Original article

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Over-interpretation of electroclinical and neuroimaging findings in syncopes misdiagnosed as epileptic seizures

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ABSTRACT – Syncope and epileptic seizures share some common clinical characteristics that may complicate the diagnostic process. In clinical practice, syncope is frequently misdiagnosed as an epileptic seizure and consequently treated with antiepileptic drugs. In this study, we identified 57 patients with syncope (diagnosis based on accepted criteria) who had come to our unit with a previous diagnosis of definite epilepsy in 30 cases (syncope misdiagnosed as epileptic seizures, SMS), or suspected epilepsy in the remaining 27 cases (unrecognized syncope, US). We attempted to identify factors underlying misdiagnosis by reviewing clinical findings, particularly potentially confounding features, and EEG/neuroimaging data. Finally, we compared these two groups of patients to search for crucial elements that had led to misdiagnosis. Although some clinical elements were found to be confounding in both groups, it was the interpretation of the EEG and MRI findings, particularly when combined with the confounding clinical features that constituted the main reasons for misdiagnosis.

Key words: syncope, epileptic seizure, neuroimaging, antiepileptic drug, misdiagnosis

Syncope and epileptic seizures are common conditions that pose diagnostic challenges for the clinician. Although the underlying pathophysiological processes are distinct, syncope and epileptic seizures share clinical characteristics that may lead to confusion during diagnosis (Britton 2004, Chadwick and Smith 2002). Although several papers have recently highlighted the crucial role of clinical semiology in the differential diagnosis of these conditions (Colman *et al.* 2004, Lempert 1996), in clinical practice syncopes are sometimes misdiagnosed, and consequently treated, as epileptic seizures (Jeavons 1983). In this study we attempted to identify

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Table 1. Questionnaire and scoring system for symptoms pertaining to loss of consciousness.

	Points
Wake with tongue biting?	**2**
Déjà vu or jamais vu?	**1**
Emotional stress associated with loss of consciousness?	**1**
Head turning during a spell	**1**
Unresponsive, unusual posture, limb movement, or amnesia of spell? (any one of these)	**1**
Confusion after spell	**1**
Lightheaded spell	**-2**
Sweating before spell	**-2**
Spell associated with prolonged sitting or standing	**-2**
If point score is ≥ 1 the likelihood was seizure or if < 1 the likelihood was syncope	

factors underlying this misdiagnosis by analysing the clinical and instrumental findings of patients with syncope who had been referred to our unit with a previously definite or suspected diagnosis of epilepsy.

Patients and methods

In this retrospective study, we selected, from a population of 2500 outpatients observed in the period between August 2003 and March 2006, sixty-two subjects with syncope who had come to our epilepsy unit because of recurrent events that had either not been diagnosed or had previously been misdiagnosed as epilepsy.

The diagnosis of syncope in all the patients had been made predominantly on the basis of clinical data and then verified according to widely accepted criteria proposed in a published questionnaire (*table 1*) (McKeon *et al.* 2006, Colman *et al.* 2004, Sheldon *et al.* 2002).

We selected 57 cases with a clinically definite diagnosis of syncope, while we excluded five patients in whom the questionnaire score did not support a diagnosis of syncope (four of these five patients had a comorbidity of epilepsy and syncope, while the fifth had anoxic-epileptic seizures).

In the selected cases we identified two subgroups:

i) patients with a previous definite diagnosis of epilepsy as demonstrated by current treatment with AEDs, whom we refer to as syncopes misdiagnosed as epileptic seizures (**SMS**): 30 cases, four males and 26 females, mean age 40.3 years, range 16-77 yrs.);

ii) patients in which a previous diagnosis of epilepsy was suspected, though not confirmed (this group had consequently not been treated), whom we refer to as unrecognized syncopes (**US**): 27 cases, six males and 21 females, mean age 31.4 years, range 16-69 yrs.).

All the patients included in this study had undergone a cardiovascular evaluation comprising a clinical assessment, electrocardiography (ECG), transthoracic echocardiography (TTE) and head up-tilt test (HUTT).

We critically reviewed the clinical data (focusing on potentially confounding features) and EEG/neuroimaging findings in an attempt to identify any factors that may have led to the misdiagnosis. We considered the following clinical data: risk factors (perinatal anoxic distress, head injury, febrile seizures), family history of epilepsy, convulsive features (motor phenomena such as tonic posture, clonic movements or myoclonic jerks; tongue-biting; sphincter incontinence), lack of precipitating factors, atypical prodromal symptoms ("ascending" epigastric sensations, olfactory, acoustic or experiential/dysmnesic phenomena), traumatic falls and post-ictal confusion/amnesia (e.g. temporo-spatial disorientation and inability to recall).

Results

Equivocal clinical data were found in both the SMS and US patients, though there was no statistically significant difference between the two groups. A review of the EEG data revealed abnormalities in 21 cases in the SMS group and in nine cases of the US group. EEG abnormalities consisted predominantly of aspecific patterns (such as diffuse or focal theta and, rarely, delta slow waves), though we also found specific patterns, both generalized (diffuse spike-and-wave and polyspike-and-wave discharges) and focal (highly-localized spikes), in a minority of patients.

