Original article

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Reflex seizures in Rett syndrome

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ABSTRACT – Reflex seizures are a rare phenomenon among epileptic patients, in which an epileptic discharge is triggered by various kinds of stimuli (visual, auditory, tactile or gustatory). Epilepsy is common in Rett syndrome patients (up to 70%), but to the authors' knowledge, no pressure or eating-triggered seizures have yet been reported in Rett children. We describe three epileptic Rett patients with reflex seizures, triggered by food intake or proprioception. One patient with congenital Rett Sd. developed infantile epileptic spasms at around seven months and two patients with classic Rett Sd. presented with generalised tonic-clonic seizures at around five years. Reflex seizures appeared when the patients were teenagers. The congenital-Rett patient presented eating-triggered seizures at the beginning of almost every meal, demonstrated by EEG recording. Both classic Rett patients showed self-provoked pressure -triggered attacks, influenced by stress or excitement. Non-triggered seizures were controlled with carbamazepine or valproate, but reflex seizures did not respond to antiepileptic drugs. Risperidone partially improved self-provoked seizures. When reflex seizures are suspected, reproducing the trigger during EEG recording is fundamental; however, self-provoked seizures depend largely on the patient's will. Optimal therapy (though not always possible) consists of avoiding the trigger. Stress modifiers such as risperidone may help control self-provoked seizures.

Key words: eating seizures, proprioception seizures, reflex seizures, Rett syndrome

Rett syndrome (RTT) is a neurodevelopmental disorder which leads to severe global delay with cognitive, motor and communication impairment. It was first described in 1966 by Andreas Rett, and has an estimated prevalence of 1/10,000 newborn girls. Diagnosis is based on clinical criteria, initially defined by Hagberg *et al*. (1983) and regularly updated (Neul *et al*., 2010). A classic form and four atypical variants (congenital, early epilepsy, preserved speech and late regression) are accepted. Three genes are involved in the development of RTT: *MECP2* (90% of classic forms), *CDKL5* (early epilepsy forms) and *FOXG1* (congenital forms), but a small percentage of Rett patients, even with classic

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forms, lack a molecular diagnosis. Autonomic dysfunction, hand stereotypies, and scoliosis often appear, and up to 75% of RTT patients present seizures, which influences social interaction and motor skills. Epilepsy patterns are different among patients with the same mutations, and may change during their follow-up. In classic RTT patients, as in other similarly disabled children, it is sometimes difficult to differentiate epileptic seizures from other abnormal movements (such as stereotypies), vacant spells caused by breathing disturbances (apnoeas or Valsalva contraction), or "voluntary" loss of social contact, which may lead to treatment of non-epileptic paroxysms with antiepileptics. Furthermore, electrographic status epilepticus in these patients is sometimes only manifested as a change of mood, or as a slight worsening of their apraxic gait, and can remain unidentified unless parents or physicians consider this possibility. It is therefore very important to identify epileptic seizures in order to undertake the most suitable therapy to prevent clinical deterioration.
To the authors' knowledge, no pressure or eating-triggered seizures have previously been described in Rett, although myoclonic reflex seizures have been reported in one patient with a mutation in *FOXG1* (Bahi-Buisson *et al*., 2010). Other types of reflex seizures have been described in different disabling disorders, such as startle reflex epilepsy in Down Syndrome and hemiparetic patients (Panayiotopoulos, 2005).
Reflex seizures were first described by Boudouresques and Gastaut (1953) and may accompany focal or generalised epileptic syndromes. In reflex epilepsy, every seizure is precipitated by a trigger, which may involve vision, proprioception, eating, or other stimuli. Although the physiopathology is not yet well understood, stimuli seem to activate the recruitment of an epileptogenic group of neurons, which may be registered as a seizure on EEG. Diffuse cortical hyperexcitability is frequently present, such that focal seizures often become secondarily generalised (Rémillard *et al*., 1998).
Eating-triggered seizures, with a prevalence of 1/1,000-2,000 epileptic patients (Ganga *et al*., 1988), may be related to one or several different parts of the meal; the trigger is stereotyped for each patient and leads to partial motor seizures or automatisms. Symptomatic epilepsy may coexist and EEG may show epileptic activity in the temporo-limbic or suprasylvian areas. Seizures can be triggered by combinations of stimuli and can sometimes be aborted by sudden manoeuvres, probably related to subcortical involvement. Brain tumours, dysplasias and opercular syndrome must be ruled out when confronting eating reflex seizures (Loreto *et al*., 2000).
Proprioception-induced seizures are usually brief tonic seizures or simple partial attacks induced by active or passive repetitive limb movements. Self-induced seizures may be associated with compulsive proprioceptive self-provocation in cases of brain lesions, non-ketotic hyperglycaemia and Rasmussen's encephalitis.
We report three Rett patients with reflex seizures.

