Journal of Nuclear Medicine, published on January 19, 2017 as doi:10.2967/jnumed.116.187492

Glucose Metabolic Profile by Visual Assessment Combined with SPM Analysis in Pediatric Patients with Epilepsy

Yuankai Zhu[1-4]†, Shuang Wu[1-4]†, Haifeng Hou[1-4]†, Jianfeng Ji[1-4], Kai Zhang[1-4], Qing Chen[1-4], Lin Chen[1-4], Haiying Cheng[5], Liuyan Gao[5], Zexin Chen[6], Hong Zhang[1-4], Jianhua Feng[5]*, Mei Tian[1-4]*

[1]Department of Nuclear Medicine, The Second Hospital of Zhejiang University School of Medicine, Hangzhou, China; [2]Zhejiang University Medical PET Center, Hangzhou, China; [3]Institute of Nuclear Medicine and Molecular Imaging of Zhejiang University, Hangzhou, China; [4]Key Laboratory of Medical Molecular Imaging of Zhejiang Province, Hangzhou, China; [5]Department of Pediatrics, The Second Hospital of Zhejiang University School of Medicine, Hangzhou, China; [6]Department of Clinical Epidemiology & Biostatistics, The Second Hospital of Zhejiang University School of Medicine, Hangzhou, China

.

†These authors contributed equally to this paper.

Running title: PET study of epilepsy

Word counts: 5827

*For correspondence or reprints contact:

Mei Tian, Department of Nuclear Medicine, The Second Hospital of Zhejiang University, 88 Jiefang Road, Hangzhou, Zhejiang 310009, China. E-mail: meitian@zju.edu.cn

or Jianhua Feng, Department of Pediatrics, The Second Hospital of Zhejiang University, 88 Jiefang Road, Hangzhou, Zhejiang 310009, China. E-mail: zeek2013@sina.com

ABSTRACT

Positron emission tomography (PET) with ^{18}F-fluorodeoxyglucose (^{18}F-FDG) has been used for presurgical localization of epileptogenic foci, however in non-surgical patients, the correlation between cerebral glucose metabolism and clinical severity has not been fully understood. The aim of this study was to evaluate the glucose metabolic profile using ^{18}F-FDG PET-CT imaging in patients with epilepsy.

Methods: One hundred pediatric epilepsy patients who have received ^{18}F-FDG PET-CT, magnetic resonance imaging (MRI) and electroencephalography (EEG) examinations were respectively included. Fifteen age-matched controls were included. ^{18}F-FDG PET images were analyzed by using visual assessment combined with statistical parametric mapping (SPM) analysis. Absolute asymmetry index (|AI|) were calculated in patients with regional abnormal glucose metabolism.

Results: Visual assessment combined with SPM analysis of ^{18}F-FDG PET images detected more patients with abnormal glucose metabolism compared to the visual assessment only. The |AI| significantly positively correlated with seizure frequency ($P < 0.001$), but negatively correlated with the time since last seizure ($P < 0.01$) in patients with abnormal glucose metabolism. The only significant contributing variable to the |AI| was the time since last seizure, both in patients with hypo-metabolism ($P = 0.001$) and hyper-metabolism ($P = 0.005$). Higher values of |AI| were found in the drug-resistant compared to the seizure remission in patients with either hypo-metabolism ($P < 0.01$) or hyper-metabolism ($P = 0.209$). In the post 1-year follow-up PET studies, significant change of |AI| (%) was found in patients with clinical improvement compared to those with persistence or progression ($P < 0.01$).

Conclusion: ^{18}F-FDG PET imaging with visual assessment combined with SPM analysis could provide cerebral glucose metabolic profile in non-surgical epilepsy patients. |AI| might be used for evaluation of clinical severity and progress in these patients. Patients with a prolonged period of seizure freedom may have more subtle (or no) metabolic abnormalities on PET. The clinical value of PET might be enhanced by timing the scan closer to clinical seizure(s).

Key Words: epilepsy, glucose metabolism, positron emission tomography (PET), statistical parametric mapping (SPM)

INTRODUCTION

Epilepsy is considered as one of the most common serious neurological condition affecting 65 million people of all ages worldwide (*1*). A major proportion of patients with epilepsy falls in the pediatric group, and approximately 20% of them have medically intractable epilepsy (*2*). So far, electroencephalogram (EEG) evaluation remains the most widely used methods in clinical practice to classify the type of seizure in patients with epilepsy, however, the frequency of epileptiform EEG discharges is weakly related to severity of epilepsy (*3*). For the localization of seizure onset and the identification of the pathologic findings underlying the epileptic brain tissue in drug-resistant epilepsy patients, a structural neuroimaging technology magnetic resonance imaging (MRI) has obviously clinical advantages. MRI is effective for identifying intracranial abnormalities commonly associated with chronic focal epilepsy (*4*). However, not all MRI abnormalities including hippocampal sclerosis, cavernomas, gliomas, and malformations cause seizures and not all seizures originate from identified structural cerebral abnormalities. It fails to reveal epileptic foci in 20% - 30% of temporal lobe epilepsy (TLE) and 20% - 40% of extra-TLE patients despite advancement of functional MRI (fMRI) and magnetic resonance spectroscopy (MRS) (*5, 6*).

Recently, interictal positron emission tomography (PET) with ^{18}F-fluorodeoxyglucose (^{18}F-FDG) has been used as a powerful neuroimaging technology for presurgical evaluation of epileptogenic foci (*7-9*), and demonstrated a sensitivity of 70–90% in patients with TLE and 33%-67% in extra-TLE patients, depending on the localization of the focus (*10-12*). The highest clinical benefit of ^{18}F-FDG PET can be achieved in patients with MRI-negative TLE, in which, ^{18}F-FDG PET correctly lateralized the lesion in 80% of the cases (*13*). However, for the non-surgical patients, especially for the non-surgical pediatric children, the clinical diagnostic and prognostic values of ^{18}F-FDG PET remain unclear.

Therefore, we hypothesized that visual assessment combined with SPM analysis (or SPM-based visual analysis) of ^{18}F-FDG PET images could be useful for evaluating the correlation between cerebral metabolism and clinical severity or progress in epilepsy patients. The aim of this study was to evaluate the glucose metabolic profile using ^{18}F-FDG PET-CT imaging in patients with non-surgical epilepsy.

