Changing Brain Metabolism Patterns in Patients With ANMDARE

Serial ^{18}F-FDG PET/CT Findings

Jing Yuan, MD, Hongzhi Guan, MD,* Xiangqin Zhou, MD,* Na Niu, MD,† Fang Li, MD,† Liying Cui, MD,* and Ruixue Cui, MD, PhD†*

Purpose: The aim of this study was to describe brain metabolic changing patterns demonstrated by serial brain FDG PET/CT scans and their relationship with the clinical course in patients with anti-*N*-methyl-D-aspartate receptor encephalitis (ANMDARE).

Patients and Methods: Eighteen serial PET scans of 8 patients with ANMDARE were reviewed. All the 18 PET scans were divided into 4 groups according to studies timing in different clinical course: group A, the acute and subacute phase; group B, early recovery phase; group C, recovery phase; and group D, relapsing phase. Antibody levels of ANMDARE of all these patients were tested at the same time. The PET images of each group were analyzed visually and also compared with 10 age- and sex-matched normal controls using voxel-wise statistical parametric mapping analysis (SPM5).

Results: Variable brain metabolic patterns and its association with the clinical course and the levels of NMDA antibody were demonstrated by FDG PET images. First, severe hypometabolism in bilateral occipital lobes and relatively mild hypermetabolism in the partial frontal and basal ganglia in acute and subacute phase, the level of antibody was high. Second, in early recovery phase when the symptoms was partially improved, extensive cortical hypometabolism was observed, and the level of antibody was low. Third, the patients in the recovery phase have no obvious neurological and psychiatric symptoms; PET images were nearly normal, and the antibodies tests were all negative, correspondingly. Fourth, 3 scans of relapsing phase presented heterogeneous brain metabolic abnormalities.

Conclusions: There existed a specific serial brain metabolic changing pattern that correlated with the clinical course and antibody level in ANMDARE.

Key Words: FDG, PET, ANMDARE

(*Clin Nucl Med* 2016;41: 366–370)

Anti-*N*-methyl-D-aspartate receptor encephalitis (ANMDARE) was first described in 2007 as an immunologically mediated disease associated with the antibody of NMDA receptor.[1] In reported cases, approximately 60% of young female patients had coexisting ovarian teratomas; testicular neoplasms and small cell lung cancers were also found in male patients. It has a set of well-defined clinical features. The patients usually develop changes of mood, behavior, and personality first, then progress to seizures, hyperkinetic episodes with featured oral-facial grimacing, autonomic instability, unconsciousness, and hypoventilation. Despite the severity of the disorder, patients often improve with immunotherapy and removal of the tumor. Brain CT scans were rarely abnormal in these patients. However, the abnormal signal in MRI scans of 55% patients were found but not characteristic.[1–3] The previous FDG PET finding about ANMDARE were all case reports and not consistent in metabolic activity changes, brain regions, and disease durations.[4–10] It was recognized that the PET findings may be influenced by multiple factors, including the stage of disease and the presence of clinical or electrical seizures. The serial FDG PET/CT images in different disease stages presented here were aimed to investigate the correlation of the brain metabolic change with the clinical courses of ANMDARE.

Received for publication August 30, 2015; revision accepted December 24, 2015.
From the Departments of *Neurology, and †Nuclear Medicine, Peking Union Medical College Hospital, Peking Union Medical College, Chinese Academy of Medical Sciences, Beijing, People's Republic of China.
Drs Jing Yuan and Hongzhi Guan contributed equally to the manuscript.
Conflicts of interest and sources of funding: Supported by the National Natural Science Foundation of China (81101075).
Correspondence to: Ruixue Cui, MD, PhD, Department of Nuclear Medicine, Peking Union Medical College Hospital, Peking Union Medical College, Chinese Academy of Medical Sciences, No 1 Shuaifuyuan, Wangfujing St, Dongcheng District, Beijing 100730, People's Republic of China. E-mail: mmdhmm@126.com.

