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FULL-LENGTH ORIGINAL RESEARCH

Eyelid fluttering, typical EEG pattern, and impaired intellectual function: A homogeneous epileptic condition among the patients presenting with eyelid myoclonia

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Summary

Purpose: This retrospective study aims to review the electroclinical features of patients presenting with eyelid myoclonia (EM) with and without absences.

Methods: The Italian chapter of the International League Against Epilepsy (ILAE) has been conducting an electroclinical study of patients with EM. Among these, we searched for and selected the patients presenting with both impairment of intellectual functions and a peculiar ictal electroencephalography (EEG) pattern, that is, a discharge of fast generalized polyspikes/polyspikes and waves.

Results: We found 18 patients matching this electroclinical picture. All the patients were photosensitive. All of them had associated generalized, mostly nocturnal, tonic–clonic seizures. During the evolution, 13 patients presented episodes of EM status. Despite adequate antiepileptic treatment, the patients remained drug resistant for many years or throughout the evolution. The degree of impairment of intellectual functions varied from borderline level to moderate mental retardation.

Discussion: The patients we described herein can be considered a homogeneous group in the more heterogeneous group of patients presenting with EM. Further clinical and, more probably, genetic studies will clarify whether this condition could be considered a specific and homogeneous condition in the more heterogeneous group of patients presenting with EM.

KEY WORDS: EMA, Eyelid myoclonic epilepsy, Intellectual impairment, Mental retardation, Generalized epilepsy.

The clinical manifestations of eyelid myoclonia (EM) can be observed in different idiopathic, symptomatic, or cryptogenic epileptic syndromes (Panayiotopoulos et al., 1996; Engel, 2001; Covanis, 2005). Within the spectrum of epilepsies with EM, eyelid myoclonia with absences (EMA) or Jeavons syndrome is considered a form of idiopathic generalized epilepsy. EMA was first described in 1977 (Jeavons, 1977) and has subsequently been confirmed by several other authors (Striano et al., 1979; Gobbi et al., 1985; De Marco, 1989; Appleton et al., 1993; Duncan & Panayiotopoulos, 1996; Giannakodimos & Panayiotopoulos, 1996; Wallace, 1996; Kent et al., 1998; Incorpora et al., 2002; Covanis, 2005). The hallmark of

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the syndrome consists of marked jerking of the eyelids often associated with jerky upward deviation of the eyeballs and retropulsion of the head (EM without absences). These seizures are brief (3–6 s) and occur mainly after eye closure and consistently many times per day (Appleton et al., 1993; Giannakodimos & Panayiotopoulos, 1996; Panayiotopoulos et al., 1996; Striano et al., 2002). EM may be associated with or followed by mild impairment of consciousness (EM with absences). Age at onset ranges between 2 and 14 years, with a peak at 6–8 years of life (Giannakodimos & Panayiotopoulos, 1996; Striano et al., 2002; Burneo et al., 2004; Covanis, 2005). The ictal electroencephalography (EEG) is characterized by generalized polyspike–wave discharges. Photosensitivity is almost invariably present, although its clinical and EEG expressivity usually decreases with age and can be modified by antiepileptic drugs (AEDs) (Appleton et al., 1993; Giannakodimos & Panayiotopoulos, 1996; Panayiotopoulos et al., 1996; Incorpora et al., 2002; Striano et al., 2002; Sevgi et al., 2007). In addition, during their life, patients with EMA may experience generalized tonic–clonic seizures, either spontaneous or photo-induced (Giannakodimos & Panayiotopoulos, 1996; Kent et al., 1998; Baykan-Kurt et al., 1999; Wakamoto et al., 1999; Kimura, 2000; Striano et al., 2002; Burneo et al., 2004; Covanis, 2005; Destina Yalcin et al., 2006; Sevgi Demirci & Saygi, 2006). Neurologic and magnetic resonance imaging (MRI) examinations are unremarkable in most cases, although patients with borderline intellectual functioning or frank mental retardation have been described (De Marco, 1989; Striano et al., 2002; Covanis, 2005; Ogura et al., 2005; Sevgi Demirci & Saygi, 2006; Termine et al., 2006; Joshi & Patrik, 2007). Herein, we describe a series of patients showing peculiar and homogeneous electroclinical features, including eyelid fluttering, typical EEG pattern, and cognitive impairment. These patients could constitute a definite and distinct subgroup in the more vast group of patients with EMA.

