

Cross-sectional Observations on the Natural History of Mucopolidosis Type IV

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Abstract

Background and Objectives

Mucopolidosis type IV (MLIV) is an ultra-rare lysosomal disorder initially described as a static neurodevelopmental condition. However, patient caregivers frequently report progressive muscular hypertonicity and functional decline. We evaluated a cohort of patients with MLIV to determine whether neurologic disability correlates with age.

Methods

We performed a cross-sectional, observational study of 26 patients with MLIV in the United States and Israel ranging in age from 2 to 40 years. Medical history was obtained from caregivers, and patients underwent a full neurologic examination. The Brief Assessment of Motor Function (BAMF), Gross Motor Function Classification System, and modified Ashworth scales were applied. Caregivers identified developmental skills on the Oregon Project for Visually Impaired and Blind Children checklist that their child had lost the ability to perform.

Results

Three patients were clinically classified as mildly affected and the remaining 23 patients as typical, severely affected cases. Timing of first symptom onset ranged from 1.5 months to 8 years of age (median 7.25 months). Across typical patients, modified Ashworth scores demonstrated a positive age dependence illustrating worsening spasticity across the lifespan. Signs of extrapyramidal motor dysfunction were also qualitatively observed. In parallel, gross and fine motor function assessed with the BAMF and Gross Motor Function Classification System scales declined across age. All typical patients had restricted tongue mobility and lacked rotary jaw movement when chewing, but BAMF scores for deglutition declined only in the oldest patients. In contrast, scores for articulation were low in all patients and did not correlate with age. Finally, loss of developmental skills frequently occurred in early adolescence.

Discussion

This cross-sectional natural history study of MLIV demonstrates worse motor function in older patients. These data support a neurodegenerative component of MLIV that manifests as developmental regression in the second decade of life. Whether the emergence of functional decline results from the cumulative, nonlinear interactions of steadily progressive neurodegenerative processes or reflects an inflection from impaired CNS development to degeneration is uncertain. However, understanding the relationship between CNS pathology and clinical course of disease will be imperative to guiding future interventional trials and optimizing patient care.

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Glossary

BAMF = Brief Assessment of Motor Function; **Cr** = creatine-phosphocreatine; **GMFCS** = Gross Motor Function Classification System; **MLIV** = mucopolipidosis type IV; **NAA** = N-acetylaspartate.

Mucopolipidosis type IV (MLIV) is an inherited lysosomal disorder characterized by hypomyelination, severe neurodevelopmental delay, progressive visual impairment, and achlorhydria.¹ The true prevalence is unknown, but MLIV is considered an ultra-rare condition with approximately 100 identified patients worldwide (personal communication from the ML4 Foundation).²⁻⁴ Low patient numbers limit our understanding of the natural history of disease, but early cohort studies have provided seminal data on the phenotypic spectrum of MLIV,⁵⁻⁷ and severe (typical) and mild (atypical) forms have been described.⁸

MLIV is an autosomal recessive disorder caused by pathologic variants in *MCOLN1*, the gene encoding the lysosomal cation channel TRPML1.^{2,9,10} TRPML1 regulates multiple lysosomal and late endosomal functions, including membrane trafficking, exocytosis, and autophagy.^{11,12} These processes play important roles in CNS development, and patients with MLIV typically reach a developmental plateau equivalent to the 18–21-month level in healthy children. Other signs of neurologic dysfunction associated with MLIV include axial hypotonia, bilateral pyramidal tract signs, cerebellar dysfunction, and retinal degeneration.^{5-7,13,14}

Whether MLIV is solely a static neurodevelopmental disorder or includes a neurodegenerative component remains unclear. Early case series and natural history studies estimated that only 15% of patients exhibit progressive neurologic symptoms and highlighted the unclear timing and extent of progression.⁵⁻⁷ However, a recent prospective brain MRI study identified signs of the cerebral white matter degeneration that correlated with worsening scores of motor function in 5 patients with MLIV.¹⁵ Furthermore, caregivers of our patients consistently report worsening muscular hypertonicity and gradual functional deterioration, suggesting that a neurodegenerative component may be more prevalent than currently appreciated. Now that gene replacement¹⁶ and small molecule therapies are under preclinical development for MLIV, defining the natural history is critical for informing future clinical trial design.

