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EPILEPSY SYNDROMES IN DEVELOPMENT

Eyelid myoclonia with absences (Jeavons syndrome): A well-defined idiopathic generalized epilepsy syndrome or a spectrum of photosensitive conditions?

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Summary

Eyelid myoclonia with absences (EMA), or Jeavons syndrome, is a generalized epileptic condition clinically characterized by eyelid myoclonia (EM) with or without absences, eye closure-induced electroencephalography (EEG) paroxysms, and photosensitivity; in addition, rare tonic–clonic seizures may also occur. Although first described in 1977 and widely reported by several authors within the last few years, EMA has not been yet recognized as a definite epileptic syndrome. However, when strict criteria are applied to the diagnosis, EMA appears to be a distinctive condition that could be considered a myoclonic epileptic syndrome, with myoclonia limited to the eyelids, rather than an epileptic syndrome with absences.

KEY WORDS: Eyelid myoclonia, Eyelid myoclonia with absences, Epilepsy, Myoclonus, Photosensitivity.

The first clinical description of a patient showing a condition recognizable as eyelid myoclonia with absences (EMA) was reported more than 70 years ago: ''A.A., 20 years old presents involuntary movements of the head and eyes under influence of sunlight. The initial manifestations date back approximately 10 years. At the age of 10–12 … his schoolfellows frequently frightened him by forcing him to gaze directly upwards. Rhythmic head movements with rotation in direction of sunlight were associated with fast eyelid blinking. … when the sunlight is brighter, he has … fall and loss of consciousness ... two to three per year'' (Radovici et al., 1932).

This description highlights the main clinical features of this condition, that is, childhood onset, unique seizure manifestations, striking light sensitivity, possible occurrence of generalized tonic–clonic seizures, and tendency to persist over the lifespan. However, only in 1977 Jeavons clearly delineated this condition: ''Eyelid myoclonia and absences show a marked jerking of the eyelids immediately after eye closure and there is an associated brief bilateral spike and wave activity …. Brief absences may occur spontaneously … accompanied by 3/sec spike-waves. The spike-waves ... after eye closure do not occur in the dark. Their presence in the EEG is a reliable warning that abnormalities will be evoked by photic stimulation'' (Jeavons, 1977).

Following this description, several authors then confirmed the identification of EMA—for which the eponym of Jeavons syndrome (JS) has been proposed—as a separate entity among idiopathic generalized epilepsies (IGEs) (Appleton et al., 1993; Giannakodimos & Panayiotopoulos, 1996; Striano et al., 2002; Covanis, 2005). However, some authors argue that eyelid myoclonia (EM) with or without absences may occur in several epileptic conditions of idiopathic, cryptogenic, and symptomatic origin, and, therefore, their occurrence alone is not sufficient to characterize a definite epilepsy syndrome (Ferrie et al., 1996; Panayiotopoulos et al., 1996). The recent International League Against Epilepsy (ILAE) proposal of Diagnostic Scheme of Epileptic

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Seizures and Epilepsy also recognizes EM without or with absences as a seizure type, but it does not list EMA among the epilepsy syndromes, merging it with other photosensitive epilepsies (but not idiopathic photosensitive occipital lobe epilepsy) under the label of ''other visual sensitive epilepsies'' (Engel, 2001).

A Definite Epilepsy Syndrome? Pros and Cons.

The pros

According to definition of key terms of the 2001 ILAE proposal, an epilepsy syndrome is ''a complex of signs and symptoms that define a unique epilepsy condition'' (Engel, 2001).

EMA or JS could be defined by the occurrence of the following triad: (1) frequent occurrence of eyelid myoclonia with or without brief absences, related to electroencephalography (EEG) generalized epileptiform activity and triggered by eye closure; (2) generalized photoparoxysmal EEG response, often in combination with a history of visually induced seizures; (3) onset in childhood.

