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Cognitive functions, electroencephalographic and diffusion tensor imaging changes in children with active idiopathic epilepsy

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ABSTRACT

Introduction: Neurocognitive impairment represents one of the most common comorbidities occurring in children with idiopathic epilepsy. Diagnosis of the idiopathic form of epilepsy requires the absence of any macrostructural abnormality in the conventional MRI. Though changes can be seen at the microstructural level imaged using advanced techniques such as the Diffusion Tensor Imaging (DTI).
Aim of the work: The aim of this work is to study the correlation between the microstructural white matter DTI findings, the electroencephalographic changes and the cognitive dysfunction in children with active idiopathic epilepsy.
Methods: A comparative cross-sectional study, included 60 children with epilepsy based on the Stanford–Binet 5th Edition Scores was conducted. Patients were equally assigned to normal cognitive function or cognitive dysfunction groups. The history of the epileptic condition was gathered via personal interviews. All patients underwent brain Electroencephalography (EEG) and DTI, which was analyzed using FSL.
Results: The Fractional Anisotropy (FA) was significantly higher whereas the Mean Diffusivity (MD) was significantly lower in the normal cognitive function group than in the cognitive dysfunction group. This altered microstructure was related to the degree of the cognitive performance of the studied children with epilepsy. The microstructural alterations of the neural fibers in children with epilepsy and cognitive dysfunction were significantly related to the younger age of onset of epilepsy, the poor control of the clinical seizures, and the use of multiple antiepileptic medications.
Conclusion: Children with epilepsy and normal cognitive functions differ in white matter integrity, measured using DTI, compared with children with cognitive dysfunction. These changes have important cognitive consequences.

1. Introduction

Epilepsy occurs as a result of excessive, hypersynchronous discharge of the brain neurons which is manifested as recurrent paroxysmal alteration of the neurologic functions [1]. The highest prevalence rate of epilepsy is recorded during childhood [2]. Cognitive dysfunction is one of the common comorbidities occurring with epilepsy. Several factors are suspected of contributing to the occurrence of cognitive dysfunction in children with epilepsy including the location of the seizure foci, the frequency of seizures, the duration of the seizure disorder, the age of onset of epilepsy, and the Antiepileptic Drug (AED) effects [3,4].

Children with idiopathic epilepsy with or without cognitive dysfunction do not have any detectable macrostructural abnormality in conventional magnetic resonance imaging (MRI) [5]. However, changes at the microstructural or the functional level can be found [6]. Diffusion Tensor Imaging (DTI) is an MRI imaging sequence that measures the diffusion properties of the water protons in tissues. The analysis of the images can provide information about the subtle white matter changes in the pathological state [7,8].

The purpose of the current research is to study the correlation between the Electroencephalographic (EEG) changes, the microstructural white matter abnormalities, detected using DTI, and the degree of cognitive dysfunction in children with active idiopathic epilepsy.

2. Patients and methods

A cross-sectional comparative study, which included 60 children with epilepsy (3–12 years) attending public hospitals in the Ismailia governorate, was carried out. Epilepsy and epileptic syndromes were classified as idiopathic depending on the age at seizure onset, the type of seizures, the electroencephalographic changes, family history, and

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the absence of any structural brain abnormality or other neurological signs or symptoms. Children with additional neurological impairment other than epilepsy (such as hypoxic ischemic EEG and developmental delay) and patients with abnormal MRI findings (such as tumor, inflammation, vascular malformation, postinfection, and congenital or developmental abnormality at the time of the study) were excluded from the study.

An informed consent was taken from the caregivers of the children with epilepsy before taking any data or doing any investigations. The research was approved by the Faculty of Medicine, Suez Canal University Health Research Ethics Board; it follows The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans.

The clinical data were collected in a preorganized data sheet for each patient including the age, gender, duration of epilepsy, age of the disease onset, type of epilepsy, frequency of seizures, and the number of antiepileptic medications. All subjects included in the study underwent neuropsychological assessment using the Stanford–Binet Intelligence Scale, fifth edition. Accordingly, children included in the study were assigned to one of the following groups according to their Intelligence Quotient (IQ):

- Children with epilepsy and normal cognitive functions (IQ > 80).
- Children with epilepsy and cognitive dysfunction (IQ < 80).

Interictal, artifact free, EEG was performed for at least 30 min. The methods used to provoke abnormalities included hyperventilation, photic stimulation, and sleep. All EEG traces were reported by a neurology consultant who was blinded to the clinical details. EEG traces were analyzed as regards the background activity frequency, the amplitude, as well as the occurrence of any defined abnormality such as the presence of epileptiform abnormalities in a focal or generalized distribution.

