

Case report

Limbic and new onset refractory tonic status epilepticus (NORSE) in anti-NMDAR encephalitis[☆]Peter W. Kaplan^{a,*}, John Probasco^b^a Johns Hopkins Bayview Medical Center, Johns Hopkins University School of Medicine, USA^b Johns Hopkins Hospital, Johns Hopkins University School of Medicine, USA

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ABSTRACT

Aims: To present a case of anti-NMDA receptor encephalitis (anti-NMDAR) with new onset refractory non-convulsive status epilepticus (NORSE).

Methods: Case report with clinical details, MRI, PET, and EEG illustrations.

Results: New onset refractory status epilepticus (NORSE) may arise from anti-NMDAR, and offers diagnostic and treatment challenges for immuno-therapy and refractory status epilepticus. Non-convulsive status epilepticus with generalized fast activity, has not been reported in anti-NMDAR, in NORSE.

Conclusions: A patient with anti-NMDAR and generalized status with stiffening, right focal weakness, high frequency alpha/beta on EEG, brain FDG-PET/CT changes in the left temporo-parietal regions and cerebellum was presented. We discuss the unique treatment challenges of anti-NMDAR. NORSE and generalized nonconvulsive status epilepticus.

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1. Introduction

Anti-N-methyl-D-aspartate receptor encephalitis (anti-NMDAR) was described in young women presenting with prodromal symptoms of possible viral infection followed by behavioral changes, hallucinations, memory deficits, seizures, coma, and central hypoventilation, many of whom were found to have ovarian teratomas (Vitaliani et al., 2005). The multiple symptoms and neurological findings of anti-NMDAR included diffuse cortical, subcortical and limbic involvement (Titulaer et al., 2013). Limbic encephalitis can result in seizures or status epilepticus (SE) as well as new onset refractory status epilepticus (NORSE) involving frontal or temporal regions, but NMDAR has not been reported to produce generalized fast patterns with focal weakness, numbness and dystonic movements. We present a patient with definite anti-NMDAR per the recent consensus criteria, and NORSE with dystonic seizures. The imaging and EEG abnormalities highlight the cortical areas of refractory ictal involvement.

2. Results – case study

A 29-year-old woman with prior migraines had two-weeks of right leg numbness, right foot “heaviness” and hand clumsiness. Head MRI was normal; over nine days, she had seven episodes of ascending right leg numbness without shaking, weakness or confusion; and three nocturnal convulsions with eye rolling and incontinence. CSF revealed 12 WBCs, glucose 58 mg/100 ml; protein and bacterial screen were normal. Several days later, she was admitted with several weeks’ history of progressive cognitive decline, a “child-like” affect, difficulty reading, emotional lability and intermittent confusion. She had had a ten kilogram weight loss over months, bronchitis a month before, but no recent travel or exposures to animals. Examination showed normal vital signs in an awake, interactive woman with several rightward head turning episodes with gaze deviation, right arm and leg posturing (stiffening), and limb jerking movements. Examination of lungs, heart, abdomen, skin and joints was normal.

Neurological examination showed her to follow simple but not complex commands, have normal naming and repetition, be unable to recall any objects at five minutes, had no visual extinction but did have double simultaneous sensory extinction in the legs. Cranial nerves were normal; motor examination showed no movement of the right leg even to pain; the other limbs were

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normal. There was a normal plantar reflex on the left but the right was equivocal.

