Natural History of Neurodevelopment in Neuronopathic Mucopolysaccharidosis Type II (MPS II): Mullen Scales of Early Learning (MSEL) Visual Reception, Expressive and Receptive Language and Fine Motor Scale Developmental Trajectories

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Introduction

Neuronopathic MPS II

- Mucopolysaccharidosis type II (MPS II), also known as Hunter syndrome, is caused by a deficiency of iduronate-2-sulfatase leading to an accumulation of glycosaminoglycans (GAGs) in tissues of MPS II patients.
- GAGs accumulate in neuronal tissue producing progressive cognitive deterioration, severe behavioral disturbances and global developmental delay.
- Initially developmental skill acquisition slows in comparison to peer development (delay stage), followed by stages of plateau and decline.[1] Limited information is available with respect to neurodevelopmental trajectories in the delay stage.
- This poster presents a retrospective, noninterventional medical records review study of the neurodevelopmental natural history of patients with neuronopathic MPS II.

Mullen Scales of Early Learning (MSEL)

- Visual reception, expressive and receptive language, fine and gross motor scales provide a comprehensive assessment of development from birth to 68 months (gross motor until 33 months).[2]
- Metrics include raw, age equivalent (AEq),T-scores and an Early Learning Composite score.
  - T-scores can be derived from each MSEL scale to compare developmental function to typically developing peers, however interpretation of decline is limited by a floor effect at a score of 20.[3]
  - AEq scores provide another metric by which to compare a given child's score on a specific scale to performance for a child the same age.[3]
- Identified as valid and reliable outcome measure for use in MPS II clinical trials.[4,5]
- Test re-test for a one to two-week interval had a correlation range from 0.84 to 0.96 and inter-rater reliability range from 0.91 to 0.99.[4]
- MSEL is widely used in children with symptoms seen in MPS II, such as behavior and attention challenges, hearing and vision loss, motor impairment and health issues.[4]
- MSEL has been used to create developmental trajectories and define key timepoints where function deviates from typically developing peers in another rare disease, Fragile X syndrome.[3]
- MSEL convergent and divergent validity is present between children with typical development and autism [6] and in children with neurodevelopmental conditions.[7]

Participants

- MSEL natural history data was available for 32 participants with neuronopathic MPS II confirmed by genotype mutation, family history or cognitive decline.
- The mean age (minimum and maximum) of first MSEL was 38 (1,117) months.
- All participants were male and 68.8% White, 9.4% Asian, 9.4% Black or African American and multiple categories were selected by 6.3% of participants.
- The genotype mutations of the participants include nonsense, frameshift, copy number variant, inversion splicing and missense.
- Three patients were treated with hematopoietic stem cell transplant (HSCT).
- All participants were receiving enzyme replacement therapy.

Methods

Step One: Create Linear Regression Models to Define ± 1 and 2 Standard Deviation (SD) Boundaries for AEq

- MSEL normative data was used to characterize SD for AEq.[8]
  - Mock data points were collected from MSEL manual normative data.
  - An algorithm was created to map each score to discrete T scores and ± 1 and 2SD boundaries were created.
  - Linear regression models were fitted between generated AEq and age.
  - Slopes from the regression line were referenced.

Step Two: Characterize the MPS II Natural History AEq Disease Trajectory Relative to Typically Developing Children

- The MPS II natural history mean AEq trajectories were plotted relative to the MSEL normative AEq standard deviations for each MSEL scale.
- The mean AEq trajectories are displayed with the following timepoints:
  - Chronological age when the AEq mean trajectory deviates below the normative mean by -1SD and -2SD.
  - The inflection timepoint where participants reach the mean maximum AEq score.
- Disease progression was further characterized by defining the developmental age when the trajectory deviates below the normal population by -1SD and -2SD.
- The estimated AEq score change per year was calculated for each MSEL scale.
- Calculated from chronological age intervals of 3 months.

Results

T-Scores (Figures 1 and 2).

- A decline in T-scores is evident very early in development.
- Individual patient developmental function may be variable between MSEL scales.

