

A reappraisal of the value of interictal EEG findings in diagnosing epilepsy plus a critical review of controversial “normal variants”, utilising long-term ambulatory EEG recordings¹

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Funding/potential competing interests: No financial support and no other potential conflict of interest relevant to this article was reported.

Summary

Utilising long-term ambulatory EEG recordings over a period of 72 hours interictal epileptiform potentials (IED's, interictal epileptiform discharges) could be recorded in 311 from 316 patients with a confirmed epilepsy diagnosis (seizures recorded). These figures allow us to calculate a PPV of 98.4%.

These results allow us to predict the chance of an unclear seizure being epileptic if we record IED's as being over 98%.

Perhaps of more use in the daily clinical practice are our results in patients with non-epileptic seizures where the chance of an unclear attack being epileptic is only 1.5% (NPV 98.5%) if there were no IED's in a 72-hour recording.

Although it still holds true that spikes without seizures are not diagnostic of epilepsy and a positive diagnosis of epileptic seizures is still based on a combination of clinical and EEG findings we can say that with unclear attacks and IED's the chances of the attack being epileptic are very high. Alternatively, if no spikes are recorded the chance of the attack being epileptic is negligible.

We identified, in three of the more controversial “normal variants” (BETS, wicket spikes and 6/s spike-and-wave) two distinct differences which only in long-term EEG recordings could be defined. Depending on morphology and topography they could be considered either to be true normal variants or pathological patterns associated with epilepsy. For practical purposes we suggest that in patients with the variations associated with epilepsy that seizures should be recorded before the final diagnosis is made.

Key words: Epileptic seizures; Non-epileptic seizures; electroencephalography; interictal epileptiform discharges; normal variants

Introduction

Our “standards” for the interpretation of the significance of interictal EEG findings are based on data mainly obtained from short-term EEG recordings.

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Since the introduction of multi-channel digital ambulatory EEG recorders we are able to obtain high-quality EEG data over a long time period, giving us the opportunity to reappraise many of our presumptions regarding the significance of interictal EEG findings in the diagnosis of epilepsy. This reappraisal concentrates on two main aspects namely the incidence and significance of interictal epileptiform potentials; (IED's) in the EEG of patients with epilepsy and those with non-epileptic attack disorders, both psychogenic and organic. The main non-epileptic attacks in the organic group in descending order of occurrence were: Convulsive syncope, paroxysmal movement disorders, sleep disorders (REM behaviour disorder), behavioural disorders and hyperkplexia.

Secondly the significance of 3 of the controversial “normal variants” or more precisely “patterns of uncertain significance”, benign epileptiform transients of sleep (BETS), wicket spikes and 6-Hz spike and waves will be critically reevaluated.

Method

The data is based on 2122 ambulatory EEG recordings which were performed either at the diagnostic level or as a control of EEG/seizures following therapeutic modifications.

Regarding the incidence and significance of normal variants all recordings were used (database search for keywords in report). For the significance of IED's patients whose habitual seizures had been recorded were evaluated, the first 350 patients with epileptic seizures, plus the first 350 with non-epileptic attacks were included.

All recordings were performed with 23 channel surface EEG (Standard 10/20 system plus T1, T2) and one channel ECG. Electrodes were fixed with collodion. Recording integrity was maintained with twice daily check of signal quality.

Recordings were performed in an inpatient setting, when the patients were in their rooms there was additional

¹ Lecture at the Joint Annual Convention of the Swiss Society for Clinical Neurophysiology SGKN and the Swiss Brain Stroke Society SHG; 185th Convention of the Swiss Neurological Society SNG, 19–21 May 2011 in Lucerne.

video recording. Protocols were filled out by the patients / nursing staff who were instructed to note all daily activities plus clinically relevant events.

Recordings lasted for a period of 72 hours or until the clinical question had been answered (seizure-recorded) average duration per patient was 53.5 hours.

Analysis was in all cases visual based with the whole EEG being analysed, there was no sampling of preselected epochs.

The definition of spikes and sharp waves from the International Federation of Societies of clinical Neurophysiology is in fact purely a morphological description of waveforms and does not distinguish the spikes and sharp waves seen in patients with epilepsy, we therefore evaluated IED's adhering strictly to the definition proposed by Gloor [1] who described 5 points which allow a differentiation between IED's and other non-epileptiform sharp transients based on a morphological analysis of spikes and sharp waves recorded in patients with a definite diagnosis of epilepsy.

