Review article

Epileptic Disord 2013; 15 (2): 114-22

Reflex myoclonic epilepsy in infancy: a critical review

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Received November 4, 2012; Accepted April 15, 2013

ABSTRACT – Benign myoclonic epilepsy in infancy, classified among the generalised idiopathic epilepsies, is characterised by the occurrence of myoclonic seizures in the first three years of life in otherwise normal infants. Some authors have described cases of myoclonic seizures as a reflex response to sudden unexpected tactile or acoustic stimuli and this clinical entity has been proposed as a separate nosographic syndrome, referred to as "reflex myoclonic epilepsy in infancy" (RMEI). We reviewed all published articles and case reports on RMEI in order to clarify clinical and electroencephalographic findings, with particular attention to outcome and treatment. RMEI appears to be a benign variant of idiopathic myoclonic epilepsy in infancy with specific features that occur in neurologically and developmentally normal children. This rare clinical entity is often under-described and under-diagnosed, and for this reason should be brought to the attention of paediatricians in order to avoid extensive investigations and reassure parents of the lack of long-term complications.

Key words: cognitive outcome, idiopathic generalized epilepsy, reflex myoclonic epilepsy in infancy, valproate treatment

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Benign myoclonic epilepsy in infancy (BMEI) is characterised by brief myoclonic attacks that occur spontaneously in otherwise healthy and developmentally normal infants, with onset between four months and three years (Dravet *et al*., 1985; Dravet *et al*., 1992; Dravet and Bureau, 2005; Guerrini *et al*., 2012). BMEI was classified among the idiopathic generalised epilepsies (IGEs) in the 1989 International Classification of the International League Against Epilepsy (ILAE) (Commission, 1989), and more recently included as myoclonic epilepsy in infancy (MEI) among the electroclinical syndromes, according to age at onset in infancy, in the recent report by the ILAE Commission on Classification and Terminology (Berg *et al*., 2010).

Cases with reflex myoclonic seizures (MS), triggered by sudden unexpected tactile or acoustic stimuli, were first reported by Ricci *et al*. (1995), who proposed to distinguish these as a separate entity, referred to as: "*reflex myoclonic epilepsy in infancy* (RMEI)".

The data presented in this review are derived from relevant articles which were selected by searching on Medline and PubMed using the term "*reflex myoclonic epilepsy in infancy*". Searches were performed

doi:10.1684/epd.2013.0584

by considering articles published from January 1995 to July 2012. Articles published in English, French, and Spanish were considered and specific review articles, systematic reviews, textbooks, and case reports were examined for cross-referencing, as were all articles identified by the literature search. All publications containing information about this topic were considered and validation was undertaken by a second review of the search results to ensure that no articles had been overlooked.

This review focuses on the emerging aspects of RMEI and briefly addresses clinical and electroencephalographic (EEG) characteristics of this clinical entity.

General remarks

RMEI is extremely rare and, to the best of our knowledge, there are at present 80 cases published in the literature (Ricci *et al*., 1995; Cuvellier *et al*., 1997; Giovanardi Rossi *et al*., 1997; Deonna, 1998; Fernández-Lorente *et al*., 1999; Zafeiriou *et al*., 2003; Kurian and King, 2003; Caraballo *et al*., 2003; Auvin *et al*., 2006; Darra *et al*., 2006; Capovilla *et al*., 2007; Korff *et al*., 2009; Verrotti *et al*., 2013; the article of Auvin *et al*. [2006] includes a patient previously described by Cuvellier *et al*. [1997]). In all cases, generalised reflex myoclonic jerks starting in the first two years of life are described. This rare clinical entity merits greater interest since it exhibits clinical and electroencephalographic (EEG) features similar to MEI, but may be differentiated based on the absence of seizures which are triggered by unexpected stimuli in MEI.

With regards to gender, boys outnumber girls: 37 males *vs* 25 females.

The genetics of RMEI is unknown. Cases are rare and no family cases of RMEI have been described. When revealed, a family history of febrile convulsions (FC) or IGE (childhood absence epilepsy [CAE], generalised tonic-clonic seizures [GTCS], and juvenile myoclonic epilepsy [JME]) is present in 43.7% of 80 cases, in first or second-degree relatives. Most patients do not have any pathological history prior to onset of reflex MS, however, the occurrence of rare FC was reported in 6/80 (7.5%) patients; these were all simple and could be observed before or after the appearance of myoclonic jerks and usually before the beginning of treatment. Only in one case were absence seizures reported a few months after the beginning of MS. Taken together, these observations suggest a complex genetic inheritance.