MATERIALS AND METHODS

Subjects

We retrospectively reviewed 142 pediatric epilepsy patients who had received ^{18}F-FDG PET, EEG and MRI examinations to detect epileptogenic areas. The inclusion criteria were as follows: clinical diagnosis of epilepsy (*14*); age between 7 and 14 y; detailed information of EEG and MRI; the last seizure occurring more than 24 h before ^{18}F-FDG PET study (*15*); completed 12-month clinical follow-up after ^{18}F-FDG PET imaging. Patients were excluded if they had no data from one of the modalities (EEG, MRI or PET). Other exclusion criteria consisted of medical illness with central nervous system impact other than epilepsy, e.g. head trauma, encephalitis, tumor, infarct, or porencephaly, since these obvious lesions preclude the normalization of ^{18}F-FDG PET images into standard template in SPM analysis. According to the type and number of seizures experienced in the 12 months, epilepsy patients were divided into the severe, moderate or mild group (*16*). Patients who had more than 20 times of seizure per year were classified as “severe”, and who without seizure in the past 12 months were considered as “mild”. At the end of the clinical follow-up, patients were considered to be in “remission” if they had no seizure during the past 12 months, or in “drug-resistant” if they were failed to achieve sustained seizure-free despite adequate antiepileptic drug (AED) (*17, 18*). A total of 100 epilepsy patients (46 girls and 54 boys; mean age: 10.4 ± 2.0 years) were included in this study. At the time of the PET scan, 49 patients received 1 type of AED, 29 patients received 2 AEDs, and 8 patients required treatment with 3 or more AEDs. The most frequently used AED was oxcarbazepine (n = 55), followed by levetiracetam (n = 22), topiramate (n = 21), valproate (n = 19), lamotrigine (n = 10), clonazepam (n = 4) and carbamazepine (n = 1). All patients underwent at least one prolonged (24 h) EEG monitoring to confirm the localization of the epileptic foci. Long-term video EEG was performed in the evaluation of 23 patients who present difficulties in localization after clinical assessment, prolonged EEG and MRI. Fifteen non-epilepsy patients (9 girls and 6 boys; mean age: 11.1 ± 3.1 years) who had no history of neurologic disorders, psychiatric illnesses, chemotherapy or radiotherapy were included as the age-matched

control subjects for SPM analysis. This age-matched control group consists of 6 patients with extracranial lymphoma and 9 with bone neoplasm. The institutional review board approved this retrospective study and the requirement to obtain informed consent was waived (ChiCTR-ORC-16009167).

PET Image Analysis

PET/CT brain images were acquired by a PET/CT scanner (Biograph mCT, Siemens Medical Solutions) at 40 min after intravenous (i.v.) injection of ^{18}F-FDG (3.7 MBq/kg) (*19, 20*). The co-registration PET and MRI images was performed by using the vender provided Fusion Registration Software implemented in the *syngo* MultiModality Workplace (Siemens Medical Solutions).

Visual Assessment. ^{18}F-FDG PET images were visually evaluated by two nuclear medicine specialists who were unaware of the findings of EEG and MRI. The glucose metabolic patterns (hypo-, hyper- or normal metabolism) of 16 major brain regions (8 in each hemisphere, corresponding to lateral and medial surfaces of the 4 lobes [frontal, temporal, parietal, occipital]) were evaluated and reported separately. Discordant results were reviewed by both experts to reach a consensus.

*SPM Analysis***.** Static ^{18}F-FDG PET image volumes were analyzed by using the SPM8 software package developed at the Well-come Department of Cognitive Neurology, Institute of Neurology (*21*). ^{18}F-FDG PET image volumes were spatially normalized into standard stereotactic space using an in-house pediatric PET template. A 16-mm full-width-half-maximum (FWHM) Gaussian kernel was used to smooth the data for statistical analysis. Individual SPM analysis was performed using an age-matched control group. Increased or decreased metabolism was regarded as statistically significant if the uncorrected *P* value was under 0.001 with cluster level above 100 voxels.

Visual assessment combined with SPM analysis. Visual assessment combined with SPM analysis were performed for re-analysis of all the PET images. A further semiquantitative analysis, absolute asymmetry index (|AI|), was performed to evaluate the intensity of the metabolic abnormality in brain

regions established by using this combined assessment. In patients with more than one cortical area showed hypo- or hyper-metabolism, the region with the most severe abnormality was selected for the calculation of |AI|. According to previous study (*22*), data were collected as nCi/cm^3 tissue for each region of interest with a 48 mm^2 circle in the original PET scans, and |AI| was calculated by using the following formula: |AI| = |(left - right)/([left + right]/ 2)|.

Statistical Analysis

Values are reported as mean ± SD. All data were analyzed by the SPSS software (IBM SPSS Statistics, Version 20.0). Comparison of gender was performed using chi-square test, and concordance between visual assessment and SPM analysis using kappa test. Two sample *t*-test was used to compare age and age of onset. Comparisons of seizure severity, seizure frequency, duration of epilepsy, number of AEDs, and time since last seizure were performed using Mann-Whitney test. Comparisons of |AI| among groups were performed using Mann-Whitney test or Kruskal-Wallis test, and followed by *post-hoc* test when appropriate. Analysis of correlation was performed using Spearman's correlation coefficients. Stepwise multivariate linear regression analysis was conducted to determine the independent contribution of individual variables (age, age of onset, duration of epilepsy, seizure frequency, time since last seizure, and number of AEDs) to the |AI|. *P* value less than 0.05 ($P < 0.05$) was considered statistically significant.

RESULTS

After carefully retrospective reviewing of EEG, MRI, PET results and clinical follow-up, a total of 100 patients were included in this study. Epileptiform activity was noted on the EEG of 86 patients (86%), with 76 (76%) of them showing focal epileptiform abnormalities. Slowing was noted on the EEG in only 5 patients, 2 were focal and 3 were generalized. The EEG and ^{18}F-FDG PET results were both abnormal in 75 patients (75%) and both normal in 5 (5%) (**Table 1**). The EEG results were significantly associated

with PET findings (Kappa = 0.237, P = 0.008). In contrast, the EEG and MRI results were both abnormal in 37 patients (37%) and both normal in 7 (7%). The association between EEG and MRI findings was not significant (Kappa = 0.051, *P* = 0.279).

Visual Assessment and SPM Analysis of ^{18}F-FDG PET Images

Abnormal cerebral metabolisms were observed by visual assessment in 70 patients (70%), including 63 with hypo-metabolism and 7 with hyper-metabolism (**Table 2**). SPM analysis identified abnormal metabolism in 71 patients (71%), including 47 with hypo-metabolism and 24 with hyper-metabolism. Among the 24 hypermetabolic patients, hypermetabolism associated with hypo-metabolism was detected in 14 patients using SPM analysis, however, primary visual assessment only demonstrated hypo-metabolic regions in these patients. A concordant result between the visual and SPM analyses was obtained in 69 patients (Kappa = 0.483, *P* < 0.001). Representative images were shown in **Figure 1**.

Correlation between Clinical Characteristics and Glucose Metabolism

The analysis of correlation between clinical characteristics and glucose metabolism was based on the combined visual and SPM analysis. Patients with abnormal glucose metabolism had significantly shorter time since last seizure (*P* < 0.05), greater severity of epilepsy (*P* < 0.05) and seizure frequency (*P* < 0.05) than those with normal metabolism (**Table 3**). No significant differences were found in gender, age, age of onset, duration of disease, or number of AEDs (*P* = 0.745, *P* = 0.293, *P* = 0.149, *P* = 0.713 and *P* = 0.127, respectively) between patients with normal and abnormal glucose metabolism. Metabolic abnormalities were detected in 25 (71.4%) of 35 patients with idiopathic epilepsy, in 35 (77.8%) of 45 patients with cryptogenic epilepsy and in 19 (95.0%) of 20 patients with symptomatic epilepsy. No significant difference of abnormal metabolism rate was found among these three types of epilepsy (Fisher's exact test, P = 0.109).