Patients and Methods

The Italian chapter of the ILAE (LICE) has been conducting a clinical study within the spectrum of epilepsies with EM (Capovilla et al., 2006). This was a retrospective study conducted in seven tertiary referral Italian epilepsy centers. In addition, another European epilepsy center (Strasbourg) participated in the study. We reviewed the databases of the centers and overall examined the video-polygraphic recordings of EMA subjects. Data from 153 EMA patients were collected. Among this group of patients, we selected those showing both a peculiar and typical electroclinical pattern, that is, a discharge of fast generalized polyspikes accompanied by very fast myoclonic jerks of eyelids resembling a flutter and an impairment of intellectual function. Patients without these features were excluded from the study. We re-called and reexamined all these patients personally. The investigators undertook personal interviews with the patient and at least one relative, usually a parent. For all patients with long lasting disease followed for many years, a seizure diary and clinical evaluation visits at least every 6 months were available. The data from each patient were tabulated with full details of seizure types, seizure frequency, response to therapy, AEDs utilized, ictal and interictal EEG recordings, and neuroradiologic findings. We also investigated gender, personal antecedents, family history, age at onset, and follow-up duration. All patients underwent prolonged and repeated video-EEG recordings during wakefulness and during diurnal sleep induced by sleep deprivation. Electrodes were placed according to the 10–20 International system. Hyperventilation (HV) and intermittent photic stimulation (IPS) were used as activators.

Results

Eighteen patients (10 F, 8 M, 11.7% of EMA patients recruited in the centers), aged 13–39 years (mean 24.3), were selected. Their clinical and electrophysiologic features are summarized in Table 1. Mean age at epilepsy onset was 6 years (range 2–13 years, median 7 years). All the patients had an uneventful personal history and were intellectually normal before epilepsy onset. None of the patients had a long (>1 year) duration of epilepsy prior to the correct diagnosis and adequate (and appropriate) treatment. A family history of epilepsy was present in 13 of the 18 cases (72%), mostly for the idiopathic generalized form. Two patients are dizygotic twins, and two are the mother and her first son.

Seizure manifestations

Eyelid myoclonia

All patients had very fast (8–10 Hz) EM occurring at eye closure, with a maximum latency of 3 s, neither accompanied nor followed by total impairment of the consciousness, as they promptly answered simple questions. Thirteen patients (72%) experienced during their life, more commonly during late childhood, prolonged episodes of EM persisting at eye closure and realizing a true status epilepticus.

Other seizure types

Most of the patients (14 of 18, 77%) also had monthly or yearly tonic–clonic seizures, usually occurring during sleep, which started frequently from the first years of the second decade of life and persisting during adulthood in nine cases, despite adequate AED treatment. Repeated and prolonged polygraphic video-EEG recordings excluded the presence of absence seizures as well as of

