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Topography of brain glucose hypometabolism and epileptic network in glucose transporter 1 deficiency

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Summary
Rationale: ^{18}F fluorodeoxyglucose positron emission tomography (^{18}F FDG-PET) facilitates examination of glucose metabolism. Previously, we described regional cerebral glucose hypometabolism using ^{18}F FDG-PET in patients with Glucose transporter 1 Deficiency Syndrome (Glut1 DS). We now expand this observation in Glut1 DS using quantitative image analysis to identify the epileptic network based on the regional distribution of glucose hypometabolism.
Methods: ^{18}F FDG-PET scans of 16 Glut1 DS patients and 7 healthy participants were examined using Statistical parametric Mapping (SPM). Summed images were preprocessed for statistical analysis using MATLAB 7.1 and SPM 2 software. Region of interest (ROI) analysis was performed to validate SPM results.
Results: Visual analysis of the ^{18}F FDG-PET images demonstrated prominent regional glucose hypometabolism in the thalamus, neocortical regions and cerebellum bilaterally. Group comparison using SPM analysis confirmed that the regional distribution of glucose hypo-metabolism was present in thalamus, cerebellum, temporal cortex and central lobule. Two mildly affected

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patients without epilepsy had hypometabolism in cerebellum, inferior frontal cortex, and temporal lobe, but not thalamus. Glucose hypometabolism did not correlate with age at the time of PET imaging, head circumference, CSF glucose concentration at the time of diagnosis, RBC glucose uptake, or CNS score.

Conclusion: Quantitative analysis of ^{18}F FDG-PET imaging in Glut1 DS patients confirmed that hypometabolism was present symmetrically in thalamus, cerebellum, frontal and temporal cortex. The hypometabolism in thalamus correlated with the clinical history of epilepsy.

Introduction

Glucose transporter 1 deficiency syndrome (Glut1DS) is a genetically determined developmental encephalopathy resulting from insufficient transport of glucose into the brain (De Vivo et al., 1991). Cardinal clinical features include infantile-onset seizures, acquired microcephaly, ataxia, dysarthria, dystonia, intellectual disability, and motor retardation (Pearson et al., 2013). The majority of Glut1 DS patients present with seizures in infancy. However, seizure onset beyond the first year of life has been also described in the number of studies with normal intelligence and alteration in SLC2A1 gene (Suls, Pong). In contrast to the earlier definition of Glut1 DS, majority of these children with late seizure onset did not have the cardinal features of the syndrome that have lead to the expansion of the clinical spectrum.

Absence seizures and generalized tonic clonic seizures are the most common seizure type in this syndrome (Leary et al., 2003). Despite the progress in clinical spectrum, diagnosis and recognition of the syndrome even in the individuals with milder phenotype; the pathophysiology underlying the epileptogenesis remains obscure.

Brain glucose metabolism in this clinical condition has been studied using ^{18}F-FDG-PET brain imaging. Qualitative analysis based on the visual interpretation of ^{18}F-FDG-PET data revealed a global decrease in glucose metabolism (Pascual et al., 2002). Regional hypometabolism was also noted in thalamus, cerebellum and neocortical regions.

Visual interpretation of ^{18}F-FDG-PET is the most traditional method for qualitative analysis. Introduction of quantitative methods to analyze ^{18}F-FDG-PET data has refined this information and provided a more precise topographical understanding of the regional vulnerability and severity of the metabolic insult in various neurological disorders and in focal epilepsy (Cummings et al., 1995; Duncan et al., 1997; Engel, 1984; McMurtray et al., 2008; Rintahaka et al., 1993; Schapiro et al., 1992). Quantitative analysis of imaging data can be achieved by Statistical Parametric Mapping (SPM), an effective, objective, and reliable method that supplements visual interpretation (Salek-Haddadi et al., 2003; Swartz et al., 1999). This quantitative method provides a voxel based analysis of metabolic activity that permits whole brain global analysis.

We hypothesized that the degree of glucose hypometabolism would vary from one region to another based on the clinical phenotype, and the regional distribution of glucose uptake would correlate with the clinical features. In this study, we searched for a correlation between the epilepsy history and regional vulnerabilities to glucose hypometabolism in an effort to map the epileptic network in Glut1DS.

Methods

Participants

Clinical features of this patient cohort were reported in our earlier study (Pascual et al., 2002). Sixteen patients diagnosed with Glut1 DS underwent ^{18}F-FDG-PET imaging. The study was approved by the Institutional Review Board of Columbia University. Informed consent was obtained from patients and their parents.

Mean age at the time of the imaging was 12.4 ± 9.9 years (range: 1.3—39). Except for two patients, cerebrospinal fluid (CSF) glucose concentration was less than 40 mg/dl. One patient was not tested and the other had a CSF glucose concentration of 52 mg/dl. Pathogenic GLUT1 mutations were demonstrated by gene sequence analysis in all patients. The demographic information, history of seizures, antiepileptic drug (AED) treatment, EEG findings and neuroimaging studies were reviewed. The Columbia Neurological Score (CNS) was used to assess the phenotypic severity of patients diagnosed with Glut1 DS (Kaufmann et al., 2004). This is a semi-quantitative tool that scores the following physical examination domains: (1) height, weight, and head circumference; (2) general medical exam; (3) funduscopic exam; (4) cranial nerves; (5) stance and gait; (6) involuntary movements; (7) sensation; (8) cerebellar function; (9) muscle bulk, tone and strength; (10) tendon reflexes, (11) Babinski sign; and (12) other findings. Results for each of these domains were scored as ''normal'' or ''abnormal'' and summarized in the CNS, ranging from 0 to 76, with 76 being perfect. It was previously shown that this instrument has good inter-rater reliability and correlates with other measures of disease severity. Based on CNS scores, the neurological phenotype was described as severe (CNS 40—49); moderate (CNS 50—59) or mild (CNS 60—69). The minimal phenotype (CNS 70—76) merged with the control subjects.

The ^{18}F-FDG-PET images of 7 healthy adults were used as the control group. Informed consent was obtained in every case. Mean age of the healthy participants was 44 ± 10.9 years (range 36—58). No neurological or other medical problems were reported in this group, and their CNS scores were normal (70—76).

PET scanning protocol: image acquisition

An interictal ^{18}F-FDG-PET scan was obtained in patients following a bolus injection of 10 mCi ^{18}F-FDG-PET after a 6-h