AEq Scores (Figures 3-6 and Table 1)

- Developmental trajectories deviate below -1SD from the normative mean at a mean chronological age range from 12.8 to 19.5 months.
  - Earliest deviation from typical development by -1SD occurs with the expressive language scale at a mean chronological age of 12.8 months.
- Developmental trajectories deviate below -2SD from the normative mean at a chronological age range from 24 to 29.3 months.
  - Earliest deviation from typical development by -2SD occurs with the fine motor scale at a mean chronological age of 24 months.
- Mean age where skill acquisition plateaus ranges by scale from 66.1(fine motor) to 74.6 (receptive language) months.
- Developmental age where skill acquisition plateaus ranges from 25.7 to 29.9 months.

Figure 1.
MSEL Visual Reception T –Scores versus Chronological Age

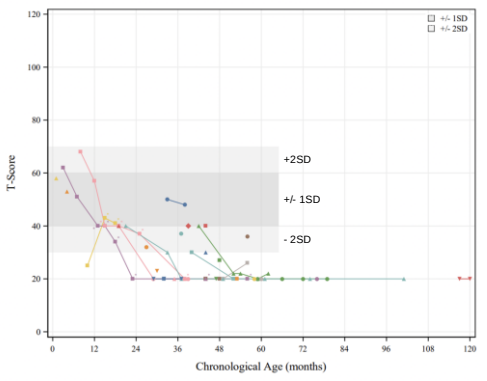

Figure 2.
MSEL Fine Motor T –Scores versus Chronological Age

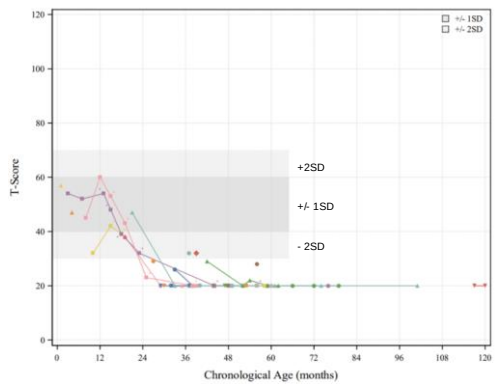

Figure 3.
MSEL Visual Reception AEq versus Chronological Age

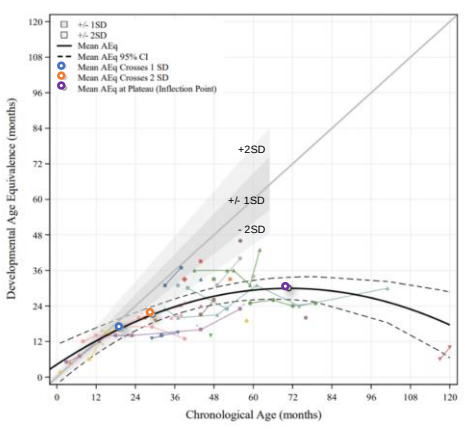

Figure 4.
MSEL Expressive Language AEq versus Chronological Age

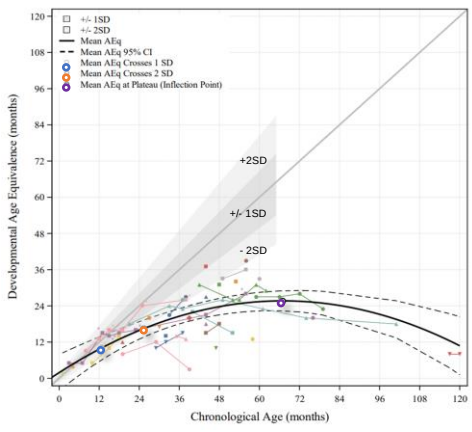

Figure 5.
MSEL Receptive Language AEq versus Chronological Age

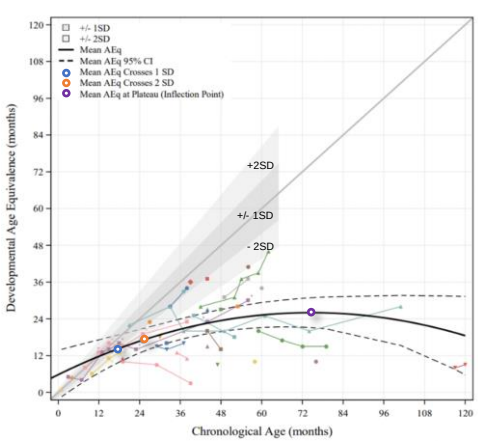

Figure 6.
MSEL Fine Motor AEq versus Chronological Age

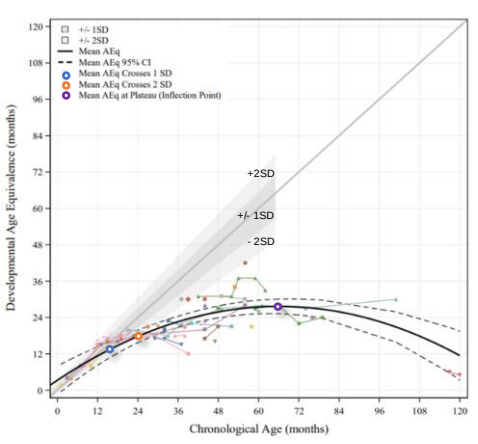

Table 1.
Chronological and Developmental Age Where Development Deviates from the Normative Mean and Where Developmental Skill Acquisition Plateaus

