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Cardiac autonomic dysfunction in drug naïve hot water epilepsy

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ABSTRACT

Purpose: This study aimed to characterize the role of autonomic nervous system dysfunction in hot water epilepsy (HWE). Heart rate variability (HRV) has been established as a good index of cardio-autonomic regulation.

Methodology: Forty-five patients with HWE (age: 24.6 ± 10.1 years; M:F = 37:8) and 45 age and gender matched controls (age: 24.17 ± 10.37 years; M:F = 37:8) were studied. Five minutes resting lead II electrocardiogram (ECG) was obtained (AD instruments) under standard conditions and analyzed for time and frequency domain HRV parameters using LabChart software.

Result: Patients with hot water epilepsy showed significant increase in LF nu (Low frequency normalized unit) and LF/HF denoting an interictal increase in sympathetic activity. In addition, reductions were noted in parasympathetic function [RMSSD (root mean square successive difference of RR intervals), HF (High frequency) nu and LF/HF].

Conclusion: This study has demonstrated an impaired sympatho-vagal balance characterized by increased sympathetic activity and reduced parasympathetic activity in patients with HWE. The present study supports the notion that the hypothalamus is involved in both, the pathogenesis of HWE and autonomic regulation.

1. Introduction

Hot water epilepsy (HWE) is an interesting type of reflex epilepsy in which a seizure is precipitated by having a bath or shower with hot water.[1–7] The condition is also known as 'water-immersion epilepsy' and 'bathing epilepsy'.[8–10] Patients affected with this condition may experience the seizures exclusively precipitated by those factors. Mani et al. published an epidemiologic study from Yelandur, a rural area near the district of Mysore from the state of Karnataka, India and reported a prevalence rate of 255 per 100,000 for HWE.[11] The diagnostic scheme proposed by the International League against Epilepsy (ILAE) in 2001 included HWE as a type of reflex epilepsy.[12] It is the second most common type of reflex epilepsy after photosensitive epilepsy.[13]

Experimental data suggests that autonomic neural discharge can be induced by inter-ictal epileptogenic activity.[14] Previous studies have shown that autonomic dysfunction plays a major role in the development of ventricular tachyarrhythmia in patients with epilepsy and may be related to the high incidence of sudden death.[15] Evidence of autonomic dysfunction like variation in heart rate or in blood pressure and even cardiac arrhythmias has also been well established in the inter-ictal period.[16] Other studies have shown that seizure control with antiepileptic drugs (AEDs) might help to improve cardiac autonomic impairment in epilepsy patients.[17] Incidence of sudden death and autonomic dysfunction is less in monotherapy than with polytherapy and gradual withdrawal is more effective than sudden withdrawal of drugs.[18]

Normal heart rate depends on the balance between sympathetic and parasympathetic systems. HRV is an important non-invasive tool for the detection of sympatho-vagal balance of the autonomic nervous system. HRV can be used as a measure of neuro-cardiac autonomic function. Several studies have documented that the analysis of time-domain and frequency-domain measures of HRV reflects sympathetic and parasympathetic functions.[19,20] HRV parameters are also suitable as tools for the quantification of physiologic, pharmacologic and pathologic changes in the autonomic nervous system.[14,20] Over the last few decades, increased emphasis has been placed on these techniques as measures of cardiovascular autonomic functions. HRV has been established as a good index of cardio-autonomic regulation.

Several studies have been done in patients with complex, simple partial and generalized tonic clonic seizures and revealed autonomic dysfunction in the inter-ictal period.[21] HRV parameters have not been used as measure of autonomic function in hot water reflex epilepsy. Hence in this study, HRV was evaluated to characterize autonomic function in HWE.

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2. Methodology

Forty-five patients with HWE (age: 24.6 ± 10.1 years; M:F = 37:8) were recruited as subjects for this study between May 2009 and September 2011, from the Neurology outpatients services of the National Institute for Mental Health and Neurological Sciences (NIMHANS), Bangalore, India. Forty-five age and gender matched healthy volunteers as controls (age: 24.17 ± 10.37 years; M:F = 37:8) were recruited for this study. The study was approved by the Institutional Ethics Committee (IEC), NIMHANS. All subjects participated voluntarily and gave their informed written consent. The diagnosis of HWE was made according to Revised International League Against Epilepsy (ILAE, 1989) guidelines.[22] Newly diagnosed patients or patients taking intermittent clobazam treatment were considered as drug naïve and were recruited for the study. None of the subjects had a history suggestive of diabetes, hypertension, cardiac disease, use of drugs or other comorbidities like head injuries, which are known to influence the autonomic functions. None of the patients met DSM-IVR criteria for depression or anxiety.

