Spectrum and time course of epilepsy and the associated cognitive decline in *MECP2* duplication syndrome

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Abstract

Objective

We characterized the epilepsy features and contribution to cognitive regression in 47 patients with *MECP2* duplication syndrome (MDS) and reviewed these characteristics in over 280 MDS published cases.

Methods

The institutional review board approved this retrospective review of medical records and case histories of patients with MDS.

Results

The average age at enrollment was 10 ± 7 years. Patients with epilepsy were older (13 ± 7 years vs 8 ± 5 years, $p = 0.004$) and followed for a longer time (11.8 ± 6.5 years vs 6.3 ± 4.2 years, $p = 0.003$) than patients without a seizure disorder. Epilepsy affected 22/47 (47%) patients with MDS. It was treatment-refractory and consistent with epileptic encephalopathy in 18/22 (82%) cases. Lennox-Gastaut syndrome (LGS) was present in 12/22 (55%) patients and manifested between late childhood and adulthood in 83% of cases. The emergence of neurologic regression coincided with the onset of epilepsy. The *MECP2* duplication size and gene content did not correlate with epilepsy presence, type, age at onset, or treatment responsiveness.

Conclusion

Epilepsy in MDS is common, often severe, and medically refractory. LGS occurs frequently and may have a late onset. Developmental regression often follows the onset of epilepsy. The *MECP2* duplication extent and gene content do not discriminate between patients with or without epilepsy. Our findings inform clinical care and family counseling with respect to early epilepsy recognition, diagnosis, specialty referral, and implementation of aggressive seizure therapy to minimize detrimental effect of uncontrolled seizures on cognitive functions or preexisting neurologic deficits.

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Glossary

EE = epileptic encephalopathy; FET = Fisher exact test; ILAE = International League Against Epilepsy; IS = infantile spasms; LGS = Lennox-Gastaut syndrome; MDS = *MECP2* duplication syndrome.

MECP2 duplication syndrome (MDS) is a severe, clinically recognizable X-linked recessive neurodevelopmental syndrome stemming from an increased *MECP2* gene copy number on the long arm of the X chromosome (Xq28).^{1,2} It has 100% penetrance in male patients, while penetrance in female patients is variable due to skewed X-inactivation.³ More than 280 cases of MDS have been described in the literature since the initial syndrome recognition in 2005 (table e-1, links.lww.com/WNL/A779).⁴ Neurologic morbidities dominate clinical features and include profound infantile hypotonia, severe intellectual disability, psychomotor regression, autism, and epilepsy.^{1,2} It is estimated that 1% of male patients with unexplained X-linked intellectual disability and 2% of male patients with severe encephalopathy and progressive neurologic symptoms have MDS.⁵ It has been reported that over 90% of children with MDS experience seizures by the time they reach adolescence,⁶ with epilepsy becoming treatment-refractory in up to 75% of patients.⁷ Severe epileptic encephalopathy represented by late-onset spasms,⁷ myoclonic-astatic epilepsy, or Lennox-Gastaut syndrome (LGS) has been reported in sporadic cases.^{5,8–10} Yet, despite the apparent frequent occurrence, severity, and detrimental effect on cognitive development, epilepsy frequency, types, and treatment responsiveness have not been systematically evaluated.

Our study stems from a partnership of medical professionals and MDS families that led to the evaluation of 47 patients with MDS. We also performed a review of all MDS cases published to date, in order to provide comprehensive context to our case series.

Methods

The Institutional Review Board of Baylor College of Medicine approved this study, protocol H-30445. Informed consent was obtained from all participants. We developed an epilepsy-focused standardized health questionnaire (appendix e-1, links.lww.com/WNL/A780) that was administered to all study participants. Parents as the primary caretakers filled out information in the questionnaire. We analyzed data related to development, behavior, epilepsy, and seizures in a convenience sample of 47 patients. Ten patients were actively followed and consented at the Blue Bird Circle Rett Center at Texas Children's Hospital and 39 patients were consented at the Third Biannual *MECP2* Duplication Syndrome Family Conference (levonslight.com/2015_MECP2conference/info.html). Thirty-seven questionnaires were returned (response rate 95%). Questionnaire-based data were cross-referenced and validated with medical records in 26/37

