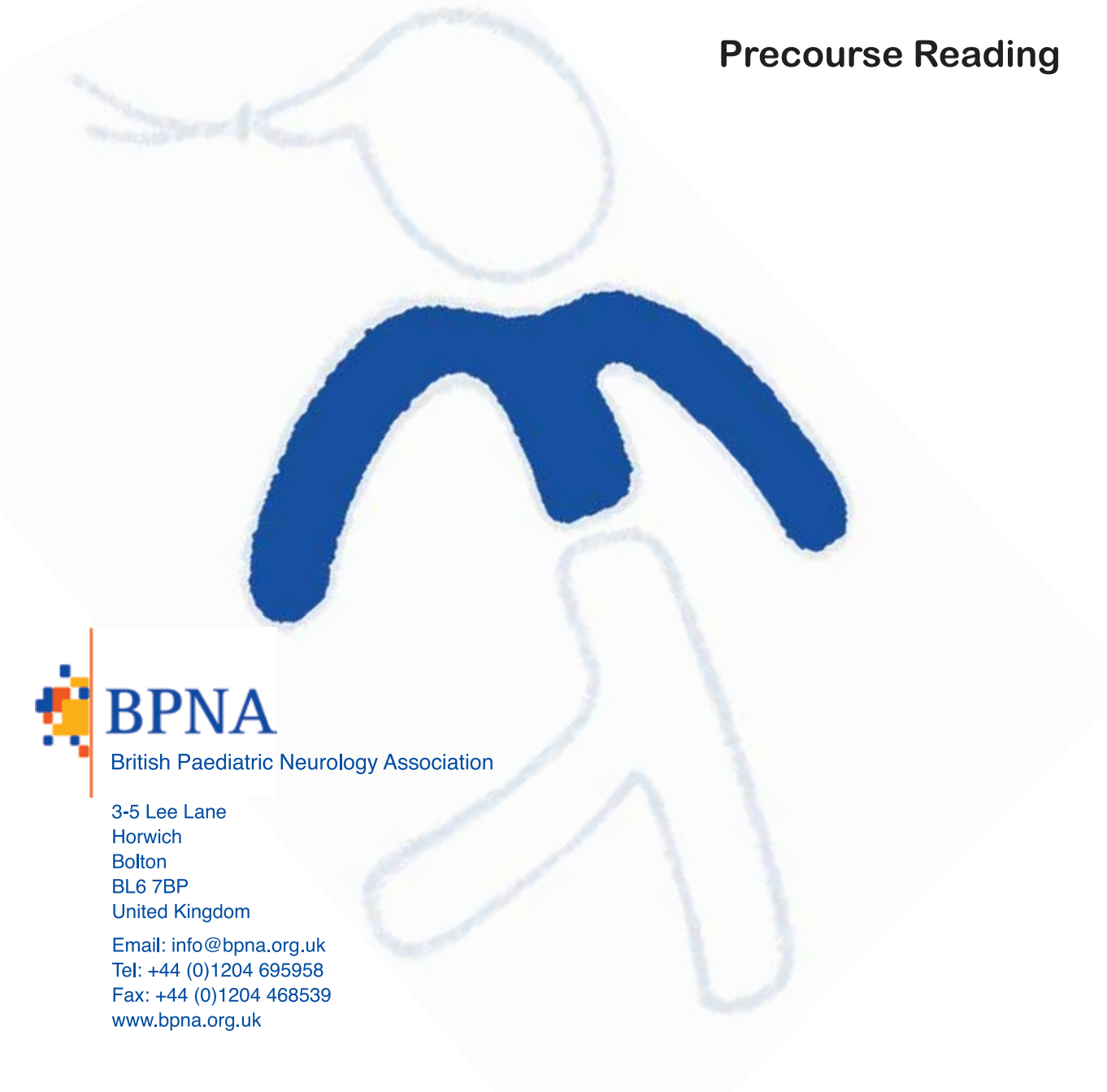
PET 1 2 3
PAEDIATRIC EPILEPSY TRAINING

PET EEG

Precourse Reading



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PET EEG Pre Course Reading

Contents

Glossary of EEG Terms

adapted from:

A glossary of terms most commonly used by clinical electroencephalographers and proposals for the report of EEG findings. In: Recommendations for the Practice of Clinical Neurophysiology: Guidelines of the International Federation of Clinical Neurophysiology. *Electroencephalography and Clinical Neurophysiology.* 1999;52

and

Glossary of Descriptive Terminology for Ictal Semiology. ILAE Epilepsy Classification & Terminology: http://www.ilae-epilepsy.org/visitors/centre/ctf/seizure_frame.html

10-20 system: System of standardised scalp electrode placement recommended by the International Federation of Clinical Neurophysiology (**Figure 1**).

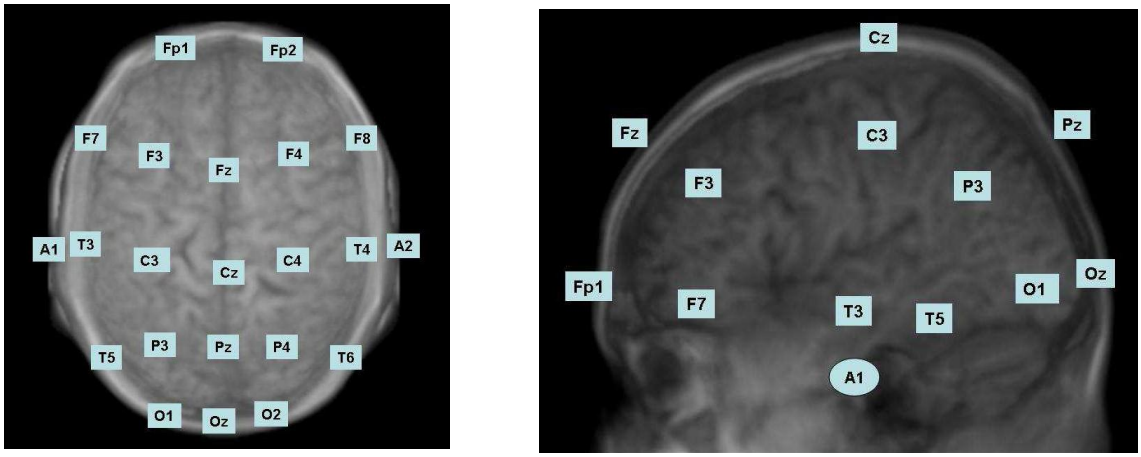

Figure 1. *Alphanumeric electrode labels:* A standardised system of labelling electrode positions based on brain region and distance from midline. F= frontal, Fp= fronto-polar; C= central; T=temporal; P= parietal; O= occipital. (A= auricular). Even nos. lie on the R, odd nos. on the L; e.g. C3 and C4 occupy homologous positions on the L and R respectively. 'z' (eg Cz) = zero, ie midline.

10-10 system: System of standardised scalp electrode placement. In this system, additional scalp electrodes are placed between the standard electrodes of the 10-20 system. Comment: also referred to as 5% system or "closely-spaced electrodes" **(Figure 2).**

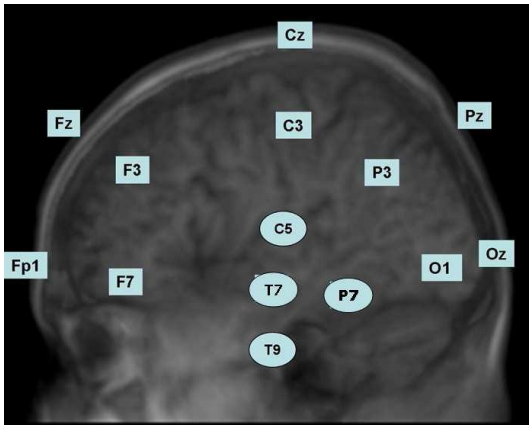

Figure 2. Amended 10-10 nomenclature as used on some figures in this glossary. Electrodes T3, T4, T5, T6 are now labelled T7, T8, P7, P8 respectively (shown (L side only) as ovals in this figure). Electrodes over the Sylvian fissures are labelled C5, C6.

Activation procedure: Any procedure designed to enhance or elicit normal or abnormal EEG activity, especially paroxysmal activity. (Examples: overbreathing, photic stimulation).

Activity, EEG: an EEG wave or sequence of waves.

Alpha rhythm: rhythm at 8 – 13 Hz coming during wakefulness over the posterior regions of the head, generally with maximal amplitudes over the occipital areas. Best seen with the eyes closed and during physical relaxation. Blocked attenuated by attention especially eye opening (**Figure 3**). Comment: there are other rhythms in the alpha band which differ from alpha rhythm as regards their topography and/or reactivity. These include physiological examples such as *mu rhythm* or *rhythms of alpha frequency* which may be abnormal, particularly in the preterm or young infant.

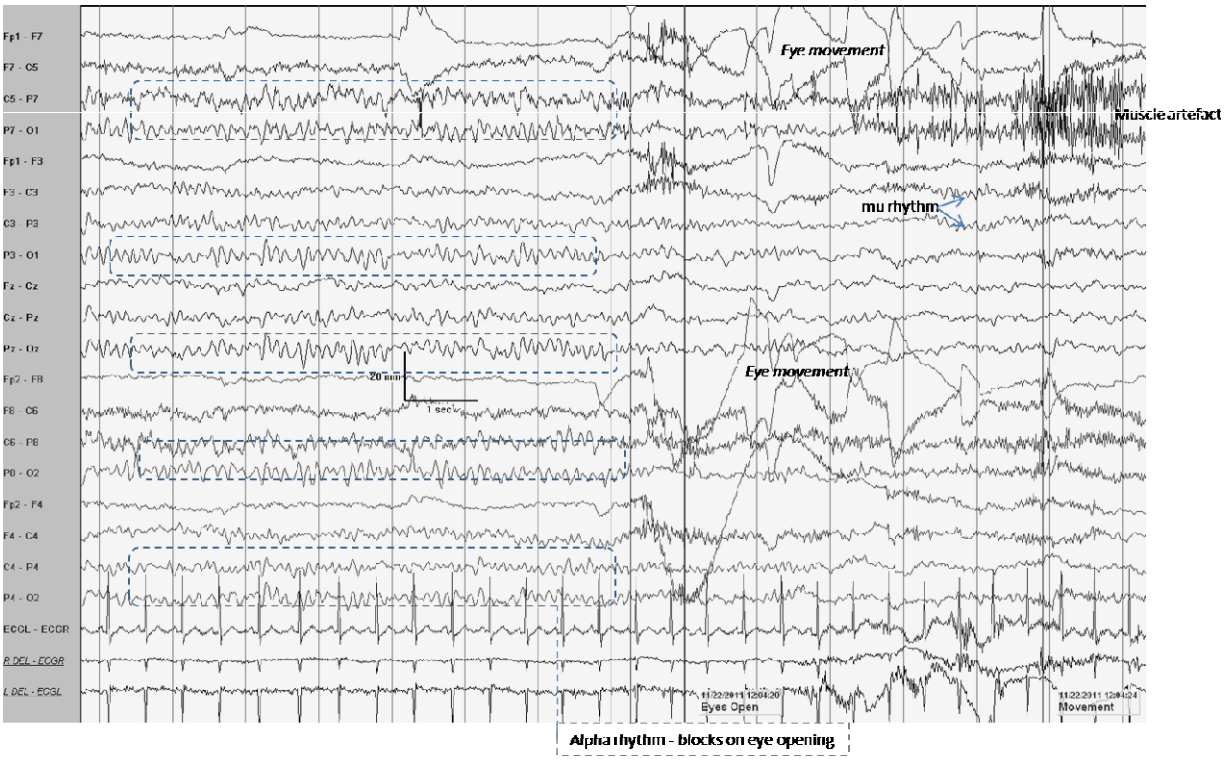

Figure 3. Change in normal EEG on eye opening. Note *alpha rhythm* is 'blocked', while *mu rhythm* remains. Note eye-movement and EMG contamination.

Amplitude: Voltage of EEG waves expressed in microvolts (μV). Measured peak-to-peak.

Arteфact: A modification of the EEG caused by extracerebral factors such as 50 Hz interference, movements, interference with electrodes (**Figure 3**).

Asymmetry: Unequal amplitude of EEG activities over homologous areas on opposite sides of the head.

Attenuation: Reduction in amplitude of EEG activity. May occur transiently in response to physiological or other stimuli or result from pathological condition.

Atypical spike-and-slow-wave complex: Paroxysms consisting of a sequence of spike-and-slow-wave complexes that occur bilaterally but do not meet the criteria of 3Hz spike-wave complexes. **(Figure 14)**

Average potential reference ("average reference") montage: Average of the potentials of all or any EEG electrodes, used as a reference.
Preferred term: *common average reference*. **(Figure 9)**

Background activity: Any EEG activity representing the setting in which a given normal or abnormal pattern appears and from which such pattern is distinguished. Comment: ***not*** a synonym for any individual rhythm such as the alpha rhythm.

Background slow activity: The frequency of the background is below the normal value.

Band: Portion of EEG frequency spectrum ie delta, theta, alpha, beta, gamma bands.

Baseline: imaginary line corresponding to the approximate mean values of the EEG activity assessed visually in an EEG derivation over a period of time. (Informal).

Bilateral: EEG changes involving both sides of the head. Comment: activity may involve homologous areas and may or may not be synchronous eg bifrontal, bitemporal spikes.

Bipolar montage: Multiple bipolar derivations, with no electrodes being common to all derivations. In most instances, bipolar derivations unlinked, ie adjacent derivations from electrodes along the same line of electrodes have one electrode in common, connected in longitudinal chains, usually antero-posteriorly (AP) or transversely across the head. **(Figure 9)**

Burst: A group of waves which appear and disappear abruptly and are distinguished from background activity by differences in frequency, form and/or amplitude.
Comment: the term does not imply abnormality. (**Figures 4, 8, 15**).

Burst suppression: pattern characterised by bursts of theta and/or delta waves, at times intermixed with faster waves, and intervening period is of low amplitude (below 20 µV).

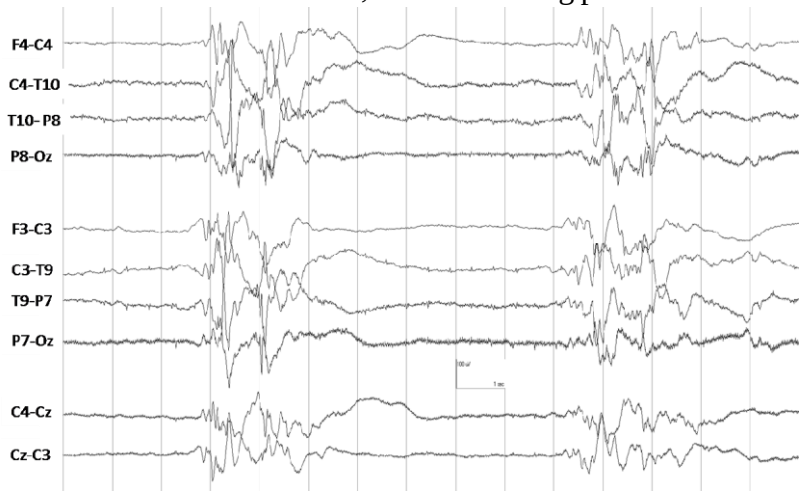

Figure 4. Burst-suppression pattern in a 4-month-old child

Comment: this EEG pattern may indicate either severe brain dysfunction or is typical of certain levels of anaesthesia. N. B. This has to be differentiated from the physiological discontinuity that is typical of early prematurity.

Channel: Complete system for the detection, amplification and display of potential differences between a pair of electrodes.

Common reference montage: Several referential derivations sharing a single reference electrode.

Complex: A sequence of two or more waves having a characteristic form or recurring with a fairly consistent form, distinguished from background activity. (**Figures 13, 14**)

Continuous slow activity: Slow activity that occurs continuously is non-responsive to external stimuli and clearly exceeds the amount considered physiologically normal for the patients each. As a rule, it is a regular (polymorphic) and lies within the frequency range of delta/theta waves.

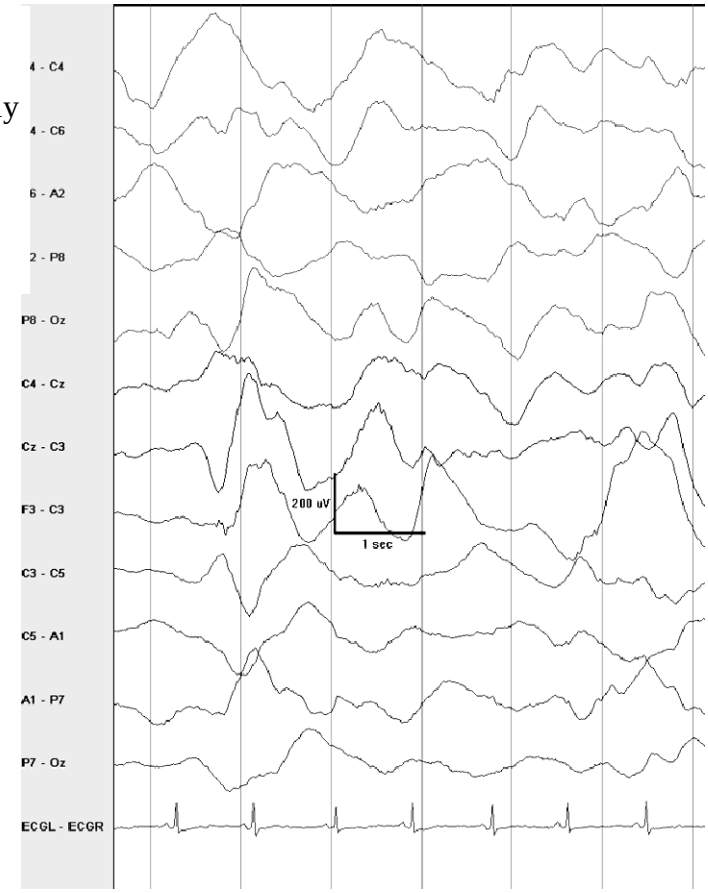

Figure 5. Continuous slow activity (in an acute encephalopathy).

Cycle: The complete sequence of potential changes undergone by individual components of a sequence of regularly repeated EEG waves or complexes.

Cycles per second: Unit of frequency. Abbreviation: c/s. Equivalent: Hz.

Derivation: (1) The process of recording from a pair of electrodes in an EEG channel. (2) The EEG record obtained from this process.

Differential amplifier: An amplifier (as used in the input stage of an EEG) whose output is proportional to the voltage difference between its two input terminals.

Digital EEG: (1) The representation of an analogue EEG signal by a series of numbers related to successive measurements of the magnitude of the signal at equal time intervals. (2) The practice of EEG using digital representation of EEG signals.

Dipole: a theoretical point-like EEGs source produced by a separation of negative and positive charge. Comment: commonly used to describe cortical source that generates an EEG field in which both negative and positive maxima can be recorded. (**Figure 6**)

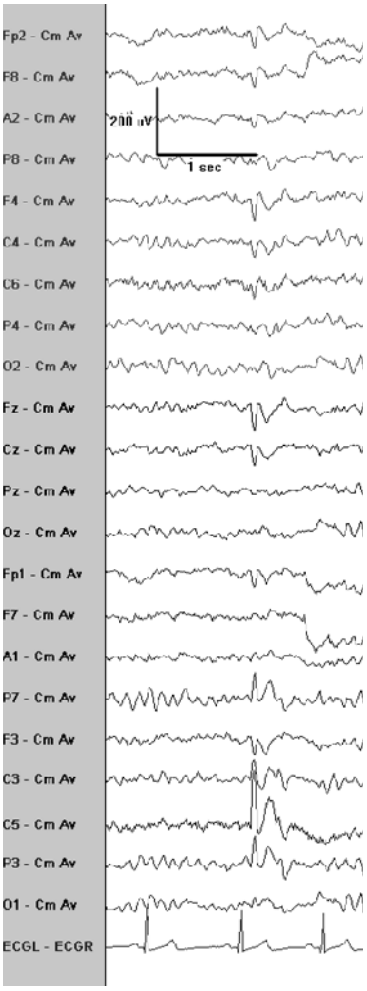

Figure 6. Focal spike seen with maximal negativity over the L Sylvian (C5) electrode. Note the corresponding positivity over the R hemisphere, maximal over the R frontal electrode F4, indicating the orientation of the equivalent dipole.

(Typical appearances of centro- temporal (Sylvian) spikes).

Discharge: Interpretive term commonly used to designate epileptiform and seizure patterns.

Disorganisation: Gross alteration in frequency, form, topography and/or quantity of physiological EEG rhythms.

Duration: (1) the interval from beginning to end of an individual wave or complex. Comment: the duration of the cycle of individual components of a sequence of regularly repeating waves or complexes is referred to as the *period* of the wave of complex. (2) The time that a sequence of waves or complexes or any other distinguishable feature lasts in an EEG record.

Electrode, EEG: A conducting device applied over or inserted into a region of the scalp/brain.

Electroencephalogram: record of electrical activity of the brain taken by means of electrodes placed on the surface of the head. Abbreviation: EEG.

Epileptiform pattern: Synonym: epileptiform discharge, epileptiform activity. Describes transients distinguishable from background activity, with characteristic spike morphology, typically, but neither exclusively nor invariably found in interictal EEGs of people with epilepsy.

Epoch: A period of time in an EEG record. Duration of epochs this is determined arbitrarily.

Equipotential: Applies to regions of the head or electrodes that are at the same potential at a given instant in time.

Evoked potential: Wave or complex elicited by and time-locked to a physiological or non-physiological stimulus on event, the timing of which can be reliably assessed (eg an electrical stimulus) delivered to a sensory receptors or nerve.

(Event-related potential): applied mainly to those evoked potential's elicited by cognitive activities. Comment: these potentials tend to be of longer, or much longer latency than those used in standard clinical EEG.

Fast activity: Activity of frequency higher than alpha (beta and gamma activity).

Focal: Limited to a small area of the brain; ie recorded in one of two intracranial electrodes.

Focus: A limited region of the scalp, cerebral cortex or depth of the brain displaying a given EEG activity, either normal or abnormal.

Frequency: Number of complete cycles of representative waves of complexes in one second. Measured in cycles per second (c/s) or Hertz (Hz). Comment: the term Hz seems appropriate when applied to sinusoidal waves such as alpha activity, but seems inappropriate when applied to complex waveforms such as spike-and-slow- wave.

Frequency spectrum: Range of frequencies composing the EEG. Divided into 5 bands termed delta (1-3/s), theta (4-7/s), alpha (8-13/s), beta (13-25 or 30Hz) and gamma (<30Hz).

Generalised: Occurring over all regions of the head, usually with frontal maximum. **(Figures 8, 10, 15).** Comment: this is a general descriptive EEG term and is not restricted to epileptiform changes.

Hypsarrhythmia: EEG pattern consisting of diffuse high voltage (<300µV) irregular slow waves interspersed with multiregional spikes/sharp waves over both hemispheres (**Figure 7**).

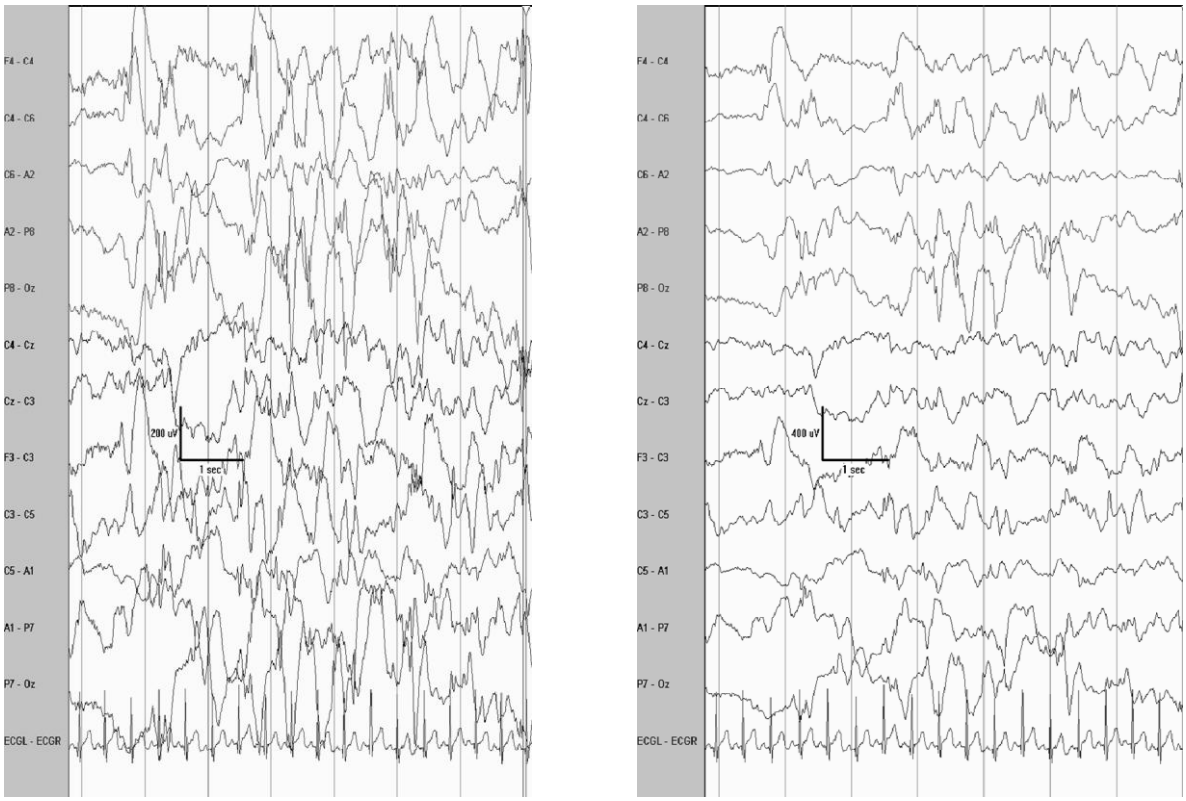

Figure 7. Hypsarrhythmia. A standard display (10µV/mm) emphasises the high amplitude of the grossly abnormal activities, with slow waves and multifocal spikes, At half the amplification (20µV/mm) the details of the distribution of the same activity are more evident.

NB Comment: EEGs which do not match the above criteria (lower amplitude, semi-organised etc) are sometimes described as 'modified hypsarrhythmia' but this term is used of records where this is found both *de* novo and following treatment and the term is therefore ambiguous.

Inactivity, total electrocerebral: Absence of identifiable electrical activity of cerebral origin, whether spontaneous or induced by physiological stimuli of pharmacological agents, over all regions of the head:
Comment: (1): requires stringent technical recording techniques. (2): tracings of electrocerebral inactivity should be clearly distinguished from low voltage EEGs and records displaying delta activity of low amplitude.

Independent (temporally): Synonym: Asynchronous.

Intermittent slow activity: Slow activity that occurs intermittently and is not caused by drowsiness. Intermittent slow can be a regular or rhythmical.

Irregular: Applies to EEG waves and complexes of inconstant period and/or uneven contour.

Isoelectric: Use of this term discouraged when describing record of electrocerebral inactivity (see above). Correctly, describes the record obtained from a pair of equipotential electrodes.

Isolated: Occurring singly.

