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Original article

Structural brain network analysis of children with localization-related epilepsy

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Abstract

Introduction: Epilepsy is considered to arise from dysfunction in neural networks. Recent advances in neuroimaging and its analysis have made it possible to investigate both functional and structural connectivity in the brain. The aim of this study was to elucidate alterations in the structural connectivity in children with localization-related epilepsy using the mathematical method of graph theoretical analysis.

Methodology: Fifteen children with localization-related epilepsy (8 female subjects; mean age, 8.5 ± 3.5 years) as an epilepsy group and 23 children without a history of seizure (12 female subjects; mean age, 8.9 ± 3.7 years) as a control group underwent three-dimensional T1-weighted brain magnetic resonance imaging (MRI). Gray matter images segmented and spatially normalized from the MRIs of both groups were analyzed using statistical parametric mapping with the Graph Analysis Toolbox. We compared global networks (global efficiency, clustering coefficient and network strength) and regional networks (betweenness centrality and clustering) between patients and controls.

Results: The global efficiency tended to be increased ($p = 0.081$) and the global modularity was significantly increased ($p = 0.017$) in the epilepsy group as compared with the control group. The epilepsy group showed locally decreased betweenness centrality mainly in the bilateral cingulate gyri, right perisylvian area, and bilateral precentral gyri, and locally increased clustering in the bilateral cingulate gyri, right perisylvian area, and medial frontal lobes as compared with the control group. The epilepsy group showed higher network resilience to random attack and targeted attack than the control group. Voxel-based morphometry did not show any difference between the two groups.

Conclusions: We observed globally increased structural connectivity along with excessive network robustness in patients with localization-related epilepsy. Local abnormality of connectivity was observed mainly in the cingulate gyrus, perisylvian area, and precentral gyrus. This alteration in the structural connectivity without any morphometric changes may be related to the underlying epileptogenicity.

Keywords: Localization-related epilepsy; MRI; Graph theory; Structural connectivity

1. Introduction

Epilepsy is among the most common neurologic disorders leading to substantial morbidity and mortality. The age-adjusted prevalence of epilepsy in developed

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countries is 4–8 per 1000 population [1]. Seizures and epilepsy are generally divided into focal and generalized according to the mode of seizure onset as well as into genetic, structural/metabolic, or unknown according to the underlying cause or etiology [2]. Most of the localization-related epilepsies are either structural or unknown, which means there is a presumed focal structural cause that cannot be identified historically or that cannot be seen with current imaging techniques. In approximately 25% of patients with localization-related epilepsy, no cause is identified, and such cases are designated idiopathic [3]. Benign localization-related epilepsies of childhood, such as benign childhood epilepsy with centrotemporal spikes or benign Rolandic epilepsy, benign occipital epilepsy of childhood and Panayiotopoulos syndrome, are electroclinical syndromes of unknown or genetic cause that occur in developmentally and neurologically normal children and have a benign course, remitting prior to adulthood. These epilepsy syndromes are distinguished from symptomatic focal epilepsy, which refers to epilepsy that results from brain injury or other structural brain disease [4]. Epilepsy is considered to arise from dysfunction in neural networks. Recent advances in neuroimaging and its analysis have made it possible to investigate both functional and structural connectivity in the brain [5]. Most commonly, structural connectivity is inferred from the magnetic resonance imaging (MRI) method known as diffusion tensor imaging (DTI) [6]. When used together with fiber tractography, DTI can reconstruct whole brain white matter networks [7]. Structural connectivity can also be inferred from more standard structural MRI sequences. In a given set of brain regions, either cortical thickness or cortical gray matter volumes can be quantified on three-dimensional T1-weighted MRI [8]. These brain regions are considered connected when they show morphologic correlations across subjects. Recently, graph theoretical analysis has been applied to structural MRI for the evaluation of networks using regional gray matter volumes [9]. This is a mathematical method that enables us to analyze connectivity networks from brain imaging or electrophysiology [10], and is expected to be very useful for the understanding of epilepsy [11]. It provided evidence for a system level disruption of patients with epilepsy. Several reports have provided evidence for a relationship between topological disruptions, clinical markers, and cognitive outcomes in epilepsy patients [12,13]. In adults, there have been a few reports about the differences in structural connectivity between patients of unilateral temporal lobe epilepsy and healthy subjects [14,15], and between patients with temporal lobe epilepsy with psychosis and without psychosis [16] based on graph theory. To our best knowledge, however, there has been no report in children using this method. In the present study, we aim to elucidate the alterations in structural connectivity in children with localization-related epilepsy using a mathematical method of graph theoretical analysis.

2. Materials/subjects

Ethical approval for this study was obtained from the St. Marianna University Graduate School of Medicine Committee on the Ethics of Human Clinical Research (No. 3148). The distribution of epilepsy and epileptic syndromes was reported according to the classification by the International League Against Epilepsy (ILAE) in 1989 [17] but new diagnostic entities such as Panayiotopoulos syndrome were included according to a previous report [2]. Patients with localization-related epilepsy ($n = 15$, 8 female subjects, mean age 8.5 $\pm$ 3.5 years, range 3–12 years) were enrolled. All patients had no abnormal MRI findings. The diagnosis of localization-related epilepsy was performed by a specialist from the Japan Epilepsy Society using clinical characteristics and abnormal electroencephalography (EEG) findings of focal sharp waves. Control subjects ($n = 23$, 12 female subjects, mean age 8.9 $\pm$ 3.6 years, range 2–14 years) without histories of either febrile or non-febrile seizures were recruited. The exclusion criteria for all subjects were as follows: (1) children under 2 years or over 15 years of age, (2) a significant brain MRI abnormality (e.g., focal cortical dysplasia, vascular malformation, tumor), (3) a history of brain surgery, meningitis, acute encephalitis, severe head trauma, cerebral stroke, hydrocephalus, or developmental abnormalities. All subjects had no concerns about development or behavior in daily life. We obtained the clinical data of all subjects, including age, gender, past history, onset age of seizures, duration from seizure onset, anti-epileptic drugs, history of present illness, and prior use of sedative drugs for brain MRI. No brain MRI images were newly obtained for purposes of this study; rather, all images were obtained through standard medical practice. The need for patient informed consent was waived in retrospective patients, and written informed consent was obtained in prospective patients.

3. Methods

3.1. MRI acquisitions, processing, and morphometry

MRI for all participants was performed on a 1.5 Tesla MR system (Achieva 1.5 Tesla, Release 3.2; Phillips Medical Systems, The Netherlands). The parameters of three-dimensional sagittal T1-weighted magnetization prepared rapid acquisition with gradient echo (MPRAGE) images were as follows: repetition time (TR)/echo time (TE) of 7.12 ms/3.4 ms; flip angle of 10°; number of excitations (NEX) = 1; 0.6-mm effective slice thickness with no gap; 300 slices; matrix of