Clinical features

The age at onset of reflex MS is usually between 3 and 24 months. All children with reflex MS were reported to be born to healthy unrelated parents after normal pregnancy and delivery, with normal perinatal history. Psychomotor and neurological development was normal in all subjects. When available, neuroradiological and metabolic investigations yielded normal findings. At onset, myoclonic jerks are usually very brief, often rare, and involve mainly head and upper limbs, rarely lower limbs, and triggered by sensory stimuli. MS may manifest within a narrow time frame and parents sometimes have difficulty in determining the precise time of onset and frequency; in the beginning, episodic "spasms" or "head nodding" are often reported (Deonna, 1998). In the majority of cases, parents contact a paediatric neurologist because of an abnormal startle response to external stimuli that causes "jumping" of arms and legs. Spontaneous attacks were reported in 26 cases (32.5%), usually appeared months after the reflex attacks, and were facilitated by drowsiness and sleep (Ricci *et al*., 1995; Cuvellier *et al*., 1997; Giovanardi Rossi *et al*., 1997; Caraballo *et al*., 2003; Darra *et al*., 2006; Capovilla *et al*., 2007; Korff *et al*., 2009; Verrotti *et al*., 2013).

Seizures are characterised by massive myoclonic jerks, involving mainly the axis of the body and arms, provoking a nod of the head and an upward-outward movement of the upper limbs, with flexion of the lower limbs, and sometimes eye-rolling. The intensity of seizures varies from one child to another and from one attack to another in the same child. The most disabling forms can cause sudden projection of objects held in the hand or sometimes a fall, while the mildest forms show only "head nodding" or blinking. Seizures are usually very brief (1-3 seconds) and consist of a single myoclonic jerk. However, they may be longer, mainly in older children, characterised by pseudo-rhythmic jerks, repeated in clusters lasting for 5-10 seconds, and consisting of repeated flexion-extension movements of the arms (Ricci *et al*., 1995). MS usually occur several times a day, in an irregular and unpredictable manner. The total number of attacks in each child varies from day to day, depending mostly on environmental precipitants.

The state of consciousness is difficult to assess due to the young age of children and short duration of seizures, but in some cases, particularly during clusters of jerks, a slight impairment of consciousness with brief interruption of activity is reported (Verrotti *et al*., 2013).

Reflex MS are triggered both in wakefulness and during sleep, with a lower threshold in stage I and a gradual increase during slower stages of sleep (Ricci *et al*., 1995).

Seizures are provoked by a sudden and unexpected acoustic and/or tactile stimuli and surprise appears to be fundamental in triggering attacks; if children expect the stimulus, they do not have a reflex seizure.

Table 1. Clinical data of all patients with RMEI reported in the literature.

Author	Patients (sex)	Family history (IGE or FC)	Age at onset (months)	Duration of RMEI (months)	Trigger stimuli	Sponta-neous jerks	Other seizures	Interictal EEG	Therapy	Follow-up (year. month)
Ricci *et al.* (1995)	6 (4M; 2F)	yes (IGE in 2 pts, FC in 3 pts)	from 6 to 21	from 3 to 12	acoustic and tactile in 5 pts; acoustic, proprioceptive and thermal in 1 pt	yes (4 pts)	FC in 1 pt	PSW during sleep	VPA in 2 pts; VPA + CZP in 1 pt	0.8-3.1
Cuvellier *et al.* (1997)	1 (F)	no	4	28	acoustic, tactile and proprioceptive	yes	FC	normal during wakefulness and sleep	VPA	0.9
Giovanardi Rossi *et al.* (1997)	2 (-)	-	-	-	acoustic	-	-	normal during wakefulness and sleep	VPA	-
Deonna (1998)	5 (4M)	-	from 4 to 13	from 4 to 36	acoustic in 1 pt; tactile in 1 pt; acoustic and tactile in 2 pts; acoustic, visual, tactile and thermal in 1 pt	yes (2 pts)	absence seizures in 1 pt	PSW during sleep in 2 pts; PSW during wakefulness and sleep in 1 pt	VPA in 3 pts; VPA + CZP in 1 pt	2.2-10.11
Fernández-Lorente *et al.* (1999)	1 (F)	FC	10	-	acoustic and tactile	no	FC	PSW during sleep	VPA	0.2
Zafeiriou *et al.* (2003)	1 (M)	no	9	1	acoustic	no	no	normal during wakefulness and sleep	VPA	3.3
Kurian and King (2003)	1 (M)	no	11	0.7	tactile	no	no	PSW during wakefulness	VPA	0.7
Caraballo *et al.* (2003)	8 (5M; 3F)	yes (IGE in 4 pts, FC in 1 pts)	from 5 to 20	from 1 to 5	acoustic in 2 pts; tactile in 5 pts; acoustic and tactile in 1 pt	yes (2 pts)	no	PSW during sleep	VPA in 6 pts; CLB in 2 pts	6