Details of seizure semiology, age at onset, types and duration of seizures, provoking factors, bathing habits, and history of febrile convulsions, family history of non-reflex epilepsy or HWE were obtained. Inter-ictal scalp EEG was performed in all subjects.

Routine electrocardiogram (ECG) was performed between 9 and 11 AM in the autonomic Laboratory, Department of Neurophysiology under standardized conditions.[23,24] ECG was performed after a minimum gap of 24 h (mean: 168 ± 25.07 h) from the last seizure. Fifteen minutes resting Lead II ECG was obtained (AD Instruments), which was analyzed offline for time and frequency domain HRV parameters using LabChart software. The recorded ECG signals were conveyed through analog digital converter (from Power Lab, 16 channel data acquisition system, AD Instruments, Australia) with a sampling rate of 1024 Hz. An artifact-free 5-min segment of the ECG was analyzed offline using LabChart software. This is an automated software program that permits visual inspection of the raw ECG and breathing signals, so as to obtain the HRV parameters in time-domain and frequency-domain, known as 'linear methods'.

2.1. Time-domain analysis

This involves comparing 2 different signals and was analyzed using descriptive statistical measures. Heart rate fluctuations were measured using various variables including (a) standard deviation of RR intervals sensitive to all sources of variation (SDNN); (b) root mean square successive difference of RR intervals – (RMSSD); (c) number of successive NN intervals that vary by more than 50 ms (NN50); and (d) percentage of NN50 counts which are more sensitive to the highest frequency component and best predictors of parasympathetic activity (pNN50).[23,24]

2.2. Frequency-domain analysis

The non-parametric Fast Fourier Technique (FFT) was performed for frequency-domain parameters. Different components of FFT with their specific frequency ranges were: (a) total power (TP) (0–0.4 Hz) which reflects sympathetic and parasympathetic tone; (b) high frequency (HF) (0.15–0.4 Hz) which is indicative of parasympathetic tone and respiration; (c) low frequency (LF) (0.04–0.15 Hz) which indicates sympathetic as well as parasympathetic tone, (d) very low frequency (VLF) (0.003–0.04 Hz) which indicates thermoregulation, and can be used to calculate LF normalized unit (LF nu) and HF normalized unit (HF nu) that represent the relative value of each component in proportion to the total power minus the VLF component; and (e) LF/HF which reflects sympathovagal balance and reflects sympathetic modulation.[19,23,24]

2.3. Data analysis

The data was analyzed using SPSS version 15. After log transformation independent sample '*t*' test was used to look for significant differences in the study parameters between patients and controls. Significance was assessed at the 5% level. Results of continuous measurements of HRV and clinical features were presented as mean ± standard error of mean (SEM) and mean ± standard deviation (SD) respectively.

3. Result

3.1. Clinical and demographic details

Forty-five subjects (age 24.6 ± 10.15 years; M:F = 37:8) of HWE and 45 age and gender matched healthy volunteers as controls (age: 24.17 ± 10.37 years; M:F = 37:8) were studied. The mean age at onset was 18.7 ± 10.2 years and the duration of illness was 69.9 ± 13.8 months. All patients had the habit of taking hot water head bath either every alternate day or at least once in a week. Thirty percent of the patients experienced 4–6 attacks per month, 10% experienced 1–2 attacks per month and the remaining experienced at least one attack every 6–12 months. 58.5% patients had complex partial seizures without secondary generalization, while 41.5% had complex partial seizures with secondary generalization. A past history of febrile convulsion was present in 22%, and a family history of non-reflex epilepsy and HWE was present in 22% and 26.8% of cases, respectively. Patients with self-induction experience a feeling of pleasure or euphoria during their hot water induced seizures, causing them to pour more hot water over themselves until they manifest with seizure. The phenomenon of self-induction in HWE is well documented and in this cohort it was noted in 32.5%.[5] The majority of the HWE patients (68%) were drug naïve while the remaining patients were on intermittent clobazam. The demographic and clinical data of the subjects are summarized in Table 1. The EEG was abnormal in 9/45 (20%) patients. In the majority of patients the abnormalities were located in the fronto-temporal region on either or both sides. The details of EEG abnormalities are mentioned in Table 2.