Among patients with hypo-metabolism, the severe group had greater |AI| than the mild and moderate groups ($P < 0.01$ and $P < 0.05$, respectively; **Fig. 2A**). In patients with hyper-metabolism, the severe group had greater |AI| than the mild group ($P < 0.01$; **Fig. 2B**), and slightly greater than the moderate group ($P = 0.051$). As shown in **Table 4**, the |AI| was significantly positively correlated with seizure frequency ($r_s = 0.516$, $P < 0.001$ and $r_s = 0.653$, $P = 0.001$, respectively) but negatively correlated with the time since last seizure in patients with hypo- ($r_s = -0.477$, $P < 0.001$) and hyper-metabolism ($r_s = -0.621$, $P = 0.001$).

Stepwise multivariate linear regression analysis was done to determine the independent contribution of individual variables (age, age of onset, duration of epilepsy, seizure frequency, time since last seizure, and number of AEDs) to the |AI|. The only significant contributing variable was the time since last seizure, both in patients with hypo- (B = -0.03; SEM = 0.01; $P = 0.001$) and hyper-metabolism (B = -0.05; SEM = 0.01; $P = 0.005$).

The Metabolic Features of TLE and RE

Based on the clinical manifestations, EEG, MRI and PET findings, 28 of 100 patients were found with temporal lobe epilepsy (TLE), 29 with rolandic epilepsy (RE), 10 with frontal lobe epilepsy (FLE), and 4 with occipital lobe epilepsy (OLE).

Of the 28 patients with TLE, 26 patients (92.9 %) showed hypo-metabolism, 1 patient (3.6 %) had hyper-metabolism in unilateral temporal lobe, and 1 patient (3.6 %) was absence of any abnormal cerebral metabolism. Among the 26 patients with hypo-metabolism, the |AI| was significantly positively correlated with seizure frequency ($r_s = 0.707$, $P < 0.001$), and negatively correlated with the time since last seizure ($r_s = -0.481$, $P < 0.05$).

Among the 29 patients with RE, four metabolic patterns were found: hyper-metabolism only (n = 6), hyper-metabolism associated with hypo-metabolism (n = 12), hypo-metabolism only (n = 5), and absence of metabolic abnormality (n = 6). Representative images were demonstrated in **Figure 3**. Of 18

patients with hyper-metabolism, the intensity was significantly positively correlated with seizure frequency (r_s = 0.597, P < 0.01), but negatively correlated with the time since last seizure (r_s = -0.569, P < 0.05). There were 20 patients were reported as “non-lesional” on MRI studies in RE patients. Among the other 9 patients with abnormal MRI, 4 patients were found with hippocampal abnormality, 2 patients with arachnoid cyst, 1 patient with enlarged temporal horn, 1 patient with demyelination and 1 patient with cortical dysplasia.

Co-registration of PET and MRI

As shown in Table 1, MRI results were abnormal in 39 children, including hippocampal atrophy (n = 10), hippocampal sclerosis (n = 5), T2WI signal abnormalities of hippocampus (n = 4), cortical dysplasia (n = 7), arachnoid cyst (n = 5), demyelination (n = 3), heterotopias (n = 1), focal cortical atrophy (n = 1), polymicrogyria (n = 1), and enlarged temporal horn (n = 2). Among the other 61 patients with normal MRI findings, however, after co-registration of PET and MRI, the guided second reading changed the MRI report as “subtle lesion” in 7 patients. The representative images of a 14-year-old patient were shown in **Figure 4**.

Visual Assessment Combined with SPM Analysis and Clinical Management

By using visual assessment combined with SPM analysis, 79 patients (79%) were found with abnormal metabolism, including 55 with hypo-metabolism and 24 with hyper-metabolism (**Table 4**).

Higher values of |AI| were found in drug-resistant patients compared to the seizure remission in patients with either hypo-metabolism (P < 0.01; **Fig. 2C**) or hyper-metabolism (P = 0.209; **Fig. 2D**). Higher value of |AI| was found in patient with add-on therapy compared to those with unchanged therapy or withdrawal (Both P < 0.01; **Fig. 5A**); and slightly higher values of |AI| was observed in patients of persistence/progression compared to those of improvement (P = 0.051; **Fig. 5B**).

There were 11 patients who had the post 1-year follow-up PET studies. Significant change of |AI| (%) was found in patients with improvement compared to those with persistence/progression (P < 0.01;

Fig. 5C).

DISCUSSION

We retrospectively evaluated the results of ^{18}F-FDG PET, MRI and EEG in 100 non-surgical epilepsy patients. We found that the visual assessment combined with SPM analysis could be an effective approach for identifying abnormal cerebral metabolic changes. Increased or decreased values of |AI| on ^{18}F-FDG PET images could be applied as an imaging biomarker for clinical evaluation of non-surgical epilepsy. Patients with a prolonged period of seizure freedom may have more subtle (or no) metabolic abnormalities on PET. The shorter interval since the last seizure, the more patients with metabolic abnormality could be detected by ^{18}F-FDG PET imaging. To the best of our knowledge, this is the first visual assessment combined with SPM analysis of ^{18}F-FDG PET study to evaluate the severity and clinical management in non-surgical pediatric epilepsy patients.

The key to successful epilepsy control is defining epileptogenic foci, whether it is an apparent anatomic focus or a more functional one, such as non-lesional epilepsy. However, the visual assessment of ^{18}F-FDG PET images in the clinical application is subjective and relies on the experience and knowledge of the readers (*23*). Therefore, it is inevitable that the interpretation of one single image by visual assessment is variable among different observers, and subtle metabolic abnormalities of epilepsy might not be identified easily. In our study, visual assessment combined with SPM analysis of ^{18}F-FDG PET images identified more patients with abnormalities compared to the visual assessment or SPM alone. Even for the non-lesional report on MRI, after co-registration of ^{18}F-FDG PET and MR images, the guided second reading could detect subtle pathologic abnormalities in 7 patients. Similarly, another group has reported that in children with MRI-negative epilepsy, co-registered ^{18}F-FDG-PET/MRI with the use of SPM could detect subtle MRI abnormalities which were not previously recognized in 9 out 31 patients (*24*). Taken their and our results together, visual assessment combined with SPM analysis of co-registrated ^{18}F-FDG-PET/MRI images could be an objective and effective method to identify subtle metabolic abnormalities corresponding to seizure foci.

