NATURAL HISTORY OF EPILEPSY IN *MECP2* DUPLICATION SYNDROME: INSIGHTS FROM THE CITIZEN HEALTH PLATFORM

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INTRODUCTION

Methyl-CpG binding protein 2 (*MECP2)* Duplication Syndrome (MDS) is caused by an increase in the copy number of the *MECP2* gene, and an elevated dosage of the MeCP2 protein.

Occurring in mostly males, MDS is characterized by infantile hypotonia, developmental delay, and severe-to-profound intellectual disability. Childhood-onset seizures, recurrent infections, and gastrointestinal symptoms contribute to disease burden. Ultimately there is a shortened lifespan.

OBJECTIVE

This medical record-based retrospective natural history study investigates the epilepsy profile in males and females with genetically confirmed MDS.

METHODS

- This study uses secondary data from Citizen Health, a patient-facing platform that extracts key data fields from predominantly U.S. medical records into a standardized longitudinal dataset from first medical contact through to the data cut.
- A data cut, taken on April 10, 2025, included 50 individuals with MDS.
- The epilepsy profile includes onset, seizure types, frequency, and concomitant medications. Hospitalizations related to epilepsy are summarized. The ages at the gain and loss of specific motor abilities or milestones are reported relative to seizure records.

Gross Motor Development Milestones

1. Ability to jump
2. Ability to walk
3. Ability to stand alone
4. Ability to pull to stand
5. Ability to pull to crawl
6. Ability to sit unsupported
7. Ability to roll
8. Ability to control head posture

DEMOGRAPHICS

Demographic Variable	**Value** N=50 mean ± standard deviation [minimum, maximum]
Age at the time of last follow-up (years)	7.2 ± 4.6 [1.1, 22.3]
Age at MDS diagnosis (years)	2.2 ± 2.8 [0.04, 15.7]
Sex, n (%)	
Male	45 (90%)
Female	5 (10%)
MECP2 Genetic Variant Structure, n (%)	
Non-terminal Duplication	35 (70%)
Terminal Duplication	14 (28%)
Unknown Variant	1 (2%)

MDS = *MECP2* duplication syndrome

SEIZURE PROFILE

Seizure Types and Frequency

- **The following Table provides a count of individuals who have experienced different seizure types**

Seizure Type / History*	Participant Count
Any (excl. provoked or febrile seizures)	24
Atonic	14
Tonic-Clonic	10
Tonic	9
Myoclonic	8
Absence	7
Focal	5
Epileptic Spasms	4

*Participants can have more than 1 seizure type / history reported.
List is not exhaustive.

Seizure Frequency at Last Record*	Participant Count
Multiple per day	11
>Weekly to Daily	2
>Monthly to Weekly	2
Monthly or less	5

*Seizure frequency information was not available for 4 participants.

Seizure frequencies ranged from ~monthly to periods of more than 100 daily.

There were 10 participants with a clinical diagnosis of **Lennox-Gastaut syndrome**; mean age at diagnosis was 8.3 years.

Anti-Seizure Medications

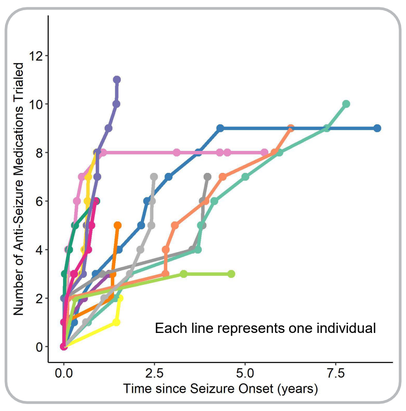
Anti-seizure medication information was reported for 21 participants

Levetiracetam and benzodiazepines are the most prescribed anti-seizure medications in children with MDS

Medication Term	Participant Count of Exposure (N=21)
Levetiracetam	15
Diazepam	13
Clonazepam	11
Valproate	10
Lorazepam	8
Clobazam	7
Epidiolex	7
Midazolam	6
Lamotrigine	5
Cannabidiol	4
Rufinamide	4
Zonisamide	4

List includes medications reported in 4 or more participants.