(70%) cases. We confirmed that questionnaire-based parental reports were accurate and thus included the remaining 11 patients with MDS with questionnaire-only data. Board-certified neurologists (D.M., D.G., A.M.G., B.S.) and a practitioner (R.S.) confirmed the diagnostic accuracy of the epilepsy and neurologic phenotypes. The investigator (D.M.) clarified data via supplemental phone interviews of caregivers as necessary. Medical records were reviewed up to the date of enrollment in both the cases enrolled at the family conference and cases enrolled in the Blue Bird Circle Rett Center. Age at diagnosis was defined as age when the patient first came to medical attention that prompted neurologic and molecular evaluations leading to the diagnosis of MDS. Age at epilepsy onset was defined as the age when seizures were either first noted by parents and subsequently confirmed by neurologic evaluation or when neurologic evaluation by a physician uncovered epileptic seizures. Length of follow-up spanned the time from the age at diagnosis to the time of enrollment into the study.

When evaluating age-based epilepsy frequency and cognition, patients were stratified into the 4 previously defined age groups⁶ according to their age at enrollment: early childhood (<3 years), late childhood (3–12 years), adolescence (13–18 years), and adulthood (>18 years).

Brain MRI studies were obtained during the initial neurologic evaluations and were classified as normal, abnormal lesional MRI, or abnormal nonlesional MRI based on the presence or absence of focal abnormalities.

Epilepsy was defined according to the 2014 International League Against Epilepsy (ILAE) guidelines¹¹ since epilepsy and seizures were originally classified using these diagnostic criteria in all patients. Patients taking one or more than one antiepileptic medication at the time of the survey were classified as being on monotherapy or polytherapy, respectively. Using the previously published ILAE definitions on epilepsy control,¹² epilepsy in MDS was classified as either drug-resistant or drug-responsive. Epileptic encephalopathy (EE) was defined according to the 2010 ILAE definition as the presence of epilepsy along with reported cognitive and behavioral decline in temporal relation with the onset of seizures.¹³ LGS was defined according to the ILAE 1989 original criteria.¹⁴ Late-onset LGS was defined as syndrome onset after 8 years of age.¹⁴

Statistical analysis was performed with Excel (Microsoft Office Professional Plus 2016; Microsoft, Redmond, WA). Group comparisons were tested with χ^2 test or Fisher exact test (FET) in the case of categorical variables and the independent samples *t* test was applied for continuous variables.

Data availability

Anonymized data not published within this article will be made available by request from any qualified investigator.

Results

We enrolled 41 male and 6 female patients with MDS. The male to female ratio of 7:1 was consistent with the sex distribution in the 286 cases published to date (table e-1, [links.lww.com/WNL/A779](https://www.lww.com/WNL/A779)). Age at enrollment was 1–27 years (average 10 ± 7 years). Accurate age at MDS diagnosis and thus the length of follow-up could be defined in 18/22 (82%) and in 22/25 (88%) cases with and without epilepsy; respectively, epilepsy was present in 22/47 (47%) patients with MDS. Patients with or without epilepsy did not differ with respect to the age at MDS diagnosis or sex (FET, $df = 1$, $p = 0.67$ [NS]). However, patients with epilepsy were significantly older at enrollment (13 ± 7 vs 8 ± 5 years, 2-tailed $t = 2.99$, $p = 0.004$) and were followed for longer time (11.8 ± 6.5 years vs 6.3 ± 4.2 years, 2-tailed $t = 3.14$, $p = 0.003$) than their peers without a comorbid seizure disorder (table 1 and figure 1). Age at onset of epilepsy in patients with MDS ranged from 1 day to 19 years with average age of 6 ± 5 years and incident epilepsy was observed in all age groups (figure 1). Among patients with epilepsy, 27% and 59% developed seizures before the age of 3 or between 3 and 12 years of age, respectively. Epilepsy emerged in adolescence or adulthood in the remaining 3/22 patients. It was treatment-resistant in 18/22 (82%) patients, of whom 17 were male. EE was common, affecting all 18 cases with drug-resistant epilepsy. LGS was the dominant EE syndrome after 3 years of age and accounted for 55% of all epilepsies. All 3 patients who developed epilepsy after the age of 13 years met the criteria for the diagnosis of LGS. EE in the 6/18 cases lacked distinguishing features for

further syndromic classification. Late-onset LGS was noted in 3 patients with MDS, including one sibpair with recurrent, maternally inherited *MECP2* duplication. Both siblings manifested autism and developmental delay in childhood followed by the onset of treatment-resistant LGS at the age of 17 and 19 years.

