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Case Report

Electroencephalographic and epilepsy findings in mecp2 duplication syndrome. A family study

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Abstract

MECP2 duplication syndrome (MECP2 DS) is an X-linked disorder characterized by early-onset hypotonia, poor speech development, recurrent respiratory infections, epilepsy and progressive spasticity. Epilepsy occurs in more than 50% of the affected patients. Generalized tonic-clonic seizures (GTCS) are the most common seizure-type described but atonic seizures, absences and myoclonic seizures have also been reported. Electroencephalographic (EEG) and seizure types occurring in MECP2 DS have been poorly investigated. Here we report on two male siblings carrying a maternally-inherited MECP2 duplication. Patients underwent several EEG recordings and long-lasting video-EEG monitoring. The most represented seizure types were myoclonic and atonic seizures. GTCS were rarely observed. In patients, we found a slowing of the background activity with multifocal paroxysmal activity, prominent on the frontal areas. In conclusion, our observations seem to suggest that MECP2 syndrome seem to have a peculiar epileptic pattern mainly characterized by the occurrence of myoclonic seizures, the recognition of which is important in order to undertake an appropriate treatment.

Keywords: MECP2 duplication syndrome; Video-EEG recording; Epilepsy

1. Introduction

MECP2 duplication syndrome (MECP2 DS) is a recently described neurodevelopmental disorder due to gain-of-function mutations of MECP2 gene, located on Xq28 region. To date more than 150 cases of MECP2 DS have been reported [1]. The syndrome is characterized by severe neurodevelopmental disorder with infantile hypotonia and progressive spasticity, recurrent severe infections, stereotyped movements, severe learning disability, and mild facial dysmorphisms [2].

Although epilepsy is a significant feature of the syndrome, electroencephalographic (EEG) pattern and ictal video-EEG recordings have been rarely described. In this perspective, the present study was focused to define epilepsy and EEG findings in MECP2 DS by describing the EEG and clinical history in two affected siblings. A review of the literature has also been performed.

1.1. Case 1

A boy born at term by vaginal delivery, after an uneventful pregnancy. Psychomotor developmental milestones were delayed. He never acquired ability to perambulate. Language was absent. During infancy

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he experienced recurrent respiratory infections with admission in hospitals. At the age of 8 years, two episodes described as GTCS occurred, which were associated with daily episodes of sudden trunk drop. He was placed under valproate (VPA), at the daily dose of 30 mg/kg, and topiramate (TPM), at the daily dose of 6 mg/kg, with an almost complete seizure control. Brain MRI was unremarkable. Array-CGH investigation detected a microduplication affecting Xq28 region, spanning around 450 Kb and encompassing MECP2 gene.

At the last clinical evaluation (9.5 years), he showed minor facial anomalies and severe psychomotor retardation and hypotonia. Stereotypic hand movements were present. The patient died at the age of 10 years for complications of a respiratory infection.

EEGs and Video-EEG monitoring. The patient underwent several EEG recordings including long-term video-EEG. Background activity was monomorphic with delta waves prominent in the posterior regions. Paroxysmal activity with multifocal onset characterized by spike, spike-wave and polyspike-and-wave were prominently observed in the frontal areas. Generalized EEG anomalies were mainly recorded during sleep. Interictal paroxysmal activity spikes, spike-waves, and polyspike-waves in the posterior regions, often occurring in long-term sequences, were also recorded (Fig. 1A). Recorded seizures were characterized by sudden head and trunk drop with ictal EEG represented by generalized spike-waves followed by delta waves. Ictal silencing on the superficial EMG signal were also recorded, which were congruent with an atonic type of seizure (Fig. 2A). During long-term video-EEG monitoring several myoclonic seizures were also observed with typical electroencephalographic and EMG findings (Fig. 1A) associated with non-paroxysmal events.

