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Full Length Research Paper

Sleep heart rate circadian rhythm variability in temporal lobe epileptic Egyptian children

Mohammed Al-Biltagi[1]*, Osama Abd Rab Elrasoul Tolba[1], Tarek mohamed Elgohary[1], Osama Abo Elmagd Elkholy[2] and Rasha Abdelgelil Abdelwanis[1]

[1]Pediatric Department, Faculty of Medicine, Tanta University, Tanta, Gharbia Governate, Egypt.
[2]Neuropsychiatry, Faculty of medicine, Alexandria University Egypt.

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The aim of this study was to measure interictal circadian rhythm variability of heart rate (HR) in Egyptian children with temporal lobe epilepsy (TLE) using a 24 hours ECG recording. A group of 40 children suffering from partial epilepsy subdivided into group A with 21 children who had controlled temporal lobe epilepsy and group B with 20 children suffered uncontrolled temporal lobe epilepsy. A third group of 40 healthy children was studied as a control group. An ambulatory two channel-5-lead electrocardiography (ECG) recording was performed in both epileptic children and the controls. A computer assisted analysis of heart rhythm and heart rate variability recorded over a 24 hours period of normal daily activity of the children was done. There was lower heart rate variability (HRV) in temporal lobe epileptic children than in normal controls. Also the HRV was lower in children with uncontrolled TLE than in children with controlled TLE. There was a disturbance of the autonomic nervous system (ANS) function in epileptic children with reduction of the vagal tone compared to normal children as indicated by the differences in HRV which suggests that the parasympathetic component of the ANS is strongly implicated in the pathogenesis of epilepsy.

Keywords: Egyptian Children; Heart Rate Variability; Sleep Circadian Rhythm; Temporal Lobe Epilepsy.

INTRODUCTION

Epilepsy is a disorder characterized by recurrent unprovoked seizures. It affects people in all ages, all nations and of all races (Haslem, 2000). Childhood epilepsy is one of the most prevalent neurological conditions affecting the growing brains, with a rate of 3.6 to 4.2 per 1000 children in developed countries, and approximately doubles these rates in developing countries (Mathiak et al., 2010). The temporal lobe is the most epileptogenic region of the brain and temporal lobe epilepsy (TLE) is characterized by recurrent seizures originating from the medial or lateral part of temporal lobe. Over 70 percent of temporal lobe seizure disorders begin in childhood which consist of simple partial seizures without loss of awareness and complex partial seizures with loss of awareness (Engel, 2001).

Autonomic dysregulation as burping, pallor or blushing, feeling of fear or panic, rising gustatory sensation including dyspepsia, apnea, or fluctuation of the blood pressure (BP) and/or HR may occur with the epileptic seizure (Opherk et al., 2002). This epilepsy- autonomic nervous system interaction is very complex. The seizure neuronal electrical activity may involve central autonomic vasomotor centers and can also affect the cortical cardiac

*Corresponding Author: Email: mbelrem@hotmail.com; Tel: +20102209797 /+973-39545472/ Fax: +973-17-590495

representation area so that the seizure can present with autonomic symptoms either initially, or during seizure propagation or postictal (Łabuz-Roszak and Pierzchała, 2009).

Sudden unexpected death (SUDEP) has accounted for at least 12% of deaths of children with epilepsy. The exact mechanisms of SUDEP are unknown; however, theories suggested have, to date, focused on autonomic instability (Ansakorpi et al., 2002). Disorders of cardiovascular and other autonomic nervous system functions are common in patients with TLE. Cardiovascular dysregulation in TLE has previously been quantified assessing traditional time and frequency domain measures of heart rate variability (HRV) from short term ECG recordings (Yang et al., 2001). Ictal changes in autonomic functions including HR are well studied in patients with epilepsy nevertheless; we need to know more about the possible interictal alterations of cardiovascular autonomic regulation. The aim of this study was to measure interictal circadian rhythm of HRV in Egyptian children with TLE using a 24 hours ECG recording.

