ORIGINAL ARTICLE

Vasovagal (neurocardiogenic) syncope in the clinical practice

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Abstract

OBJECTIVES: Vasovagal syncope (VVS) is the most common type of syncope with the incidence of 21–43%. The aim of this study was to explain difficulties of correct diagnosis of VVS.

DESIGN AND METHODS: Our group comprises 70 patients (24 men, 46 women) at the age of 15–71 years, in whom VVS was verified by the head-up tilt test (HUT-test). We evaluated the type of VVS, admission diagnoses present in the patients, interictal EEG findings and the presence of convulsions during the syncopal states. For statistical processing of the results we used binomial tests for two independent proportions, Fisher-Freeman-Haltons exact test and Cramér's V index.

RESULTS: Out of 70 VVS 35 were vasodepressoric, 19 cardioinhibitive and 16 intermediate. Admission diagnoses present in the patients were: disorders of consciousness of an unknown etiology – 42.9% cases; supposable epilepsy and epilepsy – 30% cases and syncope – 27.1% cases. Interictal EEG was normal in 51.4% cases, nonepileptiform abnormality was present in 48.6% cases. Statistical comparison among particular types of VVS revealed a significant difference in distribution and medial strong association between the type of VVS and the EEG finding (Cramér V=0.35) and also between the type of VVS and the occurrence of convulsions (Cramér V= 0.40).

CONCLUSION: The results of our study evidently suggest that interdisciplinary cooperation in accurate diagnostics in this field of medicine is needed and that HUT-test has to be in standard diagnostic algorithm in patients with failures of consciousness of an unknown cause.

INTRODUCTION

Seizure disorders with, but also without, a disorder of consciousness often represent a diagnostic problem. From a diagnostic point of view it is important to distinguish seizures of epileptic from non-epileptic origin(Angus-Leppan 2008; Bajaček *et al.* 2010; Hovorka *et al.* 2009; Perrig & Jallon 2008; van Donselaar *et al.* 2006).

Non-epileptic seizures according to etiology are divided into (EpiStop 1999):

A) Somatic
- syncopes of a various etiology
- cardiovascular disorders, mainly arrhythmia
- sleep-related disorders (narcolepsy-cataplexy, somnambulism, pavor nocturnus, physiological myoclonia when falling asleep, iacatio capitis nocturna, enuresis, etc.)
- paroxysmal dystonia and paroxysmal kinesiogenic dyskinesia
- non-epileptic myoclonus and pathological fright reaction
- tetany
- migraine (especially if headache is minimal or absent)
- paroxysmal vertigo
- transitory ischemic attacks
- transitory global amnesia
- paroxysmal endocrine dysbalance
- others

B) Psychogenic
- unaware seizures (mainly conversion and somatoform disorders)
- aware (simulated) seizures
- disorders of personality and behaviour:
  - Münchausen syndrome
  - Münchausen syndrome by proxy

Syncopal events are present in 15–25% of the population depending on the age and they represent 3% of all examinations in hospitals and up to 6% of all admissions (Cibulčík 2005; Mitro 2005). A correct and well-timed diagnosis of non-epileptic seizures has an essential significance for the prognosis of the patient. It avoids iatrogenic harm by nonadequate antiepileptic treatment and also prevents harm in psychical and social spheres (Hovorka et. al. 2004; Kollár *et al.* 2009; Kollár *et al.* 2010).

Gastaut (1974) defined syncope as a generalised anoxic-ischemic-cerebral seizure resulting from circular failure of the brain, lasting a couple of seconds which usually adapts spontaneously in a horizontal position. It occurs suddenly, unexpectedly, is reversible and associated with a loss of postural tone caused by global cerebral ischemia.

The classification of the syncopal states according to etiology is slightly modified due to the directions of European Society of Cardiology and is presented in Table 1 (Brignole *et al.* 2004).