Table 1. Electroclinical features of the 18 patients

Pt/sex/age (years)	Fam	Onset (years)	Eyelid myoclonia control	Eyelid Dis	Eyelid status	GTCS	GTCS dis	Mental status	EEG		IPS		Follow-up duration (years)
									Ictal	Interict	SC	EC	
1/F/14	E	2	No	13 years	Yes	Yes	Yes	B	PP-PPO	PO	–	+	12
2/M/13	–	2	No	No	Yes	No	–	MI	PP-PPO	PPO	–	+	11
3/F/31	E	9	No	No	Yes	Yes	No	MO	PP	–	–	+	22
4/F/31	E	13	No	No	Yes	Yes	No	MO	PP	–	–	+	18
5/F/32	E	3.6	No	No	No	Yes	Yes	MI	PP-PPO	PO	+	+	29
6/M/13	–	3.6	No	No	Yes	Yes	No	MI	PPO	–	–	+	10
7/M/27	FS	6	No	No	Yes	No	–	MI	PP-PPO	PPO	–	+	21
8/M/28	–	10.6	No	22.6 years	Yes	Yes	Yes	MI	PPO	PO	+	+	17
9/M/29	E	11	Yes	14 years	Yes	Yes	No	B	PP	–	+	+	18
10/F/22	–	7	No	No	Yes	Yes	Yes	MO	PP-PPO	PO	+	–	15
11/F/23	E	11	No	19 years	No	No	–	MI	PO-PPO	PO	+	+	12
12/F/28	E	4.6	No	No	Yes	Yes	No	B	PP	PP	+	+	24
13/M/16	E	7	No	No	No	Yes	No	MO	PO-PPO	PO	+	+	9
14/F/35	E	5	No	No	Yes	Yes	Yes	MI	PP-PPO	PPO	+	+	30
15/M/21	E	9	No	18 years	Yes	Yes	No	MI	PO-PPO	PO-PPO	+	+	12
16/M/18	E	6	Yes	8 years	No	Yes	No	MI	PO-PPO	PO	+	+	12
17/F/15	E	9	Yes	11	No	No	–	MO	PP-PPO	PPO	–	+	6
18/F/39	E	7	No	No	Yes	Yes	No	B	PP-PPO	PPO	+	+	32

Fam, familiarity; dis, disappearance; interict, interictal; SC, subclinical; EC, electroclinical; E, epilepsy; FS, febrile seizures; B, borderline mental level; MI, mild mental retardation; MO, moderate mental retardation; GTCS, generalized tonic–clonic seizures; PO, spike-waves; PPO, polyspikes-waves.

other subtle seizure manifestations, such as myoclonic jerks in other muscular districts.

Ictal EEG

In all patients, ictal EEGs during the episodes of EM showed a sequence of polyspikes with intermixed rare slow waves, prominent over the frontal regions, and occurring with a latency of 1–3 s after eye closure (Fig. 1). Their frequency was between 9 and 14 Hz. In the patients who experienced prolonged episodes of EMs (13 of 18), this peculiar EEG pattern typically continued in long runs as the eyes remained closed, disappearing only on eye opening (Fig. 2). In the 14 of 18 patients who were studied at darkness, eye closure did not induce any EEG changes (abnormal activity). Characteristically, in one of the same patients, this peculiar ictal EEG pattern remained substantially unchanged during life, with only an amplitude reduction of the polyspikes with increasing age.

Interictal EEG

In the majority of the patients (14 of 18), rare generalized interictal spike and polyspike and wave complexes were recorded. Their morphology was different from that of the ictal discharges, with a lower spike frequency and a more prominent slow wave component. The presence of interictal discharges can also be influenced by variation in the regimen of AEDs and can vary with age.

Photosensitivity

All patients in this series were photosensitive. The EEG abnormalities elicited by photostimulation at frequencies between 6 and 30 Hz differed from both interictal and ictal abnormalities, consisting of very fast, high-amplitude generalized (type 4 Waltz classification) polyspikes, often accompanied by an abrupt and isolated myoclonia involving the axial or arm muscles. Moreover, photosensitivity persisted both in darkness and at open eyes. In some cases, both clinical and subclinical photosensitivity could vary in different age periods.

Genetic investigations

Although dysmorphic features were absent in our series, the majority of the patients (15 of 18) had genetic investigations performed, usually high-definition karyotype and/or array comparative genomic hybridization (CGH), due to the presence of cognitive impairment. In addition, 10 patients were also investigated for fragile X, Angelman syndrome, and Rett syndrome. However, genetic studies were unremarkable in all cases.

Therapy

All the patients were pharmacologically treated and received appropriate and adequate therapy soon after the start of their epilepsy. The most common AEDs were valproate, ethosuximide, and benzodiazepines, used alone or in combination. All patients had undergone 1–3 adequate trials of AEDs. However, both EM and tonic–clonic seizures persisted in most of the cases (Table 1). Three patients spontaneously withdrew the therapy, with no relevant worsening of their epilepsy. In three cases only (No. 9, 16, and 17), a possible correlation between EM disappearance and AED use could be hypothesized.

