A MULTICENTER, RETROSPECTIVE MEDICAL RECORD REVIEW OF X-LINKED MYOTUBULAR MYOPATHY: THE RECENSUS STUDY

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ABSTRACT: *Introduction*: X-linked myotubular myopathy (XLMTM), characterized by severe hypotonia, weakness, respiratory distress, and early mortality, is rare and natural history studies are few. *Methods*: RECENSUS is a multicenter chart review of male XLMTM patients characterizing disease burden and unmet medical needs. Data were collected between September 2014 and June 2016. *Results*: Analysis included 112 patients at six clinical sites. Most recent patient age recorded was ≤18 months for 40 patients and >18 months for 72 patients. Mean (SD) age at diagnosis was 3.7 (3.7) months and 54.3 (77.1) months, respectively. Mortality was 44% (64% ≤18 months; 32% >18 months). Premature delivery occurred in 34/110 (31%) births. Nearly all patients (90%) required respiratory support at birth. In the first year of life, patients underwent an average of 3.7 surgeries and spent 35% of the year in the hospital. *Discussion*: XLMTM is associated with high mortality, disease burden, and healthcare utilization.

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Additional supporting information may be found in the online version of this article.

Abbreviations: AAV, adeno-associated virus; BiPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure; CRF, case report form; IPPV, intermittent positive pressure ventilation; IRB, institutional review board; LOVD, Leiden Open Variation Database; SIMV, synchronized intermittent mechanical ventilation; XLMTM, X-linked myotubular myopathy

Key words: centronuclear myopathy; congenital myopathy; disease burden; natural history; retrospective chart review; X-linked myotubular myopathy

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X-linked myotubular myopathy (XLMTM) is a centronuclear myopathy caused by pathogenic variants in the *MTM1* gene, resulting in a lack or dysfunction of the protein myotubularin.[1–8] The disorder is rare and primarily affects boys, with an estimated incidence of 1 in 50,000 live male births.[9] Infants present with severe hypotonia, weakness, and respiratory distress, and nearly half die of respiratory failure in the first year of life.[10,11] Children who survive infancy require extensive supportive care. Most never achieve independent ambulation, require respiratory support, and die prematurely.[10,11] Clinical features and comorbidities include elongated facial features, high-arched palate, ophthalmoplegia, cryptorchidism, pyloric stenosis, spherocytosis, hepatic peliosis/hemorrhage, advanced bone age, and premature adrenarche.[12–14]

XLMTM is typically diagnosed in the presence of neonatal hypotonia and weakness, muscle biopsy showing characteristic histopathologic changes, and genetic testing for pathogenic variants in *MTM1*.[13] Currently, there are no disease-modifying treatments for XLMTM. Management focuses on maximizing functional abilities and minimizing medical complications through multidisciplinary supportive care.[9,13]

Recent advances in our understanding of XLMTM have led to proof of concept and preclinical studies exploring promising approaches to therapy. Farthest along is the development of gene therapy. Delivery of a functional myotubularin gene to *Mtm1* knock out mice using an adeno-associated virus (AAV) system led to increased myotubularin expression, improved muscle pathology and strength,

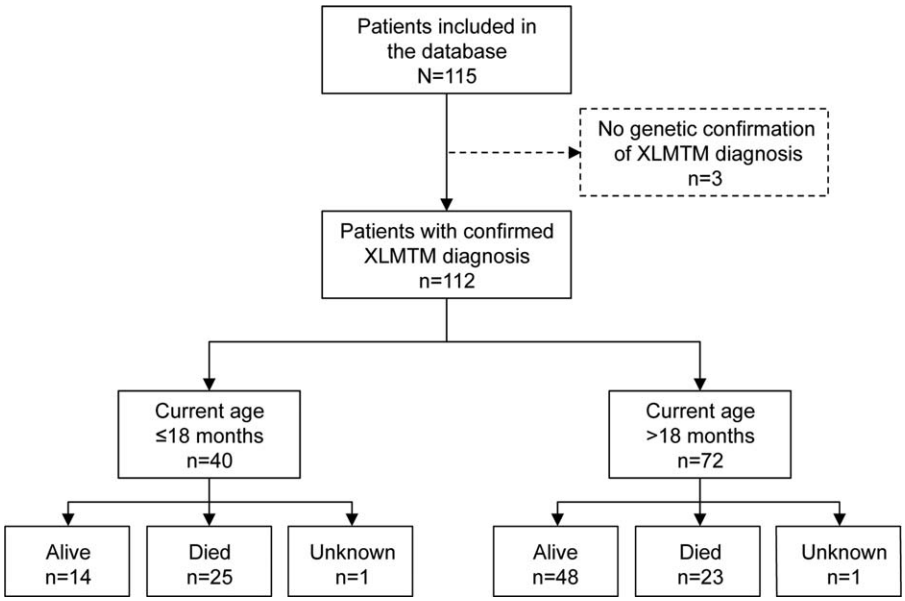

FIGURE 1. Patient disposition diagram.

greater motor activity, and prolonged survival.[15,16] Similarly, in a dog model of a naturally occurring *MTM1* variant,[17] preclinical testing of a single intravascular dose of recombinant AAV8-*MTM1* vector improved muscle weakness and respiratory impairment and prolonged life span through 4 years.[18,19] Other studies have suggested that myotubularin protein replacement,[19] down-regulation of dynamin 2 expression,[20,21] or inhibition of PIK3C2B[22] activity may be viable therapeutic strategies. With the start of the first clinical trials of a directed gene therapy for XLMTM this year,[23] there is a clear need for natural history information for this disease.