1. Epileptiform spikes and sharp waves are usually asymmetrical, the rise time to peak often being shorter than the fall from peak to baseline. Non-epileptiform sharp transients are in contrast mostly symmetrical.
2. Epileptiform spikes and sharp waves are usually followed by a slow wave, which has a longer duration than the predominant background activity.
3. Epileptiform spikes and sharp waves are polyphasic (usually 2 or 3 phases) non-epileptiform transients are mostly monophasic.
4. Epileptiform spikes and sharp waves have a different frequency (duration) from the background activity and are not simply abrupt increases in amplitude of the ongoing activity.
5. Epileptiform spikes and sharp waves interrupt the ongoing activity and there is often slowing before and after the sharp transient.

For practical purposes it can be said the more points are positive the more likely is it that the waveform is epileptiform. We considered the waveform to be epileptiform if the first 3 criteria or any other 4 were fulfilled. If this was not the case the sharp transient was not considered to be

epileptiform. In addition questionable waveforms have to be confirmed with different montages and two recording techniques (bipolar and reference) as spike-like waves can be seen or not seen depending on the montage/techniques used during review (fig. 1).

When reporting EEG's of such a long duration it is advisable that the review montage or montages used be based on a feasible hypothesis regarding possible "areas of interest" respectively where, based on seizure semiology, could IED's be expected. Figure 2 shows that with the traditionally used longitudinal montage no definite pathological findings can be seen. The seizure semiology in this case was suggestive of an involvement of the supplementary motor area and with a montage chosen to cover this area IED's can be seen.

Results

Results 1a: IED's in patients with epileptic seizures

In the first group of 350 patients with epilepsy there were 41 without IED's in their recordings. In 36 this could be explained on the following grounds:

- 34 patients with idiopathic generalised epilepsies who had been seizure-free for many years and were considering stopping anti-epileptic drugs, the referring physician requested a long-term- EEG before making this decision.
- 2 patients were receiving high doses of benzodiazepines >10 mg daily.

If we subtract these patients as not having "active epilepsy" we have from 316 with "active epilepsy", (seizures recorded in this recording session or in subsequent Video-EEG monitoring), only 5 with no IED's in the interictal EEG.

Results 1b: IED's in patients with non-epileptic seizures

In the second group, 350 patients with non-epileptic attacks, patient typical seizures recorded in this recording session or in subsequent Video-EEG monitoring, IED's were recorded in 5.

Figure 1

Change of morphology in different recording techniques. The "spike" in A (bipolar) disappears after reformatting B (reference) and is purely the result of the difference between the potentials at F7 and T3, common components being eliminated.



Probable reasons for IED's were:

- 1× clipping after subarachnoidal bleeding;
- 3× high dose antipsychotic drugs (Clozapine);
- 1× severe alcoholic.

Results 2: The significance of controversial “normal variants”

Results 2a: Benign Epileptiform Transients of Sleep (BETS)

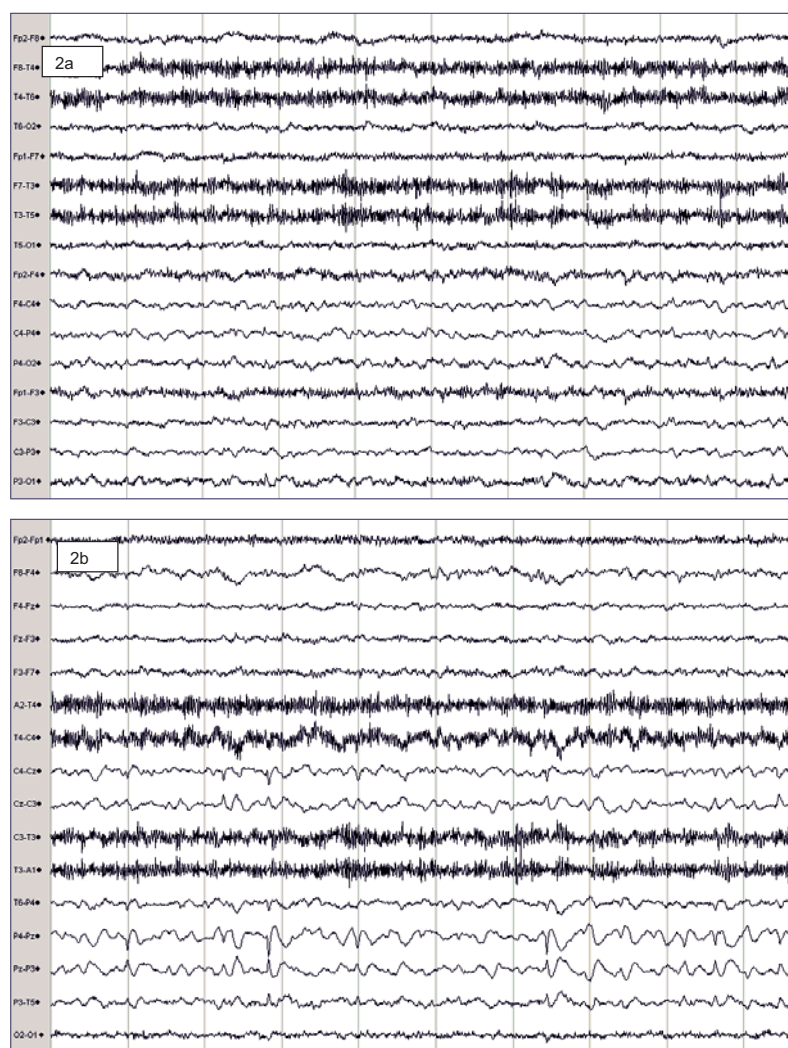
BETS occurred in a total of 82 patients (overall incidence 3.8%). Two forms could be identified.