Children with epilepsy included in the research underwent conventional MRI with a superconducting magnet with a main strength of 1.5 T (Philips Achieva R 2.5.3) to identify any structural brain abnormality. The brain was imaged in the axial, coronal, and sagittal planes with 5 mm slice thickness. TI was then carried out only for patients with no structural abnormality from both groups to assess the intrinsic properties of water diffusion in the brain using quantitative parameters. The imaging was employed in 16 noncollinear directions with a "b" value of 800 s/mm.

Voxel based analysis using FSL 5.0 was then performed based on Ubuntu 14.3 Operating systems [9]. First, the preprocessing of each volume has been employed, which includes the eddy current correction induced by the gradient coils and subject movement correction for each b-value volume in order to allow for variability of each b-value using the "eddy_correct" tool. The Brain Extraction Tool (BET) was then used to estimate the inner and outer skull surfaces and outer scalp surface and extract the brain tissue from the skull [10].

Diffusion tensors, for each voxel, were fitted using the least squares method [10] using DTIFIT tool, where the volume tensors, the eigenvalues, and eigenvectors in addition to Fractional Anisotropy (FA) and Mean Diffusivity (MD) were calculated. The FA and MD maps were then automatically coregistered and normalized with T_2 volume using FMRIB's Linear Image Registration Tool (FLIRT) [9] in order to prepare the data for the Atlas based segmentation of the regions of interest. The different white matter tracts were localized and segmented, for the extracted anisotropy maps, using FSLView tool, which employs publicly accessible white matter atlases and tractography reports [11,12]. In order to extract the masks for the neurocognitive function tracts (the superior longitudinal fasciculus, the inferior longitudinal fasciculus, the arcuate fasciculus, the uncinate fasciculus, and the inferior frontooccipital fasciculus), the Harvard–Oxford subcortical structure and JHU white matter tractography atlases were applied [13]. To segment the aforementioned tracts, FSL stat was used. Moreover, FSL stat was employed to calculate the mean and variance of the FA and MD across the different extracted tracts for the subjects of this study.

Table 1
Frequency of convulsions in patients with epilepsy with normal cognitive functions and patients with epilepsy with cognitive dysfunction.

Frequency of convulsions	Patients with epilepsy with normal cognitive functions n = 30	Patients with epilepsy with cognitive dysfunction n = 30	P value*
Weekly	0 (0%)	7 (23.3%)	0.006**
Monthly	11 (36.7%)	13 (43.3%)	
Yearly	19 (63.3%)	10 (33.3%)	

Fisher exact test.
* Statistically significant at P < 0.05.
** Highly statistically significant at <0.01.

3. Data management and statistical analysis

The quantitative data were expressed in terms of the mean ± Standard Deviation (±SD) while qualitative data were expressed as numbers. Student *t*-test was used to test the significance of the difference between the means of the 2 groups while the Chi square test was used to test the significance of the difference between qualitative data. Moreover, Spearman correlation and multivariate linear regression tests were used to assess the correlation between the EEG abnormalities, the white matter abnormalities, and the presence of cognitive dysfunction in children with epilepsy. Furthermore, Spearman's rho test was used to explore the linkage between the epilepsy-related factors and the cognitive impairment including the age of epilepsy onset, the duration of the disease, the seizure frequency, and the AED history. A probability value (P-value) < 0.05 was considered statistically significant [14].

4. Results

The current study included 60 children with epilepsy; 26 males and 32 females with age range of 3–12 years. The mean age of onset of epilepsy in children with epilepsy and normal cognitive functions was (4.93 ± 1.48 years) which is considered significantly higher than that in children with epilepsy and cognitive dysfunction (2.60 ± 1.57). There is no statistically significant difference between the durations of epilepsy in children with epilepsy and normal cognitive functions and children with epilepsy and cognitive dysfunction.

The frequency of occurrence of clinical seizures (Table 1) and the presence of interictal EEG discharges (Table 2) were significantly lower for patients with normal cognitive functions than for children with epilepsy and cognitive dysfunction.

All 30 (100%) children with epilepsy and normal cognitive functions used monotherapy. On the other hand, only 19 (63.3%) of the children with epilepsy and cognitive dysfunction were on monotherapy. Eleven (36.7%) children and epilepsy and cognitive dysfunction used multiple medications for epilepsy treatment.

Table 2
Frequency of occurrence of interictal electroencephalographic epileptogenic discharges in the studied patients.

EEG changes	Patients with epilepsy with normal cognitive functions n = 30	Patients with epilepsy with cognitive dysfunction n = 30	P value*
Normal	15 (50%)	4 (13.3%)	0.009**
Focal	8 (26.7%)	15 (50%)	
generalized	7 (23.3%)	11 (36.7%)	

Chi square test.
* Statistically significant at P < 0.05.
** Highly statistically significant at <0.01.