The RECENSUS study (NCT02231697, Audentes Therapeutics, Inc., San Francisco, CA) is a retrospective, multicenter medical chart review of patients with XLMTM. The primary objective is to characterize disease manifestations and recorded medical management. Secondary objectives are to identify prognostic disease variables, potential outcome measures for therapeutic intervention studies, and clinical disease features that warrant monitoring during therapeutic intervention. The current analysis examines disease burden and unmet medical need in XLMTM patients in RECENSUS receiving the current standard of care.

SUBJECTS AND METHODS

Study Design and Patient Eligibility. Eligible patients were males diagnosed with XLMTM based on a confirmed pathogenic variant in *MTM1* or clinically affected individuals with a combination of genetically confirmed family history of XLMTM and muscle biopsy. The study protocol was reviewed and approved by a central institutional review board (IRB) and local IRBs at participating institutions. Informed consent was obtained from the parent(s) or legal guardian(s) of each patient and/or assent by the patient (when applicable) before initiating medical record review. Further details regarding data collection, genetic testing, and statistical analysis are provided as supplementary material, available online.

RESULTS

Patient Characteristics. Data were collected from the medical records of 115 patients, including 6 affected sibling pairs, with XLMTM at 6 sites in North America. After excluding 3 patients without a genetically confirmed diagnosis, there were 112 patients. This cohort was stratified by whether the most recent patient age recorded was ≤18 months ($n = 40$) or >18 months ($n = 72$), hereafter referred to as "≤18 months old" or ">18 months old" (Fig. 1). Stratification using 18 months as a cutpoint was chosen based on the findings of McEntagart et al.[10] where survival to 18 months of age was 54%; however, in this kind of cross sectional study, many currently living patients in the ≤18 months old subgroup eventually survive long enough to enter the >18 months old group. As such, this approach was not intended to separate patients based on the severity of their conditions.

Some of these patients have been previously reported in the literature or online databases.[3,10–12,24,25] Patient characteristics are shown in Table 1. The mean (SD) age at diagnosis was 3.7 (3.7) months for patients ≤18 months old and 54.3 (77.1) months for patients >18 months old. The majority of patients in both age groups were white and nearly all lived in North America. Most XLMTM diagnoses were initially made with muscle biopsy and confirmed using genetic testing (96%), and most patients were documented as hypotonic at birth (Table 2). A greater

Table 1. Demographic and clinical characteristics.*

Characteristic	Age ≤ 18 months $n = 40$	Age > 18 months $n = 72$	All patients $N = 112$
Age at XLMTM diagnosis (months)	$n = 39$	$n = 69$	$n = 108$
Mean (SD)	3.7 (3.7)	54.3 (77.1)	36.1 (66.1)
Range (min, max)	0, 17	0, 295	0, 295
Quartiles (25th, median, 75th)	1, 3, 4	4, 21, 72	3, 6, 31
Method of diagnosis, *n* (%)†	$n = 40$	$n = 72$	$n = 112$
Genetic testing	39 (98)	69 (96)	108 (96)
Muscle biopsy	30 (75)	60 (83)	90 (80)
Clinical symptoms and family history	3 (8)	7 (10)	10 (9)
Race, *n* (%)	$n = 40$	$n = 72$	$n = 112$
White	25 (63)	53 (74)	78 (70)
Black	2 (5)	1 (1)	3 (3)
Asian	1 (3)	1 (1)	2 (2)
Unknown	4 (10)	5 (7)	9 (8)
Other‡	8 (20)	12 (17)	20 (18)
White, Native American	4 (50)	7 (58)	11 (55)
White, Black	3 (38)	2 (17)	5 (25)
White, Asian	1 (13)	1 (8)	2 (10)
White, Other Pacific Islander	0	2 (17)	2 (10)
Region of origin, *n* (%)	$n = 40$	$n = 72$	$n = 112$
North America	35 (88)	68 (94)	103 (92)
Europe	4 (10)	2 (3)	6 (5)
South America	0	2 (3)	2 (2)
Australia	1 (3)	0	1 (1)
Deaths, *n/N* (%)	25/39 (64)	23/71 (32)	48/110 (44)

*Column header counts are the number of patients found in the enrollment CRF dataset. Denominators are the number of patients with non-missing data for each characteristic. CRF datasets utilized in the table include enrollment and method of diagnosis.

†Patients may have more than one method of diagnosis.

‡These patients reported more than 1 race.

proportion of patients ≤18 months old had died compared with those >18 months old.

The time to receiving a genetic diagnosis has shortened considerably. For the 19 patients born between 1981 and 1995, before discovery of *MTM1*, the average time between birth and genetic confirmation was 11.9 years (range, 2.0–24.5 years). The average age at diagnosis was 35.1 months (range, 0–128.8 months) for children born 1996–2000, 32.4 months (range, 0.5–149.7 months) for those born 2001–2005, 7.6 months (range, 0.3–28.0 months) for those born 2006–2010, and 4.4 months (range, 0–17.1 months) for those born 2011–2014. Since the 1996–2000 birth cohort, average age at biopsy declined from 7.1 to 2.7 months and one-third of children are now diagnosed within the first 3 months of life.