Type 1: Bitemporal N = 54 (24 with epilepsy, 30 without epilepsy);

Type 2: Unilateral N = 28 (27 with epilepsy, 1 without epilepsy).

Figure 2

Choosing the correct montage: In 2a bipolar longitudinal no clear IED's can be seen in 2b the same epoch of EEG with a transverse montage show clear IED's at PZ, CZ. Patient awake ictal recordings (intracranial) confirmed seizure onset at the same localisation as the interictal IED's.



Results 2b: Wicket Spikes

Wicket spikes occurred in 150 patients (overall incidence 7.0%). Two distinct forms could be identified.

Type 1: Short runs of bilateral independent, monophasic sharp transients with a frequency ranging between 6–11 Hz sometimes occurring singly, trains showing waxing and waning (crescendo, decrescendo), mostly seen in drowsiness. This form was recorded in 136 Patients, none with epilepsy.

Type 2: Strictly unilateral no decrescendo, occurring more frequently single and in wakefulness. This form was recorded in 14 patients, all 14 with epilepsy.

Results 2c: 6-Hz spikes and wave

6-Hz S/W were recorded in 39 patients overall incidence 1.8%.

FOLD (Female Occipital Low amplitude Drowsiness) type was seen in 24 patients, none with epilepsy.

WHAM (Wake Higher in amplitude Anterior Males) was recorded in 15 patients, all with epilepsy.

Discussion

1a: IED's in patients with epileptic seizures

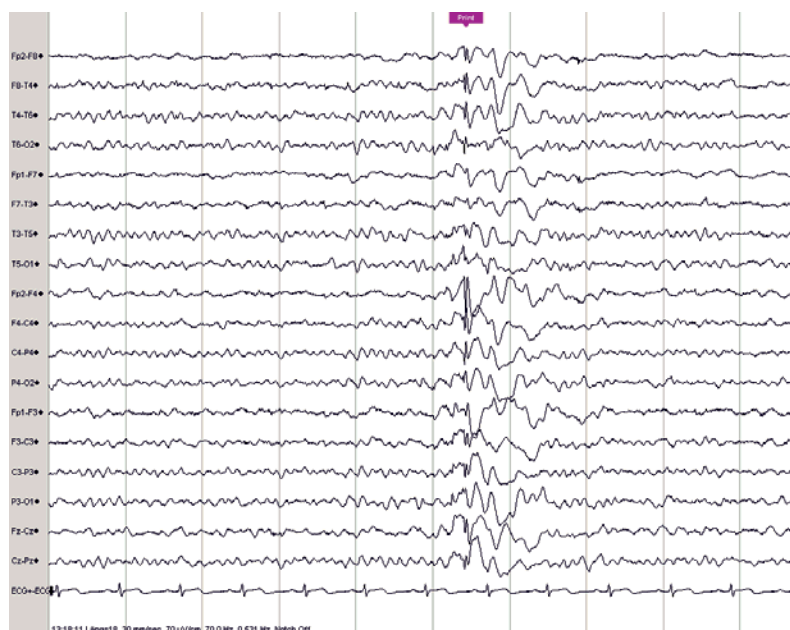
Traditionally the diagnosis epilepsy has been considered to be primarily clinical-based, the role of the interictal EEG being to [2]:

- Confirm a clinical diagnosis of epilepsy;
- Classify epilepsy type and syndrome;
- Exclude certain epilepsy syndromes;
- Detect or confirm the existence of photosensitivity;
- Detect antiepileptic drug intoxication;
- Detect potential epileptogenic cerebral lesions;
- Help to assess patients for epilepsy surgery.