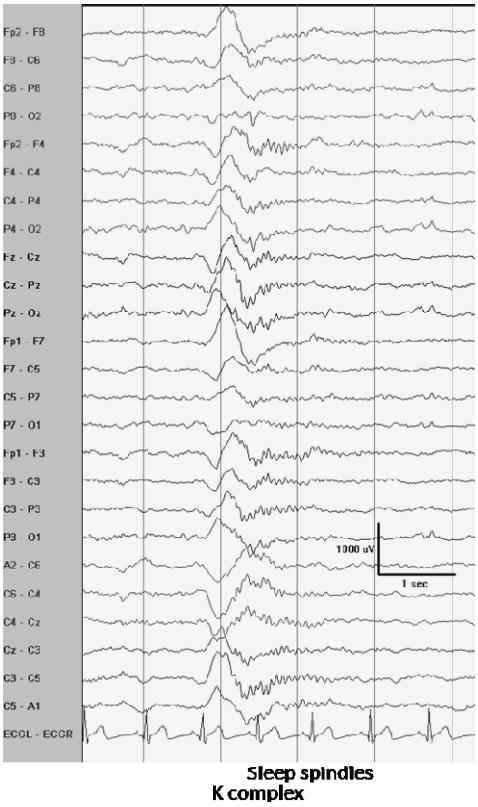

Figure 8. K complex and sleep spindles. (Features of normal stage 2 NREM sleep).

Lambda wave: diphasic sharp transient occurring over the occipital regions of the head of waking subjects during visual exploration. The main component is positive relative to other areas. Time-locked to saccadic eye movement. (**Figure 9**). Amplitude varies but is generally below 50 µV.

Laplacian montage: Montage that can be used in digital EEG recordings, consisting of a mathematical transformation involving the second spatial derivative: the Laplacian of the potential may be approximated by using the average of all neighbouring electrodes as a reference for each site on electrode. (Hence it is sometimes referred to as a 'local average reference').

Lateralised: involving mainly the right or left side of the head.

Low voltage EEG: A waking record characterised by activity of amplitude not greater than 20µV over all head regions. Comment: when related to physiological factors low voltage EEGs are susceptible to change under the influence of physiological stimuli including sleep and also to pharmacological agents and pathological processes. The term should *not* be used for tracings of electrocerebral inactivity.

Modified hypsarrhythmia: see *Hypsarrhythmia.*

Montage: The particular arrangement by which a number of derivations are displayed simultaneou sly in an EEG record.

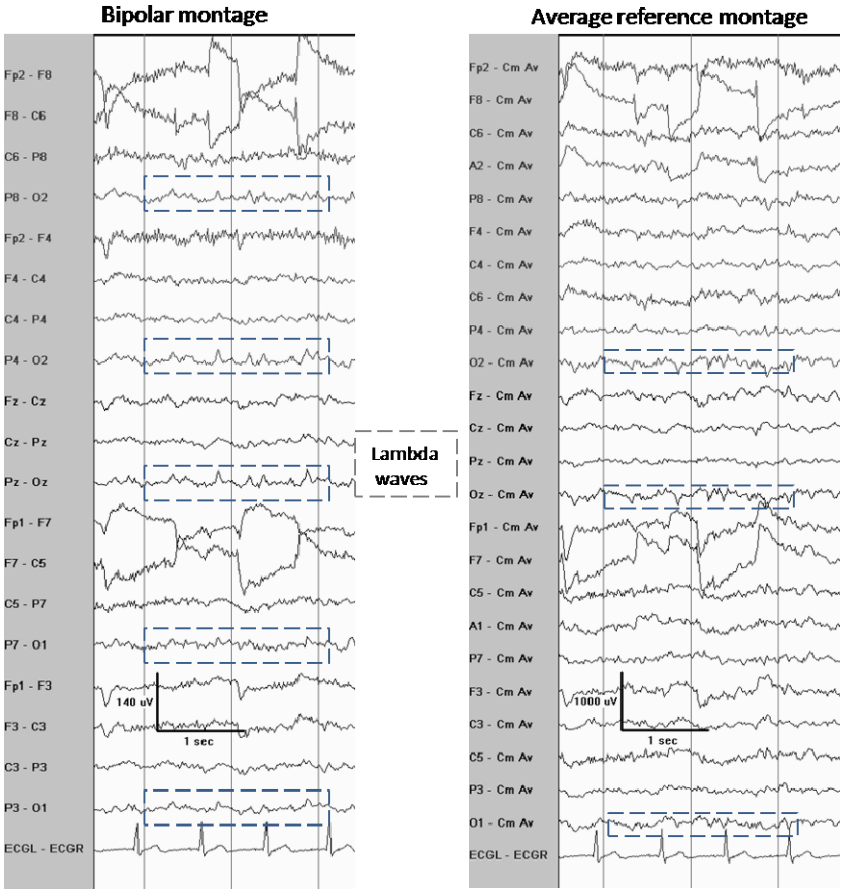

Figure 9. Lambda waves are shown with their correct surface positive polarity (down-going) at the occipital electrode in the average reference montage, but appear as an upward deflection at the end of the bipolar chain.

Mu rhythm: Rhythm at 7-11Hz composed of sinusoidal (often seen in children) *or* arch-shaped (particularly in adults) waves, occurring over the central or centro-parietal regions during wakefulness (**Figure 3**). Blocked or attenuated by contralateral movement or intention to move. (can be regarded as a sensorimotor rhythm).

Multifocal: more than two or more spatially separated foci.

Paroxysm: Phenomenon with abrupt onset, rapid attainment of a maximum, and sudden termination; distinguished from background activity. Comment: commonly used to refer to epileptiform and seizure patterns **(Figures 10, 15).**

Pattern: Any characteristic EEG activity.

Periodic: Applies to (1) EEG waves of complexes occurring in a sequence at an approximately regular rate. (2) EEG waves of complexes occurring intermittently at approximately regular intervals, generally of one to several seconds.

Periodic lateralised epileptiform discharges (PLEDs): PLEDs are sharp transients such as sharp waves of spikes, which repeat in a periodic or semi-periodic fashion. They have either a regional or lateralised distribution. They may also occur independently over both hemispheres.

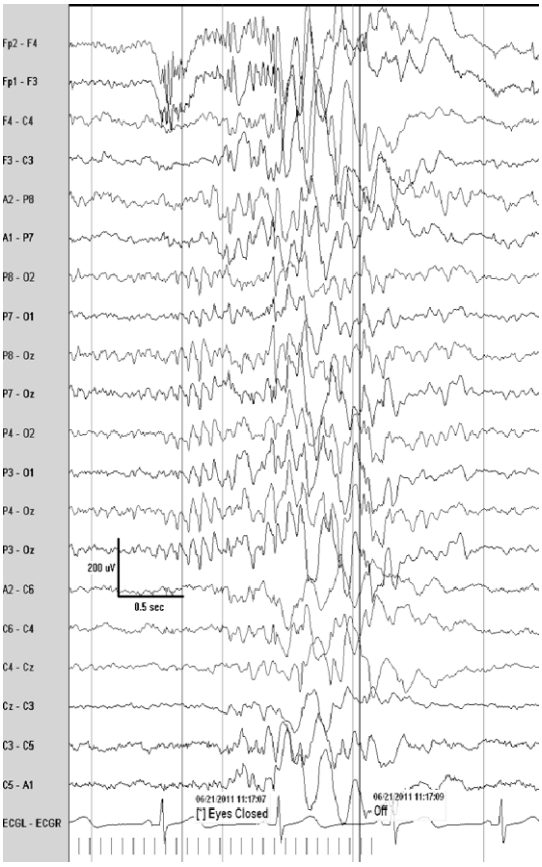

Figure 10. Photoparoxysmal response: Abnormal response to intermittent photic stimulation characterised by spike-and-slow- wave and polyspike- and slow-wave complexes. Responses are graded from occipital spikes time-locked to the flashes to generalised epileptiform discharges which may occur last the stimulus by a few seconds. Comment: only the generalised spike-and-wave response shows a strong association with epilepsy, particularly if it is self-sustaining and continues after the stimulus.

Phase reversal: Simultaneous trace deflections in opposite directions from 2 or more channels. When observed in 2 linked bipolar derivations, phase reversal indicates that the potential field is maximal or minimal at or near the electrode common to such derivations (**Figure 11**).

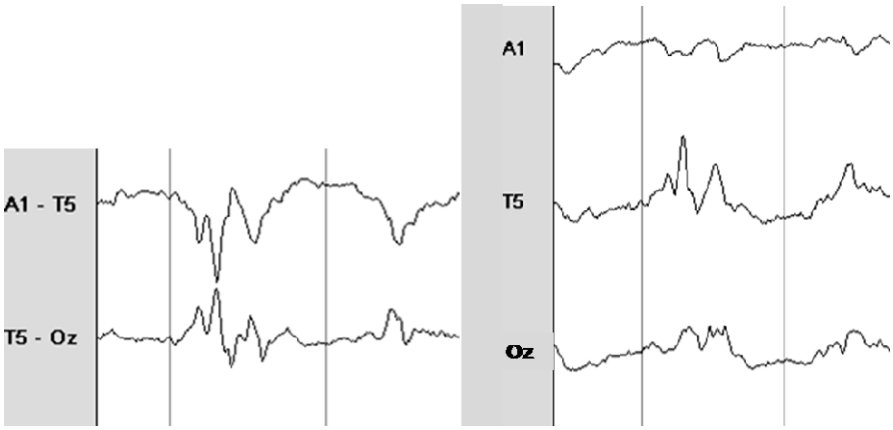

Figure 11. Phase reversal is shown in the bipolar derivation on the L. The signal arises near to the electrode in common in the bipolar chain (T5). This is confirmed in the referential derivation shown on the R.

Polarity, EEG wave: sign of potential difference existing at a given time between an electrode affected by a given potential change and another electrode not appreciably, or less, affected by the same change. Comment: the apparent "polarity" of an EEG wave is dependent upon the potential difference between two electrodes.

Polarity convention: international agreement whereby differential EEG amplifier is constructed so that negativity at the input terminal 1 to the input terminal to the same amplifier produces an upper trace deflection. Comment: this convention is contrary to that prevailing in other biological and engineering fields.

POSTS (Positive Occipital Sharp Transient of Sleep): Sharp transient maximal over the occipital regions, positive relative to other areas, apparently occurring spontaneously during sleep. May be single or repetitive. Amplitude varies.

Recruiting rhythm: One of the EEG patterns seen at ictal onset, when diffuse, rapid (10- to 13-Hz), low-amplitude activity progressively decreases in frequency and increases in amplitude (**Figure 12**). Diffuse slow waves and slow spike and waves may follow it.

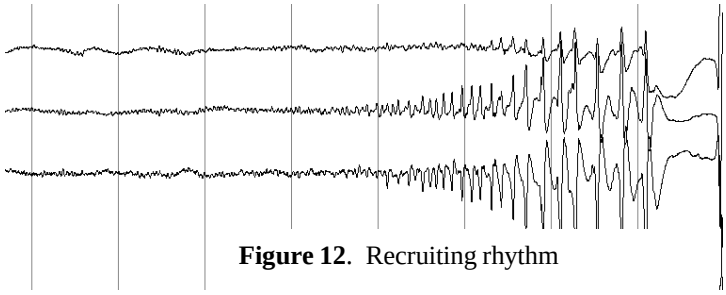

Figure 12. Recruiting rhythm

Regional: EEG activity that is limited to a region of the scalp recorded in three or more electrodes in intracranial recordings.

Rhythm: activity consisting of waves of approximately constant period.

Sleep spindle: Burst at 11-15 Hz (mostly at 12-14 Hz), generally diffuse, but of higher amplitude over the central regions of the head, occurring during sleep. (**Figure 8**). Comment: sleep spindles often occur with K complexes and essentially define stage 2 (N2) sleep.

Spatial distribution: Topography of an EEG activity across the scalp.

Spike-and-slow-wave complex: A pattern consisting of a spike followed by a slow wave. Comment: usually interpreted as epileptiform. (**Figures 13-14, 15L**).

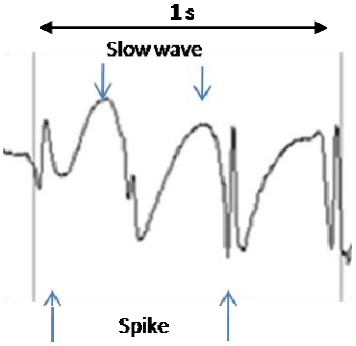

Figure 13. Typical spike-wave complexes.

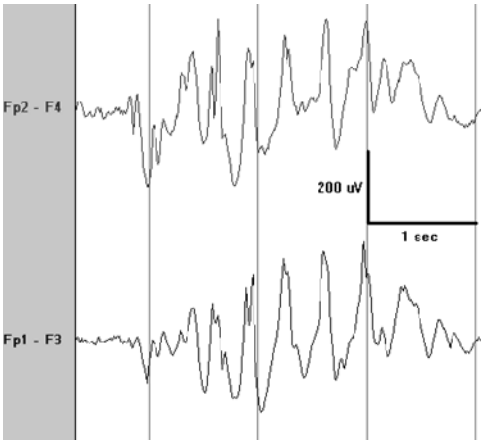

Figure 14. Atypical spike-wave complexes.

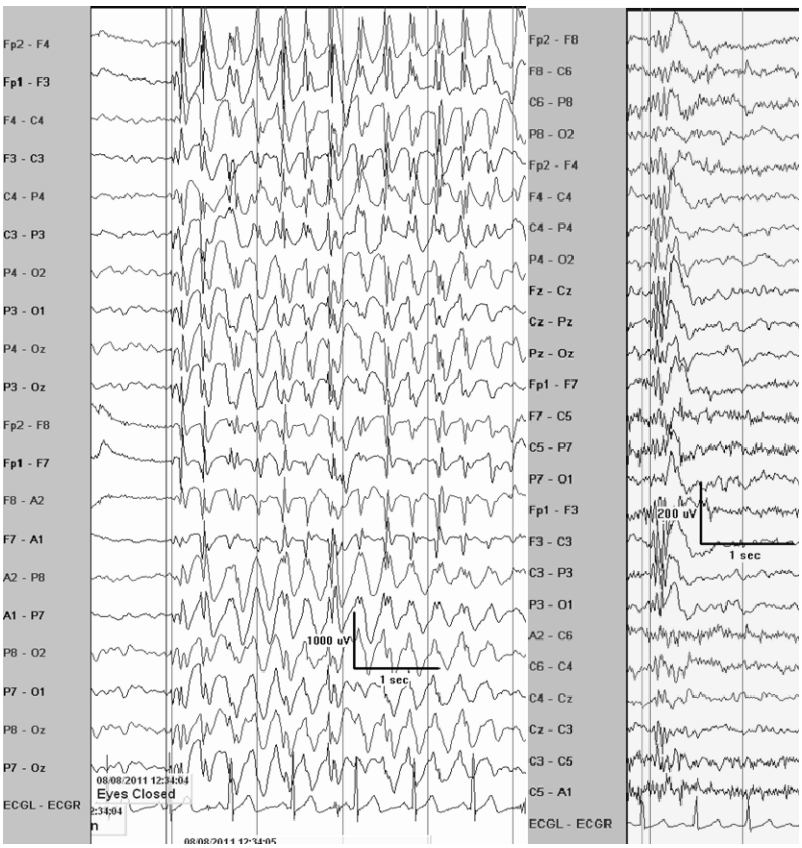

Figure 15. Generalised changes: Left: 3/s spike-wave complexes . Right: Polyspike-wave burst

Spread: Propagation of EEG waves from one region of the scalp and/or brain to another.

Synchrony: The simultaneous occurrence of EEG waves over regions on the same or opposite sides of the head. Comment: terence simultaneous only implies a lack of delay that is measurable on standard displays.

Symmetry: (1) Approximately equal amplitude frequency and form of EEG activities over homologous areas on opposite sides of the head. (2) Approximately equal distribution of potentials of unlike polarity on either side of zero isopotential axis (see phase reversal). (2) approximately equal distribution of EEG waves about the baseline.

Suppression: On-going EEG activities below 10µV (reference derivation) are termed background suppression.

Transient, EEG: Any isolated wave or complex, distinguished from background activity.

Vertex sharp transient: Sharp potential, maximal at the vertex, negative of relative to other areas, apparently occurring spontaneously during sleep or in response to a sensory stimulus during sleep or wakefulness. May be single or repetitive. Amplitude varies but really exceeds 250 µV. Abbreviation: V wave, vertex wave. Alias vertex sharp wave (use discouraged).

Voltage: Derived by multiplying the trace amplitude by the display sensitivity (Amplitude).

Volume conduction: A passive process by which electrical activity originates from a generator and spreads through a conductive medium to be picked up by a distant electrode.

Waveform: The shape of an EEG wave.

Related *clinical* terms relating to descriptions of seizures:
from: "Glossary of Descriptive Terminology For Ictal Semiology" ILAE Epilepsy Classification & Terminology –
http://www.ilae-epilepsy.org/visitors/centre/ctf/seizure_frame.html

see also Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005-2009. *Epilepsia*. 2010; 51(4):676-85

Ictus: A sudden neurological occurrence such as a stroke or an epileptic seizure.

Prodrome: A pre-ictal phenomenon. A subjective or objective clinical alteration, eg ill-localised sensation or agitation that heralds the onset of an epileptic seizure but does not form part of it.

Post-ictal Phenomenon: A transient clinical abnormality of central nervous system function that appears or becomes accentuated when clinical signs of the ictus have ended.

Epileptic Spasm (Formerly Infantile Spasm): Noun: A sudden flexion, extension or mixed extension-flexion of predominantly proximal and truncal muscles which is usually more sustained than a myoclonic movement but not as sustained as a tonic seizure ie about 1 sec. Limited forms may occur: grimacing, head nodding. Epileptic spasms frequently occur in clusters.

Tonic: A sustained increase in muscle contraction lasting a few seconds to minutes.

Myoclonic (adjective); *Myoclonus* (noun): Sudden, brief (< 100 ms) involuntary single or multiple contraction(s) of muscles(s) or muscle groups of variable topography (axial, proximal limb, distal).

*Negative Myoclonic***:** Interruption of tonic muscular activity for < 500 ms without evidence of antecedent myoclonia.

Clonic: Myoclonus which is regularly repetitive, involves the same muscle groups, at a frequency of about 2-3 c/sec, and is prolonged. Synonym: rhythmic myoclonus.

Tonic-Clonic: A sequence consisting of a tonic followed by a clonic phase. Variants such as clonic-tonic-clonic may be seen.

Atonic: Sudden loss or diminution of muscle tone without apparent preceding myoclonic or tonic event lasting one to two seconds or more, involving head, trunk, jaw or limb musculature.

Astatic: Loss of erect posture that results from an atonic, myoclonic or tonic mechanism. Synonym: drop attack.

Dystonic: Sustained contractions of both agonist and antagonist muscles producing athetoid or twisting movements which when prolonged may produce abnormal postures.

Hyperkinetic: Involves predominantly proximal limb or axial muscles producing irregular sequential ballistic movements, such as pedalling, pelvic thrashing, rocking movements. *Or:* Increase in rate of ongoing movements or inappropriately rapid performance of a movement.

Relating to *Epileptic Syndromes*:

Epilepsy syndrome: a complex of clinical features, signs, and symptoms that together define a distinctive, recognizable clinical disorder.

Epileptic encephalopathy: a condition where "the epileptiform EEG abnormalities themselves are believed to contribute to a progressive disturbance in cerebral function." T his category is not specific or limited to particular conditions, though often found in:

- early myoclonic encephalopathy, early infantile epileptic encephalopathy (Ohtahara syndrome)
- West syndrome, severe myoclonic epilepsy in infancy (Dravet syndrome), migrating partial seizures in infancy, myoclonic status in non-progressive encephalopathies
- Lennox-Gastaut syndrome (LGS), Landau-Kleffner syndrome (LKS), and epilepsy with continuous spike-waves during slow wave sleep (CSWS).

Contexts:

Terms which refer to the way in which an EEG may be **displayed:**
Derivation, Montage: *Bipolar, average reference, Common reference, Laplacian*

EEG Waveforms (activities*)* have a *morphology, amplitude* and *spatial distribution* and may have a *polarity* and/or be *rhythmic* or appear as *transients.*

The distribution of EEG activities may be described as:
Generalised, Symmetrical, Bilateral, Lateralised, Regional, Focal, Multifocal.

Normal EEG features (Wake/Sleep)
Wakefulness: *alpha rhythm, mu rhythm, lambda waves*
Sleep: *K complex, sleep spindles, Vertex waves, POSTS, (Slow activities)*

Abnormal waveforms/patterns
Spikes, Spike-wave complexes, Burst-suppression, 3/s generalised spike-wave complexes, Hypsarrhythmia, PLEDs, Recruiting rhythm.

Epilepsia, 51(4):676–685, 2010
doi: 10.1111/j.1528-1167.2010.02522.x

SPECIAL REPORT

Revised terminology and concepts for organization of seizures and epilepsies: Report of the ILAE Commission on Classification and Terminology, 2005–2009

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Summary

The International League Against Epilepsy (ILAE) Commission on Classification and Terminology has revised concepts, terminology, and approaches for classifying seizures and forms of epilepsy. Generalized and focal are redefined for seizures as occurring in and rapidly engaging bilaterally distributed networks (generalized) and within networks limited to one hemisphere and either discretely localized or more widely distributed (focal). Classification of generalized seizures is simplified. No natural classification for focal seizures exists; focal seizures should be described according to their manifestations (e.g., dyscognitive, focal motor). The concepts of generalized and focal do not apply to electroclinical syndromes. Genetic, structural–metabolic, and unknown represent modified concepts to replace idiopathic, symptomatic, and cryptogenic. Not all epilepsies are recognized as electroclinical syndromes. Organization of forms of epilepsy is first by specificity: electroclinical syndromes, nonsyndromic epilepsies with structural–metabolic causes, and epilepsies of unknown cause. Further organization within these divisions can be accomplished in a flexible manner depending on purpose. Natural classes (e.g., specific underlying cause, age at onset, associated seizure type), or pragmatic groupings (e.g., epileptic encephalopathies, self-limited electroclinical syndromes) may serve as the basis for organizing knowledge about recognized forms of epilepsy and facilitate identification of new forms.

KEY WORDS: Epilepsy, Classification, Syndrome, Seizure, Organization.

The history of classification has rested largely upon astute observations and expert opinions. First published in 1960 and last updated officially in 1981 for seizures (Commission on Classification and Terminology of the International League Against Epilepsy [ILAE], 1981) and 1989 for epilepsies (Commission on Classification and Terminology of the International League Against Epilepsy, 1989), the ILAE classifications are based on concepts that, for the most part, predate modern neuroimaging, genomic technologies, and concepts in molecular biology. The original authors foresaw that changes to the classification would be needed as new information was acquired and as new investigative technologies were developed. This is no simple task. Attempts have been made to update the 1989 and 1981 documents (Engel, 2001, 2006); however, no new proposal has been forthcoming.

A primary motivation for revising the classification in the 2005–2009 Commission term and to continue revising it in the future is to bring epilepsy out of the

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shadows of expert opinion and assertion-dominated arguments so that the classification of the epilepsies fully reflects and profits from all of the other advances being made in basic and clinical neurosciences and so that those advances can be incorporated into clinical practice. In the following report we present the main findings and recommendations of the Commission's deliberations during the 2005–2009 term accompanied by comments interleaved with the main text. The comments provide background, explanations, and justifications for these decisions and provide some insight into the variety of considerations that were addressed and why specific decisions were made.

Although changes have been made to terminology and concepts, we emphasize that no changes (other than to nomenclature) are being made to the list of epilepsy entities (''syndromes'') already recognized and updated in the 2006 Task force report (Engel, 2006). Furthermore, the revisions made to terminology and concepts in epilepsy do not have any tangible impact on how clinicians use the electroclinical syndromes that have been internationally recognized and that are applied to people with epilepsy around the world every day.

Terminology and Concepts for Classification of Seizures and Epilepsies

Mode of seizure onset and classification of seizures

Generalized epileptic seizures are conceptualized as originating at some point within, and rapidly engaging, bilaterally distributed networks. Such bilateral networks can include cortical and subcortical structures, but do not necessarily include the entire cortex. Although individual seizure onsets can appear localized, the location and lateralization are not consistent from one seizure to another. Generalized seizures can be asymmetric.

Focal epileptic seizures are conceptualized as originating within networks limited to one hemisphere. They may be discretely localized or more widely distributed. Focal seizures may originate in subcortical structures. For each seizure type, ictal onset is consistent from one seizure to another, with preferential propagation patterns that can involve the contralateral hemisphere. In some cases, however, there is more than one network, and more than one seizure type, but each individual seizure type has a consistent site of onset. Focal seizures do not fall into any

Comments: Introduction

Within the context of epilepsies and seizures, the word ''classification'' has been used to refer to at least three concepts:

1. The list of entities that are recognized as distinct forms of epilepsy: Nothing has changed in the elements of this list for specific types of electroclinical syndromes, although the list of seizures has been simplified from previous versions.

2. The concepts and structure underlying the organization and presentation of that list: The 1989 classification (Commission, 1989) was an organization built on concepts that no longer correspond to or accurately describe our increasing knowledge of seizures and the epilepsies. Consequently, the current organization and the concepts on which it is based are abandoned or revised. The dimensions by which we characterize seizures and epilepsies should represent useful, natural classes. Furthermore, the order and organization of the list of recognized syndromes need not be singular, constrained, or rigid but should be flexible to reflect our best current understanding of the neurobiology, the clinical features, prognostic implications, and any other features relevant to clinical practice or research.

3. The methods and process that determine which entities are recognized and those features by which those entities are organized: The expert-opinion review process for ''admitting'' a syndrome to the list will need to be replaced by a system based upon objective analysis and assessment of relevant evidence. This will be required to provide leads for new potential syndromes and some guidance into the natural classes and dimensions by which a scientific classification could be constructed (Berg & Blackstone, 2006). We intend to initiate such a process in the future.

In reviewing the current classifications, such as they are, and in modifying terminology and concepts, the Commission's work was aided by proceedings of the Monreale workshop (Capovilla et al., 2009). Although we set forth a revised, simplified classification for seizures, we did not find that there was an adequate knowledge base currently to propose a new classification (in the sense of organization) of epilepsies. Rather we have provided new terminology and concepts that better reflect the current understanding of these issues. A guiding principle has been to strive for clarity and simplicity so that terms refer to single qualities and are not a mixture of different concepts and dimensions. Another guiding principle has been, to the greatest extent possible, not to accept assumptions and assertions as the basis for classification and to acknowledge areas for which we do not have good information for making decisions. We present new concepts, but acknowledge them as concepts in need of further development and evidence (e.g., for generalized and focal seizures).

Comments: Classification and terminology as it relates to seizures:

The Commission accepted the ILAE definition of epileptic seizure (Fisher et al., 2005): ''a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain.'' Therefore, the comments are limited to describing epileptic seizures and are not designed to assist the clinician in distinguishing epileptic seizures from nonepileptic events. This will be treated separately in a diagnostic manual.

The terms ''focal'' and ''generalized'' have been used to express a dichotomous classification for both seizures and the epilepsies. In fact in the late 1800s, Hughlings-Jackson wrote that focal discharging lesions caused both focal and generalized seizures (see York & Steinberg, 2009). For seizures, based on current electroclinical evidence, the Commission felt that it was still of some pragmatic utility to maintain the terminology, although it was generally acknowledged that these terms likely did not represent a clear dichotomy.