Interictal hypometabolism was one of the first clinical findings during the development of PET, and in the past years, it has been noted to have predictive value independent of EEG and MRI (*25*). However, the exact mechanism underlying hypometabolism is not entirely understood. In our non-surgical pediatric population, we found that 92.9 % of TLE patients showed hypo-metabolism, 3.6 % had hyper-metabolism in unilateral temporal lobe, and 3.6 % was absence of any abnormal cerebral metabolism. A previous study has demonstrated that, despite the normal appearance of the MRI of the brain, about 40% of patients exhibit hypo-metabolism as measured by ^{18}F-FDG PET at the onset of cryptogenic TLE (*26*). The extent of cortical glucose hypo-metabolism can undergo dynamic changes, and partly related to the frequency of seizures (*27*). Interesting, hyper-metabolism could be detected in the acute phase of epileptic syndrome with continuous spikes and waves during slow sleep (CSWS), but disappear in the recovery phase (*28*). Transient hyper-metabolism was observed in 9 of 60 patients with Sturge-Weber syndrome, which was considered to reflect a period of epileptogenesis (*29*). In an autoradiography study, ^{14}C-FDG uptake was related to the general intensity of synaptic activity rather than the nature of excitation or inhibition (*30*). Therefore, either strong excitations or strong inhibitions had the potential to increase cerebral metabolism.

So far, the correlation between the regional asymmetry of ^{18}F-FDG distribution and clinical severity has not been studied in patients with hyper-metabolism. In the previous studies, the value of |AI| higher than 0.1 or 0.15 in at least one cortical region other than the cerebellum was considered abnormal (*22, 27, 31*). In our study, the majority of patients in mild and moderate groups had |AI| values lower than 0.2. The severe group had higher value of |AI| than the mild and moderate groups, and the |AI| was positively correlated with seizure frequency in patients with hyper- or hypo-metabolism. Although hyper-metabolism is frequently observed during the ictal state of epilepsy (*32, 33*), it can also be observed in absence of ictal events during tracer uptake, and correlates well with regions of high spike count, suggesting a state of increased epileptogenicity (*33, 34*). In view of the abundant sample size of patients with interictal hyper-metabolism, we assume that the |AI| value on ^{18}F-FDG PET images in patients with hyper-metabolism could be affected by the clinical severity and seizure frequency. Previous studies demonstrated that increased seizure frequency and severity were related to greater

hypo-metabolism on ^{18}F-FDG PET images, both in adult and pediatric patients (*22, 26*). Therefore, hypo-metabolism could be reversible as the seizures come under control (*27, 35*), but worsened by continuing epileptic activity (*26*). In addition, since the drug-resistant patients had significant metabolic abnormalities (especially hypo-metabolism) than those of remission, ^{18}F-FDG PET might provide valuable follow-up information for pediatric patients with epilepsy.

Most importantly, based on the results of multivariate regression analysis, we found that the timing of the last clinical seizure (rather than seizure frequency) that might primarily drive the severity of metabolic asymmetries. This finding indicated that the localizing value of ^{18}F-FDG PET may diminish in patients with prolonged seizure freedom; and, on the other hand, the clinical value of PET might be enhanced by timing the scan closer to clinical seizure(s). It should be noted that the majority of our patients who had ^{18}F-FDG PET study within less than 1 month since last seizure was found with abnormal glucose metabolism. Therefore, we recommend that the optimal timing of interictal ^{18}F-FDG PET scan might from 1 day to 1 month after the last seizure.

There were several limitations to the current study. Firstly, since this is a retrospective study, the selection bias due to specific referral patterns cannot be avoided entirely. Secondly, no pathological confirmation or invasive EEG recordings available as the gold standard to study the correlation between abnormal metabolism and epileptogenic pathology. This is inherent to our selection criteria, as non-surgical patients are unwilling to undergo invasive procedures for obvious medical and ethical reasons. Thirdly, EEG recording was performed one day before the ^{18}F-FDG PET scan, however, due to the retrospective feature of this study, simultaneous EEG was not performed. Fourthly, we used co-registered PET/MRI, which requires repositioning of the patient and might fail to eliminate significant changes in physiologic and pathological condition during the two data acquisitions. Currently, ^{18}F-FDG-PET/MRI co-registration has been recommended in the routine presurgical evaluation of epilepsy, especially in patients without lesions on MRI (*36*) Ideally, simultaneous imaging of PET and MR might yield benefits with regard to patient management and time saving (*37*). Despite these limitations, the population in this retrospective study was large enough to investigate the correlation between cerebral metabolism and severity of pediatric epilepsy, and might pave the way for a further prospective

study.

CONCLUSION

Co-registration of ^{18}F-FDG PET-MRI with visual assessment combined with SPM analysis could provide cerebral glucose metabolic profile in non-surgical epilepsy patients. |AI| might be used for evaluation of clinical severity and progress in these patients. Patients with a prolonged period of seizure freedom may have more subtle (or no) metabolic abnormalities on PET. The clinical value of PET might be enhanced by timing the scan closer to clinical seizure(s).

DISCLOSURE

This work is partly sponsored by Grants from the National Key Research and Development Program of China (2016YFA0100900), National Key Basic Research Program of China (2013CB329506), National Science Foundation of China (NSFC) (no. 81425015, 81271601) and Zhejiang Provincial Natural Science Foundation of China (LR13H180001). No other potential conflict of interest relevant to this article was reported.

REFERENCES

1. Moshe SL, Perucca E, Ryvlin P, Tomson T. Epilepsy: new advances. *Lancet.* 2015;385:884-898.

2. Rosati A, De Masi S, Guerrini R. Antiepileptic Drug Treatment in Children with Epilepsy. *CNS Drugs.* 2015;29:847-863.

3. Das JC. Electroencephalogram (EEG) in the management of epilepsy in children. *Mymensingh Med J.* 2014;23:406-411.

4. Jones AL, Cascino GD. Evidence on Use of Neuroimaging for Surgical Treatment of Temporal Lobe Epilepsy: A Systematic Review. *JAMA Neurol.* 2016;73:464-470.

5. Hong KS, Lee SK, Kim JY, Lee DS, Chung CK. Pre-surgical evaluation and surgical outcome of 41 patients with non-lesional neocortical epilepsy. *Seizure.* 2002;11:184-192.

6. Carne RP, O'Brien TJ, Kilpatrick CJ, et al. MRI-negative PET-positive temporal lobe epilepsy: a distinct surgically remediable syndrome. *Brain.* 2004;127:2276-2285.

7. Boling WW, Lancaster M, Kraszpulski M, Palade A, Marano G, Puce A. Fluorodeoxyglucose-positron emission tomographic imaging for the diagnosis of mesial temporal lobe epilepsy. *Neurosurgery.* 2008;63:1130-1138; discussion 1138.

8. Burneo JG, Poon R, Kellett S, Snead OC. The Utility of Positron Emission Tomography in Epilepsy. *Can J Neurol Sci.* 2015;42:360-371.

9. Perissinotti A, Setoain X, Aparicio J, et al. Clinical Role of Subtraction Ictal SPECT Coregistered to MR Imaging and (18)F-FDG PET in Pediatric Epilepsy. *J Nucl Med.* 2014;55:1099-1105.