Multiple seizure types were present in 19/22 cases with atonic seizures being the most frequent, occurring in 18/22 (82%) patients with MDS with epilepsy. Other commonly occurring seizure types were generalized tonic-clonic seizures (68% cases), tonic seizures, atypical absences, and myoclonic seizures (63% cases each), and focal seizures (36% cases). Infantile spasms (IS) heralded the onset of epilepsy in one patient who later developed LGS. We also found reports of either classic or modified hypsarrhythmia EEG patterns at epilepsy onset in an additional 3/12 patients with LGS.

Common seizure triggers included infections or a fever (68%), sleep deprivation (32%), feeding (27%), and emotional upset (23%). Less common precipitants were arousal from sleep (9%), facial tactile stimuli (4.5%), and sudden noise (4.5%).

While the epilepsy was successfully treated with monotherapy in 18% of cases, the majority of patients (17/22) were on polytherapy and 45% of them were taking 3 or more antiepileptic medications. Levetiracetam and valproic acid were the most commonly prescribed drugs, used in 82% and 68% of children, respectively. We did not identify a specific monotherapy or polytherapy with a sustained effect on seizure control (figure e-1, [links.lww.com/WNL/A778](https://www.lww.com/WNL/A778)). Eight patients with epilepsy were treated with one or more types of adjunct therapy. Five patients received a vagus nerve stimulator and 4/5 reported efficacy in the overall reduction of the

Table 1 Characteristics of patients with *MECP2* duplication syndrome (MDS) with and without epilepsy

	MDS with epilepsy (n = 22)	MDS without epilepsy (n = 25)	Statistics
Sex, F:M	2:20	4:21	FET, $df = 1$, $p = 0.67$
Age at study enrollment, y (all cases)			FET, $df = 3$, $p = 0.16$
<3	0	2	
3–12	12	18	
13–18	6	4	
>18	4	1	
Age at MDS diagnosis, mo, mean $\pm$ SD (range)	10.87 $\pm$ 8.9 (0.75–36.0)	11.67 $\pm$ 8.2 (4–36)	t 0.28027; $p = 0.78$
Length of follow-up, y, range (average $\pm$ SD)	2.9–25.4 (11.8 $\pm$ 6.5)	0.42–16.5 (6.3 $\pm$ 4.2)	t 3.13974; $p = 0.003$
Developmental regression, n (%) ^a	20 (91.0)	5 (20.0)	FET, $df = 1$, $p < 0.000001$
Lesional brain MRI ^b	3/14	1/8	FET, $df = 1$, $p = 0.54$

Abbreviation: FET = Fisher exact test.

^a Cognitive regression data available for 22 in the epilepsy group and 25 in the nonepilepsy group.

^b Structural MRI data available for 14 in the epilepsy group and 8 in the nonepilepsy group.

Figure 1 Frequency of epilepsy at enrollment in 40/47 patients with *MECP2* duplication syndrome and defined length of follow-up

seizure frequency, severity, and duration and an improvement in the atonic seizures, in particular. Seven patients were treated with either a ketogenic or a modified Atkins diet and parents reported modest improvement in seizure frequency and severity in 5/7 individuals.

Since cognitive impairment is a common comorbidity of MDS¹ and epilepsy,¹⁵ we analyzed data related to the intellectual functioning of our patients. We found that developmental delay was diagnosed in 85% of cases in the first year of life and in all children followed beyond 3 years of age. The average age at diagnosis of developmental delay was 11 ± 8.5 months. Detailed cognitive assessment results were available in 39/47 (83%) patients and 29/39 (74%) of these children had a global developmental delay affecting gross and fine motor functions, language, and social domains. The remaining 10 patients had less severe impairment.