Herein, we report the results of an observational cross-sectional cohort study with the primary objectives of determining whether patients with MLIV exhibit worsening motor impairment across the lifespan and defining when functional regression emerges. Our study contributes to the understanding of the natural history of MLIV and will help guide prognostic discussions with caregivers and inform the design of future clinical trials.

Methods

Standard Protocol Approvals, Registrations, and Patient Consents

This study was approved by the Mass General Brigham Human Research Committee Institutional Review Board (Federal Wide Assurance Number: 00003136). Written consent was obtained from the legal guardians or the patient if appropriate, and patient assent obtained when possible.

Inclusion and Exclusion Criteria

Patients with MLIV were made aware of our study through the ML4 Foundation from July 2018 to July 2019. Twenty-six patients contacted our team for further information and possible enrollment. Inclusion criteria included a diagnosis of MLIV established by one of the following: (1) clinical or research-based sequencing of *MCOLN1* and identification of 2 known pathogenic variants or the (2) presence of the expected constellation of clinical symptoms associated with MLIV and documentation of elevated gastrin levels, or a tissue biopsy with evidence of lysosomal inclusions consistent with MLIV. Exclusion criteria included the inability of the caregivers to give informed consent or inability of patients to undergo examination.

Patient Evaluations

A board-certified pediatric neurologist (the corresponding author) interviewed caregivers and patients, examined all patients, and applied the functional scales. Patients were examined at the Massachusetts General Hospital, the ML4 Foundation Conference, or the Tel HaShomer Hospital. When an age range was given for age at first symptom onset, the average was used as an estimate. Spasticity, defined as a velocity-dependent increase in muscle tone, was graded with the modified Ashworth scale.¹⁷ Spasticity was assessed at least 3 times for each patient over the course of approximately 1 hour and differentiated from velocity-independent rigidity that was variably present between evaluations or affected by changes in positioning. Scores on the Brief Assessment of Motor Function (BAMF)¹⁸⁻²¹ and Gross Motor Function Classification System (GMFCS)²² scores were assigned based on patient performance during the examination and caregiver report of the most consistent level of function over the previous 3 months. To quantify the number of developmental skills a patient had lost by the time of evaluation, items on the Oregon Project skill inventory, organized into gross motor, fine motor, cognitive, language, social, compensatory, and self-help skills, were given to caregivers or one atypical patient who indicated whether the patient was able to perform the skill or had previously been able to perform the skill but lost the ability. Items were presented in order, from the least to

most advanced developmental level. When a caregiver indicated that a patient had never attained the ability to perform any skill listed under a particular age category, the interview for that functional domain was terminated.

Statistics

Spearman rank correlation coefficients or Pearson correlation coefficients were calculated using Prism 8 software (GraphPad Software Inc). For calculation of Spearman rank correlation coefficients with the modified Ashworth scale, scores of 1+ were collapsed to a numerical score of one. BAMF or GMFCS scores were used in linear regression analyses using Prism 8 software. Mild or atypical patients were removed from this analysis as confounding variables.

Data Availability

The data used in this study will be made freely available on request to the corresponding author (A.L.M.) for 7 years after the date of publication.

Results

Cohort Characteristics

We identified and evaluated 26 patients with MLIV for enrollment eligibility, all of whom met the inclusion criteria and were consented into our IRB-approved study. Patients ranged in age from 2 to 40 years. Forty-two percent of patients were male, and 58% were female. Fifteen patients (58%) were of Ashkenazi Jewish descent, whereas 8 (31%) were Caucasian, and the remaining 3 were of Asian, Latin American, or mixed African American and Caucasian descent. All 26 patients were examined by a board-certified pediatric neurologist and evaluated with the BAMF scales,¹⁸⁻²¹ the GMFCS,²² and the modified Ashworth scale.¹⁷ Because of limitations associated with patient access and cost, our study was limited to a single evaluator. Caregivers of 16 patients reviewed a developmental skills inventory from the Oregon Project for Visually Impaired and Blind Children²³ and indicated which skills patients were able to perform or had been able to perform in the past but lost the ability later in life. The skills inventory was available only in English precluding review by the caregivers of 9 patients who primarily spoke Hebrew. One mildly affected patient reported no functional decline and was not given the skills inventory.