EMs are the crucial semiologic phenomena of JS and may be followed or not by brief absences, usually lasting <6 s. The recognition of EM is simple and this seizure type—once seen—cannot be missed or confused with other conditions. In addition, the characteristic eye closure–related discharges in combination with photosensitivity does not leave room for diagnostic error. Seizures occur mainly after eye closure, many times per day, and an eyelid myoclonic status epilepticus is reported in up to one-fifth of the patients; seizure self-induction is also possible (Panayiotopoulos, 2005). Generalized tonic–clonic seizures (GTCS), even if rare, occur in the majority of the patients and are often related to precipitating or facilitating factors, such as sleep deprivation, alcohol abuse, poor drug compliance, bright sensitivity, and television or video-game exposure. Myoclonic jerks other than EM are rarely reported (Covanis, 2005), and Striano and colleagues consider the occurrence of myoclonic jerks in body regions other than the eyelids, an exclusion criterion for the diagnosis of JS (Striano et al., 2002).

Ictal paroxysmal activity (PA) is characterized by high-amplitude generalized polyspikes or polyspike-wave complexes, often followed by brief discharges (3–6 s or less) of rhythmic spike- or polyspike-wave complexes at 3 or more per second. Typically, PA is triggered by active eye-closure (not by simple eye blinks), occurring immediately on closing the eyes, in a well-lit recording room; darkness abolishes totally or partially this response, whereas hyperventilation can enhance generalized paroxysmal activity and eventually give rise to EM and absences. Photosensitivity usually decreases with age and can be suppressed by antiepileptic drugs (AEDs), even if EM persist (Striano et al., 2002; Panayiotopoulos, 2005). In some patients, the fixation-off phenomenon has been reported (Panayiotopoulos, 2005).

EMA onset is typically in childhood, with a peak at 6–8 years. However, the time of seizure onset may be difficult to be exactly established, as eyelid jerks are frequently misinterpreted as tics or mannerisms, and absences may be overlooked. As expected for an IGE syndrome, mental status is usually normal, and a slight mental retardation is reported in only rare cases (Scuderi et al., 2000).

A genetic contribution to the syndrome is likely, as suggested by reports of identical twins affected (Parker et al., 1996; Striano et al., 2002; Adachi et al., 2005). However, further accurate studies are needed for a better knowledge of the precise genetic influence in EMA. As in other photosensitivity syndromes, EMA is more frequent in females and is probably a long-lasting condition.

JS should be considered a myoclonic rather than an absence epilepsy, and this concept has therapeutic consequences, supporting the good clinical efficacy of antimyoclonic drugs such as levetiracetam (Striano et al., 2008) and zonisamide (Kothare et al., 2004). Some patients show resistance to antiepileptic therapy.

Table 1. Epileptic conditions sharing common features with eyelid myoclonia with absences

Conditions with eye closure sensitivity
Eyelid myoclonia with absences
Juvenile absence epilepsy
Juvenile myoclonic epilepsy
Idiopathic generalized epilepsy with tonic–clonic seizures
Idiopathic occipital lobe epilepsy
Conditions with eyelid myoclonia (with or without absences)
Eyelid myoclonia with absences
Childhood absence epilepsy
Juvenile absence epilepsy
Juvenile myoclonic epilepsy
Sunflower syndrome(s)
Self-induced seizures
Idiopathic generalized epilepsy with phantom absences
Myoclonic status in nonprogressive encephalopathies
Conditions with photosensitivity
Eyelid myoclonia with absences
Visual reflex seizures
Sunflower syndrome(s)
Benign myoclonic epilepsy in infancy
Childhood absence epilepsy
Juvenile myoclonic epilepsy
Idiopathic generalized epilepsy with tonic–clonic seizures
Juvenile absence epilepsy
Idiopathic photosensitive occipital lobe epilepsy
Severe myoclonic epilepsy of infancy (Dravet syndrome)
Progressive myoclonic epilepsies
Alcohol or benzodiazepines withdrawal

