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RESEARCH ARTICLE

Extended head up tilt table test (HUTT) in unexplained recurrent loss of consciousness; a single centre prospective study.

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Abstract

Objectives: Recurrent loss of consciousness (rLOC) carries significant risk of injuries because of falls. On history and examination about 60% of them can be diagnosed as syncope. However history may be misleading because symptoms like head turning and jerky movement during LOC which are considered to support seizure could be associated with neurocardiogenic syncope (NCS).

Material and methods: 83 patients of rLOC without triggering factors were prospectively recruited from March 2010 to December 2014 for HUTT and using Italian protocol of HUTT.

Results: 63% of the patients with unexplained rLOC were positive on HUTT (pHUTT). Out of 15 patients with previous diagnosis of epilepsy 9(60%) turned out to have pHUTT. Tonic posturing was seen in 10 (12%) patients. The positive predictive value (PPV) of motor phenomenon for diagnosing seizure during rLOC was 40%.POTS was more common with younger age (≤ 30 years) group patients and these patients having more chance to develop NCS (p value 0.04). Severe hemodynamic compromised and LOC were significantly associated with SFS (slow flat slow) EEG pattern.

Conclusion: During LOC various types of motor phenomenon were seen including tonic posturing in 12% of patients on HUTT. Patients with POTS did not show any EEG changes during tachycardia. 9.6% of the patients with unexplained rLOC have asystole of more than 3 seconds. All patients with syncope do not show ictal EEG changes and all patients with presyncope do not have normal ictal EEG.

INTRODUCTION

The *syncope* is derived from Greek word *syncopea* meaning "to cut short". NCS defined as transient loss of consciousness due to cerebral hypoperfusion [4]. Recurrent LOC is reported by 3% of those visiting emergency and 6% of all hospital referrals [16, 17] but the etiology remains unknown in up to 40% of them. Although NCS is the most common cause of rLOC but every time a neurologist confronts patients with syncope, a possibility of seizures pops up in his mind [20]. Most of the time a history and situations in which the LOC has occurred give clues towards the possible diagnosis, however symptoms considered typical for one disease are known to occur in other, for example limb jerking, post ictal confusion and incontinence of urine thought to be pointers toward seizures are also seen in patients with syncope [6, 7].

Syncope is commonly misdiagnosed as seizures and patients are managed with long term antiepileptic drugs despite poor clinical control [7]. NCS carries significant risk of injuries and at times could be due to seizure, albeit amenable cardiac arrhythmias and need to be approached proactively.

Syncope could be acute or gradual in onset and either of them can be reproduced in controlled situation with different techniques, former with eye ball pressure and carotid massage and later by creating lower body negative pressure thereby inducing vasovagal syncope. Tilting the subject passively has become a standard procedure to evaluate gradual onset syncope. HUTT described first time by Kenny et al in 1986 [2]. While HUTT rarely has induced syncope in healthy control subjects, has stood the test for being useful in evaluation of subjects with suspected syncope [18, 19]. To further improve the sensitivity and specificity of the test later EEG and extension of test with sub lingual nitroglycerine was added. The positivity of test in NCS is 46.6% reported by J.H.Ruiter et al in his study of 528 patients [20]. Since then many investigators have used this test for classification of syncope and found to be fairly sensitive and specific for indentifying syncope [5, 20, 21, 22].Two types of EEG changes during syncope are well established SW (slow wave) and SFS (slow flat slow). However EEG changes in POTS are not well established and no significant changes observed in previous studies during HUTT.

We present our experience of 83 patients with unexplained rLOC who were prospectively evaluated with HUTT.