As a consequence the significance of interictal EEG discharges (IED's) at the diagnostic level in patients with seizure disorders is, and has been based on the accuracy of the clinical interpretation of paroxysmal events i.e., was it an epileptic seizure and respectively does the patient have epilepsy. The inherent problems of this approach are apparent, the correlation of defined interictal EEG changes to clinical events that are unsure can – and does not lead to a high specificity.

Prediction of the correct clinical diagnosis when differentiating between epileptic and non-epileptic attack disorders is difficult. It has been shown that in such patients the referring physician accurately predicted the diagnosis in 50% of cases with non-epileptic psychogenic attacks and 82% with epileptic seizures. The unit personnel (direct observation) predicted 81% of the non-epileptic attacks correctly and 80% of the epileptic attacks [3].

Even when video recordings of the attacks are available the diagnostic accuracy is not better. The same authors have shown that neurologists viewing videotapes of the attacks accurately predicted 73% of the non-epileptic psychogenic attacks and 71% of epileptic attacks. These data showing that even with video recordings or direct observation of the

Figure 3 Clozapine-induced spikes in a patient without epilepsy.

clinical attacks an accurate diagnosis cannot only be difficult, but is in many cases incorrect. These falsely diagnosed cases will of course have an impact on the figures published relating to the correlation of EEG changes to epileptic and non-epileptic seizures.

How accurate is the diagnosis if interictal EEG findings are included? Can the probability as to whether a patient with IED's in the EEG has epilepsy or not be predicted? Taking the referral population of a clinical EEG department as an example the following has been predicted.

Assuming that 1000 patients were referred for EEG's and that 50% of these have epilepsy, then from the 500 with epilepsy 275 would have IED's (55% IED's in first EEG of patients with epilepsy). Of the 500 patients without epilepsy (taking a high false positive rate of 4%) 20 would have

IED's. In this example the PPV for IED would be very high 275/295 or 93% [4].

It could therefore be said that the interictal EEG, if of a technically high enough standard and adequately reported, in the correct clinical setting can be a powerful diagnostic tool with a high PPV, if IED's are recorded. But here again the same problem remains namely the assumption that 50% of the referred patients had epilepsy.

Can these figures be reproduced in cases with unclear attack disorders in which the epilepsy diagnosis was been confirmed with seizure recordings? We have shown utilising long-term ambulatory EEG recording that in patients in which the epilepsy diagnosis was confirmed with seizure recording and whose epilepsy was active i.e., seizures still occurring, that IED's were present in 311 from 316. This allows us to calculate a PPV (the probability of having epilepsy if IED's are recorded) of 98.4%.

The length of recording may seem long but we feel that this is justified in order to be sure that the patient does or does not have IED's. It has been shown that in a 24-hour recording 11% of patients with epilepsy do not show IED's in their interictal EEGs [5]. Should these remain undiagnosed or would the recording be repeated? The alternative to reach such a high positive rate as we obtained would be serial wake and sleep recordings with a cumulative yield for IED's of 92% [6].

Our results therefore confirm, and in fact are higher than the calculated figures of Goodin and Aminoff and are also higher than those obtained with serial wake and sleep EEG's [5, 6]. They would also support the ILAE [7] proposal that epilepsy can be diagnosed after one seizure if there is evidence of an epileptogenic disturbance of function in the EEG or a potential epileptogenic lesion in MRT. It can also be said that if the diagnosis of epilepsy cannot be confirmed with a positive EEG that the diagnosis should be put in question.

1b: IED's in patients with non-epileptic seizures

One of the age-old questions of the EEG is: can epilepsy be excluded? Although often confronted with this question our answer has been No!! Is this still the case with EEG's recorded over a long period of time? In 350 patients in whom non-epileptic attacks were recorded, spikes were only seen in 5 and were explainable (1× clipping after subarachnoidal bleeding, 3× high dose antipsychotic drugs (Clozapine), 1× severe alcoholic).

These results allow us to calculate a Negative Predictive Value (NPV) of 98.5%, in other words the chance of the attack being epileptic if no spikes are recorded is only 1.5%. This figure we feel is of clinical relevance, and again we stress that with no positive EEG findings a diagnosis of epilepsy must always be held in doubt.