VVS is the most common type of syncope with the incidence of 21–43% (Disertori *et al.* 2003; Chen *et al.* 2003). It is an independent clinical entity which is often incorrectly diagnosed. In typical cases the individuals with this disorder have no structural pathology of the heart or arrhythmia and have normal interictal blood pressure (BP) and heart rate. VVS is defined as a neurogenic temporary disorder of consciousness due to vasodepression, bradycardia or asystole resulting in diffuse cerebral ischemia. A disorder of the autonomous regulation is usually clinically unapparent, but revealable by the head-up tilt test (HUT-test). HUT-test is a noninvasive diagnostic method for objectification of VVS. This test consists of passive elevation of the patient from the horizontal position, in which he remains for a couple of minutes (max. 5) on a tilt table in a quiet dark room. After tilting upright to a 60–70° vertical angle (depending on the protocol) changes of BP and heart rate (ECG) are continuously monitored for 20–45 minutes (also depending on the protocol). In case of absence of syncope in a classic HUT protocol, in effort to increase the diagnostic value, use of new irritating substances with effect on the autonomous nervous system (isoprenaline, edrophonium) is implemented into the clinical practice. In ambulatory practice nitroglycerin, which administration does not require emergency for resuscitation, is used for provocation. Nitroglycerin also positively influences sensitivity in a cardioinhibitive type of VVS. Sensitivity of the HUT-test is 40–70%, specificity is 80–100% (Hori 2000).

The pathophysiological mechanism of VVS is still not reliably revealed. A possible mechanism is irritation of the cardiac mechanoreceptors with excessive contractility of the myocard that is caused by insufficient ventricular filling as a result of stagnation of the blood in the venous system of lower limbs in a vertical position. Some authors consider also excessive irritation of atrial baroreceptors and baroreceptors in veins with a larger diameter, caused by excessive "venous pool" during orthostasis, as the main eliciting factor (Dickinson 1993). Importance of neurotransmitters (serotonine, endogenous opiates), humoral factors and impaired regulation of baroreflex is also being reconsidered. Some cases of VVS are even caused by stimulation of cerebral cortex with negative emotions (Mosqueda-Garcia 2000).

MATERIAL AND METHODS

A group comprises 70 patients (24 men, 46 women) at the age of 15–71 years, in whom VVS was verified by the HUT-test. Before performing the HUT-test, the examination by an internist (history taking, physical examination, ECG, serological examination), neuro-

Tab. 1. The classification of syncopal states according to etiology (Brignole *et al.* 2004).

A) Reflex syncope
1) vasovagal (neurocardiogenic) syncope
2) situational syncope • caused by cough, caused by sneezing • gastrointestinal (defecative, syncope caused by visceral pain, caused by vomiting) • caused by urination
3) carotid sinus syncope
4) glossopharyngeal and syncope caused by trigeminal neuralgia
B) Orthostatic syncope
1) autonomous failure (asympathicotonic orthostatic hypotension) • primary autonomous failures (Shy Drager syndrome, Bradbury Eagleston syndrome, Parkinson disease) • secondary autonomous failures (diabetic neuropathy, amyloidosis, alcoholism)
2) orthostatic hypotension unrelated to autonomous failures (sympathicotonic orthostatic hypotension) • volume depletion (bleeding, diarrhoea, dehydration, analbuminaemia) • vascular dilators and alcohol • endocrine conditioned hypotensive states (Addison disease, feochromocytoma, carcinoid, systemic mastocytosis, Verner-Morrison syndrome)
C) Postprandial syncope
D) Cardiogenic syncope - arrhythmogenic • sick sinus syndrome, AV block, paroxysmal supraventricular and ventricular tachycardia, failure of the implanted cardiostimulator or cardioverter-defibrilator
E) Cardiogenic syncope - mechanical (organic heart disease) • vault failures, hypertrophic obstructive cardiomyopathy, myxoma of the atrium, acute ischemia, pericardial fluid/ tamponade, pulmonary embolism/pulmonary hypertension
F) Vascular syncope • aortal dissection, subclavian steal syndrome, vertebrobasilar transitory ischemic attack, migraine, compression of inferior vena cava in pregnancy

Tab. 2. The classification of VVS according to HUT- test (Sutton *et al.* 1992).

