F-18 FDG Brain PET in a Para-Neoplastic Syndrome Patient with Anti NMDA Receptor Encephalitis

Devrim Ersahin and Ming-Kai Chen*

Department of Diagnostic Radiology, Yale University School of Medicine, New Haven, CT, USA

Introduction

The encephalitis associated with antibodies (Ab) against the N-Methyl-D-Aspartate Receptor (NMDAR) was first discovered in 2007 [1]. Since then, there have been several reports on clinical features and diagnostic tools for better understanding the pathophysiology of this disease. Magnetic Resonance Imaging (MRI), Magnetic Resonance Spectroscopy (MRS), Electroencephalogram (EEG), Fluoro-2-Deoxy-D-Glucose Positron Emission Tomography (FDG PET), and Single Photon Emission Computed Tomography (SPECT) with 99mTc-D,L-Hexamethyl-Propyleneamine Oxime (HMPAO) have shown a variety of abnormal findings but with no conclusion of characteristic features. High serum Ab titer for NMDA receptor and abnormal Cerebrospinal Fluid (CSF) evaluation are present in majority of the patients [2] and have been the diagnostic standard. However, non-invasive imaging diagnostic evaluation of this syndrome has not been established yet.

The prior case reports on F-18 FDG PET findings of patients with NMDAR encephalitis so far have demonstrated variable regional abnormal glucose metabolism in the brain parenchyma [3-7]. We are presenting a characteristic patient with NMDAR encephalitis showing abnormal regional F-18 FDG PET uptake of the brain.

Case Report

Our patient is a 33 year-old female who was diagnosed with NMDAR encephalitis associated with right ovarian teratoma. She was a healthy female before the onset of disease with only anxiety disorder. She presented to the Emergency Department (ED) on March 7, 2012 with headache, fatigue, myalgia, and cough for four days. She was initially thought to have a viral illness and was given lorazepam for anxiety. She returned to the ED the following day with confusion. Her family stated that she was acting “crazy” and didn’t know who people were. According to the clinical notes obtained, she was “agitated and psychotic”. She was then transferred to a psychiatric unit of another institution and was started on risperidone. Her mental status deteriorated gradually and she became more lethargic. She was taken back to ED and was noted to have trismus upon arrival. She was given intravenous benzotropine and flumazenil with immediate improvement in her mental status. However, 30 minutes later she was noted to have a generalized tonic-clonic seizure. She was intubated for airway protection and admitted to the medical intensive care unit. Initially, she was started on levetiracetam and phenytoin for continuing seizure protection and admitted to the medical intensive care unit. Initially, she was started on rituximab and cyclophosphamide as second line treatment.

A CT scan of the chest, abdomen, and pelvis was obtained as part of para-neoplastic syndrome evaluation and it showed a right ovarian mass, which was resected in April 2012. Pathologic evaluation of the mass confirmed the diagnosis of benign teratoma. The patient had several medical problems after the surgery, including gastrointestinal bleeding from gastric ulcer, episodes of hypernatremia, pseudomembranous colitis, dysautonomia, skin rash, and several episodes of various types of infection (i.e. soft tissue infection at the G-tube insertion site, central line infection, and Methicillin-sensitive Staphylococcus Aureus pneumonia). Her neurological symptoms persisted without any improvement after surgery. She was transferred to Yale New Haven Hospital for further medical care. At the time of admission, her neurologic examination revealed infrequent oculogyric movements, frequent oral dysskinetic movements with no gaze deviation. She had frequent movements of extremities and no movement to noxious stimuli. Her deep tenden reflexes were brisk throughout. She did not show significant improvement throughout her hospital stay and in May 2012, she underwent left oophorectomy for the possibility of microscopic teratoma on that side with no abnormality found on histopathological evaluation. Evaluation of her serum revealed positive NMDAR antibodies and evaluation of her teratoma for the same antibody was confirmed.

Figure 1: MRI images of FLAIR sequence in axial planes showed hyper intense signal in bilateral medial temporal lobes.

*Corresponding author: Ming-Kai Chen, Yale School of Medicine, 333 Cedar St, New Haven, CT 06520, USA, E-mail: ming-kai.chen@yale.edu

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Due to significant mental status alterations and seizures, she was referred for evaluation with F-18 FDG PET-CT of the brain in November 9, 2012. F-18 FDG PET-CT showed significant hypometabolism in bilateral occipital lobes and post central gyri as well as parietal lobes as well as parietal lobes (Figures 2 and 3). She also underwent a whole body F18-FDG PET-CT 3 weeks later, which was unremarkable. The brain portion of the whole body PET-CT demonstrates persistent hypometabolism in bilateral occipital lobes and persistent hyper metabolism in parietal lobes, but interval improvement or significantly decreased uptake of prior bilateral frontal and temporal hyper metabolism, (Figure 4 for the brain portion of the whole body scan).