Table 1. (*Continued*)

Author	Patients (sex)	Family history (IGE or FC)	Age at onset (months)	Duration of RMEI (months)	Trigger stimuli	Sponta-neous jerks	Other seizures	Interictal EEG	Therapy	Follow-up (year. month)
Auvin *et al.* (2006)	11 (-)	Yes (in 1 pt)	12	-	acoustic and tactile	-	-	PSW during sleep in 6 pts	-	-
Darra *et al.* (2006)	5 (-)	-	7	-	tactile in 3 pts; acoustic and tactile in 2 pts	yes (3 pts)	no	-	-	-
Capovilla *et al.* (2007)	8 (4M; 4F)	yes (in 8 pts)	24	-	photic	yes (3 pts)	IGE in 3 pts	PSW during wakefulness and sleep in 6 pts; PSW during sleep in 1 pt; focal abnormalities in 1 pt	VPA + CZP in 2 pts; VPA + CLB in 1 pt; VPA in 5 pts	1.4-18.11
Korff *et al.* (2009)	1 (F)	no	8	3	tactile	yes	no	normal	VPA	1.5
Verrotti *et al.* (2013)	31 (18M; 13F)	Yes (IGE in 5 pts, FC in 10 pts)	from 3 to 24	from 0.5 to 36	acoustic in 12 pts; tactile in 9 pts; acoustic and tactile in 9 pts; acoustic and thermal in 1 pt	yes (10 pts)	FC in 3 pts	PSW during sleep in 11 pts; PSW and CTS during wakefulness in 2 pts	VPA in 23 pts; VPA + CZP in 1 pt; 7 pts untreated	1.6-12.8

RMEI: reflex myoclonic epilepsy in infancy; M: male; F: female; IGE: idiopathic generalised epilepsy; FC: febrile convulsions; pt: patient; EEG: electroencephalography; PSW: polyspike-wave; CTS: centro-temporal spikes; VPA: valproic acid; CZP: clonazepam; CLB: clobazam.

Acoustic stimuli, represented mainly by sudden noise, were reported to induce MS in 17 subjects, while tactile stimuli, such as sudden touch, provoked attacks in 20 children. In 20 patients, myoclonic jerks were triggered by both tactile and acoustic stimuli. In 3 patients, MS were triggered by proprioceptive stimuli (Ricci *et al*., 1995; Cuvellier *et al*., 1997; Deonna, 1998), in 2 patients by thermal stimuli, such as cold water (Ricci *et al*., 1995; Verrotti *et al*., 2013), and only one case by a visual stimulus, represented by a flash of light (Deonna, 1998).
The threshold for MS is usually related to ambient noise level, the child's attention level (which increases the threshold), and drowsiness (which decreases the threshold). Frequent repetition of stimuli decreases the ictal response. Intermittent photic stimulation (IPS) can also provoke MS in a minority of patients. In fact, Capovilla *et al*. (2007) reported 8 patients with MS triggered by photic stimuli; in these patients, photosensitivity was invariably present at the start of ictal symptomatology, and MS were provoked exclusively by photic stimulation, both in the EEG laboratory and in controlled conditions. It is important to underline that pure EEG photosensitivity, without clinical correlate, has rarely been reported (Zuberi and O'Regan, 2006; Capovilla *et al*., 2007). Moreover, Darra *et al*. (2006) reported 3 patients who presented with occasional isolated convulsive seizures induced by IPS or television screens during the course of MEI.
Clinical features of patients with RMEI reported in the literature are summarised in *table 1*.