PATIENTS AND METHODS

The study was conducted as a case-control study. A group of children suffering from TLE (6-12 years of age) were recruited from Neurology Clinic, Children's Hospital, Tanta University from June 2009 to June 2010. An age and sex matched 40 healthy children were studied as a control group. There were two patient groups, the first patient group involved 21 children with controlled TLE (either mesial or lateral TLE) while the second patient group involved 20 children with uncontrolled TLE (either mesial or lateral TLE). All children were subjected to systematic history, clinical examination and psychomotor development assessment. Children with other types of epilepsy, chronic systemic diseases, congenital or acquired cardiac diseases, organic neurological diseases, psychiatric diseases, high body mass index (BMI), high blood pressure, abnormal hematological indices, or impaired liver or renal function tests were excluded. Children with medications that may affect the autonomic nervous system functions (e.g. choline esters, cholinomimetics, Belladonna alkaloids etc.) were also excluded. Children were diagnosed to have TLE by both typical clinical temporal lobe seizures and with the classic EEG characteristic of temporal lobe epilepsy and whether controlled or not according to the recommendations of the *International League Against Epilepsy (Yang et al., 2001)*. In all cases, EEG was performed to confirm the diagnosis and interictal EEG recordings were obtained in all subjects with the classic temporal spike or sharp-wave discharges and temporal intermittent rhythmic delta activity (TIRDA). Uncontrolled epilepsy was defined as inability to control the seizure after 9 months of optimal treatment under the care of a neurologist where the seizure occurred at least monthly despite the regular use of adequate anti-epileptic drugs (AEDs). In controlled epilepsy, the children were seizure free since starting AEDs (French, 2007).

An ambulatory two channel-5-lead ECG recording (*Medset-Cardiolight FMC Recorder version H; Hamburg; Germany*) was performed in all epileptic and control children. A computer assisted analysis of heart rhythm and HRV recorded over a 24 hours period of normal daily activity of the children was done. The parents were asked to document all the events that happened during the recorded period including possible occurrence of epileptic fits. Any artifacts were digitally removed. Time domain of HRV was automatically calculated by the computer program. The program calculated the standard deviation of all RR intervals (SDNN); the standard deviation of the averages of RR intervals in all 5 minutes segments of the entire recording (SDANN); the square root of the mean of the sum of squares of differences between adjacent RR intervals (RMSSD); and the percentage of differences between adjacent RR intervals that are greater than 50 msec. (PNN50). All parameters were compared to previously publish normal values for age and described as normal, decreased or increased (Massin et al., 2000; Silvetti et al., 2001).

For sleep recording; the children were asked to sleep in the sleep laboratory for two consecutive nights and analysis was done during the second night. Sleep stage determination was done by recording EEG, electrooculogram (EOG), and electromyogram (EMG) of the submentalis muscle. Other sleep data such as ECG, peripheral oxygen saturation and chest wall movement were also recorded. All signals were digitally recorded (sampled at a rate of 128 Hz) and also reproduced on paper by means of a polygraph (Ferri et al., 2002). Analysis of sleep staging was carried out by visual analysis of the EEG, the EOG, and the EMG according to the standard criteria of Rechtschaffen and Kales 1968 (Silvetti et al., 2001).

The sleep stage-related HRV was analyzed in 5-min epochs from sleep stages S2, SWS and REM sleep. For each subject, at least 9 epochs were selected (3 epochs from each stage). All epochs were carefully chosen during periods without evident ictal epileptiform activity in the EEG. In order to avoid gross effects on HRV, only periods without transient activation phases were chosen (Anderer et al., 2007). All parents were given and signed written informed consent before enrolment into the study. The local Institutional Research Review and Ethics Committee approved the study protocol.

