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Case Report

## Anti-NMDA Receptor Encephalitis and PET-MRI

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### Introduction

Recent recognition of specific clinical presentations and autoimmune attack of the central nervous system has furthered our understanding of the previously mysterious mixture of psychiatric and neurological symptoms where diagnosis was delayed [1,2]. Patients with anti-N-methyl-d-aspartate (anti-NMDA) encephalitis typically present with prominent psychological behaviors such as hallucinations, hyper-religiosity, aggression, catatonia, and insomnia [3,4] in addition to characteristic neurological features including seizures, autonomic instability, hypoventilation and movement disorders [5,6]. The presence of serum or cerebrospinal fluid anti-NMDA receptor antibodies confirms the diagnosis but approximately 15% of patients have only positive cerebrospinal fluid [7]. Antibody detection should prompt a search for an underlying teratoma or other neoplasm [8]. As suggested by Dalmau and colleagues, immunosuppressant therapy should also be initiated with methylprednisolone, intravenous immunoglobulin, plasmapheresis or a combination of these as the disorder is often responsive to these methods [9]. Findings on electroencephalogram (EEG) typically include focal slowing, or extreme delta brush [10]. Moreover, de novo status epilepticus and refractory epilepsy have also been associated with this disorder [11,12]. Case reports have demonstrated frontotemporal atrophy as well as hypoperfusion on MRI and SPECT during maximal neurologic disability with dramatic improvement five years later which correlated with better cognitive function [13]. PET-MRI offers greater resolution, better anatomic localization, and enhanced functional imaging compared to PET-CT (positron emission tomography-computed tomography) [14]. A case of anti-NMDA receptor encephalitis requiring multiple diagnostic techniques including EEG, MRI, SPECT (single photon emission computed tomography), and PET-CT in which PET-MRI helps define the complexity of ictal and interictal seizure activity is described.

### Case Report

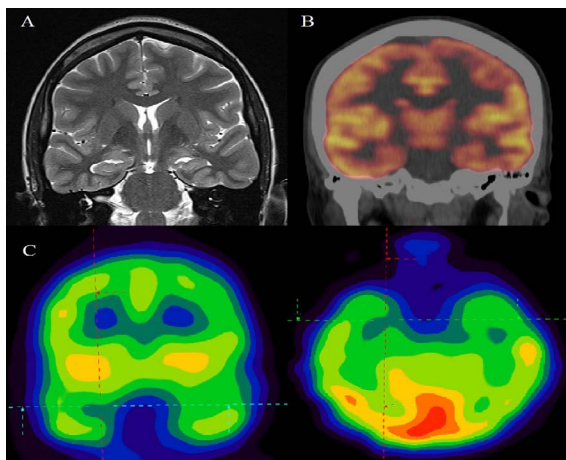
A 28-year-old female with a past medical history of epilepsy presented with 8-9 breakthrough seizures. These were described as head turning to the right, eyes rolling backward and unresponsiveness, followed by a generalized tonic-clonic

movements for two minutes. The post-ictal period lasted for approximately 25 minutes. Her epilepsy began six years prior and was extensively evaluated (MRI and EEG were reported as normal). She remained on an antiepileptic drug (unspecified) for seven months without any seizure activity. One month prior to this presentation, she was started on levetiracetam

500mg twice daily with an increase to 1000mg twice daily for increased seizure activity. There was concern that the seizure activity may have been associated with recent herbal medication use. She was admitted for video EEG monitoring which captured two right hemisphere electrographic seizures with minimal clinical correlate. Levetiracetam was increased to 1500mg twice daily with addition of lamotrigine using a slow titration to 100mg twice daily.

She returned within five days of discharge with further seizures. Video EEG again captured multiple right central parietal temporal electrographic seizures. In the interim, she became combative, aggressive and psychotic. Two additional antiepileptic medications were initiated (i.e. phenytoin and lacosamide) and levetiracetam was ceased. Repeat MRI brain and cerebrospinal fluid studies were unremarkable. She was readmitted within the same week with behavioral abnormalities including aggression, psychosis with auditory hallucinations, religiosity, inability to maintain personal hygiene, psychomotor retardation, and insomnia. EEG revealed bilateral rhythmic slowing but no electrographic correlate with her behavioral outbursts. Serum NMDA-receptor antibodies soon returned as positive. Therefore, she was provided with intravenous immunoglobulin therapy, plasma exchange and methylprednisolone 1000mg daily for five days. She improved markedly shortly afterwards.

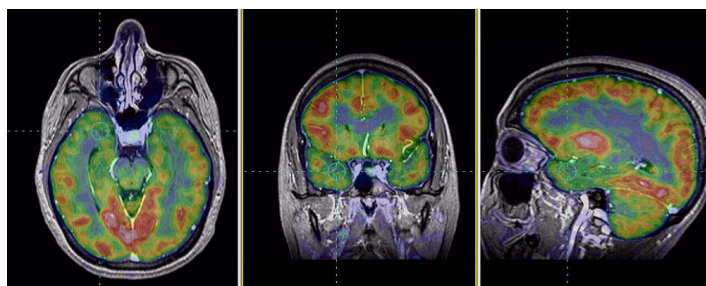
Evaluation for malignancy was negative including mammogram, CT chest/abdomen/pelvis, Papanicolaou smear, and intravaginal pelvic ultrasound. In view of continuous bilateral rhythmic slowing on EEG, SPECT-CT and PET-CT were performed. SPECT-CT showed decreased uptake in the left frontal, parietal, and superior temporal lobes. PET-CT displayed hypometabolism in the left temporoparietal region. These findings were in keeping with an ictal focus in the left temporoparietal region (Figure 1). She was discharged on lamotrigine, lacosamide, clonazepam, and quetiapine.



