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Can heart rate variability in children with epilepsy be used to predict seizures?

Ebru Kolsal [a,*], Ayşe Serdaroğlu [b], Erman Çilsal [c], Serdar Kula [c], Azime Şebnem Soysal [b], Ayşegül Neşe Çıtak Kurt [d], Ebru Arhan [b]

[a] Bakırkoy Prof. Dr. Mazhar Osman Hospital of Mental Health and Neurology, Department of Pediatric Neurology, Istanbul, Turkey
[b] Gazi University Faculty of Medicine, Department of Pediatric Neurology, Turkey
[c] Gazi University Faculty of Medicine, Department of Pediatric Cardiology, Turkey
[d] Balıkesir Atatürk State Hospital, Department of Pediatric Neurology, Turkey

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ABSTRACT

Purpose: The aim of this study was to examine interictal, pre-ictal and ictal autonomic system disturbance by comparing heart rate variability in children with uncontrolled epilepsy with that seen in healthy controls and children with controlled epilepsy.
Methods: Our study group included 20 children with refractory epilepsy, our control groups were composed of 20 children with well-controlled epilepsy and 20 healthy children. All subjects were evaluated by Holter ECG monitoring and 12-lead ECG to assess heart rate variability and QTc dispersion. The study group was also evaluated by Holter ECG during seizures.
Results: The study group exhibited significantly more pathological QTc dispersion than did the control groups. Heart rate variability was significantly suppressed: reduced parasympathetic activity with lower low frequency (LF) and high frequency (HF) band values were observed in the study group. Findings were similar in the well-controlled epilepsy group and the healthy group but differed from the uncontrolled epilepsy group. The examination of heart rate variability parameters during and before seizures revealed higher nLF and LF/HF ratio and lower nHF values demonstrating increased sympathetic activity.
Conclusion: We suggest that children with refractory epilepsy have abnormalities of autonomic nervous system functioning which could be linked to the increased risk of sudden unexpected death seen in the patient group. It is possible that a chronically reduced vagal tone predisposes patients to a more dramatic stress response during their seizures. It is possible that heart rate variability parameter arising prior to seizures could be used to predict future seizures.

1. Introduction

The mortality rate of patients with epilepsy is two- to threefold higher than that of the general population.[1,2] This increased mortality rate is caused by accidents during seizures, status epilepticus and sudden unexplained death in epilepsy (SUDEP).

SUDEP has been defined as "sudden, unexpected, witnessed or unwitnessed, nontraumatic and non-drowning death in patients with epilepsy, with or without evidence of a seizure and excluding documented status epilepticus, where postmortem examination does not reveal a toxicological or anatomical cause of death".[3] SUDEP is rare in newly diagnosed epilepsy patients but is a common cause of death that may reach rates as high as 9/1000 per year in patients with refractory epilepsy.[4–6] Ictal bradycardia, asystole and pulmonary congestion are suspected causes of SUDEP, but recent studies have demonstrated that disturbances of the autonomic system disturbance could be the root of all of these suspected causes of SUDEP.[7–9]

Normal heart rate variation depends on the balance between the sympathetic and parasympathetic systems. Spectral analysis of heart rate variability (HRV) is a non-invasive method for the assessment of autonomic cardiac control.[10] Highly variable heart rates are a sign of good adaptability and good autonomic control. There are only a small number of studies that have shown autonomic disturbances via HRV evaluation in children with epilepsy; whereas many studies of adult patients exist.[11–14] Harnod et al. found lower RR and HF levels in children with refractory epilepsy that were suggestive of parasympathetic reductions.[11] Delogu et al. showed that HRV levels are depressed in children with Dravet syndrome.[12] Assaf et al. analysed HRV changes during epileptiform events and observed no significant differences between patient and control groups.[13]

* Corresponding author. Tel.: +90 5055366258.
E-mail addresses: ebkut@yahoo.com, ebkut@hotmail.com (E. Kolsal).

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Haliloğlu et al. found suppressed HRV levels in children with epilepsy.[14]

Pathological cardiac repolarisation increases the risk of fatal ventricular tachyarrhythmia and is an established predictor of sudden cardiac death.[15] Therefore, prolongation of the QT interval during seizure can be a cause of SUDEP.[16] Moreover, the prolongation of QT dispersion (QTd) has been demonstrated in patients with epilepsy.[17,18] Increases in QTds indicate disturbances in the autonomic system that favour the sympathetic system; this phenomenon can cause ventricular tachycardia and fibrillation.

The aims of this study were to compare the severity of autonomic dysfunction by measuring heart rate variability parameters in patients with refractory epilepsy and patients with well-controlled epilepsy and to examine the cardiac changes that occur before and during the patients' seizures.

