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Cardiac autonomic dysfunction in West syndrome

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Summary
Background: West syndrome is an age-dependent epileptic encephalopathy. Autonomic changes are increasingly being recognized in patients with epilepsy: cardiac autonomic function is mediated by sympathetic and parasympathetic efferent activity to the heart and can provide information on the functional state of the autonomic nervous system. The goal of the study is to evaluate the effect of an early epileptic encephalopathy on the autonomic nervous system by measuring heart rate variability.
Methods: Cardiac autonomic function was evaluated in 13 patients with West syndrome by measuring heart rate variability during 5 min epochs of ECG in wake, stage 2 and slow wave sleep. In 5 patients who developed subsequently another type of epilepsy, a second evaluation was performed after 3 years of follow-up.
Results: Results showed a lower heart rate in stage 2 sleep in patients with West syndrome. Spectral components did not show significant differences compared to age matched controls at the moment of presentation. After follow-up of 3 years we were able to demonstrate higher low frequency (LF), lower high frequency (HF) and a higher LF/HF ratio during slow wave sleep.
Conclusion: This study shows a lower heart rate in patients presenting with West syndrome, already at the onset of the syndrome and before ACTH treatment. The epileptic encephalopathy is not sufficient to alter spectral components of heart rate at the moment of presentation. However, already after 3 years of epilepsy, chronic autonomic changes appear.
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Introduction

West syndrome is an age-dependent epileptic syndrome characterized by epileptic spasms, hypsarrhythmia on EEG and arrest or regression in psychomotor development. The epileptic spasms resolve over time but they are often replaced by other types of refractory seizures (Commission on Pediatric Epilepsy of the International League Against Epilepsy, 1992). Autonomic changes are increasingly being recognized in patients with epilepsy (Baumgartner et al.,

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2001). One way to look at the autonomic system is to study heart rate variability. Heart rate variability is defined as the fluctuation in length in consecutive RR intervals. This variability is mediated by sympathetic and parasympathetic efferent activity to the heart and can show information on the functional state of the autonomic nervous system. The vagal influences on the heart are most pronounced during sleep and reach a maximum in synchronized or slow wave sleep.

Acute changes of cardiac function at the time of a seizure in patients with epilepsy is caused by involvement of the central autonomic control centers in seizure activity. On the other hand, patients with longlasting or refractory epilepsy are prone to chronic dysfunction of autonomic cardiac control (Chroni et al., 2008; Harnod et al., 2008; Ferri et al., 2002).

The goal of this study was to investigate the immediate and long-term effect of an early epileptic encephalopathy on the autonomic nervous system. We evaluate heart rate variability at the moment of diagnosis to investigate the short-term effect of the epileptic encephalopathy on autonomic function. Furthermore, we performed a second evaluation after 3 years of epilepsy to monitor the chronic effects of epilepsy on the autonomic nervous system.

Methods

Consecutive patients who presented with infantile spasms and hypsarrhytmia on EEG at the epilepsy clinic of UZ Leuven between 2003 and 2010 were included. All patients were included and monitored before treatment with ACTH at the moment of their referral and first EEG. Control subjects were referred to the epilepsy clinic with suspicion of epilepsy but were found to have benign sleep myoclonus and had normal EEG findings. All EEGs were reviewed by 2 independent EEG specialists. The control subjects were age and sex matched to take into account age-dependent differences. EEG recordings were obtained using the 10—20 International System of Electrode Placement. Sampling rate was 250 Hz. 5 min epochs of ECG were extracted randomly during wake, stage 2 sleep and slow wave sleep of the first sleep cycle. All EEGs had continuous interictal discharges but no seizures. In patients who subsequently developed another type of epilepsy, 5 min epochs of ECG were extracted again during the three time points after minimal 3 years of follow-up. Again age-matched controls were used for comparison of the follow-up cases. Wake and sleep stages were determined by the investigator by visual analysis of the EEG and spectral analysis (OSG, Belgium). RR intervals were calculated after automatic QRS-complex detection. Finally, all RR interval time series were checked manually.