Table 1
Clinical features and demographic details of hot water epilepsy (HWE) patients.

Parameters	HWE (n = 45)
M:F	37:8
Religion (Hindu:muslim)	34:11
Age at evaluation (years)	24.6 ± 10.1[c]
Age at onset (years)	18.7 ± 10.2[c]
Duration of illness (months)	69.9 ± 13.8[c]
Mean number of HWE[d]	19.6 ± 2.36[c]
Frequency/month	5.31 ± 0.42[c]
1:1 episodes in relation to hot water head bath (%)[a]	32.5
With secondary generalization (%)	41.5
History of Febrile convulsion (%)	22
Family history of spontaneous seizures (%)	22
Family history of HWE (%)	26.8
Self-induction (%)[b]	32.8
Newly diagnosed HWE (%)	68
Abnormal EEG (%)	20

[a] 1:1 episodes in relation to hot water head bath, i.e. seizure occur every time patient have hot water bath.
[b] Patients with self-induction actually mean that while taking hot water bath they have a feeling of pleasure and euphoria, making them pour more hot water till they manifest with seizure.
[c] Values are expressed in mean ± SD.
[d] Average numbers of seizures due to hot water during their life time at the time of evaluation.

Table 2
Detailed description of EEG abnormalities and CT scan in patients of hot water epilepsy (HWE).

Sl. No.	Gender	Age (years)	Type of seizure	Duration of HWE (years)	EEG findings	CT scan
1	M	17	HWE-CPS	3	Left fronto-temporal (T1) spike	Normal
2	M	21	HWE-CPS	3	Left temporal T5 foci-spike	Not done
3	M	46	HWE-CPS with sec. generalization	6	Bi-temporal T2-5, Rt > Lt	Not done
4	M	32	HWE-CPS	3	Frontal spike arising from Lt > Rt hemisphere	Not done
5	M	17	HWE-CPS with sec. generalization	7	Independent bilateral fronto-temporal discharge	Normal
6	M	20	HWE-CPS with sec. generalization	5	Bi temporal sharp wave	Not done
7	M	39	HWE-CPS with sec. generalization	2	Left temporal sharp wave	Normal
8	M	34	HWE-CPS	1	Right frontal lobe discharge	Not done
9	M	33	HWE-CPS	2	Solitary sharp wave over T4-6	Normal

3.2. Heart rate variability parameters

The mean heart rate was higher in patients with HWE compared to controls (75 ± 3/min vs 71 ± 2/min) though statistically not significant. The time-domain parameters of HRV were significantly reduced in patients with HWE compared to the controls. SDNN was 42.8 ± 2.1 ms vs 54.4 ± 3.1 ms, $p = 0.002$; RMSSD was 33.7 ± 2.6 ms vs 72.0 ± 4.1 ms, $p = 0.012$. The frequency domain parameters were also altered in patients with HWE. LF nu was 49.3 ± 2.5 vs. 40.1 ± 2.1, $p = 0.007$; HF nu was 41.2 ± 2.5 vs 49.23 ± 2.3, $p = 0.009$ and LF/HF was 1.65 ± 0.2 vs 0.97 ± 0.1, $p = 0.004$. Results were showing predominant sympathetic overactivity with reduced parasympathetic activity and sympathovagal balance tilted toward sympathetic limb. The details are provided in Table 3.

3.3. Discussion

High variability in heart rate is a marker of a normally functioning neuro-cardiovascular system. Disturbed cardiac autonomic function might reflect as low heart rate variability, which is a marker for underlying neuro-cardiovascular diseases.

It has previously been documented that inter-ictal epileptogenic activity can induce autonomic disturbance and that cardiac arrhythmias may be associated with altered autonomic neural discharges.[25] The disturbance of the autonomic control of the heart rate might be one of the causes for the high incidence of sudden death in epileptic patients.[26,27] Historically, decreased HF power as well as RMSSD and pNN50 with increased LF/HF indicating sympathetic dominance have been documented in simple and in complex partial seizure.[28] Several other studies have showed subtle but definite cardiac autonomic dysfunction in drug-naïve and new-onset epilepsy patients.[29] A previous study of HRV in patients with newly diagnosed generalized tonic–clonic seizures reported reduced HF, increased LF and an increased LF/HF ratio.[15] However, Ansakorpi et al. showed decreased LF and HF power especially in temporal lobe epilepsy (TLE), contradicting the previous studies.[30] Even, in frontal lobe epilepsy there was reduced heart rate variability during the inter-ictal period due to reduced vagal regulation of autonomic cardiac activities.[31] Autonomic dysfunction has also been observed in refractory epilepsy.[22]

