Eating-induced epileptic spasms in a boy with MECP2 duplication syndrome: insights into pathogenesis of genetic epilepsies

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ABSTRACT – Duplication of MECP2 causes a recently described X-linked mental retardation syndrome, of which the typical features are infantile hypotonia, poor speech development, recurrent infections, epilepsy, and progressive spasticity. Recently, the associated seizure semiology and interictal EEG features have been increasingly described, whereas ictal electroclinical features remain poorly defined. We report the case of a boy carrying a maternally-inherited MECP2 duplication and describe the video-EEG sequence of a cluster of eating-induced spasms, the only epileptic manifestation of the patient. This report expands our knowledge of the epileptic phenotype of MECP2 duplication syndrome and may contribute to a better definition and comprehension of the electroclinical spectrum of patients affected by this disease. It also supports the hypothesis that in some genetic epilepsies, the electro-clinical profile can correlate with the dysfunction of limited cortical regions despite the presence of a genetic mutation over the entire brain. [Published with video sequences]

Key words: MECP2 duplication syndrome, CGH array, reflex epilepsy, eating-induced epileptic spasm, focal seizures

Duplication of MECP2 causes a recently described X-linked mental retardation syndrome, of which typical features are infantile hypotonia, poor speech development, recurrent respiratory infections, epilepsy, and progressive spasticity. Most affected males inherit the MECP2 duplication from a carrier mother; however, spontaneous de novo duplications have been reported (Ramocki et al., 2010).
Epilepsy develops in nearly 50% of affected individuals, but abnormal EEG activity is reported in almost all patients (Echenne et al., 2009, Ramocki et al., 2010) and usually precedes the onset of epileptic seizures. The most striking EEG feature is an unusual monomorphic long-lasting theta activity with absence of alpha rhythm over the parietal-occipital region (Echenne et al., 2009; Vignoli et al., 2012).

Epilepsy is often refractory to treatment and usually appears within the first two decades of life. Generalised tonic-clonic seizures are most often observed, however, other types of generalised (absence and myoclonic astatic) and focal seizures have also been described (Echenne et al., 2009; Vignoli et al., 2012).

We report, for the first time, the video EEG recording of a cluster of eating-induced epileptic spasms in a severely mentally retarded boy who carried an Xq28 duplication encompassing the MECP2 gene, with the aim of expanding our knowledge of the epileptic phenotype of children affected by this condition.

**Figure 1.** (A) Patient at 1 year and 8 months, with normal background activity at eye closure. (B) Patient at 5 years and 1 month, with a diffuse slow discharge, more evident over the fronto-central region. (C) Patient at 7 years, with erratic myoclonic jerks during wakefulness. (D) Patient at 7 years, with persistence of less intense erratic myoclonic jerks during sleep.

**Case study**

The patient was a 7-year-old Caucasian male who was referred to our institute for evaluation of developmental delay and epilepsy. He was born at 41 weeks of gestational age via spontaneous vaginal delivery to unrelated healthy parents. He presented with delayed motor development (he started walking at 24 months), absent speech, happy disposition, and several stereotyped midline hand movements, such as hand flapping. Moreover, he had circadian rhythm sleep disorders and recurrent upper-airway infections.

Since 3 years old, his EEG, which was previously normal, showed diffuse theta activity, prevalent over the central and posterior regions, independent of eye closure, with later development of an erratic myoclonus more evident over the forearms (figure 1). When he was 6 years old, eating-induced seizures appeared. These were triggered by the smell and taste of food, especially spicy food, and were characterised by muscle spasms of the neck. The epileptic spasms were accompanied by a gradual decrease of vigilance and
interaction (see video sequence). Ictal EEG patterns associated with the spasms consisted of a diffuse, irregular, ample slow-wave complex, more evident over the fronto-central regions bilaterally, and were followed by voltage attenuation (1-2 seconds). A few minutes after the beginning of food intake, spasms became pseudo-rhythmic and unrelated to the triggering stimulus. During the cluster, the EEG background activity gradually slowed down with the appearance of slow waves over the fronto-central regions (figure 2).

Seizures were pharmacoresistant and partially controlled only with high doses of valproate and clobazam, and the avoidance of spicy food.

Brain magnetic resonance imaging, performed at 4 and 6 years of age, was unremarkable.

The array CGH analysis detected a maternally inherited duplication of Xq28, spanning around 212.34 Kb and encompassing the MECP2 gene.

**Discussion**

More than one hundred cases with MECP2 duplication have been described worldwide and the characteristic features of the related syndrome are quite well-known: infantile hypotonia, poor speech development, mental retardation, recurrent respiratory infections, epilepsy, and progressive spasticity (Ramocki et al., 2010). While the clinical and neurological phenotypes seem to be quite similar among the patients reported in the literature, the seizure semiology and electroclinical patterns are extremely heterogeneous, ranging from focal to generalised seizures (tonic-clonic, atonic, and absence seizures). In addition, reflex seizures have also rarely been mentioned (Ramocki et al., 2009). EEG iconography and ictal video-EEG recordings of males with MECP2 duplication have been rarely described in the literature.

The peculiarity of our case lies in the occurrence of eating-induced epileptic spasms triggered by the smell and taste of spicy food, with neither hypsarrhythmia nor other epileptic manifestations during the observational period.

Eating-induced seizures are usually focal and associated with symptomatic epilepsies (Blauwblomme et al., 2011). Two critical functional cortical loops are likely to be involved in the pathogenesis of these types of seizures. The first is related to the interconnections between the gustatory cortex (insular, parietal, and frontal region) and the fronto-insulo-hippocampal network, of which the activation can lead to focal temporal seizures (Blauwblomme et al., 2011). The second cortical loop involves the fronto-opercular...
area, related to mouth movement (Labate et al., 2006; Enginar and Nurten, 2010; Auvin et al., 2010).

Reflex seizures, and in particular eating-induced seizures, have been rarely reported. Five patients with focal epilepsy and eating-triggered spasms have been described (Nakazawa et al., 2002; Labate et al., 2006; Auvin et al., 2010; Manyam et al., 2010); three of which presented with a focal lesion over the anterior insulo-opercular region. In these cases, repeat stimuli (such as eating), in the presence of an hyper-excitable fronto-opercular cortex (due to the lesion), could induce the activation and the recruitment of a critical neuronal mass responsible for seizure onset.

Similarly, we could infer from our patient that the genetic defect might be associated with a peculiar epileptogenic susceptibility of the fronto-opercular cortex to eating. The occurrence of spasms, rather than other types of seizures, might be due to the proximity of fronto-opercular cortex to the cortical motor strip, now considered as the main area responsible for spasm initiation (Nariai et al., 2011).

In the other cases reported in the literature, the presence of myoclonic seizures (Echenne et al., 2009) or erratic myoclonus in wakefulness and sleep (Vignoli et al., 2012) has already been stressed and this was usually coupled with common progressive limb spasticity (Ramocki et al., 2010).

These clinical features and the occurrence of eating-induced epileptic spasms in our patient could suggest that the fronto-central cortex may have a role in the pathogenesis of epilepsy and clinical picture of patients with MECP2 duplication.

Taken together, these considerations may support the hypothesis that, for genetic epilepsies, despite the presence of genetic mutation over the entire brain, the electroclinical profile correlates with the dysfunction of more limited cortical regions, as previously suggested for other syndromes such as the “ring chromosome 20 syndrome” (Vignoli et al., 2009).

Disclosures.

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