A diagnosis of MLIV was confirmed in 24 patients by identification of 2 known disease-causing *MCOLN1* allelic variants (Table 1). No novel *MCOLN1* variants were identified. Of these patients, 9 (37%) were homozygotes, and 15 (62%) were compound heterozygotes. The 16 unique allelic variants reported among the cohort included splice site (3), nonsense (2), frameshift-nonsense (2), frameshift (1), insertion (1), deletion (1), and single nucleic acid variants (6). One patient had a single disease-causing *MCOLN1* allele identified but were diagnosed based on clinical presentation and elevated serum gastrin levels. Diagnosis based on clinical presentation and corneal biopsy was made in the remaining patient.

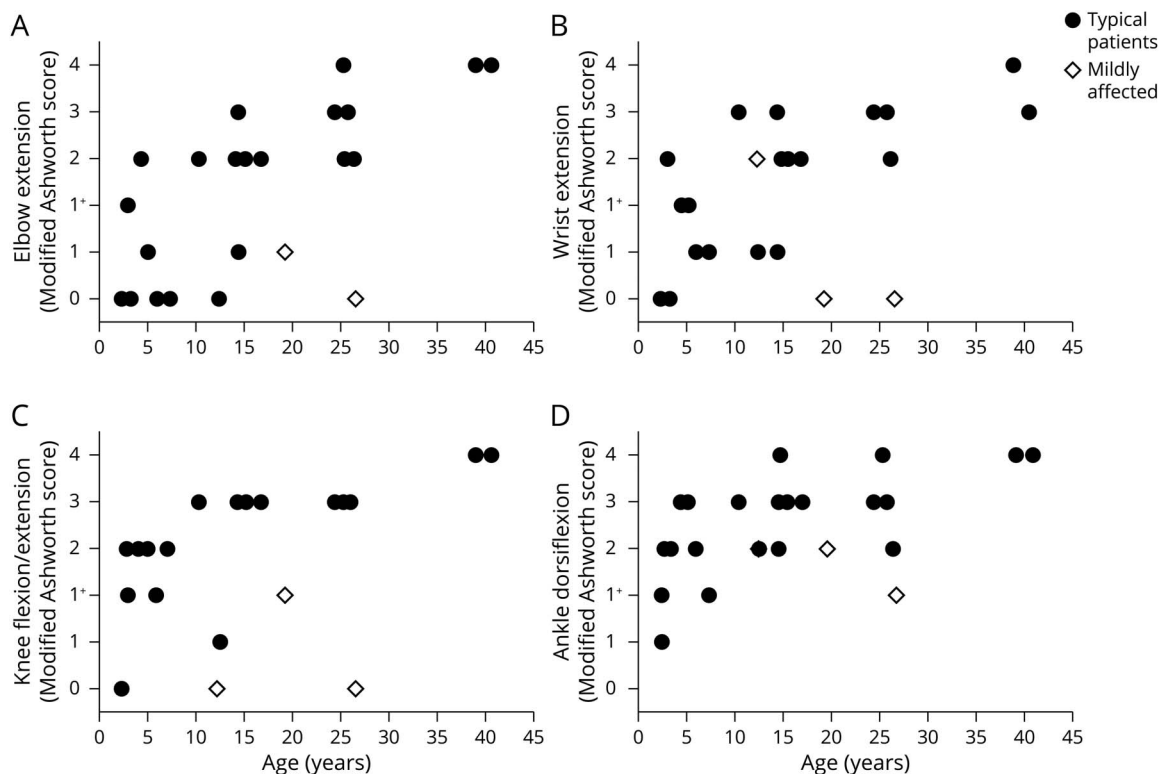
Table Patient Cohort Characteristics

ID	Phenotype	Age (y)	MCOLN1 alleles
1	Mild	10–20	c.406-2A>G; homozygous
2	Mild	10–20	c.236_237ins93; c.1207C>T
3	Mild	20–40	c.920delT; c.1615delG
4	Typical	1–10	c.429C>T; c.1405A>G
5	Typical	1–10	c.406-2A>G; homozygous
6	Typical	1–10	c.406-2A>G; c.1336 G>A
7	Typical	1–10	c.1017_1020delACGG; c.877 G>A
8	Typical	1–10	c.1135-1 G>C; g.511_6943del
9	Typical	1–10	c.984 +1 G>A; c.406-2A>G
10	Typical	1–10	c.406 -2A>G; c.964C>T
11	Typical	1–10	c.694A>C; c.785T>C
12	Typical	1–10	c.406-2A>G; homozygous
13	Typical	10–20	c.406-2A>G; homozygous
14	Typical	10–20	c.406-2A>G; g.511_6943del
15	Typical	10–20	c.406-2A>G; homozygous
16	Typical	10–20	c.406-2A>G; g.511_6943del
17	Typical	10–20	c.406-2A>G; 2nd variant unidentified
18	Typical	10–20	c.236_237ins93; c.694A>C
19	Typical	10–20	c.406-2A>G; homozygous
20	Typical	20–40	Unidentified
21	Typical	20–40	c.406-2A>G; g.511_6943del
22	Typical	20–40	c.406-2A>G; homozygous
23	Typical	20–40	c.406-2A>G; homozygous
24	Typical	20–40	c.406-2A>G; homozygous
25	Typical	20–40	c.406-2A>G; g.511_6943del
26	Typical	20–40	c.406-2A>G; g.511_6943del