10. Uijl SG, Leijten FS, Arends JB, Parra J, van Huffelen AC, Moons KG. The added value of [18F]-fluoro-D-deoxyglucose positron emission tomography in screening for temporal lobe epilepsy surgery. *Epilepsia.* 2007;48:2121-2129.

11. Drzezga A, Arnold S, Minoshima S, et al. 18F-FDG PET studies in patients with extratemporal and temporal epilepsy: evaluation of an observer-independent analysis. *J Nucl Med.* 1999;40:737-746.

12. Kim YK, Lee DS, Lee SK, Chung CK, Chung JK, Lee MC. (18)F-FDG PET in localization of frontal lobe epilepsy: comparison of visual and SPM analysis. *J Nucl Med.* 2002;43:1167-1174.

13. Won HJ, Chang KH, Cheon JE, et al. Comparison of MR imaging with PET and ictal SPECT in 118 patients with intractable epilepsy. *AJNR Am J Neuroradiol.* 1999;20:593-599.

14. Fisher RS, Acevedo C, Arzimanoglou A, et al. ILAE official report: a practical clinical definition of epilepsy. *Epilepsia.* 2014;55:475-482.

15. Leiderman DB, Albert P, Balish M, Bromfield E, Theodore WH. The dynamics of metabolic change following seizures as measured by positron emission tomography with fludeoxyglucose F 18. *Arch Neurol.* 1994;51:932-936.

16. Cramer JA, Westbrook LE, Devinsky O, Perrine K, Glassman MB, Camfield C. Development of the Quality of Life in Epilepsy Inventory for Adolescents: the QOLIE-AD-48. *Epilepsia.* 1999;40:1114-1121.

17. Kwan P, Arzimanoglou A, Berg AT, et al. Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. *Epilepsia.* 2010;51:1069-1077.

18. Dragoumi P, Tzetzi O, Vargiami E, et al. Clinical course and seizure outcome of idiopathic childhood epilepsy: determinants of early and long-term prognosis. *BMC Neurol.* 2013;13:206.

19. Gelfand MJ, Parisi MT, Treves ST, Pediatric Nuclear Medicine Dose Reduction W. Pediatric radiopharmaceutical administered doses: 2010 North American consensus guidelines. *J Nucl Med.* 2011;52:318-322.

20. London K, Howman-Giles R. Voxel-based analysis of normal cerebral [18F]FDG uptake during childhood using statistical parametric mapping. *Neuroimage.* 2015;106:264-271.

21. Kumar A, Juhasz C, Asano E, Sood S, Muzik O, Chugani HT. Objective detection of epileptic foci by 18F-FDG PET in children undergoing epilepsy surgery. *J Nucl Med.* 2010;51:1901-1907.

22. Gaillard WD, Weinstein S, Conry J, et al. Prognosis of children with partial epilepsy: MRI and serial 18FDG-PET. *Neurology.* 2007;68:655-659.

23. Archambaud F, Bouilleret V, Hertz-Pannier L, et al. Optimizing statistical parametric mapping analysis of 18F-FDG PET in children. *EJNMMI Res.* 2013;3:2.

24. Rubi S, Setoain X, Donaire A, et al. Validation of FDG-PET/MRI coregistration in nonlesional refractory childhood epilepsy. *Epilepsia.* 2011;52:2216-2224.

25. Struck AF, Hall LT, Floberg JM, Perlman SB, Dulli DA. Surgical decision making in temporal lobe epilepsy: a comparison of [(18)F]FDG-PET, MRI, and EEG. *Epilepsy Behav.* 2011;22:293-297.

26. Matheja P, Kuwert T, Ludemann P, et al. Temporal hypometabolism at the onset of cryptogenic

temporal lobe epilepsy. *Eur J Nucl Med.* 2001;28:625-632.

27. Benedek K, Juhasz C, Chugani DC, Muzik O, Chugani HT. Longitudinal changes in cortical glucose hypometabolism in children with intractable epilepsy. *J Child Neurol.* 2006;21:26-31.

28. De Tiege X, Ligot N, Goldman S, Poznanski N, de Saint Martin A, Van Bogaert P. Metabolic evidence for remote inhibition in epilepsies with continuous spike-waves during sleep. *Neuroimage.* 2008;40:802-810.

29. Alkonyi B, Chugani HT, Juhasz C. Transient focal cortical increase of interictal glucose metabolism in Sturge-Weber syndrome: implications for epileptogenesis. *Epilepsia.* 2011;52:1265-1272.

30. Bruehl C, Witte OW. Cellular activity underlying altered brain metabolism during focal epileptic activity. *Ann Neurol.* 1995;38:414-420.

31. Gaillard WD, Kopylev L, Weinstein S, et al. Low incidence of abnormal (18)FDG-PET in children with new-onset partial epilepsy: a prospective study. *Neurology.* 2002;58:717-722.

32. Meltzer CC, Adelson PD, Brenner RP, et al. Planned ictal FDG PET imaging for localization of extratemporal epileptic foci. *Epilepsia.* 2000;41:193-200.

33. Hur YJ, Lee JS, Lee JD, Yun MJ, Kim HD. Quantitative analysis of simultaneous EEG features during PET studies for childhood partial epilepsy. *Yonsei Med J.* 2013;54:572-577.

34. Bansal L, Miller I, Hyslop A, Bhatia S, Duchowny M, Jayakar P. PET hypermetabolism in medically resistant childhood epilepsy: Incidence, associations, and surgical outcome. *Epilepsia.* 2016;57:436-444.

35. Matheja P, Weckesser M, Debus O, et al. Drug-induced changes in cerebral glucose consumption in bifrontal epilepsy. *Epilepsia.* 2000;41:588-593.

36. Fernandez S, Donaire A, Seres E, et al. PET/MRI and PET/MRI/SISCOM coregistration in the presurgical evaluation of refractory focal epilepsy. *Epilepsy Res.* 2015;111:1-9.

37. Heiss WD. Hybrid PET/MR Imaging in Neurology: Present Applications and Prospects for the Future. *J Nucl Med.* 2016;57:993-995.