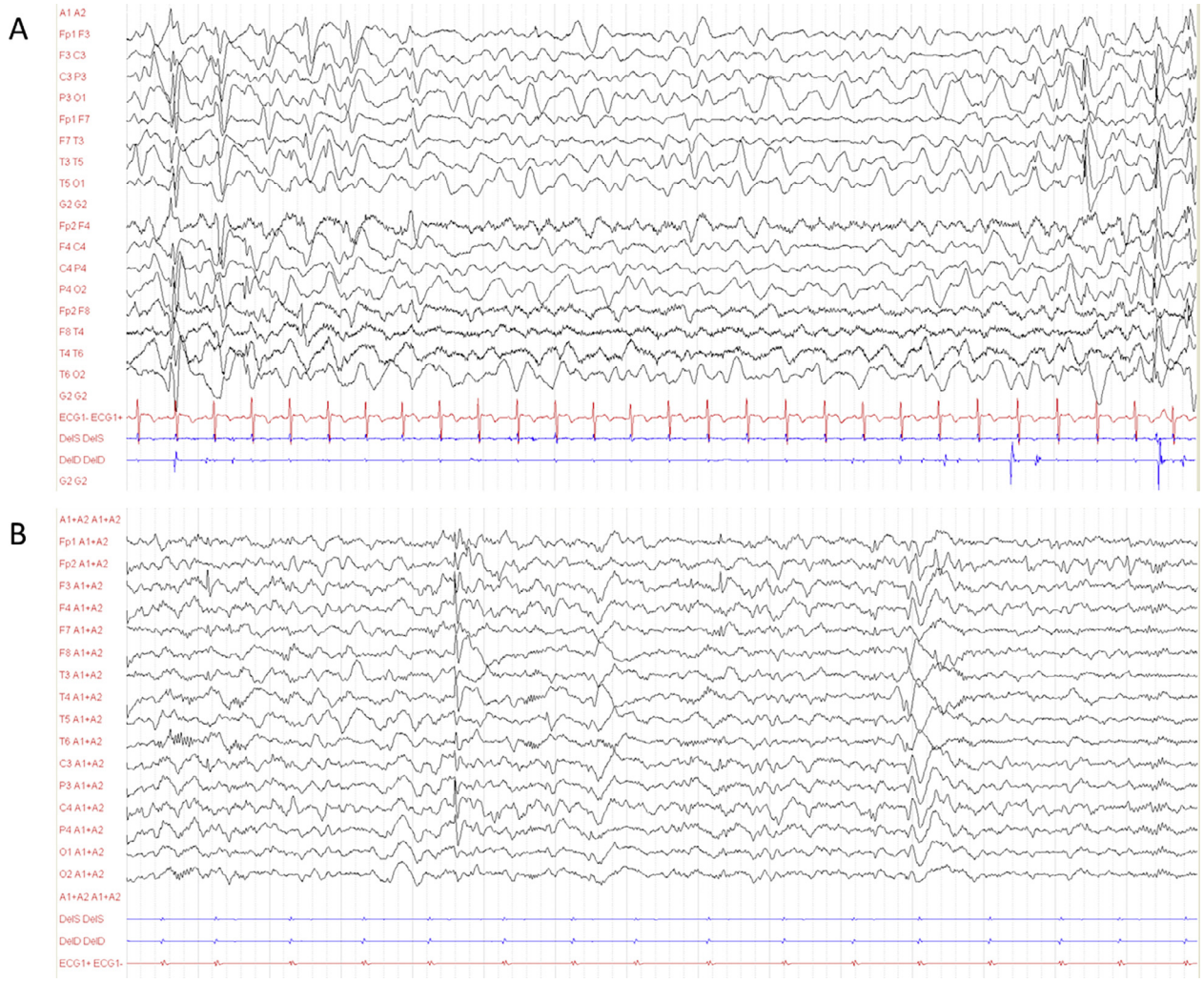

Fig. 1. A: Patient 1 EEG showing delta activity, prominent in posterior regions with multifocal paroxysmal activity, myoclonic seizures and dyskinesias. B: Patient 2 EEG showing slow background activity and paroxysmal activity with multifocal onset, prominent in the anterior regions, which also appears in short sequences in right frontopolar region.