Prenatal history and neonatal development were unremarkable in all patients. Timing of the first symptom onset ranged from 1.5 months to 8 years of age (median 7.25 months). The first symptom(s) reported by parents included inability to roll (stomach to back) or sit unsupported by 6 or 9 months of age, respectively (21 patients), strabismus (6 patients), hypotonia (5 patients), impaired vision (4 patients), inability to crawl (3 patients), weak grasp (1 patient), or inability to stand (1 patient). The mean time from symptom onset to diagnosis was 21 ± 20 months (range: 2.5 months to 7 years).

Three patients (Table 1) in our cohort exhibited a milder degree of neurologic impairment and symptom severity. Although mild phenotypic variants of MLIV have been described, formal nomenclature and classification criteria have not been established.¹ Based on the authors' combined experience with

Figure 1 Muscular Hypertonicity in Patients With Mucopolipidosis Type IV Is Positively Correlated With Age



Modified Ashworth scores of tone at the elbows (A), wrists (B), knees (C), and ankles (D) suggest worsening hypertonicity across age.

the MLIV population, patients were classified as mild if they had achieved independent ambulation at any point in life. The remaining 23 patients were classified as typical.

Muscle Tone Assessments

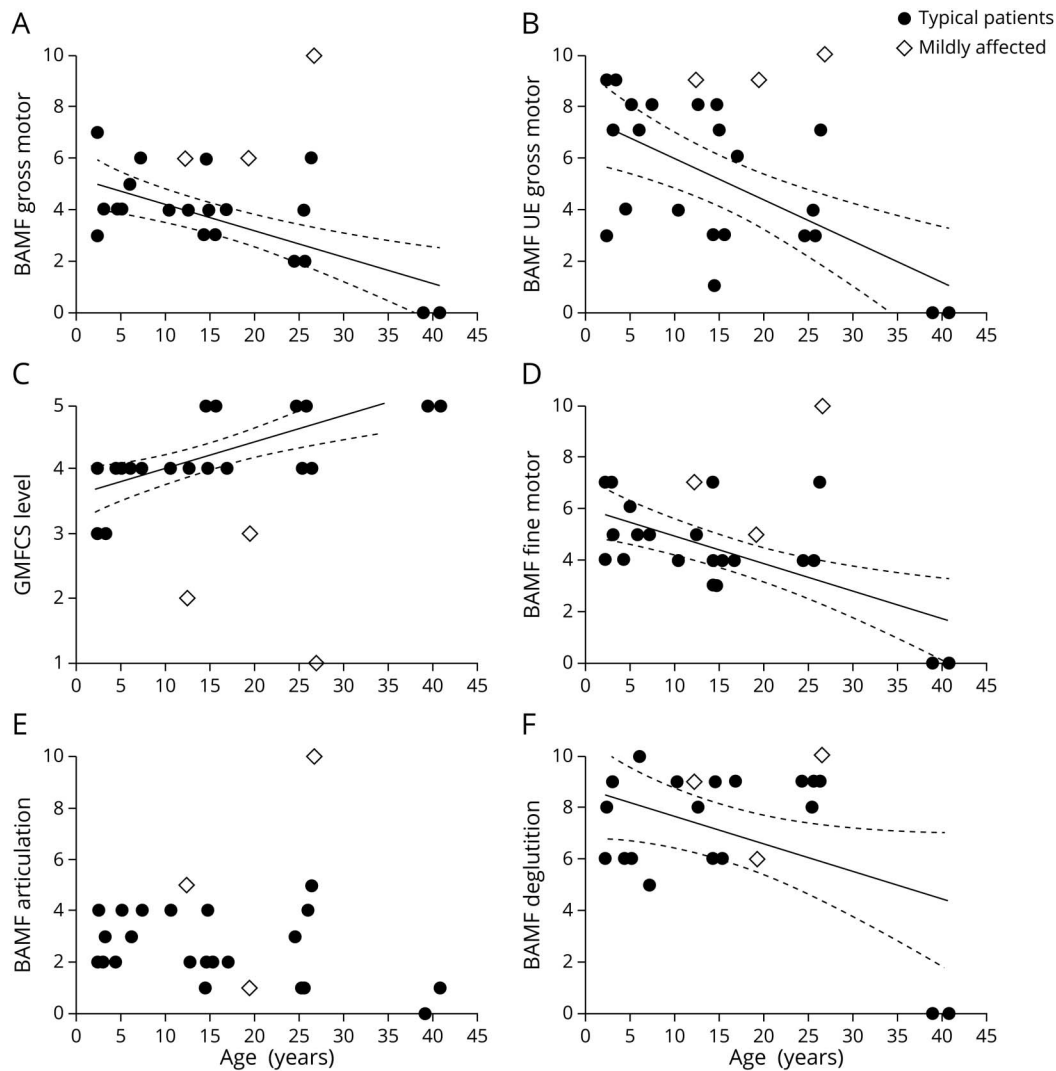
Decreased strength with volitional muscle activation, hyperreflexia, and muscular hypertonicity were frequently observed across typical patients with MLIV and appeared qualitatively worse in older patients. On examination, increased appendicular muscle tone consisted of 2 components, a velocity-dependent resistance to passive movement (spasticity) and a velocity-independent resistance to passive movement, which was variably present (rigidity). The quality of rigidity varied between patients and included cogwheel rigidity and paratonia. We quantitatively evaluated the velocity-dependent component of hypertonicity that was consistently present on repeat examination and scored the severity using the modified Ashworth scale, an ordinal measure