Many anti-seizure medications are trialed



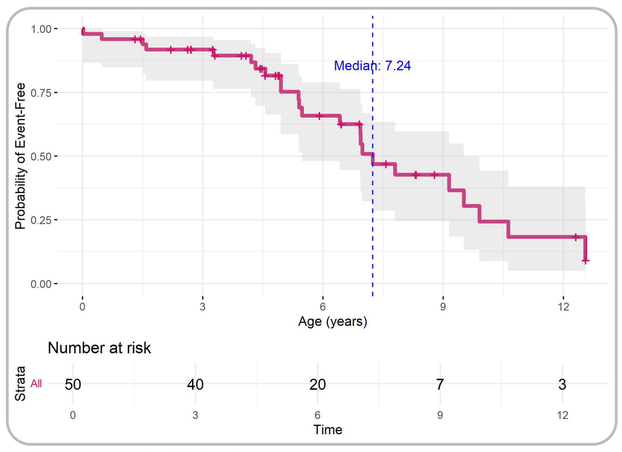
Most Individuals with MDS Who Develop Epilepsy are Hospitalized at Least Once Related to Seizures

Hospital Admission Term	Participant Count	Total Event Count
Any hospitalization related to seizures	18	43
Epilepsy monitoring unit admission	9	14
Increased seizure frequency	8	20
Seizure disorder	8	8
Status epilepticus	1	1

Hospitalizations related to seizures could be up to 1 week in duration.

SEIZURE ONSET
Age at first seizure or epilepsy diagnosis

Childhood-Onset Seizures are Near-Universal in this Population



>85% by 13 years

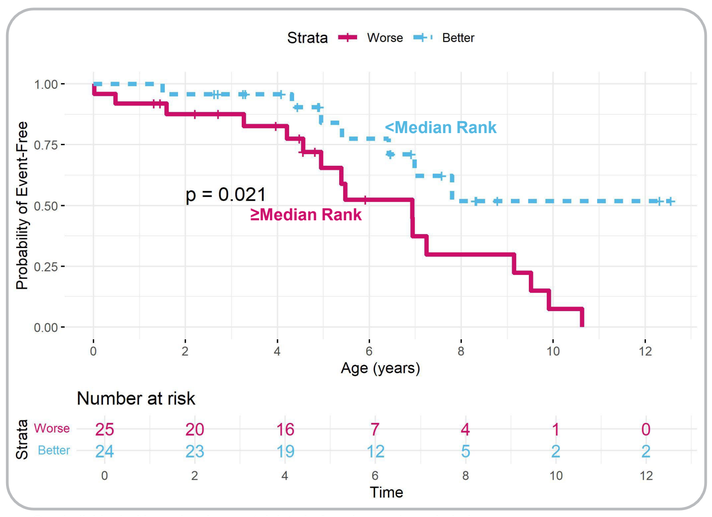
Excludes provoked or febrile seizures.

Factors Influencing Age at Seizure Onset

Subgroup / Factor	Median [95% CI] Age at Seizure Onset (years)		p-value
Genetic Variant	Terminal (n=14)	Non-Terminal or Unknown (n=36)	0.092
	6.93 [3.27 – 9.90]	7.24 [5.48 – NC]	
Microcephaly	Yes (n=15)	No (n=35)	**0.033**
	5.48 [4.21 – 9.51]	7.79 [6.41 – NC]	
Sex	Male (n=45)	Female (n=5)	0.38
	6.98 [5.40 – 9.14]	10.07 [4.56 – NC]	
Hypotonia Reported in the First Year of Life	Yes (n=32)	No (n=18)	**0.018**
	6.94 [4.56 – 9.14]	12.54 [5.39 – NC]	

Statistical procedure: log-rank test. CI = 95% log-log confidence interval.
One participant had unknown variant.
Two females had non-terminal duplications and three females had terminal duplications.

Impaired Gross Motor Development is Associated with Earlier Seizure Onset



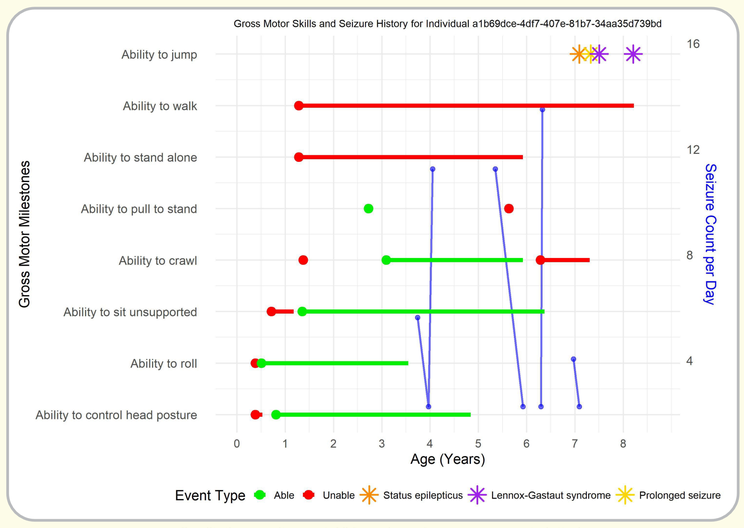
One individual with no developmental data before 4 years is excluded.