EEG findings

Video-EEG and polygraphic recordings provide us with a detailed analysis of such MS. Interictal EEG usually shows normal background activity during wakefulness; however, this was not the case for 10 reported cases (Deonna, 1998; Kurian and King, 2003; Capovilla *et al*., 2007; Verrotti *et al*., 2013) in which bursts of generalised polyspike-wave (PSW) and centro-temporal spike (CTS) activity, occurring spontaneously and without any clinical correlates, were reported. Sleep recordings show a normal organisation of sleep; in 42 reported patients, sleep was characterised by rare, generalised irregular PSW discharges, usually accompanied by brief and irregular myoclonic jerks (Deonna, 1998; Fernández-Lorente *et al*., 1999; Caraballo *et al*., 2003; Capovilla *et al*., 2007; Verrotti *et al*., 2013).
MS are always associated with an EEG discharge of generalised, high-amplitude spike-wave (SW) or PSW activity of more than 3 Hz, with fronto-central predominance, lasting for 0.5-3 seconds and synchronous with brief rhythmic bursts of electromyographic (EMG) activity (*figures 1 and 2*).

Outcome and treatment

The length of follow-up period was accurately known for 54 cases, lasting from two months (Fernández-Lorente *et al*., 1999) to 18 years and 11 months (Capovilla *et al*., 2007). The prognosis was excellent in all reported cases and reflex MS quickly disappeared, even in untreated patients. No other seizure types were observed in children with RMEI, in particular, atypical absences, tonic or atonic seizures.
The EEG normalised with the disappearance of seizures, suggesting a good correlation between clinical and EEG evolution.
Clinical examination revealed healthy children with no dysmorphic features, and when mentioned, normal postnatal head growth was reported (Kurian and King, 2003) and no abnormalities were observed on neurological examination. The neuropsychological, cognitive, and behavioural evolution has been evaluated in these children, showing excellent outcome with normal achievement of all developmental milestones.
In the majority of cases, neuropsychological development was evaluated using the Brunet-Lézine scale, Wechsler Intelligence Scales, Raven's Progressive Matrice, token test, Machover test, Vinland Adaptative Behavior scales, Bender Visual Motor Gestalt Test, oral language test, visual naming, recalling sentences, and spontaneous speech subtests. Developmental assessment was appropriate for age in all children and none demonstrated neuropsychological or intellectual disorders, such as: mental retardation or borderline IQ, fine motor skill deficits, attention deficits, language impairment, and/or learning disabilities (Verrotti *et al*., 2013).
Since myoclonic attacks are usually brief and occur only as reflex responses, some authors (Ricci *et al*., 1995; Deonna, 1998) recommended not to treat these children with antiepileptic drugs (AEDs). If the attacks persisted for more than six months, or when the duration and frequency of the seizures increased or bouts of spontaneous jerking became more frequent, valproic acid (VPA) was the first-line drug for RMEI. For all cases treated with VPA (46 patients), administered as monotherapy at low dosage (20-25 mg/kg/day), seizures stopped. Five patients benefited from clonazepam (CZP) add-on treatment (Ricci *et al*., 1995; Caraballo *et al*., 2003; Capovilla *et al*., 2007; Verrotti *et al*., 2013).
In our opinion, levetiracetam (LEV) may be useful in such cases based on the fact that the drug is widely recognised to be efficacious against generalised MS. LEV can be administered at the standard dose range in children (20-40 mg/kg/day). Compared to VPA, LEV is not associated with any life-threatening or dangerous adverse effects, such as liver failure, pancreatitis,