Case reports

For *Patient 1* (an 18-year-old girl), the clinical criteria for the congenital form of RTT (Neul *et al*., 2010) were fulfilled, without pathogenic mutations in Rett-related genes (*MECP2, CDKL5* and *FOXG1*). Partial motor seizures and infantile spasms started at seven months. Interictal EEG showed bursts of diffuse slow waves and multifocal sharp waves, without hypsarrhythmia. Seizures were controlled with valproate (discontinued after 12 months). Despite severe global delay, she acquired autonomous apraxic gait by three years of age. Brain magnetic resonance imaging (MRI) was normal. Hand stereotypes appeared at eight years of age. She remained seizure-free until 10 years old, but subsequently presented frequent generalised tonic-clonic seizures and absences, with occasional akinetic seizures. Interictal EEG showed subcontinuous high-voltage bilateral frontal sharp waves. Epilepsy was controlled at 11 years old with valproate and ethosuximide. Five years later, eating reflex seizures appeared. Upon the fourth spoonful, a cluster of seizures occurred, consisting of breakdown of social contact, sometimes followed by axial tone loss (recurrent head falls). Other episodes included upper limb recurrent tonic extension with neck flexion. Once the cluster had finished, the patient continued eating normally. Initially, this occurred at the beginning of some meals, but became more frequent over time and was not modified by the type of spoon, food, plate, caregiver or tablecloth, or by emotional stress. Interictal EEG showed brief discharges over the central and frontal areas (*figure 1*); reflex tonic seizures were confirmed using video-EEG and polygraphy recordings when the patient was asked to eat in a seated position (*figure 2*). Levetiracetam did not improve reflex seizures. Low doses of diazepam before meals did not reduce frequency or intensity. At 17 years old, after an upper respiratory tract infection treated with amoxicillin/clavulanic acid, levetiracetam dose was reduced and the patient's reflex seizures (both atonic and tonic) disappeared. At present, her generalised epilepsy remains under control with valproate, levetiracetam and ethosuximide, and reflex seizures have not reappeared in the last six months.