Genetic Variants. *MTM1* mutation data were available for 106 unrelated probands, representing 112 affected individuals. Consistent with the reporting laboratories' interpretations of likely or confirmed pathogenicity, 105 of the 106 *MTM1* sequence variants were predicted by MutationTaster[26] to be "disease causing," with the only variant of uncertain significance (VUS) being a single nucleotide intron 4 variant predicted to generate a novel splice acceptor site 16 bases proximal to the exon 5 splice acceptor. None of these variants were present in either the ExAC[27] or 1000 Genomes[28] databases but 84 have been published and/or listed in the Leiden Open Variation Database (LOVD) *MTM1* gene mutation database[3] as pathogenic variants, with the remaining 22 being novel variants not previously reported. Thirty-five pathogenic variants were familial based either on maternal sequencing or positive family history, while sequencing confirmed that a further 8 pathogenic variants were *de novo*. Information on the remaining cases was unavailable.

These 106 independent pathogenic *MTM1* variants were spread throughout the gene, affecting each of the 15 exons. Nine of these were large multi-exonic deletions, duplications or rearrangements, with the rest being mostly single nucleotide variants and small indels of up to seven nucleotides. Sixty-four variants were predicted null variants, expected to lead to complete absence of myotubularin protein, with frameshift insertions or deletions, splice site variants, and stopgain variants collectively accounting for 56 (88%) of these. The remainder were due to short frameshift indels (2), multi-exon intragenic deletions (2), deletions including exon 1 (2), a start-loss single base change, and one complex multi-exon duplication.[25]

Predicted or potential hypomorphic alleles included 37 missense variants and 1 small in-frame

Table 2. Gestational and delivery characteristics.*

Characteristic	Age ≤ 18 months $n = 38$	Age > 18 months $n = 72$	All patients $N = 110$
Decreased fetal movement, *n/N* (%)	24/38 (63)	34/72 (47)	58/110 (53)
Weeks when decreased fetal movement noted	$n = 7$	$n = 6$	$n = 13$
Mean (SD)	28.9 (5.0)	29.7 (2.9)	29.2 (4.0)
Range (min, max)	20, 34	25, 32	20, 34
Quartiles (25th, median, 75th)	25, 30, 34	28, 31, 32	28, 30, 32
Polyhydramnios, *n* (%)	19/38 (50)	38/72 (53)	57/110 (52)
Weeks when polyhydramnios noted	$n = 12$	$n = 15$	$n = 27$
Mean (SD)	31.8 (5.7)	30.7 (4.9)	31.2 (5.2)
Range (min, max)	20, 38	19, 40	19, 40
Quartiles (25th, median, 75th)	28, 33, 37	28, 30, 34	28, 31, 36
Premature delivery, *n* (%)†	13/38 (34)	21/72 (29)	34/110 (31)
Weeks at delivery (preterm only)	$n = 13$	$n = 21$	$n = 34$
Mean (SD)	31.8 (2.7)	32.9 (1.9)	32.4 (2.3)
Range (min, max)	27, 35	30, 36	27, 36
Quartiles (25th, median, 75th)	31, 33, 34	31, 33, 34	31, 33, 34
Method of delivery, *n* (%)	$n = 38$	$n = 72$	$n = 110$
Caesarian	23 (61)	42 (58)	65 (59)
Vaginal	13 (34)	21 (29)	34 (31)
Vacuum suction	0	1 (1)	1 (1)
Not documented	2 (5)	8 (11)	10 (9)
Presentation, *n* (%)	$n = 38$	$n = 72$	$n = 110$
Breech	8 (21)	14 (19)	22 (20)
Cephalic	11 (29)	7 (10)	18 (16)
Other	2 (5)	4 (6)	6 (5)
Not documented	17 (45)	47 (65)	64 (58)
Hypotonic at birth, *n* (%)‡	38/39 (97)	67/72 (93)	105/111 (95)
Apgar scores, *n* (%)	$n = 33$	$n = 48$	$n = 81$
1 min after birth	$n = 32$	$n = 48$	$n = 80$
≥7 (normal)	0	4 (8)	4 (5)
4–6 (intermediate)	3 (9)	14 (29)	17 (21)
0–3 (low)	29 (91)	30 (63)	59 (74)
5 min after birth	$n = 32$	$n = 47$	$n = 79$
≥7 (normal)	3 (9)	15 (32)	18 (23)
4–6 (intermediate)	17 (53)	28 (60)	45 (57)
0–3 (low)	12 (38)	4 (9)	16 (20)

Column header counts are the number of patients found in the gestation/birth CRF dataset. Denominators are the number of patients with non-missing data for each characteristic.

†*Premature delivery is defined as delivery before 36 weeks.*

‡*At the data cutoff June 16, 2016, 101 patients were listed as hypotonic at birth. Since then, the database has been updated to reflect 4 additional patients who were hypotonic at birth (n = 105).*

deletion, with a further 4 multi-exon in-frame duplications or deletions of unknown consequence. These were similarly distributed throughout the gene, affecting most of the known protein functional domains.[29] Of the 38 predicted hypomorphic variants, nine (23.7%) altered residues in the amino-terminal PH-GRAM domain, 11 (28.9%) were in the Ras-interacting domain, and 11 more in the phosphatase domain, including 1 affecting the catalytic P-loop. The SET-interacting domain was altered in 7 patients, and there were no variants that mapped to within the carboxy-terminal coiled-coil domain.

Gestational Characteristics. Gestational characteristics are shown in Table 2. Fetal movement was decreased in approximately half of patients overall, but in a larger percentage of those ≤18 months old than > 18 months old, and was observed at a mean 29 weeks' gestation, with little difference between age groups. Premature delivery (i.e., before 36 weeks) occurred in approximately one third of patients overall at a mean 32 weeks' gestation. Polyhydramnios was noted in approximately half of the cohort at a mean 31 weeks' gestation. Birth presentation could not be reliably characterized because it was not documented for more than half of the cohort. Cesarean delivery was the most common form of delivery in both age groups. Most patients had a low Apgar score at 1 min after birth.