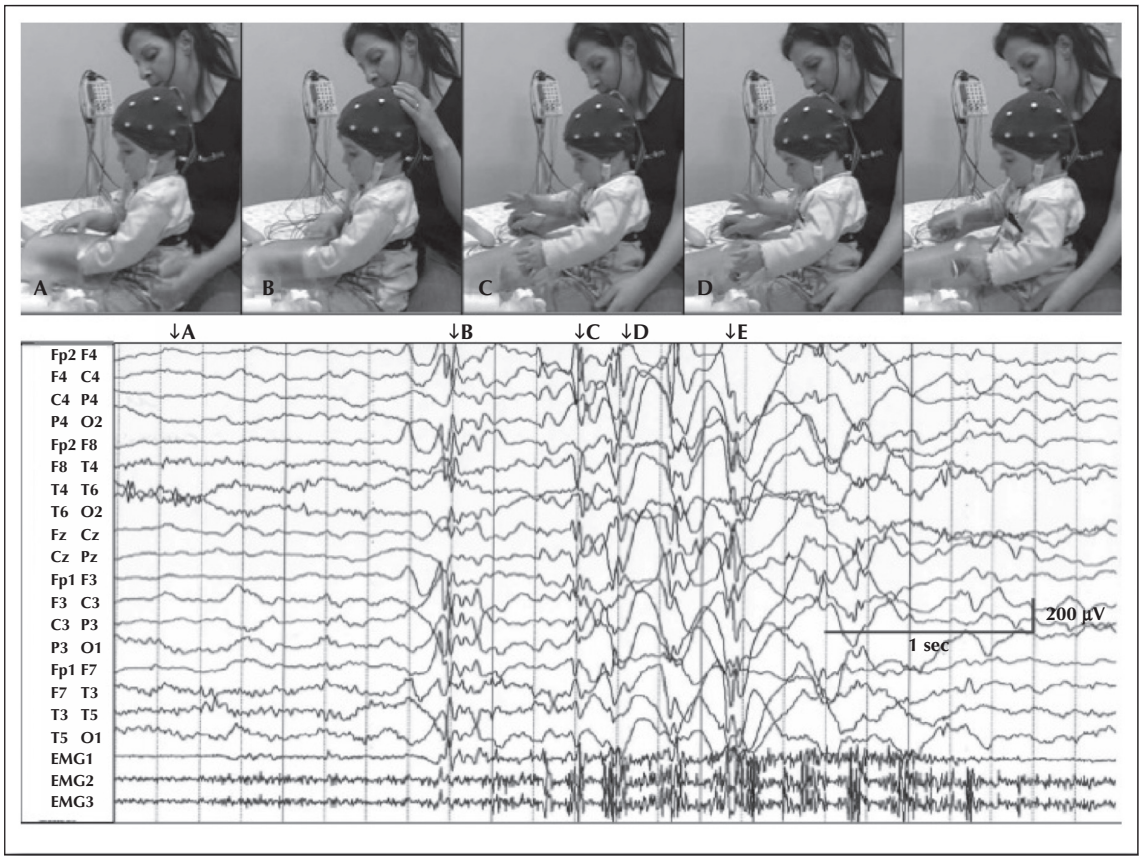

Figure 1. Electroclinical features during ictal video-EEG.
(A) Video photo: the patient is playing with toys and her mother suddenly touches her head with the left hand; (B, C, D and E) the patient immediately presents with myoclonic jerks, involving the axis of the body and limbs, and blinks. At the time of stimulus, ictal EEG shows initially an isolated spike without evidence of any clinical event and subsequently generalised, high-amplitude, 3-Hz polyspike and wave discharges, synchronous with brief rhythmic bursts on EMG.
EMG1: neck; EMG2: right deltoid; EMG3: left deltoid.

neutropenia, or bone marrow suppression, particularly in children treated under 2 years of age.

To sum up, pharmacological treatment of MS with AEDs should be managed on an individual basis, depending on the presence of epileptiform discharges, amelioration of symptoms, or change in quality of life.

The duration of the disorder ranges from 1 week to 36 months (mean: 8 months). In 11 untreated children, the myoclonic jerks disappeared spontaneously.

RMEI may be under-described and under-evaluated due to the short duration of the event, possibly misinterpreted as "excessive startle response" in otherwise healthy children.

Differential diagnosis

This clinical entity may be differentiated from other epileptic syndromes with myoclonic manifestations (myoclonic-astatic epilepsy, Dravet syndrome, intractable infantile epilepsy and neonatal myoclonic encephalopathy, West syndrome, and Lennox-Gastaut syndrome) on the basis of excellent psychomotor development, presence of reflex seizures, absence of tonic, atonic or atypical absence seizures, normal background on EEG recordings without focal or diffuse slowing-down, and absence of photosensitivity (Deonna, 1998; Verrotti *et al*., 2013).