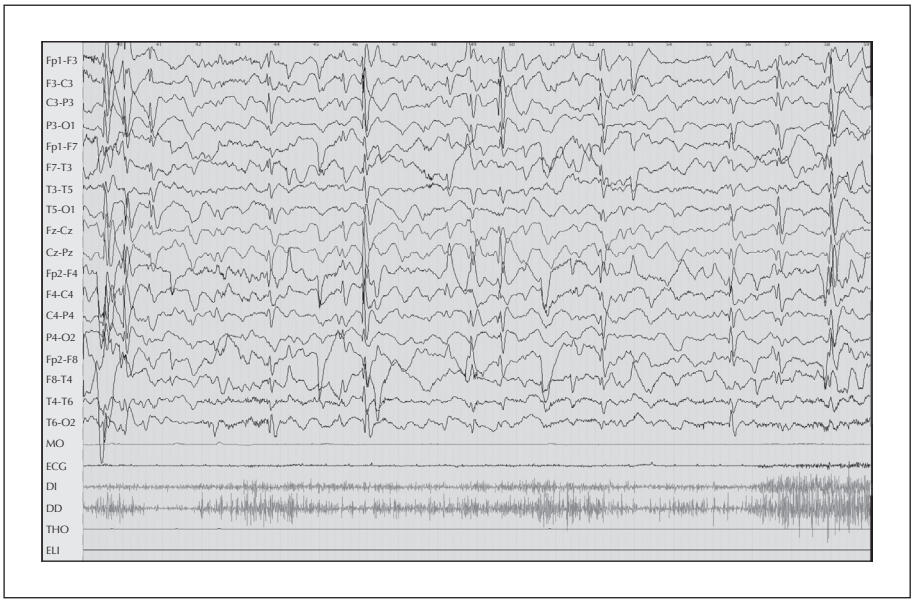

Figure 1. Interictal EEG of Patient 1 showing discharges over the midline (Cz), central, and frontal electrodes.

For *Patient 2* (a 14-year-old girl), the clinical diagnostic criteria for classic RTT were met, with severe cognitive disability and without mutations in Rett-related genes. Social withdrawal appeared at 13 months, hand stereotypes at two years and six months, and loss of acquired language by three years. Her hand skills worsened, but did not disappear. Brain MRI was normal. She presented partial motor seizures at five years old, followed by absences, which were controlled with valproate. Four years later, she presented with proprioceptive reflex seizures, self-triggered by rhythmic pressure on her left hand, which led to loss of social contact and tone, and backward falls. She self-provoked the attacks, taking someone's hand or holding onto a table. The episodes were influenced by stress, and she could prevent them at the beginning if she was asked to. Her reflex seizures were modified over the years: from the age of 13, before going to sleep, she would sit on the edge of the bed and rub the top of the bed in order to trigger a loss of social contact and fall onto a mattress. Interictal EEG showed diffuse slow background activity, multifocal spike-and-wave complexes and generalised spike-and-wave discharges. Although several EEG records were obtained, the patient never reproduced the reflex seizures while monitored. However, during both home videos and neurology consultation, she presented the above-described episodes.

Patient 3 (a 22-year-old woman) with classic Rett, with *MECP2* mutation c.880C>T/ p.Arg294Stop and X-chromosome inactivation pattern 59:41, presented a slight psychomotor delay during the first year of life with social withdrawal by 20 months, followed by instauration of severe cognitive disability. Brain computerised tomography (CT) was normal. Generalised tonic-clonic seizures started at four years and six months of age, followed shortly by partial motor seizures. Interictal EEG showed diffuse slow background activity and multifocal independent spike-and-wave complexes, and epilepsy was controlled with carbamazepine. At seven years and six months, partial epilepsy relapsed and after various combinations of drugs, seizures were finally controlled with carbamazepine alone. Eight years later, she presented proprioception reflex seizures, self-provoked by rhythmic pressure on her hands; atonic seizures were triggered while holding onto the table and falling laterally. Anxiety or stress increased their frequency. Various EEG records were obtained, but the patient did not reproduce the seizures while monitored. She did self-induce a seizure during consultation, after firmly holding the table, as described above. Her partial epilepsy remained under control with carbamazepine and reflex seizures persisted, although these were infrequent into adulthood.

Discussion

Epilepsy is frequent in RTT patients and affects 75% of the patients of the Spanish RTT database. Only 1% of epileptic Rett patients present reflex seizures, less than the 4-7% reported among the general epileptic population (Panayiotopoulos, 2005), but it is possible that some patients remain undiagnosed. Reflex seizures in our patients appeared after both generalised and partial epilepsy.