Statistical analysis

The power level of the number of cases in the study was more than 90%. Data are presented as mean (±SD)

Table 1. The demographics of the studied children

	Controls	Patients with TLE (n =41)	
	(n = 40)	Well controlled (n = 21)	Uncontrolled (n = 20)
Age (years, mean (SD))	8.0 ±1.76	8.35 ±1.7	8.15 ±1.9
BMI	19.1± 2.0	18.4 ± 2.4	18.7 ± 2.3
Resting Systolic BP	100.5 ±6.6	97.25±8.3	98.25±9.1
Resting Diastolic BP	68.5±5.2	67.5±6	67±5
Resting Heart Rate	115.5±19.1	111.4±20.5	116.7±18.2
Male/female ratio	5.3/4.7	1/1	5.5/4.5
Duration of TLE (years, mean (SD)		3.2 ± 1.2	5.8 ± 1.3 *
Seizure characteristics			
Seizure free (no. Of patients		14	0
Seizure per month (mean (SD))		0.25 ± 0.44	8.45 ± 4.3*
Psychomotor Normal		19	16
development Questionable		2	4
Antiepileptic medication			
Monotherapy			
Carbamazepine		12	0
Phenytoin		4	0
Lamotrigine		0	0
valproate		2	0
Polytherapy			
CBZ + other AED(s)		2	12
Phenytoin + other AED(s)		0	6
Valproate + other AED(s)		1	2

AED, anti-epileptic drug; CBZ, carbamazepine; OXC, oxcarbazepine
* means $p < 0.05$ and statistical difference between studied groups.

values. The two-way analysis of variance (ANOVA) with repeated measures was used to identify statistically significant differences in the different parameters among the groups. For all analysis a statistical significance of p-value < 0.05 was used. The analysis was performed using Texa Soft, WINKS SDA Software, Sixth Edition, Cedar Hill, Texas, 2007.

RESULTS

The study involved 40 healthy children as a control group, 21 children with controlled TLE and another 20 children with uncontrolled TLE. There were no statistical significant differences in age, sex, body mass index (BMI), heart rate, systolic blood pressure (SBP), and diastolic blood pressure (DBP) between control children, children with controlled TLE and those with uncontrolled TLE ($p > 0.05$). However the duration of epilepsy was significantly longer in the uncontrolled epileptic group than in the TLE controlled epileptic group. There was no significant difference in seizure type in both controlled and uncontrolled TLE (table 1).

Despite there were no significant differences between the controls and children with controlled TLE as well as those with uncontrolled TLE in SDNN parameter during different sleep stages ($p > 0.05$); the patients' values were lower than that of the control group (table 2). SDNN was also lower in the patients with uncontrolled TLE than that of controlled. The value of SDNN was lower in REM sleep stage than that of sleep stage two and slow wave sleep (Figure 1). As regard to RMSSD parameter; there was no significant difference between the patients and the controls during different sleep stages, with lower patients' values than that of the control group. The value SDNN was also lower in the uncontrolled TLE than the controlled TLE group. Also the value of RMSSD was lower during REM sleep stage (Figure 2).

On the other hand there was a significant difference of the PNN50 between the control group, the children with controlled TLE and children with uncontrolled TLE. The PNN50 was significantly lower in the patients with uncontrolled TLE than in patients with the controlled TLE. Also it was significantly lower in the patients group than that of the control group. PNN50 value shows no significant difference between different sleep stages in each patient group, except that being lower in REM sleep

Table 2. The type of epilepsy and seizure type in the studied children with temporal lobe epilepsy (TLE).

Variables	Patients with TLE (n=41)		X^2	P
	Well controlled (n = 21)	Uncontrolled (n = 20)		
Type of epilepsy:				
Symptomatic	8 (38%)	12 (60%)	0.90	0.342
Idiopathic	13 (62%)	8 (40%)		
Seizure type:				
CPS	15 (71%)	14 (70%)	0.90	0.637
SPS	3 (14%)	4 (20%)		
SPSG	3 (14%)	2 (10%)		
Side of EEG and/or Neuroimaging anomalies:				
Right	12	11		
left	8	6		
Bilateral	1	3		
Neuroimaging Anomalies:				
Mesial temporal sclerosis	2	7		
Focal cortical dysplasia	0	3		
Arteriovenous malformation	0	1		

CPS= Complex partial seizures
SPS=Simple partial seizures
SPSG= Simple partial with secondary generalization
This table demonstrates that there is no significant difference between the two groups of patients as regard the type of epilepsy and the seizure type.