Type 1 Intermediate response The heart rate descends during syncope, but does not descend below 40/min., or does descend below 40/min., but the descend of the heart rate lasts shorter than 10 s., without the rise of asystole. If the asystole rises, it lasts shorter than 3 s. BP descends before the descend of the heart rate.
Type 2A Cardioinhibitive without asystole The heart rate descends below 40/min for more than 10 s., asystole longer than 3 s. does not occur. BP descends before the descend of the heart rate.
Type 2B Cardioinhibitive with asystole Asystole lasts longer than 3 s. BP descends before the descend of the heart rate or descends at the same time.
Type 3 Vasodepressoric The heart rate does not descend more than 10% of the maximal heart rate during syncope..
Exception 1 Chronotropic incompetence During the HUT-test, the heart rate does not rise (less than 10% compared with a pre-tilt phase).
Exception 2 Syndrome of postural tachycardia The heart rate rises extremely at the beginning of the test, when tilting the patient into a vertical position (the heart rate more than 130/min.).

logical examination (thorough history-taking questionnaire, neurological examination, interictal EEG, CT or MRI of the brain, EEG recording for 1 hour after a sleep deprivation performed in 7 cases, EEG after sleep deprivation with monitoring for 24 hours in 36 cases) was performed. All patients from our group underwent a cardiological examination, echocardiography and ECG-Holter monitoring before the HUT-test was performed. The HUT-test was performed in the cases, when previous examinations had not revealed the cause of disorders of consciousness. It was performed as follows: a patient, on an empty stomach and after skipping the medication affecting the autonomous nervous system, was laid on a tilt table in a horizontal position (the beginning of the HUT-test was in all cases between 7:00 and 7:30 am). After 15 minutes of lying in a horizontal position, the patient was tilted upright to a 70° vertical angle. ECG was monitored continuously and BP was measured in intervals of every 5 minutes. When vegetative symptoms appeared, BP was measured every minute or more frequently. In cases when after 20 minutes no syncope appeared, half of a pill of nitroglycerin was administered sublingually to the patient in a vertical position. Afterwards we brought back the table to a 70° vertical angle and in case, when syncope was not provoked even after the medication, the test was terminated 25 minutes after the administration of nitroglycerin.

In cases when syncope appeared the patient was immediately returned to the horizontal position and the type of VVS was defined subsequently according to the levels of BP and heart rate (see Table 2). In patients with the diagnosis of VVS admission diagnoses present in the patients, interictal EEG findings (that were divided into normal and abnormal, in which abnormal were further divided into epileptiform and non-epileptiform and into focal and generalised) and the presence of convulsions during the syncopal states were further evaluated. The group of patients with convulsive VVS was evaluated individually.

Interictal native EEG findings and occurrence of convulsions in the groups and subgroups of patients were expressed as a proportion or percentage of the whole number of patients in the group or in the subgroup. The statistical significance of differences in proportions of occurrence of the specific sign (char-

acteristics/finding) among the groups/subgroups was tested by binomial tests for two independent proportions and for one specific group with a test for a single proportion test. Differences in frequency distribution in categories of two qualitative signs (r×c contingent tables) were tested by the Fisher-Freeman-Haltons exact test (that is generalization of the Fishers test) and the strength of the association between two qualitative signs in a contingency table was expressed by the Cramér's V index. Cramér's V varies between 0 and 1. Close to 0 it shows little association between variables. Close to 1 it indicates a strong association. Interpretation of the Cramérs V index: for independent signs is close to zero and for maximal strong association between signs it is close to 1. In all the cases of differences testing, the significance level α=0.05 was used.

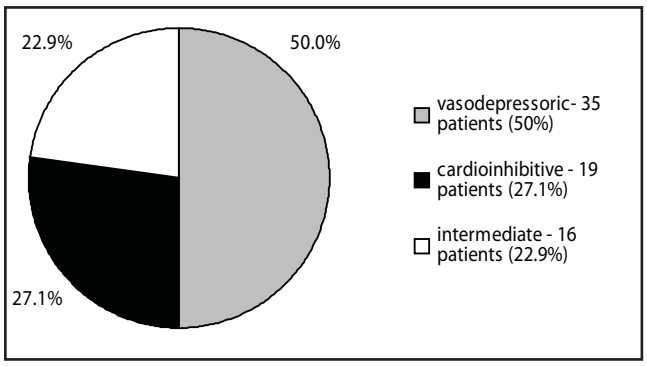

Fig. 1. The distribution of particular types of VVS in our group of 70 patients.