Effects of AEDs and epilepsy on HRV have been established.[32–34] A study of patients with TLE in which the majority of the patients were on polytherapy with different AEDs, showed lower TP and also decreased LF and HF power.[33] Heart rate and blood pressure responses were diminished in the group on AEDs, especially in the subgroup treated with carbamazepine (CBZ).[32] Impairment of cardiovascular autonomic functions studied on those who were on CBZ proved that CBZ increases the risk of cardio-respiratory changes in susceptible patients.[34] In this study, HRV was altered in patients with HWE, who were drug naïve. We therefore believe that it is likely that interictal dysautonomia in patients with HWE is likely to be caused by interictal epileptic activity.

Autonomic alterations have also been reported in children with simple and complex partial seizures.[28] Dutsch et al. showed increased LF power and LF/HF ratio, decreased HF power in TLE suggesting disturbance in hypothalamic functionality as well as in connected areas due to structural microscopic changes in limbic area.[35] However, contradicting their observations, Tomson et al. reported an excess of parasympathetic activity in TLE – either due to TLE per se or the effects of CBZ treatment.[27] The present study shows that patients with hot water induced complex partial seizures have an increased interictal sympathetic tone. Hot water epilepsy in TLE patients may also show sympathetic predominance. In our study, HWE patients were drug naïve so there was no possibility of the observed changes being due to antiepileptic drugs.

In this study, we explored both time and frequency domains of HRV in patients of HWE who were drug naïve. There was slight increase in heart rate but a significant decrease in SDNN, RMSSD and pNN50 index in time domain parameters of cases compared to healthy volunteers. Also, the frequency domain parameter results, which are more accurate if the analysis is based on short ECG recordings, showed a very significant

Table 3
Comparisons of time and frequency domain measures of heart rate variability of hot water epilepsy (HWE) and healthy volunteers.

Parameter	HWE ($n = 45$)	Healthy volunteer ($n = 45$)	p value
SD of RR intervals (SDNN)	42.8 ± 2.1	54.4 ± 3.1	0.002
Square root of mean of sum of squares of successive differences of RR intervals (RMSSD)	33.7 ± 2.6	72.0 ± 4.1	0.012
Number of successive NN intervals > 50 ms (NN50)	76.7 ± 12.2	86.3 ± 9.4	0.229
pNN50	21.64 ± 3.6	25.89 ± 3.07	0.170
Total power (TP)	3380.6 ± 572.1	3149.1 ± 457.7	0.896
LF power	836.32 ± 119.5	756.35 ± 102.83	0.642
HF power	1192.20 ± 277.1	1205.92 ± 300.20	0.614
Low frequency power normalized unit (LF nu)	49.3 ± 2.5	40.1 ± 2.1	0.007
High frequency power normalized unit (HF nu)	41.2 ± 2.5	49.23 ± 2.3	0.009
LF/HF	1.65 ± 0.2	0.97 ± 0.1	0.004

Values are expressed as mean ± SEM.

increased in LF nu and LF/HF which is an indicator of sympatho-vagal balance, indicating increased sympathetic effects on the cardiovascular system. There was a significant fall in HF nu but not in HF power because normalization tends to minimize the effect on the values of HF components of the changes in total power.[19] Hence, both time-domain and frequency-domain parameters showed increases in sympathetic tone consistent with an increased risk of cardiac arrhythmias. The relative predominance of sympathetic over-activity could predispose patients to the development of ventricular tachyarrhythmias. Increased parasympathetic activity will have long term effects on the heart leading to bradycardia and asystole if the seizures are not well-controlled.[36]

3.4. Mechanism of HWE and autonomic dysfunction

Kindling phenomena are well established in HWE and have been shown to be relevant in this condition by animal experiments.[3,37] Kindling is likely to stimulate the limbic system.[38] Simultaneously, there may be activation of the prefrontal cortex and anterior cingulate, which are involved in attention to dangerous or negative stimuli, which ultimately influence the limbic system (especially the amygdala). This could lead to an increase in the dendritic growth in the limbic system, which would lead to even greater limbic stimulation causing an increase in the excitatory post-synaptic receptors and a decrease in inhibitory pre-synaptic receptors.[39] Brain chemistry studies demonstrate that increased levels of glutamate and decreased levels of GABA lead to hot water induced seizure.[40]

Stimulation of the amygdala inhibits the hippocampus which in turn disinhibits the hypothalamus, hence causing excitation of the hypothalamus. Predominant sympathetic activity in hot water epilepsy might be due to stimulation of sympathetic center from the hypothalamus and amygdala[41,42] (Fig. 1).