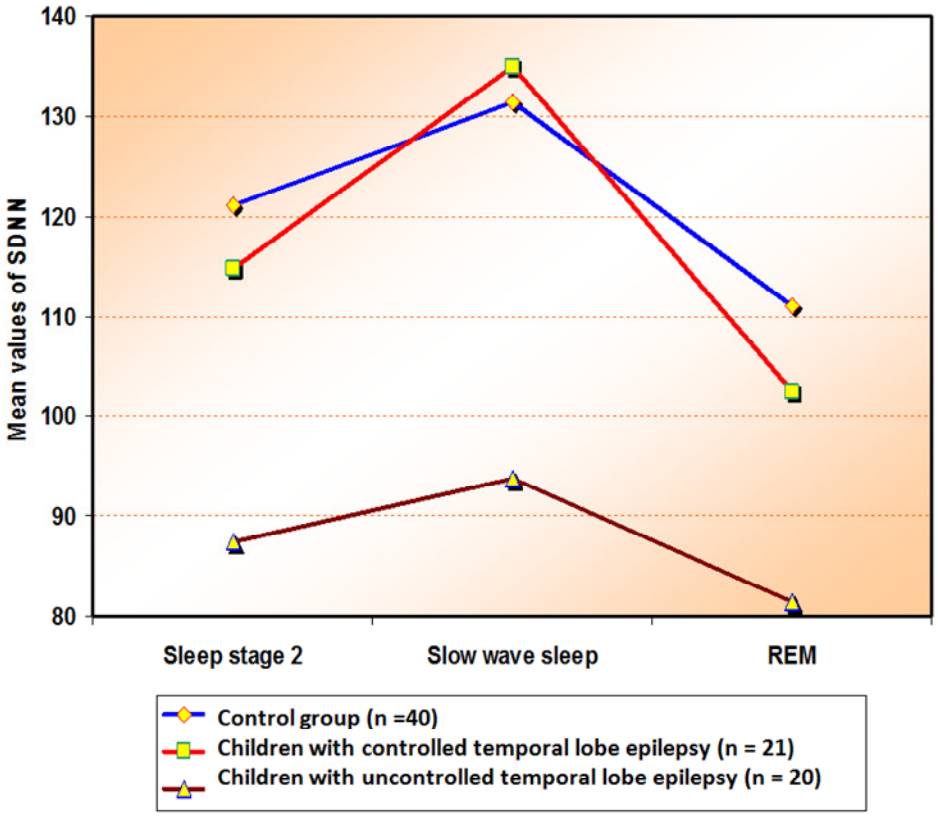

Figure 1. Standard deviation of all R-R intervals (SDNN) among the children with temporal lobe epilepsy and the control group during sleep.