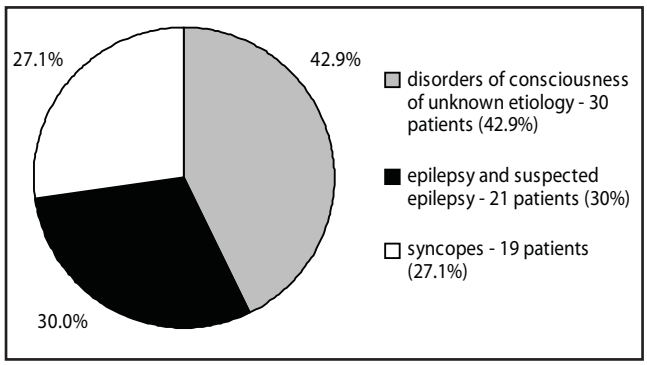

Fig. 2. Diagnoses as causes of admission of patients with VVS to our outpatient clinic.

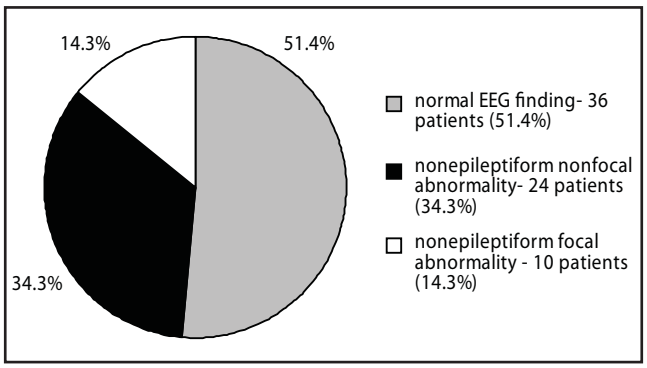

Fig. 3. Interictal "native" EEG findings in our patients with VVS.

RESULTS

1. Out of 70 VVS verified by the HUT-test, 35 were vasodepressoric (50%), 19 cardioinhibitive (27.1%) and 16 intermediate (22.9%) (see Figure 1).

2. Diagnoses present in the patients as a cause of admission were:

- disorders of consciousness of an unknown etiology: 30 cases (42.9%)
- supposable epilepsy: 12 cases (17.1%), epilepsy: 9 cases (12.9%)
- syncope: 19 cases (27.1%), 8 out of them with supposable diagnosis of VVS (11.4%) (see Figure 2).

3. Interictal EEGs findings in our patients with VVS:

- "native" interictal EEG was normal in 36 cases (51.4%), nonepileptiform abnormality was present in 34 cases (48.6%), specific epileptiform graphoelements were not present in any of the native interictal EEGs. Out of the 34 nonepileptiform EEG abnormalities, there were significantly more nonfocal, generalised abnormalities (nonepileptiform nonfocal abnormality (NNA); NNA=24; p=0.024) than focal (nonepileptiform focal abnormality (NFA); NFA=10) (see Figure 3).
- out of the 35 patients with vasodepressoric type of VVS, interictal EEG was normal in 24 cases (68.6%), out of the 19 patients with cardioinhibitive type of VVS, it was in 7 patients (36.8%), out of the 16 patients with intermediate type of VVS it was in 5 patients (31.3%) (see Figure 4). Statistical comparison among particular types of VVS revealed a significant difference in distribution (p=0.017) and medial strong association between the type of VVS and the EEG finding (Cramér V=0.35).
- EEG examinations after sleep deprivation (SD) with the time of scanning of 1 hour and 24 hours (LTM)-EEG after SD in patients with VVS revealed new information in 10 patients. In 5 of them, the diagnosis of combined epilepsy + VVS was established after the complex approach, in 4 more, with normal interictal EEG, LMT-EEG after SD suggested NNA, 1 patient with normal native EEG had NFA present in EEG after SD.