MATERIAL & METHODS:

Subject:

We studied 83 patients (male 53, female 30), from March 2010 till December 2014, who were referred to neurology outdoor with rLOC. They were subjected to detailed history & clinical examination. Patients with discernible precipitating factors (e.g. cough, micturition, emotional stress and unaccustomed physical activity), hypnogogic attacks, cardiac rhythm abnormality, valvular heart disease, and carotid stenosis & EKG evidence of coronary artery disease were excluded. Patients with motor activity during rLOC were included if the detailed history, eye witness account and other investigations did not differentiate between seizure and syncope. Such patients were, usually, referred to us as non responders to antiepileptic medications. After obtaining an informed consent, HUTT was done with an aim to reproduce the clinical syndrome and record the ictal symptoms and signs; the objectives being:

a) To assesses the usefulness of HUTT in patients with rLOC without known triggering factors.
b) To correlate EEG abnormalities with symptoms, type of syncope, change in blood pressure and heart rate.
b) To examine association of symptoms with type of syncope, change in heart rate, age, gender, hypertension and diabetes.

The study was approved by the institutional ethical committee IEC No: 12/10/01.

Protocol for HUTT:

Test; The HUTT was performed as per the Italian protocol [3]. This protocol is divided into an initial drug free phase (20 minutes) and NTG provocation phase (20 minutes) of passive 70^0 tilt on a tilt table.

Monitoring: The Blood pressure(BP) in right arm was recorded with an automated BP cuff at rest and thereafter at every five minute interval, guided by patient's symptoms additional recordings were allowed.

EEG was monitored without interruption during cool off, initial drug free phase and NTG phase. In symptomatic patients the monitoring was continued till complete clinical recovery. EEG was recorded using 10/20 system of electrode placement. While 24 channels dedicated to EEG, ocular movements were recorded on two channels and three channels were deployed for the monitoring of EMG (chin and bilateral deltoid).

ECG was monitored on a Philips Multipara Monitor and recorded on the EEG system by fixing electrodes on ventral aspect of forearm one centimeter proximal to distal wrist crease bilaterally.

End Points:

1. Precipitation of clinical syndrome
2. Occurrence of arrhythmia or symptomatic bradycardia or asystole lasting for ≥ 3 seconds, with or without NTG
3. No symptoms after 20 minutes of NTG
4. Fall in systolic BP of 40 mmHg or more.
5. Patients withdraws consent to continue further testing.

Definitions:

a. Seizures were defined as episodes of unconsciousness with or without limb jerking but associated with post ictal confusion and EEG evidence of epileptiform activity.
b. POTS is defined as an increase in heart rate ≥ 30 beats per minute (bpm) from resting state, or a rate of ≥ 120 bpm within 10 minute of tilt [14].

c. Symptoms : Self (warmth, cold, tingling, palpitation, uneasiness and black out), investigator's observations regarding motor signs (jerky limb movements, yawning, head drop, deviation of eyes, turning of head) and autonomic dysfunction (pallor, perspiration)
d. Positive test (pHUTT): Precipitation of syncope; presyncope; drop in systolic BP (≥20mmHg in initial drug free phase and ≥40 mmHg during NTG phase) or diastolic BP (≥ 10 mmHg during initial drug free phase); POTS.
e. Negative test (nHUTT): When there is no response during HUTT.
f. Presyncope defined as symptoms and/or circulatory changes without loss of consciousness.

Analysis

a) The symptoms and signs were correlated with electrophysiological findings (EEG and EKG).
b) Classification of syncope. NCS was classified in to vasodepressor (vNCS; when there is hypotension as predominant finding), cardioinhibitory (cNCS; when bradycardia and/or asystole are predominant finding) and mixed types (mNCS; when both are present) [1].
c) The EEGs were evaluated for epileptiform discharges during ictal period and changes in EEG pattern during preictal, ictal and post ictal period and classified as SW and SFS.The EEG slowing was defined as first theta or delta wave of a consistent period and the end with last theta or delta wave. Flat EEG defined as very low amplitude waves in between slow waves [4].
d) Statistical significance was determined by calculating p value through chi square, fisher exact test and student t test.

