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Case Report

MECP2 duplication syndrome: The electroclinical features of a case with long-term evolution

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ABSTRACT

MECP2 duplication syndrome (MDS) is a rare and severe neurodevelopmental disorder frequently associated with epilepsy. Different seizure types and electroencephalographic (EEG) patterns were described in patients with MDS, although it lacks a specific phenotype.

We report on an adult patient with long-term epilepsy showing an evolution of the EEG pattern that progressively changed into burst suppression (BS) during sleep. As BS has not been previously reported in MDS, this report expands the neurophysiological phenotype of MDS and further suggest the possible occurrence of a longitudinal spectrum of seizure types and EEG patterns in MDS.

Introduction

MECP2 duplication syndrome (MDS) is a rare and severe X-linked neurodevelopmental disease caused by the gain-of-function of the *MECP2* gene [1]. It has a 100% penetrance in males, whereas female penetrance is lower due to X-chromosome inactivation skewing. *MECP2* mutations in females are the primary cause of Rett syndrome but through a distinct mechanism of loss-of-function and gene deletions.

MDS is characterized by infantile hypotonia, severe intellectual disability, speech impairment and recurrent respiratory infections [2]. Seizures occur in 47% of the cases, usually as part of a developmental and epileptic encephalopathy. Despite the high prevalence of epilepsy in MDS patients, only a few studies focused on the electroclinical pattern of this disorder, perhaps owing to the lack of a specific phenotype [3,4].

We report the case of an adult patient with MDS showing an evolution of the EEG pattern that progressively morphed into burst suppression (BS) during sleep. We also provide a literature review for published cases of epilepsy in MDS focusing on EEG findings.

Case presentation

We present a male patient, the only child of healthy non-consanguineous parents, who has been referred to our institute for evaluation of developmental delay and epilepsy at age of 19 years during his transition from child to adult neurology (Fig. 1).

He was born at 39 weeks of gestation after an uneventful pregnancy. During the neonatal period, he developed feeding difficulties, frequent regurgitation and vomiting, resolved after two hiatal hernia surgeries.

Developmental psychomotor milestones were delayed, with control of the trunk and independent walking achieved at 2 and 3 years, respectively; language was limited to few words.

At 6 years, he developed seizures characterized by staring and impaired awareness lasting about 20 s, with a frequency of 2–3/year. Since the age of 7 years, he had daily episodes of atypical absence and tonic seizures resistant to multiple anti-seizures medications. Since the same period, a progressive psychomotor regression had occurred resulting in inability to walk at 9 years. Because

Abbreviations: MDS, *MECP2* duplication syndrome; EEG, electroencephalographic; MLPA, Multiplex ligation-dependent probe amplification; BS, burst suppression.

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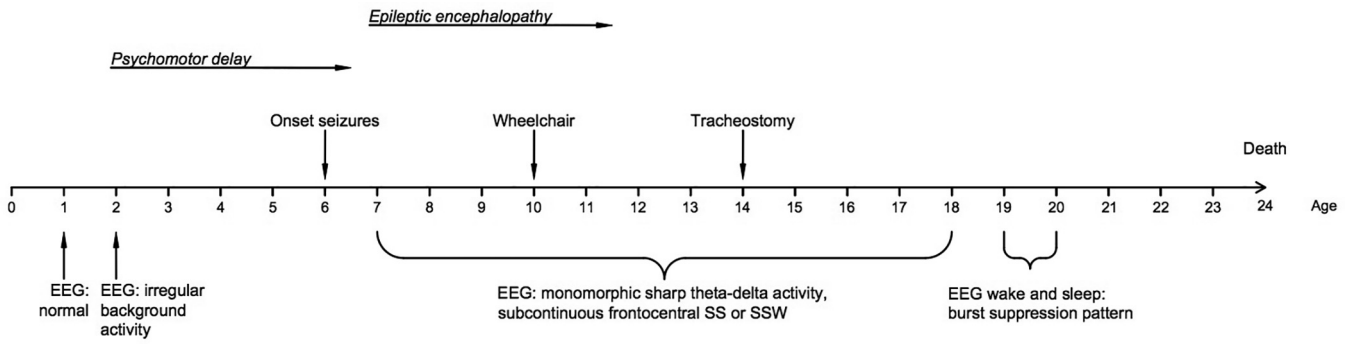

Fig. 1. Disease course and EEG findings. Abbreviations: SS: slow-spike-and-wave, SSW: spike-and-slow wave.

of recurrent respiratory tract infections, he underwent tracheostomy at 14 years.

