ELSEVIER

Cortical Hypometabolism Demonstrated by PET in Relapsing NMDA Receptor Encephalitis

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***N*-methyl-D-aspartate (NMDA) receptor encephalitis is a newly defined type of autoimmune encephalitis. Two girls (age 3 years, case 1, and 7 years, case 2) with relapsing NMDA receptor encephalitis each had the classic clinical features of encephalopathy, movement disorders, psychiatric symptoms, seizures, insomnia, and mild autonomic dysfunction. Both patients had persistent neuropsychiatric disability, despite immune therapies. Positron emission tomography (PET) scans were performed during clinical relapse at 6 weeks (case 1) and 5 months (case 2). In both cases, the scans demonstrated reduced fluorodeoxyglucose metabolism in the cerebral cortex, with the temporal regions being most affected. PET imaging was more sensitive than magnetic resonance imaging in these patients. In contrast, the one previous report of acute NMDA receptor encephalitis indicated cortical hypermetabolism. Thus, NMDA receptor encephalitis may be associated with variable PET findings, possibly dependent upon the timing of the study, or other factors. Future studies should investigate whether cortical hypometabolism is associated with a relapsing course, and whether it is predictive of a poorer outcome in NMDA receptor encephalitis.**

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Introduction

N-Methyl-D-aspartate (NMDA) receptor encephalitis is a newly defined type of autoimmune encephalitis with characteristic clinical features that include psychosis, dyskinesias, encephalopathy, seizures, and autonomic dysfunction [1]. It affects mainly children and young adults, with a strong female preponderance [1,2]. This condition is commonly associated with ovarian teratoma in women, but is less commonly paraneoplastic in children [1,2]. Patients with NMDA receptor encephalitis have prolonged hospitalization, and some require ventilatory support to manage life-threatening central hypoventilation [1,3]. The overall outcome with immunotherapy or immunotherapy plus surgery can be favorable in children and adults, but disability and death are also reported [1,2]. The diagnosis is made based on the presence of antibodies binding to the NR1 and NR2 subunits of the NMDA receptor expressed in its conformational state, identified with a cell-based assay. In the past, this entity has been known variously as *acute juvenile nonherpetic encephalitis*, *immune-mediated chorea encephalopathy*, and *dyskinetic encephalitis lethargica* [3–6].

Although MRI is a useful adjunct to diagnosing some viral encephalitides and acute disseminating encephalomyelitis [7,8], MRI findings are usually normal or mildly abnormal in the majority of patients with NMDA receptor encephalitis [1,2,4]. Reported here are [^{18}F]fluorodeoxyglucose positron emission tomography (FDG-PET) findings of cortical hypometabolism, with particular involvement of the temporal cortex, in two young girls with relapsing NMDA receptor encephalitis.

Methods

The two patients (age 3 years, case 1; age 7 years, case 2) were admitted to the authors' institution in 2007. They had a characteristic encephalitic phenotype consisting of marked agitation, encephalopathy, behavioral change, dyskinesias, intermittent seizures, and sleep disturbance. Clinical details and outcome have been previously reported in abbreviated form

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[4]. Both patients were retrospectively identified as having cerebrospinal fluid and serum antibodies against the NR1 and NR2 subunits of the NMDA receptor based on a cell-based assay as previously described [1,4]

Both patients had cerebral magnetic resonance imaging (MRI) with a 1.5 T system according to standard protocols, as well as magnetic resonance angiography and venography, with gadolinium for contrast enhancement.

Nuclear medicine imaging with FDG-PET and computed tomography (CT) was performed using a Siemens HiRez Biograph 16-slice PET-CT whole-body scanner. The FDG-PET images were analyzed according to specific anatomic regions using a Siemens esoft 10-step color scale standardized to maximal cerebral counts. All patients fasted for 4-6 hours prior to the injection of 370 MBq (scaled to weight) of [^{18}F]FDG. Blood glucose levels were within the normal range. The patient was placed in a semidarkened room for 10 minutes after intravenous insertion of a cannula and was deprived of audiovisual stimulation prior to tracer injection. The uptake time was 45 minutes prior to cerebral imaging. One patient required general anesthesia for the performance of the scan. This was given 30 minutes after the injection of [^{18}F]FDG. The studies were reviewed by an experienced nuclear medicine physician.

