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Original Article

Cardiac Autonomic Balance in Children With Epilepsy: Value of Antiepileptic Drugs

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ABSTRACT

BACKGROUND: Dysfunction of the autonomous nervous system causes arrhythmias and, although previous studies have investigated the effects of epilepsy on the autonomic control of the heart, there is still uncertainty about whether imbalance of sympathetic, vagal, or both systems occurs in epilepsy as well as the effect of anticonvulsants on the autonomic system. **AIM:** To evaluate cardiac autonomic status in children with epilepsy on antiepileptic drugs. **PATIENTS AND METHODS:** Sixty patients with epilepsy were recruited from the Outpatient Neurology Clinic at Ain Shams University and were divided into the following groups: group I, drug naive; and group II, patients with epilepsy on regular antiepileptic drugs. The second group was further subdivided into the following groups: group IIa, received monotherapy; and group IIb, received polytherapy. Forty age- and sex-matched healthy children served as controls. Included patients underwent videorecorded electroencephalograph, Holter electrocardiogram (EKG) for time and frequency domains of heart rate variability, and standard EKG recording for QTc, QTd. **RESULTS:** Mean values of all time domain, total power, and high-frequency power were significantly lower, whereas low-frequency and low-frequency/high-frequency power, QTc. and QTd were significantly higher in group I compared with group II and in patients compared with controls. No significant difference was found between patients on different antiepileptic drug regimens regarding heart rate variability values. A significant negative correlation was found between Chalfont severity score and 50% of difference between adjacent, normal RR intervals in patient groups. **CONCLUSIONS:** Children with epilepsy have cardiac autonomic dysfunction evident in their heart rate variability assessment. Patients on antiepileptic drugs had better autonomic balance than those not on antiepileptic drugs. Holter and EKG follow-up should be considered for early detection in those at high-risk cardiac complications.

Keywords: epilepsy, heart rate variability, antiepileptic drugs, autonomic imbalance

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Introduction

The electrical stimulation of various sites of the brain may cause cardiac rate and rhythm abnormalities. The most common types of cardiac autonomic dysfunction associated with seizures are tachyarrhythmia, bradyarrhythmia, and electrocardiogram (EKG) changes.[1]

Darbin et al.[2] found that the severity of convulsive seizures and seizure repetition are determinants of disordered cardiac autonomic regulation and directly influence the duration of cardiac arrhythmia during the immediate postictal state. Dysfunction in systemic and cerebral circulation physiology and seizure-induced hormonal and metabolic changes might contribute to sudden unexpected death in patients with epilepsy (SUDEP).[3]

The effect of antiepileptic drugs (AEDs) on the heart might be unpredictable. AEDs might prevent SUDEP by improving seizure control. On the other hand, AEDs might potentially contribute to SUDEP if they are suddenly withdrawn or by exerting direct effects on cardiac control.[4]

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Carbamazepine and other AEDs can slow cardiac conduction.[5] Lamotrigine has been shown to lengthen cardiac repolarization and the QT interval.[6] Certain AEDs, such as carbamazepine, rufinamide, or primidone, may induce QT shortening.[7,8]

To detect the sympathetic-parasympathetic balance of the autonomic nervous system, measuring heart rate variability (HRV) is a useful noninvasive tool.[9] It reflects the beat-to-beat alterations in the heart rate and is mainly modulated by parasympathetic and sympathetic activities.[10] HRV is analyzed by time and or frequency domain methods; the former is derived from measuring and calculating the differences in the normal to normal RR intervals and the latter involves spectral analysis of normal to normal RR interval series.[11]

The aim of this study was to evaluate interictal cardiac autonomic status in children with epilepsy receiving AEDs.

Patients and methods

This cross-sectional, case-controlled study was conducted in the Pediatric Neurology Clinic and Children's Hospital, Ain Shams University, Cairo. Sixty patients with idiopathic epilepsy were enrolled in the study and were divided into two groups. Group I comprised drug-naive patients and group II comprised patients on regular AEDs; they were further subdivided into group IIa, which included patients receiving monotherapy (valproic acid or carbamazepine), and group IIb, which included patients receiving polytherapy. Studied groups were compared to 40 age- and sex-matched healthy children and adolescents as a control group.

Patients with evidence of organic heart disease or other diseases or illnesses that might affect cardiovascular and autonomic nervous systems (e.g., systemic lupus erythematosus endocrine metabolic disorders) were excluded from the study. Also, any patients on any regular medication, other than AEDs, which could affect the cardiovascular and autonomic nervous systems were excluded. Consent was received from parents or caregivers after explaining the study requirements and details to them. The study was approved by the hospital's ethical committee.