"Minor" alterations at MRI were observed in 11 cases in the SMS group and in only one case in the US group. There was a statistically significant difference between the SMS

Table 2. Confounding clinical features, electroencephalographic and neuroimaging "pathological" findings in neurological assessment of patients with syncope.

	SMS (n = 30)	US (n = 27)	p value
A. Equivocal clinical findings	30/30	27/27	n.s.
Risk factors for epilepsy	11	10	n.s.
Family history for epilepsy	2	1	n.s.
Convulsive features	17	16	n.s.
Atypical prodromic symptoms	10	6	n.s.
Lack of precipitating factors	10	7	n.s.
Traumatic fallings	6	4	n.s.
Post-ictal confusion/amnesia	11	9	n.s.
B. EEG abnormalities	21/30	9/27	0.01*
Focal slow waves activity	4	2	n.s.
Generalized slow waves activity	10	3	n.s.
Focal epileptiform activity	3	3	n.s.
Generalized epileptiform activity	4	1	n.s.
C. MRI alterations	11/30	1/27	0.006*
"Minor" gliotic foci	5	--	0.03**
Pelludic septum cyst	--	1	n.s.
Vascular lesions	2	--	n.s.
Focal atrophy/agenesis	2	--	n.s.
Ventricular asymmetry	2	--	n.s.
D. Association of 2 or more of other items	23/30	10/27	0.005*
A+B	13	9	n.s.
A+C	4	1	n.s.
B+C	--	--	-
A+B+C	6	--	0.02**

* Yates corrected chi-square test; ** Fisher exact test ; SMS: Syncope misdiagnosed as epileptic seizure; US: unrecognized syncope.

and US groups in both the EEG and neuroimaging findings, with a higher number of EEG and MRI "abnormal" findings being observed in the SMS patients. The difference between these two groups was further highlighted by the association of clinical, EEG and MRI findings (*table 2*). The head up-tilt test, which was performed in all of the patients, was positive in 18 SMS and 18 US patients. The cardiovascular evaluation was negative in the remaining patients.

Discussion

In this study, we analyzed a high number of patients with syncope who came to our epilepsy centre with a diagnosis of epilepsy (Razvi *et al.* 2003). In accordance with previously published data, our study confirms that a differential diagnosis between syncope and epilepsy, based predominantly on the clinical history, may prove inaccurate in centres not specialised in epilepsy (Britton 2004), where a non-specific approach may result in the overinterpretation of clinical, EEG and neuroimaging data (Benbadis and Tatum 2003, Smith *et al.* 1999).

The clinical elements that are most likely to confound in clinical practice, and consequently lead to a misdiagnosis, particularly in non-specialist epilepsy units, are risk factors for epilepsy, convulsive features, lack of precipitating factors and post-ictal confusion. There is general agreement on the crucial role of clinical semiology in the differential diagnosis of syncope and epilepsy (Colman *et al.* 2004), with some authors recently emphasizing the usefulness of a very simple questionnaire for this purpose (McKeon *et al.* 2006, Colman *et al.* 2004, Sheldon *et al.* 2002). The differential diagnosis may nevertheless prove difficult, and the questionnaire unreliable, particularly in cases in which both typical syncopal features and clear epileptic phenomena coexist (e.g. in anoxic-epileptic seizures, which were not included in the present study) (Stephenson *et al.* 2004, Horrocks *et al.* 2005).

Although some clinical elements were found to be confounding in our study, the interpretation of the EEG and MRI findings constituted the main reason for misdiagnosis.

Indeed, EEG is widely recognised as contributing to the misdiagnosis of epilepsy (Kowacs *et al.* 2005). Not only does this technique have intrinsic limitations (subjective evaluation of reports and relative value of specificity/sensitivity), but EEG abnormalities (including specific patterns) are not uncommon in syncope patients (Abubakr and Wambacq 2005).

Neuroimaging was also found to contribute to the misdiagnosis, very likely because of the overestimation of negligible "alterations". This is an increasingly frequent error, probably due to the over-use of MRI, which often results in the misinterpretation of clinical features or the tendency to self-prescribe medical investigations. In accordance with previously reported data, our findings confirm the limited diagnostic role of the cardiovascular assessment (ECG, TTE etc.), which remains nonetheless mandatory, and the usefulness of head up-tilt test as a means of distinguishing syncope from epilepsy (Eiris-Punal *et al.* 2001).

In conclusion, our study confirms that the risk of misdiagnosing syncope as epileptic seizures may be reduced by a careful evaluation of the patient's clinical findings (history-taking and physical examination remain the cornerstones), and a prudent consideration of the neurophysiological/neuroimaging data (Strano *et al.* 2005). To reduce misdiagnosis, all doubtful cases should be addressed to a specialized epilepsy clinic. □

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