The significance of controversial "normal variants"

2a: Benign Epileptiform Transients of Sleep (BETS)

BETS are low-amplitude monophasic or biphasic spikes occurring mostly in adults during light sleep. The waveform has typically a simple diphasic morphology with an abrupt

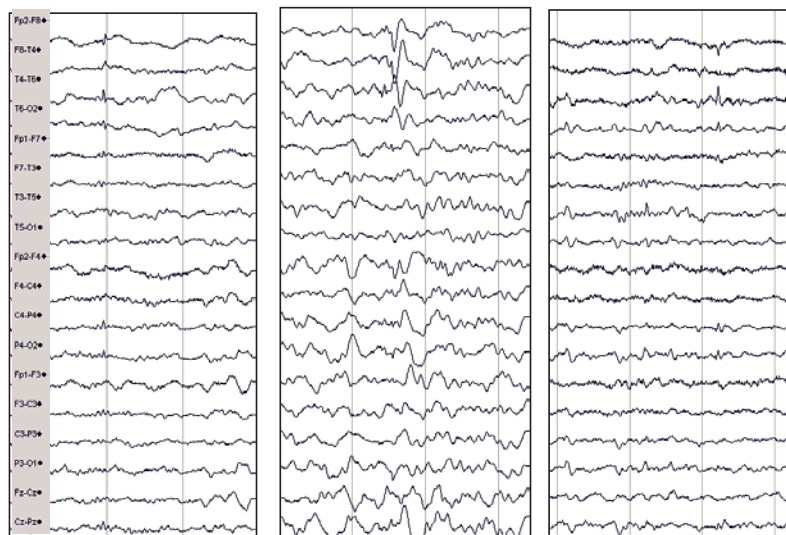
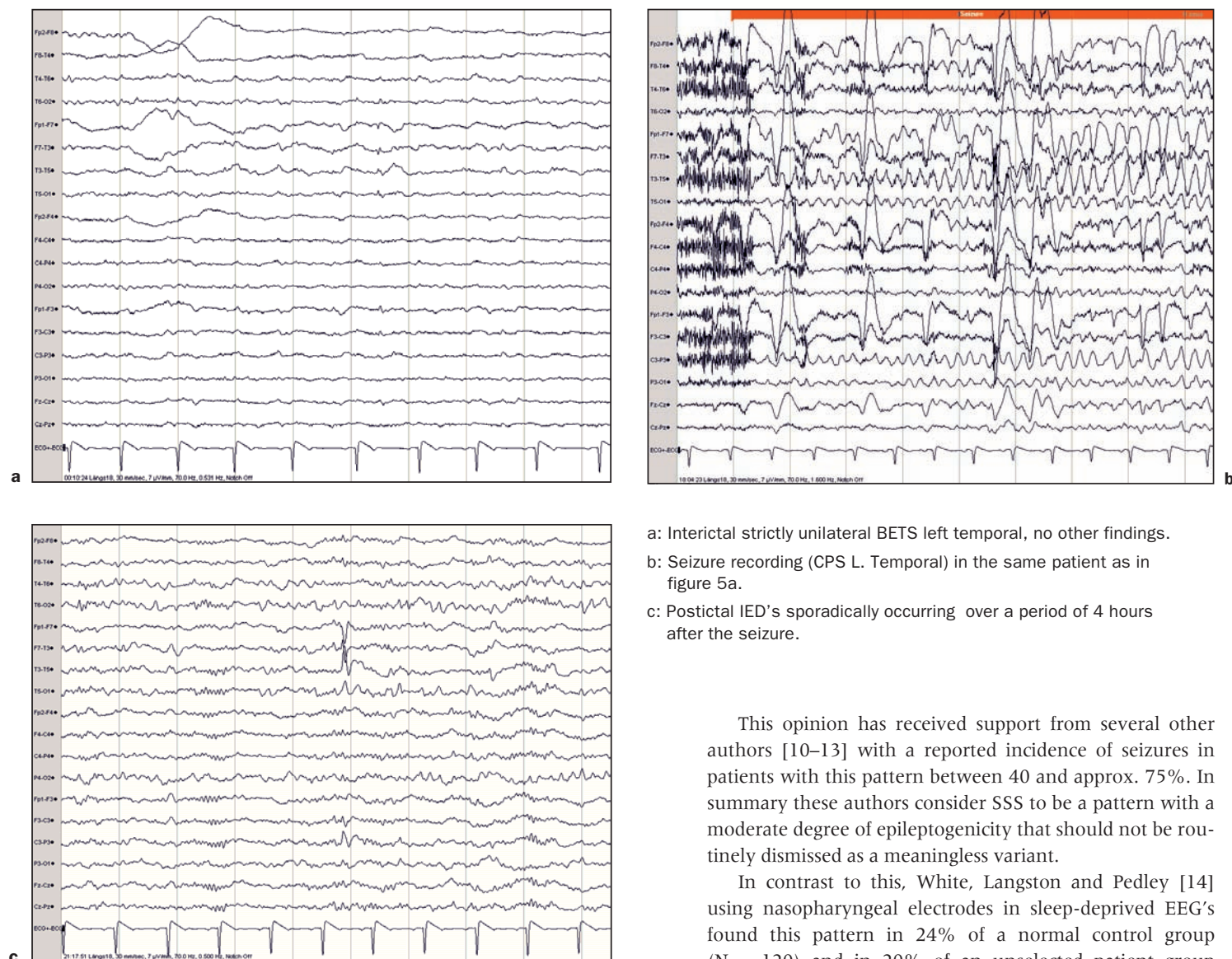
Figure 4 Dynamic progression. Preictal BETS. Postictal IED's that within a time period of 1 hour reverted to the original morphology of BETS.