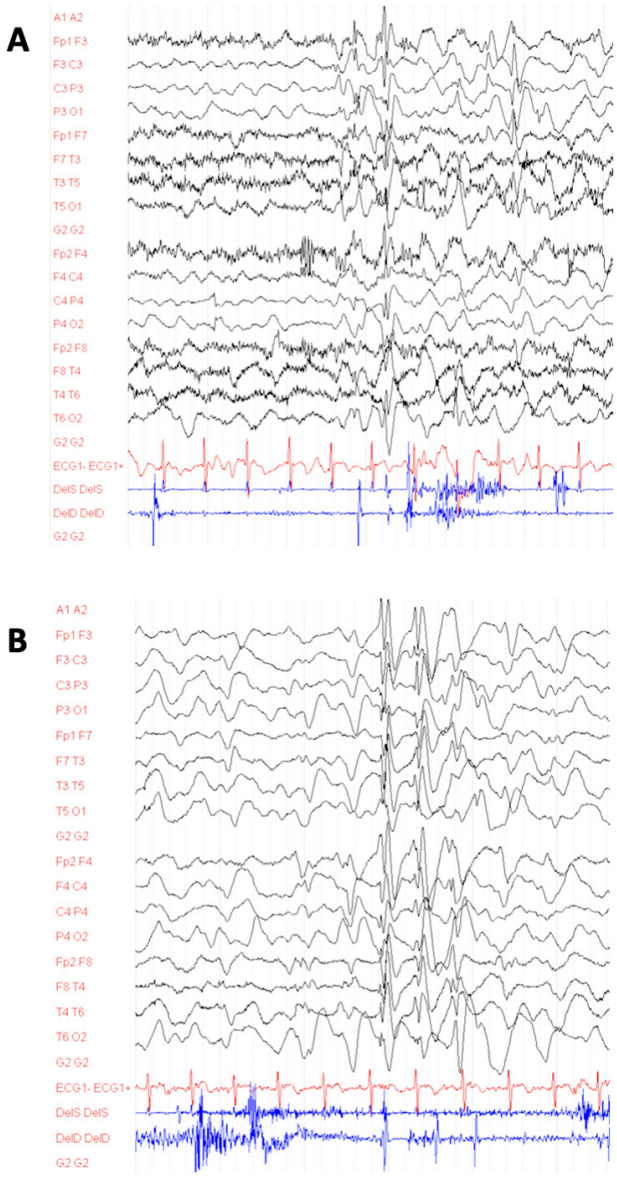

Fig. 2. A: Patient 1 EEG showing generalized spike-waves complexes followed by generalized, irregular delta-waves. B: Patient 2 EEG showing diffuse spike-and-waves activities related to myoclonic jerks.

1.2. Case 2

A boy born by vaginal delivery after an uneventful pregnancy. During the first months of life, severe psychomotor developmental was observed. Recurrent respiratory infections occurred during infancy. Seizure-onset occurred at 2.3 years of age with focal and generalized myoclonic jerks. VPA therapy (30 mg/kg per day) was started with partial seizure control. Subsequently, clobazam therapy (10 mg per day) was added, with a slight improvement of seizure control. Array-CGH analysis confirmed a microduplication affecting Xq28 region and MECP2 gene.

Physical examination showed minor facial anomalies, severe psychomotor retardation, axial hypotonia, absent speech, lower limb spasticity, and hyperreflexia.

An MRI performed at the age of 8 years showed thinning of the corpus callosum, enlargement of the periencephalic spaces and microcephaly.

EEG and long-term video-EEG monitoring. The patient underwent several EEG recordings including long-term video-EEG. Long-term video-EEG monitoring showed a slow background activity. Paroxysmal activity with multifocal onset, mainly represented by spikes and spike-and-wave in the anterior regions, prominent in the right hemisphere, was recorded (Fig. 1B). Seizures consisted in segmental and massive myoclonic jerks with typical EEG and superficial EMG findings (Fig. 2B). Non-paroxysmal events with movement disorders were also recorded.

2. Discussion

Abnormal EEG findings have been reported in almost all patients affected by MECP2 DS, while seizures seem to occur in up to 54% of them. Age at seizure-onset is variable ranging from 4 to 13 years, sometimes occurring only during the second decade of life. As a matter of fact, over 90% of affected patients who survive into adolescence has seizures [3]. GTCS are the most often described seizure type, but tonic, atonic, absence and atypical absence, partial complex, reflex, myoclonic and myoclonic-astatic seizures have also been observed [3–6].

To date, only a few studies focused on the epilepsy phenotypes and on the electroclinical pattern of affected individuals [7,8].

In the present study we describe the electroclinical features of two siblings affected by MECP2 DS. In contrast to what previously reported, GTCS appeared scarcely represented in our patients, with only two episodes described in the older brother. Myoclonic seizures, instead, play a major role in both of the patients, representing the only seizure type in younger brother. We also observed episodes of sudden head and trunk drop, defined as atonic seizures by video-EEG monitoring analysis.

Interictal EEG recording showed in both patients a slowing of the background activity, which appears to be a common feature in males with MECP2 DS [3,7,8]. In particular we confirm the occurrence of a monomorphic long-lasting delta activity over posterior regions previously described in a few affected patients [7].

Video-EEG recording analysis demonstrated that both patients had several stereotypic behaviors as well as movement disorders mainly including dyskinesias and dystonias. A correct definition of movement disor-

ders, their clinical differentiation from epileptic episodes, is mandatory to not overestimate seizures.

In most of the patients with MECP2 DS epilepsy is refractory to treatment and an effective therapeutic strategy is still lacking [3]. In our experience, a combination of VPA and TPM resulted to be effective in controlling seizures. Unfortunately, patient 1 died of respiratory infection complications, at the age of 10 years. No longer follow-up was therefore available. Over the recent years, research has focused on the identification of genetic causes for epilepsy. A better understanding of the underlying epileptogenic process will allow for the possibility of directed therapeutic approaches [9]. Hopefully, a precision or individualized medicine, based on the use of new drugs targeted at the specific genetic dysfunction, will considerably improve epilepsy treatment.

Although some common EEG characteristics among affected patients have been identified, no specific electro-clinical phenotype has emerged until now, and this is likely due to the genetic heterogeneity of the syndrome.

In conclusion, we reported on the epilepsy history and EEG findings in two siblings affected by MECP2 DS. Our observations seem to suggest that myoclonic seizures, segmental and/or massive, is the main seizure type occurring in patients with MECP2 DS. Atonic seizures can also be observed. Seizures such as GTCS or atypical absences, seem to appear marginal. Of course, further video-EEG recording analysis in MECP2 DS are needed to better understand the electro-clinical profile of the syndrome.

Ethical statement

The present study was approved by the local ethics board. Informed consent was obtained from the patients' parents.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.braindev.2018.12.008.

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