Results

Case 1

A 3-year-old girl of European origin presented with unsteadiness, chorea, and intermittent episodes of aggressive outburst over a few days. There was no prodromal illness. Her clinical examination revealed chorea and dystonic posturing. Over the following days she became mute, with persistent agitation and emotional lability. She had normal findings from cranial MRI throughout her illness, without any leptomeningeal enhancement. Cerebrospinal fluid examination revealed a mild pleocytosis (15 monocytes/mm^3), intrathecal synthesis of oligoclonal bands, and elevated neopterin indicating active cerebrospinal fluid inflammation. Findings from other microbiologic and autoimmune studies were normal.

The patient was initially commenced on antimicrobial therapy. Two weeks into her illness, she developed a generalized seizure and electroencephalography indicated epileptiform activity in the right temporal region as well as generalized slowing. She was commenced on 30 mg/kg per day of intravenous methylprednisolone at 3 weeks. Her chorea and emotional lability improved over the next 2 weeks. She started to use single words, responded to simple commands, and was more responsive. At 6 weeks, she developed a clinical relapse with increasing chorea, encephalopathy, insomnia, and self-injurious behaviors such as pulling her hair and mouth biting. Her FDG-PET scan was performed at this time (Fig 1A). She was then commenced on intravenous immunoglobulin at 2 g/kg and began to exhibit clinical improvement within 2 weeks. Her chorea and encephalopathy decreased, her emotional state improved, and she no longer exhibited self-injurious behaviors. She proceeded to exhibit a good response to monthly intravenous immunoglobulin for 12 months. At the 2-year follow-up examination, she had mild dystonic posturing and mild subjective cognitive impairment. To date, all findings from tumor surveillance with serial ultrasound imaging of her ovaries have been negative.

Case 2

A previously well 7-year-old girl of South Asian origin presented initially with new onset partial seizures with secondary generalization. Findings from neurologic examination and cranial MRI were normal. Electroencephalography indicated right temporoparietal epileptogenic activity and she was commenced on sodium valproate. Three weeks later she was readmitted with left-sided chorea and motor impersistence. Over the next few days she became encephalopathic with increasing agitation, confusion, and emotional lability. Her chorea became more generalized, and there were paroxysmal episodes of generalized dystonia with upward eye deviation without alteration of the electroencephalogram, considered to be dystonic and oculogyric crises. Electroencephalography indicated intermittent generalized slowing with left occipital spikes. A repeat MRI scan revealed subtle subcortical hyperintensities in the frontal and left temporal regions on fluid-attenuated inversion recovery (FLAIR) sequences, which were absent on follow-up imaging. There was no leptomeningeal enhancement following contrast. The cerebrospinal fluid examination was normal apart from oligoclonal bands detected in serum and cerebrospinal fluid (mirrored pattern), and elevated cerebrospinal fluid neopterin. A diagnosis of encephalitis was made, and the patient was commenced on intravenous antibiotics, acyclovir, and anticonvulsants.

Findings from all microbiologic investigations were negative, including polymerase chain reaction for herpes simplex virus. Additional autoimmune investigations were unremarkable. Because of the evolution of her encephalopathy, she was treated with intravenous methylprednisolone at 30 mg/kg per day for 3 days, which was followed by a tapering course of oral prednisolone over 8 weeks.

In the first 3 months after admission, the dominant clinical features were encephalopathy, neuropsychiatric symptoms, hyperkinetic movement disorder, and seizures. The neuropsychiatric symptoms were of agitation, mutism, reduced affect, emotional lability, and catatonia. Her movement disorder consisted of frequent unprovoked episodes of violent thrashing of her limbs, screaming, dystonia, and opisthotonic posturing. These episodes often lasted for hours, and were complicated by rhabdomyolysis. Her partial seizures and secondary generalized seizures continued, despite what would be considered adequate anticonvulsant therapy. Her other symptoms included insomnia, altered sleep-wake cycle, swallowing difficulties, and mild autonomic dysfunction consisting of hyperpyrexia, urinary retention, and tachycardia. In the fourth month, her encephalopathy, movement disorder, and psychiatric symptoms began to exhibit improvement.