The EEG revealed a background of <10 uV diffuse, sparse >20 Hz beta activity with sparse appearance of low voltage alpha and theta activity. The seizures consisted of a gradual increase in voltage of diffuse (15 uV) 10–14 Hz alpha/beta activity for runs of 1–20 s, mostly 5–10 s; occasionally slowing for the last 2–3 s to the 5 Hz theta range. These bursts occurred from one every 20–40 s to mostly up to 20–40 runs per hour. The EEG patterns were associated with worsening of clinical stiffening bilaterally, consistent with tonic status epilepticus (Fig. 1). EEG seizures subsided on the 3rd day of cEEG during ongoing levetiracetam treatment but during the day when lacosamide had been added. EEG following this showed a return of more, low voltage mixtures of alpha, beta and theta frequencies not affected by eye-blinks. Benzodiazepines had been avoided because of concern for tonic status worsening (in the literature). Repeat CSF was negative for CMV, EBV, HSV, VZV, enterovirus, cytopathology/flow, lyme titer, RPR, HIV, anti-dsDNA, ANA, c/p-ANCA, with only one WBC, protein 25; glucose 55. MRI of the brain showed no structural abnormality, or asymmetry of temporal regions (Fig. 2A and B). Chest, abdominal and pelvic CT, transvaginal ultrasound and pelvic MRI were normal. Dedicated brain FDG-PET showed relatively increased left temporo-parietal and right cerebellar activity (Fig. 2C and D), including on three dimensional stereotactic surface projections (Fig. 2E), but with only the right cerebellar brain region hypermetabolism > two SDs abnormal compared to the CortexID healthy control database (GE, Healthcare, Waukesha, WI; Fig. 2F). CSF anti-NMDAR antibody was 1:8 (normal < 1:2), supporting a diagnosis of new-onset refractory status epilepticus (NORSE) due to anti-NMDAR encephalitis. Accordingly, the patient was treated with five days of methylprednisolone, five treatments of plasmapheresis, and because of persistent confusion, with rituximab.

A year later, she had had no further seizures, was weaned off lacosamide and beginning levetiracetam wean. She was able to perform activities of daily living, and is returning to work.

3. Discussion

The patient had a recent history of generalized seizures, rapidly progressive cognitive decline, emotional lability, a child-like affect, intermittent confusion, focal sensory-motor leg weakness, and a CSF pleocytosis, followed by dystonic (stiffening) limb seizures. There were imaging abnormalities using dedicated brain FDG-PET in appropriate contralateral temporo-parietal and ipsilateral cerebellar regions (with the ipsilateral cerebellum two standard deviations abnormal relative to a control population). The EEG showed continuous high-frequency discharges supportive of a diagnosis of the tonic phase of status epilepticus (Fig. 1) in the setting of anti-NMDAR antibody positive CSF (with other encephalitides having been excluded). With a diagnosis of anti-NMDAR encephalitis, she underwent multiple immunosuppressive treatments with improvement to independence in activities of daily living, regression of seizures and reduction in anti-seizure medications.

About 70% of patients with anti-NMDAR develop seizures (Titulaer et al., 2013). A review of EEG patterns in limbic encephalitis revealed the commonest abnormalities to be slow theta and delta activity predominantly in the temporal and frontal regions (Kaplan and Sutter, 2013), and EEG of anti-NMDAR patients may demonstrate focal slowing, diffuse slowing, or disorganized activity in addition to epileptic activity and an *extreme delta brush* pattern in ~1/3rd of patients (Schmitt et al., 2012).

The clinical characteristics of LE and limbic status epilepticus (LSE) share much overlap, and a non-epileptiform EEG pattern may appear at the scalp surface even as recording from deeper structures reveals ongoing LSE (Kaplan et al., 2011; Wieser et al., 1985).

Anti-NMDAR also occurs with teratomas, sex-cord stromal tumors, Hodgkin's disease and neuroendocrine tumors (Nabbout et al., 2011; Wieser et al., 1985). For anti-NMDAR, epileptic activity occurs in about ¼ (Dalmau et al., 2008). In those patients who evolve to SE, there may be prolonged ICU stays with almost half having MRI changes, 90% with abnormal EEG changes and CSF typically showing a pleocytosis (Titulaer et al., 2013). Our patient

