturing without dyscognitive features	Steroids, IVIg	2 weeks inpatient	No information
8	13/F	Behavioral, autonomic → seizures, dyskinesia	335 wbc, 106 protein, IgG index 0.9, >5 OCB	Patchy subcortical T2 hyperintensities	Diffusely slow, EDB (224 h)	Episode of status epilepticus (~16 seizures); 6 Hz, F7/T3 and F8/T4; subclinical	Oopherectomy, steroids, IVIg, rituximab	3 months inpatient with significant ICU stay	Died during inpatient ICU admission

All patients had positive CSF antibodies to the NMDA receptor. Behavioral symptoms in patients ranged from mood liability to profound psychomotor slowing. Abbreviations: IVIg = IV immunoglobulin; OCB = oligoclonal bands unique to the CSF; EDB = extreme delta brush; PLEX = plasma exchange; OP = opening pressure.

[a] Psychogenic spells were a pre-diagnostic concern.

[b] Oligoclonal bands and IgG index were not sent.

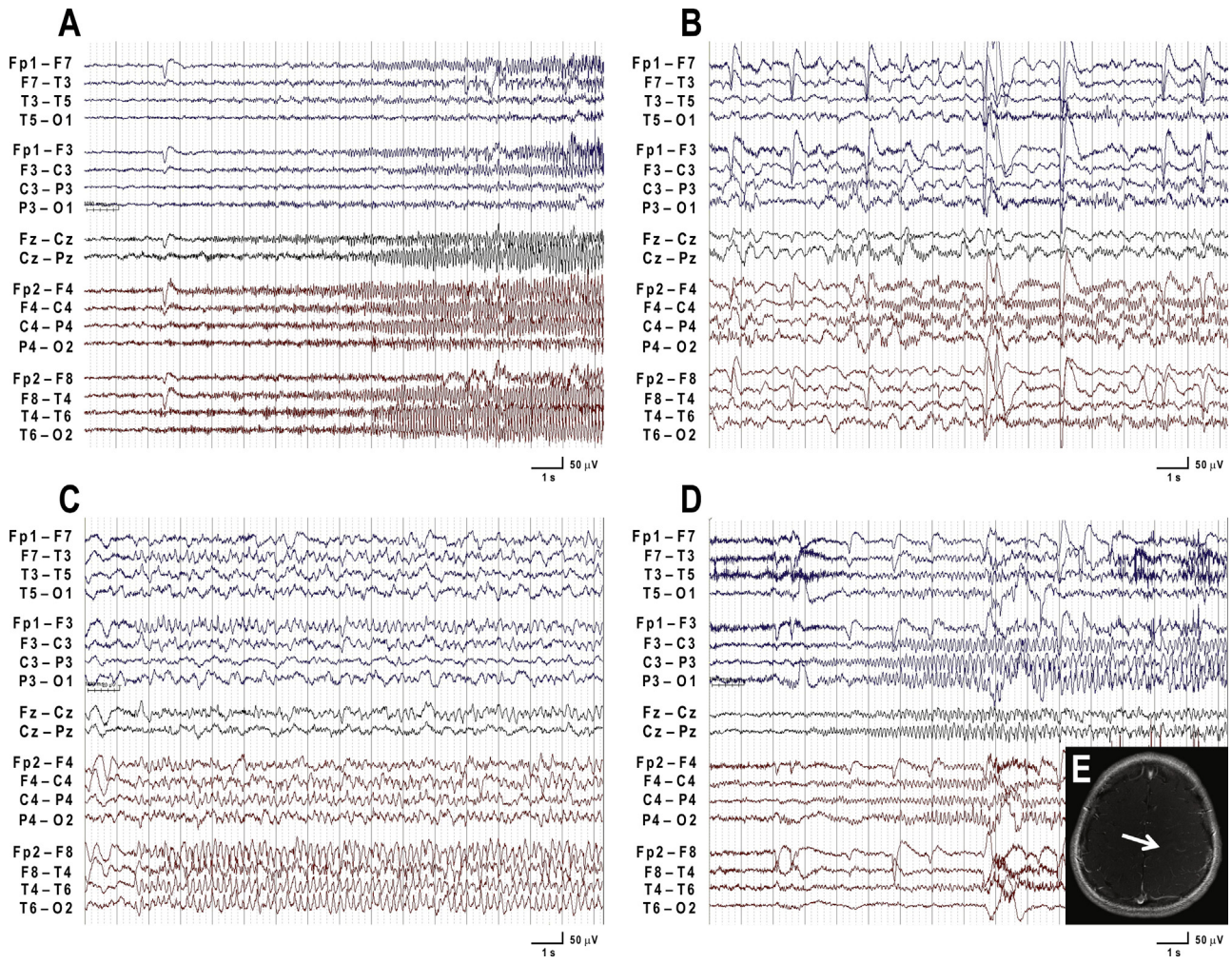

Fig. 1 *Ictal onset in children with anti-NMDA receptor encephalitis.* (A—D) Ictal EEG from four children with anti-NMDA receptor encephalitis, illustrating focal onset of rhythmic sharply contoured 6 to 12 Hz activity ((A) patient 3, F4, 12 Hz; (B) patient 5, C4, 11 Hz; patient 8, F8/T4, 6 Hz; patient 7, P3, 11 Hz). (E) T1 weighted MRI demonstrating post-contrast enhancement over the left cerebral convexity (arrow), corresponding to the site of ictal onset for patient 7 (D).

symptomatology. In support of this hypothesis, we have witnessed EEG background deterioration in conjunction with clinical progression and feel continuous EEG monitoring should be continued until the full spectrum of abnormal movements and/or behaviors have been recorded and accurately characterized.

