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Novel FDG-PET Findings in Anti-NMDA Receptor Encephalitis: A Case Based Report

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Abstract

The clinical manifestation and nuclear imaging findings in a 15-year-old boy with anti-*N*-methyl-D-aspartate receptor (NMDAR) encephalitis are described in this case report. The previously healthy patient presented with new onset hallucinations, seizure, and within a week, his mental status rapidly deteriorated to nonverbal with oro-lingual-facial dyskinesias. An extensive laboratory work-up for encephalopathy was negative. Repeated brain magnetic resonance imaging (MRI) studies were normal. On day 26 of admission, nuclear imaging using fluorodeoxyglucose positron emission tomography (FDG-PET) showed global hypometobolism with a prominent focally intense hypermetabolic lesion in the right cerebellar cortex. Diagnosis of anti-NMDAR encephalitis was confirmed with quantitative serology. The patient showed clinical signs of improvement after 2 courses of intravenous immunoglobulin therapy over 4 weeks. On day 46, repeat brain FDG-PET showed overall improvement but in contrast to the previous, the right cerebellar cortex showed focal hypometabolism. This is the first reported case of such findings using FDG-PET in anti-NMDAR encephalitis.

Keywords

anti-NMDAR encephalitis, fluorodeoxyglucose positron emission tomography, NMDAR encephalitis, glucose hypermetabolism, glucose hypometabolism

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Anti-*N*-methyl-D-aspartate receptor (NMDAR) encephalitis is an immune-mediated encephalitis within the broad category of paraneoplastic encephalitides. However, unlike classic paraneoplastic encephalitis, anti-NMDAR encephalitis affects younger patients, is often treatable, and may or may not have an associated neoplasm.[1] Most patients are young women (14-44 years) who present with a sudden onset of severe schizophrenia-like symptoms including catatonia, auditory, and visual hallucinations. There is a rapid decline in mental status as well as autonomic instability, decreased consciousness, oro-lingual-facial dyskinesia, choreoathetosis, and new onset seizures. Anti-NMDAR encephalitis is often associated with ovarian teratoma.[2] Treatment includes tumor removal and immunotherapies, with a slow and variable response.[1-5] On presentation, most patients in the pediatric population have nonspecific diagnostic findings including normal brain magnetic resonance imaging (MRI), cerebrospinal fluid (CSF) with lymphocytic pleocytosis or oligoclonal bands, and slowed disorganized activity on electroencephalography (EEG) not correlating with the abnormal movements.[3] Although young males can have anti-NMDAR encephalitis, there are no reports of tumors being discovered in any males under the age of 18 years to date.[3]

Currently, the diagnosis of encephalitis secondary to anti-NMDAR can be made only after infection (notably herpes simplex virus), paraneoplastic (limbic encephalitis), and autoimmune etiologies are excluded. There is only 1 diagnostic test to confirm cases of anti-NMDAR encephalitis that uses 3 immunohistochemical quantification techniques to confirm the presence of autoantibodies to the NMDA receptor.[2]