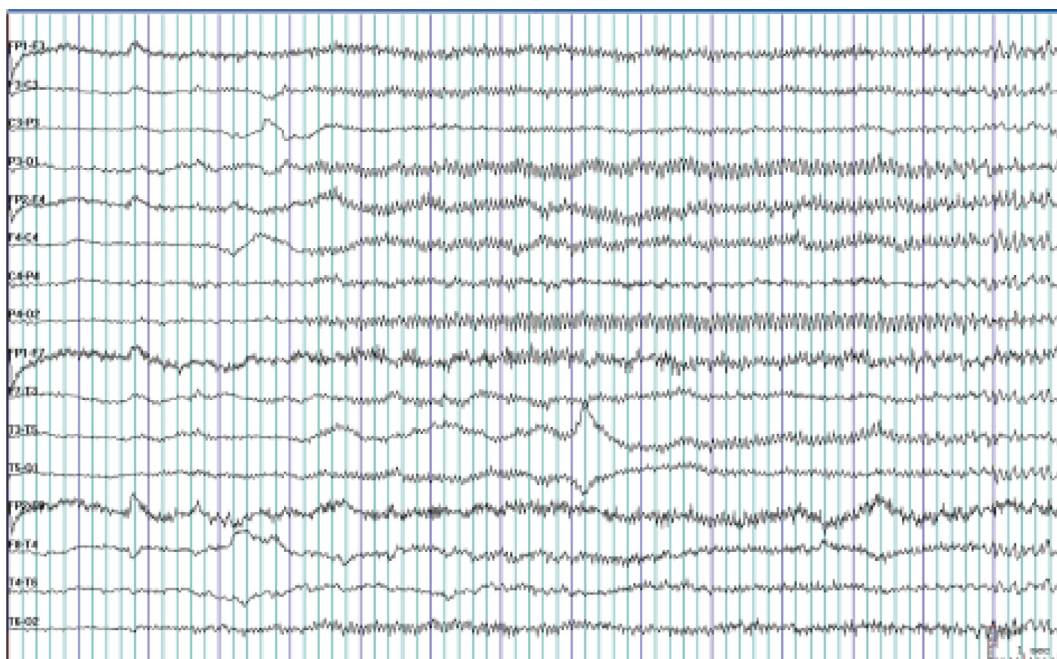


Fig. 1. High frequency diffuse beta activity with progressively increasing amplitude, typical of the tonic phase in status epilepticus, was associated in this patient with dystonic posturing and then limb numbness and paralysis.