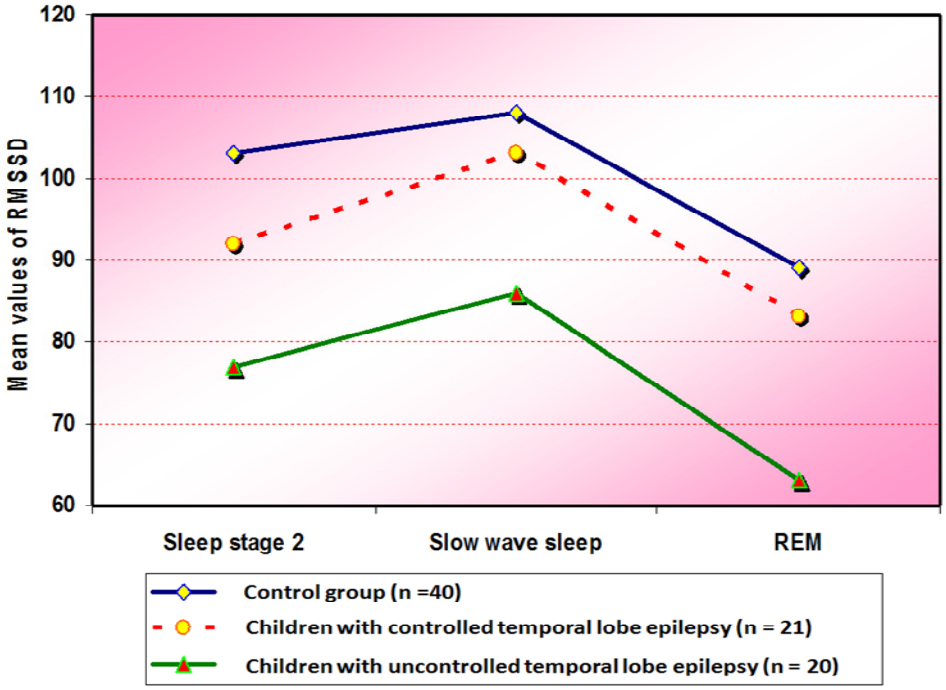

Figure 2. Square root of the mean of the sum of the squares of differences between adjacent R-R intervals (RMSSD) among the studied children with temporal lobe epilepsy and the control group during sleep.

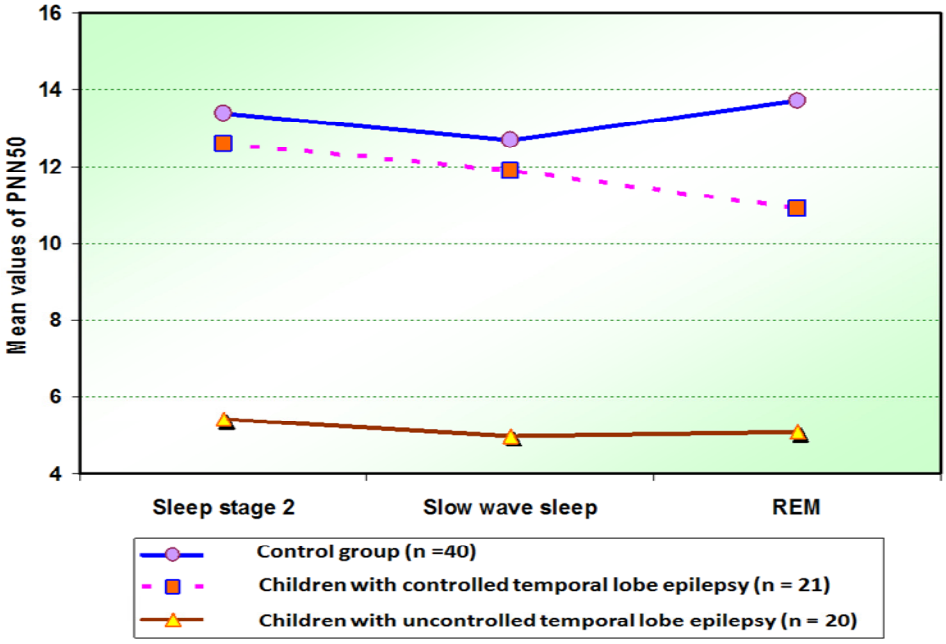

Figure 3. Number of pairs of adjacent R-R intervals differing by more than 50 ms in the entire epoch (PNN50) among the studied children with temporal lobe epilepsy and the control group during sleep.

stage (figure 3). There was no significant difference between the patients group and the control group as regard to SDANN parameter and without significant difference between the different sleep stages. However the value of SDANN was lower in the patients' groups than its values in the control group and it was lower among the uncontrolled TLE patients population than in children with controlled TLE. The value of SDANN was

