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The effect of nocturnal epileptic seizures on cognitive functions in children with idiopathic epilepsy

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Abstract

Background: Cognitive impairment is a common finding epileptic children. Studies have linked nocturnal epileptic discharges to delayed cognitive abilities in children.

Objective: The study aims to evaluate the effect of nocturnal epileptic seizures on cognitive functions in children with idiopathic epilepsy.

Patients and methods: The study was conducted on 70 children with idiopathic generalized or benign focal epilepsy. Based on seizures semiology, they were classified into cases either with nocturnal epileptic seizures (NES) ($n = 40$) or with diurnal epileptic seizures (DES) ($n = 30$). Patients receiving antiepileptic drugs (AEDs) that affect cognitive function, patients with intelligence quotient (IQ) below 70, and those having other neurological or psychiatric disorders' were excluded. All patients were subjected to neurological examination, brain magnetic resonance imaging (MRI), and electroencephalography. Cognition was assessed using Wechsler Intelligence scale for children (WISC) to measure IQ, Wisconsin card sorting test (WCST) (computerized version), Trail Making Test, and Digit spans test.

Results: There was no significant difference between both groups regarding age, sex, age of epilepsy onset, or seizure frequency. There was a significant difference in almost all cognitive variables including digit forward, digit backward, processing speed, verbal IQ, WCST perseverative responses, WCST failure to maintain set, Trail Making Test A (error), Trail Making Test B (Time), and Trail Making Test B (error). There was no significant difference regarding the associated sleep disturbances between the studied groups.

Conclusion: Children with idiopathic epilepsy suffering from predominant nocturnal seizure have overt and subtle cognitive functions impairments compared to children with predominant diurnal seizure.

Keywords: Nocturnal epileptic seizures, Cognition, Idiopathic epilepsy, Executive function, Children with epilepsy

Introduction

Epilepsy is a common neurological disorder affecting 65 million patients worldwide with a crude lifetime prevalence rate of 12.67/1000 Egyptian inhabitants [1]. Epilepsy is associated with cognitive impairment as population studies estimate the prevalence of mental

retardation with intelligence quotient (IQ) less than 70 at 20–30% of epileptic children [2].

Early age of onset, secondary epilepsy, epileptic encephalopathy, and antiepileptic drugs (AEDs) are associated with cognitive dysfunction. These dysfunctions may present at the onset of epilepsy, and they mostly affect attention, executive functions, memory, and thought process [3].

A recent study found an association between nocturnal epileptic discharges and delayed linguistic cognitive

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abilities in children [4]. Yet, limited information is available about the associations between the cognitive deficit and the seizure timing.

Aim of the study

The study aims to evaluate the effect of nocturnal epileptic seizures on cognitive functions in children with idiopathic epilepsy (idiopathic generalized epilepsy and benign focal epilepsy of childhood).

Patients and methods

This was a prospective cross-sectional study that was conducted on 70 children with idiopathic generalized or benign focal epilepsy attending to the outpatients Neurology clinic at Tanta University Hospital, Tanta, Egypt, in the period from September 2017 to September 2018. Based on seizures semiology, the patients were classified into nocturnal epileptic seizure (NES) group ($n = 40$) with more than 90% of seizures occurring predominantly at sleep time and diurnal epileptic seizure (DES) group ($n = 30$).

Exclusion criteria include patients treated with AEDs with overt cognitive adverse events, such as topiramate, phenobarbitone, or valproate [5, 6], patients with IQ less than 70 and those with a history of head trauma, and other neurological or psychiatric disorders as well as children with drug-resistant epilepsy.

All patients were subjected to meticulous history taking, neurological and general examination, and brain magnetic resonance imaging (MRI) using Magnetom Sempra 1.5 Tesla, Seimens, Germany. Electroencephalography (NicoletOne vEEG System, Natus Medical Incorporated, USA), cognitive function assessment, and sleep quality assessment by the Children's Sleep Habits Questionnaire (CSHQ) [7]. A questionnaire was designated for the assessment of sleep patterns and sleep problems in children by parents.