Heart rate variability can be used as a tool to show information on the functional state of the autonomic nervous system. Frequency domain analysis was performed using a non-parametric method of fast Fourier transformation. Borders of spectral components were defined according to age. Time and frequency domain analysis of heart rate variability was done according to the standards of the Task Force of the European Society of Cardiology (Task Force of The European Society of Cardiology and The North American Society of Pacing and Electrophysiology, 1996). Spectral analysis of heart rate can provide more information on the sympathetic and parasympathetic contribution to autonomic outflow to the heart. The high frequency (HF) components are related to parasympathetic activity, whereas the low frequency (LF) reflects sympathetic cardiac function.

Spectral components in the first cohort were defined as 0.04—0.15 Hz for LF and 0.30—1.30 Hz for the HF component, covering the breathing frequencies of all the young subjects. In the second cohort, spectral components between 0.04 and 0.15 Hz were defined as LF, those between 0.15 and 0.40 Hz were defined as HF. Normalized units were used to compare spectra with different total power. $\text{LFnu} = \text{LF}/(\text{total power} - \text{VLF}) \times 100$, $\text{HFnu} = \text{HF}/(\text{total power} - \text{VLF}) \times 100$. The LF/HF ratio was used to quantify the sympathovagal balance as an indicator of autonomic modulation. Differences between epileptic patients and the control group were obtained via the Mann—Whitney U test. $P < 0.05$ was considered statistically significant.

Results

13 patients with infantile spasms at presentation were included and an equal number of age matched controls. The mean age of onset was 7.3 months (range 4—10 months).

Ten patients developed subsequently another type of epilepsy, 9 had generalized and 1 partial epilepsy, 8 of them were refractory cases. All patients had mild to severe mental retardation. 5 of these subjects had a follow-up period of minimal 3 years. Other patient characteristics and treatment before the encephalographic evaluation is shown in Table 1.

Comparison between West syndrome patients and controls at the onset of epilepsy

Results in time and frequency domain measurements were compared between West syndrome and controls using the first set of data.

In time domain the mean RR interval was significantly higher in patients versus controls during stage 2 sleep (535.9 ± 47.5 ms versus 491.4 ± 51.4 ms; $p = 0.03$). The difference was also observed during wake (450.5 ± 46.6 ms versus 411.5 ± 41.2 ms; $p = 0.12$) and slow wave sleep (518.5 ± 56.6 ms versus 482.7 ± 39.4 ms; $p = 0.09$) but not statistically significant. Other time domain analyses showed no significant differences. In the frequency domain, there were no statistically significant differences in power spectra of patients versus controls in the different sleep stages.

Comparison between West syndrome patients who subsequently developed epilepsy and controls

Results in time and frequency domain measurements were compared between former West syndrome patients after at least 3 years of follow-up and controls, using the second set of data.

In time domain there were no significant findings. On the other hand, in frequency domain there is an important difference in LF (0.363 ± 0.154 versus 0.160 ± 0.109; $p = 0.03$) and HF (0.494 ± 0.157 versus 0.737 ± 0.153; $p = 0.01$) power

Table 1 Patient characteristics.

Case no.	Age at onset (months)	Sex (male/female)	Treatment	Etiology	Subsequent epilepsy	Treatment	Age at first EEG evaluation (months)	Age at second EEG evaluation (years)
1	6	M	Vigabatrin, Sodiumvalproate	Cryptogenic	Yes, generalized	Sodiumvalproate, clobazam, sulthiame	8	4.5
2	5	F	Sodiumvalproate	Cryptogenic	Yes, generalized	Sodiumvalproate	6.5	7.5
3	8	M	Vigabatrin, sodiumvalproate	Symptomatic: trisomy 21	Yes, generalized	Topiramate	9	6.5
4	9	M	Sodiumvalproate	Cryptogenic	No	—	9	—
5	7	M	Vigabatrin, sodiumvalproate	Symptomatic: ACM infarct	Yes, generalizee	Sodiumvalproate, topiramate, clobazam	9	—
6	10	M	Sodiumvalproate	Symptomatic	Yes, generalized	Sodiumvalproate, vigabatrine, clonazepam	10	—
7	10	M	Vigabatrin, sodiumvalproate	Symptomatic	No	—	10	—
8	10	M	Vigabatrin, carbamazepine	Symptomatic: tuberous sclerosis	Yes, partial	Sodiumvalproate, topiramate, clobazam	11	6
9	6	F	Vigabatrin	Symptomatic: tuberous sclerosis	Yes, generalized	Sodiumvalproate	6	3
10	5	M	Sodiumvalproate, topiramate	Symptomatic: tuberous sclerosis	Yes, generalized	Sodiumvalproate, topiramate	10	—
11	6	M	Sodiumvalproate	Cryptogenic	No	—	7	—
12	4	F	Vigabatrin	Symptomatic: trisomy 21	Yes, generalized	Sodiumvalproate	4	—
13	9	M	None	Symptomatic: trisomy 21	Yes, generalized	Sodiumvalproate, levetiracetam	10	—

