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Thalamic hypoperfusion and disrupted cerebral blood flow networks in idiopathic generalized epilepsy: Arterial spin labeling and graph theoretical analysis

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ABSTRACT

Purpose: The aim of this study was to investigate interictal cerebral blood flow (CBF) distributions and graph theoretical networks in idiopathic generalized epilepsy (IGE) using arterial spin labeling (ASL) imaging and anatomical covariance methods of graph theoretical analysis.
Material and methods: We recruited 19 patients with IGE and 19 age-/gender-matched healthy controls. Their CBF images were obtained by pseudo-continuous ASL imaging and compared using statistical parametric mapping 8 software (SPM8) and Graph Analysis Toolbox (GAT).
Results: The ASL imaging could detect interictal hypoperfusion in the thalamus, upper midbrain, and left cerebellum in IGE. Additionally, the graph theoretical analyses revealed characteristic findings of the CBF network of IGE, including significantly reduced resilience to attacks and changes of regional clustering especially in the bilateral temporo-occipital areas and lateral frontal lobes. There was no significance in the comparisons of network metrics.
Conclusion: These findings could contribute to a better understanding of the pathophysiology of IGE.

1. Introduction

Idiopathic generalized epilepsy (IGE) is a group of age-related epilepsy syndromes with non-focal mechanisms and no identifiable cause other than genetic predisposition. IGE is characterized by primarily generalized seizures and discharges on electroencephalography (EEG) (Panayiotopoulos, 2005). Although conventional MRI typically produces normal results for IGE, several studies of voxel-based morphometry (VBM) have reported subtle gray-matter abnormalities in group comparisons (Betting et al., 2006; Huang et al., 2011; Kim et al., 2007). However, the pathophysiology of IGE is not yet clear.

A previous study of cerebral blood flow (CBF) in IGE by single photon emission computed tomography (SPECT) revealed interictal hypoperfusion in several areas including the thalamus (Joo et al., 2008), where multiple imaging modalities have identified abnormalities in IGE (Bernasconi et al., 2003; Huang et al., 2011;

Abbreviations: IGE, idiopathic generalized epilepsy; EEG, electroencephalography; VBM, voxel-based morphometry; CBF, cerebral blood flow; SPECT, single photon emission computed tomography; ASL, arterial spin labeling; GTCS, generalized tonic-clonic seizures; MS, myoclonic seizures; AbS, absence seizures; pCASL, pseudo-continuous arterial spin labeling; DARTEL, diffeomorphic anatomical registration using the exponentiated lie; GAT, graph analysis toolbox; BC, betweenness centrality; SPM8, statistical parametric mapping 8; AUC, areas under a curve; JME, juvenile myoclonic epilepsy; NAA, *N*-acetylaspartate; Cr, creatine; DTI, diffusion tensor imaging; JAE, juvenile absence epilepsy.

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Kim et al., 2013; Wang et al., 2012). Although regional CBF can also be evaluated noninvasively by arterial spin labeling (ASL) imaging (Ota et al., 2013), studies on differences in interictal ASL findings between subjects with and without IGE are limited. Verifying the reliability of CBF findings by ASL would be meaningful for future noninvasive investigation of IGE.

Graph theoretical analysis has recently attracted attention in the study of epilepsy (Bernhardt et al., 2015), and can be used to evaluate CBF networks (Melie-Garcia et al., 2013). Several studies have revealed graph theoretical differences on other modalities in IGE (Caeyenberghs et al., 2015; Chowdhury et al., 2014b; Zhang et al., 2011), but CBF networks in IGE are still poorly understood. Thus, we expected that network findings about CBF would contribute to better understanding of the pathophysiology of IGE. The aim of this study was to investigate CBF distributions and graph theoretical findings related to IGE by using ASL imaging and graph theoretical analysis.

2. Methods

2.1. Subjects

We recruited 19 patients with IGE (6 males, 13 females, mean ± SD age: 26.4 ± 7.7 years) at our institute between March and April 2016. The diagnosis of IGE was based on (1) the presence of primarily generalized seizures with no focal symptoms, (2) diffuse (poly)spike-wave complex on interictal conventional scalp EEG, and (3) no focal abnormality on conventional MRI. Of the 19 patients, 9 had only generalized tonic-clonic seizures (GTCS), whereas 7 had myoclonic seizures (MS) and 3 had typical absence seizures (AbS) in addition to GTCS. All patients were treated with anti-epileptic drugs (monotherapy/polytherapy, 12/7: sodium valproate 16, lamotrigine 4, levetiracetam 3, zonisamide 1, phenobarbital 1, clonazepam 1). We also recruited 19 age- and gender-matched healthy volunteers as controls (6 males, 13 females, mean ± SD age: 26.8 ± 6.6 years). There were no significant differences in age and gender between the two groups ($p = 0.88$ by unpaired *t*-test, $p = 0.73$ by Pearson's χ^2 with Yates' correction, respectively).