Respiratory Support. Use of respiratory support is shown in Table 3. The vast majority of patients in both age groups required respiratory support at birth. In the first 24 h after birth, a majority required intermittent positive pressure ventilation

Table 3. Respiratory and ventilator support.*

Type of support	Age ≤ 18 months $n = 38$	Age > 18 months $n = 70$	All patients $N = 108$
Respiratory support required at birth, *n* (%)	$n = 38$	$n = 70$	$n = 108$
Yes	37 (97)	60 (86)	97 (90)
No	1 (3)	4 (6)	5 (5)
Not documented	0	6 (9)	6 (6)
Type of respiratory support in first 24 h after birth, *n* (%)	$n = 37$	$n = 66$	$n = 103$
IPPV/SIMV/pressure support	25 (68)	37 (56)	62 (60)
CPAP/BiPAP	9 (24)	15 (23)	24 (23)
Supplemental oxygen	0	5 (8)	5 (5)
Not documented	3 (8)	9 (14)	12 (12)
Type of respiratory support at any time,† *n* (%)	$n = 29$	$n = 47$	$n = 76$
CPAP/BiPAP	18 (62)	33 (70)	51 (67)
IPPV/SIMV/pressure support	18 (62)	31 (66)	49 (64)
Supplemental oxygen	7 (24)	22 (47)	29 (38)
Other	18 (62)	23 (49)	41 (54)
Tracheostomy, *n/N* (%)	13/38 (34)	52/70 (74)	65/108 (60)
Age at tracheostomy (months)	$n = 13$	$n = 48$	$n = 61$
Mean (SD)	3.8 (2.2)	15.1 (35.9)	12.7 (32.2)
Range (min, max)	1, 8	1, 197	1, 197
Quartiles (25th, median, 75th)	2, 3, 5	2, 3, 12	2, 3, 8
Ventilator dependent 24 h/day, *n* (%)	$n = 38$	$n = 70$	$n = 108$
Yes	22 (58)	30 (43)	52 (48)
No	12 (32)	25 (36)	37 (34)
Not documented	4 (11)	15 (21)	19 (18)
No. of hours off ventilator (average day)	$n = 8$	$n = 25$	$n = 33$
Mean (SD)	18.3 (8.8)	14.6 (8.2)	15.5 (8.3)
Range (min, max)	2, 24	2, 24	2, 24
Quartiles (25th, median, 75th)	12, 24, 24	6, 16, 24	8, 16, 24
Age at first ventilator support (months)	$n = 29$	$n = 46$	$n = 75$
Mean (SD)	0.5 (1.9)	20.1 (52.6)	12.5 (42.1)
Range (min, max)	0, 9	0, 239	0, 239
Quartiles (25th, median, 75th)	0, 0, 0	0, 0, 1	0, 0, 0

**Column header counts are the number of patients found in the respiratory support CRF dataset. Denominators are the number of patients with non-missing data for each characteristic.*

†Patients may have more than one type of respiratory support.

(IPPV) or synchronized intermittent mechanical ventilation (SIMV) and approximately one-quarter required continuous positive airway pressure (CPAP) or bilevel positive airway pressure (BiPAP) support, with little difference between age groups. Among patients with respiratory support data, reported lifetime incidence of respiratory support was high in both age groups, including a majority of patients using IPPV/SIMV support and CPAP/BiPAP.

Overall, more than one-third of patients had used supplemental oxygen at some point, with greater use among patients >18 months old. Ten patient records did not indicate whether they had respiratory support at any time, but all 102 remaining patients required it at some point in their lives. Tracheostomy, performed in 60% of patients, was more than twice as common among patients >18 months old and was performed at an older mean age in these patients, although the median age was the same for both age groups. Nearly half of patients required ventilator support 24 h per day at some time. Among patients who were not 24-h ventilator dependent, patients ≤18 months old had more hours off the ventilator than those >18 months old.

Motor and Cognitive Development. Motor milestones were inconsistently documented in the medical records. The ability to sit without support for 10 s was achieved in only 1 patient (at 11.8 months) among the 11 patients ≤18 months old for whom these data were documented. This milestone was achieved in 41 of 48 patients >18 months old at a mean of 19.9 (13.1) months among the 28 patients with data on timing. The ability to walk ten yards was not achieved by any of the 7 patients ≤18 months old for whom these data were documented; 13 patients achieved independent walking among the 42 patients >18 months old for whom these data were available. The 6 patients who had data regarding timing, walked independently at a mean 25.4 (10.1) months. Among the 33 patients (46%) >18

Table 4. Other conditions in the medical record classified as related to XLMTM and reported in ≥5% of patients.*