At 19 years, he developed repeated episodes during wakefulness characterized by impaired awareness, staring, sudden flexion of truncal muscles with the abduction of arms lasting few seconds, consistent with epileptic spasms. Neurologic examination revealed severe intellectual disability with absent speech, sporadic purposeless limb movements, diffuse hypotonia and brisk tendon reflexes. At that time, he was bedridden, dysphagic and required respiratory support.

All assessed laboratory parameters and brain MRI study excluded mitochondrial, metabolic and lipid storage diseases. Karyotype, *FRAXA, ATR-x*, *CDKL5* and *ARX* genes analysis were normal. According to the patient's phenotype and clinical evolution we performed at 19 years a multiplex ligation-dependent probe amplification (MLPA) analysis which reaveled a microduplication of the region on Xq28 including *GDI1, FLNA, MECP2, IRAK1, L1CAM* and *IDH3G* genes.

The patient died at 24 years due to pneumonia, a common complication of dysphagic and severely cognitively impaired patients.

EEG features

The first EEG study at 1 year of age was normal. At the age of 2 years, awake and sleep study showed a poorly organized cerebral activity without epileptiform discharges and normal sleep structure.

Follow-up EEGs performed between 7 and 18 years revealed a slow background activity characterized by monomorphic sharp theta-delta activity, with subcontinuous epileptiform abnormalities of slow spike-and-waves asynchronously over the frontocentral head regions. Seizures characterized by diffuse tonic contraction lasting 1–2 s were recorded; ictal EEG showed spike-and-slow waves followed by a sudden depression of activity and superimposed generalized paroxysmal fast activity prevalent over the frontocentral regions. Sleep activity observed during daytime recordings was characterized by a synchronism of the epileptiform abnormalities enhancing the generalized paroxysmal fast activity. Physiological sleep elements were poorly represented.

At 19 years, EEG recording showed an alternating appearance of bursts with frequent paroxysmal activities of diffuse spike-and-slow waves or polyspike-and-slow waves lasting 10–15 s followed by background activity attenuation lasting approximately 1 second. This EEG activity did not always correlate with clinical changes. Several spasms and asynchronous myoclonic jerks were recorded (Fig. 2A-B).

A 24-hour EEG monitoring study performed at this age documented a total time of sleep of 4.5 h during nighttime with some protracted awakenings, of which the longest lasted up 48 min (sleep efficiency 56%). Sleep architecture was characterized by all non-rapid eye movement (NREM) and REM sleep stages (5% stage 1 NREM, 72% stage 2 NREM, 13% stage 3 NREM, 10% stage REM); two sleep cycles were recorded. Physiological sleep figures were poorly represented. EEG recordings were characterized by a gradual increase of suppression phases duration, which morphed into a burst suppression (BS) pattern in NREM stage 2 and REM (Fig. 2C). Burst suppression index (BSI, number of burst suppression per hour of sleep) was 443. Specific BSIs for stage 2 NREM and REM were 485 and 741, repectively. Spike-and-wave index (SWI, number of spike-and-wave per hour of sleep) was 528. BS pattern was not associated with any muscular activities or vegetative changes. Spasms were recorded also during nighttime, though arising from phases of wakefulness.

Discussion

We report on an adult male patient with MDS and long-term epilepsy documented by repeated clinical and EEG evaluations over time. Literature on epilepsy in MDS is mainly focused on childhood, while data about patients with long-term epilepsy or its natural history are lacking (Supplementary Table).