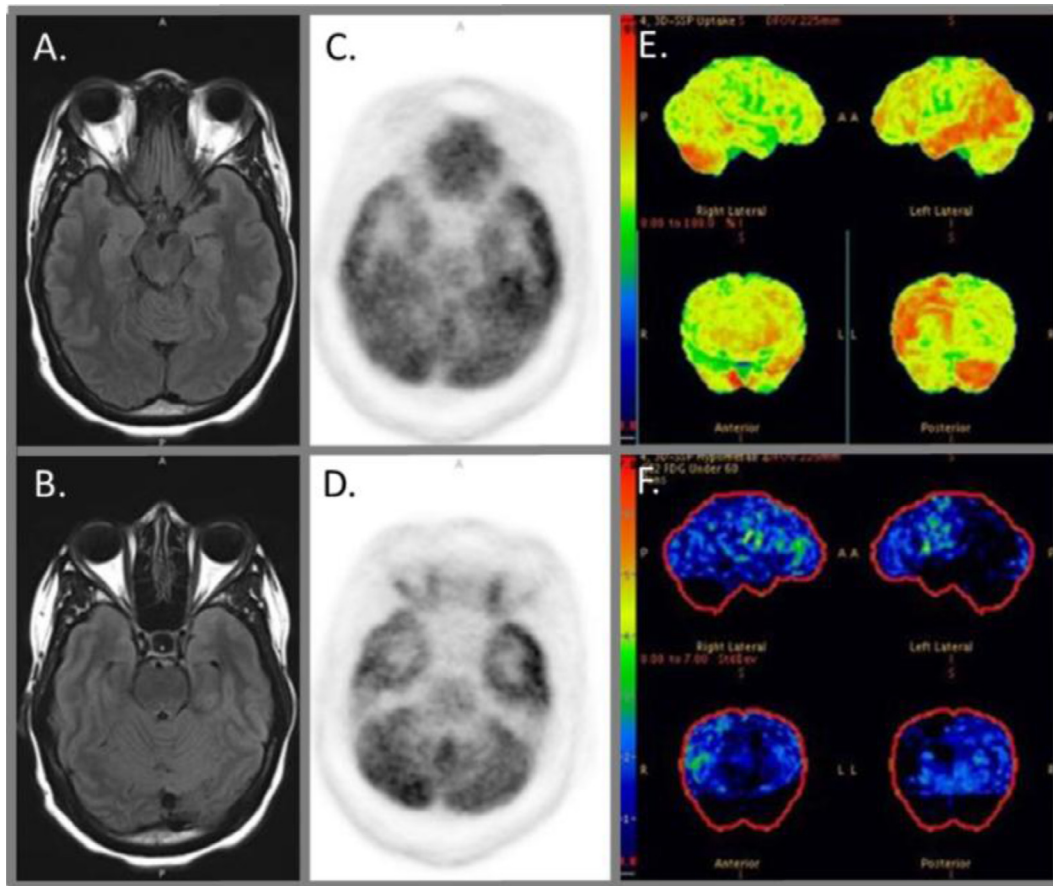


Fig. 2. MRI FLAIR sequences demonstrating normal mesio-limbic temporal regions (A and B), with relative hypermetabolism in the left temporoparietal cortex and right cerebellum qualitatively on -inverted dedicated brain FDG-PET/CT images (C and D) and three-dimensional statistical mapping (3D-SSP, E) but with only right cerebellum regional hypermetabolism greater than two standard deviations elevated compared to the Cortex ID (GE, Healthcare, Waukesha, WI) control population (F).

also had behavioral and cognitive/psychiatric changes that can be seen in the majority of patients (Nabbout et al., 2011), with a psychosis attributable to changes in NMDA receptor activity. Anti-NMDAR presents with partial or generalized seizures more frequently in men (Spatola and Dalmau, 2017), although the entity is commoner in women, but SE in particular, occurs in a minority of those with anti-NMDAR. Nonetheless, EEG appears ineffective in differentiating autoimmune etiologies of seizures from those without (Baysal-Kirac et al., 2016). SE in anti-NMDAR is reportedly difficult to control, and often requires, in succession, benzodiazepines, non-sedating second line AEDs (phenytoin, valproate levetiracetam, lacosamide), even progressing in some cases, to 3rd line anesthetic agents. Meanwhile, the patient is often treated with a succession of immunotherapies, including steroids, PLEX, IVIG and rituximab. Nonetheless, about 70% may be successfully improved (Byun et al., 2016). Continuous EEG may be extremely helpful in diagnosing intermittent seizures, identifying SE and in monitoring the effects of treatment in obtunded patients. The risk for chronic epilepsy appears to be <15%.

Regarding this patient's particular EEG pattern and dystonic seizures, the diffuse high-frequency beta activity accompanying the tonic phase during status epilepticus (and in this patient, right body paralysis) is rarely if ever reported in adults, and rarely appears *de novo*. Some features of this clinical pattern may occur in LGI1 limbic encephalitis (Andrade et al., 2011). Of note, tonic status epilepticus may worsen with benzodiazepines, further complicating NORSE management. NORSE presents clinical and diagnostic challenges, with strategies directed at potential infectious causes. Paraneoplastic and autoimmune causes are those most frequently found with anti-NMDAR being the commonest

identified (Gaspard et al., 2015). NORSE patients often have poor functional outcome (>3 modified Rankin Scale), but newer management approaches may portend improved prognoses.

4. Summary

A patient with anti-NMDAR presented with seizures, and new onset refractory dystonic seizures and status epilepticus (NORSE). Tonic status epilepticus is rarely recognized in either NORSE or anti-NMDAR, and in our patient, was correlated with high frequency alpha/beta activity on EEG, left temporo-parietal, and cerebellar FDG-PET/CT increased uptake. Treatment of encephalitis and dystonic seizures resulted in gradual improvement over 1 year.

Disclosures

No conflicts of interest regarding the case report and topic.

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