MedDRA system organ class/preferred term	Age ≤ 18 months *n* = 38 *n* (%)	Age > 18 months *n* = 70 *n* (%)	Total *N* = 108 *n* (%)
Any conditions related to XLMTM	30 (79)	48 (69)	78 (72)
Musculoskeletal and connective tissue disorders	18 (47)	25 (36)	43 (40)
Bone development abnormal	12 (32)	9 (13)	21 (19)
Head deformity	9 (24)	12 (17)	21 (19)
Congenital, familial, and genetic disorders	16 (42)	25 (36)	41 (38)
Dysmorphism	11 (29)	17 (24)	28 (26)
Macrocephaly	2 (5)	6 (9)	8 (7)
Cryptorchism	3 (8)	2 (3)	5 (5)
Gastrointestinal disorders	5 (13)	8 (11)	13 (12)
Gastroesophageal reflux disease	4 (11)	4 (6)	8 (7)
Salivary hypersecretion	1 (3)	4 (6)	5 (5)
Nervous system disorders	2 (5)	10 (14)	12 (11)
Facial paresis	1 (3)	7 (10)	8 (7)
Hepatobiliary disorders†	2 (5)	6 (9)	8 (7)
Respiratory, thorasic, and mediastinal disorders†	3 (8)	5 (7)	8 (7)

*Column header counts and denominators are the number of patients found in this dataset. Because only the preferred terms reported in ≥5% of patient are included for each MedDRA system organ class, the total for the class may not equal the sum of the terms shown here. Hypotonia, dysphagia, and respiratory failure were scored but not included here due to inability to distinguish between primary disease presentations versus secondary comorbidities or masking of conditions by successful therapy (i.e., G-tube placement for dysphagia).

†The MedDRA system organ class reached ≥5%, although no single condition within the class reached ≥5%.

months old with cognitive assessments available, 6 (18%) were reported "above grade level," 22 (67%) were "at grade level," 9 (27%) were "below grade level," and 3 (9%) were "significantly below grade level."

Related Conditions in the Medical Record. Other medical conditions considered related to XLMTM were present in 72% of patients (Table 4). The most common related conditions (grouped by MedDRA System Organ Class[30] were musculoskeletal and connective tissue disorders and congenital, familial, and genetic disorders. In general, related medical conditions were more frequent in patients ≤18 months old compared with patients >18 months old for most major MedDRA system organ classes, with the greatest difference for abnormal bone development. Among patients >18 months old, facial paresis was more common. Dysmorphism, head deformity, macrocephaly, gastroesophageal reflux disease, and salivary hypersecretion occurred in similar proportions of patients in both age groups. Hepatic peliosis, a serious and often fatal complication in older patients with XLMTM,[12,13] was documented in 6 patients in the RECENSUS cohort ranging in age from 1.8 years to 22.0 years. Similarly, thin or fractured ribs[31] were reported in 10 patients.

Hospitalizations and Procedures. The annual percentage time in the hospital per patient for all patients, and for only patients with records including information on hospitalizations, was highest in the first year of life (35% and 47%, respectively) (Fig. 2A), declined in Year 2, and continued to decline through Year 5. Sixteen patients spent their entire first year of life in the hospital. The most frequently reported (≥5%) reasons for hospitalization were respiratory in nature (Table 5). After discharge, home-based nursing or physical therapy support was reported for 37% of patients.

The mean number of surgeries ranged between 2.0 (1.5) and 3.7 (2.5) per year (Fig. 2B). The most frequently reported (≥5%) surgical procedures are shown in Table 6. Surgeries performed more often among patients >18 months old, included esophagogastric fundoplasty, tracheostomy, myringotomy with or without ear tube insertion, bronchoscopy, laryngoscopy, orchidopexy, spinal fusion, adenotonsillectomy and laparoscopy. Only gastrointestinal tube insertion was performed in a greater percentage of patients ≤18 months old. Gastrostomy, circumcision, muscle biopsy, myringotomy, inguinal hernia repair, and ventriculoperitoneal shunt were performed in similar proportions of patients in both age groups.

DISCUSSION

Findings demonstrate high mortality and substantial disease burden in patients with XLMTM, particularly in those ≤18 months of age at last follow-up, where mortality was 64%; this is similar to the 18-month survival rate of 54% observed by McEntagart et al.[10] The clinical disease burden includes respiratory support at birth for 90% of patients, 24-h ventilator dependence for 48%, tracheostomy for 60%, other medical conditions related to XLMTM in 72%, and high rates of healthcare use, hospitalization and surgical