In our patient, epilepsy with atypical absences started at age of 6 years, as commonly seen in MDS [3]. Childhood EEGs showed a diffused slowing with paroxysmal epileptiform activity over the frontocentral regions. However, after 10 years, seizures and EEG pattern changed featuring late-onset epileptic spasms, with multifocal epileptiform abnormalities mixed with suppression phases in wake and a BS pattern during sleep.

While spasms were recently described in other patients with MDS, the BS pattern has not been reported in the literature to our knowledge [5–7]. BS typically occurs in the behavioral state of loss of consciousness secondary to severe cerebral dysfunction or anesthetic-induced [8]. It is uncommon in epilepsy syndromes, apart from early infantile epileptic encephalopathies (Ohtahara syndrome, Early Infantile Myoclonic Encephalopathy), where BS represents a sign of incomplete brain development, and typically evolves to hypsarrhythmia at 3–6 months [9]. Some cases of reversible BS pattern associated with sleep have been described in West syndrome, since cortical disconnection occurring during sleep facilitates the emergence of suppression phases [10].

Unlike what typically happens in epileptic encephalopathies, where BS commonly represents the EEG pattern at disease onset, in our case BS pattern likely reflects a severe cerebral dysfunction secondary to advanced disease progression. As clinical worsening with older age has been suggested, studies on the natural history of epilepsy could potentially point out a progression of EEG findings [11]. Serial EEGs of 9 patients with MDS have been recently reviewed reporting an evolution from normal to abnormal activity