	Visual Reception	Expressive Language	Receptive Language	Fine Motor
Chronological age (months) where developmental skill acquisition plateaus	70.9	67	74.6	66.1
Developmental age equivalence score (months) where developmental skill acquisition plateaus	29.9	25.7	26	27.7
Chronological age (months) when the AEq mean trajectory deviates from normative mean (below Mean -1 SD)	19.5	12.8	17.4	15.9
Developmental age equivalence score (months) when the AEq mean trajectory deviates from normative mean (below Mean -1 SD)	16.4	10.1	14.1	13.6
Chronological age (months) when the AEq mean trajectory deviates from normative mean (below Mean -2 SD)	29.3	25.3	24.9	24
Developmental age equivalence score (months) when the AEq mean trajectory deviates from normative mean (below Mean -2 SD)	21.1	16.4	17	17.8

Mean AEq Change per Year (Table 2)

- Mean change is estimated in each MSEL scale AEq score after 1 and 2 years based on age of first assessment.
- In all MSEL scales at all age ranges, skill acquisition per year is less than 12 months. This slowing of skill acquisition per year is even evident at the youngest age range of 6 to <9 months.
  - On the visual reception scale from 6 to <9 months chronological age, the mean change for 12 months is only 7.2 months, and for 24 months is 13 months, indicating a slowing in the rate of skill acquisition compared to typically developing peers.
- Rate of skill acquisition per year decreases further as chronological age increases.