While it is desirable to diagnose anti-NMDA receptor antibody encephalitis early in its course, our results highlight certain challenges. Strikingly, three of four patients from whom we recorded focal seizures were initially diagnosed or suspected to have psychogenic spells. We attribute this to a combination of factors, all of which we observed in our cohort. Patients may have preservation of awareness with their focal seizures, which can raise skepticism amongst some providers. They may have comorbid involuntary movements that are not convincing for seizure either clinically or on EEG. The interictal EEG may lack epileptiform discharges, the background may be normal, and the seizures may get worse despite escalation of appropriate medical management. Finally, we note that the clinical impression can be colored by the presence of mild behavioral symptoms (e.g. emotional liability).

We found extended inpatient telemetry to be an indispensible tool in the optimal care of this patient population for several reasons. In patients presenting with paroxysmal episodes, it was possible to readily demonstrate ictal activity in some. For others, it demonstrated their non-epileptic spells to be more consistent with an unusual movement disorder than with a psychogenic event and prompted us to continue monitoring and to conduct the lumbar puncture that led to diagnosis. Our cases highlight the importance of keeping anti-NMDA receptor antibody encephalitis on the differential in children referred for evaluation of unexplained movements or psychogenic spells. We recommend monitoring such patients with video EEG to record and evaluate their attacks carefully, as inpatients for several days if necessary to capture a typical event, and suggest having a low threshold to test for CSF antibodies against the NMDA receptor, regardless of the EEG background at presentation.