The cons

The more impressive symptom, EM (followed or not by a brief absence), induced by eye closure and by intermittent photic stimulation (IPS), is observed in several common forms of idiopathic, symptomatic, and cryptogenic epilepsy syndromes, either generalized or focal (i.e., occipital) (Kasteleijn-Nolst Treinté et al., 2001). In addition to EMA, eye closure sensitivity has been reported also in juvenile myoclonic epilepsy (JME), in IGE with tonic–clonic seizures, in juvenile absence epilepsy, and in idiopathic photosensitive occipital lobe epilepsy (IPOLE) (Sevgi et al., 2007). Fixation-off phenomenon, the putative trigger mechanism of PA in Gastaut-type childhood OLE, is sometimes described in patients with EMA (Panayiotopoulos, 2005). Therefore, some epileptic conditions with photosensitivity or with eye closure sensitivity share some seizure types with EMA, making the boundaries of this syndrome not completely clear (Table 1). In addition, some variations in activation functional magnetic resonance imaging (fMRI) patterns in EMA patients have been seen (Liu et al., 2008). Destina Yalçin et al. report some cases of EMA overlapping with JME, and suggest that these are two dynamic syndromes evolving one into another (Destina Yalçin et al., 2006).

Furthermore, the above-described typical electroclinical pattern is often modified by the effect of age and/or therapy; therefore, epileptiform activity frequently becomes subclinical, particularly in response to eye closure, or may appear limited to the occipital regions; photoparoxysmal response decreases in intensity, appearing only confined on occipital areas [i.e., shifting from Waltz 4 to Waltz 1–2 response (Waltz et al., 1992)] and may also disappear (Striano et al., 2002). These factors can additionally contribute to make more difficult the identification of EMA as a unique epileptic syndrome. Finally, Capovilla et al. recently described a homogeneous population with eyelid fluttering, various seizure types,

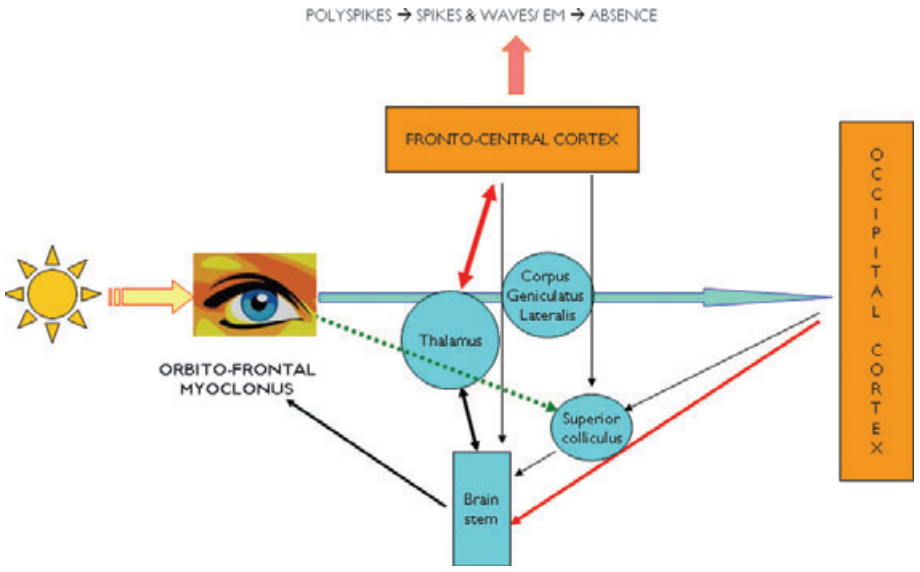

Figure 1.