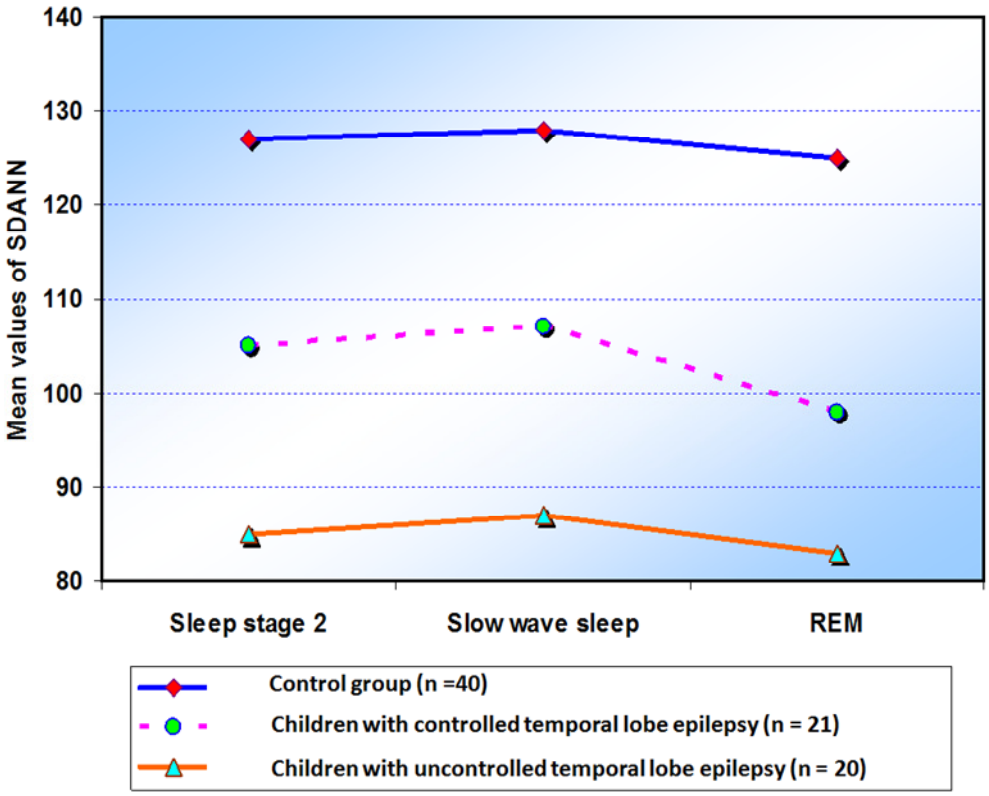

Figure 4. Standard deviation of the averages of NN intervals in all 5 min. segments of the entire recording (SDANN) among the studied children with temporal lobe epilepsy and the control group during sleep.

lower in REM sleep stage than other sleep stages. Taken as a whole from the previous figures, there was a lower HRV in temporal lobe epileptic children than in normal controls; and HRV was also lower in children with uncontrolled TLE than in children with controlled TLE (figure 4).

DISCUSSION

The autonomic nervous system (ANS) plays a complex and vital role in the homeostasis of the human body. Repetitive seizures can alter the regulation of cardiac activity by their effects on ANS, partly due to a direct spreading of seizure activity to the ANS and partly due to an evolved physiological response by time (Evrengul et al., 2005). Several early studies had described alterations of autonomic control of cardiac functions and described both ictal and interictal modifications of heart rate regulation in epileptic adult patients (Van Buren, 1958; Van Buren and Ajmone-Marsan, 1960). Fewer studies described such changes in pediatric age and to our best knowledge, there was no studies explored these changes in Egyptian epileptic children. Heart rate variability in epileptic children during wakefulness was studied by Yang TF et al (2001). They found a disturbed sympatho-vagal balance documented by lower low frequency component (LF) of heart rate variability in children with epilepsy when compared to the normal children. They owed these changes to the disturbed modulating effects of the cerebral hemisphere on autonomic function (Yang et al., 2001).