This is the first study in which heart rate variability was compared between patients with hot water epilepsy and healthy volunteers. The results reveal a reduced vagal tone during the inter-ictal period in patients with HWE. Hypothalamic functions, which play a role in regulating autonomic and thermoregulation, may be altered in HWE. This study supports an earlier hypothesis of hypothalamic dysfunction[5] and a distinctive sympathetic dysfunction in patients with HWE. This also supports the hypothesis of a common neuro-anatomical and neuro-physiological region for HWE and autonomic dysfunction.

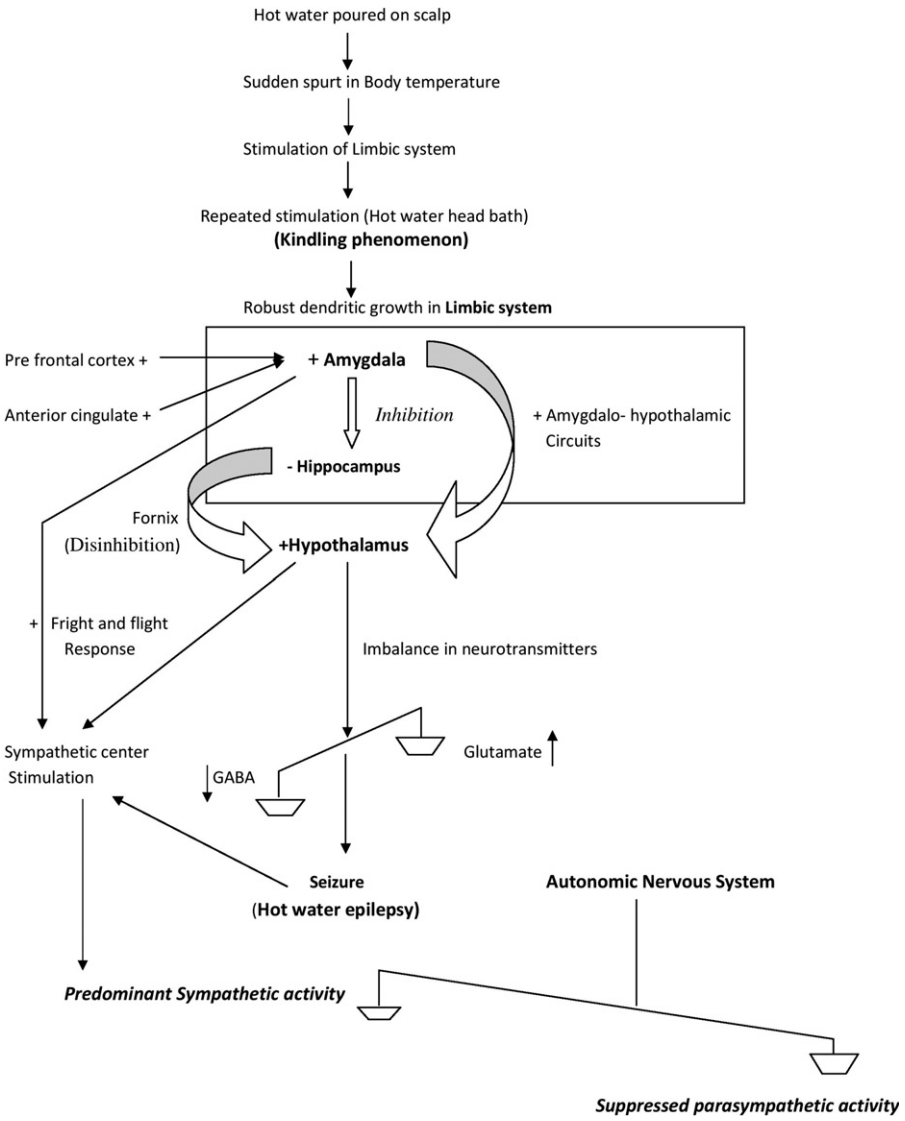

Fig. 1. Schematic diagram showing possible mechanism of autonomic dysfunction in hot water epilepsy (HWE).

Conflict of interest

None.

Financial disclosure

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