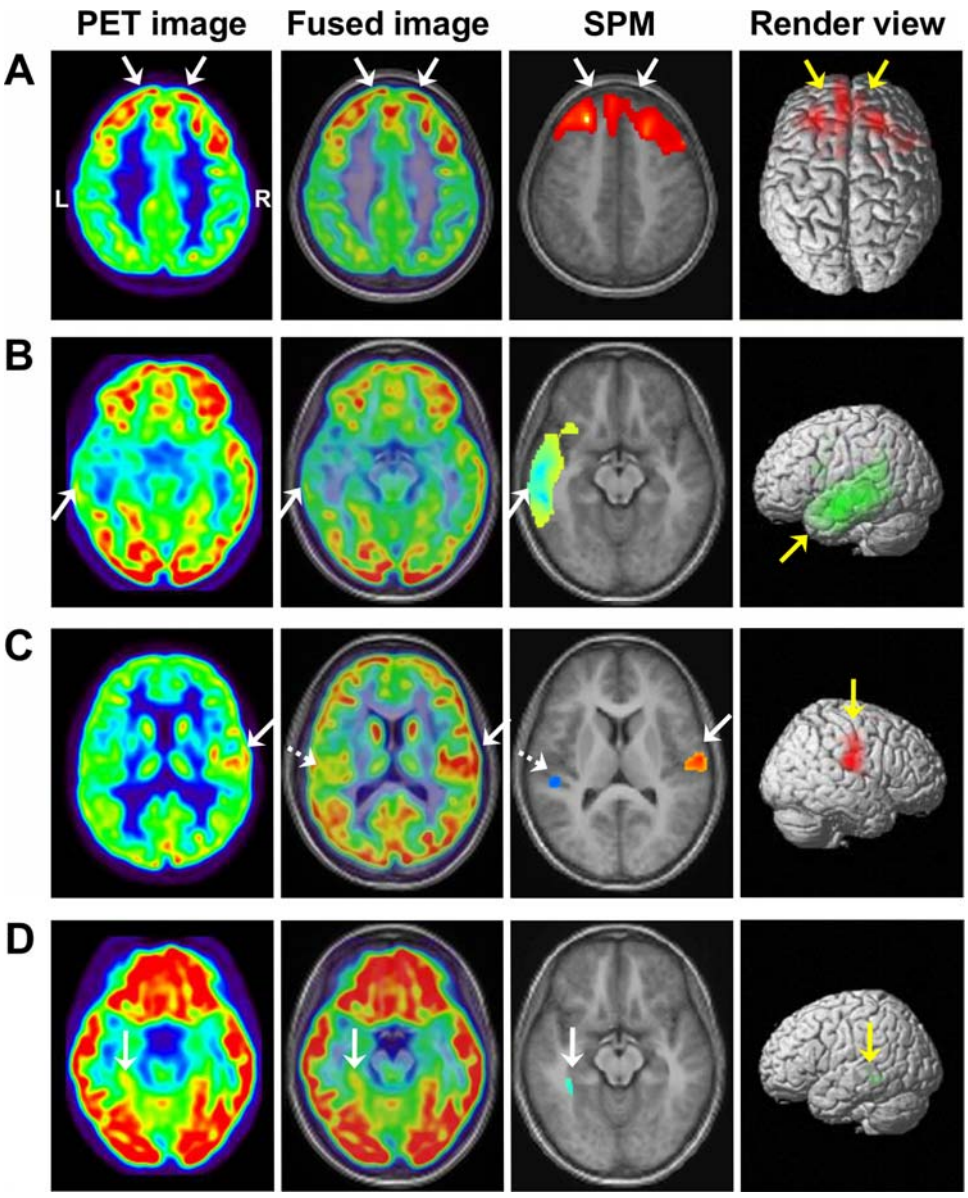

FIGURE 1. Comparison between visual and SPM analysis of ^{18}F-FDG PET Images. **(A)** Hyper-metabolism in bilateral frontal lobes (solid arrow) was detected by both visual and SPM analysis. **(B)** Hypo-metabolism in the left temporal lobe (solid arrow) was detected by both visual and SPM analysis. **(C)** Hypo-metabolism was found in the left rolandic area (dashed arrow) by visual assessment, and hyper-metabolic region was further identified in the right rolandic area (solid arrow) by SPM analysis. **(D)** Hypo-metabolic region undetected by visual assessment was identified in the left mesial temporal lobe (solid arrow) by SPM analysis.