In the current study, there was no statistically significant difference in SDNN and SDANN between TL epileptic children and normal children. However, values of SDNN and SDANN were lower in patients' population than that of the controls population. These values were also lower in patients with uncontrolled TLE than those of controlled TLE patients. This implies that overall autonomic nervous system activity that was expressed by SDNN was decreased in TLE children. On the other hand PNN50 was significantly decreased in patients with uncontrolled TLE compared to patients with controlled TLE and that of the normal children. The values of RMSSD showed no significant difference between the control and the patients' population; however, these values were lower in the patients than the control group, and it was lower in patients with uncontrolled TLE than that of the patients with controlled TLE. These HRV were mostly observed during REM sleep stage. This decreased HRV may be related to the imbalance

between the sympathetic and vagal systems with a preponderance of sympathetic and reduction of vagal system and changes in the respiratory sinus arrhythmia and parasympathetic activity (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology 1996). TLE is associated with reduced variability in heart rate, and the difference with control patients is greater at night than in the day. Low heart rate variability is considered to be a risk factor for sudden cardiac death (Ronkainen et al., 2005; Stein and Kleiger, 1999).

The results of our study agreed with a previous Italian study done on 2002 by Ferri R et al. They studied the cardiac autonomic function during sleep without ictal epileptiform EEG activity in 11 children with partial epilepsy and 11 healthy control children. They have found a lower HRV in epileptic patients than in normal controls. In their study there was a tendency towards statistical significance for the difference between RMSSD which was lower in the patients than in normal controls during S2 without statistically significant difference between the two groups during SWS. On the contrary, the difference between the values of RMSSD obtained in the two groups was statistically significant while SDNN, NN50 and pNN50 almost reach statistical significance during REM sleep (Ferri et al., 2002).

The same finding was documented in a Finnish study done by Ansakorpi H, at 2002 but was conducted in adult patients with uncontrolled and well controlled TLE. They found that traditional time and frequency domain measures, the power law slope and approximate entropy (ApEn) were lower in patients with TLE than in controls. These parameters were also more reduced in patients with uncontrolled TLE than in patients with well-controlled TLE (Ansakorpi et al., 2002).

However a more recent Sweden study done by Persson H et al at 2007 found no significant difference between the patients and the controls in any of the analyzed measures of HRV. Also, they found no significant difference between the daytime and nighttime recordings. These differences may be because of the different type of epileptic patients (partial epilepsy, generalized epilepsy and undetermined types) as well as the different age group (Cechetto and Saper, 1990).

Explanation of cardiovascular autonomic dysfunction in TLE is not completely understood. However, the epileptic focus that arises close to the frontal and temporal regulatory cortical area of the autonomic nervous system may alter and interfere with their function. These changes were observed in both controlled and uncontrolled TLE children but were more prominent in the uncontrolled cases. This may denote that TLE may be the cause (Cechetto and Saper, 1990, The Cardiac Arrhythmias Suppression Trial (CAST) investigators, 1989). These changes also may be related to the long lasting antiepileptic treatment as all TLE children included in the study were under antiepileptic medications. The anti-epileptic drugs used to treat the included cases act by blocking cardiac sodium channels exactly the same like many commonly used antiarrhythmic agents; and may affect the cardiac conduction system. Children with uncontrolled TLE are more liable to use more than one antiepileptic drug to achieve epilepsy control which in turn may have more effects on ANs as well as cardiac functions. They also may be more hesitant to participate in sports or may behave inactively with resulting small variation of heart rate in the 24-hour study (The Cardiac Arrhythmias Suppression Trial (CAST) investigators, 1989; The Cardiac Arrhythmias Suppression Trial II Investigators, 1992; Ansakorpi et al., 2000).

CONCLUSION

There is disturbance of the ANS function of epileptic children with reduction of the vagal tone compared to normal children which suggests that the parasympathetic component of the ANS is strongly implicated in the pathogenesis of epilepsy. This altered cardiovascular regulation seems to be related to the epileptic process itself rather than to the severity or duration although the parameters of HRV seem to be lower in patients with uncontrolled TLE than in patients with well controlled TLE. The methods used in this study may be useful in evaluating abnormal HR dynamics in patients with TLE especially with the higher risk of sudden unexpected death related to epilepsy. However, further studies are needed to assess the association between altered HR dynamics and risk for sudden death in patients with TLE. However we recommend further studies to detect the effect of sympathetic component of the ANS in epileptic children using other modalities of HRV and to conduct more studies of HRV assessing the frequency domain to study the sympathetic and parasympathetic control of the heart rate.

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