ISSN: 0363-9762/16/4105–0366
DOI: 10.1097/RLU.0000000000001164

PATIENTS AND METHODS

Subjects and Clinical Diagnosis

Patients diagnosed with ANMDARE in our hospital during 2011 to 2013 were retrospectively reviewed. The diagnosis was based on clinical manifestations and the presence of antibodies binding to the NMDA receptor. The indirect immunofluorescence method was used for testing antibodies against the NMDA receptor with substrates including rat hippocampus, rat cerebellum, and HEK293 cells transfected with NR1 (EUROIMMUN, order number FA111m-3). The serum samples were diluted 1:10 in PBS-Tween, and CSF samples were undiluted during the test. Positive test result was defined as positive reaction to all 3 substrates. The diagnosis was confirmed by positive anti-NMDA receptor antibodies both in blood and in CSF samples of all cases. Whole-body CT and Brain MRI scan were performed to rule out other possible neurological diseases and screen potential tumors. Eight patients (3 women and 5 men, aged 12–35 years) with serial FDG PET/CT scans (totally 18 PET scans) were included. All the 18 PET scans were divided into 4 groups according to the time point in clinical course when the studies were performed: group A consisted of 6 scans in the acute and subacute phase (5–6 weeks from onset of illness), group B consisted of 5 scans in early recovery phase (9–13 weeks from onset of illness), group C included 4 scans in recovery phase (more than 20 weeks from onset of illness), and group D has 3 relapsing scans. The antibodies were tested in the same periods when PET studies were done. PET scans of 10 age- and sex-matched healthy individuals without neurological or psychiatric illnesses were also obtained.

FDG PET/CT Imaging

FDG PET images were acquired using Biograph 64 PET/CT scanner (Siemens), starting 40 minutes after IV injection of 5.55 MBq/kg (0.15 mCi/kg) ^{18}F-FDG. The PET scan duration is 15 minutes. Subjects fasted for at least 4 hours before PET imaging. All the patients were required to close eyes after tracer injection to eliminate the influence of eyes opening to occipital lobe uptake of FDG. FDG PET images were reconstructed using OSEM. Attenuation correction was performed with CT attenuation (120 KV, 380 mA). The different uptake in the occipital cortex is more possible due to change of the clinical course and because the similar change in the occipital cortex could also be seen in other patients.

PET Data Analysis

SPM Analysis of Regional Glucose Metabolism

Before statistic analysis, using SPM5 (Wellcome Department of Cognitive Neurology, Institute of Neurology, University College London) implanted in a Matlab 7.0 environment (MathWorks, Inc), all images were preprocessed for spatial normalization into the Montreal Neurological Institute template to remove intersubject anatomic variability, then smoothed with a full width half maximum of 2 × 2 × 2 mm, Gaussian kernel to increase the signal-to-noise ratio. The typical plane of normalized images of the serial 18 PET scans for 8 patients were shown in Figure 1. The scans of 3 groups (A, B, and C) were compared with those of the same healthy control group (n = 10), respectively, in a voxel-wise manner using SPM5. A 2-sample *t* test was used to detect differences between the PET images of different clinical phases and those of healthy control groups ($P < 0.05$, uncorrected). For visualization of the *t* score statistics (SPM {*t*} map), significant voxels were projected onto the 3-dimensional rendered brain template provided by SPM5, thus allowing anatomic identification (red color represented the hypermetabolic region, and green color depicted the hypometabolic region; Fig. 2).