All participants gave written informed consent, and this study was approved by the institutional review board at the National Center of Neurology and Psychiatry Hospital.

2.2. MRI acquisition and processing

The MRI for all participants was performed on a 3.0-T MR system with a 32-channel coil (Philips Medical Systems Achieva, Best, The Netherlands). We confirmed that the patients had no seizures within the 24 h prior to the examination by interview, and no seizures were observed during the scan.

The CBF estimation was performed using the pseudo-continuous arterial spin labeling (pCASL) technique. The imaging parameters for the pCASL experiments were single-shot gradient-echo planar imaging in combination with parallel imaging (sensitivity encoding factor 2.0), repetition time/echo time 4000/12 ms, number of excitations 32, matrix 64 × 64, field of view 24 × 24 cm, 7-mm slice thickness with 1-mm gap, 20 slices, labeling duration 1650 ms, postspin labeling delay 1520 ms, time interval between consecutive slice acquisitions 32.0 ms, radio frequency duration 0.5 ms, pause between radio frequency pulses 0.5 ms, labeling pulse flip angle 18°, bandwidth 3.3 kHz/pixel, echo train length 35. Thirty-two pairs of control/label images were acquired and averaged. For measurement of the magnetization of arterial blood and also for segmentation purposes, an echo planar imaging M0 image was obtained separately with the same geometry and the same imaging parameters as the pCASL but without labeling.

We transferred the collected data to CBF maps using ASLtbx software working on Matlab 2014a (Wang et al., 2008). As the slice gap that we used was somewhat large, simple 2D median filtering (3 × 3 voxels) was used. Subsequently the CBF maps were normalized with the DARTEL (diffeomorphic anatomical registration using the exponentiated lie) registration method (Ashburner, 2007) using a template made from the average CBF maps of healthy subjects previously recorded at our institute. Each map was then spatially smoothed with a 4-mm FWHM Gaussian kernel.

2.3. Graph theoretical analysis

This study used the Graph Analysis Toolbox (GAT) (Hosseini et al., 2012), which is an open-source package that provides a graphical user interface to facilitate analyses and comparisons of anatomical brain networks. We applied the normalized CBF images of both groups to GAT running in MATLAB 2014a, with age and gender as nuisance covariates. The region of interest (ROI) scheme comprised 90 cortical and subcortical regions from the Automated Anatomical Labeling template (Tzourio-Mazoyer et al., 2002).

GAT was used to analyze all 90 ROIs, and a 90 × 90 association matrix for each group and modality was generated using the Pearson correlation coefficient. The matrices were thresholded at multiple densities (ranging from 0.10 to 0.50 at intervals of 0.02) and converted into binary adjacency maps. GAT was also used to quantify the network hubs based on measures of betweenness centrality (BC).

Subsequently, the following network metrics were calculated: the clustering coefficient (*C*), a measure of the number of edges that exist between each node's nearest neighbors; the characteristic path length (*L*), which is the average shortest path length between all pairs of nodes as a measure of network integration; the global efficiency (E_{glob}), a measure of the exchange of information across the whole network, which is inversely related to the path length; and the small-worldness (σ), which was calculated as $[C/C_{rand}]/[L/L_{rand}]$, where C_{rand} and L_{rand} are the mean clustering coefficient and the characteristic path length of 20 random networks, respectively. Here, $[C/C_{rand}]$ is the normalized clustering coefficient (γ), and $[L/L_{rand}]$ is the normalized characteristic path length (λ).

In addition, the network resilience to random failure and to targeted attack was evaluated. Random failure was assessed by randomly removing one node from the network and measuring changes repetitively, whereas a targeted attack was assessed by removing the nodes in rank order of decreasing nodal BC.

For regional comparisons between the IGE and control groups, GAT was used to perform nonparametric permutation tests and assess the regional difference in the clustering between the two groups.

The above analyses were fully automatic; the details of the processes are described in a previous paper (Hosseini et al., 2012).

2.4. Statistical analyses

CBF maps comparisons: To confirm morphological differences between the IGE and control groups, we subjected normalized CBF images to two-sample *t*-test analysis in the statistical parametric mapping 8 software program (SPM8; http://www.fil.ion.ucl.ac.uk/spm/), with age and gender as nuisance covariates. Differences that met the following criteria were deemed significant: a height threshold of $p < 0.001$ (uncorrected) and an extent threshold of $p < 0.05$.

Graph-Theoretical Comparisons: GAT compared the areas under a curve (AUC) of each network measure of both groups. To test the