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Short communication

Follow-up study of idiopathic generalized epilepsy with associated absence seizure and myoclonic epilepsy of infancy

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ABSTRACT

We evaluated the long-term prognosis of patients featuring the association of absences and myoclonic epilepsy of infancy. Our cohort consisted of 10 male subjects with mean age at seizure onset of 29 months. Follow-up data included seizure outcome and EEG findings. All individuals received antiepileptic drugs (AEDs) as monotherapy (6 patients) or polytherapy (4 patients) for a mean period of 24 months. Over a 30–60 month evaluation period (mean: 43 months), all patients were seizure-free. Follow-up data after withdrawal of antiepileptic therapy were obtained for a mean period of 22 months. None of the children did develop other age-related epileptic syndrome after AEDs discontinuation. Furthermore, follow-up EEG data after drugs withdrawal were normal and none of the patients showed cognitive impairment. In conclusion, we confirm that absence seizures may occur in association with myoclonic epilepsy of infancy. This condition shows excellent prognosis with either favourable neurologic development and seizure outcome in these children.

1. Introduction

Myoclonic epilepsy of infancy (MEI) is a well-defined epileptic syndrome with a likely genetic origin and characterized by myoclonic seizures (MS) without other seizure types, except rare simple febrile seizures (FS), in the first three years of life. First described by Dravet and Bureau in 1981, MEI was included in the International Classification of Epilepsies and Epileptic Syndromes within the group of idiopathic generalized epilepsies (IGE) and syndromes with age-related onset (Guerrini et al., 2012). MEI is usually self-limited and shows a good outcome in terms of seizure control and neuropsychological profile. Generally, in this syndrome the ictal electroencephalography (EEG) shows a generalized discharge of polyspikes, polispikes-and-waves, or spikes-and-waves, although the interictal EEG is usually normal (Auvin et al., 2006). MSs are predominantly located in the upper limbs and head and they are usually very brief (1–3 s); however they may be longer and, when they are repeated, children may be unresponsive, with interruption of ongoing activities such as, clinically, it occurs in absence seizures (ASs). On the other hand, ASs are generalized seizure of sudden onset and termination, lasting for seconds with the transients impairment of consciousness and interruption of ongoing activities (Caraballo et al., 2011). They may be isolated or associated with other signs, especially motor manifestations (complex ASs). ASs most frequently occur between 4 and 9 years of age and the youngest age at onset has been set at 3 years and can occur in several well-defined idiopathic generalized epileptic syndromes, such as childhood absence epilepsy (CAE), epilepsy with myoclonic absences (EMA), juvenile absence epilepsy (JAE) and juvenile myoclonic epilepsy (JME) (Engel, 2001; Panayiotopoulos, 2001, 2008). Although some authors have reported that ASs may be associated with myoclonic jerks in MEI patients (Caraballo et al., 2011; 2013; Belcastro et al., 2015) this issue remains matter of debate (Guerrini et al., 2012). Although hundreds of MEI patients have been reported, the coexistence of MEI and ASs has been rarely observed (Belcastro et al., 2015; Caraballo et al., 2011, 2013a).

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In particular, Belcastro et al. ([2015]) found that in their series of 37 subjects myoclonic seizures can be accompanied by brief ASs of variable frequency and intensity in a percentage of roughly 20% of the patients. Nevertheless, long-term follow-up and long-term prognosis data are very rare.

The aim of this study is to evaluate the long-term prognosis of patients with clinical association of ASs and MEI.

2. Materials and methods

A retrospective chart review was conducted in 7 pediatric epilepsy centres on patients recruited between January 2002 and April 2017. Written informed consent was provided by parents or guardians. All the patients showed the electroclinical features of MEI and the co-existence of ASs, as reported (Belcastro et al., 2015), according to the following criteria: (Agostinelli et al., 2012) normal development until seizure onset; (Auvin et al., 2006) seizure onset between 4 months and 4 years of life; (Belcastro et al., 2015) myoclonic (including reflex) seizures; (Caraballo et al., 2013a) absence seizures(Panayiotopoulos, 2008); (Caraballo et al., 2013b) EEG: generalized paroxysms of polyspike (PS) or spike-and-wave (SW) complexes; (Caraballo et al., 2011) no evidence of structural or metabolic aetiology. Patients with both myoclonic and atonic seizures were excluded.

ASs were defined according to the following criteria: i) sudden onset and interruption of ongoing activities; ii) bilateral PS or SW complexes at 2–4 Hz; iii) duration ranging from 3 to 30 s (Panayiotopoulos, 2008). All patients underwent sleep and awake video-EEG recordings. Ictal video-EEG recordings were reviewed in 'ad hoc' sessions and collegially discussed. Seizure onset, semiological features, frequency, distribution, duration of the seizures, and ictal EEG recordings were analyzed. Evaluation of consciousness impairment included: 1) the presence of upward deviation of the eyes accompanied by the sudden arrest of ongoing activities; 2) interrupted speech accompanied by the arrest of ongoing activities.