Table 2.
Mean AEq Change per Year by Chronological Age

Age of First MSEL	Visual Reception Estimate (Gain)		Expressive Language Estimate (Gain)		Receptive Language Estimate (Gain)		Fine Motor Estimate (Gain)		Gross Motor Estimate (Gain)	
Assessment (months)	After 1 Year	After 2 Year	After 1 Year	After 2 Year	After 1 Year	After 2 Year	After 1 Year	After 2 Year	After 1 Year	After 2 Year
6 - <9	15.6 (7.2)	21.4 (13)	12.9 (7)	18.4 (12.5)	14.4 (5.5)	18.8 (9.9)	14.8 (7.2)	20.4 (12.9)	12.9 (9)	19.6 (15.7)
9 - <12	17.2 (6.9)	22.6 (12.3)	14.4 (6.6)	19.5 (11.7)	15.6 (5.2)	19.7 (9.4)	16.3 (6.8)	21.6 (12.1)	14.8 (8.4)	21 (14.6))
12 - <15	18.7 (6.5)	23.7 (11.5)	15.9 (6.2)	20.6 (10.9)	16.7 (4.9)	20.6 (8.8)	17.8 (6.4)	22.6 (11.3)	16.6 (7.9)	22.2 (13.5)
15 - <18	20.1 (6.1)	24.7 (10.8)	17.2 (5.9)	21.5 (10.2)	17.8 (4.7)	21.4 (8.3)	19.1 (6)	23.6 (10.5)	18.2 (7.3)	23.2 (12.4)
18 - <21	21.4 (5.8)	25.7 (10)	18.4 (5.5)	22.3 (9.4)	18.8 (4.4)	22.1 (7.8)	20.4 (5.6)	24.4 (9.7)	19.6 (6.7)	24.1 (11.2)
21 - <24	22.6 (5.4)	26.5 (9.3)	19.5 (5.1)	23.1 (8.6)	19.7 (4.2)	22.8 (7.3)	21.6 (5.2)	25.2 (8.9)	21 (6.2)	24.9 (10.1)
24 - <27	23.7 (5)	27.3 (8.6)	20.6 (4.7)	23.7 (7.9)	20.6 (3.9)	23.4 (6.7)	22.6 (4.8)	25.8 (8.1)	22.2 (5.6)	25.5 (9)
27 - <30	24.7 (4.7)	27.9 (7.8)	21.5 (4.3)	24.3 (7.1)	21.4 (3.6)	24 (6.2)	23.6 (4.4)	26.4 (7.3)	23.2 (5.1)	26 (7.9)
30 - <33	25.7 (4.3)	28.5 (7.1)	22.3 (3.9)	24.8 (6.4)	22.1 (3.4)	24.5 (5.7)	24.4 (4)	26.8 (6.5)	24.1 (4.5)	26.4 (6.7)
33 - <36	26.5 (3.9)	29 (6.4)	23.1 (3.6)	25.1 (5.6)	22.8 (3.1)	24.9 (5.2)	25.2 (3.6)	27.2 (5.6)	24.9 (3.9)	26.6 (5.6)
36 - <39	27.3 (3.5)	29.3 (5.6)	23.7 (3.2)	25.4 (4.8)	23.4 (2.8)	25.2 (4.6)	25.8 (3.2)	27.5 (4.8)	25.5 (3.4)	26.6 (4.5)
39 - <42	27.9 (3.2)	29.6 (4.9)	24.3 (2.8)	25.6 (4.1)	24 (2.6)	25.5 (4.1)	26.4 (2.8)	27.6 (4)	26 (2.8)	26.6 (3.4)
42 - <45	28.5 (2.8)	29.8 (4.2)	24.8 (2.4)	25.6 (3.3)	24.5 (2.3)	25.7 (3.6)	26.8 (2.4)	27.7 (3.2)	26.4 (2.2)	26.4 (2.2)
45 - <48	29 (2.4)	29.9 (3.4)	25.1 (2)	25.6 (2.5)	24.9 (2.1)	25.9 (3.1)	27.2 (2)	27.6 (2.4)	26.6 (1.7)	26 (1.1)
48 - <51	29.3 (2.1)	29.9 (2.7)	25.4 (1.7)	25.5 (1.8)	25.2 (1.8)	26 (2.5)	27.5 (1.6)	27.5 (1.6)	26.6 (1.1)	25.5 (0)
51 - <54	29.6 (1.7)	29.9 (1.9)	25.6 (1.3)	25.3 (1)	25.5 (1.5)	26 (2)	27.6 (1.2)	27.2 (0.8)	26.6 (0.6)	24.9 (-1.2)
54 - <57	29.8 (1.3)	29.7 (1.2)	25.6 (0.9)	25 (0.3)	25.7 (1.3)	26 (1.5)	27.7 (0.8)	26.9 (0)	26.4 (0)	24.1 (-2.3)
57 - <60	29.9 (1)	29.4 (0.5)	25.6 (0.5)	24.6 (-0.5)	25.9 (1)	25.9 (1)	27.6 (0.4)	26.4 (-0.8)	26 (-0.6)	23.2 (-3.4)
60 - <63	29.9 (0.6)	29.1 (-0.3)	25.5 (0.1)	24.1 (-1.3)	26 (0.7)	25.7 (0.5)	27.5 (0)	25.9 (-1.6)	25.5 (-1.1)	22.1 (-4.5)
63 - <66	29.9 (0.2)	28.6 (-1)	25.3 (-0.3)	23.5 (-2)	26 (0.5)	25.4 (-0.1)	27.2 (-0.4)	25.2 (-2.4)	24.9 (-1.7)	20.9 (-5.7)

