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Review

Electroencephalography in clinical epilepsy research ☆

Susan T. Herman [a,b], Masanori Takeoka [c], John R. Hughes [d], Frank W. Drislane [a,b,*]

[a] Comprehensive Epilepsy Program, Department of Neurology, Beth Israel Deaconess Medical Center, Boston, MA, USA
[b] Harvard Medical School, Boston, MA, USA
[c] Division of Epilepsy and Clinical Neurophysiology, Department of Neurology, Children's Hospital Boston, Boston, MA, USA
[d] Department of Neurology, University of Illinois at Chicago, Chicago, IL, USA

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ABSTRACT

Electroencephalography (EEG) remains central to the investigation of epilepsy. This review discusses two clinical problems at the temporal extremes of neurophysiologic recording: evaluation of the clinical significance of individual spike discharges in benign epilepsy of childhood with centrotemporal spikes (BECTS), and prolonged (several days) continuous EEG monitoring in the ICU. BECTS is misdiagnosed often, and probably mis-treated often as well. Though the long-term outcome is usually excellent, it remains unclear whether the individual epileptiform discharges have a clinical effect. Answering this question is difficult, in part because of the natural evolution of the epilepsy and its different appearance depending on wakefulness or sleep state, and also due to substantial methodologic problems in measuring short and long-term cognitive effects. Continuous EEG (CEEG) recording has grown remarkably over the last 10 years. It has proved crucial in the diagnosis of nonconvulsive status epilepticus (NCSE), especially in the ICU, given the usual lack of obvious clinical signs of seizures in most of these patients, many of whom are critically ill. Much progress has been made in agreeing on terminology for the EEG findings, but diagnosis is still complicated. More efficient and reliable technology is being developed to help process the massive amount of data captured by CEEG and make it more useful (and in a timely fashion) clinically. Still, it is not completely clear which patients should be monitored, for how long, and what is the best role for CEEG in assessing and adjusting treatment once the diagnosis has been made. Investigators are using CEEG to study "seizure burden," to help determine what are the long-term effects of nonconvulsive seizures and NCSE, and to help guide treatment and improve outcome.

1. Introduction

Clinical neurophysiology, particularly electroencephalography, has been intimately involved with epilepsy research since the invention and development of the electroencephalogram (EEG) by Berger 80 years ago. Although many other research techniques, including several types of sophisticated imaging, have been brought to bear on problems in clinical epilepsy over the ensuing decades, electroencephalography remains central to the investigation of patients with epilepsy, in diagnosis and clinical management and also in understanding the physiology of brain processes. Electroencephalography has unmatched temporal resolution and remarkable variety in its neurological correlations, many giving important insights into the function of brain processes and also into the clinical function of human patients.

This article focuses on extremes in the temporal span of electroencephalography and neurophysiological phenomena. Dr. Hughes and Dr. Takeoka discuss the clinical significance and meaning of spikes (lasting no more than a quarter of a second) in understanding the neurological function of children with benign focal epilepsy of childhood with centrotemporal spikes and current research in this area. Then, Dr. Drislane and Dr. Herman review long-term (often over days) EEG monitoring, primarily in intensive care units, in the search for nonconvulsive seizures and nonconvulsive status epilepticus and in guiding their management.

2. Benign epilepsy of childhood with centrotemporal spikes

Benign epilepsy of childhood with centrotemporal spikes (BECTS) is often misdiagnosed. A child may be brought to a neurologist because of poorly sustained attention, school difficulties, or a behavior disorder. Clinical episodes suggestive of seizures may not have been noted, and even parents may remain unaware of the typical nocturnal attacks. A diagnosis of seizures might be made (even without a

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* Corresponding author at: Comprehensive Epilepsy Program, Department of Neurology, Beth Israel Deaconess Medical Center, 330 Brookline Avenue, Boston, MA 02215, USA. Fax: +1 617 667 7919.
E-mail address: fdrislan@caregroup.harvard.edu (F.W. Drislane).

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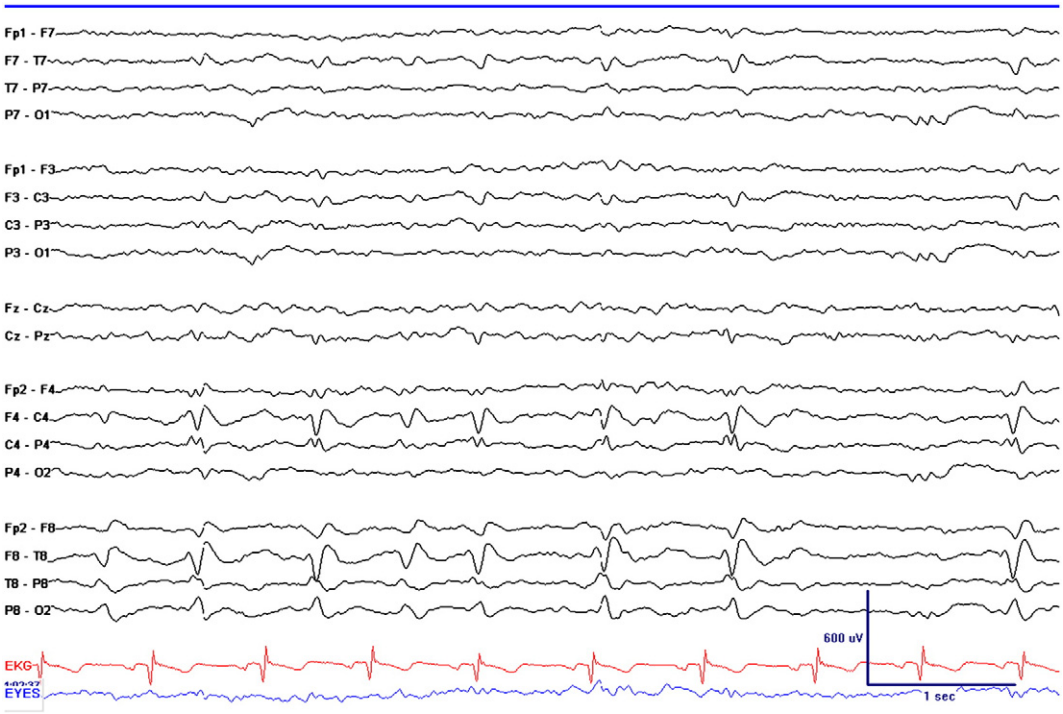

