Absence Semiologies

Factors Influencing Clinical Features of Absence Seizures. Sadleir LG, Scheffer IE, Smith S, Carstensen B, Carlin J, Connolly MB, Farrell K. *Epilepsia* 2008;49(12):2100–2107. PURPOSE: The clinical features of absence seizures in idiopathic generalized epilepsy have been held to be syndrome-specific. This hypothesis is central to many aspects of epilepsy research yet has not been critically assessed. We examined whether specific factors such as epilepsy syndrome, age, and state determine the features of absence seizures. METHODS: Children with newly presenting absence seizures were studied using video electroencephalography (EEG) recording. We analyzed whether a child's epilepsy syndrome, age, state of arousal, and provocation influenced specific clinical features of their absence seizures: duration, eyelid movements, eye opening, and level of awareness during the seizure. RESULTS: Seizures (509) were evaluated in 70 children with the following syndromes: Childhood absence epilepsy (CAE), 37; CAE plus photoparoxysmal response (PPR), 10; juvenile absence epilepsy (JAE), 8; juvenile myoclonic epilepsy (JME), 6; unclassified, 9. Seizure duration was associated with epilepsy syndrome as children with JME had shorter seizures than in other syndromes, independent of age. Age independently influences level of awareness and eye opening. Arousal or provocation affected all features except level of awareness. Specific factors unique to the child independently influenced all features; the nature of these factors has not been identified. DISCUSSION: The view that the clinical features of absence seizures have syndrome-specific patterns is not supported by critical analysis. We show that confounding variables profoundly affect clinical features and that syndromes also show marked variation. Variation in clinical features of absence seizures results from a complex interaction of many factors that are likely to be genetically and environmentally determined.

Childhood Absence Epilepsy: Behavioral, Cognitive, and Linguistic Comorbidities. Caplan R, Siddarth P, Stahl L, Lanphier E, Vona P, Gurbani S, Koh S, Sankar R, Shields WD. *Epilepsia* 2008 Nov;49(11):1838–1846. PURPOSE: Evidence for a poor psychiatric, social, and vocational adult outcome in childhood absence epilepsy (CAE) suggests long-term unmet mental health, social, and vocational needs. This cross-sectional study examined behavioral/emotional, cognitive, and linguistic comorbidities as well as their correlates in children with CAE. METHODS: Sixty-nine CAE children aged 9.6 (SD = 2.49) years and 103 age- and gender-matched normal children had semistructured psychiatric interviews, as well as cognitive and linguistic testing. Parents provided demographic, seizure-related, and behavioral information on their children through a semi-structured psychiatric interview and the child behavior checklist (CBCL). RESULTS: Compared to the normal group, 25% of the CAE children had subtle cognitive deficits, 43% linguistic difficulties, 61% a psychiatric diagnosis, particularly attention deficit hyperactivity disorder (ADHD) and anxiety disorders, and 30% clinically relevant CBCL broad band scores. The most frequent CBCL narrow band factor scores in the clinical/borderline range were attention and somatic complaints, followed by social and thought problems. Duration of illness, seizure frequency, and antiepileptic drug (AED) treatment were related to the severity of the cognitive, linguistic, and psychiatric comorbidities. Only 23% of the CAE subjects had intervention for these problems. CONCLUSIONS: The high rate of impaired behavior, emotions, cognition, and language and low intervention rate should alert clinicians to the need for early identification and treatment of children with CAE, particularly those with longer duration of illness, uncontrolled seizures, and AED treatment.

COMMENTARY

The study by Sadleir et al. found that absence semiology varied more with the circumstances of occurrence (e.g., clinical features, age) than specific syndrome type. Their results reflect an earlier video-EEG finding of semiology variability among patients with childhood absence epilepsy as well as variability in the same child (1). Multiple components among the several systems involved in producing absence seizures with spike-waves likely bring about this pleomorphism. The following reviews some of the relevant components.

The mechanism underlying absence epilepsy with spike-waves involves abnormal oscillatory rhythms in thalamocortical

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circuits, including the nucleus reticularis thalami, thalamic relay neurons, and cortical pyramidal neurons. Perturbations at one or multiple sites within this circuit can evoke bisynchronous spike-waves (2). During wakefulness, photic stimulation, and hyperventilation may evoke absence seizures with spike-waves; sleep also elicits bisynchronous spike-waves.

Epileptic activity evoked by visual stimuli in humans appears to be initiated by synchronously activated magnocellular pathways from the occipital cortex, thus it is part of the dorsal stream of efferents stemming directly to the frontal cortex or through the brainstem reticular formation (3). In the baboon Papio papio, the only known species with naturally occurring light sensitive seizures similar to those in humans, the light-induced epileptic discharges arise in the frontal Rolandic region but require visual afferents for their precipitation. Subsequent discharge propagates to the brainstem reticular formation, at which point the clinical seizure occurs. Involvement of the thalamus in this process has been documented in the Papio papio (4).