REGRESSION
Permanent loss of gross motor skills relative to seizure onset and seizure types

Determining Gross Motor Skill Loss Events from Medical Records

- Defined as “Able” then “Unable” with no regain of the ability
  - With no higher-level ability that is concurrently or later defined as "Able”

Example: Individual a1b69dce had skill loss events of “pull to stand” and “ability to crawl” around 6 years of age. The seizure frequency and major seizure events are overlaid in time by the right y-axis. Unspecified, absence and tonic-clonic seizures were reported since 3 years old; Atonic seizures were first reported at 5.9 years old.



Qualitative results e.g. ‘>X’ for seizure frequency are not plotted.

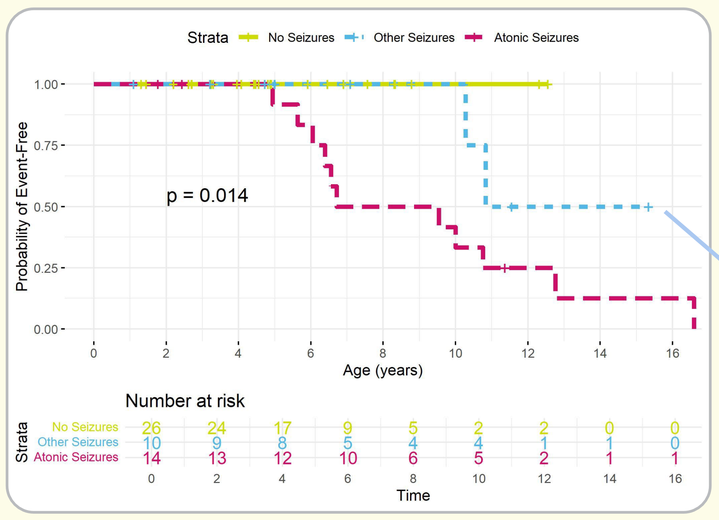
Seizures Precede Gross Motor Regression

Permanent gross motor skill loss events occur more frequently in children who experience seizures

- There were **21 events in 12 children** <u>after</u> the onset of seizures (**Table**)
- 1 event was reported in 1 child at 9 months before an epilepsy diagnosis. The child subsequently developed treatment-refractory atonic seizures (up to 15 per day) and Lennox-Gastaut syndrome.

	Number of Skill Loss Events
No Seizures	0
Before Seizures	1
After Seizures	21

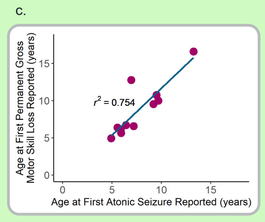
Time to Gross Motor Skill Loss is Earlier for Children who Develop Atonic Seizures (vs. No Seizures or Other Seizures)



a. No seizure type information was available for these two events; both individuals had a hx of status epilepticus or prolonged seizure > 5 min as well as hospitalization for seizures.

b. Times from first atonic seizure reported to last available medical record were 69, 213, and 1086 days.

c.



There is a Temporal Relationship between Gross Motor Skill Loss and Atonic Seizure Onset

Atonic Seizure	No Skill Loss	Skill Loss
No	34	2[a]
Yes	3[b]	11[c]

LIMITATIONS

- Follow-up is of variable length.
- Study has selection bias for those who opted in to the Citizen Health Platform.
- Approximately half of children have developed seizures in the dataset; the majority of children in the dataset have not yet experienced permanent skill loss events.

CONCLUSIONS

1. Childhood-onset seizures are near-universal in this population (>85% by adolescence). Microcephaly, hypotonia in the first year and impaired gross motor development may be associated with earlier seizure onset.
2. Atonic seizures may be temporally associated with gross motor regression.
3. Further research is required to understand relationships between seizure type, frequency, severity, and functional outcomes.

Disclosures

PM, FL and CC are full-time employees of Ionis and may hold Ionis stock or options
EB is a full-time employee of Citizen Health

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