Neurometabolic disorders such as mitochondriocytopathies (MERRF [myoclonic epilepsy with ragged red fibres]), storage disorders, neuronal ceroid lipofuscinosis, non-ketotic hyperglycinaemia, infantile hexosaminidase deficiency (Tay-Sachs disease and Sandhoff disease), and biopterin deficiency may all present with MS. However, unlike RMEI, these are not usually the only seizure type and MS are usually spontaneous. Neurometabolic disorders are usually accompanied by developmental arrest or regression, whereas children with RMEI have an excellent

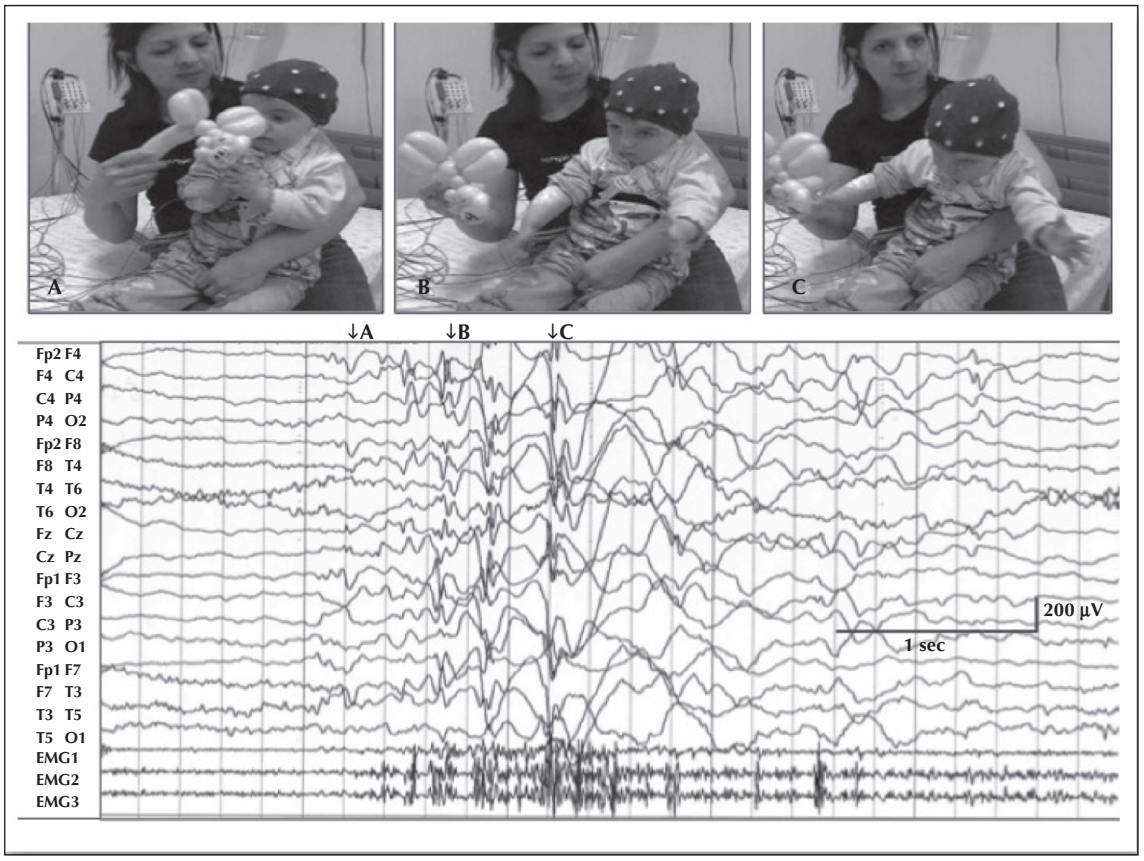

Figure 2. Electroclinical features during ictal video-EEG-EMG.
(A) Video photo: the child's mother suddenly touches the face of the child with a balloon; (B and C) the child immediately presents with myoclonic jerks, involving the axis of the body and upper limbs, with an upward-outward movement and head nodding. Ictal EEG shows a discharge that clearly starts from the right fronto-central area and rapidly spreads with generalised, high-amplitude, polyspike and wave discharges, synchronous with brief rhythmic bursts on EMG.
EMG1: neck; EMG2: right deltoid; EMG3: left deltoid.