The conceptualization of generalized seizures as arising in and rapidly engaging bilaterally distributed networks was, in part, an attempt to address the apparently generalized nature of spasms in the context of a focal lesion. This could represent a paradigmatic breakthrough in thinking about manifestations versus underlying pathology. There was much lively discussion and at times bitter disagreement over how best to classify spasms, as generalized or focal or both. In the end, the considerable collective knowledge of spasms represented by the various Commission members was still not up to the task of resolving this issue precisely because of inadequate information. Spasms are thus left on their own.

The 1981 seizure document used the terms simple partial, complex partial, and partial seizures secondarily generalized (Commission, 1981). This terminology was imprecise, as the terms ''simple'' and ''complex'' were often misused or misunderstood. Moreover, the distinction based on impairment of consciousness or awareness, although of great pragmatic social importance (e.g., for driving), was impossible to define precisely (Gloor, 1986). The term ''secondarily'' generalized is poorly understood and inconsistently used. Currently, we have inadequate information to create a *scientific classification* within focal seizures. Instead, we recommend that focal seizure be described according to features that are the most useful for a given specific purpose. For example, in many circumstances such as the differential diagnosis of epileptic versus nonepileptic events or in presurgical evaluation it is often useful to describe the specific elemental features of seizures and their sequence of occurrence (Luders et al., 1993). Others may wish to recognize terms to describe degree of disability caused by the seizures. We encourage those interested to consult the Glossary of Ictal Semiology (Blume et al., 2001) for well-defined descriptive terms.

recognized set of natural classes based on any current understanding of the mechanisms involved.

The following specific changes to the 1981 classification of seizures have been made.

1. Neonatal seizures are no longer regarded as a separate entity. Seizures in neonates can be classified within the proposed scheme.

2. The previous subclassification of absence seizures has been simplified and altered. Myoclonic absence seizures and eyelid myoclonia are now recognized.

3. Spasms were not explicitly acknowledged in the 1981 classification of seizures. They are now included. The term ''epileptic spasms,'' which includes infantile spasms, was recognized previously (Blume et al., 2001). Because spasms may continue past or even occur de novo after infancy (Camfield et al., 2003, Goldstein & Slomski, 2008), the more general term ''epileptic spasms'' is used. There was inadequate knowledge to make a firm decision regarding whether spasms should be classified as focal, generalized, or both; consequently, they have been placed in their own group as unknown.

4. For focal seizures, the distinction between the different types (e.g., complex partial and simple partial) is eliminated. It is important, however, to recognize that impairment of consciousness/awareness or other dyscognitive features, localization, and progression of ictal events can be of primary importance in the evaluation of individual

Table 1. Classification of seizures[a]

Generalized seizures
Tonic–clonic (in any combination)
Absence
Typical
Atypical
Absence with special features
Myoclonic absence
Eyelid myoclonia
Myoclonic
Myoclonic
Myoclonic atonic
Myoclonic tonic
Clonic
Tonic
Atonic
Focal seizures
Unknown
Epileptic spasms

[a]Seizure that cannot be clearly diagnosed into one of the preceding categories should be considered unclassified until further information allows their accurate diagnosis. This is not considered a classification category, however.

Comments: Terminology and concepts for underlying cause:

The terms idiopathic, symptomatic, and cryptogenic have taken on a variety of meanings and connotations laden with presumptions which, at times, conflate multiple concepts into a single word. This has resulted in considerable contradiction and confusion. The term idiopathic was defined in the 1989 document: ''There is no underlying cause other than a possible hereditary predisposition. Idiopathic epilepsies are defined by age-related onset, clinical and electrographic characteristics, and a presumed genetic etiology.'' We now state a minimum threshold for presuming a form of epilepsy does in fact have a genetic basis. Undocumented assertions are not accepted. Examples of epilepsy syndromes that would be classified as genetic epilepsies include childhood absence epilepsy, autosomal dominant nocturnal frontal lobe epilepsy, and Dravet syndrome. Note that in the 1989 classification, Dravet syndrome was not classified as idiopathic epilepsy. Dravet is now considered as a genetic epilepsy.

The term ''idiopathic'' was also used to convey the idea of a highly pharmacoresponsive form of epilepsy. Many, although not all, of the traditional ''idiopathic'' epilepsies also spontaneously remit during a predictable age range (a separate quality or dimension) and were generally thought to be unaccompanied by other consequences or disabilities, although this is clearly not the case, as a variety of subtle cognitive and behavioral disorders are seen in association with these epilepsies.

The new terminology and concepts require that the concept of cause contain only one dimension and not be used to imply others. Cause is no longer equated with prognosis, and the implication that ''idiopathic'' confers the quality of ''benign'' is intentionally discarded. It is possible that the genetic defect may have other effects in addition to the seizures but, as best we can tell, these other effects are not interposed between the genetic effect and the seizures.

The term ''symptomatic'' is a truism; all epilepsy is symptomatic of something. It is often substituted for the concept of a poor prognosis. The term ''structural and metabolic'' is intended to highlight that there is a separate disorder the relationship of which to epilepsy is not as direct. The grouping of structural and metabolic disorders together is only to distinguish this concept from that of genetic (i.e., genetic vs. all else). Depending on the purposes, it will be necessary to subdivide these heterogeneous causes further starting with separate groups for structural and for metabolic. Within each of these subdivisions, further taxa will be elaborated (e.g., for malformations, gliomas, and mitochondrial disorders). Other ILAE Commissions and other groups around the world are tackling these very issues.

''Cryptogenic'' was defined in 1989 as ''presumed symptomatic,'' apparently meaning ''lesional.'' It is, however, from among these ''cryptogenic'' epilepsies that genetic electroclinical syndromes such as autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) and autosomal dominant epilepsy with auditory features (ADEAF) have been discovered (Scheffer et al., 1995; Ottman et al., 1999). In replacing the term ''Cryptogenic'' with ''unknown,'' the Commission discarded the notion that a clinical hunch should be the basis of a scientific classification.

Examples of syndromes that would be classified as ''of unknown cause'' include epilepsy of infancy with migrating focal seizures and myoclonic epilepsy in infancy [formerly benign myoclonic epilepsy of infancy, (Engel, 2006)]. At the present time, it might be reasonable to include some of the traditional electroclinical syndromes previously classified as ''idiopathic'' in the unknown category as well. These include benign rolandic epilepsy (Vadlamudi et al., 2006), Panayiotopoulos syndrome, and benign occipital epilepsy of the Gastaut type (Taylor et al., 2008). It is likely that genetic factors are involved in these syndromes. Current *evidence* (e.g., low or absent concordance in siblings) does not suggest that genetic factors are paramount. This issue will be revisited if high quality evidence supporting the hypothesis of a genetic contribution comes to light.

As new genetic contributions to epilepsy are recognized, it may often be difficult to know how best to characterize them with respect to the preceding distinctions. For example, *ARX*, a homeobox gene, is associated with phenotypic heterogeneity including West syndrome and lissencephaly (Stromme et al., 2002). *STXBP1* encodes a protein involved in synaptic vesicle release and is associated with Ohtahara syndrome (Saitsu et al., 2008). Both syndromes involve severe encephalopathic forms of epilepsy. In the first case, one might consider the *ARX* mutation in the structural/metabolic category. In the case of *STXBP1*, because of the function of the protein product, one might associate this with the concept of genetic epilepsy. No determination has been made in either case at this time. Instead the role of the specific genetic error should be recognized, but it is not necessary to pigeon-hole the cause of the disorder further unless there is an adequate basis for doing so. We advocate a focus on mechanisms. This focus should ultimately reveal the natural classes. The overly simplistic designation of ''genetic'' versus ''structural-metabolic'' will then be replaced by a more precise characterization of the underlying cause.

patients and for specific purposes (e.g., differential diagnosis of nonepileptic events from epileptic seizures, randomized trials, surgery). Nothing in this recommendation precludes describing focal seizures according to these or other features.

5. Myoclonic atonic (previously called ''myoclonic astatic'') seizures are now recognized.

Table 1 presents the list of recognized seizure types.

Descriptors of focal seizures

For pragmatic reasons and to facilitate continuity with the 1981 classification of seizures, descriptors of focal seizures may be used, individually or in combination with other features depending on the purpose. We have listed *examples* chosen to facilitate continuity with the 1981 seizure document and which have been drawn from the glossary of ictal semiology (Blume et al., 2001) (Table 2).

The classification of status epilepticus will be the subject of a separate report in the future.

Underlying type of cause (etiology)

Instead of the terms idiopathic, symptomatic, and cryptogenic, the following three terms and their associated concepts are recommended:

1. Genetic: The concept of genetic epilepsy is that *the epilepsy is, as best as understood, the direct result of a known or presumed genetic defect(s) in which* seizures *are the core symptom of the disorder. The knowledge regarding the genetic contributions may derive from specific molecular genetic studies that have been well replicated and even become the basis of diagnostic tests (e.g., SCN1A and Dravet syndrome) or the evidence for a central role of a genetic component may come from appropriately designed family studies.* Designation of the fundamental nature of the disorder as genetic does *not* exclude the possibility that environmental factors (outside the individual) may contribute to the expression of disease. At the present time, there is virtually no knowledge to support specific environmental influences as causes of or contributors to these forms of epilepsy.

2. ''Structural/metabolic'': Conceptually, there is a *distinct other structural or metabolic condition or disease* that has been demonstrated to be associated with a substantially increased risk of developing epilepsy in appropriately designed studies. Structural lesions of course include acquired disorders such as stroke, trauma, and infection. They may also be of genetic origin (e.g., tuberous sclerosis, many malformations of cortical development); however, *as we currently understand it*, there is a separate disorder interposed between the genetic defect and the epilepsy.

3. ''Unknown cause'': Unknown is meant to be viewed neutrally and to designate that *the nature of the underlying cause is as yet unknown;* it may have a fundamental genetic defect at its core or it may be the consequence of a separate as yet unrecognized disorder.

Table 2. Descriptors of focal seizures according to degree of impairment during seizure[a]

Without impairment of consciousness or awareness
With observable motor or autonomic components. This roughly corresponds to the concept of ''simple partial seizure. ''Focal motor'' and ''autonomic'' are terms that may adequately convey this concept depending on the seizure manifestations).
Involving subjective sensory or psychic phenomena only. This corresponds to the concept of an aura, a term endorsed in the 2001 Glossary.
With impairment of consciousness or awareness. This roughly corresponds to the concept of complex partial seizure. ''Dyscognitive'' is a term that has been proposed for this concept (Blume et al., 2001).
Evolving to a bilateral, convulsive[b] seizure (involving tonic, clonic, or tonic and clonic components). This expression replaces the term ''secondarily generalized seizure.''

[a]For more descriptors that have been clearly defined and recommended for use, please see Blume et al., 2001.

[b]The term ''convulsive'' was considered a lay term in the Glossary; however, we note that it is used throughout medicine in various forms and translates well across many languages. Its use is, therefore, endorsed.

Diseases, syndromes, and epilepsies

Disease versus syndrome

Although there is reason to distinguish the concepts of disease and syndrome, these terms are not consistently used in medicine. *Ultimately, it was decided not to insist on the disease–syndrome distinction in referring to the epilepsies at this time, although either or both terms have been and will continue to be used depending on the context and custom.* Instead, there are at least three or four groupings that may be invoked in this context and as described below:

Electroclinical syndromes: Henceforth, the use of the term ''syndrome'' will be restricted to a group of clinical entities that are reliably identified by a cluster of electroclinical characteristics. Patients whose epilepsy does not fit the criteria for a specific electroclinical syndrome can be described with respect to a variety of clinically relevant factors (e.g., known etiology and seizure types). This does not, however, provide a precise (syndromic) diagnosis of their epilepsy.

Constellations: In addition to the electroclinical syndromes with strong developmental and genetic components to them, there are a number of entities that are not exactly electroclinical syndromes *in the same sense* but which represent clinically distinctive *constellations* on the basis of specific lesions or other causes. These are diagnostically meaningful forms of epilepsy and may have implications for clinical treatment, particularly surgery. These include mesial temporal lobe epilepsy (with hippocampal sclerosis), hypothalamic hamartoma with gelastic seizures, epilepsy with hemiconvulsion and hemiplegia, and Rasmussen ''syndrome.'' Age at presentation is not a defining feature in these disorders, as we understand them; however, they are

sufficiently distinctive to be recognized as relatively specific diagnostic entities. *Whether or not they are considered* ''*electroclinical syndromes*'' *now or in the future is less important than that they be recognized by clinicians who are treating patients.*

Structural/metabolic epilepsies: The next group includes epilepsies secondary to specific *structural or metabolic lesions or conditions* but which do not, given our current understanding, fit a specific electroclinical pattern, although that may change in the future. Therefore, these entities represent a lower level of specificity than the two previous groups.

Epilepsies of unknown cause: Those epilepsies, which in the past were termed ''cryptogenic,'' will now be referred to as being of ''*unknown*'' *cause*.

Dimensions for classifying epilepsies and organizing information

In referring to syndromes, the dichotomy of focal versus generalized will be abandoned, that is, ''the focal or generalized epilepsies.'' This is intended to separate the manifestations from the underlying pathology that produced them.

Each syndrome and each patient can be characterized according to a large number of other features, which are often routinely part of any patient's evaluation and which are essential features in distinguishing among established syndromes. These include the age at onset, cognitive and developmental antecedents and consequences, motor and sensory examinations, EEG features, provoking or triggering factors, and patterns of seizure occurrence with respect to sleep.

Comments: Reestablishing the concept of ''electroclinical syndrome'' and recognizing the precision or imprecision of diagnosis.

Electroclinical syndromes: The 1989 report used the terms ''syndromes'' and ''epilepsies'' almost interchangeably. The result was that the term ''syndrome'' took on a broad and very imprecise meaning to the point where very specific and highly recognizable entities (such as childhood absence epilepsy) and poorly differentiated and not well-described epilepsies (such as cryptogenic parietal lobe epilepsy) tended to be treated as though they represented the same level of diagnostic precision. The result was a veneer of equivalency bestowed upon all entities identified within that document.

An electroclinical syndrome, however, is a complex of clinical features, signs, and symptoms that together define a distinctive, recognizable clinical disorder. These often become the focus of treatment trials as well as of genetic, neuropsychological, and neuroimaging investigations (e.g., Scheffer et al., 1998, 2008; Guerrini et al., 2007; Ottman et al., 2008). These are distinctive disorders identifiable on the basis of a typical age onset, specific EEG characteristics, seizure types, and often other features which, when taken together, permit a specific diagnosis. The diagnosis in turn often has implications for treatment, management, and prognosis. It would be inappropriate to refer to, for example, epilepsy with a frontal lobe focus and not otherwise specified as a ''syndrome.'' The currently recognized electroclinical syndromes are presented in the first part of Table 3 organized by typical age at onset, as this is one of the most distinctive and clinically salient dimensions for organizing these entities, but this is just an example of one way to organize them.

Constellations: Whether these entities should be considered syndromes or nonsyndromic epilepsies was the subject of considerable disagreement. Ultimately, these conditions can and should be recognized based on their clinical features. What they are called as a group in no way detracts from their clinical importance.

Epilepsies associated with structural or metabolic conditions: Previously, many such epilepsies were grouped together as ''symptomatic focal epilepsies'' and distinguished on the basis of localization. We recommend less emphasis be given to localization and more to the underlying structural or metabolic cause. Terms such as ''symptomatic temporal lobe epilepsy'' are replaced by longer but more precise expressions such as ''epilepsy with focal seizures secondary to cortical dysplasia in the temporal lobe.'' Localization is not, based on current knowledge, the primary factor of importance for understanding the cause and prognosis of these epilepsies. Further organizations might consider type of lesion, age at onset, localization, seizure type, specific ictal and interictal EEG patterns, or other factors.

Epilepsies of unknown cause: These epilepsies account for one-third or more of all epilepsy, are the most poorly understood, and represent perhaps the most fertile area for future research in imaging and genetics. For such research to be feasible, however, it will require that the simple characterization by localization of interictal focus (e.g., cryptogenic parietal lobe epilepsy) be replaced with a detailed characterization of all relevant features (see next section). Among these poorly differentiated epilepsies are likely to be additional genetic electroclinical syndromes (such as ADNFLE and ADEAF); however, they cannot be recognized until they are adequately characterized. This approach should also facilitate identification of nongenetic determinants of epilepsy.

Table 3. Electroclinical syndromes and other epilepsies

Electroclinical syndromes arranged by age at onset[a]
Neonatal period
Benign familial neonatal epilepsy (BFNE)
Early myoclonic encephalopathy (EME)
Ohtahara syndrome
Infancy
Epilepsy of infancy with migrating focal seizures
West syndrome
Myoclonic epilepsy in infancy (MEI)
Benign infantile epilepsy
Benign familial infantile epilepsy
Dravet syndrome
Myoclonic encephalopathy in nonprogressive disorders
Childhood
Febrile seizures plus (FS+) (can start in infancy)
Panayiotopoulos syndrome
Epilepsy with myoclonic atonic (previously astatic) seizures
Benign epilepsy with centrotemporal spikes (BECTS)
Autosomal-dominant nocturnal frontal lobe epilepsy (ADNFLE)
Late onset childhood occipital epilepsy (Gastaut type)
Epilepsy with myoclonic absences
Lennox-Gastaut syndrome
Epileptic encephalopathy with continuous spike-and-wave during sleep (CSWS)[b]
Landau-Kleffner syndrome (LKS)
Childhood absence epilepsy (CAE)
Adolescence – Adult
Juvenile absence epilepsy (JAE)
Juvenile myoclonic epilepsy (JME)
Epilepsy with generalized tonic–clonic seizures alone
Progressive myoclonus epilepsies (PME)
Autosomal dominant epilepsy with auditory features (ADEAF)
Other familial temporal lobe epilepsies
Less specific age relationship
Familial focal epilepsy with variable foci (childhood to adult)
Reflex epilepsies
Distinctive constellations
Mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE with HS)
Rasmussen syndrome
Gelastic seizures with hypothalamic hamartoma
Hemiconvulsion–hemiplegia–epilepsy
Epilepsies that *do not* fit into any of these diagnostic categories can be distinguished first on the basis of the presence or absence of a known structural or metabolic condition (presumed cause) and then on the basis of the primary mode of seizure onset (generalized vs. focal)
Epilepsies attributed to and organized by structural-metabolic causes
Malformations of cortical development (hemimegalencephaly, heterotopias, etc.)
Neurocutaneous syndromes (tuberous sclerosis complex, Sturge-Weber, etc.)
Tumor
Infection
Trauma
Angioma
Perinatal insults
Stroke
Etc.
Epilepsies of unknown cause
Conditions with epileptic seizures that are traditionally not diagnosed as a form of epilepsy per se
Benign neonatal seizures (BNS)
Febrile seizures (FS)

[a]The arrangement of electroclinical syndromes does not reflect etiology.

[b]Sometime referred to as Electrical Status Epilepticus during Slow Sleep (ESES).

Natural evolution of the disorder

Among the many dimensions that may be used for organizing forms of epilepsy, ''natural'' evolution is highlighted here because of its considerable importance in reflecting our growing understanding of the full nature of the epilepsies.

Epileptic encephalopathy. The concept of epileptic encephalopathy has grown in acceptance and use. It was formally recognized in the 2006 report and is now defined within this document. Epileptic encephalopathy embodies the notion that *the epileptic activity itself may contribute to severe cognitive and behavioral impairments above and beyond what might be expected from the underlying pathology alone (e.g., cortical malformation), and that these can worsen over time.* These impairments may be global or more selective and they may occur along a spectrum of severity. Although certain syndromes are often referred to as epileptic encephalopathies, the encephalopathic effects of seizures and epilepsy may potentially occur in association with any form of epilepsy.

Other concepts and terms. The terms catastrophic and benign *are not* recommended. The first has strong emotional overtones and thus is not considered an appropriate term for a diagnostic label or category. The second belies the growing understanding of the relationship between the epilepsies and a wide variety of brain disorders including cognitive, behavioral, and psychiatric illnesses as well as sudden death and suicide. ''Benign'' can be misleading and leave physicians, patients, and families unaware of and unprepared to address these associated disorders. That said, names of syndromes have not, at this time, been changed.

An interim organization (''classification'') of the epilepsies

In a departure from the 1989 classification of the epilepsies, there is no one specific organization proposed for the revised classification. Instead, the various forms of epilepsy (at all levels of specificity) will be organized according to those dimensions that are most relevant to a specific purpose. These may be comparable to those in the 1989 classification (seizure onset, ''etiology,'' and age at onset), a different hierarchical arrangement of these same dimensions, a more detailed version of these dimensions, or by entirely different dimensions as needed. For example, Table 3 provides a list of epilepsies from the Task Force on Classification and Terminology (Engel, 2006) according to level of specificity and within those designations, by age where meaningful.

Acknowledgments

During the Commission's 2005–2009 term, input was sought from experts in the genetics of epilepsy, neuroimaging, therapeutics, pediatric and adult epileptology, as well as statistics and research design. The results

Comments: Other dimensions for classifying epilepsies and organizing information:

The commission decided to discard the terms generalized and focal for modifying the epilepsies themselves. ''Generalized'' spasms arising from a focal lesion as occurs in West syndrome and focal seizures arising from a diffuse genetic disorder as occurs in Dravet syndrome were some of the prime examples of why and how these terms do not adequately reflect the processes underlying the epilepsies.

In addition to the traditional dimensions and features, each syndrome and each patient can be characterized according to a large number of other features, which are often routine parts of any patient's evaluation and essential features in distinguishing among established syndromes. These include the cognitive and developmental antecedents and consequences, motor and sensory examinations, EEG features, provoking or triggering factors, and patterns of seizure occurrence with respect to sleep. There is also an important traditional cluster of syndromes that might be convenient to maintain, the ''idiopathic generalized epilepsies;'' however, we recommend that they be called the ''genetic generalized epilepsies.''

Natural evolution: Epileptic Encephalopathy. The term ''epileptic encephalopathy'' can be used to characterize syndromes and also be applied to individuals. As a *domain for clustering and describing syndromes*, an epileptic encephalopathy is an electroclinical syndrome associated with a high probability of encephalopathic features that present or worsen after the onset of epilepsy. Separately but important to note, as a group, they tend to be pharmacoresistant, but this is another quality or dimension. Inclusion of a specific syndrome in the domain of ''epileptic encephalopathy'' does not imply that all individuals with these disorders will appear encephalopathic; however, the risk is often quite high. *Diagnosing an individual* as having an *encephalopathic course* requires demonstration of a failure to develop as expected relative to same-aged peers or to regress in abilities. Note that it is not necessary for an individual to have a syndrome identified as being one of the ''epileptic encephalopathies'' (e.g., West, Dravet) in order to have an encephalopathic course. Epileptic encephalopathy can present along a continuum of severity and may occur at any age. The phenomenon is most common and severe in infancy and early childhood, where global and profound cognitive impairment may occur. Adults, however, can also experience cognitive losses over time from uncontrolled seizures (Hermann et al., 2006). Whether these involve similar or different mechanisms as those early in development remains to be seen, but the phenomenon should be recognized.

Inherent in the concept of epileptic encephalopathy is the notion that suppression of epileptic activity may improve cognition and behavior. Early effective intervention may in fact improve seizure control and developmental outcome in some cases (Jonas et al., 2004; Freitag & Tuxhorn, 2005; Jonas et al., 2005; Lux et al., 2005).

''Epileptic encephalopathy'' should be viewed as a concept and a description of what is observed clinically with the recognition that, we are rapidly approaching a clearer understanding of the effects of epilepsy on brain function and the potential for lasting deleterious impact in the developing brain. We must, however, recognize that the source of an apparent encephalopathy is usually unknown. It may be the product of the underlying cause, the result of epileptic process, or a combination of both.

The argument against the term, ''*Benign*''*:* One of the new research Benchmarks of the National Institutes of Health for epilepsy research is to understand the various comorbidities of epilepsy including cognitive, behavioral, and psychiatric disorders as well as mortality (Kelly et al., 2009). There are international efforts underway to understand the mechanisms of sudden death and to educate patients and families of this risk and how it may be mitigated. Increasingly, basic science and clinical studies are illuminating the shared mechanisms between epilepsy and these various other disorders.

Self-limited: The terms ''idiopathic'' and ''benign'' captured important features of clinical relevance. We recommend that, instead of designating a group of syndromes as ''benign,'' we recognize the different qualities that make up the concept of benign and apply them specifically and consistently to individual forms of epilepsy. One of these features is predictable spontaneous remission. Instead of benign, we recommend the descriptive term ''self-limited'' to mean having a high likelihood of spontaneously remitting at a predictable age. If a better term is devised, that can be considered in the future.

Pharmacoresponsive: In syndromes designated as idiopathic, most cases tend to be pharmacoresponsive. Diagnosis of one of these syndromes allows, within a reasonable certainty, the prediction that the seizures will rapidly come under control with appropriate medication. As yet, we do not have perfect prediction, so some patients diagnosed with a particular syndrome may not be pharmacoresponsive; however, clinical prognostication was never an exact science. Labeling these syndromes as pharmacoresponsive may be more meaningful to clinicians and provide anticipatory guidance to families better than the term ''idiopathic,'' which requires explanation.

Of note, the inclusion of features that are descriptive of the natural evolution of a form of epilepsy is not, strictly speaking, based upon natural classes but rather on repeated observations and impressions. *They are included for pragmatic purposes*.

Age at onset: For grouping syndromes or individuals, age at onset categories are recommended as per standard use: neonate (<44 weeks of gestational age), infant (<1 year), child (1–12 years), adolescent (12–18 years), and adult (>18 years). For some purposes, it may be helpful to distinguish a category for elderly (>60 or >65). The age ranges are approximate and meant to be used only for convenience in describing already characterized forms of epilepsy. For individual patients, the exact age at onset or best approximation should be used, and greater precision for electroclinical syndromes is encouraged when possible.

Other features: Many other dimensions and features will ultimately be used in describing, classifying, and grouping the different forms of epilepsies and may prove to be more useful for organizing the epilepsies than those used in the 1989 Classification. We may ultimately classify by specific cause, for example, ion channelopathies and by specific ion channel genes, as is being done with prolonged QT syndrome (Johnsons et al., 2009). Alternatively, one could organize a subgroup of epilepsies by age at onset and association with s*pecific* types of cortical malformations (Lerner et al., 2009). Other dimensions would include but are not limited to detailed aspects of ictal and interictal EEG, structural neuroimaging findings, neurologic examination, and cognitive and psychiatric status.

A syndrome is characterized with respect to many factors. Knowing a given patient's syndromic diagnosis, provides key information about that patient's epilepsy, for example, likely age at onset, EEG patterns, likely responses to medications, and cognitive and developmental status. We can organize our information about these syndromes along the many dimensions by which they are characterized. The benefits of this approach for developing a diagnostic manual are considerable.

For epilepsies that do not fall into clear electroclinical syndromes and which are associated with structural–metabolic causes, the most natural and rational primary approach to organizing them seems to be by specific underlying cause or lesion. For epilepsies of unknown cause and predominately characterized by seizure onset, there is no natural class that validly sorts them into more homogeneous groups. The revised recommended approach explicitly acknowledges this. Forcing these partially or poorly characterized epilepsies into a system of classification for which they are not yet ready suggests greater knowledge than we currently have and impedes progress. Much greater effort should be invested in characterizing individual patients sufficiently to facilitate objective research into identifying previously unrecognized entities. This information can then be used as the basis for objective analyses to identify potential new ''syndromes'' (Berg & Blackstone, 2006). It will also greatly facilitate the use of the planned diagnostic manual, which will provide a guide with specific definitions and examples that will encourage clinicians to make the necessary, precise observations on all patients in order to make or exclude specific diagnoses.