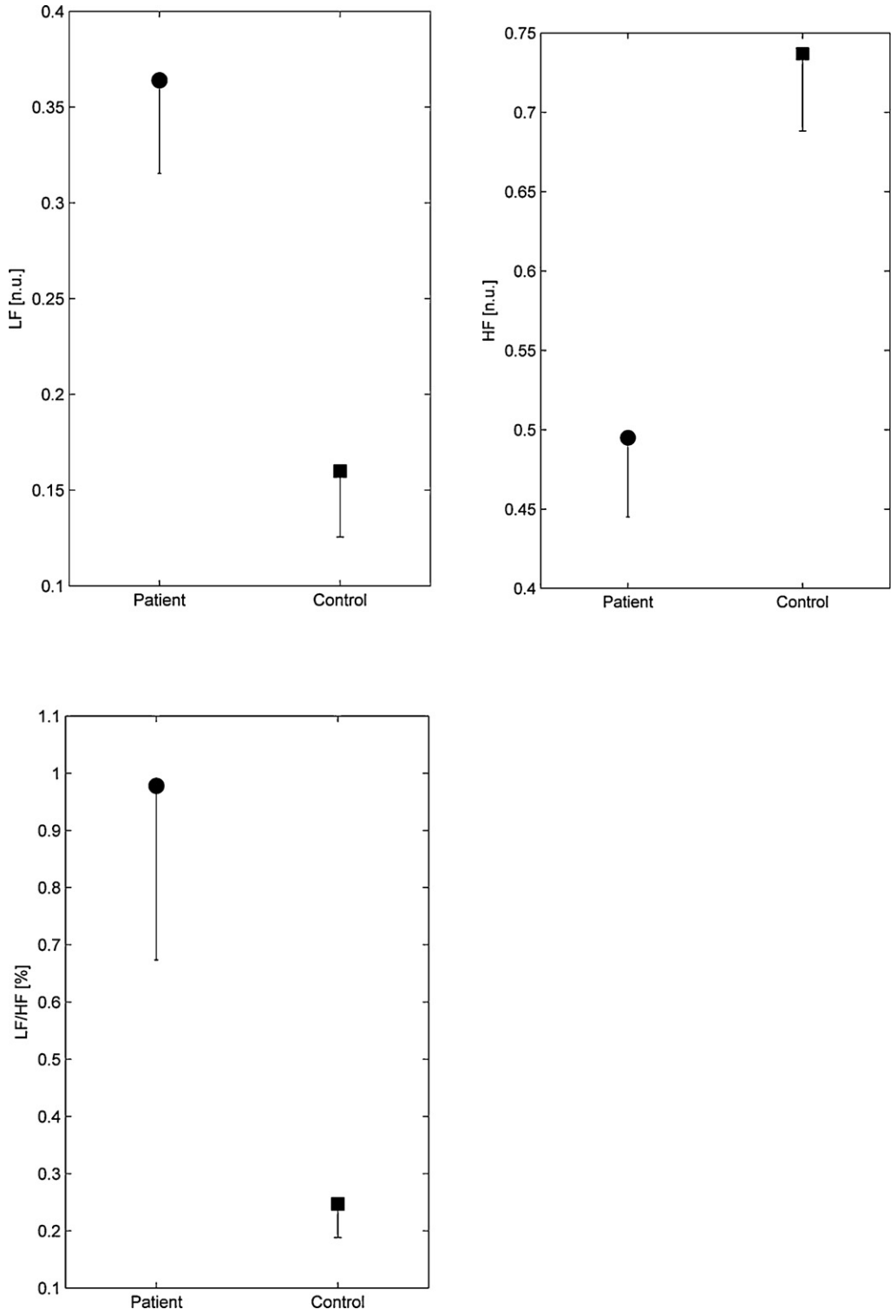


Figure 1 LFnu, HFnu and LF/HF ratio in patients and controls after 3 years of follow-up. Figure shows the higher contribution of LF and lower contribution of HF components to the spectral power of patients with West compared to controls. This leads to a higher LF/HF ratio.

in patients with epilepsy during slow wave sleep compared to controls. This is also observed in the LF/HF ratio (patients 0.997 versus controls 0.247; $p = 0.03$). These findings are not observed in wake or stage 2 sleep (see Fig. 1).

