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Review

Absence seizures: A review of recent reports with new concepts

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ABSTRACT

Absence seizures with bilateral spike–wave (SW) complexes at 3 Hz are divided into the childhood form, with onset at around 6 years of age, and the juvenile form, with onset usually at 12 years of age. These seizures typically last 9–12 s and, at times, are activated by hyperventilation and occasionally by photic stimulation. Generalized tonic–clonic (GTC) seizures may also occur, especially in the juvenile form. There may be cognitive changes, in addition to linguistic and behavioral problems. Possible mechanisms for epileptogenesis may involve GABAergic systems, but especially T-calcium channels. The thalamus, especially the reticular nucleus, plays a major role, as does the frontal cortex, mainly the dorsolateral and orbital frontal areas, to the extent that some investigators have concluded that absence seizures are not truly generalized, but rather have selective cortical networks, mainly ventromesial frontal areas and the somatosensory cortex. The latter network is a departure from the more popular concept of a generalized epilepsy. Between the "centrencephalic" and "corticoreticular" theories, a "unified" theory is presented. Proposed genes include T-calcium channel gene CACNA1H, likely a susceptible gene in the Chinese Han population and a contributory gene in Caucasians. Electroencephalography has revealed an interictal increase in prefrontal activity, essential for the buildup of the ictal SW complexes maximal in that region. Infraslow activity can also be seen during ictal SW complexes. For treatment, counter to common belief, ethosuximide may not increase GTC seizures, as it reduces low-threshold T-calcium currents in thalamic neurons. Valproic acid and lamotrigine are also first-line medications. In addition, zonisamide and levetiracetam can be very helpful in absence epilepsy.

1. Introduction

In the past 3 years, a number of studies have challenged prevailing concepts of generalized epilepsy, especially with respect to the classic absence seizure with its bilateral spike–wave (SW) complexes at 3 Hz. Characteristics of the cognitive, behavioral, and motor changes in these patients have recently been more carefully explored. The purpose here was to review recent studies on clinical absence seizures and also to deal with new concepts that challenge the generalization aspect of these seizures. This review deals only with the human condition of absence seizures and is not concerned with animal studies, especially those involving the WAG/Rij rat, whose generalized seizures may or may not be equivalent to human absence seizures.

As different types of absence seizures, such as the childhood form, the juvenile form, and eyelid myoclonia, are discussed, the review deals with epilepsy syndromes with absence seizures. With respect to mechanisms, the emphasis is on epileptogenesis but also ictogenesis.

2. Methods

For this review Medline was surveyed for studies dealing with human absence seizures, published from 2005 to 2008. Animal studies, especially those dealing with the WAG/Rij rat [1], were disregarded because their relevance to human absence seizures remains controversial.

3. Characteristics of the human absence seizure

3.1. General

In a study of 51 patients with absence seizures, Duŕa Travé and Yoldi Petri [2] reported a relatively high proportion of females (73%), different from the 59% in another study [3]; the mean age at onset was 7.5 years and 80% had multiple seizures per day with a mean duration of 12 s. School performance was impaired in 20% of these patients, hyperventilation activating the ictal bilateral SW complexes at 3 Hz in a relatively high and unexpected number (98%) and photic stimulation in only 16%. Seizures were controlled with valproic acid at 26 mg/kg/day (mean) in 84%. In the great majority (84%) medication was withdrawn in 3 years; only 7% relapsed. The authors added that absence seizures can impair learning, as might be expected.

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3.2. Incidence

The same authors [2], in a different publication [4], reported the incidence of absence epilepsy in children <15 years of age. Of the nearly 200 children with seizures, 19% had absence epilepsy. The latter value was very different from the incidence of 4% in 8285 children reported by Caraballo et al. in Argentina [5]. In the United States [6], the study by Tanaka et al. reported values midway between 19 and 4%, namely, 10–12%, [6]. In the Spanish study [4] involving 14 years of experience with 7562 neuropediatric patients, 10% had epilepsy, and among the latter, 6.5% had absence seizures. As absence seizures are known to have a prominent inheritance, differences from one laboratory to another may be expected with different populations sampled. From these values, 10% is indicated as the average incidence of absence seizures in pediatric epilepsy.

3.3. Types

3.3.1. Childhood versus juvenile absence seizures

For the childhood form, Sadleir et al. [7] found that the average ictal duration was 9 s for the absence, and clinical features consisted of arrest of activity, loss of awareness, staring, 3-Hz eyelid movements, and, of course, 3-Hz bilateral SW complexes on the EEG.