**Figure 1.** Imaging results during psychiatric behavior abnormalities due to anti-NMDA receptor encephalitis. A) MRI shows no structural abnormality. B) Hypometabolism in left temporoparietal region on

PET. C) SPECT demonstrated decreased uptake on left frontal, parietal, and superior temporal lobes.

During routine clinical review, aside from mild cognitive impairment, her marked clinical recovery persisted. Therefore, clonazepam and quetiapine were discontinued. At this time, there existed a discrepancy between right hemispheric seizure activity on EEG and SPECT/PET demonstrating interictal hypoperfusion/hypometabolism in the left temporal region. Simultaneous PET-MRI showed decreased uptake in the right mesial temporal lobe consistent with the ictal focus evident on EEG (Figure 2). In retrospect, it is likely that the apparent decreased perfusion/metabolism on the left seen on nuclear imaging studies was not an interictal finding. Rather, it reflected the asymmetrically increased perfusion/metabolism on the right.



**Figure 2.** Simultaneous PET-MRI following treatment and recovery displays decreased uptake in right mesial temporal lobe.

## Discussion

Our NMDA receptor encephalitis case report again demonstrates typical findings of psychological behaviors including altered mental status, insomnia, and agitation without any prior psychiatric history [1-4]. Despite a prior history of seizures in our patient, complete remission occurred for multiple years without antiepileptic treatment. Subsequently, recurrent seizure with de novo psychosis was likely due to NMDA receptor encephalitis rather than reactivation of her seizure disorder. Initial EEG monitoring showed right temporoparietal focal ictal activity that resolved with adequate antiepileptic drug use. Diffuse rhythmic slowing was only observed when she returned with sustained altered mental status. Continuous EEG monitoring typically reveals focal abnormalities when clinical seizure activity is apparent but may only show non-specific findings of global dysfunction such as diffuse slowing when cognitive deficits alone are observed [15]. In our case, there was some confusion regarding the underlying etiology of her continued altered mental status as her initial work up including MRI and CSF profile were unremarkable but results of other diagnostic studies were pending. Rhythmic slowing without clear evolution on EEG was considered to likely represent an interictal finding. Nevertheless, the rhythmic slowing could also be due to atypical non-convulsive status epilepticus, which led to additional studies utilizing nuclear medicine techniques. PET and SPECT performed in a subset of patients with

T2-hyperintensity on MRI related to status epilepticus associated with paraneoplastic autoimmune encephalitis demonstrated increased perfusion and metabolism overlapping the inflammatory lesions [16]. Complete resolution of abnormal SPECT and FDG-PET findings in addition to atrophy identified on MRI have occurred with prompt and adequate immunosuppressive therapy [13]. Neuroimaging findings in autoimmune encephalitis are inconsistent with MRI results ranging from normal to both hyperintense signal in limbic areas as well as extra limbic involvement. This heterogeneity in imaging may be due to the cellular localization of target antigens of the autoantibodies. Autoantibodies against intracellular antigens were associated with mesiotemporal abnormalities, while autoantibodies against surface antigens were more often associated with either normal findings or abnormalities outside the mesiotemporal region [17]. Our initial findings were difficult to interpret without having a prior baseline of nuclear medicine studies. However, retrospective analysis of SPECT and PET results revealed that the hyperdynamic/hypermetabolic activity over the right temporal lobe was consistent with the ictal focus on the prior EEG as opposed to an interictal finding of decreased perfusion/metabolism on the left. To our knowledge, this is the first case to demonstrate the correlation of ictal SPECT and PET-CT with interictal PET-MRI which clarified the initially conflicting results from imaging and electrographic data. Our study supports the implication that simultaneous PET-MRI offers particular advantages with spatial and temporal correlation of a measured signal [14]. Furthermore, detection of epileptogenic foci may also occur with simultaneous studies if the MRI brain is negative or there are several possible structural abnormalities. By improving in vivo assessments utilizing changes in hemodynamics [18], specific application in neuropsychiatric abnormalities such as autoimmune encephalitis may prove invaluable.

## Conclusion

Ictal-interictal SPECT and interictal PET-CT are useful in detecting an epileptogenic focus but rely on the occurrence of seizure activity. We report on the usefulness of PET-MRI imaging in the detection of an ictal focus missed on SPECT/PET-CT. We propose that PET-MRI may provide valuable information regarding seizure foci in patients with conflicting EEG and traditional nuclear medicine imaging modalities. Moreover, negative baseline cerebral MRI does not preclude the use of MRI-PET in detecting epileptogenic foci.

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