4. Convulsions were observed in 20 patients during the HUT-test. In 14 cases there was also a history of convulsions, in 6 cases there was no previous history of convulsions. In patients with convulsions already present in their history and also during the HUT-test, 6 were already treated for epilepsy and in 3 cases epilepsy was supposable, 4 were referred to an additional examination for disorders of consciousness of an unknown etiology, the diagnosis of syncope was correctly established only in 1 case out of these patients. Convulsions

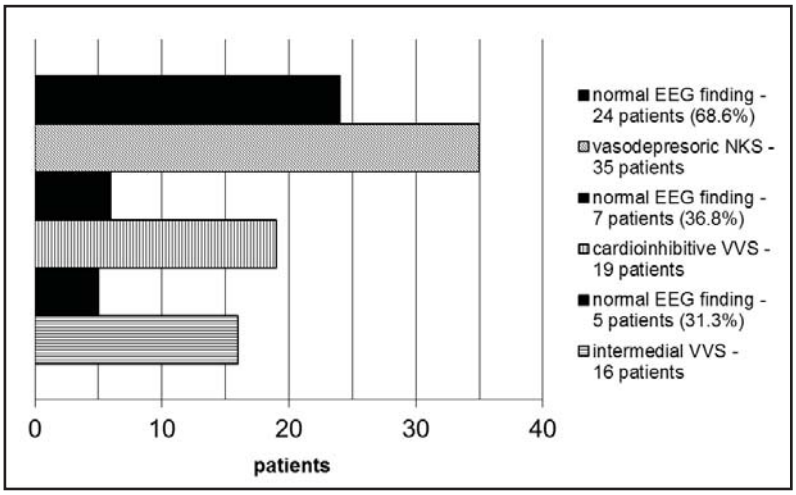

Fig. 4. EEG findings in particular types of VVS.

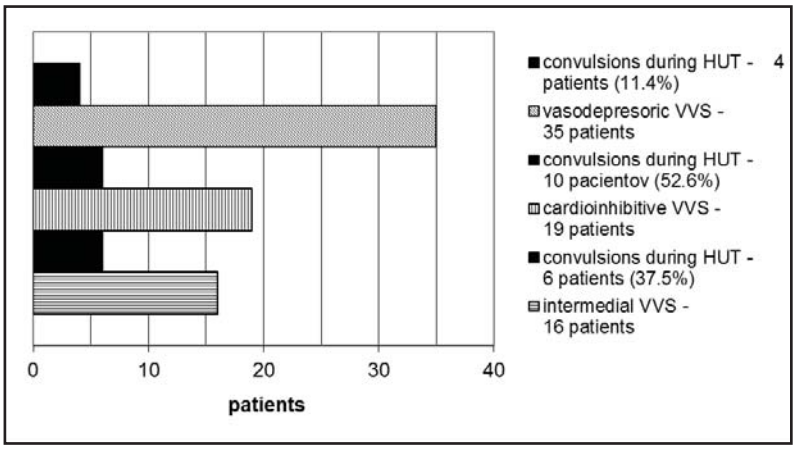

Fig. 5. Occurrence of convulsions in particular types of VVS.

during the HUT-test were recorded in 4 out of the 35 patients with vasodepressoric type of VVS (11.4%), in 6 out of the 16 patients with intermediate type of VVS (37.5%) and in 10 out of the 19 patients with cardioinhibitive type of VVS (52.6%) (see Graph 5). Statistical comparison of particular types of VVS showed a significant difference in the frequency distribution of occurrence of convulsions (p=0.003) and medial strong association of the type of VVS and the occurrence of convulsions (Cramér V=0.40). Interictal EEG finding was normal in 6 cases (30%) out of the patients with the occurrence of convulsions during the HUT-test.

DISCUSSION

VVS is considered to be a relatively common cause of relapsing disorders of consciousness. The fact that VVS is frequently associated with diagnostic errors can be certified also from the number of diagnoses that were the causes of admission to our outpatient clinic. Only in 19 out of all (27.1%) a possible diagnosis of syncope was established correctly. In 21 cases (30%) an incorrect diagnosis of epilepsy was established or suspected. Incorrect final diagnosis of this clinical unit is described also by other authors. Kuba *et al.* (2001) demonstrates this fact on a group of 21 patients. The most common diagnosis as a cause of admission and additional diagnostic process was epilepsy. Only in 2 cases syncope was suspected. Razvi *et al.* (2003) suggested, with his study on a group of 132 patients, with the HUT-test performed due to disorders of consciousness of an unknown origin, that an adequate diagnostics of the reflexive syncopal states is needed. He found out that as many as 27 of them were treated by antiepileptic drugs in spite of the fact that they suffered no type of epilepsy.