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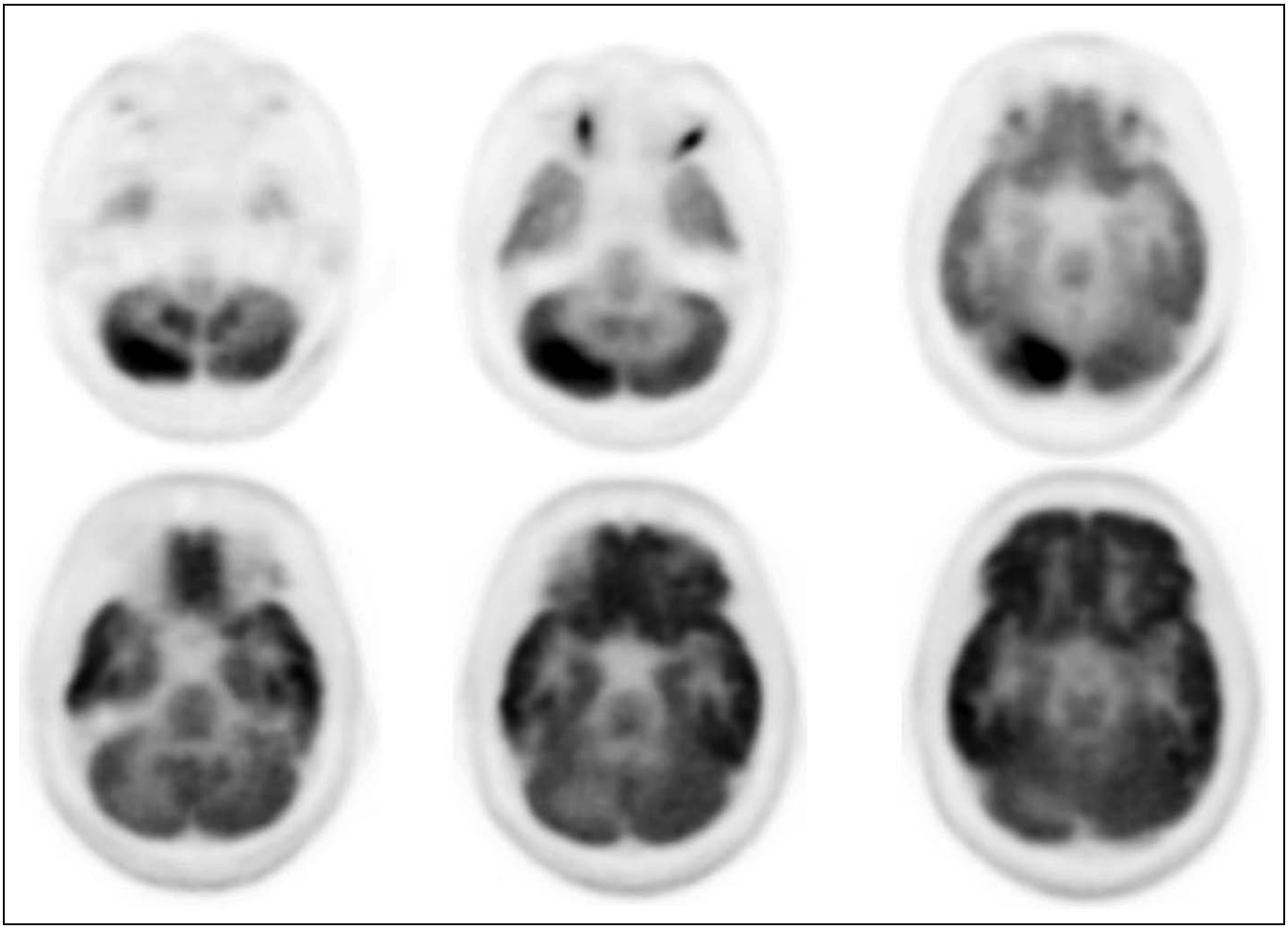

Figure 1. FDG-PET scan. Top row: focal intense hyper-metabolism in right cerebellar cortex and diffuse hypo-metabolism of bilateral cerebral hemispheres. Bottom row: focal hypo-metabolism in the right cerebellar cortex, corresponding with the initially hyper-metabolic region.

Conventional brain imaging studies on anti-NMDAR encephalitis patients are frequently normal and nondiagnostic. However, we report a case of anti-NMDAR encephalitis with unique glucose metabolism using fluorodeoxyglucose positron emission tomography (FDG-PET).

Clinical Course

A 15-year-old African American male presented with new onset visual and auditory hallucinations, and had 2 witnessed generalized tonic-clonic seizures during admission to a community hospital. Past medical history revealed a diagnosis of attention-deficit hyperactivity disorder (ADHD) at the age of 12 years. During initial presentation, the patient had slurred speech that rapidly deteriorated to incomprehensible babble to mutism within the first 2 weeks of admission. Initial diagnostic imaging included brain MRI and computed tomography (CT) were normal and EEG showed generalized disorganization. The patient remained afebrile and with a normal white blood cell count. However, at the time, index of suspicion was high for meningitis secondary to infection and started on prophylactic broad-spectrum antibiotics and acyclovir. Analysis of the CSF revealed 61 nucleated cells (92% lymphocytes, no neutrophils) with a normal protein (20 mg/dL) and glucose (57 mg/dL). Infectious work up on the CSF included bacterial, fungal, and viral culture, as well as polymerase chain reaction (PCR) testing for herpes simples virus type 1 and 2 (HSV1 and HSV2)—all were negative. Patient became increasingly agitated and received risperidone and chlorpromazine for aggressive behavior.

