Poster **#194**

DISEASE COURSE OF MECP2 DUPLICATION SYNDROME: INSIGHTS FROM A RETROSPECTIVE NATURAL HISTORY STUDY

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INTRODUCTION

MECP2 Duplication Syndrome (MDS) is a severe X-linked neurodevelopmental disorder primarily affecting males, caused by increased copies of the *MECP2* gene. Early signs often include infantile hypotonia, developmental delays, gastrointestinal issues, and feeding difficulties. As children grow, they typically exhibit severe to profound intellectual disability along with recurrent infections requiring hospitalization. The condition worsens with age, with most children developing refractory seizures and experiencing developmental regression by adolescence. Lifespan is substantially shortened with half of children not surviving past 25 years of age.

Objective

To characterize the clinical phenotype and disease course of MDS

METHODS

- This study uses secondary data from Ciitizen, a patient-facing platform that extracts key data fields from pre-dominantly U.S. medical records into a standardized longitudinal dataset from first medical contact through to the data cut.
- A data cut, taken on June 27, 2024, included 24 individuals with MDS.
- The following data sets were analyzed: demographic information, clinical diagnoses, seizure history, and developmental milestones.

Demographics

Demographic Variable	Value N=24 mean ± standard deviation [minimum, maximum]
Age at the time of last follow-up (years)	6.7 ± 5.0 [1.1, 22.3]
Age at onset of developmental delay (years)	0.72 ± 0.36 [0.32, 1.88]
Age at MDS diagnosis (years)	2.5 ± 3.2 [0.34, 15.7]
Sex, n (%)	
Male	22 (91.7%)
Female	2 (8.3%)

Presenting Signs/Symptoms

The most common signs and symptoms in the year leading up to MDS diagnosis are:

- Soft Tissue Disorders (79.2%)
- Developmental Delay or Regression (70.8%)
- Diseases of the Digestive System (62.5%)
- Diseases of the Respiratory System (50.0%)
- Symptoms & Signs Concerning Food & Fluid Intake (50.0%)
- Abnormalities of Breathing (50.0%)
- Dependence on Enabling Machines & Devices, Not Elsewhere Classified (41.70%)

The Clinical Phenotype Includes Effects on Multiple Body Systems

	Current Study (N=24)	Ta et al., 2022
Neurological Signs		
Hypotonia	95.8%	≥ 88% (Infantile hypotonia)
Abnormal gait	58.3%	58% (Ataxia or ataxic/ wide-based gait)
Spasticity	29.2%	45%
Abnormal involuntary movement	58.3%	63% (Choreiform movements)
Autistic Features		
Autism spectrum disorder diagnosis	54.2%	68%
Stereotypy	75.0%	55% (Stereotypical behaviors)
Bruxism	54.2%	65%
Gastrointestinal Problems		
Feeding problems	95.8%	52%
Constipation	91.7%	72%
Gastro-esophageal reflux	87.5%	54%
Sialorrhea	62.5%	70% (Drooling)
Infections		
Respiratory infections	Not determined	74%
Otitis media	29.2%	30%
Urinary tract infections	16.7%	25%
Breathing and Sleep Disturbances		
Abnormal breathing	41.7%	31% (breathing problems)
Obstructive sleep apnea	62.5%	36%
Sensory Impairment		
Hypermetropia	25.0%	49%
Astigmatism	33.3%	29%
Hearing loss	29.2%	33%

Global Developmental Delay is Observed Followed by Regression in Adolescence

(Loss of Acquired Motor or Language Skills)

Ability to …	Age (months) when the function was first reported as "Able"	
	n[a] (%)[b]	median [minimum, maximum]
Gross Motor		
Crawl	17 (77%)	15.3 [9.2, 30.9]
Pull to Stand	15 (79%)	15.4 [9.0, 41.1]
Walk	15 (71%)	28.8 [13.1, 75.2]
Expressive Communication		
Babble	22 (100%)	9.2 [5.8, 28.3]
Use at Least One Word	12 (52%)	21.5 [11.0, 152.7]

[a] number of subjects who achieved the milestone (function/ability reported as "Able" at one point during the follow-up period).
[b] frequency determined using the total number of subjects with non-missing records for the ability.

Frequent hospitalizations contribute to disease burden

Number of Hospitalizations by Age Range

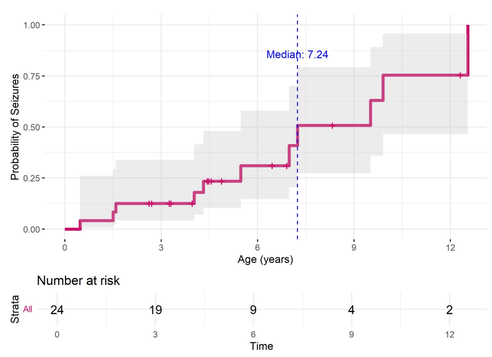
Age Range	N[a]	Hospitalization Count mean (median) [minimum, maximum]
0 to <1	24	1.4 (1) [0, 7]
1 to <2	22	1.0 (0) [0, 6]
2 to <5	11	1.6 (1) [0, 6]
5 to <10	5	1.4 (1) [0, 4]
10 to <15	2	(7.5) [6, 9]
15 to <20	1	(14)