Eyelid myoclonia with absences (EMA): from to semiology to neural networks. The role of occipital cortex (OC) in EMA, and, more in general, in photosensitive epilepsies, is of crucial importance. Eye closure and intermittent photic stimulation (IPS) "synchronize" OC neurons. Activation of OC depends on light intensity, volume of cortex activated, and level of excitability. Therefore, light attenuation inhibits response to eye closure in EMA, and monocular stimulation or optical lenses reduce response to IPS in photosensitive patients. Some antiepileptic drugs (AEDs) (and age-related reduction of excitability) reduce spreading of discharges, thereby limiting paroxysmal activity to the posterior cortex. Spreading of the visual response to the cortex, and in particular to the frontorolandic (FR) cortex, is possible by either transcortical or subcortical (reticulothalamic) pathways, inducing generalized or predominantly FR paroxysmal discharges. Reciprocal thalamocortical interactions are likely essential to generate rhythmic spike and waves (and absences) following initial polyspike (and myoclonia) discharges. The role of the brainstem in generating photomyoclonic response is also important, as demonstrated by the photosensitive fowl model and by mesencephalic chimeras (Naquet & Batini, 2004).

distinctive EEG features, and impaired intellectual function, suggesting the existence of a definite subgroup of epileptic patients with EM, but separate from EMA (Capovilla et al., 2009).

From Semiology to Neural Networks

In 1929, Clementi was able to induce EM by visual stimulation after strychninization of occipital cortex in dogs (Clementi, 1929). The importance of occipital cortex in the initiation of paroxysmal discharges triggered by intermittent photic stimulation was also confirmed by clinical and experimental studies on humans as well as on *Papio papio* baboons. In EMA, a possible alpha-rhythm generator malfunction has been hypothesized (Panayiotopoulos, 2005). Therefore, the response to occipital (hyper)excitation in genetically ''predisposed'' beings produces: (1) photomyoclonic response (EM); (2) subclinical paroxysmal activity confined to occipital areas (Waltz 1–2 response); (3) clinical and EEG occipital seizures; (4) photoparoxysmal response, with generalized polyspikes and polyspike-wave complexes, often associated with massive myoclonias (and sometimes absences); and (5) generalized tonic–clonic seizures. The sequence of electrical and clinical events is different in humans and in *Papio papio*; in photosensitive fowls the role of ''epileptic'' brainstem is essential to produce myoclonus and convulsions without EEG paroxysmal activity (Naquet & Batini, 2004). On the other hand, diffuse cortical hyperexcitability (''cortico-reticular system,'' as postulated by Gloor and coworkers) in IGEs is not necessarily uniform, as shown by both spontaneous and reflex epileptogenesis as well as by local functional abnormalities demonstrated by functional neuroimaging (Binnie, 2004; Liu et al., 2008). The role of corpus callosum, corticocortical, and thalamocortical pathways is also crucial in ''primarily generalized'' epilepsies. In this view, generalized epilepsies involve ''functional systems'' and their supporting circuitry (Wolf, 2006; Liu et al., 2008). A schematic representation of system and circuits possibly involved in EMA is proposed in Fig. 1.

Conclusions

The characteristics of EMA favor the idea that it represents a unique epileptic condition, with onset in childhood and long-lasting duration. The distinctive type of seizure (even if possible in other conditions), the specific EEG pattern associated, the modalities of seizure provocation, and the photosensitivity allow one to configure a cluster of signs customarily recurring together, fulfilling the definition of an epilepsy syndrome. According to current classifications, EMA can be correctly classified in the field of IGEs. However, the role of occipital cortex, in a context of diffuse cortical hyperexcitability, seems to be fundamental. On the other hand, the role of specific cortical areas or of neuronal networks is a common observation in IGEs and, more in general, in the group of idiopathic epilepsies; thus the concept of ''system epilepsies'' rather than generalized or focal syndrome has been proposed for these conditions (Wolf, 2006). In this view, the not clear-cut boundaries with other epileptic conditions, either generalized (other photosensitive or self-induced epilepsies) or focal (e.g., IPOLE), could be justified.

Acknowledgments

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

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