Cognition was assessed using the following: (A) Wechsler Intelligence scale for children (WISC) to measure IQ in children, adolescent, and adult patients. WISC is one of the most widely used tests of intelligence for school-age children and adolescents. The third edition of the Wechsler Intelligence scale for children (WISC-III-R) (verbal IQ, a performance IQ, and a combined full-scale IQ) was applied. (B) Wisconsin card sorting test (WCST) (computerized version) to evaluate set shifting, working memory, conceptual problem-solving ability, use of feedback, the ability to modify incorrect strategies, flexibility, and inhibition of prepotent but incorrect responses. (C) Trail Making Test: part A can measure visual search through drawing lines in ascending order from 1 to 25 (standard test sheet). The score of the test consists of the number of seconds taken by the subject to solve the problem. Errors are not

corrected, but the stop watch is running while the subject corrects them. Part B is the same as part A but with lines drawn from 1 to 13 and from A to L to be connected by alternating between numbers and letters in ascending order. The results are scored in seconds as in part A. This part was used to assess distracted attention and set shifting components of executive functions. (D) digit spans (DS) subtest of the Wechsler scales which is comprised of digits forward (DF) and digits backward (DB) components that yield separate raw scores but they are combined to give a single scaled score. DF is a task of short-term auditory memory, sequencing, and simple verbal expression, while DB is more sensitive to deficits in verbal working memory. The DS scaled score, the longest digits forward raw score, and the longest digits backward raw score were used in this study.

All cognitive assessments were done while the patients were seizure-free for at least 1 month before participation in the current study. The study protocol was approved by the ethical committee in Tanta University, Egypt, under the code number (31398/02/17) on February 2017. Participation was voluntary and all contributors' parents received detailed information about the aims of this research work, and an informed written consent was obtained prior to the commencement of the study.

Statistical analysis was conducted using SPSS version 19, 2011, created by IBM, Chicago, IL, USA. For numerical values, the range and mean \pm SD were calculated. Correlation analysis was performed using Pearson's correlation test. P value < 0.05 was considered statistically significant.

Results

This study included 70 idiopathic epileptic patients with age ranging from 6 to 18 years. Based on seizures semiology, they were classified into NES group ($n = 40$) with more than 90% of seizures occurring predominantly at sleep time and DES group ($n = 30$). There were no significant differences between both groups regarding age and sex as shown in Table 1.

In the NES group, 22 patients had benign focal epilepsy (15 had benign childhood epilepsy with centrotemporal spikes, 6 had benign occipital epilepsy of childhood (Gastaut syndrome), and 1 had Panayiotopoulos syndrome), while 18 patients had idiopathic generalized epilepsy (12 with generalized tonic clinic fits, 4 with juvenile myoclonic epilepsy, and 2 with childhood absence epilepsy).

In the DES group, 14 patients had benign focal epilepsy (9 had benign childhood epilepsy with centrotemporal spikes, 2 had benign occipital epilepsy of childhood (Gastaut syndrome), and 3 had Panayiotopoulos syndrome), while 16 patients had idiopathic

Table 1 Demographic data in the studied groups

Demographic data		Nocturnal epileptic seizure	Diurnal epileptic seizure	P value
Age (years)	Range	6–18	6–18	0.61
	Mean \pm SD	11.7 \pm 3.61	11.13 \pm 3.51	
Sex	Males	17(42.5%)	15(50%)	0.751
	Females	23(57.5%)	15(50%)	

generalized epilepsy (6 with generalized tonic clinic fits, 1 with juvenile myoclonic epilepsy, and 9 with childhood absence epilepsy).

No one of our patients was diagnosed as drug-resistant epilepsy as most of seizures in the 6 months before the study were due to the poor compliance of medication or concurrent illness (common cold, fever gastroenteritis). The frequency of seizure was calculated by dividing the total number of seizure in the last year on 12 months.

There were no significant differences between both groups regarding age of epilepsy onset or the duration since epilepsy was diagnosed. Also, there were no significant differences between both groups in the types and frequency of seizure as shown in Table 2.

Regarding cognitive functions, when comparing both group, there was a significant difference in almost all cognitive variables including digit forward, digit backward, processing speed, verbal IQ, WCST perseverative responses, WCST failure to maintain set, Trail Making Test A (error), Trail Making Test B (Time), and Trail Making Test B (error), but there were no statistically significant differences in performance IQ, total IQ, and Trail Making Test A (time). Also, no statistically significant differences were observed between the studied groups regarding the associated sleep disturbances as measured CSHQ as shown in Table 3.