The studied groups were subjected to the following.

- A complete history, which placed stress on a detailed history of the patient's epilepsy (age of onset, seizure type, type and severity of seizures rated according to the Chalfont seizure severity scale,[12] details of drug therapy in terms of duration, dose, and preparations).
- A thorough clinical examination with detailed neurological and cardiac examinations.
- Twenty-four hour EKG (Holter) recording for time and frequency domains; HRV indices and dysrhythmia assessments were done using a Holter monitor (circadian, model number HR1 recorder) that recorded two channels of EKG into a standard 60-minute cassette tape for 24 hours. Parents of patients and controls kept notes of 24-hour events. Holter tapes were analyzed using a Hyundai computer/delux 145 with a HillMed inversion DFA 3.3).

Time domain measures of HRV included the following: standard deviation of all normal RR intervals (SDNN, ms) in the entire 24-hour EKG recording; standard deviation of averaged normal sinus RR intervals for all 5-minute segments of entire recording (measured in ms); mean of standard deviations of all normal RR intervals for all 5-minute segments of the entire recording (measured in ms); root mean square of successive RR interval differences (the square root of the mean of the sum of the squares of differences between adjacent normal RR intervals over the entire recording, measured in ms), and the percentage of difference between adjacent normal RR intervals that are greater than 50 ms computed over the entire 24-hour EKG recording (pNN50, measured in percentage), according to Silvetti et al.[13]

Frequency domain measures of HRV included the following: Total power (TP) values (ms^2); high-frequency power (HF) values (ms^2) (a marker of parasympathetic activity), low-frequency power (LF) values (ms^2) (a measure of sympathetic activity), and the ratio between LF and HF (an index of the balance between sympathetic and parasympathetic influences).[13]

Analysis of Holter data for other variables describing cardiac changes and arrhythmias was done as premature atrial contractions and premature ventricular contractions, bigeminy, trigeminy, and any other dysrhythmias.

A 12-lead EKG recording for P wave amplitude and duration, PR interval, QRS duration, QTc and QTd estimation, and QTc assessment were done according to Bazett's formula: [QTc measured = QT/squared root RR interval]. The upper limit of normal QTc was considered 0.44 seconds.[14]

Instructions were given to parents before recording and emphasized not missing drug doses, if received, and avoiding conditions that might induce stress and any caffeine containing beverages so as not to affect patients heart rate.

Statistical analysis of data

Statistical analysis was carried out using SPSS, version 17.0 (SPSS Inc., Chicago, IL). The collected data were statistically managed as follows. Descriptive statistics were calculated as the mean ± standard deviation for quantitative variables; the number and % were used for qualitative variables. For analytic statistics, to assess the differences in frequency of qualitative variables, the chi-square test was used, whereas Fisher's exact test was applied if any expected cell values in a two by two table was <5.

To assess differences in means of quantitative variables between cases and controls, independent samples *t* test was applied. The relation between quantitative variables within the case group was analyzed using one-way analysis of variance test. Pearson's correlation coefficient was used to correlate various quantitative variables within the case group. The statistical methods were verified, assuming a significance level of $P < 0.05$ and a highly significant level of $P < 0.001$.

Results

The patients included in our study (32 males and 28 females) had ages ranging from 4 to 12 years (median 8 years; mean 8.4 ± 2.6 years). They were compared with 20 healthy controls (21 males and 19 females), with ages ranging from 4 to 13 years (median age 8.2 years; mean 8.6 ± 2.8 years).

Regarding EKG data, 22 patients (36.7 %) had premature atrial contractions, 15 (25.0%) had premature ventricular contractions, three (5.0 %) had one couplet, and one patient (1.7 %) had one triplet, six patients had prolonged QTc (more than 0.44 seconds) and five had prolonged QTd (more than

TABLE 1.
Distribution of Normal and Abnormal Holter Data of the Patients with Epilepsy Group

Variables		Patients (n = 60)	
		No.	%
PACs	Absent	38	63.3
	Present	22	36.7
PVCs	Absent	45	75.0
	Present	15	25.0
Couplets	Absent	57	95.0
	Present	3	5.0
Triplets	Absent	59	98.3
	Present	1	1.7

Abbreviations:
PACs = Premature atrial contractions
PVCs = Premature ventricular contractions