of spasticity. Across typical patients, worsening hypertonicity correlated with increasing age at all joints tested (Figure 1). Spearman rank correlation coefficients were estimated between ages and modified Ashworth scores across typical patients at the elbows ($r = 0.880$, 95% CI = 0.728 to 0.949), wrists ($r = 0.771$, 95% CI = 0.518 to 0.900), knees ($r = 0.828$, 95% CI = 0.631 to 0.924), and ankles ($r = 0.664$, 95% CI = 0.348 to 0.845) and demonstrated a positive age dependence of spasticity.

Motor Function Evaluations

Gross motor development was impaired in all patients except 1 mildly affected patient who had lost vision but was otherwise developmentally normal (patient 3). Across typical patients, Pearson correlation coefficients between age and BAMF gross motor function scores ($r = -0.658$, 95% CI = -0.841 to -0.337) or upper extremity gross motor scores ($r = -0.646$, 95% CI = -0.836 to -0.320) showed a negative age dependence, consistent with worsening function across time (Figures 2, A–B). GMFCS scores demonstrated a positive age dependence ($r = 0.691$, 95% CI = 0.390 to 0.859), also consistent with worsening gross motor function (Figure 2C). Scores were then fit to a linear model to estimate the rate of decline across age in the entire cohort (Figure 2, A–C). Among atypical patients, gross motor function varied ranging from a normal gait with the use of a white cane to ambulating only with assistance at the time of examination.

Similar to gross motor function scores, BAMF scores for fine motor function showed a negative age dependence ($r = -0.644$, 95% CI = -0.835 to -0.316), consistent with worse function in older typical patients (Figure 2D). Finger articulation was impaired in all typical patients, and none demonstrated a superior pincer grasp, 14 (61%) an inferior pincer grasp, 1 (4%) a tripod grasp, and 8 (35%) could not grasp objects with their fingers. Among atypical cases, only 1 demonstrated a superior pincer grasp and normal fine motor function. The remaining 2

Figure 2 Gross and Fine Motor Function Decline Across Age in a Cohort of Patients With Mucopolidosis Type IV