In the NES group, there was a significant correlation between focal seizures and digit forward, digit backward, performance and verbal IQ, total IQ, WCST (failure to maintain set, perseverative responses), Trail Making Test A (time, error), and Trail Making Test B (time), while in DES group, we found a significant correlation between focal seizures from one side and performance and verbal IQ, total IQ, and Trail Making Test A (time, error) from the other side (Table 4).

In the NES group, the duration of epilepsy was in negative correlation with digit forward, processing speed, and performance and verbal IQ, while it was positively correlated with WCST perseverative responses and WCST failure to maintain set. The DES group showed the same results in addition to a significantly negative correlation of the duration of epilepsy with digit backward and total IQ (Table 4).

Frequency of seizures in NES showed a significantly negative correlation with digit forward, digit backward, processing speed, verbal IQ, performance IQ, and total IQ, and it was positively related with WCST failure to maintain set, which was the same in DES except the positive correlation of frequency of seizures with WCST perseverative responses, instead of WCST failure to maintain set (Table 4).

Discussion

Studies examining the cognitive and behavioural outcomes of epileptic children show that children with epilepsy perform more poorly than their peers; however, the general intellectual function tends to be less affected [8]. Cognitive problems in affected children exist from the beginning of epilepsy, and their progression afterwards depend on the underlying pathology, disease dynamics, AEDs side effects, and seizure control [9].

Children with NES have behavioral, cognitive, and academic impairments. They may, moreover, experience regression in previously acquired skills. Furthermore, the cognitive consequences of NES can depend on brain maturation at NES onset [4]. However, there is an ongoing debate regarding the causal relation between NES and cognitive impairment [10].

Aiming to study the effect of NES on cognitive function in children, we conducted this study on 70 children with idiopathic epilepsy, and they were classified into cases either with NES or with DES.

Table 2 Seizure characteristics in the studied groups

Clinical data		Nocturnal epileptic seizure	Diurnal epileptic seizure	P value
Age of onset (years)		8.26 \pm 2.84	11.13 \pm 3.51	0.81
Type	Generalized	18(45%)	16(53.4%)	0.76
	Focal	22(55%)	14(46.6%)	
Duration(years)		3.56 \pm 0.89	3.56 \pm 1.15	0.98
Frequency per month		1.1 \pm 0.46	0.85 \pm 0.77	0.31

Table 3 Cognitive functions in both groups

Cognitive functions	Nocturnal epileptic seizure	Diurnal epileptic seizure	t value	p value
Digit forward	3.8 ± 0.48	4.3 ± 0.66	4.78	0.0001
Digit backward	2.17 ± 0.78	3 ± 0.78	4.11	0.0002
Processing speed	82.57 ± 6.13	87.35 ± 5.83	3.51	0.0012
Performance IQ	85.21 ± 6.04	85.76 ± 5.59	1.34	0.188
Verbal IQ	85.93 ± 5.26	86.65 ± 5.09	3.54	0.0011
Total IQ	85.36 ± 5.9	86 ± 5.52	1.38	0.174
WCST(PR)	24.09 ± 4.82	15.19 ± 5.01	5.57	0.0001
WCST (FMS)	7.21 ± 1.67	3.18 ± 0.98	8.61	0.0001
TMTA (TIME)	3.52 ± 1.06	3.56 ± 1.09	0.11	0.909
TMT A (error)	4.29 ± 1.04	2.12 ± 0.71	7.24	0.0001
TMTB (Time)	6.30 ± 1.14	3.18 ± 0.83	9.28	0.0001
TMTB (error)	7.43 ± 1.53	3.75 ± 0.93	8.56	0.0001
CSHQ total score	44.7 ± 3.8	43.82 ± 2.4	4.35	0.514

IQ intelligent quotient, *WCST* Wisconsin card sorting test, *PR* perseverative responses, *FMS* failure to maintain set, *CSHQ* Children’s Sleep Habits Questionnaire, *TMT* Trail Making Test

Table 4 Correlation between Cognitive domains, Seizures characteristics and in both groups