Discussion

Looking at short-term effects in our patient population, we were able to demonstrate a lower heart rate in patients

with West syndrome already before ACTH treatment, in contrast to the findings of Hattori et al. (2007). The decrease in heart rate can be a sign of parasympathetic predominance on the autonomic outflow to the heart. The finding is most significant during stage 2 sleep, where vagal components are physiologically less pronounced. During slow wave sleep vagal components are physiologically most prominent. Our findings suggest that there is already a difference in heart rate regulation in patients presenting with West syndrome. One of the pathophysiological hypotheses in West syndrome is the activation of a stress response and release of corticotropin releasing hormone (CRH). An early insult on the brain e.g. cerebral infarction provokes a stress response. This mediates an excessive release of CRH. In the developing brain, this excessive release can cause epileptic spasms and neuronal cell death, most important in amygdalae and hippocampus (Rho, 2004; Brunson et al., 2001). A high level of CRH will cause a rise in cortisol through production of ACTH. The autonomic vagal response could be a counterbalance for the cortisol-induced effects on bloodpressure and cardiac function. This is comparable with the findings in patients with Cushing, who also have a relatively increased parasympathetic activity and lower heart rate (Fallo et al., 2009). Treatment with ACTH could make these findings even more pronounced, as observed by Hattori.

Looking at the follow-up data, we were able to demonstrate higher LF, lower HF and a higher LF/HF ratio during slow wave sleep in patients who developed epilepsy after West syndrome compared to controls. These findings are already present after 3 years of epilepsy. In normal sleep, vagal components are always most pronounced during synchronized or slow wave sleep. This normal phenomenon is no longer visible in our cohort of patients with former West syndrome. Vagal reduction in patients with longlasting epilepsy has been previously observed in adults as well as in children (Tomson et al., 1998; Evrengül et al., 2005; Jansen and Lagae, 2010). The explanation of this phenomenon is still uncertain. A possible mechanism is that disruption of normal autonomic function is due to chronic epileptic activity. In a study by Sathyaprabha et al. (2006), the autonomic changes were more severe, the longer the duration of epilepsy was. In this study patients with longer duration of epilepsy (23.2 years) had more severe dysfunction than patients with relatively shorter duration (17.5 years) of epilepsy. Therefore, it is not impossible that chronic dysautonomia can already be present after a relatively short phase of severe epileptic encephalopathy.

The clinical relevance of these changes in patients with epilepsy remain an open question. Reduced heart rate variability is a marker of dysfunction of the autonomic nervous system and can be considered a risk factor in chronic disease e.g. myocardial infarction (Buccelletti et al., 2009). Various diseases including epilepsy are now known to be accompanied by a loss of autonomic functionality and reduced HRV (Chroni et al., 2008). One of the possible mechanisms underlying sudden unexplained death (SUDEP) are seizure related cardiac arrhythmias with tachyarrhythmias leading to ventricular fibrillation and bradycardia and ictal asystole (Tomson et al., 2008).

We did consider the possible effect of confounding factors e.g. the etiology of the West syndrome and the difference between cryptogenic and symptomatic cases, the number of seizures or influence of medication, but we were unable to investigate this further due to sample size constraints. However the observed results are so consistent that we believe that these factors can only be responsible for insignificant differences.

Although our results are consistent, we need more studies to show how the epileptic encephalopathy change the ANS in detail.

In conclusion, our results show that there is a lower heart rate in patients with West syndrome, already at the onset of the syndrome, even before treatment with ACTH. The epileptic activity at onset itself is not sufficient to alter spectral components of heart rate on the short term. However, after follow-up of 3 years of epilepsy, chronic autonomic changes appear.

Conflicts of interest

The remaining authors have no conflicts of interest.

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