RESULTS:

Subjects:

Out of 83 (male 53, female 30, male to female ratio1.76:1, p 0.638) who completed the study, clinical symptoms could be replicated in 53 patients by HUTT, giving a sensitivity of 63%. The mean age of total cohort was 38.78 (SD±17.21). Difference in the mean age of the pHUTT (36.32, SD±17.75)) and nHUTT (43.28, SD±15.18) was statistically non significant (p value 0.067). However patients under 30 years of age were more likely to have pHUTT as compared to the older population (p 0.042). Hypertension appears to be a risk factor for syncope (P value <0.005). PHUTT cohort comprised of NCS (31; 37.34%, male=20, female=11), presyncope (10; 12.04%; male=7, female=3), orthostatic hypotension (3; 3.61%, male=3) and POTS in 27 patients (32.53%, male=16, female=11). The vNCS was present in 8 (25.80%, male=5, female=3); cNCS in 2(6.45%, male=2) and mNCS in 21(67.74%, male=13, female=8). Out of 53 pHUTT, only 31 patients had LOC (58%), remaining 22 patients either had presyncope or asymptomatic POTS (n=8).

15 patients were referred to us with a possibility of epilepsy, 9 (60%) of them had pHUTT but only 5 (33.33%) had convulsive syncope. In addition 18 patients without any clinical history of motor symptoms showed involuntary motor activity during the test, PPV of HUTT to reproduce motor phenomenon was only 22%.

Symptoms and type of NCS: Uneasiness, visual, motor symptoms and LOC are significantly associated with vNCS. Motor symptoms and LOC are significantly associated with mNCS and autonomic with LOC is significantly associated with cNCS (Figure 1).

Postural orthostatic Tachycardia:

POTS (n=27) was significantly common in subjects under 30 years of age (p<0.01), no gender specific difference was found in its occurrence. None of the patient had any symptoms during the epoch of postural tachycardia however 19 of them had presyncope (n=6, 22%) or syncope (n=13, 48%) on continued tilt.

Electroencephalographic changes:

No time locked EEG changes were seen during the episode of postural tachycardia and during orthostatic hypotension. Ictal EEG changes were seen in 35 patients of pHUTT (35/53) and which could be classified into SW (n=27) or SFS (n=8) pattern. SFS was exclusively associated with mNCS (n=7) and cNCS (N=1), while all patients with vNCS showed SW pattern. Sensory symptoms, uneasiness was significantly more common in those with ictal SW. Other symptoms were seen with both EEG patterns but autonomic was associated with SFS (table 2). While deviation of eyes, yawning and head turning was more common with SFS, head drop, myoclonic jerks, tonic and clonic limb movements were often seen with SW (table 3). No EEG pattern was associated with blood pressure change; however patients with SFS had significantly slow ictal heart rate (p 0.04); (Figure 2). While asystole of five seconds were seen in SFS (5/8), asystole of ≤3 seconds was present in SW (3/27).

Table 1: Relation of age, gender and clinical features with HUTT

	NO.(n)	p HUTT			n HUTT	SW EEG	SFS EEG	Normal EEG
		Syncope	Presyncope	POTS				
Male	53	35			18	18	6	30
		20	7	16				
Female	30	18			12	9	2	18
		11	3	11				
<30 years	32	26			6	14	3	15
		14	4	23				
30-49 years	29	15			14	6	3	20
		10	3	3				
>50 years	22	12			10	7	2	13
		7	3	1				
History of rLOC	68	44			24	21	7	40
		26	7	22				
History of rLOC with motor phenomenon	15	9			6	6	1	8
		5	3	5				
Hypertension	13	10			3	6	1	6
		5	3	2				
Diabetes	3	-			3	-	-	-
		-	-	-				
Hypothyroidism	2	2			0	1	-	1
		1	1	-				

Table 2: Symptom correlation with SW and SFS EEG pattern, (S): Statistically significant i.e. P-value <0.05.

(NS): Statistically non significant. LOC: Loss of consciousness

Symptoms	SW EEG (n=27)	*P*-Value	SFS EEG (n=8)	*P*-Value
Uneasiness(n=21)	12	**0.005**	3	0.563
Blackout, Visual symptoms (n=15)	10	**0.001**	5	**0.0005**
Autonomic(n=33)	18	**0.0005**	8	**0.00025**
Motor symptoms(n=23)	15	**<0.05**	7	**0.0003**
Sensory symptoms(n=3)	3	**0.01**	0	-
LOC (n=31)	21	**<0.05**	8	**0.0001**

Table 3: Motor symptoms association with SW and SFS EEG pattern.