Cognitive functions	Seizure timing	Nocturnal epileptic seizure				Diurnal epileptic seizure			
		Age of onset	Type	Duration	Frequency	Age of onset	Type	Duration	Frequency
Digit forward	<i>r</i>	0.74	0.74	-0.88	-0.83	0.52	0.44	-0.75	-0.78
	<i>p</i>	0.0001	0.0009	0.0017	0.005	0.038	0.082	0.018	0.011
Digit backward	<i>r</i>	0.832	0.862	-0.8	-0.8	0.55	0.41	-0.78	-0.79
	<i>p</i>	0.0001	0.0001	0.009	0.009	0.027	0.113	0.012	0.01
Processing Speed	<i>r</i>	0.734	0.35	-0.76	-0.75	0.45	0.49	-0.59	-0.67
	<i>p</i>	0.0002	0.09	0.017	0.018	0.07	0.051	0.005	0.0012
Performance IQ	<i>r</i>	0.78	0.862	-0.62	-0.69	0.56	0.56	-0.55	-0.53
	<i>p</i>	0.0001	0.0001	0.07	0.036	0.021	0.021	0.010	0.014
Verbal IQ	<i>r</i>	0.671	0.866	-0.85	-0.84	0.58	0.515	80.78	-0.72
	<i>p</i>	0.0012	0.0001	0.0034	0.0041	0.017	0.041	0.011	0.02
Total IQ	<i>r</i>	0.84	0.73	-0.82	-0.85	0.57	0.51	-0.79	-0.74
	<i>p</i>	0.0001	0.0001	0.0068	0.0036	0.019	0.040	0.010	0.02
WCST (PR)	<i>r</i>	-0.85	0.93	0.68	0.62	-0.47	0.25	0.68	0.68
	<i>p</i>	0.0008	0.0002	0.04	0.07	0.063	0.34	0.03	0.04
WCST(FMS)	<i>r</i>	-0.75	0.83	0.71	0.72	-0.64	0.48	0.71	0.08
	<i>p</i>	0.0075	0.0053	0.02	0.02	0.0068	0.054	0.02	0.66
TMTA (TIME)	<i>r</i>	-0.78	0.84	0.65	0.64	-0.514	0.560	-0.32	-0.12
	<i>p</i>	0.0043	0.0045	0.05	0.05	0.041	0.0102	0.08	0.51
TMT A (error)	<i>r</i>	-0.71	0.89	0.61	0.27	-0.168	0.583	-0.05	-0.16
	<i>p</i>	0.013	0.0011	0.08	0.47	0.53	0.0069	0.75	0.38
TMTB (Time)	<i>r</i>	-0.64	0.74	0.36	0.32	-0.47	-0.263	-0.15	-0.32
	<i>P</i>	0.033	0.021	0.33	0.39	0.06	0.32	0.42	0.07
TMTB (error)	<i>r</i>	-0.83	0.77	0.26	0.14	-0.38	-0.24	0.12	0.23
	<i>P</i>	0.0014	0.013	0.49	0.7	0.138	0.36	0.502	0.212

IQ intelligent quotient, *WCST* Wisconsin card sorting test, *PR* perseverative responses, *FMS* failure to maintain set, *TMT* Trail Making Test

In the current study, children with NES had a significant lower verbal IQ than children with DES. This is matching with the findings of *Verrotti and colleagues* [11] who studied language delay in children with idiopathic childhood epilepsy with centrotemporal spikes (BCECTs), and they reported that language delay was more apparent in the children with NES than those with DES. Language impairment is observed in several epilepsy syndromes that are characterized by nocturnal epileptiform activities, such as Rolandic epilepsy and nocturnal frontal lobe epilepsy, yet it is not known whether there is a causal relation between NES and language impairment, or it is just an epiphenomenon [12].

Executive functions, a set of skills that is necessary for efficient and goal-directed behaviour, are less studied, despite being affected in epileptic patients [13]. In the current study, processing speed, digit forward, digit backward, WCST perseverative responses, WCST failure to maintain set, Trail Making Test A (error), Trail Making Test B (Time), and (error) were affected in a significant manner in NES group in comparison to DES group.