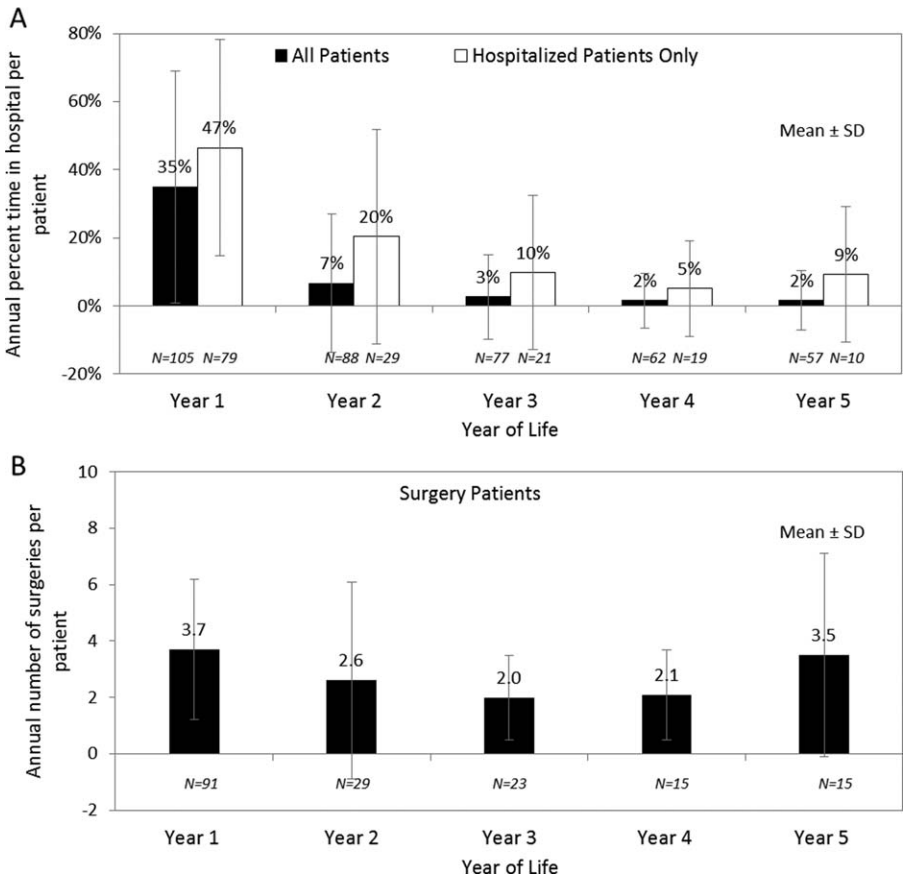

FIGURE 2. Hospital and Surgical Burden: Annual Percentage Time in the Hospital per Patient (A) and Annual Number of Surgeries per Patient (B). "All Patients" = all study participants. "Hospitalized patients only" = patients with recorded hospitalization start and end dates. "Surgery patients" = patients with surgical data and known dates for their surgical procedures.

intervention, with patients hospitalized for 35–47% of their first year of life. As such, the RECENSUS dataset confirms perinatal and respiratory findings of earlier studies and provides important insights into healthcare use, medical intervention, diagnostic trends, and the extent of related medical conditions.

Perinatal Complications. XLMTM often involves a prenatal history of polyhydramnios and weak or infrequent fetal movements.[10] As in previous studies, perinatal complications were commonplace in RECENSUS and frequencies were higher than for pregnancies in the general population.[10,12] Polyhydramnios and decreased fetal movement were each noted in roughly 50% of RECENSUS pregnancies comparable to 45% and 58%, respectively, in a previous study.[12] Although statistics on decreased fetal movement are not widely available, polyhydramnios is estimated to occur in only 0.2–1.6% of pregnancies overall.[32] Preterm birth was reported for 31% of RECENSUS patients, 24–31% of XLMTM patients in previous studies,[10,12] and only 9.6% of U.S. births overall.[33] Similarly, Caesarean delivery was performed for 59% of births in RECENSUS and 45% in a previous study,[12] compared with 32% of U.S. births overall.[33] In addition, the majority of patients had a low Apgar score at 1 min after birth, signaling a need for extensive, immediate and aggressive resuscitation management in the newborn period.

Respiratory Support. A primary presentation of XLMTM is inability to establish spontaneous respiration. The near-universal (90%) need for respiratory support at birth in the RECENSUS population is consistent with this, and with findings of McEntagart et al. that 85% of patients required respiratory support at birth regardless of eventual survival or degree of disease severity.[10] These data also illustrate that respiratory compromise at birth is not a reliable predictor of later severity, a fact that may lead to prognostic uncertainty during the assessment of newly diagnosed infants. Although data were unavailable for 10 patients, all 102 of the remaining cohort required respiratory support at some point in their lives, underscoring the severity of this disease. Nearly half of RECENSUS patients required 24-h ventilator support, consistent with the rate of 57% reported by Herman et al.[12] The decision to undergo tracheostomy may be driven by both medical and philosophical or logistical considerations, but the procedure was uniformly

Table 5. Primary reason for hospitalization reported for ≥5% of patients.*

MedDRA system organ class/preferred term	Age ≤ 18 months *n* = 36 *n* (%)	Age > 18 months *n* = 62 *n* (%)	Total *N* = 98 *n* (%)
Any hospitalization, *n* (%)	36 (100)	62 (100)	98 (100)
Respiratory, thoracic and mediastinal disorders	29 (81)	52 (84)	81 (83)
Respiratory failure	19 (53)	33 (53)	52 (53)
Respiratory distress	10 (28)	22 (35)	32 (33)
Acute respiratory failure	1 (3)	7 (11)	8 (8)
Hypoxia	0	5 (8)	5 (5)
Respiratory arrest	1 (3)	4 (6)	5 (5)
Infections and infestations	5 (14)	39 (63)	44 (45)
Pneumonia	3 (8)	26 (42)	29 (30)
Respiratory tract infection	0	5 (8)	5 (5)
Surgical and medical procedures	5 (14)	28 (45)	33 (34)
Surgery	0	7 (11)	7 (7)
Orchidopexy	1 (3)	5 (8)	6 (6)
Ear tube insertion	0	5 (8)	5 (5)
Procedure not specified	2 (6)	3 (5)	5 (5)
Nervous system disorders	7 (19)	12 (19)	19 (19)
Hypotonia†	6 (17)	5 (8)	11 (11)
Injury, poisoning and procedural complications‡	1 (3)	16 (26)	17 (17)
Investigations‡	1 (3)	13 (21)	14 (14)
Cardiac disorders‡	3 (8)	7 (11)	10 (10)
Hepatobiliary disorders‡	0	6 (10)	6 (6)
Metabolism and nutrition disorders‡	1 (3)	5 (8)	6 (6)
Gastrointestinal disorders‡	0	5 (8)	5 (5)
General disorders and administration site conditions	1 (3)	4 (6)	5 (5)
Pyrexia	1 (3)	4 (6)	5 (5)

**Column header counts and denominators are the number of patients found in the hospitalizations CRF dataset.*

A patient is counted at most once in each row. Because only the preferred terms reported in ≥5% of patient are included for each MedDRA system organ class, the total for the class may not equal the sum of the terms shown here.