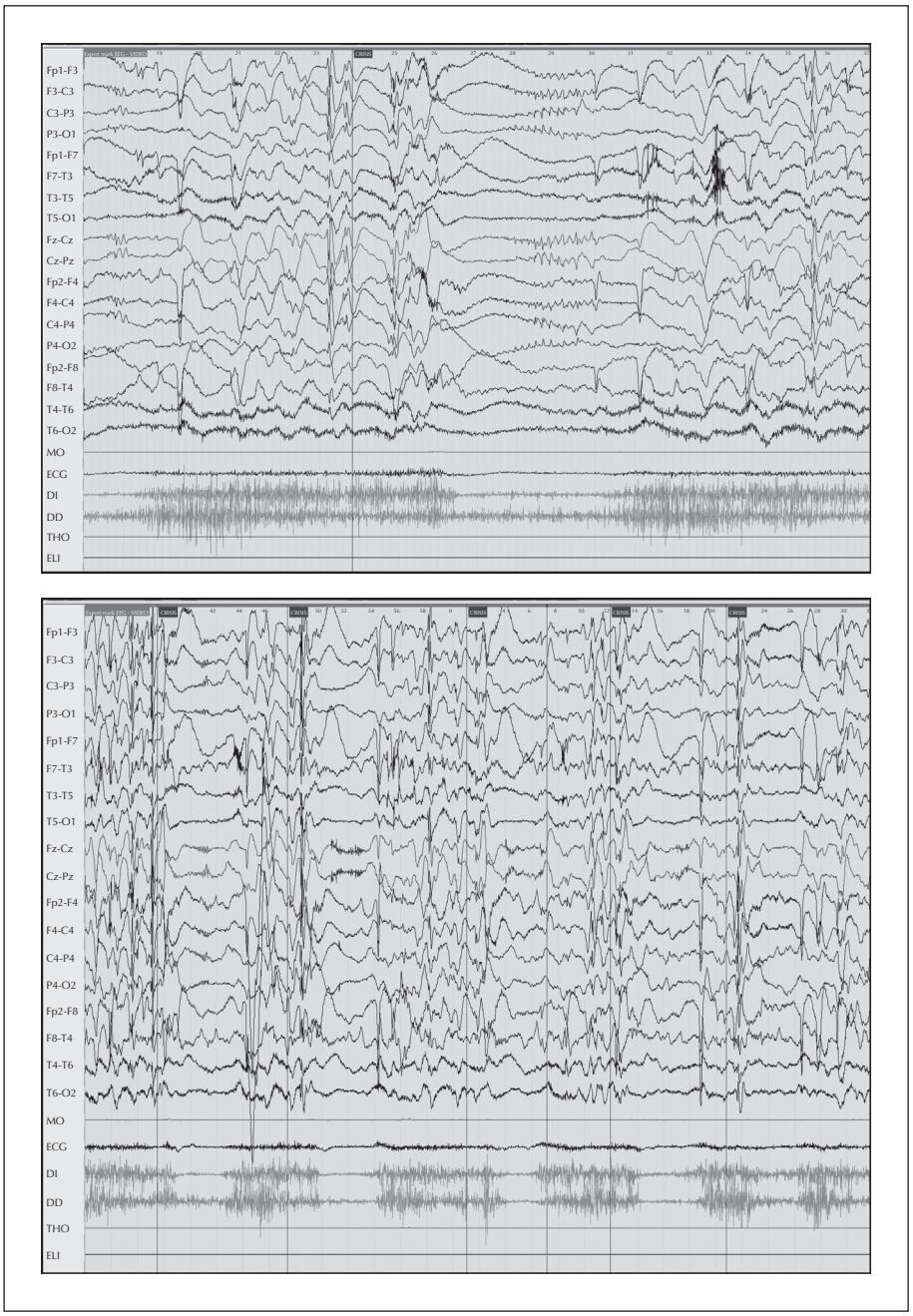

Figure 2. Ictal EEG of Patient 1.
Polygraphic electrodes placed at para-vertebral cervical muscles showing the disappearance of the previous interictal epileptiform abnormalities immediately at the beginning of food intake. Ictal EEG shows a generalised high-voltage slow wave component, which was sometimes preceded by epileptiform abnormalities. Cephalic and axial loss of tone was associated with a peak of this slow component, followed by an event with rhythmic sharp waves of low or medium amplitude. Polygraph recording revealed sudden interruption of the electromyographic (EMG) potentials; this EMG silencing was more evident when the seizures were more prolonged (400 msec). A total of 12 seizures were registered; generalised high-voltage slow-wave activity was observed on the EEG following each seizure.