development outcome and extensive metabolic testing is negative (Kurian and King, 2003).
RMEI and startle epilepsy are two distinct entities, despite a common excessive startle response. Startle epilepsy (Commission, 1989) occurs across a wide age range and is usually drug-resistant. It arises from brain damage, particularly hypoxic-ischaemic pre- and perinatal lesions. Clinical and EEG patterns are variable (partial, tonic, atonic, and myoclonic) (Yang *et al*., 2010). Distinctive EEG and EMG findings also allow differentiating between RMEI and non-epileptic manifestations characterised by an excessive startle response; hyperekplexia or startle disease and benign non-epileptic myoclonus. Hyperekplexia is an autosomal dominant disease characterised by exaggerated startle reflex and neonatal hypertonia. The EEG does not show epileptic discharges during attacks (Zhou *et al*., 2002). Benign non-epileptic myoclonus is a benign condition comprising a variety of episodic motor phenomena in normal and healthy children with normal EEG recordings (Caraballo *et al*., 2009).

Discussion

Some authors (Dravet *et al*., 1992; Auvin *et al*., 2006; Darra *et al*., 2006) do not support the designation of RMEI as a separate syndrome from MEI, and thus consider the two as a single clinical and nosographic syndrome. On the contrary, many other authors (Ricci *et al*., 1995; Deonna, 1998; Verrotti *et al*., 2013; Zuberi and O'Regan, 2006) propose that these two clinical entities should be distinguished from one another. Despite the apparent similarity between the conditions, they differ based on numerous findings, particularly the absence of triggering factors in MEI. However, the duration of MEI is the same as that of RMEI; less than one year, with the exception of only three cases (Guerrini *et al*., 2012). These exceptional cases are interesting, since these patients were not treated for many years, in contrast to RMEI, in which MS may disappear even in untreated patients. Moreover, the mean onset of RMEI (10 months) is earlier than that of MEI (20 months). Pharmacological treatment

with VPA appears to be more effective in RMEI than in MEI, and treatment duration may be shorter; MEI often requires long-term treatment and discontinuation of therapy in MEI may cause seizures to relapse (Giovanardi Rossi *et al*., 1997; Verrotti *et al*., 2013; Auvin *et al*., 2006). The cognitive outcome is much less certain, with neuropsychological complications present in a third of children affected by MEI (Mangano *et al*., 2005; Auvin *et al*., 2006; Zuberi and O'Regan, 2006), while patients with RMEI showed excellent cognitive outcome (Verrotti *et al*., 2013).

RMEI may be associated with a genetic factor. Recently, MS were hypothesised to result from a focus associated with dysfunction of the afferent sensorial pathways, up to the contralateral parietal cortex, however, in patients with RMEI, this does not appear to be the case, as demonstrated by normal findings based on neuroimaging and neurophysiological examination (Korff *et al*., 2009). In a recent review (Ferlazzo *et al*., 2005) on cortical triggers in generalised reflex seizures and epilepsies, it was proposed that these patients may have a genetically determined hyperexcitability of the sensorimotor cortex and an excessive startle response. Cortico-reticular or cortico-cortical networks may be involved, and in some cases, generalised responses are triggered by a signal propagation from a localised area to bilateral motor regions. Moreover, some of these sensory cortical regions may be more excitable than others. Finally, with regards to generalised seizures, a group of experts working on IGE recently concluded that "*available data support the idea of a trigger zone within a given thalamocortical system that has a particular genetically determined epileptogenic susceptibility*" (Bertram *et al*., 2008). These authors proposed the concept of "system epilepsy".

Conclusion

The present data suggest that a benign variant of idiopathic reflex myoclonic epilepsy occurs in otherwise normal children. This starts most often in the first year of life. Most sensory stimuli can evoke myoclonic jerks and an element of surprise or startle seems to be important.

Long-term follow-up of reported children does not show late recurrence of seizures or other forms of epilepsy. Cognitive development appears excellent, and the response to AEDs, usually VPA, is good. However, a limitation of the reviewed data is the lack of detailed indication of age of neuropsychological assessment for all reported patients.

Further data on long-term outcome and other investigations, such as evoked potentials, magnetoencephalography or functional magnetic resonance imaging, may be helpful to better understand the underlying pathophysiological mechanisms of reflex MS. On the other hand, since this type of epilepsy is benign, such investigations are not recommended during the clinical care of these patients.

The close age-dependency, high genetic predisposition, clinical and EEG findings, and normal neuropsychological development suggest that this rare entity constitutes an early form of IGE.

RMEI should be brought to the attention of paediatricians in order to carefully manage these patients, to avoid extensive investigations and reassure parents regarding the lack of long-term complications. □

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