Discussion and Conclusions

- A limitation of this retrospective study is that participants have been evaluated at different intervals and frequencies and data is both cross-sectional and longitudinal.
- The MSEL developmental trajectories are similar to those reported by Seo et al (2020) using the Kyoto Scale of Psychological Development.9 Their data include 7 children <3 years old at initial assessment, with developmental quotients from 60-86, indicating early developmental delay.[9]
- The MSEL data in this study provide a comprehensive, multi-domain developmental picture of neuronopathic MPS II.
  - Expressive language and fine motor scales provide the earliest indication of delay and precede a deviation from the normative mean for visual reception and receptive language.
  - Mean developmental AEq trajectories for each MSEL scale support a deviation below -1SD from the normative mean at a chronological age of 12.8 months (expressive language), 15.9 months (fine motor), 17.4 months (receptive language), and 19.5 months (visual reception).
  - MSEL mean developmental AEq trajectories support a deviation below -2SD from the normative mean at a chronological age of 24 months (fine motor), 24.9 (receptive language), 25.3 months (expressive language), and 29.3 months (visual reception).
  - The mean gain per year in AEq for every MSEL scale, at all age ranges illustrates that the rate of skill acquisition in children with neuronopathic MPS II slows early in development and the delay becomes more substantial over time.

References

1. Shapiro EG, Escolar ML, Delaney KA, Mitchell JJ. Assessments of neurocognitive and behavioral function in the mucopolysaccharidoses. Mol Genet Metab. 2017 Dec;122S:8-16
2. Mullen EM, Mullen Scales of Early Learning, Pearson, Bloomington MN, 1995
3. Wheeler AC, Gwaltney A, Raspa M, Okoniewski KC, Berry-Kravis E, Botteron KN, Budimirovic D, Hazlett HC, Hessl D, Losh M, Martin GE, Rivera SM, Roberts JE, Bailey DB Jr. Emergence of Developmental Delay in Infants and Toddlers With an *FMR1* Mutation. Pediatrics. 2021 May;147(5).
4. Janzen D, Delaney KA, Shapiro EG. Cognitive and adaptive measurement endpoints for clinical trials in mucopolysaccharidoses types I, II, and III: A review of the literature. Mol Genet Metab. 2017 Jun;121(2):57-69.
5. van der Lee JH, Morton J, Adams HR, Clarke L, Eisengart JB, Escolar ML, Giugliani R, Harmatz P, Hogan M, Kearney S, Muenzer J, Muschol N, Rust S, Saville BR, Semrud-Clikeman M, Wang R, Shapiro E. Therapy development for the mucopolysaccharidoses: Updated consensus recommendations for neuropsychological endpoints. Mol Genet Metab. 2020 Sep-Oct;131(1-2):181-196.
6. Akshoomoff N. Use of the Mullen Scales of Early Learning for the assessment of young children with Autism Spectrum Disorders. Child Neuropsychol. 2006 Aug;12(4-5):269-77.
7. Burns TG, King TZ, Spencer KS. Mullen scales of early learning: the utility in assessing children diagnosed with autism spectrum disorders, cerebral palsy, and epilepsy. Appl Neuropsychol Child. 2013;2(1):33-42.
8. Cho Y et al. Beyond the normative data: understanding the Mullen Scales of Early Learning. ICIEM Virtual Congress.2021
9. Seo JH, Okuyama T, Shapiro E, Fukuhara Y, Kosuga M. Natural history of cognitive development in neuronopathic mucopolysaccharidosis type II (Hunter syndrome): Contribution of genotype to cognitive developmental course. Mol Genet Metab Rep. 2020 Jul 29;24:100630