Developmental regression, as noted in the medical records and reported by parents, affected 25/47 (53%) patients, with an average age at onset at 6 ± 5 years. In 20/22 children, it was linked to either the onset or a progression to treatment resistance of epilepsy while an apparently spontaneous regression occurred in 5/25 patients without epilepsy, and this difference was statistically significant (20/22 vs 5/25; FET, $df = 1$, $p < 0.0001$) (table 1). With the exception of 2 patients with drug-responsive epilepsy, continued decline in life skills and cognition was seen in the rest of the patients. Behavior could be reliably assessed in 41/47 patients and behavioral problems or autism were frequent and present in 44% and 41% of patients with and without epilepsy, respectively. Autism and epilepsy were comorbid in 27% of children with MDS.

The emergence of epileptic seizures combined with cognitive decline prompted genetic investigations and MDS diagnosis in 32% of patients. We performed an analysis of the *MECP2*

duplication characteristics to better understand a possible correlation between the genotype and the presence and severity of epileptic phenotype. The original genetic testing reports were available in 28/47 (59%) patients, of whom one patient was adopted. Thus the inheritance pattern could be assessed in 27/47 (57%) patients. The *MECP2* duplication was inherited in 20/27 children, and occurred de novo in 7 cases. It was recurrent in 3 sibpairs. Inheritance pattern could not be determined due to insufficient information in 20 patients. Precise genetic coordinates and duplication length were available in 24 individuals, of whom 10 were patients with epilepsy and 8/10 had LGS. The length of the duplicated interval on Xq28 varied between 119 kb and 11.2 MB (mean $\pm$ SD = 2.295 ± 3.232 MB). Three patients harbored *MECP2* duplication due to de novo unbalanced interchromosomal translocations, namely $t(20;X)(p13;q28)$, $t(X;Y)(q27.3;q11.22)$, and $t(3;X)$. There were no apparent sex or clinical differences among patients with intrachromosomal vs interchromosomal *MECP2* duplications. Epilepsy genotype-phenotype correlation showed that the minimal and maximal sizes of the duplicated regions did not differ between individuals with or without epilepsy (figure e-2A, [links.lww.com/WNL/A778](https://www.lww.com/WNL/A778)). Minimal and maximal sizes of the duplicated regions were 119 kb and 11.2 MB, respectively, in the group without epilepsy and 187 kb and 9.9 MB, respectively, in the group with epilepsy. Mean duplication sizes did not differ ($p = 0.45$) between the 2 groups. Genetic coordinates were available in 8/12 individuals with LGS and the length of the duplication varied between 187 kb and 3 MB. However, duplication sizes again did not differ from those without epilepsy ($p = 0.26$). The duplicated genetic region, common to all individuals with epilepsy, contained the following genes: *ARHGAP4*, *NAA10*, *REBP*, *DL490658*, *HCFC1*, *TMEM187*, *MIR3202-1/2*, *IRAK1*, *MIR718*, and *MECP2* (figure e-2B). The region duplicated in all individuals without epilepsy encompassed *IRAK1*, *MIR718*, and *MECP2* genes. Yet, in 12/14 individuals without epilepsy, their duplicated

genetic regions spanned, at least, the minimal duplicated region of those with epilepsy mentioned above. Also, aside from the *MECP2* gene, no other genes affected by the duplication appear to confer additional risk for the development of epilepsy (appendix e-2, links.lww.com/WNL/A781). Hence, we could not detect a significant difference with respect to the minimally affected region between the 2 patient groups. In addition, there was no apparent correlation between the length of a mutation and the age at onset of epilepsy ($R^2 = -0.00098567$), the presence of LGS, or the most prevalent seizure type ($R^2 = -0.379993852$).

Finally, we reviewed available imaging data in search for possible MDS-specific structural abnormalities. Results of brain MRI obtained at the time of initial neurologic evaluation were available in 21/47 patients and the study was reported normal in one case only. The imaging showed diffuse non-specific changes in 15/21 individuals while heterogeneous focal findings were identified in the remaining 5 patients (figure e-3, links.lww.com/WNL/A778). There were no statistically significant differences in the frequency or character of imaging findings between patients with and without epilepsy (FET = 1, $p = 0.54$, NS) (table 1).