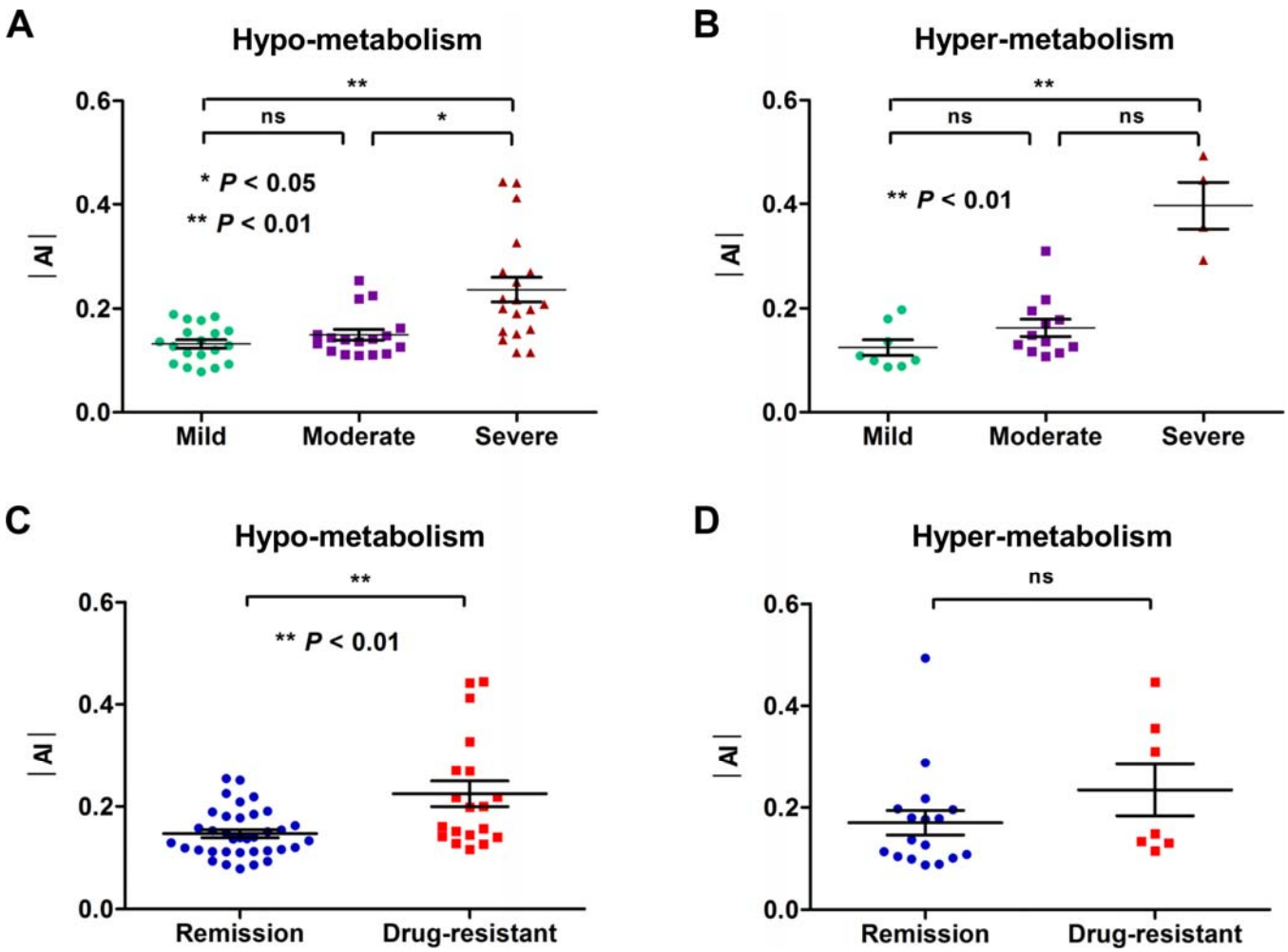

FIGURE 2. The clinical value of ^{18}F-FDG PET in the severity and outcome of pediatric epilepsy. **(A)** In patients with hypo-metabolism (n = 55), the severe group had higher value of |AI| than the mild and moderate groups (*P* = 0.001 and *P* = 0.030, respectively). **(B)** In patients with hyper-metabolism (n = 24), the severe group had higher value of |AI| than the mild group (*P* = 0.002), and slightly higher than the moderate group (*P* = 0.051). **(C)** Based on follow-up, in patients with hypo-metabolism, the drug-resistant patients had higher |AI| than those with seizure remission (*P* = 0.002). **(D)** In patients with hyper-metabolism, the drug-resistant patients had slightly higher |AI| than those with seizure remission (*P* = 0.209).

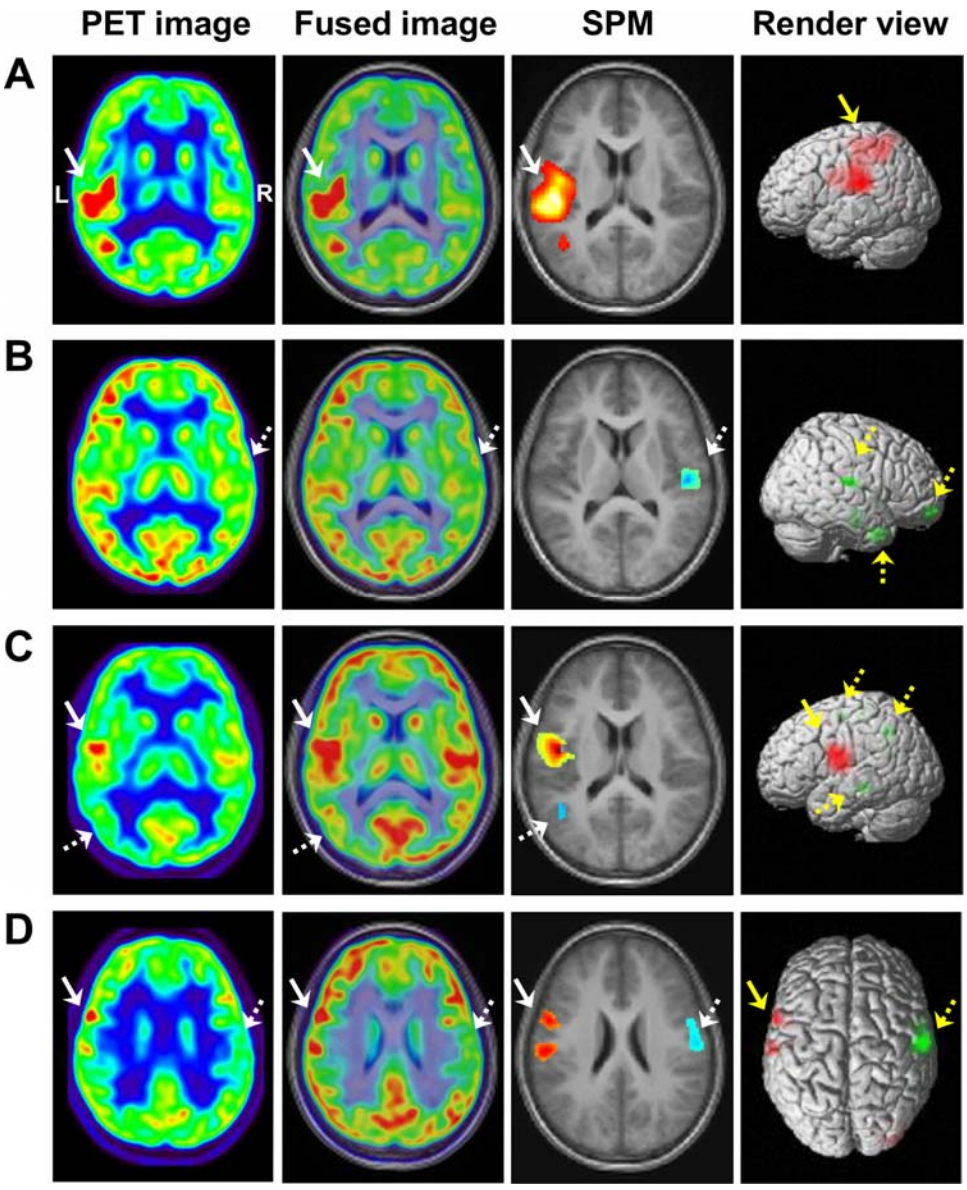

FIGURE 3. The metabolic features of rolandic epilepsy. **(A)** Hyper-metabolism was found in the left rolandic area (solid arrow). **(B)** Hypo-metabolic regions were found in the right frontal, temporal lobes and rolandic areas (dashed arrow). **(C)** Hyper-metabolism (solid arrow) with associated surround hypo-metabolism (dashed arrow) was observed in the left rolandic area. **(D)** Hyper-metabolism and its associated remote hypo-metabolism were found in the left (solid arrow) and right (dashed arrow) rolandic areas, respectively.

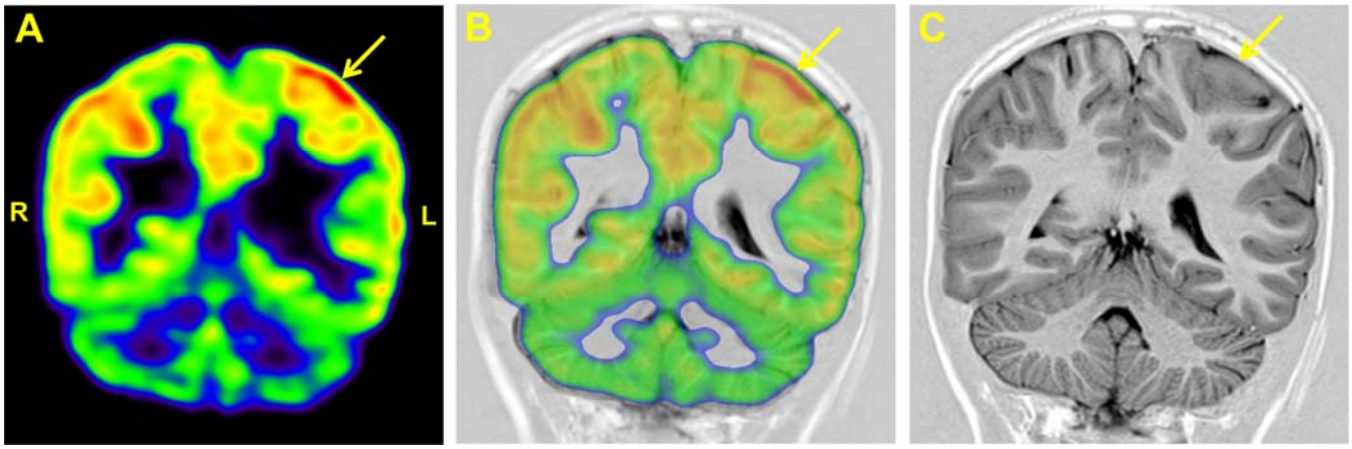

FIGURE 4. Interictal ^{18}F-FDG PET and MRI studies of a 14-year-old girl who experienced 6 times of right hemifacial contraction with drooling during the past 4-month. ^{18}F-FDG PET image (A) and PET/MRI co-registration (B) guided the second reading of MR images, in which detected a previously missed cortical thickening in the left parietal lobe (solid arrow) on T1-weighted image (C).