Comments: Classification in the future:

The previous ''classifications'' of seizures and epilepsies were often treated as rigid doctrine. Epilepsy classification was dominated by expert opinion and assertion. Advances in all areas of investigation (epidemiology, electrophysiology, imaging, developmental neurobiology, genomics, computational neuroscience, and neurochemistry) have made it clear that such a simple and often autocratic approach does not do justice to the complexity of the underlying developmental and physiologic processes. Therefore, any classifications put forth by this Commission should be viewed as a guide to summarize our current understanding about seizures and epilepsies in a useful manner, one that is responsive to the needs to which it is put and flexible enough to incorporate new information as it develops.

Unfortunately, this remains an area where long-held beliefs and ignorance often clash with reason and evidence. For example, an overly melodramatic comment posted on the website stated that the Commission's rejection of the term ''benign'' to characterize epilepsy was ''*… a stone of death to all of us, who have campaigned for year that on evidence, a significant number of patients and mainly children have some forms of epilepsies … that are entirely benign with little or no detrimental consequences as documented with long term prospective studies over the last 50 years (…). The main consequences … are psychosocial resulting from equating them with epilepsy.*'' Such emotional assertions actively ignore the last several years of very productive research in the neurosciences and represent the kind of arguments that are no longer acceptable.

In the future, the Classification of the Epilepsies will essentially be a database. The features discussed earlier and other essential pieces of information will form the basis for a diagnostic manual. In the interim, we encourage people to conceptualize a future classification as a flexible, multidimensional catalog of features for organizing information about different epilepsies (or seizures) as appropriate for purposes of drug development, clinical and basic research, and of course, clinical practice.

of those deliberations were presented at the ICE in Budapest, 2009. Following comments received at the meeting, a written report was disseminated to the many ILAE chapters with an invitation to respond with feedback. The report was also posted on the ILAE website, again with an invitation to comment, and comments were posted on the website. We owe a special debt of gratitude to the many colleagues around the world who took the time to consider our proposals and convey their thoughts, suggestions, and critiques to us throughout this process. We also thank our colleagues Pawel Matykiewicz, Ruth Ottman, Philippe Ryvlin, and Peter Wolf for their input into some of our meetings. The process for approving this report followed that outlined in the Commission Operations Manual of the ILAE, 2009.

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Disclosure

None of the authors has any conflict of interest to disclose.

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Interictal Epileptiform Discharges in Persons Without A History of Seizures: What Do They Mean?

Elson L. So

Abstract: Interictal epileptiform discharge (IED) is rarely observed in healthy volunteers without a history of seizures, but higher rates of occurrence are reported in children than in adults. Higher rates are also observed among neurologic inpatients and outpatients without a seizure history, but the risk of subsequent unprovoked seizures or epilepsy is low in healthy volunteers and patients. An exception is the patients with autism spectrum disorders, attention deficit/hyperactivity disorder, or cerebral palsy, who are predisposed to epilepsy development. However, it is currently unclear whether epilepsy risk is higher for patients with incidentally detected IED than for the patients without IED. Hospitalized patients with IED but no prior seizures often have underlying acute or progressive brain disorders. Although they have increased risk of acute seizures, the risk for subsequent unprovoked seizures or epilepsy is unknown and requires assessment on an individual basis. For patients who have psychogenic spells but no seizure history, the rate of IED detection is low, similar to that of healthy volunteers. The association between IED and transitory cognitive impairment has not been established in nonepileptic persons. Evidence thus far does not suggest that routine EEG screening of pilot candidates reduces risk of flight-related accidents.

Key Words: EEG, Epilepsy, Interictal epileptiform discharges, Seizures.

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The best known types of interictal epileptiform discharge (IED) are the spike and sharp wave, either of which can occur with or without a subsequent slow wave. Spikes have been defined as "a transient clearly distinguished from the background activity, with pointed peak at conventional paper speeds and a duration from 20 to under 70 milliseconds, i.e., 1/50–1/14 seconds, approximately. Main component is generally negative [compared] to other areas" (International Federation of Societies for Electroencephalography and Clinical Neurophysiology, 1983) (Fig. 1). A sharp wave discharge differs from a spike only in its longer duration, with a range of 70 to 200 milliseconds (Fig. 2). It should be considered a variation of spike activity; as such, both have the same clinical significance. More importantly, descriptions of sharp wave discharge as an IED should be distinguished from those of normal background activity, which uses terminology such as "sharply contoured waves" and "sharp transients."

Spike and sharp wave discharges are more commonly focal in distribution, but they can also be generalized, either as independently appearing waveforms or as components of complexes of different waves. Examples of the latter are generalized, atypical, spike-and-slow-wave discharges (Fig. 3) and, uncommonly, 3-Hz spike-and-wave discharges.

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Detection of IED in the clinical practice is invaluable for diagnosing epilepsy, classifying seizure type, and localizing the seizure focus. However, IED are also encountered in persons with no seizure history. The detection of IED in such persons raises questions regarding the probability of future seizures and whether that probability justifies treatment with antiepileptic drugs (AED) or restriction of activities such as driving, flying aircraft, or playing sports. The objective of this article is to review the prevalence of IED in persons without a seizure history and to discuss the implications of IED detection in these persons.

NONSEIZURE SETTINGS IN WHICH IEDs MAY BE IDENTIFIED

EEG has endured the rapid advances in brain imaging technology because of its unique role in evaluating abnormal brain function, its wide availability, and relatively low cost. Therefore, EEG is regularly used in many clinical practice situations other than evaluation of epileptic seizure disorders (Box). The yield of EEG in some of these conditions is arguable, but EEG is still commonly performed in these scenarios.

All too often, the question of an unrecognized seizure disorder is raised as the indication for performing EEG (Williams et al., 2002). For children, inattention, unsatisfactory school performance, or behavioral disorders often lead to neurologic evaluation that includes EEG. This course of action is not totally unfounded. Children with epilepsy have a 2.5-fold higher risk of attention deficit/hyperactivity disorder (ADHD) than children without epilepsy (Hesdorffer et al., 2004). The increased risk of ADHD is antecedent to epilepsy onset; therefore, the ADHD risk cannot be attributed to seizure episodes or AED treatment.

EEG is also used as a screening test for aircraft pilot candidates. The advent of clinical EEG in the late 1930s coincided with the rise in deployment of military aircraft during World War II. The next decades saw the establishment and expansion of civilian air travel. With these developments, both civilian and military authorities assumed that EEG would be a good screening test to help with pilot selection.

Syncopal and psychogenic events frequently are encountered in clinical practice, especially in neurologic practice. Up to 30% of patients undergoing spell evaluation receive the diagnosis of psychogenic spells (Lancman et al., 2001). With or without simultaneous video-recording, EEG is regularly conducted to evaluate syncope and psychogenic spells. EEG and video features of these conditions have been well characterized (Brenner, 1997; French, 1995), but limitations in the reliability between video-EEG reviewers for psychogenic spells have been reported (Benbadis et al., 2009). The observation of IED always raises concern of misdiagnosis in a patient who otherwise has evidence only of psychogenic spells (Iriarte et al., 2003).

Standard EEG is no longer routinely required before initiating electroconvulsive therapy. The risk of a prolonged seizure that is induced during the first electroconvulsive therapy session is only 1% to 2%, and prolonged seizures are usually shorter than 3 minutes

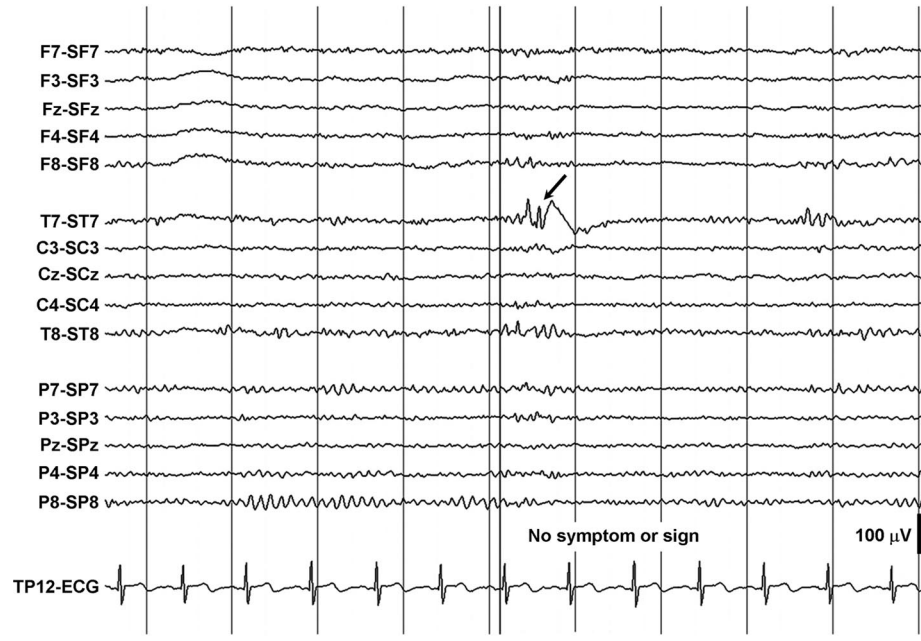

FIGURE 1. EEG Tracing in a Laplacian montage. The arrow denotes a left temporal spike. The interval between grid lines represents 1 second. The patient was a 78-year-old woman. EEG was performed to help evaluate a 5-year history of episodic visions of serrated wheel-like phenomena, with alternating areas of dark and light that would enlarge slowly and migrate inferiorly in her visual field. The visual experience was followed more recently by head or eye pain. The patient recalled that an EEG, performed when she was 50 years old, had shown abnormalities on the left side of her head. She was advised to initiate antiepileptic drug treatment at that time, but she declined the advice.

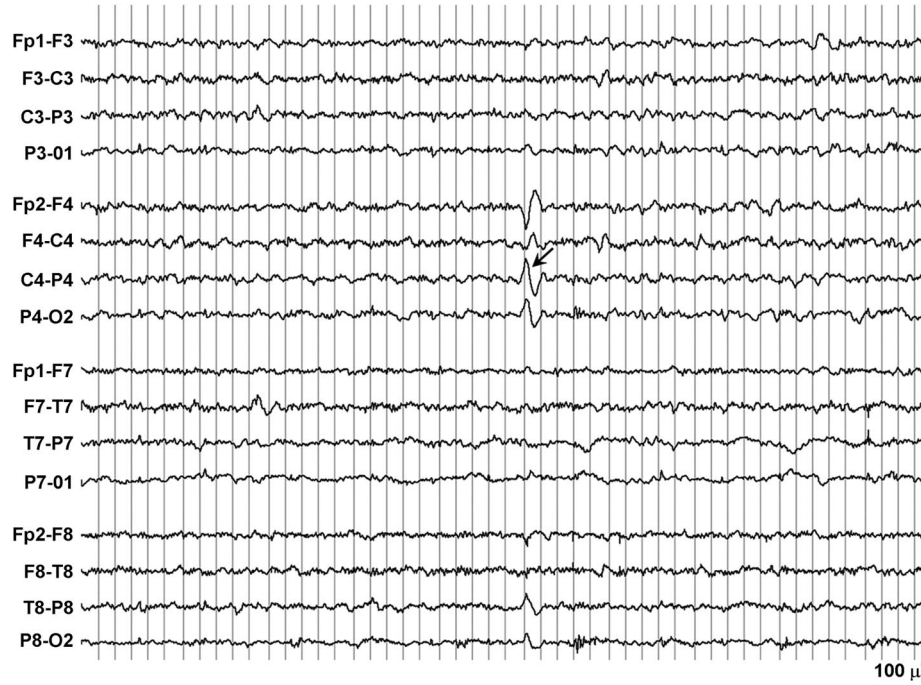

FIGURE 2. EEG tracing. The arrow denotes a right temporal sharp wave. The interval between grid lines represents 200 milliseconds. The patient was a 24-year-old man with easily provoked outbursts of anger.

(Whittaker et al., 2007). Nonetheless, a history of episodic behavioral dysfunction or behavioral change after electroconvulsive therapy has warranted EEG recording.

An established indication for EEG is the evaluation of traumatic and nontraumatic encephalopathy (Kaplan, 2006; Young, 2007). EEG provides diagnostic and prognostic information for different types of obtundation or coma (Young, 2000). The increasing use of EEG monitoring in patients with encephalopathies and coma is due to the observation that subclinical seizures or status epilepticus are not uncommon in these patients (Jirsch and Hirsch, 2007). Some centers have implemented routine EEG monitoring of critically ill patients.

A recent critical review of the literature described numerous studies of EEG in the evaluation of dementia (Jelic and Kowalski, 2009). Although the usefulness of routine EEG in patients with dementia has not been convincingly established, patients with Alzheimer disease and other dementias have a sixfold higher risk of unprovoked seizures than the general population (Hesdorffer et al., 1996). Consequently, EEG is still performed to assess episodic behavioral changes in patients with dementia. Also, the usefulness of clinical and quantitative EEG in differentiating between various types of dementia continues to be investigated (Gawel et al., 2009; Pijnenburg et al., 2008; Schreiter Gasser et al., 2008).

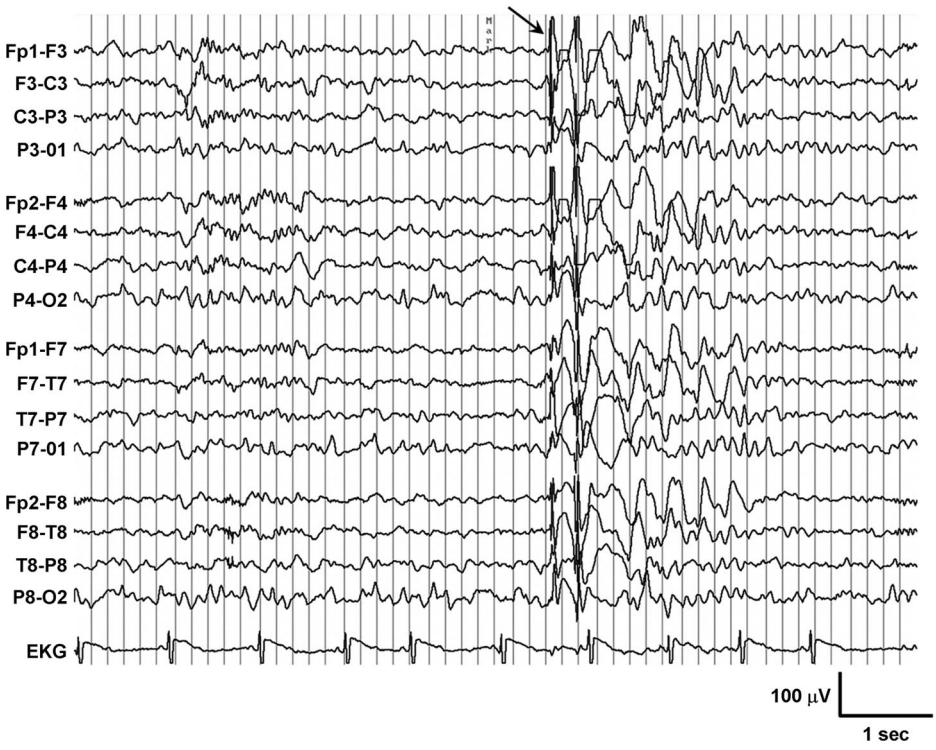

FIGURE 3. EEG tracing. The arrow denotes a generalized, atypical, spike-and-slow-wave discharge during sleep. The patient was a 40-year-old woman who was considered for electroconvulsive treatment for intractable depression. Her son had childhood-onset epilepsy.

BOX. Clinical Practice Settings in Which Interictal Epileptiform Discharges May Be Identified[a]

1. School-age children—screening, attention deficit and hyperactive disorder, performance issues
2. Air crew and air traffic controller candidates
3. Spell evaluations, especially psychogenic events, syncope, and sleep-related events
4. Before electroconvulsive therapy
5. After head trauma
6. Acute encephalopathies
7. Dementia evaluations
8. Polysomnograms

[a]These patients do not have a history of seizures.

The standard protocol of polysomnogram review is not ideal for detection of IED because of limited scalp coverage of the recording and the compressed time scale of EEG display. However, given that nocturnal seizures are often in the differential diagnosis of parasomnias and other sleep-related events (Bazil, 2004; Nobili, 2007), a montage of full-head EEG recordings has been selectively used in polysomnographic recordings for patients with nocturnal paroxysmal events. The longer duration of EEG recording in polysomnograms, especially of sleep activity, is considered an advantage over routine EEG recordings for detecting IED.

TYPES OF IED STUDIES IN PERSONS WITHOUT A SEIZURE HISTORY

IED have been detected in various groups of persons without a seizure history and in different settings. A review of the literature in 2001 showed that these persons with IED range from young children to adults (Table 1) (Sam and So, 2001). In 1940s, clinical application of EEG was just beginning, two decades after its discovery by Hans Berger. Clinicians and investigators needed to assess the specificity of IED for clinical disorders. Therefore, many EEG studies were subsequently performed in healthy volunteers for the purpose of determining the prevalence of IED in the general population. Some studies assessed only children (Brandt and Brandt, 1955; Brandt et al., 1961; Cavazzuti et al., 1980; Corbin and Bickford, 1955; Doose et al., 1968; Eeg-Olofsson et al., 1971; Herrlin, 1954; Okubo et al., 1985, 1993), whereas others confined the study population to adults (Gibbs et al., 1943; Jabbari et al., 2000; Kooi et al., 1964).

In addition to healthy children and adult volunteers, two particular cohorts of persons without a seizure history were also studied with EEG for IED: neurologic patients and aircrew candidates. In the first group, inpatients and outpatients were studied, mostly in an attempt to gauge the specificity of IED for seizure disorders and to assess the prognosis for seizure occurrence in those who had brain injury (Bridgers, 1987; Doose et al., 1968; Iida et al., 1985; Sam and So, 2001; Zivin and Marsan, 1968). As mentioned earlier, EEG routinely was used to screen military and civilian aircrew candidates, but fewer countries now use EEG for this purpose.

PREVALENCE OF IED IN PERSONS WITHOUT A SEIZURE HISTORY

The prevalence of IED in persons without a seizure history must be assessed according to patient age and health status. Also, a distinction should be made between IED that are spontaneous and those that are activated by photic stimulation or hyperventilation. A review of the literature shows that the prevalence rates of spontaneous IED in healthy children volunteers vary from 0% to 5.6% (Table 1) (Brandt and Brandt, 1955; Cavazzuti et al., 1980; Corbin and Bickford, 1955; Doose et al., 1968; Eeg-Olofsson et al., 1971; Herrlin, 1954; Okubo et al., 1993; Sam and So, 2001). Similarly, the

TABLE 1. Summary of Studies of IED of Persons Without Epilepsy[a]

Study	Type of Patient	No. Patients	Benign Transients	Patients With IED (%)					Duration of Follow-Up	Seizure Development (%)
				EEG Recording State						
				Unspecified	Wake and Drowsy	Sleep	Photic Stimulation	Hyperventilation		
Gibbs et al. (1943)	Volunteers, ≥20 years	1,000	Not excluded	0.4[b]	—	Not done	Not done	—	None	NA
Williams (1944)	Healthy aircrew	241	Not excluded	0.8	—	—	—	—	None	NA
Buchthal and Lennox (1953)	Predominantly male air force applicants	682	Not excluded	NA	2.6	Not done	2.2	0.3	None	NA
Herrlin (1954)	Nonepileptic children	70	Not excluded	NA	0	Not done	1.4	0	None	NA
Brandt and Brandt (1955)	Healthy children, <5 years	135	Not excluded	—	0.7	Not done	Not done	Not done	None	NA
Corbin and Bickford (1955)	Healthy children, 1–10 years	71	—	NA	5.6	Not done	Not done	0	None	NA
Larsson and Weden (1958)	Control subjects, ≥7 years	120	Not excluded	0.8	—	Not done	Not done	—	None	NA
Kooi et al. (1964)	Predominantly male volunteers, 26–81 years	218	Not excluded	—	6.6	—	—	—	None	NA
Bennett (1967)	Predominantly male aviators	1,332	Not excluded	0.6	—	—	—	—	None	NA
Doose et al. (1968)	Neurologically healthy children	118	Not excluded	0.8	—	Not done	—	—	None	NA
Zivin and Marsan (1968)	Inpatients in tertiary care	6,497	Not excluded	2.0	—	—	0.2[c]	0	Few months to 10 years	14.1
Eeg-Olofsson et al. (1971)	Healthy children, 1–15 years	743	Excluded 14 and 6 positive spikes	NA	1.9	8.1[d]	8.3[d]	0.3	None	NA
Cavazzuti et al. (1980)	Neurologically healthy children, 6–13 years	3,726	Excluded 14 and 6 positive spikes, high-voltage nonepileptiform synchronous activities, and "excessive sensitivity" to hyperventilation	—	3.5	Not done	Not done	0	—	5.3
Iida et al. (1985)	Nonepileptic outpatients	10,473	Not excluded	8.1	—	—	—	—	—	1.5[e]
Bridgers (1987)	Nonepileptic psychiatric inpatients, 11–85 years	3,143	Excluded	1.0	—	—	—	—	None	NA
Gregory et al. (1993)	Aircrew trainees, 17–25 years	13,658	Excluded 6-Hz spike-wave and positive spikes	0.2	—	—	0.3	—	5.0–29.0 years	2.3
Okubo et al. (1993)	Healthy children, 6–12 years	1,057	Excluded, except small sharp spikes	5.0	—	—	—	—	1.0–5.8 years	6.0
Jabbari et al. (2000)	Healthy male volunteers, 18–45 years	100	Excluded	0	0	0	0	0	None	NA
Sam and So (2001)	Community outpatients and inpatients	521	Excluded	—	10.5	1.2	0.6	0	230.8 person-years	6.3 acutely provoked seizures, no unprovoked seizures

Adapted from Sam and So (2001) with permission. [a]Excluding studies of (1) only relatives of persons with epilepsy, (2) the effect of pharmacologic and photic stimulation in healthy subjects, and (3) patients with brain injury (e.g., cerebral palsy, mental retardation, perinatal brain damage, or brain trauma). [b]Spike-wave discharges, 3/s. [c]Spontaneous discharges: 0.13% with and 0.07% without. [d]Includes nonepileptiform paroxysmal activities. [e]Based on 202 patients who had two separate EEGs with abnormal findings. ED, epileptiform discharges; NA, not applicable.

rates of spontaneous IED in healthy adult volunteers vary from 0% to 6.6% (Gibbs et al., 1943; Jabbari et al., 2000; Kooi et al., 1964). The prevalence rates of spontaneous IED reported in patient groups are overall higher than those of healthy volunteers. The rates in groups of inpatients and outpatients (or both) range from 2% to 12% (Bridgers, 1987; Iida et al., 1985; Sam and So, 2001; Zivin and Marsan, 1968). The higher prevalence rates observed in patients is expected because these nonseizure patients would still have had some neurologic complaint or condition to warrant referral for EEG. In one study, nearly three-fourths of nonseizure patients with IED had acute or progressive brain disorders (Sam and So, 2001).

Shelley et al. (2008) recently conducted a review of the extensive literature on EEG in nonseizure patients with psychiatric disorders and in children with neurobehavioral disorders. EEG abnormalities had been observed in up to 50% to 70% of patients with psychiatric and neurobehavioral disorders, but many of the abnormal EEG findings were not epileptiform. They included slowing of the background, which could be due to drowsiness, concomitant nonepileptic cerebral disorders, or medication effects. One retrospective study reported that 60% of patients with autism spectrum disorders (but no prior seizures or EEG abnormality) had IED detected by 24-hour ambulatory digital EEG (Chez et al., 2006). The majority of the IED (55%) were temporal in location. The EEG normalized in approximately 47% of a subgroup of patients who received valproic acid, with another 17% showing EEG improvement. The remarkably high IED rate of 60% may be partly explained by the high association between autism and epilepsy, with nearly 40% of autistic persons reported to have epilepsy (Danielsson et al., 2005). The other explanation for the high IED rate detected in the study is that the EEG performed were 24-hour, prolonged, ambulatory recordings (a routine EEG procedure typically records for an hour or less). The authors of the study had commented that their yield of IED detected with 24-hour, ambulatory recording was twice that detected with routine EEG.

Definite epileptiform abnormalities have been reported in 30% of children with ADHD but no prior seizures (Hughes et al., 2000). Most of the IED detected were focal at the occipital or temporal regions. Other EEG studies of nonseizure ADHD children showed lower IED rates of 5% to 15% (Hemmer et al., 2001; Holtmann et al., 2003; Richer et al., 2002). The value of EEG and the implications of IED in this subgroup of patients remain uncertain (Richer et al., 2002).

Many studies omitted or did not mention photic stimulation or hyperventilation procedures (Sam and So, 2001). The prevalence of photoparoxysmal response (PPR) ranges from 2.0% to 8.9% (Verrotti et al., 2004). Higher rates may include nonepileptiform abnormalities such as EEG slowing (Eeg-Olofsson et al., 1971). The risk of seizure occurrence after incidentally recorded PPR is very small. A study of 33 nonepileptic persons with PPR showed that none had seizures develop during an average follow-up duration of 9 years (So et al., 1993). However, this favorable finding is most likely age dependent. PPR in many persons is due to an autosomal, inherited trait that has age-dependent penetrance (Waltz and Stephani, 2000). In that study, seizure onset of the patients with PPR and epilepsy occurred at an average age of 9 years, whereas PPR was recorded incidentally in nonepileptic persons at an average age of 17 years. Therefore, incidentally recorded PPR in the first decade of life (or soon after) may still be associated with seizure risk, although the risk is generally believed to be small (Verrotti et al., 2004).

PPR discharge that exceeds the end of photic stimulation initially was thought to be associated with a higher seizure risk than when the entire discharge was confined to the stimulation period (Reilly and Peters, 1973). Findings of two later studies failed to support this notion (Jayakar and Chiappa, 1990; So et al., 1993). In fact, the waveform appearance of PPR in persons without seizures is indistinguishable from the PPR in persons with epilepsy (So et al., 1993).

Two studies reported rare IED activation by hyperventilation, affecting only 0.3% of persons without a seizure history (Buchthal and Lennox, 1953; Eeg-Olofsson et al., 1971). One study reported an unusually high rate of 8% activation by hyperventilation (Eeg-Olofsson et al., 1971). However, the high rate also included nonepileptiform abnormalities.

LIMITATIONS OF IED PREVALENCE STUDIES IN PERSONS WITHOUT A SEIZURE HISTORY

Although it can be said that IED prevalence in persons without a seizure history is generally low, the prevalence rates among studies vary by as much as eightfold. The wide variation suggests differences in EEG recording techniques and differences in the subjects studied. Few studies specifically excluded benign transients that resemble IED (Cavazzuti et al., 1980; Eeg-Olofsson et al., 1971; Gregory et al., 1993; Jabbari et al., 2000; Okubo et al., 1993; Sam and So, 2001; Shelley et al., 2008). Only one or two types of benign transients were specifically excluded in some of the studies. Many types of benign transients are frequently mistaken for epileptiform discharges (Benbadis, 2007); wicket waves are probably the patterns most frequently interpreted as epileptiform sharp waves (Fig. 4) (Benbadis, 2007; Krauss et al., 2005). Even nonspecific fluctuations of the background EEG could be mistaken for epileptiform discharges. Benbadis and Lin (2008) reported a series of 34 nonepileptic patients with background EEG fluctuations that were misinterpreted as temporal sharp waves (n = 30), frontal sharp waves (n = 2), and generalized sharp waves (n = 2).

