

FOCAL AND GENERALIZED: BOTH HERE AND THERE

Generalized-Onset Seizures with Secondary Focal Evolution. Williamson R, Hanif S, Mathews GC, Lagrange AH, Abou-Khalil B. *Epilepsia* 2009;50(7):1827–1832. The international seizure classification recognizes that partial-onset seizures can become secondarily generalized, but generalized-onset seizures are expected to remain generalized. We report six patients who had recorded seizures with generalized onset, but subsequent evolution into a focal discharge. The clinical seizure onset was generalized absence or myoclonic, and the most common subsequent clinical pattern was prolonged behavioral arrest with mild automatisms, and then postictal confusion. The ictal discharge started with generalized spike-and-wave activity and then acquired a focal predominance. Interictal epileptiform activity was generalized. There were no focal magnetic resonance imaging abnormalities. Four patients were misdiagnosed with complex partial seizures. All patients were initially refractory, but three became seizure-free and three improved after treatment with antiepileptic medications appropriate for absence or myoclonic seizures. Generalized-onset seizures that acquire focal features are easily misdiagnosed as complex partial. These seizures have a more favorable response to medications effective against generalized absence and myoclonic seizures.

COMMENTARY

The interesting observations of this paper by Williamson and colleagues, together with others described here, illustrate the continuum between generalized and focal seizures that may be encountered in clinical practice, creating difficult diagnostic and management decisions. Relative physiological data, also presented in the following, only partially clarify such gradations.

Figure 1B in the paper by Williamson et al. illustrates generalized paroxysmal fast activity as well as sequential spike

waves during the absence seizure. The EEG suggests reduced cortical inhibition as compared to what usually accompanies spike waves (1), possibly with the reduced inhibition precipitating a seizure in a cortical area (left occipital in this image) having a lesion-based or inherently low seizure threshold. The region of seizure offset may reflect onset: a study by Blume and Pillay on secondary bilateral synchrony—an EEG phenomenon in which focal spikes proceed to bisynchronous spike waves—found hemispheric or focal offsets in 27 (47%) of 57 patients, with the offsets appearing ipsilateral to focal onsets in 26 of 27 (96%) of the patients (2). This study suggests that regional epileptogenesis may underlie a focal offset, even in the absence of an apparent focal onset. Scalp EEG may miss a focal origin, especially if the initial discharge is of low voltage and

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high frequency (3). A mesial hemispheric origin may also be missed because of only distant scalp EEG electrode coverage and a likely tangential dipole orientation (4–6).

“One-sided generalized epilepsy,” as described by Gastaut et al., also illustrates the gradation between generalized and focal epilepsy (7). Among otherwise neurologically normal patients with clinical and EEG evidence of primary generalized epilepsy, Gastaut found about 15 patients per year whose seizures had identical clinical and EEG features to the other subjects except that some were confined to one hemisphere and the contralateral limbs, with the hemisphere and contralateral motor phenomena shifting among seizures. In contrast to most focal seizures, the proximal extremities are chiefly involved, without a Jacksonian march. Various sensory phenomena have been described among patients whose awareness is somewhat preserved during absence attacks with bisynchronous spike waves (8). Other studies have shown that spike waves, which usually occur bisynchronously, may also appear regionally as the same pattern, with the field shifting among paroxysms (9,10).

The gradation between focal and generalized epilepsy is further exemplified by so-called hemispheric epilepsy. This entity is defined as bisynchronous EEG spike waves that, when lateralized, take place consistently over the same hemisphere in at least four recordings and never principally occur contralaterally (11). This constellation initially was identified in 13 patients; clinical examinations and MRI were normal in all. Bilaterally symmetrical motor seizures occurred in 13 of the 13 patients and absence in 10. An aura for absence occurred in 3 of these 10 individuals, exemplifying the apparently discordant juxtaposition of semiologies that may appear in these bridging circumstances. Similarly, a study of sequential field potentials of human spike waves, with onsets (visually assessed) that appeared bilaterally synchronous and symmetrical, showed that there were distinct regional frontal onsets in one-third of the subjects (12). Moreover, among patients with idiopathic generalized epilepsy, hemifield pattern stimulation revealed an asymmetrical threshold for initiating a photoparoxysmal response in 50% of subjects (13). These clinical studies illustrate that one hemisphere may be more epileptogenic than the other, even though bisynchronous clinical and EEG expression also exist.

Spike waves represent abnormal synchronous thalamocortical oscillations involving the thalamic reticular, relay, intralaminar, anterior, and mediodorsal neurons as well as the association cortex (14–16). It appears that spike-wave generation does *not* require a bilateral mechanism; bisynchrony of spike-wave expression appears to be principally mediated by the corpus callosum (12,17). However, under some circumstances the corpus callosum may inhibit homotopic propagation of epileptic discharges, potentially leading to an asymmetrically bilateral or unilateral EEG expression and clinical semiology (18).

Current classifications of epileptic seizures, which are based on a comprehensive compilation of epileptic semiologies and distinctive features, have essential educative and heuristic value for the practicing physician (19,20). However, the demarcations inherent in classification tend to obscure the interplay between entities created by CNS complexity and may contribute to the few epilepsy patients whose disorders remain unclassifiable under these systems. Engel et al. indicate that the distinction between focal and generalized seizures is: “. . . not an absolute dichotomy. It can be difficult to determine whether some ictal phenomena are partial or generalized or to account for the continuum from discrete focal, to diffuse hemispheric, to multifocal bilateral to bilaterally symmetrical epileptogenic abnormalities” (19). Such classifications specifically exclude a role for EEG (19,20).

The article by Williamson et al., which illustrates regional offsets of bisynchronous spike-wave onsets, carries significance beyond the mere six subjects described in the report. It brings to mind Jasper and Kershman’s seminal, yet currently applicable, correlation of seizure type with the nature of the EEG abnormalities: over 80% of patients with focal spikes had partial seizures, while a similar proportion with bilaterally synchronous spike waves had absence or nonlateralized tonic–clonic seizures (9). To redefine the role of EEG within a now much enhanced clinical and laboratory capability constitutes a challenge.

Painstaking review of the sequential features of generalized tonic–clonic seizures may disclose the lateralizing features previously described. Questioning patients with partially controlled absence may reveal curious sensory phenomena. Such measures may disclose focal cortical-like or hemispheric features in a greater proportion of patients than is currently realized, which may subsequently expand therapeutic options for some cases.

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