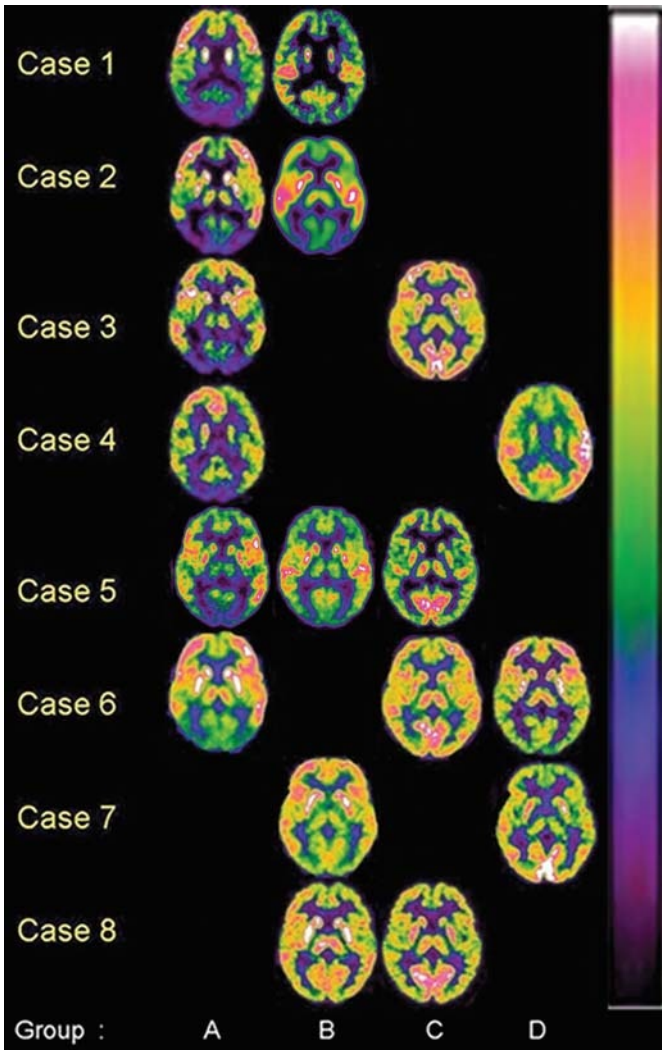

FIGURE 1. Typical transaxial planes of serial FDG PET scans after spatial normalization for each individual patient was presented according to the clinical course. Group A, acute and subacute phase; group B, early recovery phase; group C, recovery phase; and group D, relapsing phase.

RESULTS

The typical transaxial plane of 18 FDG PET scans of the 8 patients were displayed according to the courses of disease (Fig. 1). Various brain metabolic changes in different phases were observed in each patient. In Figure 1, the selected plane can showed the metabolic change in both cortex and basal ganglia. To facilitate comparison between the scans visually, the raw images of each scan were processed for spatial normalization into the Montreal Neurological Institute template provided by SPM 5 to remove intersubject anatomic variability and interscan spatial displacement. The general intensity of these scans is the original true status of each study. The uptake level of FDG changed a lot between the serial scans due to the different timing of clinical course, which was also proved by the result of group analysis presented in Figure 2.

The group analysis was performed by using "2-sample *t* test" to detect differences between the PET images of different clinical phases (groups A, B, and C) and those of healthy control groups, respectively ($P < 0.05$, uncorrected). For visualization of the *t* score statistics (SPM {*t*} map), significant voxels were projected onto the 3-dimensional rendered brain template provided by SPM5.

The clinical manifestations, FDG PET findings, and the levels of the antibodies are described later.

Acute and Subacute Phase

Six PET scans were performed at 5 to 6 weeks from the onset of the disease when patients were at the peak stage of their symptoms with various degree of severity including psychosis, intermittent involuntary movements, rigidity, tremor, unconsciousness, generalized seizures, and instability of autonomous nervous system.

Severe hypometabolism of the bilateral occipital lobes as well as hypermetabolism of the partial frontal, temporal lobe cortex, and basal ganglia were found in FDG PET/CT studies (Figs. 1A, 2A). During this period, a high level of antibody was observed in all the patients.

Early Recovery Phase

Five PET scans were performed at 9 to 13 weeks from onset. During this phase, the symptoms were resolving but still present, including small-scale involuntary movement, improved but limited language output, memory deficit, and intermittent psychiatric symptoms of anxiety, agitation, and hallucination. For PET studies, previous hypometabolism of bilateral occipital lobes and hypermetabolism of partial frontal lobe and temporal lobe cortex evolved to diffuse cortical hypometabolism with relative hypermetabolism in basal ganglia (Figs. 1B, 2B). The antibody levels of these patients were weak positive at the same time.

Recovery Phase

Four FDG PET/CT scans were performed at more than 20 weeks. At this period, the 4 patients only had memory deficit but without other symptoms. The metabolism of the brain almost returned to normal in PET findings (Figs. 1C, 2C). The antibody levels of these patients were all negative at this time.