Mutations in *MECP2, CDKL5* or *FOXG1* genes have been identified in 70% of the Spanish database patients. Although the three patients were clinically characterised as RTT patients (one congenital variant and two classic forms, following the recently revised diagnostic criteria), only one had a molecular diagnosis. Reflex epilepsy among Spanish Rett patients without mutations (2/123) is more prevalent than in those with mutations in any of the Rett-related genes (1/423), with a ratio of almost 7:1. The molecular and

biochemical pathways involved in neuronal migration and maturation are currently under study in these RTT patients.

Eating-triggered seizures are rare. They can be simple or complex partial seizures, with or without secondary generalisation. Physiopathological mechanisms involve oral proprioception, emotional and digestive organ stimuli, as well as psychological inferences. Clinical control is difficult because avoidance of stimulus is not always possible. Some patients may improve by changing the context of food, or administrating benzodiazepines (Ganga *et al*., 1988) or clobazam before meals (which was of no use in our patient). Other patients have shown some improvement after vagal nerve stimulation (Cukiert *et al*., 2010).

Our patient presented "akinetic-tonic seizures", confirmed by video-EEG recording, while other groups observed a series of tonic spasms and both generalised and focal seizures. Previous non-reflex epilepsy could influence this variability.

Afferent information in an "abnormal" sensorimotor cortex may provoke an epileptic discharge and either a focal or generalised seizure. Our patients with proprioception reflex seizures presented with spontaneous seizures at around five years old (the typical age for epilepsy onset in RTT); reflex seizures appeared between four and eight years afterwards. A delay of five years was also previously observed (Ahuja *et al*., 1988), which reinforces the hypothesis of reflex seizure development in a "hyperexcitable" brain, such as in RTT patients.

It remains intriguing why some patients with proprioception reflex seizures provoke an attack. This may bring secondary benefits or induce a seizure-free postictal period. Our two patients appeared happy before self-provocation and upset when asked not to do so. They were able to abort seizures at the beginning of their self-provocation. Guerrini's group observed stereotyped behaviour, as in Rett patients (*eg*. rocking, limb rotation, tapping, *etc*), in three grown-up males, some years before the onset of reflex proprioceptive seizures (Guerrini *et al*., 1992). This co-occurrence of stereotypies and self-induced seizures could be explained as a relief of tension and anxiety, and escape from a disturbing or an overexciting situation.

Reactions of patients with severe mental disability are often difficult to interpret and epileptic Rett children are sometimes misdiagnosed: respiratory or stereotyped events may mimic seizures and seizures may be described as vacant spells. EEG with video and polygraph recording with the suspected trigger is very useful to confirm the diagnosis of reflex seizures. However, self-induced seizures depend on the patient's mood and cooperation and can be difficult to reproduce in severely disabled or uncooperative children. Video recording (at home or at consultation) can be a useful tool to identify reflex seizures.

Response to antiepileptics is poor in reflex seizures, although non-reflex epilepsy was controlled in our patients. Both patients with self-provoked seizures were controlled with one antiepileptic drug (valproate or carbamazepine), but the patient with eating reflex epilepsy remains under triple therapy.

Risperidone reduced our patients' anxiety levels with partial or good response and may thus help to reduce self-provoked attacks related to stress. However, avoiding the trigger remains the best treatment, although this is not always possible. □

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