Early EEG studies of IED in persons without a seizure history were very limited in terms of the recording duration and the number of recording electrodes. Studies were as short as 10 minutes or were obtained using only three scalp electrodes (Bennett, 1967; Gibbs et al., 1943). One study was conducted using EEG samples from awake activity only (Brandt and Brandt, 1955). Activation procedures such as hyperventilation and photic stimulation were not consistently conducted across studies during the EEG procedure (Sam and So, 2001). Many of the early EEG studies were also performed before the establishment of diagnostic criteria that defined specific clinical entities, especially for psychiatric, cognitive, and behavioral disorders.

The type of study population strongly influences the rate of EEG detection of IED. The reported rates increase from healthy adult and children volunteers (up to 6%), to nonseizure and non-predisposed patients (up to 12%), to nonseizure but predisposed patients (up to 60%). Moreover, retrospective studies are most likely to be influenced by referral or selection bias, when patients with seizure risks are more frequently referred for EEG procedures. This probability was underscored by authors who reported a very high IED rate of 60% in their patients with autism spectrum disorders (Chez et al., 2006).

A type of IED that has not been reported in persons without a seizure history is temporal intermittent rhythmic delta activity (TIRDA) (Fig. 5) (Reiher et al., 1989). This type of IED was not widely recognized until the past decade. It is currently unclear whether TIRDA occurs in persons without a seizure history. If future studies of TIRDA should determine that it does not occur in persons without seizures, TIRDA may be designated as a more specific correlate of seizure history than other types of IED.

RISK OF SEIZURES SUBSEQUENT TO IED DETECTION IN PERSONS WITHOUT A SEIZURE HISTORY

The important issue raised by incidentally recorded IED is how to determine the risk of subsequent epileptic seizure occur-

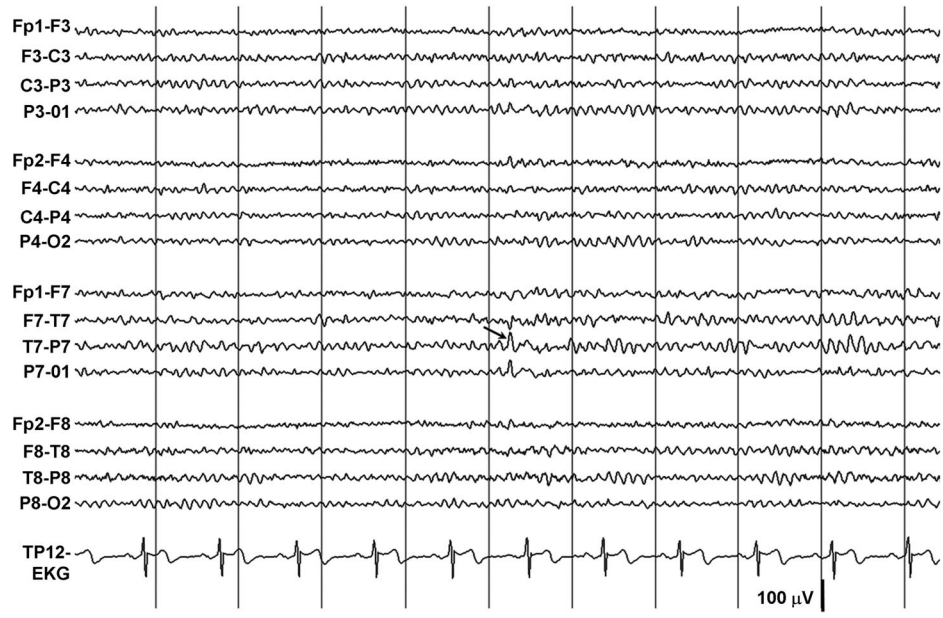

FIGURE 4. EEG tracing. The arrow denotes a wicket wave. The interval between grid lines represents 1 second. The patient was a 65-year-old woman who had daily, prolonged spells of feeling distant from her surroundings. She also had a history of panic attacks and anxiety.

rence. Few studies have reported rates of seizure occurrence after IED observation. Differences in seizure occurrence rates seem to be influenced by the populations being studied. The highest seizure rate reported was 14%, but the study involved a referral hospital and patients who were more likely to have cerebral disorders than subjects from other studies (Zivin and Marsan, 1968). In contrast, a study of nonseizure outpatients and inpatients in a nonreferral community population showed a much lower rate for provoked seizures (6.3%) and no unprovoked seizures or epilepsy (Sam and So, 2001). Of note, that study specifically asked whether seizure occurrence was provoked or unprovoked. Provoked seizures are due to acute structural or functional disturbance of the brain (e.g., stroke, head trauma, and electrolyte imbalance), whereas acute cerebral disturbance is absent in unprovoked seizures. The distinction between provoked and unprovoked seizure occurrence has important therapeutic and prognostic implications (So, 2006). Compared with persons who had an unprovoked seizure occurrence, persons with provoked seizures are five times less likely to subsequently experience unprovoked seizures (Hesdorffer et al., 2009). Moreover, the acute factors that underlie provoked seizure occurrence are often remediable. Therefore, chronic AED therapy is generally not necessary for provoked seizure occurrences (So, 2006).

Compared with nonseizure patients, healthy volunteers generally have lower rates for seizures after IED detection. Among healthy volunteers, children have higher seizure occurrence rates than adults (approximately 6% versus 2%) (Cavazzuti et al., 1980; Gregory et al., 1993; Iida et al., 1985; Okubo et al., 1993). The reason for the difference in the seizure occurrence rates is not clear. Duration of follow-up may be a reason, but the "survival phenomenon" may also contribute to the difference (i.e., IED hypothetically develop early in life in all subjects, and the risk of seizure occurrence may be higher in the first few years after IED development). The types of IED observed in healthy children volunteers may also be different from IED observed in healthy adult volunteers.

Unfortunately, no information is available regarding the rate of subsequent seizure development in nonseizure patients who are reported to have high IED rates (Shelley et al., 2008). With rare exceptions, the studies are retrospective, and many patients were empirically treated with AED.

IED DETECTION IN AIRCREW CANDIDATES

Pilot applicants make up the largest group of aircrew and traffic controller candidates who have been evaluated with EEG. A review of the literature shows that the rate of IED in these candidates ranges from 0.5% to 5.0% (Table 2) (Hendriksen and Elderson, 2001; Sam and So, 2001). The high rate of 5.0% is clearly an outlier (Buchthal and Lennox, 1953), considering that most studies reported rates of approximately 1% or less, and a few reported rates of 2.0% to 2.5% at the highest. The unusually high rate of 5% is almost certainly because of the administration of a convulsant, pentylenetetrazol, to subjects in the study.

Information regarding seizure occurrence after IED detection in aircrews is sparse. Follow-up is rarely performed for aircrew candidates who fail medical screening tests because of IED detection. Nevertheless, one report indicated that 1 in 20 aircrew candidates with IED subsequently had a seizure disorder develop during 10 years of follow-up (Robin et al., 1978). One review estimated a 25% probability of an aircrew candidate with IED subsequently having seizures (Hendriksen and Elderson, 2001). However, this high rate of seizure development could be due to selection bias in the type of patients whose follow-up information was available. Small sample sizes in many studies also reduce the reliability of the estimates of subsequent seizure rate.

Although only 1% or less of all aviation accidents is due to sudden incapacitation of the pilot (Hendriksen and Elderson, 2001), an epileptic seizure event is the most common medical disorder that causes sudden incapacitation because of loss of consciousness. This is likely the reason that EEG is used by many countries to scrutinize pilot candidates for risk of epileptic seizures. The crash rate because of pilot error is reportedly fourfold higher in pilots with abnormal EEG findings than in those with normal findings (Lennox-Buchthal et al., 1960). However, the association between EEG abnormalities and higher crash rates was not corroborated by results of a later study (Weber, 2002). The case-control study showed that serial EEG findings from 33 pilots killed in crashes were not different from 66 matched control pilots. In his review of publications on EEG as a screening tool in pilot applicants, Zifkin (2005) concluded that no evidence suggested that the practice reduced risk of flight-related

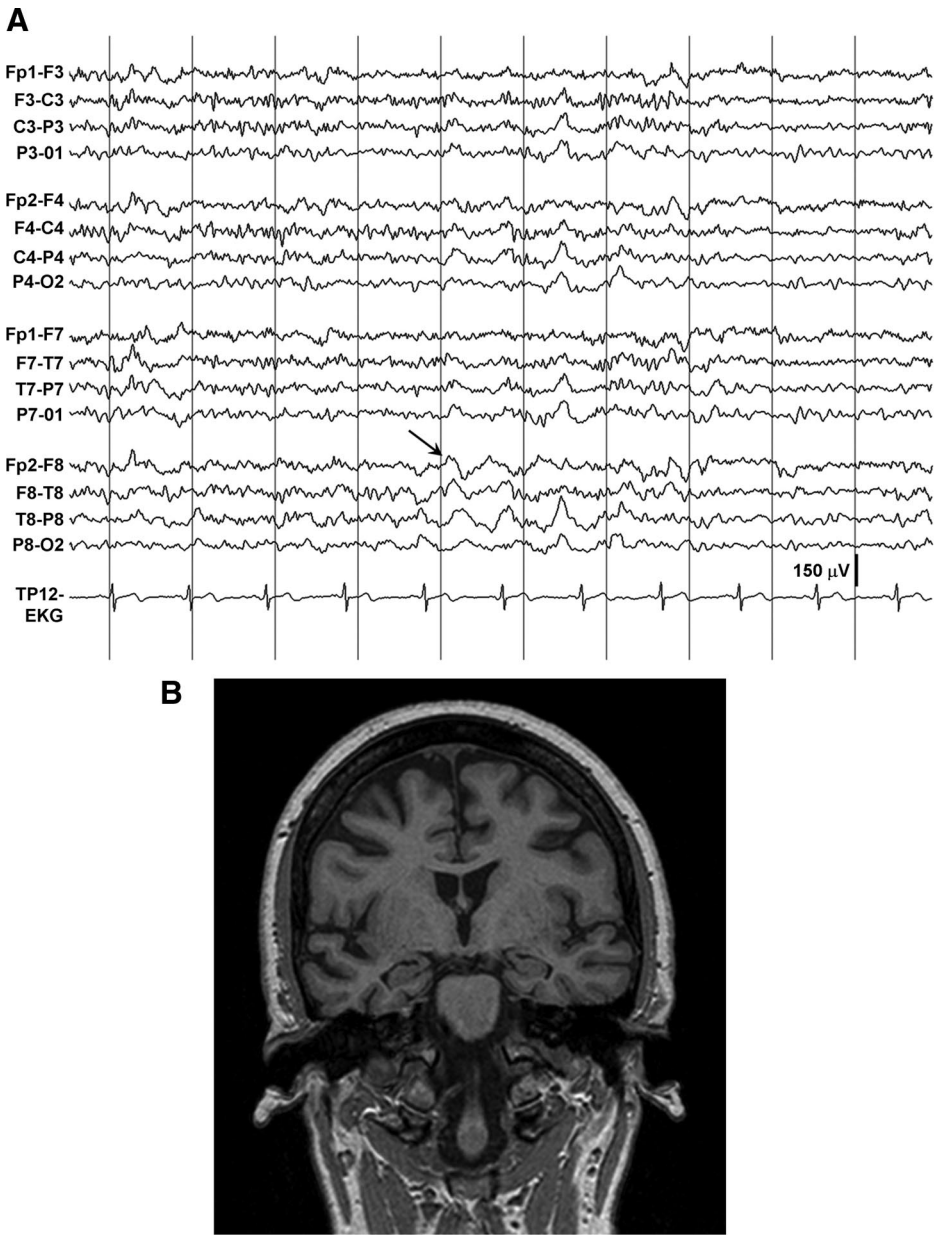

FIGURE 5. **A**, EEG tracing. The arrow denotes temporal intermittent rhythmic delta activity on the right side. The interval between grid lines represents 1 second. **B**, Magnetic resonance image. Marked, diffuse atrophy is apparent. The patient was a 56-year-old woman who presented with a 5-year history of progressive memory loss and fainting spells.

accidents. The low IED detection rate of 0.5% to 2.5% among young, healthy aircrew candidates and the low rate of subsequent seizure occurrences question the cost-effectiveness of routine EEG screening for qualifying aircrew candidates. Furthermore, aviation medical experts often disagree when interpreting EEG for pilot candidate assessment (Zifkin et al., 2005). The use of EEG as a screening tool in pilot candidates has been abandoned in the United States, Canada, and Australia, but it continues in many countries in Europe and Asia.

IED IN PATIENTS WITH PSYCHOGENIC SPELLS

Epileptic seizures are often included in the differential diagnosis when evaluating patients with psychogenic spells, and the converse is also true. Among all patients evaluated at referral epilepsy programs, the proportion with psychogenic spells is reportedly as high as 30% (Lancman et al., 2001). Moreover, at least 10% of patients with epilepsy have concomitant psychogenic spells (Lesser et al., 1983). Therefore, the detection of IED greatly influences the diagnosis and treatment of patients with suspected psychogenic spells. Ten percent of patients with psychogenic spells have been reported to have IED (Lesser, 1985). The proportion is even higher (26%) among elderly patients undergoing prolonged video-EEG monitoring (McBride et al., 2002). However, an exceptionally rigorous study that used multiple EEG reviewers who were blinded to clinical data showed that the rate of IED detection in patients with psychogenic spells is very low (2%), about the same as the rate in healthy control subjects (Reuber et al., 2002).

ARE IED REALLY CLINICALLY SILENT?

Generally, IED are considered to be clinically silent. However, several studies have shown that IED occurrence is associated with a transient alteration of behavior or mental performance (Aarts

TABLE 2. Incidence of Abnormal and Epileptiform EEGs and Follow-Up Results in Pilot Groups

Study	Subjects	Abnormal EEG	Epileptiform EEG	Follow-Up
Lachaud et al. (1971)	French pilot candidates, 18–22 years	152/2,700 (5.6%)	73/2,700 (2.7%)	—
LeTourneau and Merren (1973)	Naval aviation students, 19–29 years	38/28,658 (0.1%)	21/28,658 (0.1%)	1 of 31 with an abnormal EEG located had a seizure in 11 years of follow-up
Oberholz (1976)	German AF candidates, 17–57 years	61/973 (6.3%)	13/973 (1.3%)	—
Maulsby et al. (1976)	French AF pilots and other crew members	2,050/10,000 (20.5%)	250/10,000 (2.5%)	No seizures after 4–10 years
Robin et al. (1978)	US AF male aviators, 18–55 years	166/7,760 (2.1%)	76/7,760 (1.0%)	1 of 20 had a seizure during 10 years of follow-up
Everett and Akhavi (1982)	US AF Academy cadets, fourth year	85/2,947 (2.9%)	14/2,947 (0.5%)	No seizures after 10–15 years
Trojaborg (1992)	Royal Danish AF male applicants, 17–28 years	142/5,893 (2.4%)	Mainly paroxysmal (≤2.4%)	Four applicants had a seizure during EEG recording
Gregory et al. (1993)	Royal AF (United Kingdom) candidates, 17–25 years	—	69/13,658 (0.5%)	1 of 38 had a seizure during 5–29 years of follow-up
Ribeiro (1994)	AF pilot applicants and other crew applicants	92/2,015 (4.6%)	38/2,015 (1.9%)	One with a normal initial EEG had a seizure during 15 years of follow-up

Adapted from Hendriksen and Elderon (2001) with permission. AF, air force.

et al., 1984; Binnie et al., 1991). The observation has been termed "transitory cognitive impairment" (TCI). TCI can be observed with IED that are as brief as 0.5 seconds (Kasteleijn-Nolst Trenite and Vermeiren, 2005). In some patients undergoing driving simulation tests, TCI has resulted in lateral deviation of the simulated vehicle.

The association between IED and TCI in nonepileptic persons has not been established. TCIs have been observed mostly in patients with epilepsy who have frequent IED; furthermore, the observations are often made in the laboratory setting, using complex tasks to elicit the phenomenon. To increase the likelihood of observing TCI, subjects undergo rigorous testing, up to the limits of their capabilities (Binnie, 2003).

DOES AED TREATMENT OF IED HAVE A ROLE IN PERSONS WITHOUT SEIZURES?

Clinicians generally adhere to the principle of "treating the patient, not the EEG." Nonetheless, AED treatment of persons without a seizure history is considered for two reasons: (1) to prevent future seizure occurrence and (2) to improve behavior and cognition. Theoretically, partial blockade of *N*-methyl-D-aspartate receptors could potentially reduce long-term risks of seizure development (Staley and Dudek, 2006). Still, AED treatment for seizure prevention has not been pursued clinically because of the overall low risk of epilepsy development in nonseizure patients with IED and because of the frequent absence of IED on follow-up EEG, especially in children. Besides, experience with AED treatment to prevent the development of epilepsy in patients with brain trauma suggests that long-term compliance with AED intake is poor when the aim of treatment is prevention of epilepsy development (compliance is better for those seeking to control active epilepsy) (Temkin et al., 1990).

In contrast, persons with and without epilepsy have been treated with AED for the purpose of improving behavior or cognition through suppression of IED. The reason for the treatment is the suspicion that IED has the potential of disrupting behavior and impairing cognition. A double-blind, placebo-controlled study of children with epilepsy treated with lamotrigine showed that reduction in IED was associated with improved global ratings of behavior (Pressler et al., 2005). Although seizure improvement could have accounted for the behavioral improvement, patients reportedly did not have significant changes in seizure frequency during the study period. Cognitive decline in the number of epileptic syndromes with frequent IED, generally termed "epileptic encephalopathies," can sometimes be improved or arrested if AED treatment is associated with reduced IED (Holmes and Lenck-Santini, 2006).

Studies of AED effects on persons without epilepsy, which included IED, cognition, and behavior, consisted of only small numbers of patients. Although AED treatment could reportedly normalize EEG in persons with autism but no seizure history (Chez et al, 2006), no evidence suggests that EEG improvement is accompanied by cognitive or behavioral improvement (Binnie, 2003; Shelley et al., 2008). Also, IED are infrequent in many persons without seizures, and the effect of infrequent IED on baseline cognition or behavior is questionable. Moreover, many AED do not predictably suppress IED, especially focal IED. Also, the potential adverse effects on cognitive and behavioral function by AED treatment are well known.

COMMENTS

Currently, no evidence supports AED treatment of incidentally detected IED in persons without seizures, either for the prevention of subsequent epilepsy or for improving behavior or cognition. Moreover, if IED is detected in persons without seizure history, they often occur infrequently on the EEG recording and may not be observed in subsequent recordings.

The prognostic significance of IED in patients without a history of seizures deserves further study, particularly for patients with conditions such as cerebral palsy, autism spectrum disorder, or ADHD, which predispose them to epilepsy development (Boutros, 2009; Shelley and Trimble, 2009). However, the shortcomings of earlier studies of IED in persons without a seizure history should be avoided. EEG must be performed and reviewed using a standardized protocol that specifies the different types of epileptiform and nonepileptiform abnormalities. Reviews of the EEG recordings should

be performed while blinded to clinical findings, and IED should be quantitated. The value of AED treatment must be assessed with a randomized, double-blind, controlled trial with a large enough sample size to reasonably expect meaningful results.

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Prognostic Significance of Interictal Epileptiform Discharges in Newly Diagnosed Seizure Disorders

Elaine C. Wirrell

Abstract: EEGs performed for new-onset seizures show epileptiform discharge in approximately 18% to 56% of children and 12% to 50% of adults. An EEG after sleep deprivation improves detection of epileptiform abnormalities, showing discharge in 13% to 35% of patients whose standard EEG findings were normal. Some studies have also shown a higher yield with EEG performed within 24 hours after the seizure. The EEG is a useful diagnostic study in this clinical setting for a number of reasons. First, specific EEG abnormalities help characterize the seizure type and epilepsy syndrome, which allows more informed decisions regarding therapy and more accurate prediction of seizure control and ultimate remission. Second, in certain cases, the EEG may detect more subtle seizures, including absence, myoclonic, or partial seizures. Third, specific EEG patterns may alert the clinician to the presence of a focal cerebral lesion. Fourth, most studies have shown that an epileptiform discharge is predictive of seizure recurrence, particularly in patients with idiopathic epilepsy. In the presence of epileptiform discharge, the recurrence risk is approximately double what would be predicted after a normal EEG. The predictive value of nonepileptiform abnormalities is not clearly established.

Key Words: EEG, Epileptiform discharge, First seizure, New-onset epilepsy.

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Prospective, population-based studies have estimated the incidence of unprovoked seizures and epilepsy to be approximately 20 to 80 per 100,000 person-years (Adelow et al., 2009; Annegers et al., 1999; Christensen et al., 2007; Forsgren, 1990; Forsgren et al., 1996, 2005; Hauser et al., 1993; Jallon et al., 1997, 2001; Keranen et al., 1989; Olafsson et al., 1996, 2005; Oun et al., 2003; Sander et al., 1990; Sidenvall et al., 1993; Zarrelli et al., 1999). Many nonepileptic events can mimic seizures, including cardiogenic or vasovagal syncope, neurogenic syncope, transient ischemic attacks, sleep disorders, panic attacks, or behavioral events. A recent review showed that diagnosis of a "first seizure" is subject to considerable interobserver disagreement, with a misdiagnosis rate of up to 23% (van Donselaar et al., 2006). Diagnostic accuracy is crucial to facilitate appropriate investigations and management of the underlying condition.

The usefulness of an EEG in patients presenting with a first unprovoked seizure is a subject of debate (Fountain and Freeman, 2006). A meta-analysis addressing information gained with an EEG after a first unprovoked seizure in childhood concluded that neither positive nor negative findings were informative enough to affect recommendations for treatment (Gilbert and Buncher, 2000). However, a report from the Quality Standards Subcommittee of the American Academy of Neurology, Child Neurology Society, and American Epilepsy Society criticized this conclusion (Hirtz et al., 2000). They stated, "where the EEG is used as one of several variables, it can identify children with very high and very low recurrence risks." Furthermore, they noted that "the EEG is not used solely to determine recurrence, but

TABLE 1. Prevalence of Epileptiform Abnormalities in Children With New-Onset Seizures

Study	No. of Patients	EEG Timing	Epileptiform Abnormalities (%)
Scotoni et al. (2004)	213 first seizure	Late	18
Ramos Lizana et al. (2000)	217 first seizure or new-onset epilepsy	<48 hours	31[a]
Shinnar et al. (1994)	321 first seizure	Most late	32
Hamiwka et al. (2007)	94 first seizure or new-onset epilepsy	Most late	39
Camfield et al. (1985)	168	Not specified	43
Winckler and Rotta (2004)	109 first seizure	<7 days	46
Carpay et al. (1997)	552 first seizure or new-onset epilepsy	Not specified	56

[a]Did not distinguish epileptiform from other abnormalities.

TABLE 2. Prevalence of Epileptiform Abnormalities in Adults With New-Onset Seizures

Study	No. of Patients	Epileptiform Abnormalities (%)
van Donselaar et al. (1992)	157	12
Das et al. (2000)	76	16
Neufeld et al. (2000)	91	21
Schreiner and Pohlmann-Eden (2003)	157	27
Hopkins et al. (1988)	295	27 on first EEG
Forsgren et al. (1991)	103	27
Hui et al. (2001)	132	28
Lindsten et al. (2001)	104	30
Bora et al. (1995)	147	33
King et al. (1998)	300 (80% were age >16 years)	35
Kim et al. (2006)	1,420	43 on first EEG[a]
First Seizure Trial Group (1993)	387	50

[a]Did not distinguish epileptiform abnormalities from other abnormalities.

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also helps differentiate a seizure from other events, is essential to the diagnosis of a syndrome, and provides information on long-term prognosis; it influences the decision to perform subsequent neuroimaging studies and may influence counseling about management of the child." As such, they recommended performing an EEG after the first nonfebrile seizure in children. Similarly, a recent practice parameter from the American Academy of Neurology suggests routine performance of EEG in adults with new-onset seizures (Krumholz et al., 2007).

In this article, I review how frequently epileptiform abnormalities are identified in patients with new-onset seizures. Further, I address how EEG findings assist the clinician, specifically in the identification of seizure type and syndrome, in guiding further investigations and therapy, and in predicting seizure recurrence.

FREQUENCY OF EPILEPTIFORM ABNORMALITIES IN PATIENTS WITH NEW-ONSET SEIZURES

Numerous studies have documented EEG findings from children with first unprovoked seizures and new-onset epilepsy. These data are summarized in Tables 1 and 2. Overall, 18% to 56% of children and 12% to 50% of adults presenting with new-onset seizures showed epileptiform abnormalities on EEG, with abnormalities being slightly more common in patients presenting with new-onset epilepsy than patients presenting with the first unprovoked seizure.

Most studies have shown that an EEG obtained after a period of sleep deprivation improves detection of epileptiform abnormalities. Carpay et al. (1997) reported that 60 of 177 (34%) children with normal findings during a standard recording showed epileptiform abnormalities after sleep deprivation. Similarly, King et al. (1998) reported that 35% of adults and children whose initial EEG findings were normal showed epileptiform abnormalities on a subsequent study performed after sleep deprivation. However, sleep deprivation may be more important in patients with focal discharge. Shinnar et al. (1994) described 148 children who had both sleep and wakefulness recorded on a single EEG. Epileptiform discharge was identified in only one state in 30% of subjects, with generalized discharge more common during the awake state and focal discharge more common during the sleep state.