Discussion

Our study is the first systematic retrospective analysis of age-based epilepsy frequency, types, and treatment responsiveness in a large case series of individuals with MDS. The diagnosis of epilepsy was common, identified in 47% of patients, and this finding is commensurate with the 49% estimated epilepsy frequency we found in the review of 286 published patients with MDS (table e-1, links.lww.com/WNL/A779). Similarly to the previously published studies,^{6,16} we found incident cases of epilepsy in all age categories but with important differences in age-based epilepsy frequency. For example, epilepsy onset before 3 years of age in MDS has been considered rare,⁶ yet it was observed in 6/22 (27%) patients with epilepsy in our study. Importantly, we found that 38% of all individuals met criteria for EE. This finding is in contrast to the estimated 10% EE frequency in the published cases (table e-1).^{3-7,9,10,17-25} There are several possible reasons underlying the differences in the frequency of epilepsy and EE observed in our case series and that estimated from review of published cases summarized in table e-1. (1) Ascertainment bias—the epileptic phenotype was scrutinized systematically and in detail in this study while published case reports and case series differ in their focus and depth of investigation. Moreover, children evaluated in a specialty clinic often undergo more detailed or frequent evaluations that may lead to a higher frequency and precision in the detection of epilepsy.⁶ (2) Referral bias—the patient population referred to our highly specialized center is likely enriched for children with more severe developmental and neurologic problems. (3) Self-selection bias—close to 80% of the enrolled patients entered the study at the *MECP2* Duplication Syndrome

Family Conference. While the 95% response rate and the chart-based validation of parental reports support epilepsy frequency detected in this study, it is possible that families with children on a more severe disease spectrum were more likely to attend the family conference, thus inadvertently inflating the observed frequency and severity of epilepsy in MDS. As patients in our study may be representative of more severely affected patients with MDS, it is important to note that our patients with epilepsy were significantly older and had on average a longer follow-up when compared to their peers without a documented seizure disorder (table 1 and figure 1). Only 20% of cases without epilepsy were followed beyond 13 years of age. It is thus possible that the epilepsy frequency seen in our more severely affected patients is an underestimate as it does not take into account incident cases of epilepsy that may emerge as children mature. A prospective long-term follow-up will be needed to address these issues.

Given the high frequency of EE in our cases, it was not surprising to find that more than half of patients with epilepsy had 4 or more seizure types, with atonic seizures being the most common (82%). In our case series, LGS emerged as an especially frequent EE type that was present in 10/22 (45%) patients with MDS and epilepsy. This is in contrast to the 7/286 (<3%) patients with MDS with LGS identified in the literature (table e-1, links.lww.com/WNL/A779), and 3%–10% estimated frequency of LGS among all childhood epilepsies.²⁶ LGS with onset in teenagers and adults occurred in 3/22 (14%) patients with epilepsy and was the dominant epilepsy syndrome in a new-onset epilepsy after the age of 13 years. This finding is of special relevance for an adult clinical practice when considering treatment options in sudden onset of intractable epilepsy in teenage patients with intellectual disability. Interestingly, we also identified one patient with IS. While Caumes et al.⁷ described late-onset epileptic spasms in 4 cases of MDS, early-onset spasms have not been previously reported and this finding has implications for genetic testing.

In harmony with the frequently severe epileptic phenotype, 82% of patients with epilepsy were treatment-resistant. This finding corroborates previously published estimates derived from smaller patient populations.^{1,6,7} In our review, we could not identify a particularly effective monotherapy or polytherapy (figure e-1, links.lww.com/WNL/A778). A few reports commented on the use of adjuvant therapy, such as vagus nerve stimulation, deep brain stimulation, ketogenic diet, or corpus callosotomy.^{6,9,21,25,27} In our study, parents reported an improvement in seizure frequency and severity in 4/5 patients treated with vagus nerve stimulation and in 5/7 children treated with the ketogenic diet. However, larger collaborative studies are needed for a truly objective assessment of therapeutic efficacies.