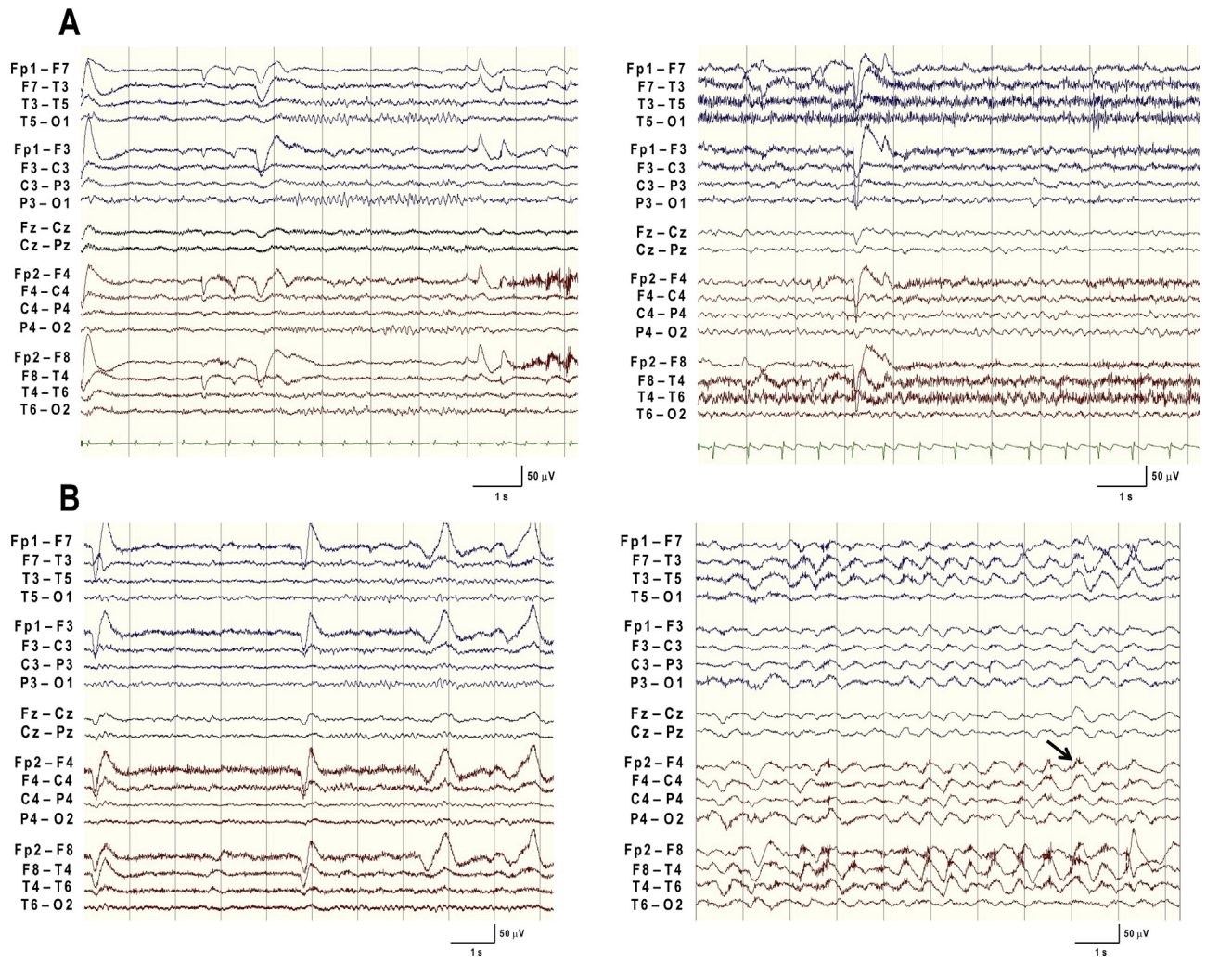

Fig. 2 *Background evolution in children with anti-NMDA receptor encephalitis.* (A and B) EEG background may be normal early in the clinical course (left panels), but deteriorates with progression of disease (right panels). Patient 6 (A) develops a non-specific slowing, while patient 3 (B), acquires more pronounced slowing, including ''extreme delta brush'' (arrow).

Seizures are common in anti-NMDA receptor antibody encephalitis, but the electroclincal features have not previously been described. In our small cohort, we found these seizures to be universally focal in onset. Focal status epilepticus was common and could occur explosively after many hours of recording without interictal discharges. There was a characteristic EEG onset, manifesting as runs of rhythmic 6—12 Hz activity from stable foci within individual patients. The disease is thought to exert its effects through selective disruption of NMDA receptor mediated neurotransmission and this has been shown to result in a reduction in inhibitory synapses (Moscato et al., 2014). Perhaps this reduced inhibitory tone permits the rhythmic oscillations we observed. Our study shares the inherent limitation of any small case series and it will be important to confirm our findings with larger cohorts of pediatric and adult patients.

Conflict of interest statement

None of the authors has any financial conflict of interest to disclose.

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