	SW EEG (n=27)	*P- Value*	SFS EEG (n=8)	*P- Value*
Eye deviation/up rolling(n=7)	3	0.542	3	**0.001**
Yawning(n=1)	0	0.484	1	**0.002**
Head drop (n=9)	8	**0.0001**	1	0.87
Turning of head (n=5)	2	0.713	2	**0.01**
Tonic limb movement(n=10)	7	**0.006**	2	0.23
Clonic limb movement(n=7)	5	**0.021**	1	0.663
Myoclonic jerks(n=2)	2	**0.039**	0	-

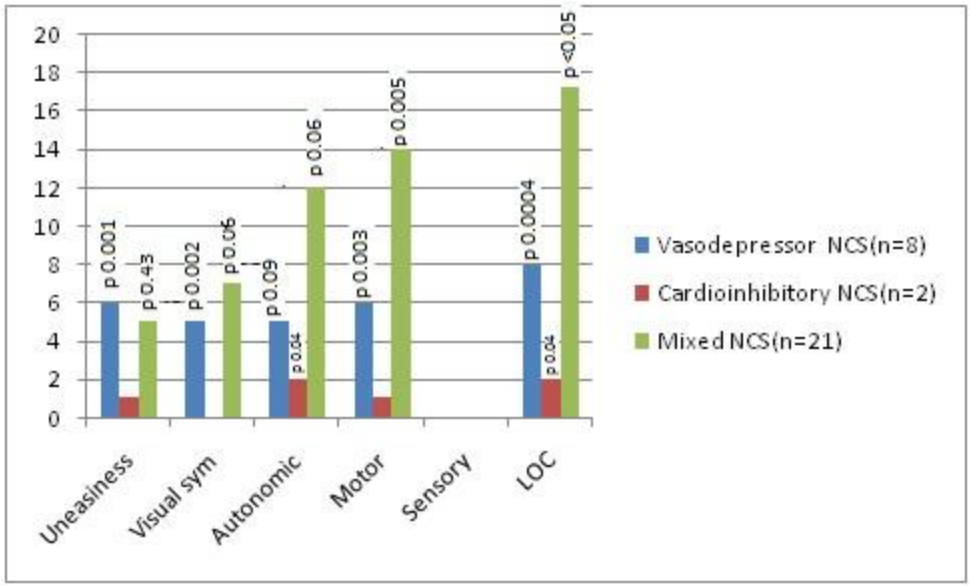

Figure 1: Symptoms in different types of NCS. P value <0.05 is statistically significant.

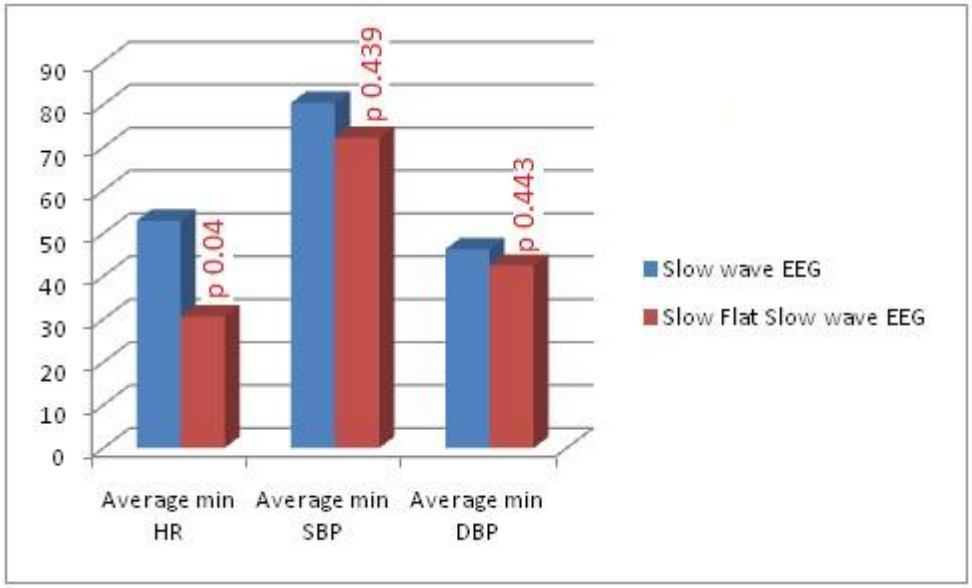

Figure 2: Association of hemodynamic changes with type of EEG pattern. P value <0.05 is statistically significant.