At 5 months, she had a clinical relapse with worsening dystonia. She began to manifest parkinsonism with cogwheel rigidity, bradykinesia, shuffling gait, and an expressionless face, but no resting tremor. Her FDG-PET scan was performed at this time (Fig 1B). Her MRI scan revealed

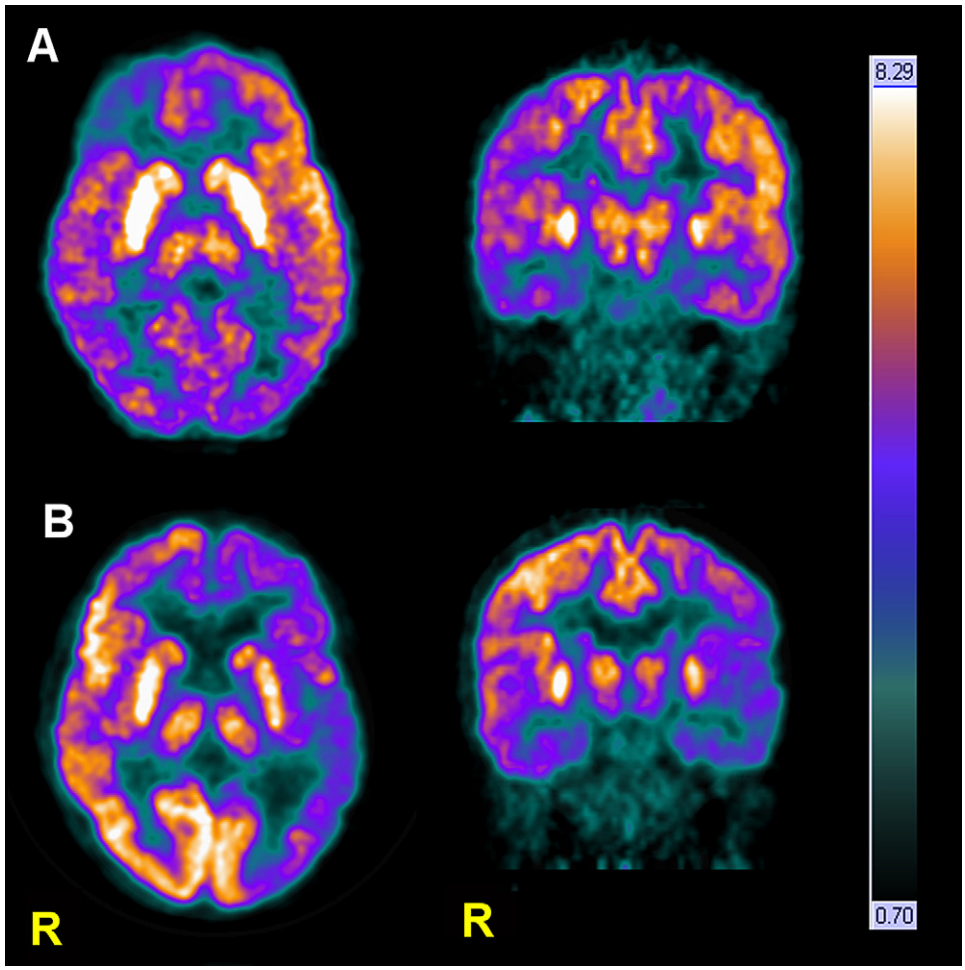

Figure 1. [^{18}F]Fluorodeoxyglucose PET-CT images from case 1 (A) and case 2 (B): transaxial and coronal views in warm metal display. White to orange color represents normal metabolism. R indicates right side. (A) Case 1 exhibited generalized marked reduction in cortical metabolism in both hemispheres, the right more than the left, involving bilateral frontal, temporal, parietal, and occipital regions. Both thalami have symmetric mildly reduced metabolic activity. The basal ganglia exhibited normal symmetric activity. (B) Case 2 exhibited a marked reduction in cerebral metabolism in the entire left hemisphere, both temporal lobes, and the right frontal lobe. The thalami exhibited a mild reduction in metabolism. The basal ganglia exhibited normal symmetric activity.

progressive cerebral atrophy; cerebrospinal fluid analysis revealed no pleocytosis, but oligoclonal bands were detected in both cerebrospinal fluid and serum, and elevated cerebrospinal fluid neopterin compatible with ongoing central nervous system inflammation. She was commenced on dopamine replacement therapy, with marginal improvement. She was given 2 g/kg of intravenous immunoglobulin given over 5 days with some improvement of her movement disorder and general condition. Six months into her illness, she was commenced on a selective serotonin reuptake inhibitor because of her persistent psychiatric symptoms of mutism, reduced affect, withdrawal, and anxiety. Her insomnia and altered sleep-wake cycle exhibited improvement. A follow-up MRI scan indicated no progression, but also no resolution of the cerebral atrophy.