The literature is less clear on whether prevalence of epileptiform discharge on EEG is influenced by the time elapsed between the seizure and the EEG recording. In a large Australian study of children and

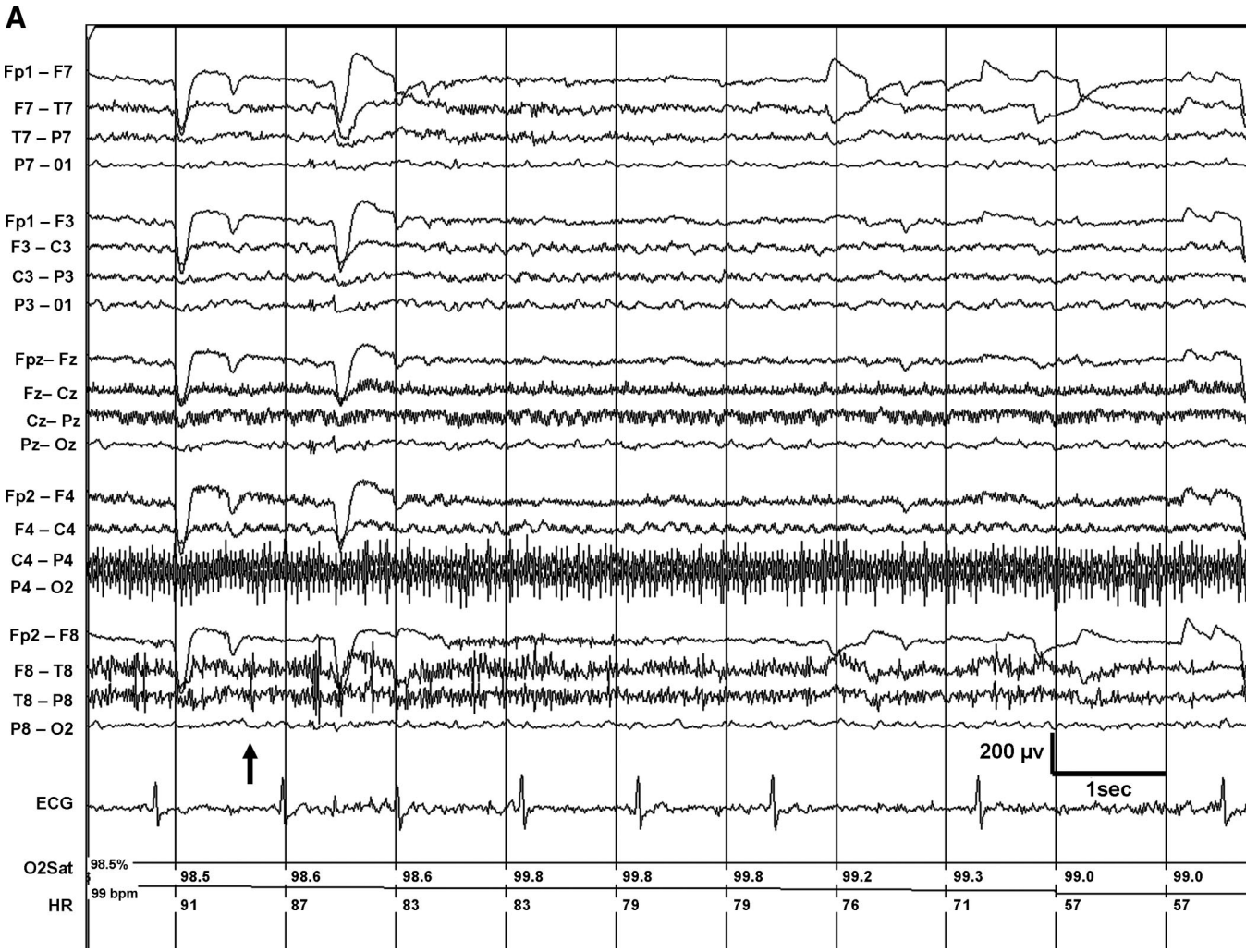

FIGURE 1. EEG of a 16-year-old girl with a recent loss of consciousness. The ECG lead shows bradycardia, followed by asystole (17 seconds) and spontaneous recovery. **A**, During the EEG, she indicated she felt another episode beginning (arrow). **B**, After asystole, the EEG shows generalized slowing and the patient fell (arrow). EEG suppression followed the slowing. ECG, electrocardiogram; HR, heart rate; O_2Sat, oxygen saturation.

adults after a first seizure, King et al. (1998) reported a higher rate of epileptiform abnormalities in EEGs performed within 24 hours (51%) than those performed after 24 hours (34%). However, another study of children compared diagnostic yields of early (<48 hours) versus late EEG and did not measure a significant difference in the rate of epileptiform abnormalities identified (Hamiwka et al., 2008). In many cases, scheduling of early EEG is not feasible because of late referral, difficulty contacting families, and parent work schedules. An early EEG often limits the opportunity to evaluate the patient in a sleep-deprived state; this limitation may offset the benefit of an early EEG. Furthermore, a very early EEG may show transient abnormalities (e.g., postictal slowing), which must be interpreted cautiously.

Although the prevalence of epileptiform abnormality is not significantly different between those with idiopathic versus symptomatic causes, nonepileptiform abnormalities are more common in the latter—25% versus 7% (Carpay et al., 1997; Shinnar et al., 1994). Specific seizure types also influence the likelihood of seeing epileptiform abnormalities on EEG, with higher rates in patients with absence seizures (92%) and atonic or myoclonic seizures (85%) compared with partial complex seizures (59%) or generalized tonic-clonic seizures (44%) (Carpay et al., 1997).

In summary, approximately one-third of patients presenting with new-onset seizures will show epileptiform abnormalities on the initial EEG. For patients with normal findings after a standard EEG, a subsequent recording after sleep deprivation will identify abnormalities in another third.

HELPFUL EEG FINDINGS FOR THE CLINICIAN

Identification of Nonepileptic Spells

Rarely, nonepileptic spells may occur during a routine EEG recording. In most laboratories, one channel is dedicated to electrocardiographic monitoring for detection of heart rate abnormalities in patients with cardiogenic syncope (Fig. 1). Recording respiration patterns may assist in the diagnosis of breath-holding spells or apnea. In addition, patients with nonepileptic behavioral spells often have events during the EEG recording. These spells are frequently triggered by suggestion, and normal occipital dominant activity is present during the period of apparent loss of consciousness.

Identification of Seizure Type

Accurate classification of seizure type helps guide decisions regarding the need for further investigations (e.g., blood tests and imaging studies). Unfortunately, the clinical history is often limited in patients with a presumed first seizure because seizure onset is either not witnessed or observers may be too frightened to recall specific details accurately. Thus, it can be difficult to determine whether a generalized tonic-clonic seizure

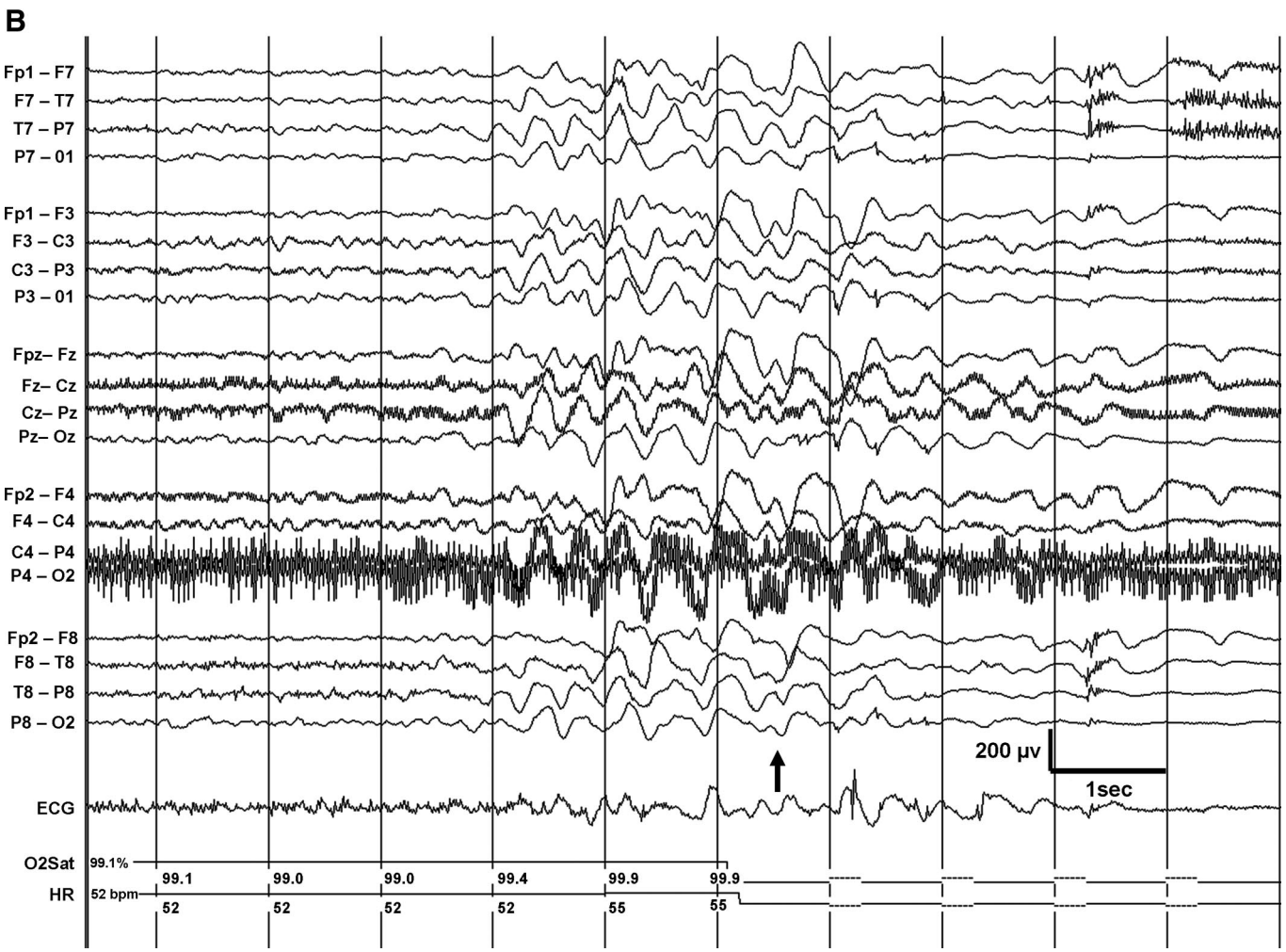

FIGURE 1. (*Continued*).

began focally. A partial onset is suggested by an EEG showing a focal epileptiform abnormality or focal slowing. In contrast, the presence of generalized spike-wave discharge would be consistent with generalized epilepsy.

In their first seizure cohort, King et al. (1998) were able to classify seizures into generalized versus partial in only 47% of cases after considering the medical history and physical examination findings alone. When EEG findings were considered, correct classification was possible in an additional 30%; thus, only 23% of seizures remained unclassified.

Identification of Epilepsy Syndrome

Classification of a seizure disorder into a specific epilepsy syndrome provides important clues about the presumed cause, needed investigations, probable responses to specific antiepileptic medications, likelihood of seizure control, and, in children, likelihood of eventual remission. Specific syndromes have a fairly characteristic EEG signature that, in conjunction with a supportive clinical history, may allow classification of a seizure disorder.

An example of this is shown in Fig. 2. Two 5-year-old boys presented with their first nocturnal, secondarily generalized seizures; both seizures began with twitching of the left side of the face. Figure 2A shows a normal background with characteristic right centrotemporal spikes and a morphology highly suggestive of benign, rolandic epilepsy. This child was neurologically and developmentally normal. He and his parents were reassured that he had an idiopathic, partial epilepsy that might not require prophylactic antiepileptic medication and would be outgrown by the teen years. In contrast, Fig. 2B shows signs of symptomatic partial epilepsy, with diffuse slowing, maximally in the right posterior temporal region, and right temporal sharp waves. A magnetic resonance image showed a right temporal lesion; during resection, a ganglioglioma was identified.

In the first seizure cohort of King et al. (1998), EEG and neuroimaging data were used to identify the specific epilepsy syndrome. Of 68 subjects with generalized epilepsy, 30 (44%) could be further classified into a specific syndrome. Of 175 subjects with partial epilepsy, 13 (7%) were classified as having a specific idiopathic partial

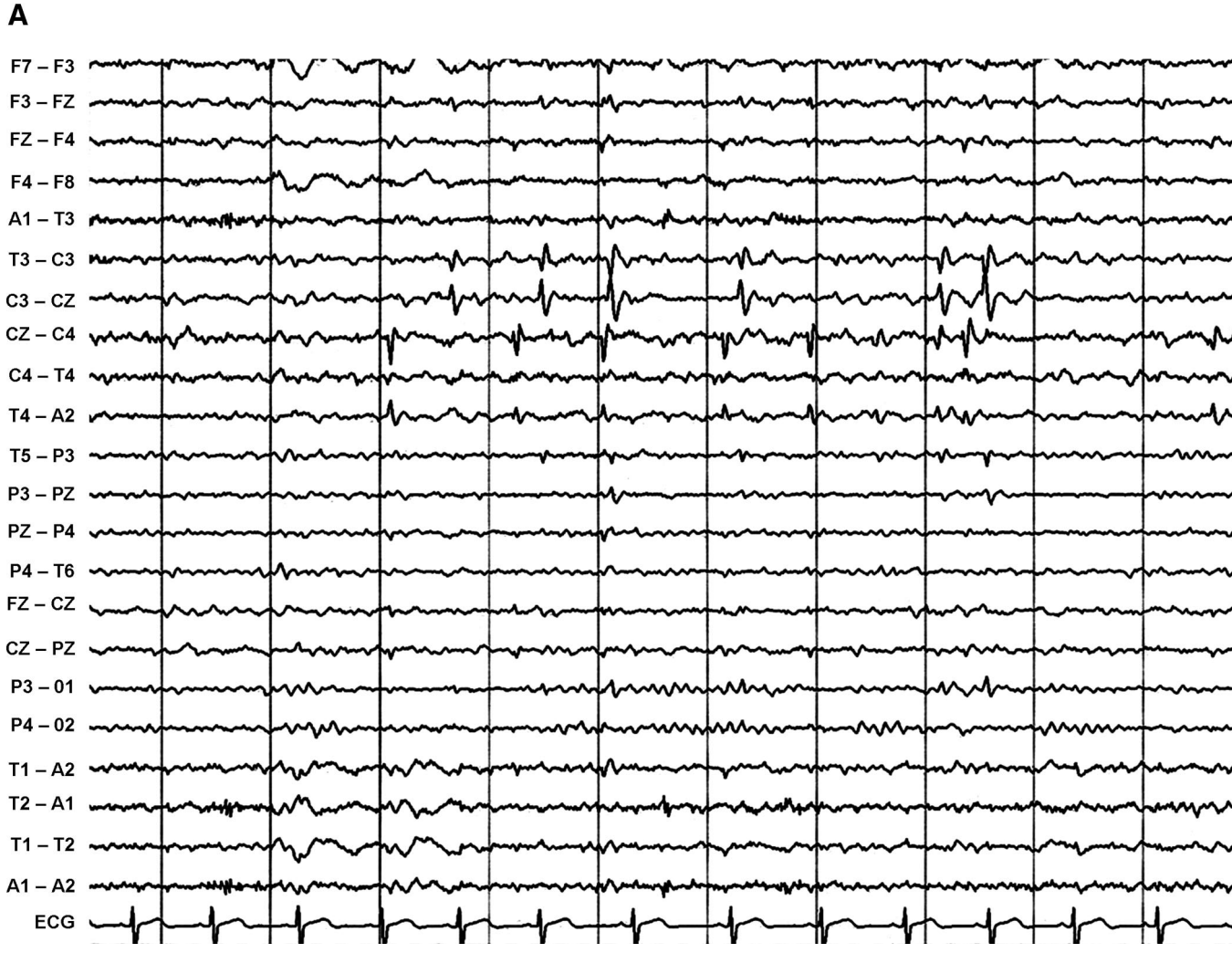

FIGURE 2. EEGs of two 5-year-old boys who had secondarily generalized seizures. **A**, The background is normal. Independent left central and right centrotemporal discharges are seen; these increased substantially during sleep (not shown) and are suggestive of benign, rolandic epilepsy with centrotemporal spikes. **B**, The background is slow, maximally in the right temporal region, and right temporal sharp waves are suggestive of symptomatic partial epilepsy. ECG, electrocardiogram; HR, heart rate; O_2Sat, oxygen saturation.

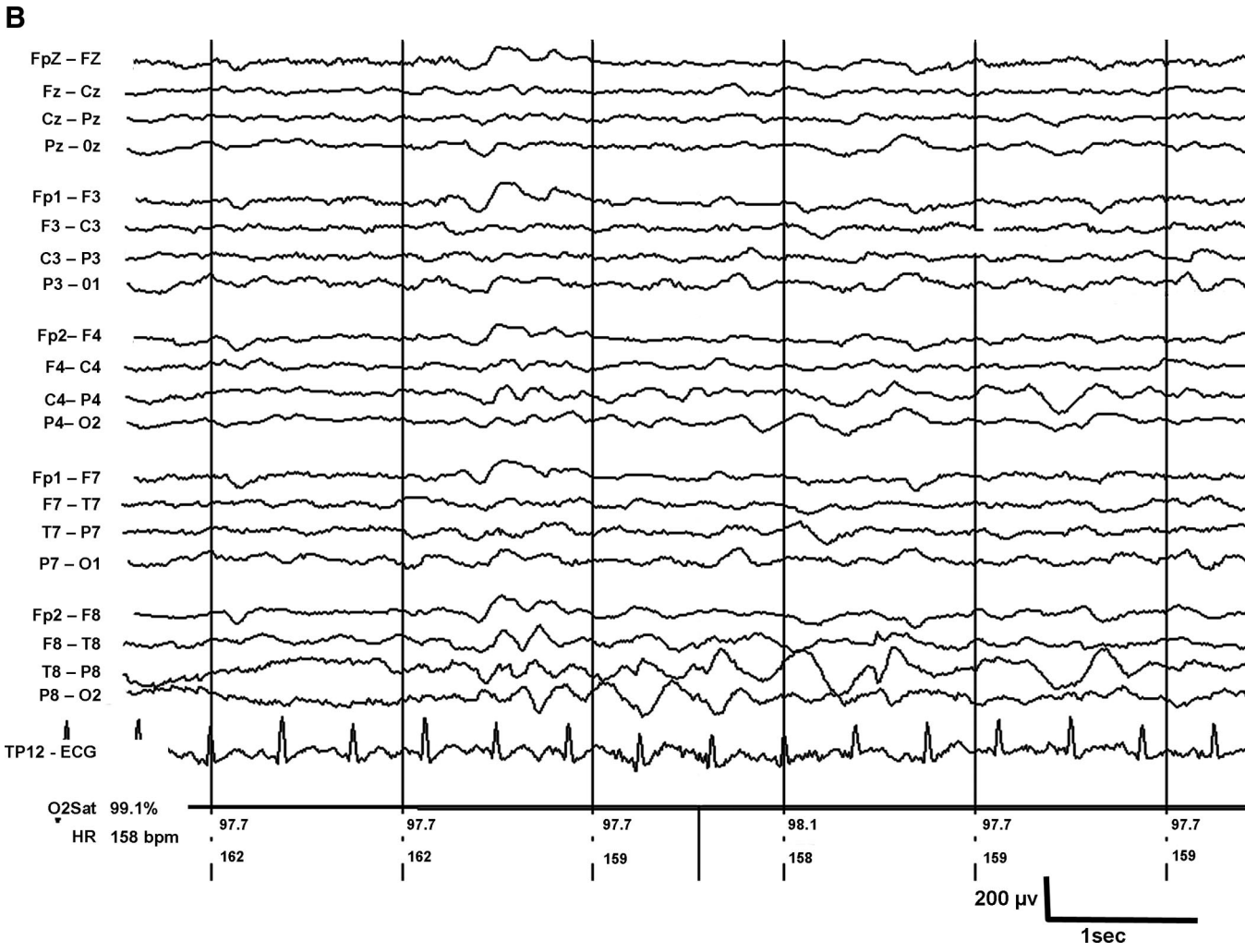

FIGURE 2. (*Continued*).

epilepsy syndrome, and 126 (72%) could be further localized to a specific lobe. In a large, French, multicenter study of new-onset seizures, Jallon et al. (2001) were able to assign epilepsy syndromes to just over half the patients on the basis of EEG and imaging results.

Detection of More Subtle Seizure Types

The first seizure that causes a patient to seek medical attention is frequently not the patient's actual first seizure (Hamiwka et al., 2007; King et al., 1998). Patients presenting to a first-seizure clinic often have a history of more subtle seizures (e.g., absence seizures and myoclonic or partial seizures) that were not recognized by the patient or the patient's family. These seizure types are commonly observed during routine EEG. Children with untreated childhood or juvenile absence epilepsy typically will have an absence seizure that is triggered by hyperventilation (Fig. 3), and those with untreated juvenile myoclonic epilepsy often have a series of myoclonic jerks that can be induced by photic stimulation (Fig. 4). Less commonly, partial seizures may occur (Fig. 5). Detection of more subtle seizures changes the diagnosis from first unprovoked seizure to epilepsy, and they usually prompt consideration of initiating antiepileptic medication.

Detection of Abnormalities That Alter Investigation or Treatment

In most cases, neurologists abide by the adage "treat the patient, not the EEG." However, certain EEG patterns may alert the clinician to other diagnoses. Electrical status epilepticus denotes an EEG pattern of nearly continuous epileptiform discharge in slow-wave (non rapid eye movement) sleep (Fig. 6). This EEG pattern can be associated with two epilepsy syndromes—Landau-Kleffner syndrome and continuous spike-wave in slow sleep, both of which present in early to mid-childhood with regression and seizures. Early, appropriate treatment is indicated to attempt to ameliorate the electrical status and improve the child's cognitive function.

Specific EEG patterns may indicate a certain type or location of epileptiform discharges. Focal slowing not restricted to the postictal period is suggestive of a focal lesion and should prompt neuroimaging. In their study of adults presenting with a first seizure, Schreiner and Pohlmann-Eden (2003) identified EEG abnormalities in 60 of 94 patients with normal findings after a neurologic examination. Neuroradiologic examination identified previously unknown lesions in 19 of these patients, and pathologies included brain tumor, ischemic stroke, trauma, and subcortical vascular encephalopathy.

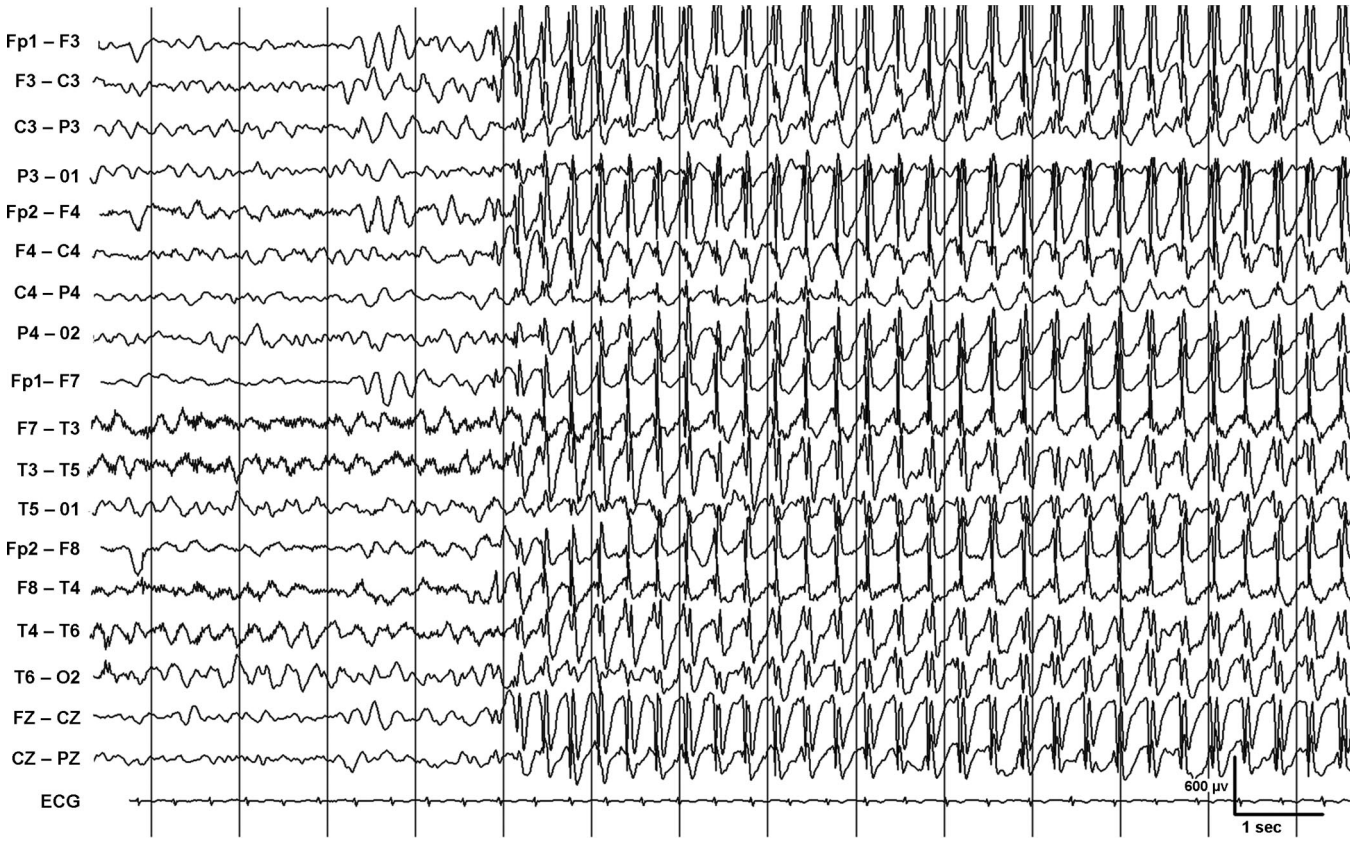

FIGURE 3. EEG of a 12-year-old girl after her first generalized tonic-clonic seizure. During hyperventilation, a typical absence seizure was recorded, showing a 3-Hz generalized spike-wave discharge. ECG, electrocardiogram.

PREDICTION OF SEIZURE RECURRENCE

Approximately 40% to 50% of patients who experience a first unprovoked seizure will have a recurrence within the subsequent 2 years (Berg and Shinnar, 1991). Numerous studies have examined seizure recurrence after the first seizure in childhood (Table 3); the risk of recurrence increases from 27% to 42% if the EEG is normal and increases to 60% to 71% if epileptiform abnormalities are seen. Two studies further subdivided causes into idiopathic or cryptogenic versus symptomatic and reported that epileptiform abnormalities were predictive of recurrence only in the idiopathic or cryptogenic group (Ramos Lizana et al., 2000; Shinnar et al., 1996). Most studies examining this same question in adults presenting with a first unprovoked seizure determined a higher recurrence rate if the EEG was abnormal (Table 4).

A meta-analysis of 16 studies assessed recurrence risk after the first unprovoked seizure and showed that the strongest predictors of recurrence were seizure cause and EEG findings (Berg and Shinnar, 1991). Overall, the risk ratio for seizure recurrence with an epileptiform EEG compared with a normal EEG was significant at 2.0 (95% confidence interval [CI], 1.6–2.6). Although higher recurrence rates were observed with nonepileptiform abnormalities (risk ratio, 1.3; 95% CI, 0.9–1.8), it was not significantly different from the rate of recurrence after normal findings.

The American Academy of Neurology and American Epilepsy Society more recently issued practice parameters regarding evaluation of a first unprovoked seizure in adults and reached similar conclusions (Krumholz et al., 2007). The posttest probability of seizure recurrence was 49.5% in adults with epileptiform abnormalities on EEG versus 27.4% in those with normal EEGs. Other nonspecific EEG abnormalities such as slowing were not significantly predictive of recurrence.

PREDICTING EVOLUTION TO INTRACTABLE EPILEPSY

Specific features on the initial EEG may be predictive of intractability. Berg et al. (2001) studied 613 children with newly diagnosed epilepsy; at 2 years, 10% of the total group and 13.3% of the nonidiopathic group had intractable epilepsy. In the full cohort, focal EEG slowing was predictive of intractability (risk ratio, 2.31; 95% CI, 1.13–4.74). Among those with nonidiopathic, localization-related epilepsy, 22% with focal slowing had intractable epilepsy. In another study comparing initial EEGs of 39 children with well-controlled seizures to 144 children with intractable epilepsy, Ko and Holmes (1999) reported that diffuse background slowing and a focal spike and wave were independently predictive of intractability. Similarly, in a study comparing initial EEGs of 150 patients with controlled epilepsy and 150 with uncontrolled seizures, Hughes and Fino (2003) noted that frequent focal spikes and focal slowing were both seen more frequently in the group with uncontrolled seizures.