Figure 5



a: Interictal strictly unilateral BETS left temporal, no other findings.

b: Seizure recording (CPS L. Temporal) in the same patient as in figure 5a.

c: Postictal IED's sporadically occurring over a period of 4 hours after the seizure.

rise and fall. They do not interrupt the background activity, unlike IED's they do not show a predominant aftergoing slow wave and do not occur in trains. The amplitude maximum is in the majority of cases mid-temporal if the recording is of long enough duration, BETS are almost always seen bilaterally [8].

Gibbs and Gibbs [9] first described this waveform and gave it its original name of "Small Sharp Spikes" (SSS). They originally described this pattern as follows: "Small sharp spikes are usually bilaterally independent. As a rule they are widespread, but predominate in the mid-temporal and frontal areas. Small sharp spikes are found mainly in adults, and they often occur in association, but independent of, anterior temporal spiking. This is an epileptic pattern, but it occurs occasionally among supposedly normal adults. Impairment of memory is the only outstanding non-epileptic symptom. When small sharp spikes are the sole abnormality and epileptic seizures are present, the response to anticonvulsant drugs is usually good. The aetiology is non-specific."

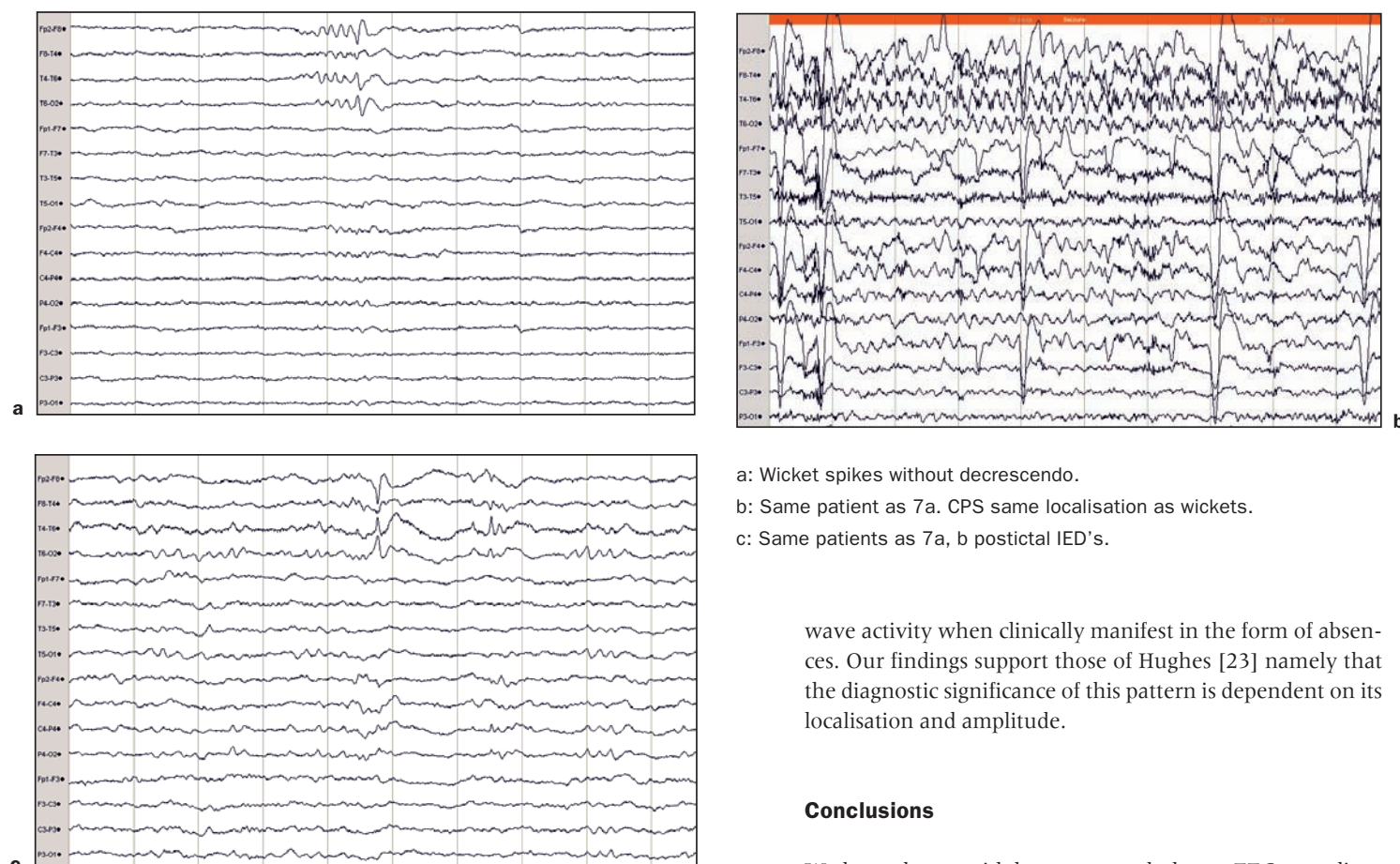
This opinion has received support from several other authors [10–13] with a reported incidence of seizures in patients with this pattern between 40 and approx. 75%. In summary these authors consider SSS to be a pattern with a moderate degree of epileptogenicity that should not be routinely dismissed as a meaningless variant.