Admissions for Term birth of newborn, Birth, and Research are excluded
[a] Number of individuals with age at last follow-up ≥ the upper limit of the range

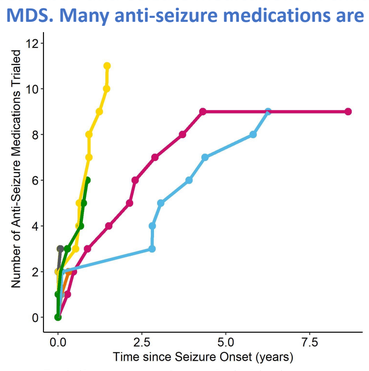
The most frequently reported reasons for admission were for planned procedures, pneumonia, respiratory distress/failure, seizure-related disorders, and constipation

By Adolescence, Most Children Experience Refractory Seizures

Median age at seizure onset is 7 years

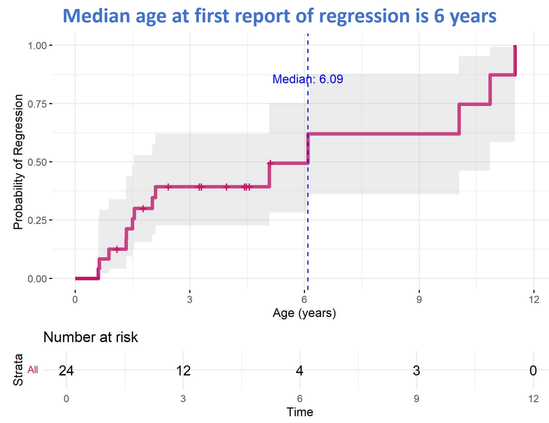


Levetiracetam and benzodiazepines are the most prescribed anti-seizure medications in children with MDS. Many anti-seizure medications are trialed



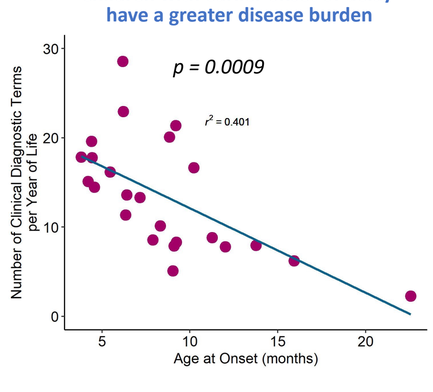
Each line represents one individual

Median age at first report of regression is 6 years

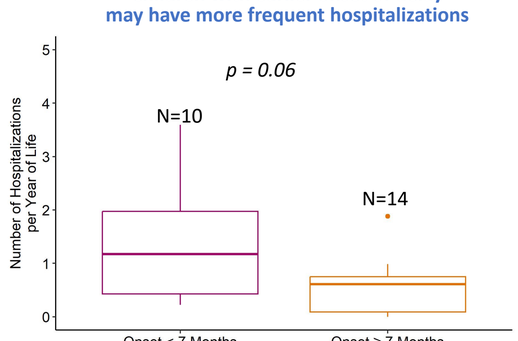


Age at Onset of Developmental Delay May Represent a Novel Prognostic Variable

Children with earlier onset of delay have a greater disease burden

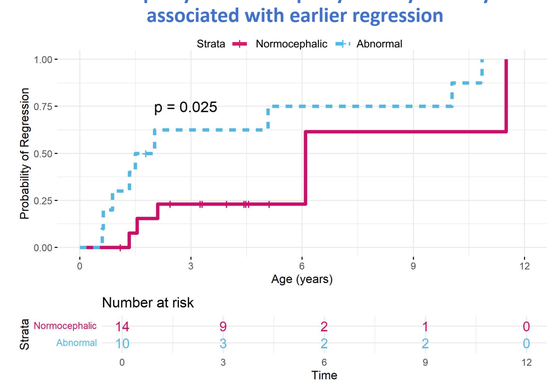


Children with earlier onset of delay may have more frequent hospitalizations



Admissions for Term birth of newborn, Birth, and Research are excluded
Statistical procedure: t-test

Microcephaly or macrocephaly in early life may be associated with earlier regression



CONCLUSIONS

1. This interim analysis highlights the broad spectrum of neurological and systemic symptoms of MDS, confirming previous literature findings and providing valuable insights about progression into adolescence
2. The integration of real-world data and medical records from platforms like Ciitizen offers new opportunities for advancing translational research in rare diseases
3. Further analysis with the full dataset is required to explore the relationship between onset of developmental delay and increased disease burden, which could guide future clinical trials and therapeutic strategies

LIMITATIONS

- Sample size is small; preliminary analysis of 24 individuals
- There are few individuals older than 13 years of age (n=2), and few females (n=2)
- Genetic variant structures are unknown

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 Ciitizen

ACKNOWLEDGEMENTS

- Participants in the Ciitizen Heart, Brain, and Rare Disorders Databank
- Cure MDS and MECP2 Duplication Foundation

Ta D, Downs J, Baynam G, Wilson A, Richmond P, Leonard H. A brief history of MECP2 duplication syndrome: 20-years of clinical understanding. *Orphanet J Rare Dis*. 2022;17(1):131.

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