Figure 1.
Ictal electroencephalography (EEG) of patient 14. Occurrence of generalized polyspikes with intermixed rare slow waves, more evident in the frontal regions, two seconds after eye closure. Disappearance after eye opening.

Follow-up and neuropsychological evolution

All patients had a long follow-up, ranging from 6–32 years (mean 17, median 16 years and 3 months). Moreover, follow-up duration was more than 10 years in the large majority of subjects (16 of 18) and more than 15 years in 10 of 18 patients. All the patients showed varying degrees of impaired intellectual functioning. In particular, a mild or moderate mental retardation was evident in nine and five subjects, respectively (Table 1). The remaining four patients showed borderline intellectual functioning. In addition, the patients showed behavioral disturbances with hyperkinetic features. At the last observation, 14 of 18 patients were in adulthood. In addition to three patients pharmacologically controlled, EM disappeared during or after adolescence in four. In the other 11 patients, EM remained unchanged or reduced only. Tonic–clonic seizures decreased in their frequency after the third decade of life, but completely disappeared in only five patients.

Discussion

We reported a series of patients showing peculiar and homogeneous electroclinical features, including eyelid fluttering, a typical EEG pattern, and impaired intellectual function. All patients had fast EM occurring at eye closure, in association with ictal generalized polyspikes with intermixed rare slow waves on EEG. Although it may be difficult to depict the possible impairment of consciousness related to the ictal EEG discharge, a complete loss of consciousness did not seem to occur during this clinical phenomenon. Moreover, possible cognitive impairment was tested with numbers or words called as quickly as possible after the onset of the discharges, which patients are asked to repeat after the end of the discharge. Notably, during their life, most of the subjects experienced prolonged episodes of EM persisting at eye closure, realizing a true status epilepticus. Unfortunately, polygraphic recordings available in our cases do not allow us to establish a close correlation between the EEG discharges and the myoclonic manifestations, owing to the presence of muscular artifacts. However, in all cases, video-polygraphy excluded the occurrence of myoclonic jerks in muscular districts other than eyelids. Moreover, video-EEG recordings allowed us to differentiate our cases from fixation-off sensitivity (FOS, i.e., clinical and/or EEG manifestations elicited by the elimination of central vision and fixation) patients for the presence of EM that are instead