In contrast to this, White, Langston and Pedley [14] using nasopharyngeal electrodes in sleep-deprived EEG's found this pattern in 24% of a normal control group (N = 120) and in 20% of an unselected patient group (N = 599) and therefore considered it to be of no diagnostic significance and suggested the term Benign Epileptiform Transients of Sleep (BETS). In a more recent glossary of terms most commonly used by clinical electroencephalographers [15] BETS have been described as low amplitude spikes of short duration followed in the majority of cases by a low amplitude theta wave, occurring mostly in drowsiness. This pattern is of little clinical significance.

The current consensus [16–20] is that BETS/SSS are indeed benign even when occurring in combination with a theta wave, and have no significance in the diagnosis of epileptic seizures, and are considered in patients with epilepsy to be a coincidental finding. The above authors, both pro and contra diagnostic significance, have reported an overall incidence ranging between 1% and 25%. With such blatant discrepancies it could be postulated that different forms of BETS exist.

Our results would support this hypothesis as we found BETS in a total of 82 patients (overall incidence of 3.8%). Two forms could be identified. The classical bilateral form of BETS was seen in a total of 54 patients, 24 with epilepsy, 30 without epilepsy.

Figure 7



a: Wicket spikes without decrescendo.

b: Same patient as 7a. CPS same localisation as wickets.

c: Same patients as 7a, b postictal IED's.

wave activity when clinically manifest in the form of absences. Our findings support those of Hughes [23] namely that the diagnostic significance of this pattern is dependent on its localisation and amplitude.

Conclusions

We have shown with long-term ambulatory EEG recordings over a period of 72 hours that IED's could be recorded in 311 from 316 patients with a confirmed epilepsy diagnosis (seizures recorded). These figures allow us to calculate a PPV of 98.4%.

Therefore our results allow us to predict the chance of an unclear seizure being epileptic if we record IED's as being over 98%. Perhaps of more use in the daily clinical practice are our results in patients with non-epileptic seizures where the chance of an unclear attack being epileptic if there were no IED's in a 72-hour recording is only 1.5% (NPV 98.5%).

