Syncope or seizure? The diagnostic value of the EEG and hyperventilation test in transient loss of consciousness

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Abstract

In a prospective study of consecutive patients (age 15 or over) with transient loss of consciousness 45 patients had a history of seizure and 74 patients had a history of syncope. All patients had an EEG, ECG, laboratory tests and a hyperventilation test and were followed for an average of 14·5 months. Epileptiform activity in the interictal EEG had a sensitivity of 0·40 and a specificity of 0·95 for the diagnosis of a seizure. Epileptiform activity nearly doubled the probability of a seizure in doubtful cases. If no epileptiform activity was found, this probability remained substantially the same. The hyperventilation test had a sensitivity of 0·57 and a specificity of 0·84 for the diagnosis of syncope. A positive test increased the probability of syncope half as much in doubtful cases. A negative test did not exclude syncope. Laboratory tests were not helpful except for an ECG which was helpful in elderly patients.

Syncope and related conditions where cerebral blood flow is impaired are usually distinguished from seizures on the history alone. The wide variety of epileptic manifestations and the clonic jerks that may be seen in fainting patients cause problems.[1 2] When the diagnosis remains in doubt, other diagnostic tests are needed.

The finding of epileptiform activity—spikes, spike-waves, sharp waves—in the EEG must reinforce the diagnosis of a seizure,[3-5] though the extent remains uncertain, as some patients with this finding never have seizures.[6]

Anxiety or hyperventilation attacks are mistaken for seizures.[7-9] Many of the so-called pseudoseizures are actually hyperventilation attacks.[10] When associated with fainting the differentiation from epilepsy is particularly difficult.[11] A hyperventilation test provoking characteristic symptoms (such as paresthesia, giddiness and dyspnoea) is used for the diagnosis. Does this test really help to distinguish seizure from (hyperventilation) syncope?

Cardiac syncope may be mistaken for a seizure.[12 13] An ECG cannot exclude cardiac syncope, but may suggest a cardiac disorder.

We carried out a prospective study of patients with transient loss of consciousness to assess the diagnostic value of a single interictal EEG, of the hyperventilation test, of a standard ECG and of the routine laboratory examination.

Methods

Patients

From March 1987 to March 1988 we included all consecutive patients ($\geqslant 15$ years of age) referred to the neurological department because of one or more episodes of transient loss of consciousness. Transient loss of consciousness was defined as an episode of less than one hour with inability to maintain posture and to recall events during the episode. We excluded patients with loss of consciousness due to trauma or subarachnoid haemorrhage and patients with epilepsy. We studied 119 patients. General practitioners referred 55 (46%) and other physicians 14 patients to our outpatient department. We interviewed in the emergency department 28 and on admission 22 patients. We followed all until December 1988. The mean period of follow up was 14·5 months (range: 8-21).

Diagnostic criteria

A gold standard for the diagnosis of a seizure does not exist. Long-term EEG and video monitoring are unrealistic in patients with a single or rare event.[14] The international classification of seizures has no explicit criteria to distinguish seizures from syncope.[15] We classified a patient in the seizure group as follows:
if an eyewitness observed more than a few movements during loss of consciousness and identified clonic movements from a range of movements imitated by the interviewer;
if an eyewitness observed automatisms, such as chewing or lip smacking, during loss of consciousness;
if the patient reported an unequivocal aura, such as a strange smell, preceding the event;
if the patient felt confused immediately after the event (inability to recognise familiar persons or environment);
if the patient had tongue biting. We classified all other patients in the syncope group.

Table 1   Checklist of symptoms provoked by hyperventilation

Complaints before, during or after the test
—Tingling in hands, feet or circumoral
—Cold sweat in hands or feet
—Stiffness or cramps in hands or feet
—Twitching in hands or feet
—Dizziness
—Light-headedness
—Faintness
—Headache
—Fullness in the head
—Dry mouth
—Palpitations
—Pain or strangling sensation in the chest
—Breathlessness
—Sweating
—Shivering
—Shaking
—Nausea
—Other complaints

Symptoms seen before, during or after the test
—Visible hyperventilation
—Tremor
—Chvostek's sign (tapping facial nerve causes twitching face)
—Tetanic spasm of the fingers and wrist
—Cold hands

Evaluation

One of us (WAJH) interviewed all patients and eyewitnesses, using a standardised questionnaire. A routine interictal EEG (21 channel, 30 minutes) was recorded in all patients. A neurophysiologist, without knowledge of the clinical details, coded the EEG using a conservative interpretation according to the following scheme:[16] EEG within normal limits? Yes/no. If abnormal:
is there localised epileptiform activity?
is there generalised epileptiform activity?
is there localised slowing without epileptiform activity?