Tovia et al. [8] reported that 59% of their patients with the juvenile form were female; the mean age at onset was 12 years, and 29% of the patients had a family history of epilepsy. Generalized tonic–clonic (GTC) seizures occurred in nearly one-half (47%), and at follow-up (usually after 6 years), 44% were seizure free. Among patients who had had GTC seizures (compared with no GTC seizures), fewer (38% vs 56%) were seizure free, so that GTC seizures were a predictor of a poorer outcome. Also, outcome was generally less favorable for the juvenile than for the childhood form. Another group [9] reported on the characteristics of idiopathic generalized epilepsy including absences, claiming patients often showed a mild impairment of cognitive functions, especially verbal memory. They also had characteristic personality traits, including neglect of physical needs, were poorly compliant with therapy often with obstinacy, and were often relatively impressionable. Many of the latter characteristics were suggestive of involvement of the frontal lobe. Mullins et al. [10] reported a higher incidence of females (61%) in the juvenile type than the childhood form (55%), similar to the results of Tovia et al. [8].

Valentin et al. [11] studied patients of all ages with absence seizures and reported that more (53%) had the juvenile than the childhood form. Among the patients in the latter category, the 1989 criteria were first applied and, then later, the stricter 2005 criteria were used, according to the International League Against Epilepsy (ILAE), and this change reduced the number considered to have the childhood form by 32%. With the stricter 2005 criteria, a better outcome was evident, and thus, diagnostic criteria used to classify these children had prognostic significance. During the next year in 2008, Malik et al. [12] concluded similarly that patients with childhood absence seizures had a favorable prognosis. Other investigators [13] compared children with absence seizures classified with the early criteria with those classified with the later stricter criteria with respect to different variables, including gender, family history of generalized epilepsy, and history of febrile seizures. As a group, patients classified with the stricter criteria had better seizure control, better remission rates, fewer GTC seizures, and shorter periods of treatment. As did the other study [11], Grosso et al. [13] indicated that patients with a stricter definition of their absence type constituted a more homogenous group and had an excellent prognosis.

3.3.2. Frequency and duration changes

Bosnyakova et al. [14] differentiated ictal bilateral SW complexes according to their frequency and duration. One group of complexes lasting >4 s quickly decreased in frequency from 5 to 3.5 and then to 3 Hz. The other group with a shorter duration (<4 s) also decreased in frequency from a similar 5 to 2–2.5 Hz. The authors concluded that the different types "most likely represent different dynamics in the corticoreticular-cortical loop".

3.3.3. Typical versus atypical absences

Sinclair and Unwala [15] compared typical and atypical childhood absence seizures in 119 patients (not those with Lennox–Gastaut syndrome), according to ILAE criteria, emphasizing the less abrupt onset and offset of the ictal atypical form. No differences were noted between these two groups with respect to complex automatisms, changes in tone, incontinence, attention-deficit hyperactivity disorder (ADHD), learning disorders, remission in 2 years, and enuresis. However, the typical group showed less developmental delay and responded better (83% vs 51%) to medication. The authors concluded that the clinical and EEG characteristics are similar and the two forms are part of a continuum. Although the eventual outcomes were similar, seizures in the atypical variant may *initially* be more difficult to control.

3.3.4. Idiopathic generalized epilepsy with absences versus GTC seizures

Koutroumanidis et al. [16] compared groups with idiopathic generalized epilepsy with phantom absence seizures with groups with GTC seizures and found that those with only GTC seizures never had absence seizures, even though they reviewed many EEGs searching for SW complexes. The GTC seizures tended to occur on awakening; a hereditary risk was found in 30%, compared with only 7% in those with absence seizures. The conclusion was that these two groups are distinct entities.

3.3.5. Absences with and without eyelid myoclonia

Burneo et al. [17] described two patients with absence seizures and eyelid myoclonia (EM): in one the clinical seizures occurred only in daylight, and in the other some rare focal discharges were observed along with the ictal SW complexes. Valproic acid only partially controlled the seizures, and lamotrigine was ineffective in both cases. A few years later, Joshi and Patrick [18] studied 288 patients with idiopathic generalized epilepsy and reported that 9% had both absence seizures and EM, concluding that the condition was not uncommon. Compared with those without EM, patients with EM were older at the first EEG, were more likely to have had bilateral paroxysms on their routine EEG, had a higher prevalence of developmental delay, but more often had a normal EEG background. Developmental delay was also emphasized by Mourente-Diaz et al. [19] in patients with EM "with marked jerking of the eyelids, often associated with jerky upward deviation of the eyeballs," triggered often by eye closure, and described by another group as well [20]. The ictal EEG pattern was consistent with generalized polyspike–waves at 3–6 Hz. Ogura et al. [21] noted that paroxysmal bursts on the occipital areas preceded the more generalized SW complexes. In 2008, Striano et al. [22] further described patients with absence seizures and EM, characterized by eye closure-induced EEG paroxysms and photosensitivity (Jeavons syndrome). There were 35 patients and 66% were female. Most of the patients (77%) had been administered one to five AEDs; the median number of days per month on which seizures occurred was 12, with the majority also experiencing GTC seizures. Levetiracetam was well tolerated; 80% responded and two-thirds had no more GTC seizures over the next 12 weeks.