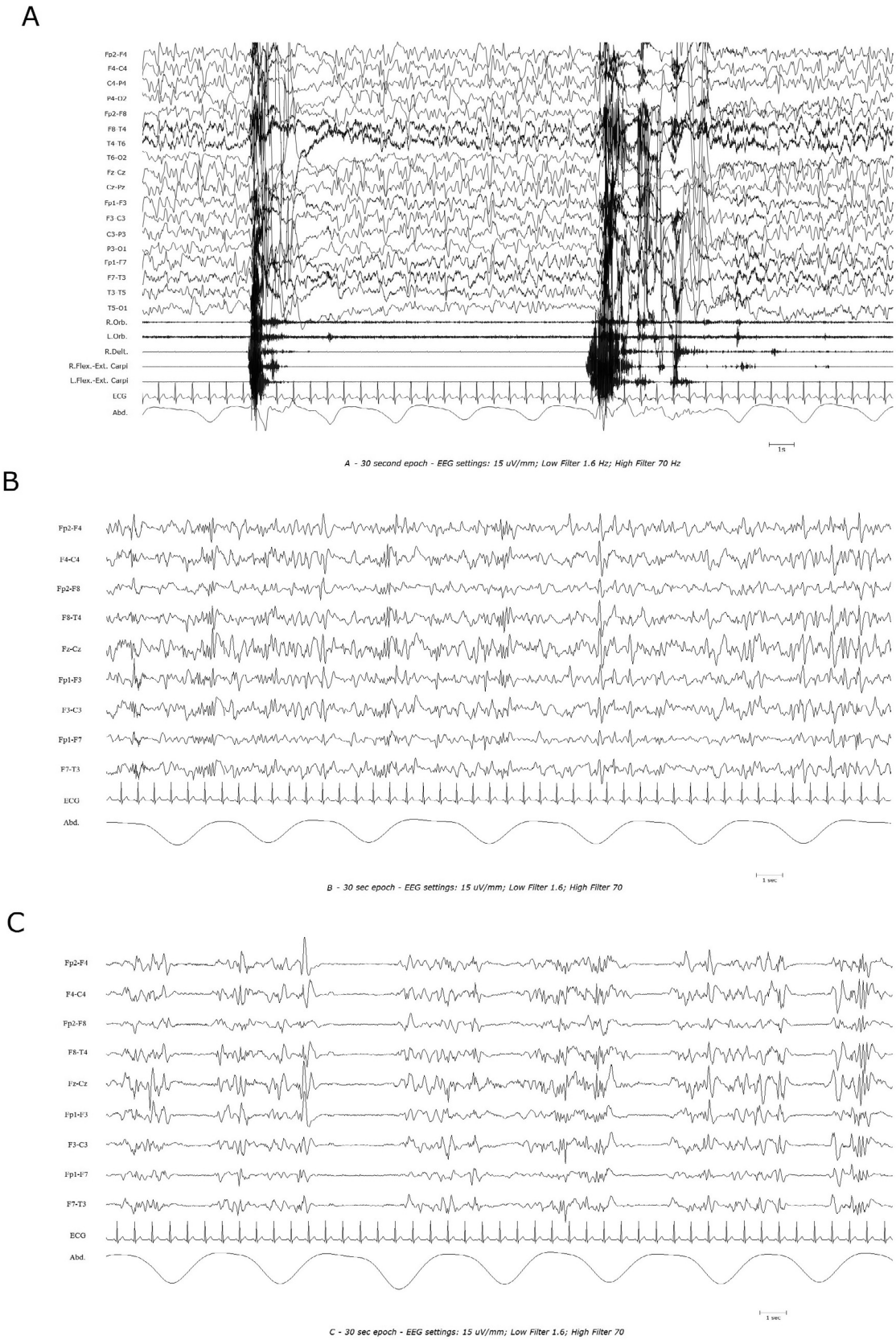

Fig. 2. Wake and sleep EEG recordings showing suppression phases in wake and burst suppression pattern during sleep. A) Diurnal polygraphic awake recording showed diffuse spike-and-slow wave or polyspike-and-slow wave discharges; on two occasions, a bilateral brief contraction of proximal and truncal muscles lasting 1–2 s (spasm) was recorded with no related epileptiform activity. B) Prolonged monitoring of sleep-wake cycle in wake showed bursts with frequent paroxysmal activities of diffuse spike-and-slow waves or polyspike-and-slow-waves lasting 10–15 s followed by symmetric voltage attenuation lasting 1 second. C) Prolonged monitoring of sleep-wake cycle during NREM 2 stage showed a burst-suppression pattern with phases of suppression lasting up to 4 s during sleep. *Abbreviations:* Abd.: abdominal respirogram, Delt: deltoid muscle, ECG: electrocardiogram, Ext. Carpi: extensor carpi muscle; L.: left, Orb.: orbicularis oculi muscle, R., right.

within 1–8 years of age in half of the patients [7]. However, our report is the only description of progression of EEGs to BS in a patient with MDS and long-term epilepsy. Two other patients over 20 years have been reported in the literature, one case focused on phenotyping of seizures in MDS, the other centered on the management of seizures with deep brain stimulation [4,12]. Further studies are needed to better characterize the electroclinical pattern of this rare disease, possibly including the implementation of sleep studies.

Conclusions

We reported the electroclinical evolution of an adult patient with MDS, pointing out a unique EEG pattern, consisting of suppression phases and sleep BS pattern, that appearred only in the later stages of disease. To our knowledge, these findings have not been previously described in the literature. This feature expands the neurophysiological phenotype of patients with MDS known so far, and highlights the possible occurrence of a longitudinal spectrum of seizure types and EEG patterns in MDS. We speculate a BS pattern on EEG may have similar prognostic implications for other patients with MDS.

Declarations of interest

None.

Disclosure

The authors report no relevant disclosures or conflicts of interest for this manuscript.

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Declarations

Ethics approval and consent to participate: Written informed consent was obtained from patient's relatives for the inclusion of deidentified clinical data in a scientific publication, in accordance with the Declaration of Helsinki.

Consent for publication: All authors agreed with this final version.

Competing interests: The authors declare that they have no competing interest.

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Authors' contributions: IC, FB and FP conceived and designed the study. IC analyzed the data and drafted a significant portion of the manuscript, figures, and table. LM, FM and LL helped in the acquisition and analysis of the data. FB and FP contributed to revising the manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ebr.2022.100541.

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