Clinical records were reviewed to obtain information including previous febrile seizures (FS), first-degree family history of IGE, treatment (AED monotherapy versus polytherapy) and outcome variables. Repeated EEGs were performed during follow-up, after withdrawal of antiepileptic therapy.

3. Results

3.1. General features

Our cohort consisted of 10 male patients showing the clinical association of ASs and MS in patients with adiagnosis of MEI. The mean age at seizure onset was 29 months (range 11–36). Three patients (30%) had family history of FS while a family history of IGE was reported in 4 subjects (40%) and 1 patient (10%) showed IGE plus FS; two subjects (20%) had negative history of epilepsy and/or FS (Table 1).

3.2. Seizure manifestations

At least one ictal polygraphic video-EEG recording was available in all the patients. Overall the patients have both MSs and ASs both captured as part of the same seizure. Isolated MSs, unlike ASs, were also recorded at different times in this cohort. The MSs were predominantly located in the upper limbs and head, with variable intensity in the same child and when comparing children, and from one episode to the next. In all patients, during the occurrence of some MSs, the ongoing activities were interrupted and alertness was reduced. ASs were mainly recognized by the occurrence of upward deviation of the eyes accompanied by the arrest of ongoing activities or impairment of consciousness manifested mainly with arrest of speech and ongoing activities in relation to the onset of the EEG discharge. ASs were captured both during a brief cluster of rhythmic MSs than after single myoclonic jerks. No reflex myoclonus was observed in our series.

3.3. EEG data

EEG background activity was normal in all patients both awake and during sleep. All the patients at onset showed ictal EEG abnormalities, while only 4 patients (40%) showed interictal EEG anomalies and only 2 subjects did not show any electroclinical pathologic feature at sleep EEG. Noteworthy, the ictal EEG abnormalities associated with seizures were very similar to the interictal EEG paroxysms. In particular, the ictal EEG abnormalities observed in patients with ASs were similar to the ictal EEG patterns associated with only myoclonias.

3.4. Follow-up

Follow-up data were available for all patients recruited in our series and they included clinical outcome (seizure free or not seizure free) and electroclinical features (presence or not of EEG anomalies). We evaluated the evolution of the patients over a 30–60 months period of follow-up with a mean of 43 months (DS ± 11.7 months). We observed that all patients became seizure free after several months: 1 patient (10%) resulted seizure free when he was 44 months old, 2 patients (20%) at age of 42 months, 2 patients (20%) resulted seizure free when they were 38 months old, 2 patients (20%) at age of 36 months, 1 subject (10%) at age of 32 months, 1 subject (10%) at age of 30 months and 1 patient (10%) at age of 18 months, with a mean age at seizure freedom of 36 months (range 18–44). Concerning therapy, all patients received AEDs therapy from seizure onset and all children did so for a mean period of 24 months (range 12–60): 6 subjects (60%) used AEDs monotherapy with valproic acid (VPA) or ethosuximide (ESM) (4 *vs* 2) and 4 patients received AEDs polytherapy with VPA plus ESM or VPA plus levetiracetam (LEV). The mean duration of AEDs monotherapy was 23 months (range 12–60) *vs* 25 months of AEDs polytherapy (range 12–38). Follow-up data after withdrawal of antiepileptic therapy were obtained for a mean period of 22 months (range 12–36) and children of our series did not show any age-related epileptic syndrome after AEDs discontinuation. Follow-up EEG data after drug withdrawal remained unremarkable. Neurological examination were constantly normal at last follow-up and neuropsychological examinations (Wechsler Test Scale-WPPSI-III subtype) performed in all patients were normal as well as brain MRI. Moreover, we contacted all patients with a telephonic interview to collect more recent data: all patients (at the date of 1 July 2017) continued to be seizure free in absence of any treatment. In particular, 3 of 10 patients have completed pubertal development (according to Tanner's stages) confirming the good prognosis also in adolescence.

4. Discussion

Our series confirm an extremely rare clinical association, so far unknown, and for that reason it is important to consider this combination of two types of seizures among described epileptic syndromes. The best tool to identify this clinical association is ictal video-EEG recording, as conducted in our series. Lastly, the male predominance, the early onset and the good response to treatment, as reported in the literature were also confirmed in our series. The follow-up period observed in our study (mean 43 months) allowed us to evaluate our series for a long time, with clinical examinations, serial EEGs, neuropsychological tests and neuroimaging that showed the excellent outcome of this condition in terms of seizure freedom and neuropsychological profile, confirming the data obtained in previous studies (Caraballo et al., 2011, 2013a, 2013b). Notably, EEG features and the clinical outcome of patients with association of MEI and ASs were similar to the typical clinical course of patients with MEI. Caraballo et al. (2011) recently reported 18 patients with particular myoclonic seizures associated with absences. The electroclinical features of this group were