On day 4, the patient was transferred to Children's Hospital of Michigan in Detroit. On admission evaluation, it was noted that he had a flat affect and gave single word responses. The patient also had choreoathetoid movements on his left side. A full encephalitis infectious disease work up was performed, including a repeat PCR of HSV1 and HSV2 in the CSF, which remained negative. In addition, the CSF was analyzed for antibodies to known potential viral causes of encephalitis (West Nile virus, cytomegalovirus, etc) as well as serum anitbodies (Lyme, hepatitis panel, rapid plasma reagin, human immunodeficiency virus [HIV], etc)—all serological studies and cultures were negative. The only notable exception was a positive

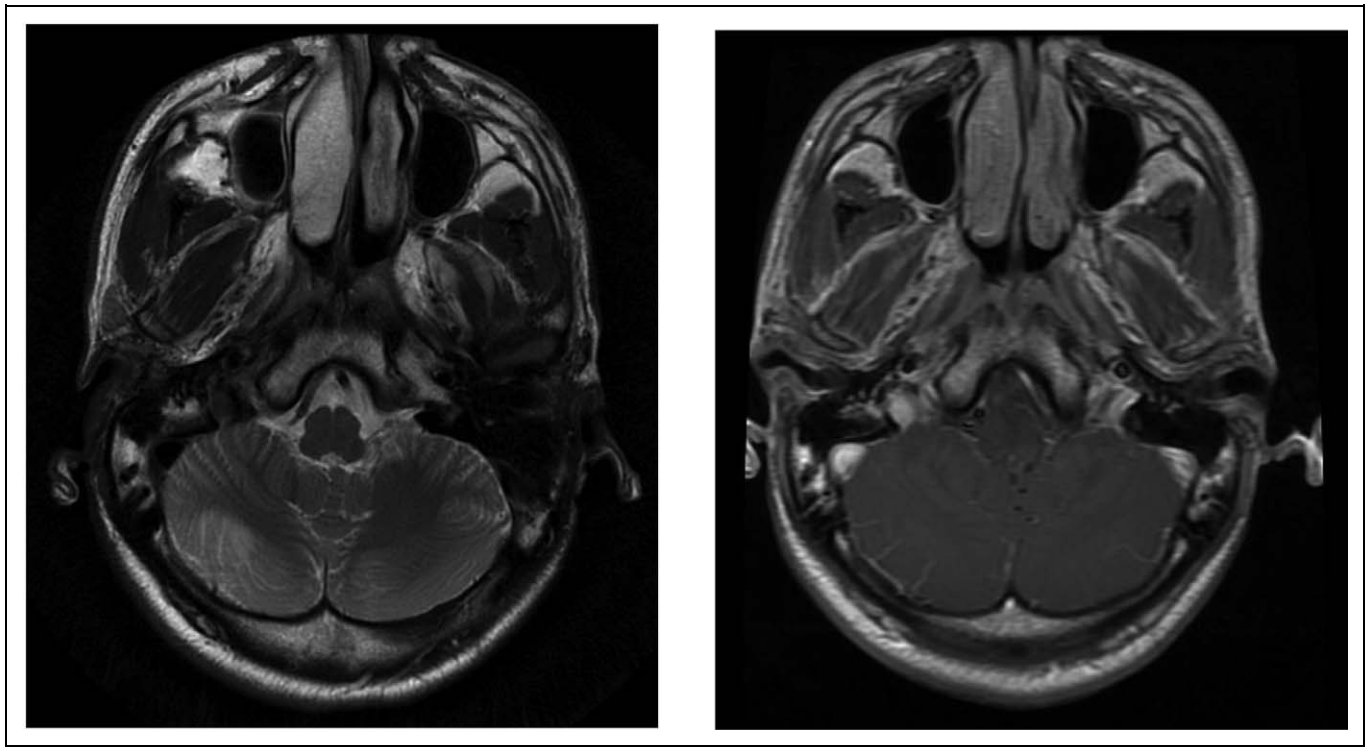

Figure 2. MRI scan. Left: T2 weighted (noncontrast) magnetic resonance imaging (MRI) showing an abnormal signal in the right cerebellar hemisphere correlating with the initially hyper-metabolic and later hypo-metabolic region of cerebellum. Right: T1-postcontrast MRI showing right cerebellar enhancement.

serology for mycoplasma IgG with a negative mycoplasma IgM. The patient, however, had completed a 5-day course of azithromycin one day before this test.

During week 2 of admission, a repeat brain MRI was normal and angiography and venography were negative for possible vacuities autoimmune etiology. The patient was no longer responsive to verbal commands and became nonverbal. The patient developed noticeable oro-lingual-facial dyskinesia and the choreoathetotic movements continued. At this time, infectious etiology was unlikely as the patient continued to deteriorate, remained afebrile, and a potential autoimmune cause was aggressively worked up. The patient was started on a 5-day course of high dose prednisolone, while possible autoimmune etiologies were being pursued. The patient showed no improvement in behavior or level of consciousness, and was started on a second 5-day course of prednisolone without improvement.