Relapsing Phase

Three FDG PET/CT scans were performed for 3 patients with relapsing disease proved by positive changes of the antibody and clinical manifestations. The PET findings were different, and the symptoms of these 3 patients were also different. In case 6, hypometabolism of occipital lobe recurred (Fig. 1D, case 6). This patient had paroxysmal seizure discharge accompanied by

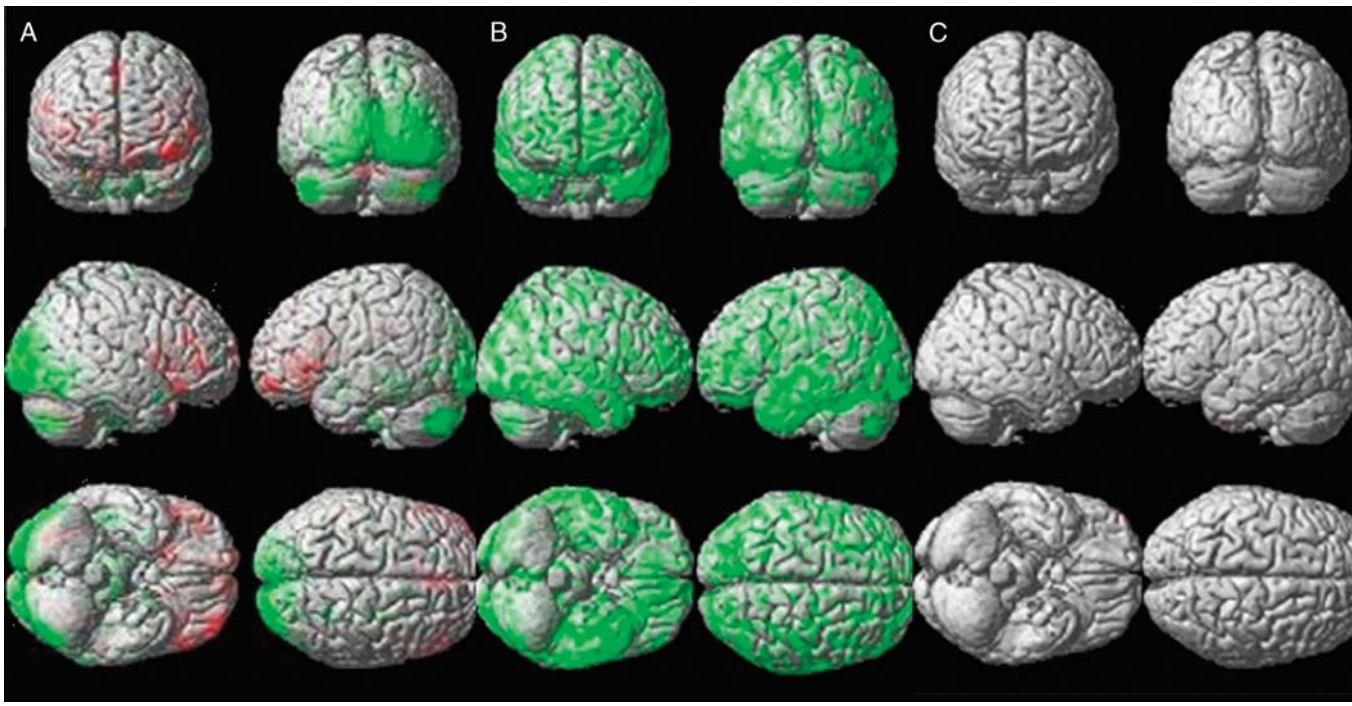

FIGURE 2. Results of 2-sample *t* test group analysis using SPM5 for scans of each group comparing with healthy control. The significant metabolic change regions were displayed on 3-dimensional surface-rendered templates ($P < 0.05$, $t = 1.87$, uncorrected). **A**, The relatively hypermetabolic (red color) and relatively hypometabolic regions (green color) in scans of group A. **B**, Hypometabolic regions (green color) in scans of group B; **C**, There was no significant metabolic change presented in group C.

unconsciousness and abnormal behaviors, similar to his original symptoms. For case 4, focal hypermetabolism of the left temporal lobe over the background of the diffusively decreased cortical uptake was observed because he was in a state of prolonged status epilepticus during the whole course of PET study (Figs. 1D, case 4; 3). Although his original occipital lobe hypometabolism had returned to normal (after eliminating the influence factor of eyes opening during study), newly emerging focal hypermetabolism of the left hippocampus was observed in case 7, who complained of headache and aggravated memory decline (Figs. 1D, case 7; 4).