Patients younger than 65 years of age had an additional hyperventilation test.[17] After an initial spiro- and capnogram patients were asked to ventilate, in the sitting position, at a rate of 40 breaths per minute for at least three minutes. The end tidal CO_2 percentage was monitored and had to be lower than 2·5% after hyperventilation. Blood gases were measured by fingerprick before and after the test and after the recovery phase. A pulmonary physiologist graded the test, using a predefined checklist[18] (table 1). If patients did not reach 90% of the baseline value of the end tidal CO_2 percentage after three minutes recovery, the test was considered positive if two or more symptoms were provoked and were recognised by the patient as (part of) his complaint and as dubious if only one symptom was provoked or symptoms were not recognised. The test was considered negative if the end tidal CO_2 restored to >90% of baseline value after three minutes recovery. A final diagnosis of hyperventilation syndrome was made if the patient responded to training in abdominal breathing and relaxation and no other cause was found during follow up.

A cardiologist assessed the standard ECG with computerised measurement of the QT-interval of all patients as normal or as abnormal.

The laboratory examination included serum sodium, potassium, calcium, phosphate, glucose, urea, sedimentation rate, liver func-

tions, blood count. The attending physician decided if cerebral CT scan or 24 hour cardiac monitoring were necessary. All patients gave informed consent to participate. The ethical committee of the hospital approved the study.

Statistical methods

The sensitivity is the true-positive rate and the specificity is the true-negative rate of a test. The positive likelihood ratio is the ratio of the probability that a test is positive in diseased persons to the probability that a test is positive in non-diseased persons (sensitivity/1-specificity). The negative likelihood ratio is the ratio of the probability that a test is negative in diseased persons to the probability that a test is negative in non-diseased persons (1-sensitivity/specificity). The likelihood ratio is used in the odds ratio form of Bayes' theorem, which is a simple way to calculate the effect of new information on diagnostic uncertainty: Post-test odds = pre-test odds × likelihood ratio.[19] The more the likelihood ratio deviates from 1 the greater the predictive value.[20] We calculated the 95% confidence intervals (CI) of the likelihood ratios according to the method for relative risks.[21] If the CI includes 1·0, the test is not significant.

Results

The final diagnoses of the patients in this study are listed in table 2. We classified 45 patients (17 women, 28 men) in the seizure group (38%) and 74 patients (39 women; 35 men) in the syncope group (62%).

EEG

One patient refused an EEG after receiving a pacemaker. Table 3 presents the results of the EEG in the remaining 118 patients. No patient was receiving antiepileptic drugs before the EEG was taken. If the pre-test probability of a seizure is 50% and epileptiform activity is found the post-test probability of a seizure becomes 88%. If no epileptiform activity is found the post-test probability of a seizure in this case becomes 38%. The predictive value of the EEG is shown in the figure for different pre-test probabilities. Epileptiform activity was found in 12 out of 23 patients with recurrent seizures and in six out of 22 patients with a

Table 2   Final diagnosis

1. Seizure group: 45 patients
   Recurrent seizures 23 (51%)

Generalised epilepsy	7	
Partial epilepsy	16	
—"idiopathic"		9
—glioma		2
—meningioma		1
—Metastases (melanoma)		1
—"old" cerebral infarct		3

   Single seizure 22 (49%)

—related to alcohol	4

2. Syncope and related conditions group: 74 patients

Hyperventilation syndrome	21 (28%)
Vasovagal syncope	15 (20%)
Cardiac syncope	3
Postural hypotension	1
Vertebrobasilar ischaemia	2
Micturition/cough syncope	4
Unexplained	28 (38%)

Table 3 Interictal EEG

A Results of interictal EEG

	seizure n = 45	syncope n = 73
Normal	15	55
Localised epileptiform activity	10	4
Generalised epileptiform activity	8	0
Localised slow activity	12	14

B Diagnostic value of epileptiform activity for a seizure

Sensitivity	0·40 (18/45)
Specificity	0·95 (69/73)
Positive likelihood ratio (CI)	7·3 (2·6–20·3)
Negative likelihood ratio (CI)	0·6 (0·5–0·8)

CI = 95% confidence interval

single seizure (chi square: P > 0·1); accordingly, epileptiform activity did not predict recurrence of seizures in our small group of patients.

Hyperventilation test

Ninety two patients were younger than 65 years of age. In the seizure group four patients and in the syncope group five patients failed this test for various reasons (unable to lower the end tidal CO_2 percentage < 2·5% or did not keep the appointment). Table 4 presents the results of the remaining 83 patients. When dubious results are considered negative and the pre-test probability of syncope is 50% a positive test gives a post-test probability of 77% and a negative test gives one of 33%. The diagnostic value of this procedure was slightly better than a simple question about attacks of breathlessness (IVC).

ECG

Eighteen recordings were abnormal, but only one was diagnostic, showing a second degree atrioventricular (Mobitz II) block. This 77 year old patient had a 24 hour recording showing symptomatic bradycardia and received a pacemaker. In one 71 year old patient a sick sinus syndrome was found after a third 24 hour recording. A third patient with cardiac syncope was an 86 year old hypertensive man who suddenly turned his head and lost consciousness. A carotid sinus syncope was presumed, but not confirmed as loss of consciousness did not recur. No case of prolonged QT-interval syndrome was found.
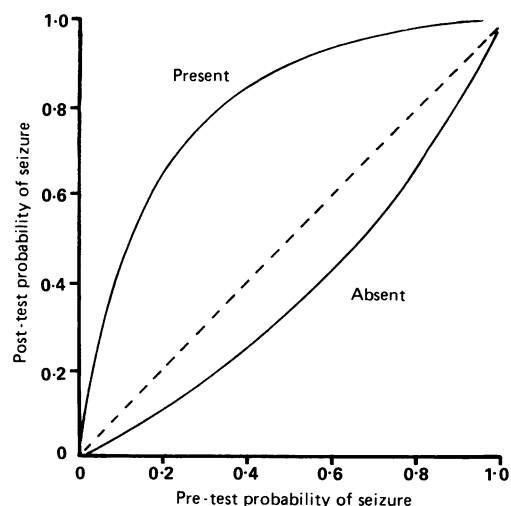
Laboratory examination