Given the sex-based differences in MDS penetrance, we analyzed possible sex bias with respect to epilepsy. Our review of published cases indicates that male patients are more than

twice as likely to be affected by EE. Of the 34 published cases of female patients with MDS, we identified 10 (29%) female patients with drug-resistant epilepsy and possible EE and one case of LGS in a female patient¹⁰ (table e-1, [links.ww.com/WNL/A779](https://www.ww.com/WNL/A779)). We were able to determine exact age at onset of epilepsy and intractability in 7/10 published female patients and found that in 86% of cases, an equal proportion developed drug-resistant epilepsy in infancy and between the ages of 6–9 years, and one girl at the age of 16. The 6 female patients in our case series were ascertained between the ages 3 and 18 years. Yet, we observed a lower frequency (1/6 female patients) of a medically intractable epilepsy in our case series. This difference may be due to a small sample size, limited length of follow-up, or regional differences in the case referral for molecular diagnostics and epilepsy care. It is possible that the lower frequency of severe epilepsy in female patients reflects a diagnostic bias towards female patients with a more severe neurocognitive phenotype, while female patients with epilepsy appearing neurologically intact or showing a milder cognitive compromise may remain genetically undiagnosed. Another possibility is an inherently lower frequency of epilepsy in female patients with MDS. Some studies suggest that female carriers of *MECP2* duplication are more likely to manifest behavioral or psychiatric symptoms rather than epilepsy.²² Future studies focused on a natural history of MDS may be better suited to address these factors.

Vignoli et al.⁶ made a tentative association between the phenotypic severity and the duplication length. However, the careful analysis of the duplication data in 24/47 (51%) of our cases is consistent with prior studies that showed lack of correlation between the *MECP2* gene duplication size and MDS disease burden.^{1,25,28} Given that the proportions of cases with epilepsy and LGS in the 24/47 patients analyzed for duplication characteristics reflected the epilepsy and LGS proportions in the overall case series, it is unlikely that we would have missed an important association. Still, the absence of a genotype–phenotype correlation in MDS is intriguing. In Rett syndrome caused by *MECP2* gene deletions and point mutations, a genotype-dependent symptom severity has been established.²⁹ However, the mechanisms by which *MECP2* gene duplications modulate the spectrum and severity of neurocognitive phenotype remain unclear.

Limitations of our study are inherent to retrospective reviews and to data based on parental reporting and recall. We tried to minimize these shortcomings by careful cross-validation of reported information with medical records, original diagnostic reports, and studies, and by detailed review and comparative analysis of our case series with the 286 cases of MDS published to date. Ideally, future studies in MDS will be longitudinal and prospective, designed to evaluate the natural course of MDS and MDS-related epilepsy using standardized tools to limit bias.

Epilepsy in MDS is common, often severe, drug-resistant, and coincident with developmental regression. Individuals with

MDS may experience severe forms of epilepsy including EE and LGS with onset in later childhood or adulthood.

Conventional therapy with antiseizure medications is frequently not sufficient to control seizures. Adjuvant interventions, including ketogenic diet and vagus nerve stimulator, may provide additional therapeutic benefit. This study emphasizes the importance of awareness of the frequent occurrence of epilepsy in MDS as we observed that the presence of epilepsy placed children at substantial risk for regression of their developmental milestones. However, our case series may reflect neurologic comorbidities of more severely affected children and may thus not represent all individuals with MDS. This highlights the need for genetic diagnostics across the syndrome spectrum and for an improved understanding of the natural course of the syndrome and associated epilepsy. In the age of gene-targeted therapies, a careful longitudinal follow-up of affected children will be essential when designing MDS-specific treatment trials and evaluating their efficacy.

Author contributions

Dana Marafi: study concept and design, acquisition of data, analysis and interpretation of data, drafting the manuscript. Bernhard Suter: study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript. Rebecca Schultz: study concept and design. Daniel Glaze: critical revision of manuscript for intellectual content. Valory Pavlik: data analysis and interpretation, critical revision of manuscript for intellectual content. Alica Goldman: study concept and design, analysis and interpretation of data, drafting of the manuscript, critical revision of manuscript for intellectual content.

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Disclosure

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