Unfortunately, the patient has struggled with multi-organ failure during the prolonged admission and abdominal compartment syndrome. She died in February 2013.

Discussion

The encephalitis associated with NMDAR was first discovered in 2007 [1] and since then, a few case reports have been published [1-6]. It is most commonly seen in young women with akinetic mutism, refractory seizures, abnormal movements, and autonomic signs [2,8]. In approximately 60% of patients, clinical workup may reveal teratoma, which the patient presented here also had [2,8]. Our patient is a young female who initially presented with “viral-like” prodromal symptoms and had changes in her mental status. She eventually showed psychotic behaviors, which gradually evolved into lethargic state and she also developed seizures. This pattern of disease evolution has been reported in several publications [1-6,8].

Brain MRI is unremarkable in half of patients, and the other half might show T2 or FLAIR signal hyper intensity in the hippocampi, cerebellar or cerebral cortex, fronto-basal and insular regions, basal ganglia, brain stem, and, infrequently the spinal cord [3,9,10]. Our patient had several MRI evaluations since her initial presentation. Initially she had subtle increased T2 and FLAIR signal abnormality within bilateral medial temporal lobes (including the uncus and hippocampi), right greater than left. These findings improved significantly over time and the most recent brain MRI on November 6, 2012 was demonstrating interval improvement of high Flair and T2 signal involving medial portion of the bilateral temporal lobes with atrophy of bilateral hippocampi and cerebral hemispheres.

F-18 FDG PET-CT of the brain has been used in diagnostic workup of some patients with encephalitis associated with NMDAR. Case reports so far have demonstrated areas of abnormal glucose metabolism in several areas of the brain. In a case report by Iizuka et al.
[3] patient had symmetric hyper metabolism in the frontal cortex; findings from follow-up F-18 FDG PET study during convalescence were normal. The patient reported by Maeder-Ingvar et al. had 3 PET-CTs over the course of her disease. These studies showed a striking bilateral increase of the basal ganglia metabolism during sub-acute phase. Subsequently, a follow-up scan demonstrated a relative diffuse cortical decreased uptake during the recovery phase. Eventually, the diffuse cortical hypo metabolic pattern was normalized with a similar metabolic activity in both basal ganglia and cerebral cortex [7]. Other studies also demonstrated abnormal findings in localized areas of the brain or sometimes generalized decreased metabolism [3-7]. In addition, Leypoldt et al. reported a small retrospective study of six NMDAR encephalitis subjects and summarized a characteristic pattern of FDG uptake in the brain with hyper metabolism in both frontal and temporal cortices and hypo metabolism in occipital cortices. They also reported the utility of ratios of front-o-temporal to occipital cortices, which correlated well with clinical severity [11]. Two of the subjects had follow-up PET scans which demonstrated normalization of abnormal FDG uptake as well as decreased front-o-temporal to occipital ratios. The authors concluded that the pattern of FDG uptake in brain as a result of NMDAR deficits, similar to the patients who received NMDAR antagonists such as ketamine [11].

Our patient had significant hypo metabolism in bilateral occipital lobes and post central gyri as well as relative hyper metabolism in bilateral frontal, temporal, and even parietal lobes, consistent with the characteristic feature from the retrospective study [11]. We did not observe increased uptake in the basal ganglia. It is reasonable to assume that the differences in abnormal F-18 FDG uptake in the brain in previous case reports might be due to imaging being performed at different stages of the disease. In this case report, hyper intense FLAIR in medial temporal lobes in early MRI study may represent earlier sub-acute encephalitis phase and is consistent with previous case reports. The later FDG PET brain demonstrated characteristic regional hypo metabolism might represent sequela of encephalopathy with NMDAR impairment. From previous reports and our case experience, it appears that the NMDAR encephalitis has a hypermabolic phase reflecting an inflammatory process in the early phase. The regional hyper metabolism is mostly seen anteriorly in temporal and frontal cortices [11] and even parietal lobes and basal ganglia. The follow up PET scan of the subject demonstrated normalization of front of temporal hyper metabolism but persistent occipital hypo metabolism. The characteristic hypo metabolism of bilateral occipital lobes may represent a consequence of NMDAR impairments in late stage. The pattern of occipital hypo metabolism may last for a long time if no recovery from encephalitis such as in our patient. Serial PET studies during the entire course with pathologic correlation are needed to better understand the disease process.

In conclusion, we present a case of anti-NMDA receptor encephalitis with characteristic feature of occipital hypo metabolism and relative hyper metabolism in frontal, temporal, parietal cortices in the FDG PET brain scan. This regional metabolic feature is believed to be somehow unique in this disease and may provide useful clinical diagnostic value.

References