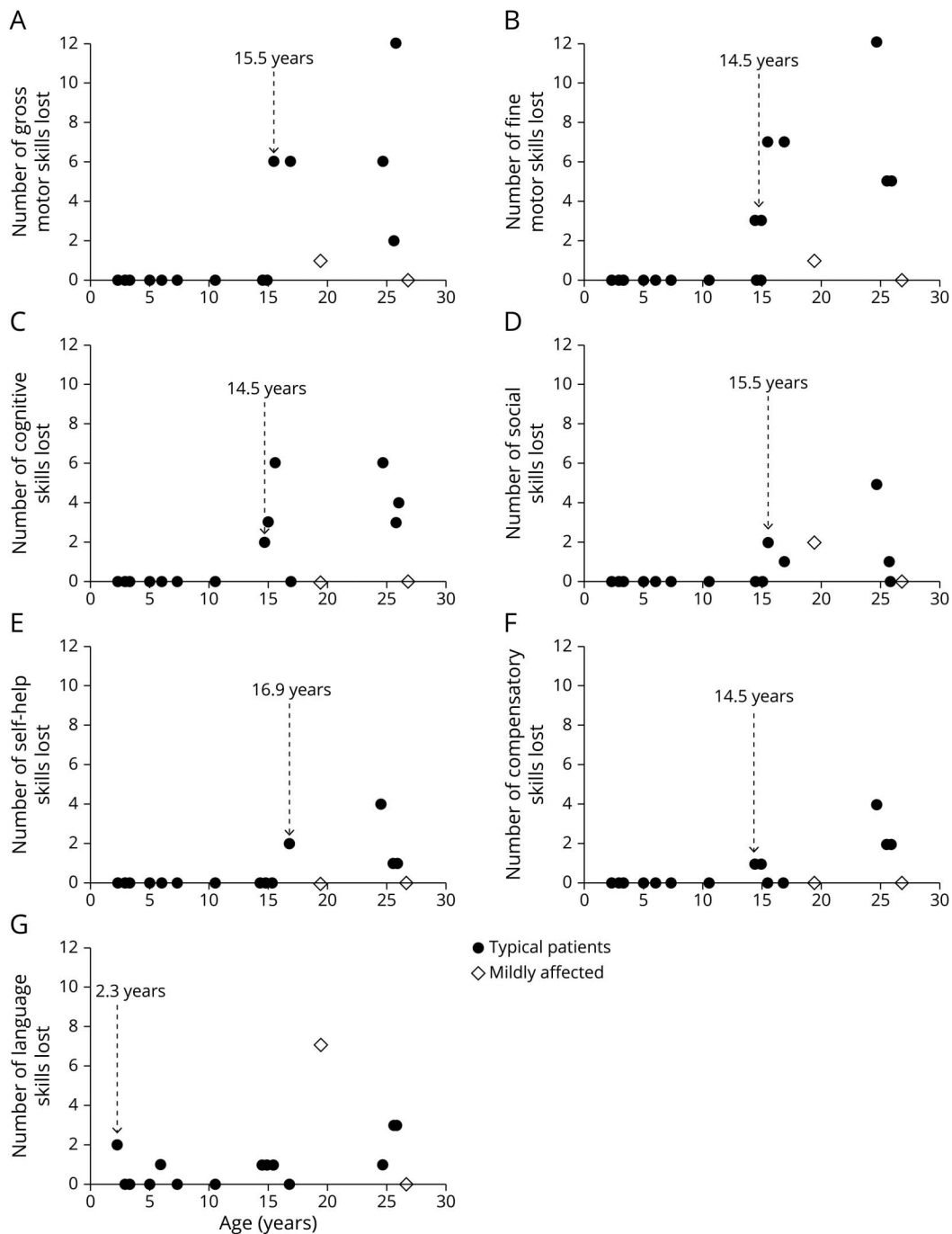
Linear regression analysis performed with BAMF scores of gross motor function (slope = -0.102 , 95% CI = -0.155 to -0.050) (A), BAMF scores of upper extremity (UE) gross motor function (slope = -0.164 , 95% CI = -0.252 to -0.076) (B), and Gross Motor Function Classification System levels (slope = 0.041 , 95% CI = 0.021 to 0.060) (C) demonstrated deteriorating gross motor function across age. BAMF scores for fine motor function also declined with age (slope = -0.106 , 95% CI = -0.163 to -0.489) (D). In contrast, BAMF scores for articulation did not significantly vary (slope = -0.045 , 95% CI = -0.094 to 0.003) (E). Linear regression analysis of BAMF scores for deglutition suggested a decline with age (slope = -0.106 , 95% CI = -0.202 to -0.011) (F), but the significance was heavily influenced by the low scores of the 2 oldest patients, which created an outlier effect. All linear regression analysis excluded atypical patient scores. BAMF = Brief Assessment of Motor Function.

used an inferior pincer grasp, although both had more advanced fine motor control compared with typical patients and were able to eat with normal utensils.