It is obvious, that the occurrence of convulsions during syncope (so-called convulsive syncopes), is a significant symptom that can lead to incorrect diagnosis of epilepsy. It is fully in accordance with our findings. Only in 1 out of our 14 patients, with convulsions in a history, the diagnosis at admission was established correctly. As many as 6 of them were treated incorrectly with the diagnosis of epilepsy, in 3 more cases was epilepsy suspected. The character of convulsions was already described in 1957 by Gastaut and Fisher-Williams. They described myoclonies, tonic-clonic spasms, generalised tonic flexional and extensional postures (Gastaut & Fisher-Williams 1957). Ictal EEG findings were explored by Kuba *et al.* (2001) who in accordance

with previous studies noticed no association between convulsions and the occurrence of specific epileptiform graphoelements. The genesis of convulsive manifestation during syncope is localised with the support of experimental studies into the location of the brainstem and the rostral medulla. A diffuse delta activity was the typical ictal EEG finding in these patients. The authors confirmed that a faster presyncopal period is associated with a higher likelihood of convulsions during the failure of consciousness (Kuba *et al.* 2001). In this context it is necessary to mention a term "malignant neurocardiogenic syncope", where the impairment of consciousness occurs suddenly, without any prodromes or only with a short period of prodromes and with a common coincidence of convulsions, enuresis and defecation. Convulsions during syncope are quite common. Grubb *et al.* (1991) even observed them in patients with syncope during the HUT-test in 67% of cases. We observed convulsions during the HUT-test in 20 out of 70 patients (28.6%). A significantly lower percentage of convulsions during the HUT-test in our group of patients with VVS (p=0.004) is due to the fast horizontalization of a tilt table after the occurrence of disorders of consciousness.

A high percentage of abnormal EEG findings in the group of other than epileptic seizures with or without failure of consciousness was frequently noticed also previously (Cibulčík 2005; Kollár *et al.* 2010). Interictal "native" EEG findings in the group of our patients were nonspecifically abnormal (nonepileptiform) in 34 out of 70 patients with VVS (48.6%). The proportion that we found does not differ significantly (p=0.47) from the findings of Kuba *et al.* (2001), who describe interictal occurrence of nonspecific abnormality in 58% of the cases with VVS, yet the character of recording did not change qualitatively during hyperventilation and photostimulation, which was the same in our group of patients. It is clear that simultaneous occurrence of abnormal interictal EEG finding with anamnestic presence of convulsions, or also presence of enuresis and defecation during the syncope, is the most common source of diagnostic errors and many times leads to incorrect diagnosis of epilepsy. The statistical comparison of the occurrence of normal EEG findings and convulsions among particular types of VVS suggests that clinically the patients with vasodepressoric VVS, in whom a significantly higher number of normal EEG findings and also a significantly lower number of convulsions were found, are less hazardous in term of establishing the incorrect diagnosis than the patients with VVS, in whom a tendency to cardioinhibition is observed. While establishing the correct diagnosis it is necessary to consider contemporary presence of epileptic and nonepileptic seizures in the same case as a complication of the diagnostic process. In our study it occurred in 5 cases (7.1%).

CONCLUSION

Diagnostics of failures of consciousness, solitary or repetitive, belongs to the most difficult in clinical practice. In our study we wanted to suggest the difficulties and pitfalls of the correct diagnostics of VVS, particularly in cases, when the syncopal states are accompanied with a convulsive manifestation and at the same time an abnormal finding in interictal EEG examination is present. The results of our study evidently suggest that interdisciplinary cooperation of a neurologist and an internist (cardiologist) in accurate diagnostics is needed. We also want to emphasize the importance of the HUT-test in standard diagnostic algorithm in patients with failures of consciousness of an unknown cause. The HUT-test itself can in a number of such cases avoid incorrect establishing of diagnosis of epilepsy and following harm to patients as a result of an incorrect therapy.

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