DISCUSSION

ANMDARE was first described in 2007 with an increasing number of cases now being reported. Clinical workup may disclose an underlying neoplasm, usually an ovarian tumor, in approximately 60% of patients. It represents a new category of immune-mediated disorder that is often paraneoplastic and treatable. In this study, we retrospectively reviewed serial FDG PET/CT images of 8 patients with ANMDARE in different clinical course, and found a specific variable pattern of brain metabolic abnormalities correlating with the clinical course in these cases, which was different from other previously reported unspecified paraneoplastic encephalitis.[11–13]

Previous case reports about FDG PET results for ANMDARE were inconsistent.[4–10] Mohr et al[4] described a case with obvious hypometabolism in bilateral occipital lobes. Focal hypermetabolism in the left prefrontal cortex and the anterior cingulate cortex[5] and asymmetric hypermetabolism in the superior right frontal lobe[6] were also reported. Maeder-Ingvar et al[7] reported the hyperactivity in basal ganglia. There was another finding that described the abnormal metabolic feature as diffuse cortical hypometabolism in the relatively chronic state.[8,9]

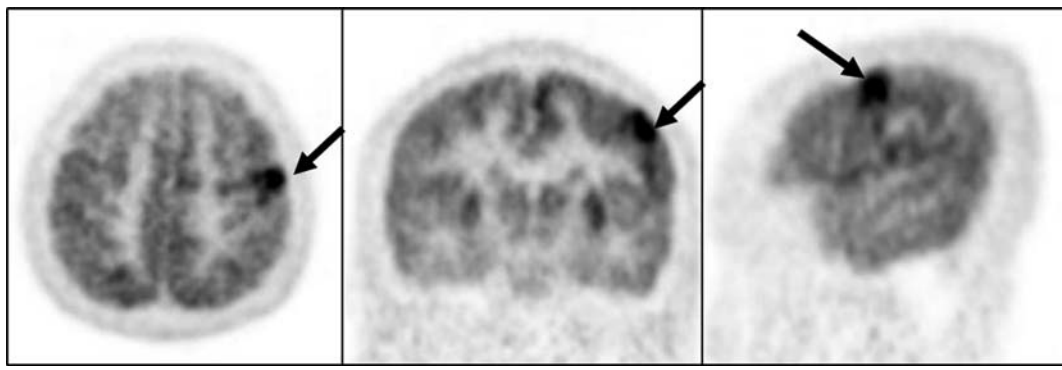

FIGURE 3. The hypermetabolic regions due to ictal seizure state during PET study for case 4 in relapsing phase. Increased uptake foci of left frontal lobe was showed in transaxial, coronal, and sagittal slice of PET images (arrow).

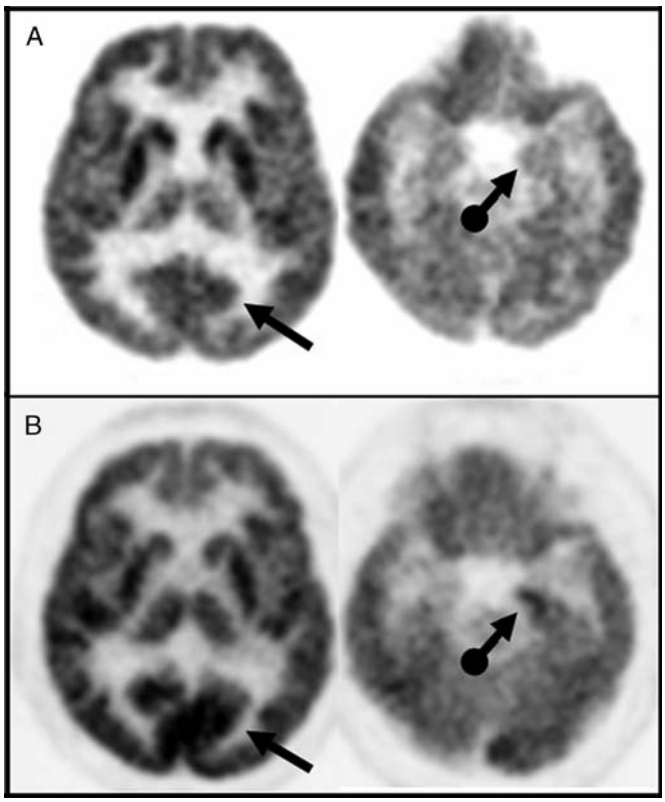

FIGURE 4. Brain metabolic changes in early recovery phase and relapsing phase of case 7. **A**, Mildly decreased activity in occipital lobes (arrow) and normal symmetric distribution of FDG in bilateral hippocampus (arrow with round tail) in early recovery phase. **B**, Normal uptake in occipital lobe (arrow) and obviously increased uptake of FDG in left hippocampus (arrow with round tail) in relapsing phase.