Articulation and deglutition (swallowing) are 2 separate oromotor functions that share common anatomic structures. Articulation encompasses all motor processes involved in the production of sounds, whereas deglutition starts with mastication and includes all subsequent motor processes involved in moving food or liquid from the mouth to stomach. In contrast to gross and fine motor function, BAMF scores for articulation did not show a significant correlation with age ($r = -0.0389$, 95% CI = -0.690 to 0.030) (Figure 2E). BAMF scores for deglutition did show a

significant correlation ($r = -0.451$, 95% CI = -0.728 to -0.047) (Figure 2F), but this was largely driven by the low scores of the 2 oldest patients and was interpreted as an outlier effect. Scores for articulation were consistently in the lower half of the range among all patients except for the most mildly affected atypical patient. In contrast, scores for deglutition were consistently in the upper half of the range except for the 2 oldest patients who were completely dependent on a gastric tube for feeding. With the exception of the 2 oldest patients, aspiration of thin liquids or foods was not reported. All typical patients lacked rotary jaw movements while chewing, exhibited limited lateral tongue movement, and had poor control of oral secretions. These findings were also observed in 2 mildly affected patients.

Figure 3 Loss of Functional Skills in Patients With MLIV Begins in Adolescence



Caregiver-reported numbers of lost functional skills suggest that patients with MLIV begin to exhibit functional regression in gross motor (A), fine motor (B), cognitive (C), social (D), self-help (E), and compensatory (F) skills during adolescence. In contrast, caregivers reported loss of language skills at various times across age (G). Dotted arrows label the youngest patient to have lost skills in each domain. MLIV = mucopolipidosis type IV.

Timing of Developmental Regression in MLIV

Given the suggestion of declining motor function with age, we sought to identify the range of ages during which patients with MLIV lose specific developmental skills across different functional domains. Caregivers reviewed a developmental skills inventory from the Oregon Project for Visually Impaired and Blind Children and for each listed skill, indicated whether

1) the patient was able to perform that skill at the time of exam, 2) the patient had never been able to perform the skill, or 3) the patient had performed the skill in the past but lost that ability by the time of exam. In all domains except for language, functional regression emerged early in the second decade of life (Figures 3, A–F). In contrast, language skills were lost across the age range (Figure 3G).

Discussion

We report a cross-sectional, observational study of 26 patients with MLIV that demonstrates a positive correlation between age and worsening motor function and developmental regression beginning in the second decade of life. Although MLIV has been primarily described as a static neurodevelopmental condition,⁵ our data highlight a neurodegenerative component that should be considered in prognostic discussions and the design of future clinical trials. In our study, patients most commonly presented with delayed motor development in the first year of life. Across the first decade, the severity of appendicular spasticity positively correlated with age, whereas measures of gross and fine motor function negatively correlated with age. However, caregivers did not report loss of developmental skills until early adolescence. Based on our current study and the existing published data, we postulate that the natural history of MLIV can be described in 3 general stages. First, patients make slow developmental gains in the first years of life while exhibiting signs of CNS dysfunction (i.e., abnormal muscle tone and impaired vision). Second, patients reach a developmental plateau while muscular hypertonicity worsens, and motor function gradually declines. Third, in early adolescence, the compounding effects of worsening hypertonicity, motor function, and visual impairment result in functional regression.