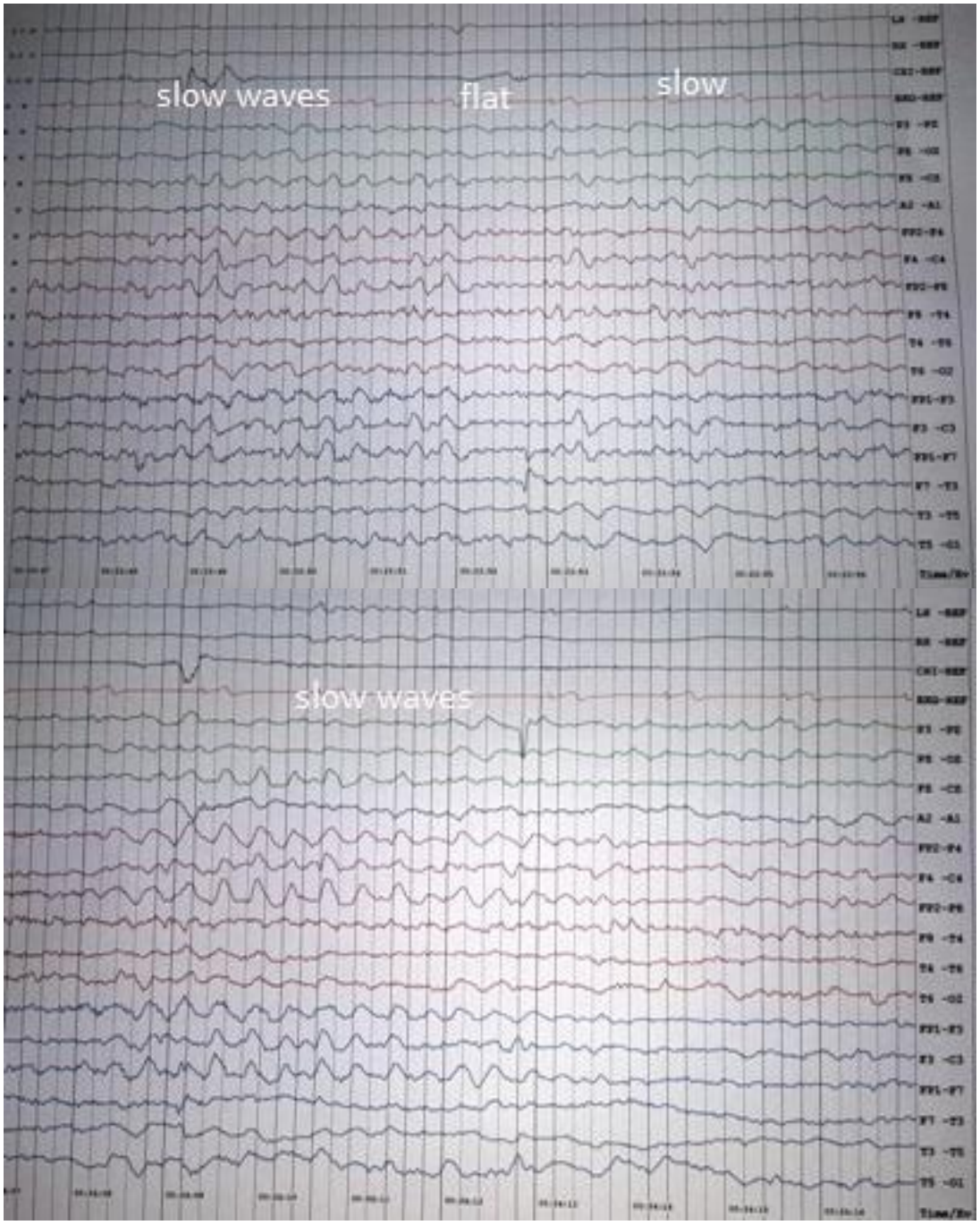

Image 1: SW and SFS EEG pattern.