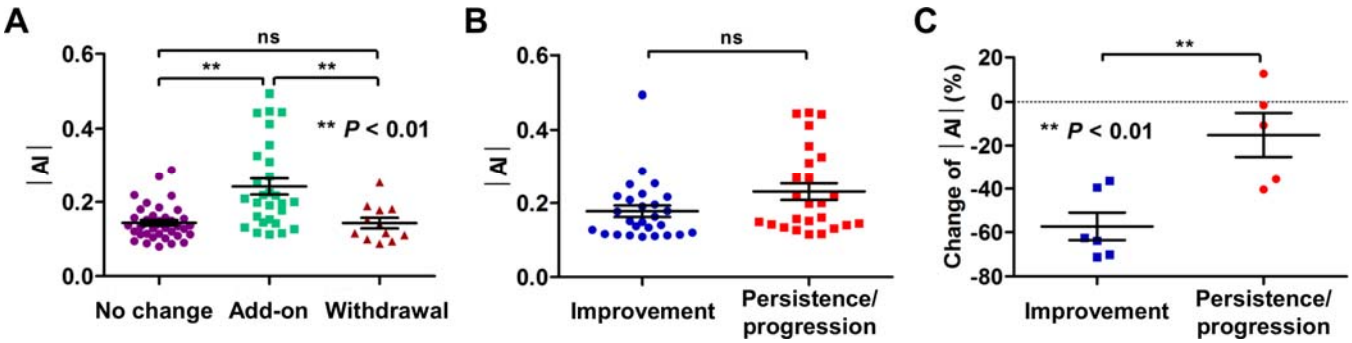

FIGURE 5. The diagnostic value of ^{18}F-FDG PET imaging during the clinical course of pediatric epilepsy. **(A)** The patients with add-on therapy after ^{18}F-FDG PET study had higher value of |AI| than those with unchanged therapy or withdrawal (P = 0.006 and P < 0.001, respectively), but no significant difference in |AI| was found between patients with unchanged therapy and those at withdrawal (P = 1.0). **(B)** The improvement course was defined as remaining seizure-free throughout the follow-up of patients in the moderate or severe group; and persistence/progression course was defined as drug-resistant throughout the follow-up. Patients with persistence/progression course had slightly higher value of |AI| than those with improvement (P = 0.051). **(C)** Of the 11 patients who also had the post 1-year follow-up PET scans, significant change of |AI| (%) was found in patients with clinical improvement compared to those with persistence or progression (P = 0.005).

TABLE 1

Comparisons of EEG, ^{18}F-FDG PET and MRI Findings

in Pediatric Epilepsy Patients (n = 100)

EEG findings	^{18}F-FDG PET findings*		MRI findings#		Total
	Normal	Abnormal	Normal	Abnormal	
Normal	5	4	7	2	9
Abnormal	16	75	54	37	91
Total	21	79	61	39	100

*Kappa = 0.237, P = 0.008; #Kappa = 0.051, P = 0.279

TABLE 2

Comparison between Visual Assessment and SPM Analysis of ^{18}F-FDG PET Studies in Pediatric Epilepsy Patients (n = 100)

Visual assessment	SPM analysis			Total
	Normal	Hypo-metabolism	Hyper-metabolism	
Normal	21	6	3	30
Hypo-metabolism	8	41	14	63
Hyper-metabolism	0	0	7	7
Total	29	47	24	100

Kappa = 0.483, P < 0.001

TABLE 3

Clinical Characteristics and ^{18}F-FDG PET Findings

in Pediatric Epilepsy Patients (n=100)

Clinical Characteristics	Abnormal (n = 79)	Normal (n =21)	*P* value
Gender			0.745
Female / Male	37 / 42	9 / 12	
Age (y)	10.3 ± 2.0	10.8 ± 2.0	0.293
Age of onset (y)	6.7 ± 2.6	7.7 ± 2.5	0.149
Duration of epilepsy (y)	3.6 ± 2.4	3.2 ± 2.1	0.713
Seizure frequency (times/y)	6.0 ± 13.4	1.0 ± 1.4	0.034
Seizure severity			0.026
Mild	27 (19 / 8)*	12	
Moderate	28 (16 / 12)*	7	
Severe	24 (20 / 4)*	2	
Time since last seizure			0.010
1d – 1m	38 (25 / 13)*	3	
1m – 1y	14 (11 / 3)*	6	
> 1 y	27 (19 / 8)*	12	
Antiepileptic drug			0.127
Drug naive	11 (7 / 4)*	3	
Single drug	35 (25 / 10)*	14	
Combined drugs	33 (23 / 10)*	4	

* Number in parentheses refers to the number of patient with hypo- vs. hyper-metabolism

TABLE 4

Correlation between |AI| and Clinical Severity in

Pediatric Epilepsy Patients with Abnormal Glucose Metabolism (n = 79)

	Seizure frequency		Time since last seizure	
	r_s	*P* value	r_s	*P* value
Abnormal metabolism				
Hypometabolism (n = 55)	0.516	< 0.001	-0.477	< 0.001
Hypermetabolism (n = 24)	0.653	0.001	-0.621	0.001

Supplemental Materials

Glucose Metabolic Profile by Visual Assessment Combined with SPM Analysis in Pediatric Patients with Epilepsy

RESULTS

According to interval between ^{18}F-FDG PET study and the time since last seizure, we dived the patients into 3 subgroups: (1) 1d – 1m, (2) 1m – 1y, (3) more than 1y. We found that patients with a prolonged period of seizure had more subtle metabolic abnormalities on ^{18}F-FDG PET images (**Fig. 1A and B**).

Figure Legend

Supplemental Figure 1. Hypo- or hyper-metabolic changes on ^{18}F-FDG PET images in pediatric epilepsy patients who had different period since last seizure. **(A)** In patients with hypo-metabolism, significantly lower value of |AI| was found in patients with more than 1 year of time since last seizure, compared to those with a much shorter period since the last seizure. **(B)** In patients with hyper-metabolism, significantly lower value of |AI| was found in patients with more than 1 year of time since last seizure, compared to those with a much shorter period since the last seizure.