Our studies show that the inconsistence of brain metabolic change pattern maybe mainly due to the different scan timing in clinical course. For our cases, at acute and subacute phase, it presented the obvious hypometabolism in bilateral occipital lobes and, relatively, hypermetabolism of the bilateral frontal, temporal, and parietal lobes and basal ganglia. With the clinical status improvement, diffuse cortical hypometabolism in the relatively chronic state and the follow-up PET images demonstrated gradually improvement paralleled with the level of the antibody and clinical recovery. For the clinical relapsing cases, focal hypermetabolism was observed, and the hypometabolism of the bilateral occipital lobes recurred. The study by Leypoldt et al[10] reported a case with a similar pattern as ours. They found relative frontal and temporal glucose hypermetabolism associated with occipital hypometabolism and longitudinal analysis showed normalization of the pattern of cerebral glucose metabolism with recovery.

According to these specific brain metabolic characteristics, it may provide help in diagnosis, monitoring disease process, and management in the setting of ANMDARE. In fact, for case 7, it was the hypermetabolic foci in the temporal lobe that proved his replasing status and pushed the doctor to make decision for further treatment because he only complained of mild headache and memory decline, and the antibody level was low at that time.

The reversibility of the disorder suggests an immune-mediated neuronal dysfunction rather than irreversible degeneration. The variable metabolic change in the duration of the illness demonstrated that the change is mainly functional and reversible, which is consistent with the reversible clinical course and the antibody level. The molecular mechanism of the effect of antibody in ANMDARE had been investigated in previous study in vitro and in vivo, and it was proved that patients' antibodies reversibly and selectively reduce surface NMDA receptor clusters and protein in a titer-dependent fashion without affecting the number of synapses. The antibody's binding, capping, and cross-linking to NMDARs result in their internalization, which in turn decreases the synaptic function without a substantial loss of synapses.[2,14–16] These findings undergird the reversible clinical process and the FDG PET manifestation.

The pathophysiological basis of this metabolic signature of ANMDARE is not known. Hypometabolism in the occipital lobes and hypermetabolism in the frontal lobes, temporal lobes, and basal ganglia might be due to different distribution of NMDA receptor or differential glucose utilization in different location of the human brain. Based on the observation that ketamine, which is an NMDAR antagonist, applied to healthy human subjects, demonstrated the similar symptoms and frontal-to-occipital gradient of glucose metabolism detected by FDG PET, ketamine increases the glucose metabolism most dramatically in the cingulate anterior and frontal cortex, and to a lesser extent in the insular, parietal, and temporal cortex. The smallest increase was found in the occipital medial cortex.[17,18] This is similar to the observation in patients with ANMDARE. So we hypothesize that the pattern of abnormal brain glucose metabolism detected in ANMDARE might be a direct result from disrupted NMDAR signaling.

The relationship between changes in glutamatergic function and glucose metabolism in ANMDARE patients is not clear. Study by Iasevoli et al[19] found that ketamine might affect the gene expression of hexokinase 1 (Hk1) and glucose transporter 3 (GLUT3), which are crucially involved in the glucose utilization in brain tissues. The results show that HK1 and GLUT3 are extensively and differentially affected by the ketamine dose, and these molecules may play a role in the pathophysiology of ketamine-induced behavioral abnormalities. The results indicate that NMDA receptor pathway may affect glucose metabolism through HK1 and GLUT3, and the differential changes of glucose metabolism related with the dosage of ketamine indicate that the varied FDG PET findings might be associated with different levels of antibodies and disease severities.

CONCLUSIONS

Thus, specific changes in brain metabolism patterns were found in ANMDARE, possibly dependent upon the timing of the study and phase of the illness. This is consistent with the evolution of antibody titers and clinical symptoms. The specific metabolic changes may provide insights into the function of the neurotransmitter receptor targeted by antibodies. Given the small sample size in our study, this needs to be further tested by other larger studies.