CONCLUSIONS

In children and adults presenting with new-onset seizures, approximately one-third will show epileptiform abnormalities on EEG. If the standard EEG shows normal findings, a recording after sleep deprivation should be considered. The EEG is a useful investigation in patients presenting with a first unprovoked seizure; it may assist in establishing the diagnosis of epilepsy syndrome, thus helping to guide further investigations and management. It may also provide important prognostic information and may allow identification of more subtle seizures that previously were unrecognized. If

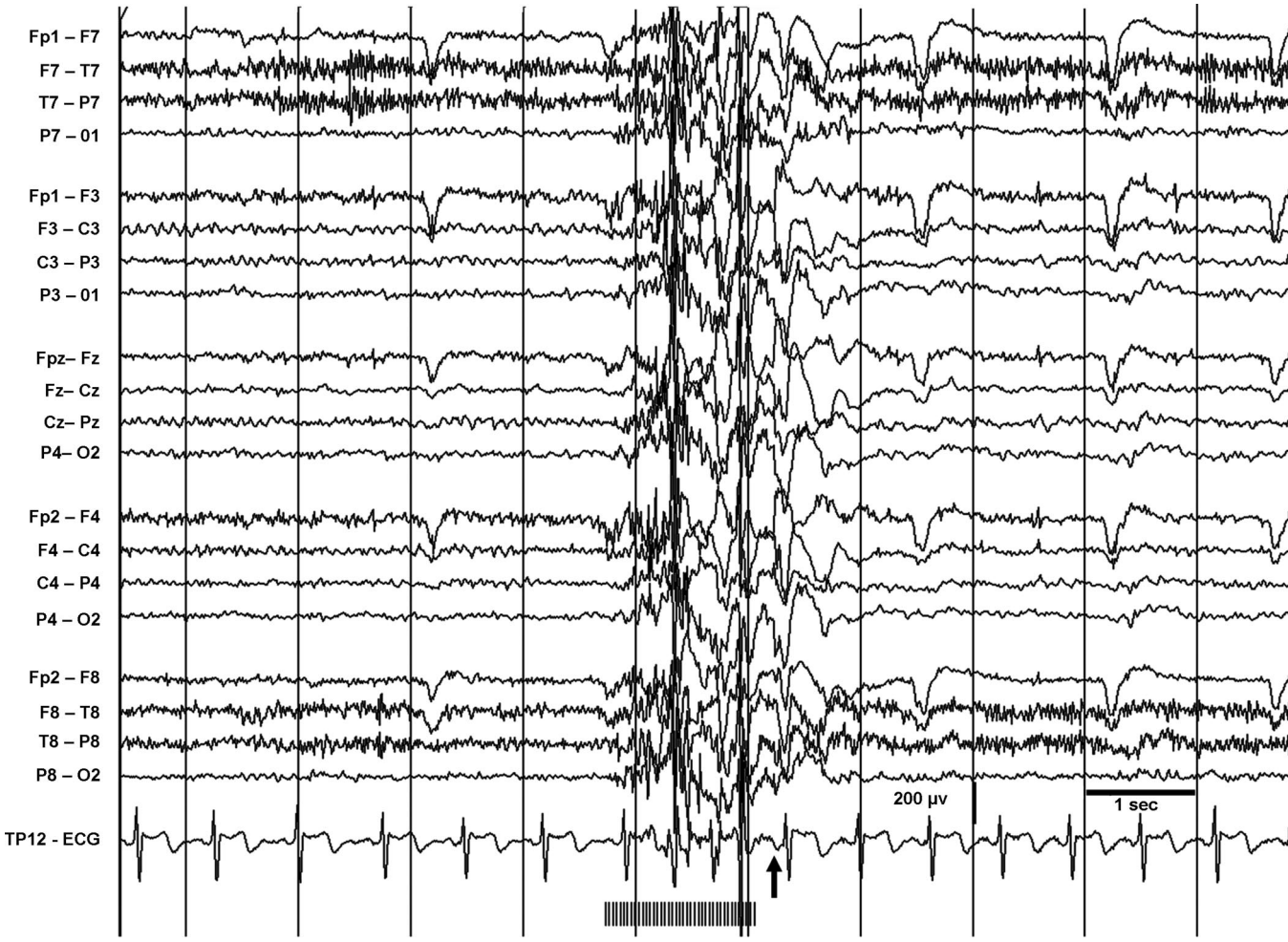

FIGURE 4. EEG of a 15-year-old girl after her first generalized tonic-clonic seizure. During photic stimulation (represented on the EEG as short vertical lines), she had a series of myoclonic jerks with generalized spike-wave discharge (arrow), consistent with the clinical diagnosis of juvenile myoclonic epilepsy. Because of this finding, she began taking antiepileptic medication. ECG, electrocardiogram.

epileptiform abnormalities are observed with EEG, the recurrence rate increases approximately twofold, from approximately 35% to 65% in children and from approximately 27% to 50% in adults. Epileptiform abnormalities are most predictive of recurrence among patients with idiopathic or cryptogenic seizures.

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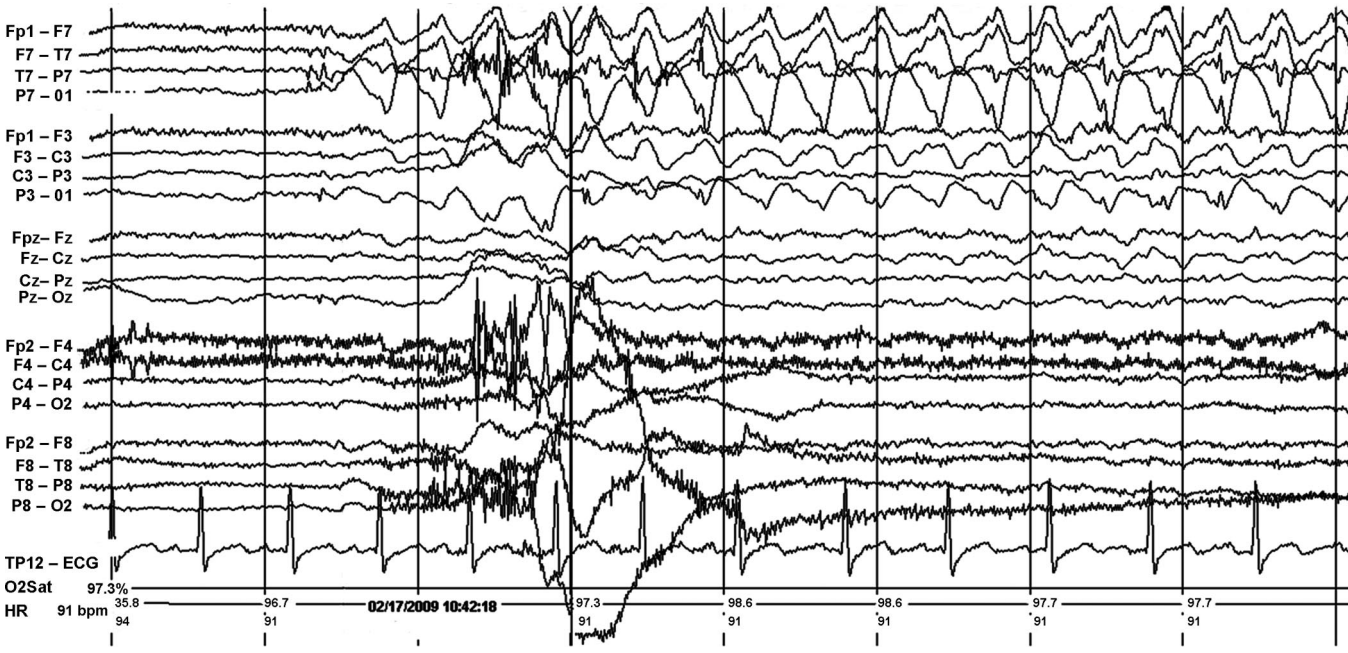

FIGURE 5. EEG of a 14-year-old girl after a single, generalized, tonic-clonic seizure. The patient had global, moderate to severe developmental delays and spastic quadriparesis. Her parents denied other seizures. During the EEG, she had a partial complex seizure with onset in the left temporal region that consisted of unresponsive staring and subtle oral automatisms. ECG, electrocardiogram; HR, heart rate; O_2Sat, oxygen saturation.

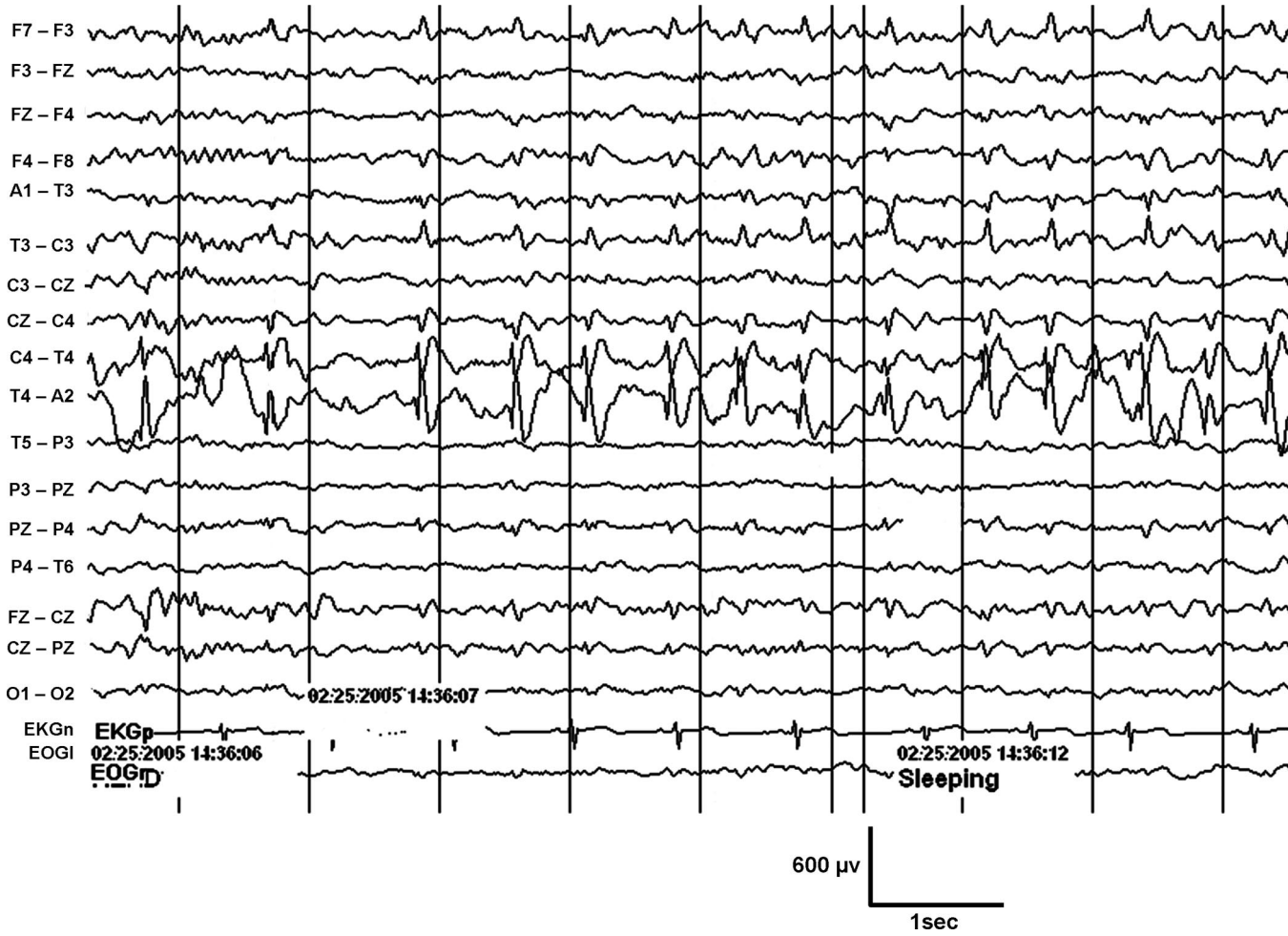

FIGURE 6. EEG of a 7-year-old boy presenting after his first secondarily generalized seizure. His magnetic resonance image was normal, but the EEG showed a pattern of electrical status epilepticus in slow sleep, with maximal discharge in the right centrotemporal region. He had shown increased impulsiveness and other behavior problems, along with left upper extremity apraxia, during the prior month. He was treated with high-dose diazepam with resolution of his apraxia and electrical status epilepticus. EKG, electrocardiogram; EOG, electrooculogram.

TABLE 3. Pediatric Seizure Recurrence After a First Unprovoked Seizure

Study	No. of Patients	Recurrence
Camfield et al. (1985)	168	EEG is normal or shows nonspecific changes only, 41% Epileptiform abnormalities are present, 66%
Shinnar et al. (1996)	407	2-year recurrence rate Cryptogenic EEG is normal, 28% Epileptiform abnormalities are present, 60% Symptomatic EEG is not predictive of recurrence
Stroink et al. (1998)	156	2-year recurrence EEG is normal, 40% Epileptiform abnormalities are present, 71%
Ramos Lizana et al. (2000)	217	2-year recurrence Idiopathic-cryptogenic EEG is normal, 42% Epileptiform abnormalities are present, 62% Symptomatic EEG is not predictive of recurrence
Scotoni et al. (2004)	213	EEG is normal, 27% EEG is abnormal, 60%
Boulloche et al. (1989)	119	Those with epileptiform abnormalities tend to have higher recurrence rates than those with normal EEG or nonspecific slowing

TABLE 4. Adult Seizure Recurrence After First Unprovoked Seizure

Study	No. of Patients	Recurrence
Annegers et al. (1986)	424	Idiopathic Abnormal EEG is predictive of seizure recurrence: RR, 2.2 (95% CI, 1.1–4.3) Symptomatic Abnormal EEG not predictive of recurrence
van Donselaar et al. (1992)	157	EEG is normal, 12% Epileptiform abnormalities are present, 83%
Das et al. (2000)	76	EEG is normal, 17% EEG is abnormal, 75%
Schreiner and Pohlmann-Eden (2003)	157	EEG is abnormal: RR, 4.5 (95% CI, 1.8–11.3) Focal but not generalized epileptiform abnormalities are predictive of recurrence
Kim et al. (2006)	1,443	EEG is abnormal: RR, 1.54 (95% CI, 1.27–1.86)
Hopkins et al. (1988)	408	EEG is not significantly predictive, but an abnormal EEG may be associated with greater risk of recurrence
First Seizure Trial Group (1993)	193	Patients with epileptiform abnormalities had 1.7-fold higher recurrence rate
Bora et al. (1995)	147	Abnormal EEG may be associated with greater risk of recurrence
Hui et al. (2001)	132	Patients with epileptiform abnormalities may have a higher recurrence rate
Lindsten et al. (2001)	107	Abnormal EEG may be associated with greater risk of recurrence

CI, confidence interval; RR, relative risk.

Original article

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Photosensitivity in epileptic syndromes of childhood and adolescence

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ABSTRACT – *Purpose.* Photosensitivity, a reaction of the brain to external photic stimulation, can be graded from 1 to 4, and is most frequently seen in the first decades of life. This study investigated photosensitivity in children with epilepsy. *Methods.* A retrospective study performed in the neuropaediatric department of the largest paediatric hospital in Kiel, treating patients at all medical care levels. The clinical data and EEG records of 566 patients with the most common epileptic syndromes were analyzed, in particular regarding photosensitivity. Their EEGs included application of intermittent light stimulation using standard techniques at twice the minimum. *Results.* The proportion of photosensitive patients was significantly higher in the paediatric cohort than in adult patients, as published in the literature: 46% of patients with generalized epilepsies showed photosensitivity as compared to 20% with focal epilepsies. Photosensitivity was more common in idiopathic generalized epilepsy (IGE), (epilepsy with *grand mal* on awakening, 74%; juvenile absence epilepsy, 56%; juvenile myoclonic epilepsy, 50%; childhood absence epilepsy, 44%) than in focal types (idiopathic partial – Rolandic epilepsy, 23%; symptomatic/cryptogenic type of epilepsy, 16%), while in patients who experienced occasional seizures (neonatal/febrile seizures), this ranged between 40% and 23%, respectively. The generalized photoparoxysmal response, (PPR), grades 3 and 4 were found significantly more often in patients with IGE (92%) than in patients with focal epilepsies. Finally, the female preponderance was confirmed (37% to 27% of all epilepsies). *Conclusions.* Photosensitivity can be detected both in patients with IGE, with idiopathic and symptomatic/cryptogenic types of focal epilepsies, and with epileptic (occasional) seizures. PPR grades 3 and 4 are the most common in IGE.

Key words: photosensitivity, epileptic syndromes, childhood, adolescence, adulthood, photoparoxysmal response

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On electroencephalography (EEG), photosensitivity (photoparoxysmal response, [PPR]) is a common genetic trait in about 8% of healthy children (Doose and Gerken 1973). It is defined as the occurrence of irregular spikes or spikes-and-waves in response to intermittent photic stimulation (IPS), ranging from the localized form of occipital spikes (grade 1) to the

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most generalized form (grade 4) of generalized spikes-and-waves or polyspike waves (Waltz *et al.* 1992, Doose and Waltz 1993).

Many studies on photosensitivity have been performed in children and adolescents, the periods during which the prevalence of photosensitivity is highest (for review see Kasteleijn-Nolst Trenité, 1989). However, studies investigating the distribution of the photoparoxysmal response within the different epileptic syndromes have been confined to adult patients (Wolf and Gooses 1986, Obeid *et al.* 1991, Harding *et al.* 1997). The purpose of this study was to examine the relationship between photosensitivity and the epileptic syndromes in childhood and adolescents, in particular, generalized and focal epilepsies and idiopathic, symptomatic, cryptogenic forms of epileptic syndromes, and epileptic syndromes with occasional seizures such as neonatal and febrile seizures. Furthermore, the grades of the PPR in different epileptic syndromes were analyzed.

Methods and material

Patients

This is a retrospective study performed in the neuropaediatric department of the largest paediatric hospital in Kiel, treating patients at all medical care levels. We analyzed the clinical charts and EEGs involving photostimulation of all 1241 patients who were treated from 1975 to 2002 (*table 1* with age distribution), and met the following criteria: 1) at least two EEGs with intermittent photic stimulation (IPS) were performed in individuals aging from five to 15 years; 2) patients were clearly classified as suffering from one of the more common epileptic syndromes, including occasional seizures (*i.e.* neonatal seizures and febrile seizures), West syndrome, Lennox-Gastaut syndrome, myoclonic-astatic epilepsy, childhood absence epilepsy, juvenile absence epilepsy, juvenile myoclonic epilepsy, *grand mal* on awakening, Rolandic epilepsy, or epilepsy with complex-focal seizure; 3) the definition of epilepsy syndrome was consistent with the revised classification of epilepsy, epileptic syndrome, proposed by the International League Against Epilepsy (1989). The charts of the patients were analysed carefully in order to rule out the possibility of their being wrongly diagnosed with epilepsy. In particular, the group with "occasional seizures" referred to those patients who had experienced neonatal seizures and febrile seizures, without being associated with other epileptic seizures. Neonatal seizures were considered as all types of seizure within a postnatal period of four weeks. Febrile seizures were defined as fever-induced seizures at the age of six weeks to five years. The percentage of the photosensitivity rate in those children without a definite diagnosis of an epileptic syndrome was not determined in this study.

In some patients (e.g. those with absence seizures and febrile seizures), repeated EEGs had been performed in the Kiel neuropaediatric department for scientific studies. Because of the huge amount of data available, only every third patient with childhood absence epilepsy, with Rolandic epilepsy, and with febrile seizures was randomly selected for further analysis, which resulted in a cohort of 566 patients, with 122, 103, and 117 patients being diagnosed respectively *(table 2)*.

Electroencephalographic assessment of the PPR

IPS stimulation had been carried out with standard photostimulators (Knott or Grass PS22 stimulator) in a dim room; lamp distance was approximately 25 cm (Waltz *et al.* 1992, Doose *et al.* 1969). For 30 sec, the flash frequency was slowly increased up to 20/sec, and for the next 30 sec reduced to 4/sec. Thereafter, flash frequencies of 5, 10, 12, 15, 20, and 25/sec (in a few patients examined with a new device, up to 50/sec) were used for 20 sec each and irregular frequencies for a period of 30 sec. During each 30-sec period the effect of three eye conditions (eye closure, eyes closed, and eyes open) was tested once. The quantitative expression of the age-dependent PPR was graded on a scale of 1 to 4, ranging from solely occipital-spikes within the occipital alpha rhythm (grade 1), parieto-occipital spikes followed by biphasic slow waves (grade 2), parieto-occipital spikes followed by biphasic slow waves and spreading to the frontal region (grade 3), to generalized spikes-and-waves and polyspike waves discharges (grade 4) (Waltz *et al.* 1992). The EEG recordings of the patients were re-analysed and only patients with unambiguous findings were included.

Table 1. Number of EEGs with photic stimulation in relation to photosensitive patients in different age groups.

Age group	EEGs with photostimulation	PS+ -EEGs		Investigated patients	Patients with PPR	
		Nr.	%		Nr.	%
1-3 years	209	8	4	146	6	4
4-6 years	694	116	17	430	70	16
7-9 years	520	116	22	338	83	25
10-12 years	261	68	26	186	52	28
13-15yars	195	70	36	124	41	33
> 15 years	18	4	22	17	4	24
	1 897	382		1 241	256	

Table 2. The classification and clinical data of epileptic patients and epileptic syndromes.

Epileptic syndrome	Gender		Age of onset	
	Male	Female	Mean	Range
Occasional seizures				
Neonatal seizures (n = 15)	7 (47%)	8 (53%)	4 days	1 day to 14 days
Febrile seizures (n = 117)	71(61%)	46 (39%)	2.2 years	1.5 months to 6 years
Epilepsies				
Generalized epilepsy				
Symptomatic/ cryptogenic				
West syndrome (n = 17)	13 (76%)	4 (24%)	8months	1.5 months to 12 months
Lennox-Gastaut syndrome (n = 7)	5 (71%)	2 (29%)	2 years	2 months to 7 years
Idiopathic				
Myoclonic-astatic epilepsy (n = 11)	7 (64%)	4 (36%)	3.4 years	7 months to 8 years
Childhood absence epilepsy (n = 122)	54 (44%)	68 (56%)	5.5 years	3 years to 9 years
Juvenile absence epilepsy (n = 25)	10 (40%)	15 (60%)	11 years	10 years to 15 years
Juvenile myoclonic epilepsy (n = 12)	6 (50%)	6 (50%)	13 years	11 years to 15 years
Grand mal on awakening (n = 31)	17(55%)	14 (45%)	9.6 years	4 years to 15 years
Focal epilepsy				
Idiopathic				
Rolandic epilepsy (n = 103)	63(61%)	40 (39%)	6 years	2 days to 13 years
Symptomatic/ cryptogenic				
Complex focal seizures (n = 106)	69 (65%)	37 (35%)	6 years	1 day to 14 years
Total (n = 566)	322(57%)	244 (43%)	5.3 years	1 day to 15 years

Statistic analysis

Chi-squared tests and Fisher's exact tests were performed. A P-value less than 5% was considered as significant.

Results

Patients

Our cohort contained 566 patients, comprising 322 males and 244 females. Eleven epileptic syndromes were classified into two groups; occasional seizures and epilepsies. *Table 2* lists the distribution of the different epileptic syndromes and age-at-onset in the male and female patients. IPS was performed twice in 100%, three times in 67% and four times or more in 33% of the patients.

Photosensitivity

Photosensitivity in different epileptic syndromes

Thirty-one percent of the total 566 patients had a PPR *(table 3)*. The frequency of the PPR in generalized epilepsy (46%) was significantly higher than in focal epilepsy (20%). Of the patients with idiopathic generalized epilepsy (IGE), 49% showed photosensitivity. This was significantly different from the rate of 23% photosensitivity in patients with idiopathic focal Rolandic epilepsy ($p < 0.0001$). The patients with generalized or focal symptomatic/cryptogenic epilepsies had similarly low PPR rates (17% to 16%).

The highest rate of PPR was 74% in patients with *grand mal* on awakening (IGE), followed by patients with juvenile absence epilepsy (56%), patients with juvenile myoclonic epilepsy (50%), and patients with childhood absence epilepsy (44%). A statistically significant difference was observed between the patients with *grand mal* on awakening and those with childhood absence epilepsy ($p < 0.015$).

Photosensitivity was found in 20% of all patients with focal epilepsies, (23% of patients with Rolandic epilepsies). There was no significant difference between the occurrence of the PPR in Rolandic epilepsy as compared to symptomatic/cryptogenic epilepsies with complex-focal seizures (16%).

Twenty-five percent of patients with occasional seizures (neonatal seizures and febrile seizures) were photosensitive. The PPR rate was higher in patients with neonatal seizures (40%), but the difference, compared to patients with febrile seizures (23%), was not significant.

Photosensitivity in male and female patients

Overall, the PPR rate was significantly higher in females (37%) than in males (27%) *(table 3)*. The incidence of the the PPR in female patients with *grand mal* on awakening was much higher than that found in male patients (93% *versus* 59%, $p < 0.001$). In the subgroup of juvenile

Table 3. Photosensitivity in the epileptic syndromes and the respective sex distribution.

Epileptic syndrome	Photo-sensitivity	Male		Female	
	Nr. (%)	Nr.	Nr. (%) of PPR	Nr.	Nr. (%) of PPR
OCCASIONAL SEIZURES					
Neonatal seizures (n = 15)	6 (40)	7	3 (43)	8	3 (37)
Febrile seizures (n = 117)	27 (23)	71	17 (24)	46	10 (22)
Total (n = 132)	33 (25)	78	20 (26)	54	13 (24)
EPILEPSIES					
Generalized epilepsy					
Symptomatic/ cryptogenic					
West syndrome (n = 17)	3 (18)	13	1 (8)	4	2 (50)
Lennox-Gastaut syndrome (n = 7)	1 (14)	5	1 (20)	2	0 (0)
Total (n = 24)	4 (17)	18	2 (11)	6	2 (33)
Idiopathic					
Myoclonic-astatic epilepsy (n = 11)	2 (18)	7	2 (29)	4	0 (0)
Childhood absence epilepsy (n = 122)	54 (44)*	54	21 (39)	68	33 (49)
Juvenile absence epilepsy (n = 25)	14 (56)	10	8 (80)$^{+}$	15	6 (40)$^{+}$
Juvenile myoclonic epilepsy (n = 12)	6 (50)	6	2 (33)	6	4 (67)
Grand mal on awakening (n = 31)	23 (74)*	17	10 (59)$^{++}$	14	13 (93)$^{++}$
Total (n = 201)	99 (49)**	94	43 (46)	107	56 (52)
Total (generalized epilepsies, n = 225)	103 (46)***	112	45 (40)	113	58 (51)
Focal epilepsy					
Idiopathic					
Rolandic epilepsy (n = 103)	24 (23)**	63	12 (19)	40	12 (30)
Symptomatic/ cryptogenic					
Complex focal seizures (n = 106)	17 (16)	69	11 (16)	37	6 (16)
Total (focal epilepsies, n = 209)	41 (20)***	132	23 (17)	77	18 (23)
Total (n = 566)	177	322	88 (27)$^{+++}$	244	89 (37)$^{+++}$

* $p < 0.015$ between *grand mal* on awakening and childhood absence epilepsy; ** $p < 0.0001$ between idiopathic generalized epilepsy and idiopathic focal Rolandic epilepsy; *** $p < 0.0001$ between generalized epilepsies and focal epilepsies; $^{+}$ shows the PPR incidence higher in males with juvenile absence epilepsy than in females, $p < 0.0001$; $^{++}$ shows the PPR incidence in female patients with *grand mal* on awakening higher than that of male patients, $p < 0.0001$; $^{+++}$ overall the PPR rate significantly higher in females than in males, $p = 0.002$.

absence epilepsy, the incidence of the PPR was higher in males than in females (80% *versus* 40%, $p < 0.001$).