†While the primary reason for hospitalization was reported on some CRFs as hypotonia, these were typically initial neonatal intensive care unit admissions at birth and additional information on the forms indicate that most of these patients were hospitalized for complications related to hypotonia, including pneumonia, premature birth, club foot, dysphagia, respiratory and feeding support, respiratory distress, feeding insufficiency, respiratory failure/secretion management, feeding difficulties, and bilateral diaphragmatic paralysis.

‡The MedDRA system organ class reached ≥5%, although no single event within the class reached ≥5%.

common in both the RECENSUS cohort (60%) and the study by McEntagart et al. (50%).[10] Of interest, tracheostomy was performed for twice the proportion of patients aged >18 months compared with those ≤18 months. Additionally, older patients were more likely to be using supplemental oxygen, but less likely to be dependent on ventilator support 24 h per day. Herman et al. also found that among patients surviving past 1 year, 57% were 24-h ventilator dependent.[12] Increasing cumulative lifetime need for ventilation and tracheostomy with age place a substantial quality-of-life burden on patients and their families, likely including cost, anxiety about the machines failing, difficulty communicating, and limitations on mobility and social activities.

Motor and Cognitive Function. The medical records of XLMTM patients in RECENSUS contained limited data on motor milestones. This is unfortunate given that hypotonia, weakness and grossly delayed motor development are hallmarks of the disease.[10,12] Nonetheless, available data for patients who survived beyond 18 months demonstrated delays in the ability to sit without support and to walk 10 yards. Similarly, despite a dearth of information on cognitive function, available data suggest that among children living beyond 18 months, approximately 37% were below grade level. Herman et al. reported 20% (7 of 35) of children surviving past 1 year had delayed cognitive development.[12] Motor function and cognitive development are important developmental features that should be regularly and consistently assessed in XLMTM patients using standardized assessment tools to better understand the long-term motor and cognitive development of these children.

Healthcare Use and Medical Intervention. The average length of hospital stay for all newborn infants in the United States has been reported as 4.3 days, extending to 7.7 days for sick infants, and 15.3 days for premature only infants.[34] In contrast, the average time spent in the hospital for XLMTM newborns ranged from a third to almost half of the first year of life, depending on whether

Table 6. Types of surgical procedures reported for ≥5% of patients.*

MedDRA high-level term/preferred term	Age ≤ 18 months *n* = 37 *n* (%)	Age > 18 months *n* = 68 *n* (%)	Total *N* = 105 *n* (%)
Any surgery, *n* (%)	37 (100)	68 (100)	105 (100)
Gastric therapeutic procedures	35 (95)	64 (94)	99 (94)
Gastrostomy	35 (95)	64 (94)	99 (94)
Esophagogastric fundoplasty	14 (38)	36 (53)	50 (48)
Tracheal therapeutic procedures	12 (32)	51 (75)	63 (60)
Tracheostomy	12 (32)	51 (75)	63 (60)
Middle ear therapeutic procedures	3 (8)	38 (56)	41 (39)
Ear tube insertion	2 (5)	37 (54)	39 (37)
Myringotomy†	2 (5)	5 (7)	7 (7)
Respiratory tract and thoracic imaging procedures	7 (19)	25 (37)	32 (30)
Bronchoscopy	7 (19)	22 (32)	29 (28)
Laryngoscopy	1 (3)	15 (22)	16 (15)
Penile therapeutic procedures	10 (27)	18 (26)	28 (27)
Circumcision	10 (27)	18 (26)	28 (27)
Musculoskeletal and soft tissue histopathology procedures	5 (14)	10 (15)	15 (14)
Muscle biopsy‡	5 (14)	10 (15)	15 (14)
Testicular and scrotal therapeutic procedures	1 (3)	14 (21)	15 (14)
Orchidopexy	1 (3)	13 (19)	14 (13)
Spine and spinal cord therapeutic procedures	0	11 (16)	11 (10)
Spinal fusion surgery	0	6 (9)	6 (6)
Tonsillar therapeutic procedures	0	8 (12)	8 (8)
Adenotonsillectomy	0	6 (9)	6 (6)
Gastrointestinal and abdominal imaging procedures	1 (3)	6 (9)	7 (7)
Laparoscopy	0	5 (7)	5 (5)
Hernia repairs	1 (3)	6 (9)	7 (7)
Inguinal hernia repair	1 (3)	4 (6)	5 (5)
Cerebrospinal fluid therapeutic procedures	2 (5)	4 (6)	6 (6)
Ventriculoperitoneal shunt	2 (5)	4 (6)	6 (6)
Chest wall and mediastinal therapeutic procedures§	3 (8)	3 (4)	6 (6)
Diaphragmatic therapeutic procedures§	1 (3)	4 (6)	5 (5)

**Column header counts and denominators are the number of patients found in the surgical procedures CRF datase. A patient is counted at most once in each row. Because only the preferred terms reported in ≥5% of patient are included for each MedDRA system organ class, the total for the class may not equal the sum of the terms shown here. NEC: not elsewhere classified.*

†Five patients who had myringotomy also had ear tube insertion; two patients had only myringotomy.

‡Category reflects idiosyncratic reporting of muscle biopsy as a surgical procedure. Muscle biopsy as a method of diagnosis is captured in Table 1.