Fig. 1. Routine EEG of a child with BECTS during stage 2 sleep shows right centrotemporal spikes with triphasic morphology, maximum at C4 and T8. The field of these spikes involves the left centrotemporal area, as well, at C3 and T7. A tangential dipole is seen, with negative phase reversal at C4 and positive reversal at F4.

confirmatory EEG) and the child placed on an antiepileptic drug (AED) such as carbamazepine, only to worsen clinically [1]. An experienced neurologist with thorough EEG training, however, would more likely recognize this common childhood seizure disorder, with its typical spells of unilateral facial movements and speech arrest [2]. The experienced epileptologist/electroencephalographer would also recognize that carbamazepine may complicate or worsen treatment and precipitate the appearance of de novo generalized discharges in these patients [1].

Generalized tonic–clonic seizures (GTCSs) occur in nearly one-fifth of these children. If Gowers was correct that "seizures beget seizures" [3], the very frequent focal seizures could facilitate the development of GTCSs. One study [4] compared treated patients with BECTS with untreated patients with BECTS and found, with statistical significance ($P<0.001$), that one-half of the untreated group had GTCSs versus 19% of the treated group. Accordingly, many investigators of BECTS favor treatment with AEDs, but others do not, except with GTCSs [5]. It is also unclear if individual interictal epileptiform discharges have a clinical effect on patients, for example, in cognitive function. The work described below concerns the clinical significance of interictal epileptiform discharges in BECTS.

Benign focal epilepsy of childhood with centrotemporal spikes, or benign rolandic epilepsy, is a common type of focal epilepsy in childhood, with a prevalence as high as 24% of schoolchildren with epilepsy. It has a mean age at onset of about 7 years [6,7], and 75% of seizures occur after children fall asleep or just before they awaken [7]. Other seizure types occur in 20–54%, and about 16% have secondarily generalized seizures [8].

On the EEG, typical spikes have a biphasic or triphasic appearance over the lower part of the rolandic strip, in the central and temporal EEG electrodes, and are thus termed *centrotemporal* [9] (Fig. 1). The spike's electrical dipolar field may produce a spike of the same or opposite polarity in the contralateral homologous region as well, in the same or different records [10]. Some children have such EEG findings without clinical seizures and are considered to have a "BECTS trait."

Benign focal epilepsy of childhood with centrotemporal spikes usually has a hereditary pattern for the seizures and traits. A mutation in the gene for elongator protein complex 4 has been associated with increased genetic susceptibility to BECTS [11]. The seizure semiology, EEG pattern (including location of the epileptiform spikes, morphology and sleep potentiation, normal background rhythm, and sleep features), and lack of other neurological conditions, such as structural brain abnormalities, developmental delay, and obvious focal neurological deficits, are all consistent features of typical BECTS. Such consistency of features supports the concept of BECTS as a relatively homogeneous disorder.

There is a wide range of *atypical* forms of BECTS, but their frequency varies greatly, depending on how strict the inclusion criteria are. Rare cases present with clinical and EEG features of BECTS but later evolve into Landau–Kleffner syndrome (LKS) with electrical status epilepticus of slow wave sleep (ESES). Considering LKS, ESES, and other severe epilepsy syndromes, atypical BECTS constitutes about 1–7% of all BECTS [12,13]. When these extreme cases are excluded, but cases with subtle cognitive deficits are still evaluated, the frequency of "atypical cases" ranges from 9 to 52% [8,13].

Here, we focus on children with typical BECTS, BECTS with only subtle cognitive changes, and BECTS traits, and exclude the more severe atypical cases, such as BECTS associated with Landau–Kleffner syndrome, continuous spikes and waves during slow sleep, or other severe clinical epilepsy syndromes.

2.1. Promising areas of research and young investigators

Masanori Takeoka

Cognitive changes in benign focal epilepsy of childhood with centrotemporal spikes

Although most children with BECTS develop normally and have no obvious cognitive or neurobehavioral problems, a subset has cognitive impairment. Many studies on BECTS have reported a variety of neuropsychological deficits, but no uniform profile of impairment has been identified. Cognitive changes have been noted in attention,