Discussion:

Syncope is transient loss of consciousness characterized by rapid onset, short duration, and spontaneous complete recovery [1]. Reflex syncope remains the most common cause of rLOC and it is suggested that about half of them can be diagnosed on the basis of history in presence of normal physical examination [21, 23]. In patients without classical triggers, evidence of cardiac abnormality or autonomic dysfunction diagnosis of syncope based on history and clinical findings alone may be difficult. It has been suggested that about a third of the patients, with unexplained rLOC, test positive on HUTT even without pharmacological provocation [26]. 53 (63%) patients were tested positive on HUTT. Of these 5 were positive during initial drug free phase and 48 persons could be classified as pHUTT following administration of NTG (57% of total cohort and 90% of total pHUTT p value<0.05). Oraii S et al studied effect of pharmacological provocation in patients with vasovagal syncope as well as normal subjects and found that almost 5% of normal subject have syncope with or without NTG, while 31% patients had syncope during initial phase only. In normal persons, upon standing, roughly 300-800 ml of blood is displaced into vasculature of abdomen and lower extremities, resulting into fall in the venous return to the heart. This is compensated by mechanoreceptors in cardiac chambers, redistribution of blood from adipose tissues, skin and muscles as well as activation of rennin angiotensin aldosterone system [25]. Persons with abnormality in any of these adoptive processes are prone to experience syncope in stress situation, like cough micturition, emotional stress and humid condition, pain, unaccustomed exercise etc. By excluding those who have a forthcoming history of syncope in these situations, we actually excluded persons with severely abnormal adoptive mechanism, which explains the lower number of persons in our study cohort with pHUTT during initial drug free phase. NTG provocation seems essential to diagnose syncope in cohort of persons with rLOC in whom diagnosis remain unclear after history and clinical examination. A study by M.Lelonek et al shows that arterial hypertension in less than 65 years of age is a risk factor for syncope [9]. We also found significant association of hypertension with syncope (P <0.005).

Symptoms and type of NCS (Fig1)

A clinical rating system has been evolved wherein a score greater than 1 is proposed to favor seizure and that less than 1 suggests syncope in persons presenting with unexplained LOC. Furthermore, symptoms like tongue bite, head turning, jerking of limbs are proposed to favor a possibility of seizure [23]. In our study population 15 patients (18%, 15/83) had history of motor activity with rLOC, while in remaining (n=68) there was no historical evidence of motor activity during syncope, 9 of the former (60%) tested positive on HUTT. Thus the PPV of motor phenomenon for diagnosing seizures is only 40%, even if it is assumed that remaining patients (n=6) had seizures. Furthermore 18 persons from the later group (26%) had syncope with motor phenomenon during HUTT (table 1). Motor movements during syncope have been reported with varying frequency of 5.57% to almost 90% [27, 28]. Focal or multifocal myoclonic jerks and eye deviation are the most frequently reported during syncope. In our study tonic limb movements and head drop were most frequent followed by clonic limb movement and eye deviation (table3). Motor phenomenon was seen in all three types of NCS (Fig 1) but was significantly associated with vNCS (p=0.003) and mNCS (p=0.0005).

Postural orthostatic tachycardia

In normal persons heart rate increases in response to upright posture and an early sustained increase in heart rate ≤18 beats per minute (bpm) predicts nHUTT with a specificity of 100% and sensitivity of 86.6% [25, 29]. Increase in heart rate beyond 30 bpm during initial 10 minutes of tilt is suggestive of dysfunctional autonomic nervous system this newly recognized syndrome POTS is frequently seen in younger persons. Persons with POTS often report orthostatic intolerance such as palpitation or light headedness [14, 15]. 35% (n=27) of our patients fulfilled the diagnostic criterion of POTS and most were ≤30 years in age. Neither any symptom (except single patient) nor any EEG abnormality was seen during the epoch of tachycardia. Other investigators also did not find any EEG abnormality in POTS [14, 15]. Incidence of syncope in POTS has been reported to vary between 6% and 62.6% [8, 26]. In our study 66.6% (n=18) of POTS went on to develop syncope on continued tilt. Our results suggest that POTS is significantly associated with NCS (p= 0.04).