The disturbance of executive functions in epileptic children may be caused by a number of factors, such as the underlying lesion and/or its neuro-developmental effects, interictal epileptic activity, the total drug load, drug interactions, and the lack of drive and motivation due to depression [9–14]. Recently, impaired executive functions were reported in newly diagnosed drug naïve epileptic children [15]. In the current study, children treated with AEDs that affected cognitive function or those having secondary epilepsy were excluded so we can assume that epilepsy per se plays a fundamental role in the development of cognitive deficit irrespective of other associated factors including sleep disturbance. However, we should clarify that we did not aim to study the effect of interictal epileptic discharges on cognitive functions as our primary concern was to investigate the relation between seizure timing and cognitive function.

Previous studies related the cognitive deficit to the associated sleep abnormalities, but our results showed non-significant difference among studied patients regarding CSHQ scores so we can assume that other factors, such as metabolic disruption induced by NES play a role in the regression of cognitive skills more than abnormal memory consolidation during sleep alone [16]. The results of the current study are supported with the previous works by *Holleys and colleagues* [17] and *Licchetta and colleagues* [18] who studied the effect of nocturnal seizure on executive functions; they reported that the infection of these functions in children with NES was not related to sleep disturbances, and this was the same in epileptic and control groups.

The age of seizure onset is related to cognitive impairment as shown in our results. Childhood-onset epilepsy

is associated with several cognitive disorders compared to healthy peers, and it affects mainly linguistic and semantic functions as well as motor and visual functions. This is going with many neuropsychological investigations of children done at earlier stage of life showing cognitive abnormalities even in epilepsy syndromes that were previously considered to be idiopathic and uncomplicated [19].

The hippocampus (HPC) has been increasingly seen to be involved in executive tasks through its connectivity with the prefrontal cortex (PFC), and there is growing evidence for protracted maturation of HPC-PFC circuits through adolescence. While PFC has long been associated with cognitive control tasks, accumulating research suggests that HPC has a role in supporting both working memory and executive functions [20].

Studies in humans and animals suggest that epileptogenic pathology results in specific functional and anatomic abnormalities affecting the maturing hippocampus. The hippocampus has an essential role in the acquisition of new memories which later on become encoded in neocortical regions. This process has been shown to be related to sleep spindles and the duration of slow-wave sleep. During the slow-wave sleep, protein synthesis required for long-term potentiation also appears to be increased which in turn results in facilitating synaptic reorganization and memory consolidation [21]. Also, childhood-onset TLE has reduced the total volume of white matter associated with the poorer cognitive performance [22].

Conclusion

Children with idiopathic epilepsy suffering from predominant nocturnal seizure have overt and subtle cognitive functions impairments especially the executive functions compared to children with predominant diurnal seizure.

Study limitation

The absence of a control group of age and sex in healthy children is to evaluate the cognitive deficit in children with NES in relation to their healthy peers.

The limited number of patients regarding the diversity of seizure semiology and type of epilepsy. Hence, another large study with recruiting more patients is highly recommended.

Abbreviations

AEDs: Antiepileptic drugs; CSHQ: Children's Sleep Habits Questionnaire; DB: digits backward; DES: Diurnal epileptic seizures; DF: Digits forward; MRI: Magnetic resonance imaging; NES: Nocturnal epileptic seizures; WCST: Wisconsin card sorting test; WISC: Wechsler Intelligence scale for children; IQ: Intelligent quotient; PR: Perseverative Responses; FMS: Failure to maintain set; TMT: Trail Making Test; HPC: The hippocampus; PFC: prefrontal cortex

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Authors' contributions

All authors have participated in designing of the study, acquisition of data, data interpretation, and revising. AA recruited the patient and carried out clinical, neurological evaluation and editing the manuscript. SA carried out cognitive function assessment. KR recruited some patient and carried out clinical, neurological evaluation and participated in interpretation of the study results. OR recruited the patient and carried out clinical, neurological evaluation and editing the manuscript. The authors read and approved the final manuscript.

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Availability of data and materials

All raw data will be available on the editor request.

Ethics approval and consent to participate

The study protocol was approved by the ethical committee in Tanta University, Egypt, under the code number (31398/02/17) on February 2017. Participation was voluntary and all contributors' parents received detailed information about the aims of this research work, and an informed written consent was obtained prior to the commencement of the study.

Consent for publication

Not applicable.

Competing interests

The authors have no conflict of interest to disclose.

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