Photosensitivity in individual age groups

The finding of a PPR was an age-related trait in our selected cohort *(table 1)*. The incidence of PPR was low (4%) in children 1-3 years of age, and increased gradually with increasing age until the maximal PPR penetrance appeared in EEGs in 13-15-year-old patients (33%). Thereafter, the incidence of the PPR decreased by 24% in patients older than 15 years of age. However, photostimulation was performed most frequently in patients 4-6 years of age.

Effect of medication on photosensitivity

The incidence of the PPR in 355 patients who had received at least one IPS without drug therapy was 51%. IPS was performed in another 211 patients during drug treatment; the PPR rate was 59%. The difference in the frequency of the PPR in patients with and without medication was not significant.

Of the patients with classical IGE syndromes (childhood and juvenile absence epilepsies, juvenile myoclonic epilepsy, *grand mal* on awakening), 49 (44%) of a total of 111 patients on valproic acid (VPA) were photosensitive as compared to 48 (60%) of 79 patients not receiving VPA therapy *(table 4A)*. Of the patients with mixed non-IGE-syndromes (neonatal seizures, febrile seizures, West-syndrome, Lennox-Gastaut syndrome, myoclonic astatic epilepsy, Rolandic epilepsy, symptomatic/cryptogenic focal epilepsy) 4 (18%) of 22 patients receiving VPA were photopositive as compared to 75 (21%) of 354 patients not receiving VPA *(table 4B)*.

Table 4. The PPR in patients with and without VPA.

A) Idiopathic generalised epilepsies (IGE)				
Epileptic syndrome	**With VPA**		**Without VPA**	
	Nr.	**Nr. (%) of PPR**	**Nr.**	**Nr. (%) of PPR**
Childhood absence epilepsy (n = 122)	84	33 (39%)	38	21 (55%)
Juvenile absence epilepsy (n = 25)	18	11 (61%)	7	3 (43%)
Juvenile myoclonic epilepsy (n = 12)	7	4 (57%)	5	2 (40%)
Grand mal on awakening (n = 31)	2	1 (50%)	29	22 (76%)
Total (n = 190)	111	49 (44%)	79	48 (60%)
B) Mixed non-IGE syndromes				
Epileptic syndrome	**With VPA**		**Without VPA**	
	Nr.	**Nr. (%) of PPR**	**Nr.**	**Nr. (%) of PPR**
Neonatal seizures (n = 15)	0	0 (0%)	15	6 (40%)
Febrile seizures (n = 117)	2	1(50%)	115	25 (22%)
West syndrome (n = 17)	0	0 (0%)	17	3 (18%)
Lennox-Gastaut syndrome (n = 7)	2	0 (0%)	5	1 (20%)
Myoclonic-astatic epilepsy (n = 11)	5	1 (20%)	6	1 (17%)
Rolandic epilepsy (n = 103)	4	1 (25%)	99	23 (23%)
Complex focal seizures (n = 106)	9	1 (11%)	97	16 (16%)
Total (n = 566)	22	4 (18%)	354	75 (21%)

Different grades of photosensitivity

In a total of 177 patients with a PPR, 82% showed a generalized PPR grade 3 and 4 reaction, and 18% individuals demonstrated a PPR grade 1 and 2 reaction *(figure 1)*.

Grade 3 and 4 reactions were found in 92% of photosensitive patients with IGE, in 100% of such patients with symptomatic/cryptogenic generalized epilepsies, in 71% each with idiopathic and symptomatic/cryptogenic partial epilepsies, and 67% and 63% with neonatal seizures and febrile seizures, respectively.

Grade 4 reaction was found significantly more often in IGE (59%) than in idiopathic focal Rolandic epilepsy (38%).

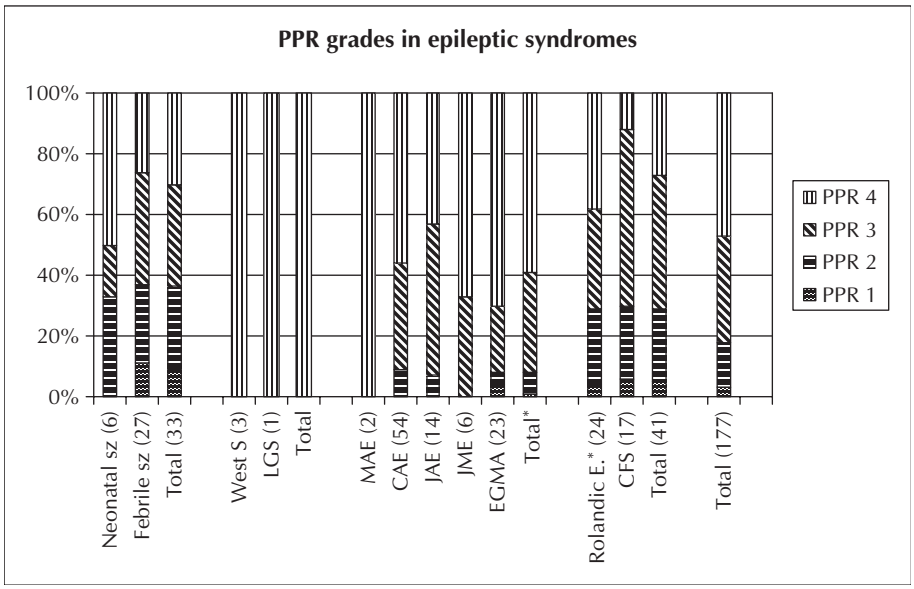

Figure 1. PPR grades in epileptic syndromes.
(Nr): absolute numbers of patients; sz: seizures; Total: summarizes the left sided bars of each Total; West S: West syndrome; LGS: Lennox-Gastaut-syndrome; MAE: myoclonic astatic epilepsy; CAE: childhood absence epilepsy; JAE: juvenile absence epilepsy; JME: juvenile myoclonic epilepsy; EGMA: epilepsy with *grand mal* on awakening; Rolandic E.: Rolandic epilepsy; CFS: complex focal seizures. PPR 1-4: PPR grades 1-4. * Shows that the PPR grade 4 reaction is significantly higher in patients with idiopathic generalized epilepsy than with idiopathic focal Rolandic epilepsy, $p < 0.001$.

Grade 1 and 2 reactions were seen in 8% of patients with IGE with a PPR, in 29% of patients each with idiopathic and symptomatic/cryptogenic partial epilepsies and a PPR, and in 33% and 37% with neonatal and febrile seizures, respectively.

Photosensitive seizures

Of 177 photosensitive patients, eight had photosensitive seizures (PSS), and all suffered from IGE. Among them, three photosensitive patients with childhood absence epilepsy had absence seizures during IPS; three photosensitive patients with *grand mal* on awakening showed tonic-clonic seizures during IPS; and myoclonic seizures were provoked by IPS in another two photosensitive patients with juvenile myoclonic epilepsy.

Discussion

Photosensitivity

According to published reports, a PPR can be elicited in about 1.6% of healthy adults and patients with neurological-psychiatric disorders in general, but in 7.4%-9.9% of adult patients with epilepsy (Buchthal and Lennox 1953, Gastaut *et al.* 1958, Rabending and Klepel 1978, Obeid *et al.* 1991, Wolf and Gooses 1986). Higher rates of photosensitivity have been reported in children. Of a total of 662 healthy children and adolescents, 7.6% showed photosensitivity, with the maximal PPR penetrance in the age range of 5-15 years (Doose and Gerken, 1973). A similar rate for the PPR, 8.3%, was also reported in healthy children younger than five years of age (Eeg-Oloffson *et al.* 1971). Within a mainly adult population, Klepel found the highest PPR rate in patients with neurological-psychiatric disorders in the age range of 10-20 years (Klepel and Rabending 1989).

In the present study, 31% of patients with epilepsy had a PPR. This high rate of PPR might be explained by the following:

– repeated IPS procedures might result in higher PPR rates than fewer or single investigations (33% of all the analyzed patients had received four or more EEGs with IPS). Therefore, those studies which deal only with routine clinical aspects probably overlook the higher rate of PPR;

– a PPR may be missed in a given individual if photic stimulation is performed before age-related appearance of the PPR or after remission of the electroencephalographic trait (Harding *et al.* 1997). We selected patients, who had been investigated at least twice at the age of maximum penetrance of the photoparoxysmal response (three times between the age of four and 18 years as a rule, in the unselected patient cohort) (Doose and Waltz 1993). It is reasonable to admit that investigations involving patients, who had only been investigated at a younger or older age (Wolf and Gooses 1986) will report a lower rate of photosensitivity;

– some older PPR studies do not consider grade 1 and 2 PPR (Wolf and Gooses 1986, Kasteleijn-Nolst Trenité 1989). This might be a selection bias in other studies.

Photosensitivity in different epileptic syndromes - comparison of adult and children groups

As was already shown in previous investigations (Wolf and Gooses 1986, Stephani *et al.* 2004), the present study confirms that PPR rates are significantly higher in patients with generalized epilepsy than in patients with focal epilepsies. Moreover, the present study shows that generalized types of PPR are more prevalent in generalized epilepsies than in symptomatic/cryptogenic focal epilepsies.

The distribution of the photosensitivity rate among the different syndromes of IGE was somewhat different from the data reported by Wolf and Gooses (1986) and Waltz *et al.* (1990) in adults. The rate of photosensitivity in absence epilepsies is higher than previously reported. Thus, investigation of patients in childhood shows that a PPR occurs more frequently in childhood absence epilepsies (*e.g.* pycnolepsy) than in adult patients (*e.g.* spaniolepsy). In the studies of Wolf and Gooses (1986) and Waltz *et al.* (1990), the epileptic syndrome with the highest rate of photosensitivity was JME (Waltz 2000, Appleton *et al.* 2000), whereas in the present study the highest rate of photosensitivity was found in epilepsy with *grand mal* on awakening. However, our study included only a small number of patients with JME. Furthermore, some of our young patients with *grand mal* on awakening only, may have developed JME later in life.

In our investigation, a PPR was found in 20% of patients with focal epilepsy; this is much higher than in other reports; 2.7% in the study by Wolf; 0.6% in Obeid's studies. The reason for the great difference might not just be the age of patients. The investigations of Wolf and Gooses (1986) and Obeid *et al.* (1991), did not include patients with Rolandic epilepsy, who, in our study, showed the highest rate of photosensitivity among the focal epilepsies.

Our study, including nongeneralized grades of photosensitivity as proposed by current classification systems (Waltz *et al.* 1992, Kasteleijn-Nolst Trenité *et al.* 2001) shows a high proportion of grade 1 and grade 2 PPR in focal epilepsy. Thus, previous studies that excluded nongeneralized grades of PPR may have underestimated the rate of the PPR in focal epilepsies. However, the higher rate of photosensitivity in focal epilepsies is restricted to photosensitivity as an electroencephalographic trait. The presence of a PPR in focal epilepsies may represent a contributing factor in the multifactorial pathogenesis of epilepsy in such children (Andermann and Straszak 1982, Doose et Waltz 1993). None of the patients with focal epilepsy in this study showed photosensitive seizures.

Some patients with occasional seizures (neonatal and febrile seizures) are also photosensitive. Indeed, the PPR rate reached 42% in young patients with febrile seizures

(Doose *et al.* 1983). In our investigation however, the PPR rate in patients with febrile seizures is somewhat lower, at only 23%.

Photosensitivity in male and female patients

It is generally accepted that the PPR rate is higher in females than in males (Newmark and Penry 1979, Klepel and Rabending 1989, Wolf and Gooses 1986). In line with those findings, the overall incidence of a PPR was also higher in females than in males in the present study.

In patients with IGE, the PPR in females is predominant, except for in the group of juvenile absence epilepsy. However, this group comprised only 25 patients. Therefore, it is hard to draw any conclusions from this finding.

VPA effect on photosensitivity

The expected decline of the PPR rates in patients taking VPA was moderate in both IGE syndromes and mixed non-IGE syndromes. The PPR was lower in patients receiving VPA than in those not receiving VPA (44 to 60% in patients with IGE and 18 to 21% in non-IGE patients). Those patients who received VPA belong mainly to the IGE group, which shows higher PPR rates than other types of epileptic syndromes. In addition, a prospective comparison before and after VPA was administered was not performed in this study. Therefore, we cannot make conclusions about the extent of the effect of VPA on the PPR.

Photosensitive seizures

Patients with PSS mainly display generalized seizures, such as myoclonic, tonic-clonic seizure, or absence seizures: photosensitive focal seizures occurring only rarely (Kasteleijn-Nolst Trenité 1989 and 1994, Newmark and Penry 1979), with myoclonic seizures being the most frequent PSS (Kruse 1991). However, photosensitive partial seizures with secondary generalization have been observed in a small cohort (Kosaburo *et al.* 1994). The aim of the present study was to investigate the EEG-trait of photosensitivity.

The rate of photosensitive seizures may be underestimated in the present study for several reasons: we did not analyze video documentation of photic stimulation. Short seizures may therefore have been missed by our technicians. Furthermore, in our laboratory, technicians have to stop IPS when generalised spikes and waves occur twice (PPR grade 3 and 4) during the photic stimulation.

In conclusion, this study shows high rates of the PPR in young patients investigated at least twice for photosensitivity with generalized epilepsies, focal epilepsies, and neonatal and febrile seizures. PPR grade 3 and 4 reactions were predominant. Grade 4 PPR is found more often in IGE than in Rolandic epilepsy. The greatest penetrance of the PPR is seen in the 13-15 year age group. □

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The misdiagnosis of epilepsy in children admitted to a tertiary epilepsy centre with paroxysmal events

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ORIGINAL ARTICLE

The misdiagnosis of epilepsy in children admitted to a tertiary epilepsy centre with paroxysmal events

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Aims: To determine the proportion of children admitted with difficult to treat paroxysmal events to a tertiary epilepsy centre who did not have epilepsy.

Methods: In an observational retrospective study, all case notes of 223 children admitted in 1997 were examined. The referral was made from the local paediatric department in 51% of cases, other departments in 27%, and from general or specialist practitioners in 22%. Doubt regarding the diagnosis of epilepsy was expressed in the referral note in 17%. On admission, 86% were on antiepileptic drug treatment. During admission all children were subjected to a comprehensive intensive observation and 62% had EEG monitoring.

Results: In total, 39% (87/223) were found not to have epilepsy. In 30% of children (55/184) referred without any doubts about the epilepsy diagnosis, the diagnosis was disproved. Of the 159 children admitted for the first time, 75 (47%) were discharged with a diagnosis of non-epileptic seizures. Of 125 children admitted for the first time with no doubts about the diagnosis of epilepsy, 44 (35%) did not have epilepsy. Staring episodes were the most frequently encountered non-epileptic paroxysmal event. Psychogenic non-epileptic seizures were found in 12 children. A total of 34 (15%) had their medication tapered off; a further 22 (10%) had tapered off medication before admission.

Conclusion: The present study supports the view that misdiagnosis of epilepsy is common. The treating physician should be cautious in diagnosis, especially of staring episodes. A diagnostic re-evaluation should be undertaken in difficult cases with continuing paroxysmal events in order to avoid unnecessary drug treatment and restrictions on the child's lifestyle.

Epilepsy is a common neurological disorder in children, with a prevalence of about 0.5%. The epilepsies form an array of more or less discrete epilepsy syndromes, characterised by age of onset, hereditary factors, seizure types, electroencephalogram (EEG) abnormalities, and prognosis.[1]

The diagnosis of epilepsy is often difficult.[2 3] A good seizure history depends on descriptions by parents or other observers, mainly staff in day care centres or schools. Direct observations by trained medical staff will add considerably to the value of history, but they are difficult to obtain in a normal paediatric ward setting. Hence, the diagnosis must often be made in the outpatient clinic, based on clinical history taking and interictal EEG. The diagnostic information obtained from a single interictal EEG is low; it is frequently normal in children with epilepsy and 2–5% of children without epilepsy present with epileptiform EEG discharges, especially in the centrotemporal regions.[4 5] Furthermore, a number of benign variant patterns not related to epilepsy are often misinterpreted as epileptiform.[6]

In specialised units, video-EEG or ambulatory long term EEG monitoring to obtain an ictal recording are very helpful,[7] but these techniques are not available in most cases. It is therefore not surprising that epilepsy frequently is misdiagnosed in children. Many paroxysmal events may be mistaken for epilepsy, for example, tics, staring, syncope, dystonia, psychogenic seizures, and behavioural disturbances during sleep.[8]

In the UK, it was recently disclosed that one physician had misdiagnosed 618/1948 children (31.7%).[9] As documented in an evidence report for the Center for Disease Control,[10] our knowledge of the amount of misdiagnosis of epilepsy in children with ongoing paroxysmal events is unknown due to the lack of studies with information on the reasons for referral, medications, and the degree of representative value of the population studied.

The aim of this observational retrospective study was to describe the results of a diagnostic evaluation in children from a well defined population with difficult to treat paroxysmal events, admitted to a tertiary epilepsy centre.

PATIENTS AND METHODS

The Dianalund Epilepsy Centre is the only tertiary centre of its kind in Denmark (population 5.2 million).[11] The case notes of 223 children admitted to the Paediatric Department during 1997 were examined in an observational retrospective study. For children admitted more than once that year, only data from the first admission were included.

The median age was 8 years and 6 months (range 8 months to 17 years and 8 months) and 54% were boys. The pattern of referral was evenly spread from all over Denmark. The rate for the first admission per 100 000 inhabitants was 3.1 (total population). The referral was issued by the local paediatric department in 113 children (51%), other hospital departments in 16 (7%), and general practitioners in 36 (16%); 45 (20%) came from the outpatient clinic of the Epilepsy Hospital and 13 (6%) from non-hospital based paediatricians and neurologists. Table 1 shows the reasons for referral. On admission, 14% of the children had never tried any antiepileptic drug (AED), 34% had been treated with one or two AEDs, 26% three or four AEDs, and 26% more than four AEDs. Drugs used for acute treatment were not included.

During hospital stay all the children were subjected to general observation and recording (including video in the ward) of seizures and other events by trained nurses, nursery

Abbreviations: AED, antiepileptic drug; EEG, electroencephalogram; PNES, psychogenic non-epileptic seizures

Table 1 The main reasons for referral to the Paediatric Department of the Dianalund Epilepsy Centre

	n	%
Improvement of epilepsy treatment	69	31
Doubt about the diagnosis of epilepsy	39	17
Classification of epilepsy	61	27
Psychological problems	17	8
Epilepsy surgery evaluation	10	4
Follow up of EEG, cognitive, and behavioural problems	27	12
Total	223	

staff (kindergarten), teachers, and physicians. All children of school age attended the hospital school. One of the parents was always co-admitted except for some of the older children. In total 56 of the children (34.8%) were examined by a child neuropsychologist.

All children had one or more interictal EEGs performed during the admission, which lasted for an average of three weeks. Furthermore, during admission 62% of the children had intensive EEG monitoring (video-EEG, ambulatory EEG, or cognitive testing during video-EEG while having paroxysmal discharges). A few had a multiple sleep latency test done as part of an evaluation for narcolepsy.

The final decision on whether the child had epilepsy or not was taken based on the comprehensive evaluation during the admission by two of the authors (PU, JB).

RESULTS

On discharge, 87 of the 223 children (39%) were found not to have epilepsy, excluding three children with epilepsy and psychogenic non-epileptic seizures (PNES). As seen from table 2, 30% of the children were diagnosed as non-epileptic, even when the referring doctor had expressed no doubt about the epilepsy diagnosis in the referral note. Of the 159 children admitted for the first time, 75 (47%) were thought to have non-epileptic seizures. Of the 125 children admitted for the first time with no doubts about the diagnosis of epilepsy, 44 (35%) did not have epilepsy. The distribution of the referring doctor's clinic or specialty among these 44 children showed no difference from the total referrals as mentioned in the methods section.

Table 3 shows the diagnoses of non-epileptic events in the 87 children without epilepsy. The most frequently encountered paroxysmal events were staring episodes in mentally retarded children. PNES were found in 12 children (10 girls). Their median age was 14 years (range 8–17). Of these, only three children with concomitant epilepsy were mentally retarded.

Of the 87 children without epilepsy, 35 were treated with AEDs at the time of admission. Among 34 children taken off drugs, seven had been treated with two or more AEDs. In 16 of these cases the referring doctors were in doubt about the diagnosis of epilepsy. One patient with dystonia was continued on clonazepam because of its muscle relaxant effect. Thus a total of 34 (15%) of the 223 admitted children had their medication tapered off. A further 22 (10%) had previously been treated with AEDs but had been tapered off before admission.

Table 2 Reasons for referral versus diagnosis at discharge among 223 children admitted for possible epilepsy

	Epilepsy confirmed	Epilepsy not confirmed
Doubt about diagnosis of epilepsy in referral note	7 (18%)	32 (82%)
No doubt of epilepsy expressed in referral note	129 (70%)	55 (30%)

Table 3 Diagnosis of 87 children discharged without a diagnosis of epilepsy

Diagnosis	No.
Staring episodes	46
Mental retardation (n = 22)	
Autism/Asperger syndrome (n = 4)	
Learning disorder (n = 3)	
Self stimulation (n = 2)	
Abnormal EEG (n = 7)	
Normal child (n = 8)	
Psychogenic non-epileptic seizures (PNES)	9
Syncope	4
Dystonia	4
Parasomnias	4
Hyperventilation attacks	3
Migraine	3
Breath holding spells	2
Munchhausen by proxy	2
Narcolepsy, Gilles de la Tourette, benign tremor, febrile convulsions	4
Not clarified	6

DISCUSSION

In Denmark, most children with epilepsy and other paroxysmal events are treated in the local paediatric departments. Admission to the only tertiary epilepsy centre in Dianalund is free for the patients. All medical doctors can refer a child to the centre. This means that if the parents want a second opinion they can go to their general practitioner for a referral to Dianalund, even though the local paediatrician may not find a referral necessary.

The total annual incidence of childhood epilepsy in Denmark is about 600. Expecting about 25% (150) of these to be difficult to treat, the number of children (159) admitted to Dianalund for the first time in 1997 seems to indicate that the majority of the ''intractable'' cases in Denmark will be admitted at least once during their lifetime. Furthermore, the geographical distribution of the children was evenly spread from all over Denmark. Even though this is not a strict population based study we believe that the figures in the present study are reasonably representative for Danish children with continuing seizures treated by paediatricians.

The difficulties of obtaining a final decision of the epilepsy diagnosis are illustrated by the fact that 12 of the 87 non-epileptic children had been admitted in previous years. Some of these children had been misdiagnosed at the previous admission; new clinical observations emerged during the admission in 1997 that made it possible to discard the epilepsy diagnosis. Others are thought to have outgrown a previously possible epilepsy. This is in accordance with a prospective study in which experienced child neurologists had to change their first diagnosis of epilepsy to non-epileptic paroxysmal events in 4.6% at later follow up.[12] It has also been shown by the same study group that among child neurologists the agreement was only fair to moderate[13] on the diagnosis of epileptic seizures based on the description of 100 first paroxysmal events. The agreement improved somewhat using predefined descriptive definitions of epilepsy and panel discussions. In contrast to the Dutch study our results are based on a comprehensive evaluation during admission of children with continuing paroxysmal events. In spite of this

some uncertainty on the diagnosis seems to exist in a small number of cases. In a prospective study it would be reasonable to include a category of children where no firm diagnosis could be made. This might reduce the percentage of misdiagnosis. We doubt, however, that a prospective study with predefined work up of the children would have changed the results. A planned ictal video-EEG would, for instance, seldom be possible to obtain, even during a three week admission.

The incidence of 30% where the referring doctor expressed no doubt about the diagnosis is surprisingly high. We have not found any study calculating the percentage of misdiagnosis where the referral cases all were thought to be epilepsy.

The results of a diagnostic evaluation of suspected epilepsy after a referral to a tertiary epilepsy centre are better documented. In a Scottish study only 54% referred with paroxysmal phenomena had epilepsy.[14] Among 666 Australian children who had intensive EEG monitoring done, 43% had non-epileptic seizures.[15] In a study from the USA, 22.5% of 199 children were discharged without epilepsy diagnosis after video-EEG.[16] However, in these studies the reasons for referral were not specified. Other small observational studies have documented the problem of misdiagnosis in childhood epilepsy.[2 17]

Disproving the diagnosis of epilepsy is important from several points of view. Unnecessary drug treatment as well as concerns about development and social coping and restriction imposed on the child's lifestyle can come to an end. In our series, medication could be stopped in 34 children (15% of all admitted). This is a somewhat higher percentage than found in the US study of 883 children referred for EEG monitoring (5%)[16] and children evaluated at the adolescent clinic in the UK (4%).[17] The explanation for their lower figures is probably that more children were referred to these clinics for an early diagnostic evaluation.

The majority of non-epileptic events in the present series were staring episodes, confirming results from other studies.[15 16] Most often this is seen in mentally retarded children with non-specific EEG abnormalities which are over-interpreted as ''epileptiform''. One study showed, however, that it was found just as often in normal children.[7] Another study found some descriptive features distinguishing epileptic from non-epileptic events; the sensitivity was low, however.[18] PNES were found less often than in other studies,[16] probably because of our strict definition of PNES: paroxysmal events of non-physiological nature, but which are regarded and treated as epileptic *and* play an important role in the emotional interaction between the child and the parent/environment. This means that the diagnosis was only used if a psychological evaluation could add these positive criteria. Except for gastro-oesophageal reflux, shuddering attacks, paroxysmal torticollis, tonic upward gazing, long Q-T syndrome, and alternating hemiplegia, all the differential diagnoses most frequently mistaken for epilepsy seem to be represented in our material.

The problem of misdiagnosis in epilepsy is not restricted to children. A recent study has shown high figures in adults as well, syncopal episodes being among the most frequent.[19] In the present study, video-EEG monitoring played an important role as 62% of the children had this investigation done. In the remainder, the diagnostic work-up was based on clinical observation combined with careful history taking, and interictal EEG. The role of each diagnostic procedure is difficult to evaluate because each forms part of a comprehensive procedure.

What is already known on this topic

- The diagnosis of epilepsy is difficult
- A consultant paediatrician in England misdiagnosed 618/1948 (31.7%) children as having epilepsy

What this study adds

- The rate of misdiagnosis of epilepsy in a national sample of difficult-to-treat patients from a developed country is extremely high, with more than 30% of those with definite epilepsy not having epilepsy at all

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The co-author Jette Buchholt has passed away since this paper was accepted.

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