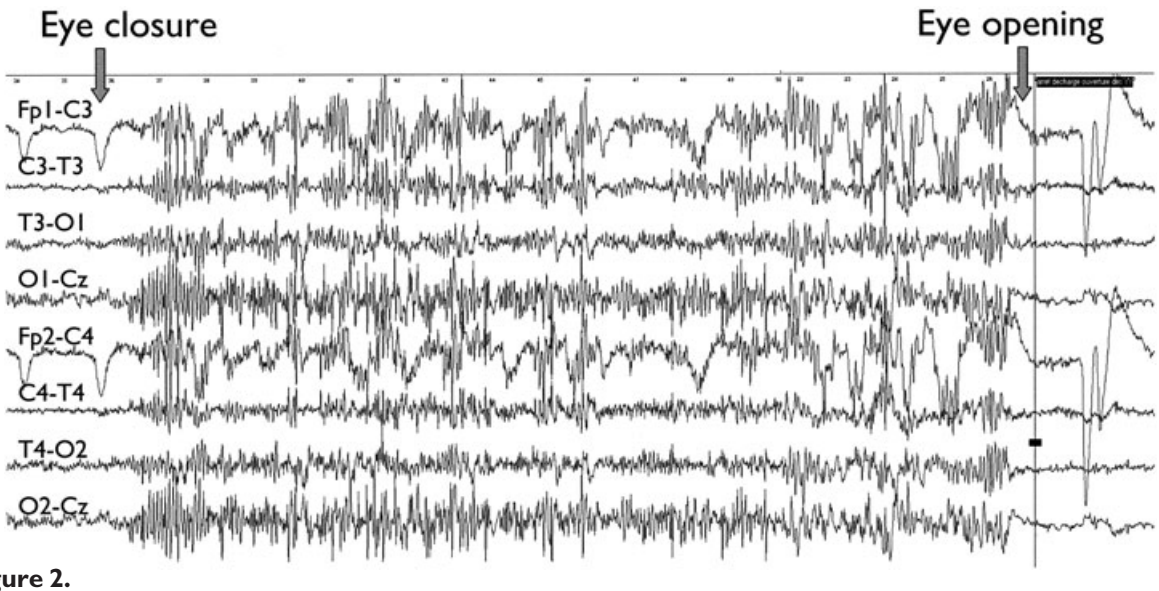

Figure 2.
Ictal electroencephalography (EEG) of patient 3. Appearance of fast polyspikes after one second from eye closure and disappearance after eye opening.
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absent in FOS patients. Moreover, EEG abnormalities in FOS are described mainly as diffuse alpha-like rhythms, intermixed with bisynchronous sharp and spike/polyspike components, which are clearly different from those observed in our series. In addition, FOS is observed mainly in the early and late-onset forms of focal benign childhood epilepsies and is usually not associated with photosensitivity (Panayiotopoulos et al., 1996). On the contrary, a marked photosensitivity was constant in our patients and was often related to massive myoclonic jerks. The clinical manifestations in our patients tended to be drug-resistant and to persist throughout adult life. However, a tendency to seizure reduction may be observed in an advanced stage, more probably related to the natural evolution of epilepsy rather than to the effect of the AED regimen. Accordingly, self-withdrawal of the therapy in some cases did not result in significantly worse epilepsy. In many series describing patients with Jeavons syndrome, a description of clinical and electrophysiologic features similar to that observed in our series can be found. For example, the finding of fast polyspike discharges on EEG is reported by several authors (Appleton et al., 1993, patient No. 4; Panayiotopoulos et al., 1996, Figure 2; Ming & Kaplan, 1998; Striano et al., 2002, Figure 5). Furthermore, in several reports (De Marco, 1989; Striano et al., 2002; Covanis, 2005; Joshi & Patrik, 2007), some patients are referred to as mentally retarded. Although tonic–clonic seizures and marked photosensitivity are often mentioned, the clinical and EEG features of these cases are not reported in detail. Therefore, at this stage, it remains speculative to suggest that at least a subgroup of patients from other series share homogeneous characteristics similar to that described in the present report. Nevertheless, anecdotal cases showing the coexistence of fast EM with childhood onset, mild or borderline intellectual functioning, generalized fast discharges of polyspikes with rare intermixed slow wave at eye closure, and tonic–clonic seizures have often been reported (Ogura et al., 2005; Sevgi Demirci & Saygi, 2006; Termine et al., 2006). Moreover, Scuderi and coworkers described three EMA patients with mental retardation and abnormal MRI examinations (Scuderi et al., 2000). Therefore, these authors concluded that EMA can sometimes represent a peculiar phenomenon in symptomatic epilepsies. However, in our series, neuroradiologic study was unremarkable in all cases and, therefore, mental retardation cannot be explained by the presence of structural brain abnormalities. Furthermore, although it is also well-known that epileptic myoclonic manifestations may occur in mentally retarded patients carrying different chromosomal rearrangements, genetic studies were unremarkable in the subjects from our series. It remains speculative whether the long-lasting EEG abnormalities, persisting through the years, may play a role in determining the impaired intellectual functions in our patients.

The patients we present here pose again the Hamletic doubt between lumping or splitting in a specific syndromic context. They share both a peculiar electroclinical profile and a stereotyped evolution with an unfavorable outcome, but they have a peculiar main

seizure manifestation, EM, which has been considered a syndrome in itself. However, it is also true that they greatly differ from the ''typical'' cases of EM patients, from the electroclinical, prognostic, and therapeutic point of view. So we feel that our cases represent a well-characterized and homogeneous subgroup in the larger group of patients who presented, at various age of life, with eyelid myoclonic manifestations. Further clinical and, more probably, genetic studies will clarify whether this condition could be considered a specific and homogeneous condition in the heterogeneous group of patients presenting with EM.

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

Conflicts of interest: The authors have no conflicts of interest to declare.

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