During the third week of admission, the patient continued to be combative and unresponsive to voice or command. The patient started to have self-limited episodes of hypertension, tachycardia, tachypnea, and hyperthermia—the beginning of autonomic instability. A comprehensive paraneoplastic panel of known causes of paraneoplastic encephalitis (antibodies to Hu, Yo, voltage-gated calcium channel, potassium channel, etc) panel was negative. The patient's serum was also tested for all possible known autoimmune etiologies that could cause an encephalopathy—including, but not limited to, antinuclear antibody (ANA), anti-thyroid antibodies, and anti-neutrophil cytoplasmic antibodies were also negative.

On day 26, FDG-PET of the brain showed a large focal lesion of intense metabolic activity in the right cerebellar cortex with hypometabolism of most of the supratentorial structures, with the most pronounced decrease of normal metabolic activity in the bilateral occipital lobes (Figure 1, top row). The following day, repeat brain MRI revealed an increased T2/FLAIR signal in the right cerebellar hemisphere with contrast enhancement involving both gray and white matter (Figure 2). The patient's serum was sent out to the Dalamau Laboratory at the Children's Hospital of Philadelphia and was reported as positive for the presence of antibodies to the NMDA receptor.

After confirmation that the patient had adequate immunoglobulin A levels to reduce the risk of analphyaxis to the intravenous immunoglobulin (IVIG), the patient was started on IVIG on admission on day 30 (2 g per kg divided over 5 days).[1,3-5] After a total of 2 courses of IVIG over the period of 4 weeks in conjunction with aggressive physical rehabilitation and supportive care by the family, the patient started to show some physical (stable vital signs, walking, eating) and cognitive (answering simple questions) improvements. A follow-up brain FDG-PET scan was performed on day 46 (Figure 1, bottom row), which showed significant hypometabolism of the right cerebellum cortex correlating with the area of prior abnormal increase in metabolic activity. Overall, the

FDG-PET on day 46 was improved yet still grossly hypometabolic in the bilateral cerebral hemispheres. A total of 4 courses of IVIG were given over a period of 8 weeks, with no significant clinical improvement after the fourth course. Based on the clinical response after the final IVIG treatment with no significant improvement after the treatment, we believe that IVIG was no longer providing any additional therapeutic benefit. Subsequently, the patient was transferred to an inpatient psychiatric facility for continued intensive behavioral, cognitive, and physical rehabilitation 10 weeks after the initial presentation.

Discussion

In previous studies of other paraneoplastic syndromes (eg, limbic encephalitis, paraneoplastic cerebellar degeneration), brain FDG-PET revealed focal areas of hypermetabolism during the acute phase of illness, with the lesion resolving to an area of depressed metabolic activity during the stable or nonencephalopathic phase of their illness.[6-7] Notably, cerebellar hypermetabolism was described on FDG-PET 3 weeks after presenting symptoms with corresponding normal brain MRI.[7]

Furthermore, PET studies in Fisher Miller syndrome (autoantibody to ganglioside) described similar metabolic uptake patterns as described in our case—hypermetabolism in the cerebellar hemispheres in the acute phase with demonstrated bilateral occipital hypometabolic activity not otherwise described in the other paraneoplastic syndromes.[8] Global hypometabolism on FDG-PET in anti-NMDAR encephalitis within adults has recently been described.[9] However, review of the literature has yet to describe brain FDG-PET abnormalities in this condition in the pediatric population.

Only a handful of brain FDG-PET studies have been performed in the adult population with anti-NMDAR encephalitis, and the focal finding of intense hypermetabolic activity present unilaterally in the cerebellar cortex is a unique finding and not previously described in the literature. In a recent study of an adult patient with anti-NMDAR encephalitis, FDG-PET showed symmetric hypermetabolism in the primary motor, premotor, and supplementary motor areas. However, this increase of metabolic activity was notably absent in the basal ganglia during the time that the patient had severe oro-lingual-facial dyskinesias,[10] and no abnormal metabolic uptake was appreciated in repeat FDG-PET during convalescence.[10]

The very focal finding of hypermetabolism unilaterally in the cerebellum during the acute phase of illness in a pediatric patient with anti-NMDAR encephalitis has not been previously reported. We recommend that brain FDG-PET be used in other cases of anti-NMDAR encephalitis to elucidate whether specific brain regions are selectively more vulnerable in this disorder.

Author Contributions

The authors of this case report actively participated in patient care and post-discharge follow up.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the authorship and/or publication of this article.

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Ethical Approval

No ethical approval was necessary.

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