Hyperventilation was associated with more absence seizures with spike-waves than any other state in the Sadleir et al. study. Although the mechanisms by which hyperventilation activates spike-waves and absence seizures remain unresolved, the resulting alkalosis as well as the decreases in pO_2 and pCO_2 may play significant roles (5,6). Alkalosis promotes gap-junction opening, and gap-junctions have been shown to enhance seizure activity both in the cortex (7) and the reticular nucleus of the thalamus (8). About one-third of seizures recorded in the study by Sadleir and colleagues occurred during drowsiness or sleep and correlated with the transition from the tonic mode of thalamic neuronal firing to an oscillatory mode, from which spike-wave burst firing can emerge (9,10). The distinct mechanisms of these precipitants of the thalamocortical spike-wave circuitry likely perturb its malfunction differently, thus affecting various semiologies associated with absence with spike-waves. However, there are other potential variables.

Systemic pentylenetetrazol evokes bisynchronous spike-wave discharges prior to convulsive seizures. Experimental evidence suggests that the mediodorsal and midline thalamic nuclei are involved in the generation of the convulsive phase. Neuroimaging studies also have demonstrated thalamic involvement (10). In convulsive seizures, cortical afferents likely arise from these thalamic nuclei as well as from thalamic relay nuclei. However, the mediodorsal nuclei do not form a functional unit: there are several subdivisions, each supplying a different part of the prefrontal cortex (11). Thus, the basis for another potential semiological variable is added.

Microelectrode recordings of feline cortical layers (using systemic penicillin) disclosed correlations with each of several components of resultant spike-wave complexes: 1) surface negative spike: excitation in upper cortical layers, 2) positive trough: excitation in lower cortical layers, and 3) wave: lower cortical layer inhibition (12). Corticofugal impulses from the motor cortex correlate with lower cortical layer excitation in a study of focal epilepsy (13). Therefore, motor phenomena associated with absence epilepsy with spike-waves indicate involvement with its lesser-known trough complex and any variability connected with this spike-wave component.

The anterior–posterior expression of spike-waves also may influence its associated motor manifestations. Bilateral placement of acute epileptogenic foci on monkey anterior frontal cortex produced absence seizures with no motor components, while progressively more posterior placements were associated with increased motor features from myoclonus to tonic–clonic events (14). Additionally, the range of spike-wave frequency (1.5–4 Hz) likely influences absence motor manifestations. Clinical and experimental data indicate an inverse relationship between spike-wave frequency and cortical excitability—thus, with associated absence motor manifestations (15,16).

Among descending tracts that originate in the brainstem, motor manifestations of generalized seizures principally involve the reticulospinal system. The cortical afferents to the reticulospinal tract arise chiefly from the Brodmann areas 4 and 6 of the motor cortex (17). Data suggest that the motor components of seizure output of the reticulospinal tract are influenced by the level of arousal, strength of cortical afferents, and location of cortical involvement.

Brainstem stimulation studies indicate that myoclonic seizures arise principally from the mesencephalic reticular formation. Velasco and Velasco demonstrated that tonic and atonic attacks reflect caudal involvement (18), corresponding to the motor excitation property of the pons and mesencephalon and to the motor inhibition property of the ventral medial medulla (19,20). GABA experimental injection into rat lateral dorsal tegmental nucleus of the mesencephalic reticular formation incites myoclonus (21), confirming the localization findings of myoclonus in the Velasco and Velasco study (18). Thus, ocular and facial phenomena, such as eyelid myoclonia, are likely mediated by interneurons in periaqueductal gray of the mesencephalic reticular formation (22). A neuronal pool in the lower brainstem may integrate masticatory automatisms, while reticular formation stimulation may elicit stereotyped limb movements (17,23).

However, the anatomical complexity of the brainstem reticular system, which is a wickerwork of long dendrites and axons with multiple collaterals, produces a moderate overlap of excitatory and inhibitory areas (14). As was similar in the other potential mechanism sites, a complex interplay among reticular formation areas likely contributes to the variable motor accompaniments that occur with absence epilepsy with spike-waves. Moreover, the strength of stimulus to the brainstem

reticular formation also influences resulting motor features. One study found that mild reticular formation stimulation evoked myoclonic phenomena, moderate stimulation produced a tonic response with limb flexion, and a strong stimulus elicited tonic limb extension (24). Nonetheless, in some patients, a relatively consistent sequence of automatisms during absence seizures with spike-waves has been found: ocular, oral, and non-oral automatisms, in that order (25). This finding suggests possible seizure progression within at least one of the involved systems described here.

From the number and extent of systems involved in the production of absence epilepsy with spike-waves, the substantial proportion of afflicted children with cognitive, attention, and related deficits described in the Caplan et al. study is not surprising. In addition, antiepileptic drugs likely impair learning and school performance to various degrees (26). Antiepileptic drugs may disrupt normal sleep architecture. For instance, valproate was shown to increased stage 1 sleep (27). Finally, stigma afflicts all patients with epilepsy, leading to anxiety and depression (28), which also may impair cognitive performance at school or at work.

Physiological and anatomical variables at each stage of absence-spike wave production, from precipitant to brainstem, likely contribute to the inconsistency in both inter-patient and intra-patient motor manifestations, as seen in the study of Sadleir et al. and others (1,25). Therefore, the current classification system of absence syndromes that contains only distinct categories appears insufficiently flexible to portray such varying phenomena. Instead, a codification system with multiple arms has been proposed; it takes advantage of the multifaceted programmable database systems presently in use (29). The Caplan et al. findings underscore the need for practicing physicians to monitor social aspects of all young patients with a seizure disorder, even those that appear to be relatively benign.

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