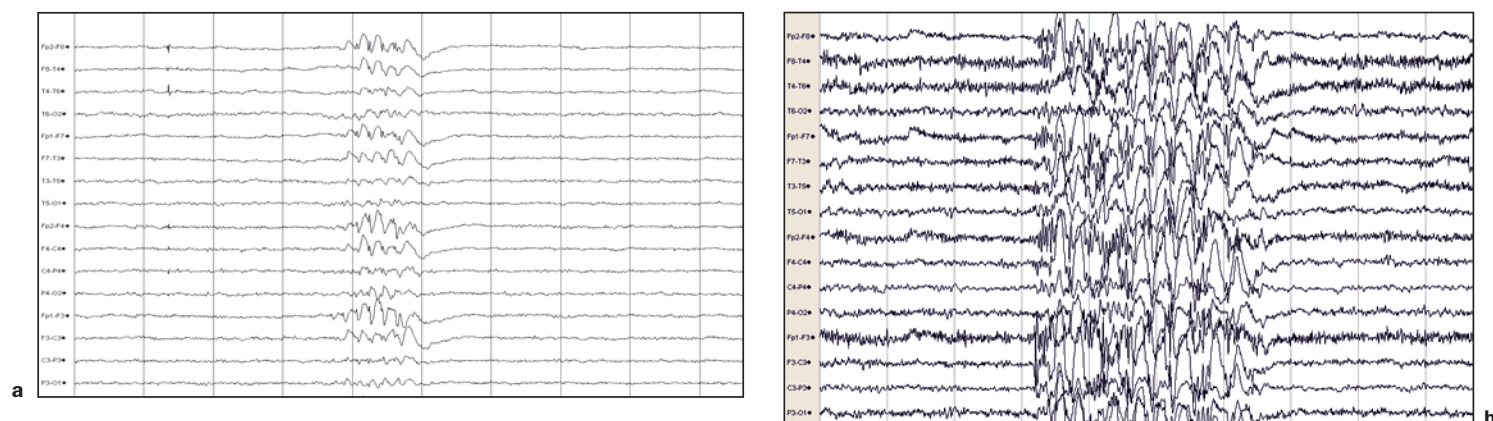
Although it still holds true that spikes without seizures are not diagnostic of epilepsy and a positive diagnosis of epileptic seizures is still based on a combination of clinical

normal variant (36% with seizures), WHAM however being associated with epilepsy (75% with seizures). In a glossary of terminology for EEG interpretation [14] these topographical differences are mentioned but both forms are considered to be of no diagnostic significance regarding epilepsy.

We recorded 6 Hz S/W in a total of 39 patients (overall incidence 1.8%). The FOLD type was seen in 24 patients, none of whom had epilepsy. WHAM was recorded in 15 patients, all with epilepsy.

During the long-term recordings all patients with WHAM showed at some time or other diffuse bilateral spike-and-

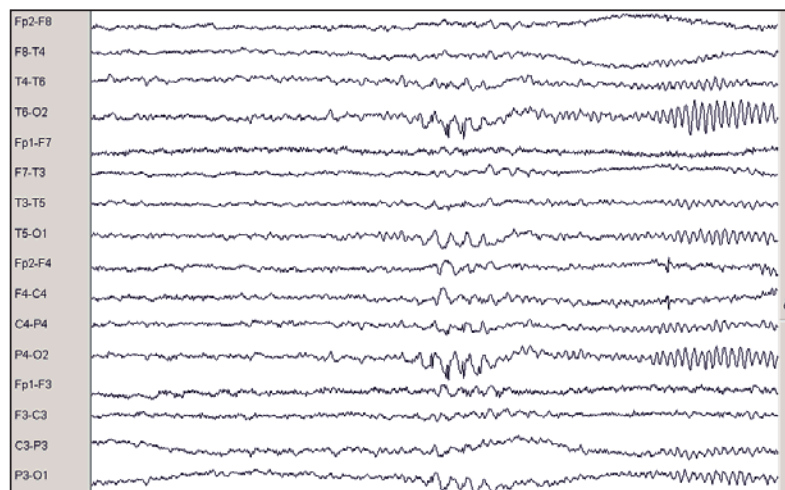
Figure 8



a: Six per second spike-and-wave, type WHAM.

b: Same patient as 8a. During long-term EEG diffuse bilateral spike/poly spike-and-wave.

Figure 9 Six per second spike-and-wave, type FOLD, during the 72 hour recording no other findings, seizure recorded in this patient was a convulsive syncope.



and EEG findings, we can say that with unclear attacks and IED'S the chances of the attack being epileptic are very high, alternatively if no spikes are recorded the chance of the attack being epileptic are negligible. If however, the clinical semiology remains highly suggestive of an epileptic seizure ictal recordings should, if possible, be performed.

As far as normal variants are concerned we could identify in three of the more controversial or misleading patterns (BETS, wicket spikes and 6/s spike-and-wave) two distinct differences which only in long-term EEG recordings could be identified. Depending on morphology and topography they could be considered either to be true normal variants or pathological patterns associated with epilepsy. For practical purposes we suggest that in patients with the variations associated with epilepsy that seizures should be recorded before the final diagnosis is made.

Utilising EEG recordings of long duration (72 hours) we can, in patients with unclear attack disorders, with a high degree of certainty say whether there are IEDS' or not, this allowing more certainty in the diagnostic decision as to whether the attack was epileptic or non-epileptic.

The alternatives available to obtain comparable results are either, multiple sleep/wake recordings or Video-EEG monitoring. We feel our results can position ambulatory

EEG as cost-effective and the optimal form of assessing interictal EEG activity especially IED's in the diagnosis of unclear attack disorders.

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