2. Methods

This study included 40 consecutive children with epilepsy who were referred to our institute for evaluation and treatment between January to June 2011. Patients were divided into two groups: group 1 was composed of 20 children with refractory epilepsy who were admitted to the video EEG unit of the paediatric neurology department for the evaluation of potential surgical interventions, and group 2 was composed of 20 patients with controlled epilepsy. An additional group (group 3) of 20 healthy children were included as the control group. Study group consists of children with refractory epilepsy who are using three or more antiepileptic drugs without seizure control. Group 2 consists of children with epilepsy who are using only one antiepileptic drug and had no seizure within last 6 months. Brain MRI findings, antiepileptic drug types and number and names of antiepileptic drugs used were also evaluated.

All patients were evaluated by a paediatric cardiologist via a standard 13-derivation ECG (including V4 R derivation) and a complete blood count. Echocardiographic examination was conducted using M-mode, 2-dimensional, colour, pulse and continuous wave Doppler echocardiograms with a GE Vivid 7 (Wisconsin, USA). Two-dimensional echocardiographic pictures were recorded in standard parasternal long axis, short axis, apical 4-chamber, subcostal and suprasternal views. ECG sampling was made only for one time.

The T morphologies, PR, QRS, QT, and corrected QT intervals and QT dispersions of all participants were evaluated from the ECG records. QTc was calculated via "Bazzet" ($QTc = QT/RR^{1/2}$) formula.

2.1. Heart rate variability

Twenty-four hour cardiac holter monitorization was done by "Medilog FD-2 (Oxford Instruments Medical Sytem)" digital holter device. Heart rate variability analyse was based on 24 h digitally recorded ECG signal with 100 Hz sampling rate. Holter Data acquisition and analysis were performed using the MediLog Cardiology Information System V 1.41 PC-compatible software that was developed by Oxford Instruments Medical System (USA). The processed signal was derived from surface electrodes on the chest. QRS complexes were automatically identified and labelled by the software and reviewed manually to limit any potential artefacts. The temporal parameters analysed were the mean of the RR interval (mean RR), the standard deviation of RR interval (SDNN), the standard deviation of the difference between consecutive RR intervals (SDANN), and the root mean square of difference between successive normal intervals (RMSSD). Both absolute and normalised low frequency (LF: 0.04–0.15 Hz) and high frequency (HF: 0.15–0.4 Hz) spectral powers were evaluated. The LF value mainly provides a measure of sympathetic activity but is somewhat influenced by the parasympathetic nervous system. The HF value solely reflects parasympathetic activity. To remove the influence of parasympathetic activity in the LF spectral power, the LF/HF ratio was calculated, and high LF/HF ratios reflects the predominance of sympathetic activity. Triangular index measurement is the integral of the density distribution (that is, the number of all NN intervals) divided by maximum of the density distribution. It can be used as estimate the overall HRV.

We analysed the HRV parameter for 24 h. Also parameters were evaluated again in two different time periods as daytime (between 7:00–12.00 am), and nighttime (between 12:00–7:00 am).

Holter monitorization of the study group was done simultaneously during the video EEG monitorization. Therefore we could also evaluate the HRV parameters during the seizure.

Fourteen refractory epilepsy patients had seizures during Holter monitoring. In total, 17 seizures were observed, for which heart rate variability data were collected 15 min before, during, and 30 min after the seizure. This periictal period lasted about a hour. These data from the seizure time periods were compared with the all-day mean values.

Data are expressed as proportions or the means ± the S.D. Student's *t*-tests were used for the evaluation of continuous variables. Chi-square analysis and Student's unpaired *t*-tests were used to compare variables between groups in univariate analyses. *P*-values lower than 0.1 were considered as statistically significant. All statistics were calculated with the SPSS 16.0 program.

3. Results

This study involved 60 children under the age of 18 years old. The demographic data, seizure semiology and antiepileptic drug therapy of the subjects are summarised in Table 1. There were no significant differences in the demographic data between the three groups (Table 1).

Corrected QT dispersions were calculated for groups 1 and 2. Ten patients in group 1 and five patients in group 2 exhibited QTc dispersions greater than 50 ms. Statistically significant lengthening was found in group 1 (Table 2).

All groups were evaluated with echocardiography, and no functional cardiac disorders were found.

Holter monitoring was performed in all groups and revealed that three patients in group 1 exhibited sinus tachycardia during seizure and that one patient exhibited T wave inversion.

All groups were evaluated for time- and frequency-domain heart rate variability. Statistical analyses were performed with student's *t*-tests (Table 3).

Table 1
Demographic data of the groups.

	Group I (refractory epilepsy)	Group II (controlled epilepsy)	Group III (healthy children)
Number of subjects	20	20	20
Age (years mean ± SD)	9.55 ± 5.02	10.1 ± 4.18	10.35 ± 4.39
Gender (female/male)	8/12	8/12	8/12
Partial/generalised seizure	15/5	9/11	No seizure
Median number of AED	3.25	1	0

Table 2
Patients' QTc dispersion values.

Groups	<50 ms	>50 ms	Total
Group 1	10	10	20
Group 2	15	5	20
Total	25	15	40

$p < 0.1$ (difference between groups' QTc dispersion values).