She was discharged from the hospital after 7 months. A formal developmental assessment using the Griffiths Mental Development Scales revealed global delay across her profile; locomotor and personal social domains were consistent with a developmental age of 17 months, but eye and hand coordination with a developmental age of 46 months. At 2-year follow-up, she had significant cognitive, anxiety, and behavioral problems, with minimal dystonia in her left hand.

Nuclear Medicine: PET-CT Imaging

Cases 1 and 2 had FDG-PET-CT studies at 6 weeks and 5 months into their illness, respectively, in both cases during a clinical relapse. Neither patient had clinical seizures in the days prior to the study. The studies were displayed using a warm metal color display (Fig 1). The FDG-PET-CT study in case 1 (Fig 1A) indicated an overall generalized reduction in cortical metabolism in both hemispheres, the right more than the left, involving bilateral frontal, temporal, parietal, and occipital regions. Both thalami had symmetrically reduced metabolic activity, compared with the basal ganglia. The FDG-PET-CT in case 2 (Fig 1B) revealed a significant marked reduction in cortical metabolic activity in the entire left cerebral hemisphere, both temporal lobes, and to a lesser degree in the right frontal lobe. The metabolic activity in the thalami was mildly reduced and

the basal ganglia were normal and symmetric in uptake. In both patients, the temporal lobes were the most affected area.

Discussion

These patients presented with the well described clinical phenotype of NMDA receptor encephalitis consisting of psychiatric symptoms, movement disorders, seizures, encephalopathy, and mild autonomic dysfunction [2,4]. Both patients had NMDA receptor antibodies in serum and cerebrospinal fluid. Repeated surveillance yielded no evidence of occult teratoma. Both patients exhibited a variable response to immunotherapy, both had a clinical relapse, and both had residual cognitive impairments.

The findings of FDG-PET in encephalitis in the literature are varied [9,10]. Lee et al. [9] investigated six patients with limbic encephalitis of unknown etiology and reported FDG-PET hypermetabolism in the temporal lobes as a dominant finding, although focal hypometabolism was also observed. There have been other PET studies in limbic encephalitis of unknown etiology, some of which may have been NMDA receptor encephalitis: these cases usually had hypermetabolism in the temporal lobes [11]. A recent PET report of a very young child with suspected autoimmune limbic encephalitis identified focal hypermetabolism acutely in temporal and limbic structures, followed by hypometabolism during convalescence; NMDA receptor antibody testing was not performed in this case [12].

The present article is, to our knowledge, the first report of PET imaging in children with NMDA receptor encephalitis. Iizuka et al. [3] described the case of a woman with paraneoplastic NMDA receptor encephalitis with psychiatric symptoms, dyskinesia, hypoventilation, and a single episode of status epilepticus at 5 months. She was treated with steroids and intravenous immunoglobulin without improvement, received ventilation support for 6 months, and returned to work after 4 years. In that case, the FDG-PET study (which was performed during a period of severe dyskinesia, in the first few months) identified symmetric hypermetabolism in the frontal cortex; findings from follow-up FDG-PET study during convalescence were normal, but MRI revealed fronto-temporal atrophy.

The present finding of diffuse cortical hypometabolism during clinical relapses contrasts with findings of previous studies [3,9,11]. It is possible that cortical hypometabolism may be a feature of subacute or chronic disease, in contrast to cortical hypermetabolism in acute disease [10–12]. It is recognized that the PET findings may be influenced by multiple factors, including the stage of disease and the presence of clinical or electrical seizures. Unfortunately, neither of the present patients had follow-up PET scans to document whether the cortical hypometabolism persisted or resolved. It would be important to know from a larger prospective study whether such changes are associated with a relapsing course or a poor outcome. Although the whole of the cortex was affected in the present patients, the temporal lobes appeared to be the cortical region most affected.

In conclusion, NMDA receptor encephalitis is an important diagnosis to consider in children with encephalitis. In these two patients, FDG-PET was more sensitive than MRI. A larger study involving serial FDG-PET imaging in patients with NMDA receptor encephalitis is required to determine whether cortical hypometabolism may be associated with relapsing disease, or a poor outcome.

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