§The MedDRA system organ class reached ≥5%, although no single event within the class reached ≥5%.

complete hospitalization data were available for this period (Fig. 2A). While the annual percentage time in the hospital per patient declined after the first year of life, the number of surgeries per child ranged between 2.0 and 3.7 per year over the first 5 years of life, which contrasts with reported rates of 429 total surgical procedures per 10,000 infants less than 1 year of age, and 294/10,000 children aged 1 to 4 years in the U.S. general population.[34] These RECENSUS data highlight the significant proportion of young lives spent in the hospital and undergoing procedures during their early years, demonstrating the high disease burden for young children and their families, and the likely adverse impact on quality of life and healthcare system costs.

As might be expected in a disease characterized by hypotonia and inability to establish spontaneous respiration, the most common reasons for hospitalization were respiratory distress, respiratory failure and pneumonia. The most commonly performed surgeries (gastrostomy in 94% and tracheostomy in 60%) are higher than reported by McEntagart et al., in which 56% and 50% of patients, respectively, had undergone gastrostomy and tracheostomy.[10] It is important to note that the number of surgeries reported in RECENSUS may underrepresent the true burden, as each surgery may have multiple procedures performed under a single episode of anesthesia, and some case records, particularly on older patients, may have contained incomplete data. On the other hand, surgical procedures captured on some case report forms (CRFs) also included muscle biopsy (a routine diagnostic procedure in XLMTM) and circumcision, which, in some cases, may not be a therapeutic procedure.

Genetic Findings. The mutational spectrum of the RECENSUS cohort largely mirrors what has been

published previously.[3,10] The LOVD *MTM1* mutation database currently lists 153 missense substitutions and 209 frame shift or nonsense variants among 529 *MTM1* variants (28.9% and 39.5%, respectively),[3] comparable to 37/106 missense (34.9%) and 40/106 frame shift + nonsense changes (37.7%) in the RECENSUS cohort. It is likely that large duplications and rearrangements are underrepresented in both groups as a result of difficulty identifying these by Sanger and next generation sequencing methods. The LOVD includes one large multi-exonic duplication, while the RECENSUS cohort includes four, all of which were diagnosed in 2010 or later, reflecting the recent availability of clinical deletion/duplication testing.[25] Genotype–phenotype correlations are complex, and it will be important to further explore whether particular variants are associated with mild or severe clinical presentations. However, both null and missense variants were found in roughly equal proportions among cases in the $\leq$18 or >18 month age groups.

A striking finding from RECENSUS is the substantial decrease in time to genetic diagnosis since the gene was identified in 1996.[1] Today, one-third of genetic diagnoses are made within the first 3 months of life and sometimes before muscle biopsy results are returned. Earlier diagnosis has important implications for strategies to improve clinical outcomes and quality of life, and helps families and clinical teams make appropriate decisions regarding ongoing care and potential future children.

Benefits and Limitations of Retrospective Chart Reviews. While retrospective studies are particularly valuable for rare diseases, they have inherent limitations. Data collection may be hindered by inconsistent documentation and data extraction or missing data. RECENSUS collected a comprehensive range of data using robust methodology;[35] however, many of the primary clinical records had been assembled by a preexisting research study or by a registry, many were incomplete, and underreporting is likely. For example, hospitalization data on patients with at least one reported event might be more representative of the group as a whole, as some records contained diagnostic information but relatively little retrospective clinical data. Data on comorbidities in retrospective data collection are subject to a high degree of missing data, as many conditions are not documented in patient medical records or may be masked by successful management strategies. For example, the proportion of patients with reported dysphagia (which typically persists despite the insertion of a G-tube) was <15%, which is lower than the incidence of G-tube insertion typically used to manage that symptom. Similarly, hypotonia and respiratory failure, which were primary or presenting findings in a large majority of cases, were also sometimes reported as comorbidities in the medical records of some of those same patients. Therefore, although recorded as comorbidities, these findings were omitted from Table 4.

Finally, with small datasets, results from one or two patients can skew the results, e.g., in RECENSUS, the mean age at diagnosis (36.1 months) was substantially greater than the median (6 months). Such studies may be biased toward living, "healthier" patients, due to increased likelihood of consent from these parents, and difficulty obtaining IRB approval for deceased patients. There may also be selection bias; for example, the patients at the very mildest end of the spectrum of disease manifestations may be under-diagnosed or there may be other confounding factors (e.g., most RECENSUS patients were white from North America), meaning that regional differences in patient characteristics, treatment patterns and outcomes may not be represented. Finally, evolution of the disease natural history with increasingly sophisticated medical care is unlikely to be captured adequately.

Despite the above limitations, retrospective chart reviews are valuable tools to address challenges inherent in rare disease research, including small numbers of geographically isolated patients and inadequate knowledge about the clinical disease course.[36] Indeed, as these studies can identify variables that correlate with disease and outcomes in the absence of treatment,[37] they also help define objectives, outcome measures, and feasibility for future prospective studies[38] and have provided historical control populations for interventional studies of treatments that have since received regulatory approval.[39] The RECENSUS data characterize measures of XLMTM that might be useful as potential outcome measures for therapeutic interventional trials. Future analyses from RECENSUS will provide valuable information on predictors of survival in these patients.

In conclusion, the RECENSUS study has more completely defined the disease burden and medical management of XLMTM, and reinforces earlier findings that XLMTM is a severe disorder of childhood with substantial mortality, morbidity, and burden on patients, families, and healthcare systems. With no currently approved treatments for XLMTM, there are significant unmet medical needs for this population. This comprehensive data set will inform prospective studies of treatments for XLMTM.

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