REFERENCES

1. Dalmau J, Tüzün E, Wu HY, et al. Paraneoplastic anti-*N*-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. *Ann Neurol*. 2007;61:25–36.
2. Florance NR, Davies RL, Lam C, et al. Anti-*N*-methyl-D-aspartate receptor (NMDAR) encephalitis in children and adolescents. *Ann Neurol*. 2009;66:11–18.
3. Dalmau J, Gleichman AJ, Hughes EG, et al. Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. *Lancet Neurol*. 2008;7:1091–1098.
4. Mohr BC, Minoshima S. F-18 fluorodeoxyglucose PET/CT findings in a case of anti-NMDA receptor encephalitis. *Clin Nucl Med*. 2010;35:461–463.
5. Chanson JB, Diaconu M, Honnorat J, et al. PET follow-up in a case of anti-NMDAR encephalitis: arguments for cingulate limbic encephalitis. *Epileptic Disord*. 2012;14:90–93.

6. Padma S, Sundaram PS, Marmattom BV. PET/CT in the evaluation of anti-NMDA-receptor encephalitis: what we need to know as a NM physician. *Indian J Nucl Med*. 2011;26:99–101.
7. Maeder-Ingvar M, Prior JO, Irani SR, et al. FDG-PET hyperactivity in basal ganglia correlating with clinical course in anti-NDMA-R antibodies encephalitis. *J Neurol Neurosurg Psychiatry*. 2011;82:235–236.
8. Pillai SC, Gill D, Webster R, et al. Cortical hypometabolism demonstrated by PET in relapsing NMDA receptor encephalitis. *Pediatr Neurol*. 2010; 43:217–220.
9. Maqbool M, Oleske DA, Huq AH, et al. Novel FDG-PET findings in anti-NMDA receptor encephalitis: a case based report. *J Child Neurol*. 2011; 26:1325–1328.
10. Leypoldt F, Buchert R, Kleiter I, et al. Fluorodeoxyglucose positron emission tomography in anti-*N*-methyl-D-aspartate receptor encephalitis: distinct pattern of disease. *J Neurol Neurosurg Psychiatry*. 2012;83: 681–686.
11. Dadparvar S, Anderson GS, Bhargava P, et al. Paraneoplastic encephalitis associated with cystic teratoma is detected by fluorodeoxyglucose positron emission tomography with negative magnetic resonance image findings. *Clin Nucl Med*. 2003;28:893–896.
12. Scheid R, Lincke T, Voltz R, et al. Serial ^{18}F-fluoro-2-deoxy-D-glucose positron emission tomography and magnetic resonance imaging of paraneoplastic limbic encephalitis. *Arch Neurol*. 2004;61:1785–1789.
13. Basu S, Alavi A. Role of FDG PET in the clinical management of paraneoplastic neurological syndrome: detection of the underlying malignancy and the brain PET-MRI correlates. *Mol Imaging Biol*. 2008;10:131–137.
14. Dalmau J, Lancaster E, Martinez-Hernandez E, et al. Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. *Lancet Neurol*. 2011;10:63–74.
15. Hughes EG, Peng X, Gleichman AJ, et al. Cellular and synaptic mechanisms of anti-NMDA receptor encephalitis. *J Neurosci*. 2010;30:5866–5875.
16. Moscato EH, Peng X, Jain A, et al. Acute mechanisms underlying antibody effects in anti-*N*-methyl-D-aspartate receptor encephalitis. *Ann Neurol*. 2014; 76:108–119.
17. Vollenweider FX, Leenders KL, Oye I, et al. Differential psychopathology and patterns of cerebral glucose utilisation produced by (S)- and (R)-ketamine in healthy volunteers using positron emission tomography (PET). *Eur Neuropsychopharmacol*. 1997;7:25–38.
18. Vollenweider FX, Leenders KL, Scharfetter C, et al. Positron emission tomography and fluorodeoxyglucose studies of metabolic hyperfrontality and psychopathology in the psilocybin model of psychosis. *Neuropsychopharmacol*. 1997;16:357–372.
19. Iasevoli F, Latte G, Avvisati L, et al. The expression of genes involved in glucose metabolism is affected by *N*-methyl-D-aspartate receptor antagonism: a putative link between metabolism and an animal model of psychosis. *J Neurosci Res*. 2012;90:1756–1767.