Apart from abnormal liver functions in all four patients with alcohol related seizures, none of the other abnormalities found had diagnostic or therapeutic consequences.

Discussion

Epileptiform activity in the EEG is specific, but not sensitive for the diagnosis of a seizure as the cause of transient loss of consciousness. It follows that an interictal EEG can be used to confirm, but not to dismiss the clinical diagnosis of a seizure. Unfortunately, the EEG cannot predict recurrence of seizures, which confirms the study of Hopkins *et al* in a much greater group of patients.[22] We do not agree with their conclusion that the EEG is not necessary, because of the often weak nature of a clinical diagnosis of a seizure and the value of the EEG to diminish diagnostic uncertainty. This is important because if the first event is considered a seizure the next recurrence will result in a diagnosis of epilepsy.

A hyperventilation test should only be considered as positive if the patient recognises more than one of the symptoms that preceded or followed loss of consciousness. A negative test does not exclude (hyperventilation) syncope. We cannot recommend the hyperventilation test as a routine diagnostic procedure because the diagnostic gain is marginally better than questioning the patient about episodes of breathlessness. The patient may, nevertheless, be reassured by the test.[23] Routine laboratory examination is not necessary; an ECG is only indicated in elderly patients.

Some aspects of this study deserve further comment. First, the study has been conducted in an academic neurological setting, which biased the selection of patients. In a similar study from an emergency room, however, a seizure was diagnosed in 58 out of 198 patients (29%).[24] The difference with the proportion of seizures (38%) in our study is not significant (chi square: P > 0·1).

Second, there is doubt about the final classification of patients. In four patients of the syncope group (6%, CI from 2% to 13%[25])

Figure Relation between pre-test and post-test probability of the diagnosis of a seizure. Upper curve shows post-test probability if epileptiform activity is found. Lower curve shows post-test probability if epileptiform activity is absent. Dotted line shows post-test probability if the EEG would provide no information at all.

Table 4 Hyperventilation test

A Results of hyperventilation test

	Negative	Dubious	Positive
Seizure (n = 37)	18	13	6
Syncope (n = 46)	12	8	26

B Diagnostic value of the hyperventilation test for syncope
I = if dubious results are considered as negative
II = if dubious results are considered as positive

	I	II
Sensitivity	0·57 (26/46)	0·74 (34/46)
Specificity	0·84 (31/37)	0·49 (18/37)
Positive likelihood ratio (CI)	3·5 (1·6–7·6)	1·4 (1·0–2·1)
Negative likelihood ratio (CI)	0·5 (0·4–0·7)	0·5 (0·3–1·0)

C "Did you ever have episodes of breathlessness?"

	yes	no	don't know
Seizure (n = 41)	5	36	0
Syncope (n = 51)	19	31	1

Diagnostic value of this question for syncope

Sensitivity	0·38 (19/50)
Specificity	0·88 (36/41)
Positive likelihood ratio (CI)	3·1 (1·3–7·6)
Negative likelihood ratio (CI)	0·7 (0·6–0·9)

CI = 95% confidence interval

epileptiform activity was found. This activity consisted of sharp waves meeting most of the described epileptiform criteria.[26] Their history did not suggest epilepsy and follow up seemed long enough to exclude epilepsy in these patients. The confidence interval shows the range of this false-positive percentage. If in reality the percentage is 2%, it is the same as the percentage found by Zivin and Ajmone Marsan.[6] We believe that 6% or an even higher percentage is closer to reality as their study was retrospective and carried the risk of "circular reasoning": the finding of epileptiform activity may have been used to diagnose epilepsy in patients with obscure symptoms. Our study confirms that epileptiform activity in the EEG is not synonymous with epilepsy.[27] The false-negative rate of 60% (CI from 44% to 74%) of patients in the seizure group is comparable with the false-negative rate of 45% (CI from 40% to 50%) in another study.[28]

Third, an important limitation of our study is the relatively small number of patients. Nevertheless, the specificity of the EEG in our study is the same as in the larger study of Goodin and Aminoff, who reported a higher sensitivity of 0·52.[5] Their retrospective study carried the same risk mentioned above of circular reasoning which may lead to a higher true-positive rate.

The starting point of a diagnosis of epilepsy is often the evaluation of transient loss of consciousness. If the clinical diagnosis of a seizure is in doubt, the interictal EEG is a very useful diagnostic tool. Our findings apply to normal clinical practice as the spectrum of transient loss of consciousness is well represented.[29]

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