Electroencephalogram in NCS (table 2, 3 and fig 2)

Duration of LOC was between30-50 seconds, which is similar to the study of Ammirati et al. We also found post ictal slowing for average duration of 10-20 seconds even when the patient was tilted back to supine position. Post ictal slowing was present in a total of 17 patients and consisted of theta wave in 8, delta waves in 5 and theta delta both in 4 patients. Only in three patients EEG changes were of gradual onset starting with alpha drop out followed by slowing but in rest of patients it is sudden change in background with the appearance of slow waves.

Two types of ictal patterns have been reported SW or SFS with syncope [4, 11]. Out of this SW pattern was seen in 27 (77.14%) and SFS was present in 8 (22.86%). It is noteworthy that 2 of the persons with NCS did not develop any EEG abnormality, while 60% of patient with presyncope had SW pattern in EEG. In a study by Sheldon et al to observe EEG changes during syncope induced by tilt table testing shows all 18 patients with syncope had EEG

changes of slowing but 13 out of 14 patients with presyncope had EEG slowing [10]. While we found SFS pattern to be associated with lower average heart rate and bradycardia was found to outlast the EEG slowing. No epileptiform discharges were seen during the syncope associated with motor phenomenon. Head drop and tonic limb movements were significantly more common with SW (table 3), deviation of eyes correlated significantly with SFS (table 3). Van D et al evaluated 69 patients with HUTT and EEG monitoring. They found eye deviation, verbalization, and head turning as significant motor phenomenon in SFS [4]. In their study, head drop was seen in 27.5 % and 34.2% of SW and SFS respectively, and the difference was not statistically significant. Tonic limb posturing is not reported in their cohort. Asystole of more than 3 seconds was found to be significantly associated with SFS pattern, as reported by other investigators [4, 11]. No pattern of EEG slowing was specific for cNCS and mNCS but SW pattern was present in 100% vNCS. Increasing amplitude and duration of slow waves suggest increasing network failure and appearance of flat waves suggest there is complete network failure and very few functioning neurons maintain network activity. EEG becomes flat when hemispheric blood flow falls below 0.16-0.17 ml/kg/minute [4, 12, 13]. SFS is thus a manifestation of severe cerebral hypoperfusion, which is supported by its association with long asystole and significant bradycardia.

Conclusion:

HUTT with NTG challenge is able to diagnose NCS in 63% of unexplained rLOC. The NTG provocation would raises the sensitivity of test and in our study out of 53 pHUTT, 48 (90%) of them turned out positive after NTG use. Hypertension is a definite risk factor for syncope and targeted control of it with antihypertensive drugs will decrease the rLOC episodes.

Postural orthostatic tachycardia is usually asymptomatic and found more in younger age group with male preponderance. Patients with POTS did not show any EEG changes during tachycardia and these patients were more prone to develop syncope. During LOC various types of motor phenomenon were seen including tonic posturing. The occurrence of motor phenomenon is usually thought to be associated with seizures. However, in patients with rLOC it is common and probably cannot be used in refuting the diagnosis of syncope. All patients with syncope do not show ictal EEG changes and all patients with presyncope do not have normal ictal EEG. SFS type EEG pattern significantly associated with blackout, autonomic, motor symptoms and LOC as compare to SW pattern. Symptomatic bradycardia and asystole of more than 3 seconds significantly associated with SFS pattern suggest severe hemodynamic compromised. The ability of HUTT to pick up life threatening situations like this, in itself justifies it been offered as screening test in rLOC.

Limitation of study: Present study was conducted at a single centre and video monitoring not done in all patients.

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