Although limited, the available radiographic data on patients with MLIV support the existence of a late-onset neurodegenerative component in corroboration with our clinical findings. In the early stages of MLIV, brain MRI studies typically demonstrate a profound paucity of subcortical white matter, hypoplasia of the corpus callosum, and iron deposition in the basal ganglia with relative preservation of the cortical gray matter.^{15,24} This constellation of findings is consistent with a hypomyelinating leukodystrophy and brain iron accumulation, which conceptually align with younger patients' impaired neurodevelopment and extrapyramidal signs, respectively. Although cortical gray matter atrophy is absent in younger patients, a study using MR spectroscopy in 11 children and 3 adults with MLIV suggests that loss of TRPML1 channel activity does impair neuronal function in the CNS across all stages of disease.²⁵ In this study, a diffuse reduction in the N-acetylaspartate (NAA) to creatine-phosphocreatine (Cr) ratio was measured in most gray and white matter regions. NAA is a neuron-specific metabolite, and a decreased NAA/Cr ratio is indicative of dysfunction or damage in the neuronal cell bodies or axons. A subsequent prospective study in 5 patients younger than 20 years demonstrated stable or increasing cortical gray matter volumes, but decreasing subcortical white matter and cerebellar volumes with age.¹⁵ Taken together, these data suggest that loss of TRPML1 compromises the function of cortical neurons (decreased NAA/Cr in the cortex and axonal tracts) without causing neuronal death (preserved gray matter volume) in the early stages of disease. Degeneration of axonal tracts (subcortical white matter volume loss) and cerebellar atrophy

develop later around the time that functional regression emerges in adolescent patients.

Progressive visual impairment due to retinal degeneration is a well-documented feature of MLIV^{13,14,26,27} that likely contributes to the functional decline in patients. Although the rate of progression has not been delineated, in our experience, most patients are legally blind by the second decade of life. The nadir of visual function coincides with the emergence of functional regression that we demonstrate in the current study. Our study design was unable to accommodate the assessment of visual function, but we assume that degree of visual impairment contributes to functional regression. As engaging the environment becomes more challenging with loss of vision, a vicious cycle of decreased engagement and worsening motor function likely ensues.

We found that patients with MLIV in our cohort demonstrated appendicular hypertonia that consisted of both pyramidal (spasticity) and extrapyramidal (rigidity) qualities. Extrapyramidal motor signs in MLIV are not conspicuously documented in the literature. However, ferric iron deposition in the basal ganglia of patients with MLIV appears similar to that demonstrated in neurodegeneration with brain iron accumulation disorders where extrapyramidal signs are prominent.²⁸ Whether iron deposition and extrapyramidal dysfunction worsen across age in MLIV is not known. In our older patients, the prominent and persistent spasticity observed may have masked extrapyramidal features that were easier to discern in younger patients with milder spasticity. Further characterization of pyramidal and extrapyramidal features in MLIV merits further investigation as patients would benefit from appropriately targeted medical interventions.

Our study has limitations that need to be acknowledged. First, limited patient access and cost permitted only a single evaluation of each patient by one evaluator, precluding an analysis of intrarater and interrater variability. Next, all typical patients scored low on the BAMF and GMFCS scales, suggesting that these instruments lack the sensitivity to track disease progression in the MLIV population. Clinical scales with higher resolution in the lower functional range may avoid floor effects and could be tested in future studies. Alternatively, disease-specific scales, which have been highly successful in defining the natural history of other rare diseases,²⁹⁻³¹ could be developed for MLIV. Finally, the low number of participants limits the significance of our results. However, the 26 patients in our cohort represent roughly 25% of all patients currently identified through the ML4 Foundation, the only international patient advocacy group and registry for patients with MLIV.

Despite our studies limitations, our results provide quantitative clinical measurements demonstrating a positive correlation between worsening neurologic disability and age in patients with MLIV. The results of our study support a neurodegenerative component of MLIV that manifests as developmental regression in the second decade of life. Whether

the emergence of functional decline results from the cumulative, nonlinear interactions of steadily progressive neurodegenerative processes or reflects an inflection from impaired CNS development to degeneration is uncertain. However, understanding the relationship between CNS pathology and clinical course of disease will be imperative to guiding future interventional trials and optimizing patient care. Further investigations into the molecular mechanisms connecting lysosomal dysfunction and late-onset neurodegeneration are also merited and may provide new insights into the importance of TRPML1 function in the disease relevant developmental contexts of MLIV. Finally, our study highlights the need for identifying or developing suitable clinical instruments to track disease progression and aid in the development of clinical trial end points for future therapeutics targeting MLIV.

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Disclosure

The authors have declared that no conflict of interest exists except for Y.G. who is an inventor on patent application (PCT/US2020/057839) filed through Mass General Brigham Corporation. Go to [Neurology.org/NG](https://www.neurology.org/NG) for full disclosures.

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Appendix (continued)

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Florian Eichler, MD	Department of Neurology and Center for Genomic Medicine, Massachusetts General Hospital and Harvard Medical School, Boston, MA	Drafting/revision of the manuscript for content, including medical writing for content, and study concept or design

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