A Multicenter, Retrospective Medical Record Review of Patients with X-Linked Myotubular Myopathy (XLMTM): The RECENSUS Study

Alan H. Beggs, PhD,[1] Barry J. Byrne, MD, PhD,[2] Sabine de Chastonay, PhD,[3] Tmirah Haselkorn, PhD,[4] Imelda Hughes, MB, BCh,[5] Emma James, PhD,[6] Nancy L. Kuntz, MD,[7] Jen Simon, MPH,[8] Lindsay C. Swanson, MS,[1] Michele L. Yang, MD,[9] Zi-Fan Yu, ScD,[8] Sabrina W. Yum, MD,[10] Suyash Prasad, MD[6]

[1]Boston Children's Hospital, Harvard Medical School, Boston, MA; [2]Children's Research Institute, University of Florida, Gainesville, Gainesville, FL; [3]Cure CMD, Torrance, CA; [4]EpiMetrix, Inc., Los Altos, CA; [5]Royal Manchester Children's Hospital, Manchester, UK; [6]Audentes Therapeutics, San Francisco, CA; [7]Ann and Robert H. Lurie Children's Hospital of Chicago, Chicago, IL; [8]Statistics Collaborative, Washington, DC; [9]Children's Hospital Colorado, Aurora, CO; [10]Children's Hospital of Philadelphia, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA

AUDENTES

Background

- XLMTM is a rare, inherited centronuclear myopathy caused by mutations in the *MTM1* gene that result in lack or dysfunction of the myotubularin protein.[1-3] The incidence is estimated to be 1 in 50,000 live male births.[4]
- Infants present with severe hypotonia, weakness, and respiratory failure, which leads to death of approximately half of affected children in the first year of life.[5-6] Most children who survive beyond infancy never achieve independent ambulation, require ventilatory and nutritional support, and die prematurely.[5-6]
- Management focuses on maximizing functional abilities and minimizing medical complications through multidisciplinary supportive care.[4,7]
- Gene therapy to increase myotubularin levels and ameliorate disease manifestations is under development.
- RECENSUS is an ongoing, retrospective, non-interventional, multicenter medical chart review of patients with XLMTM.

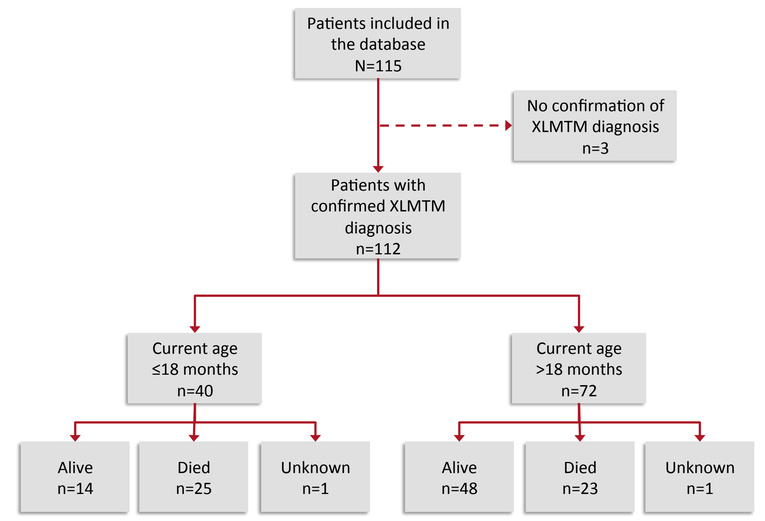
Objective

- To examine disease burden and unmet medical need in patients with XLMTM.

Methods

- Patients: males diagnosed with XLMTM based on confirmed pathogenic variant in the *MTM1* gene or clinically affected individuals with a combination of genetically confirmed family history of XLMTM and muscle biopsy
- Data collection: Sept. 10, 2014 to Jun. 16, 2016.
- Data collection was standardized across sites, performed by trained data extractors, and included demographics, diagnosis, gestation, pulmonary function, hospitalizations, surgeries, motor function, and more.
- Variants were evaluated and confirmed pathogenic or likely pathogenic based on frequency in the Leiden Open Variation (LOVD) *MTM1* Database, the 1000 Genomes and Exome Aggregation Consortium (ExAC) databases and bioinformatic analyses including MutationTaster2.

Disposition



≤18 months: patients currently aged ≤ 18 months or who died before 18 months of age
>18 months: patients currently >18 months of age
Stratification of patients using age 18 months was based on findings from McEntagart et al., in which survival at 18 months was 54%.[5]

Results

Demographics and Clinical Characteristics

A total of 112 patients were included in the analysis. Overall mortality was 44% (64% of patients ≤18 months; 32% of patients >18 months).

Table 1	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 (%)[a]	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[b]	8 (20)	12 (17)	20 (18)
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.
[a] Patients may have more than one method of diagnosis.
[b] These patients reported more than one race, including White/Native American (11), White/Black (5), White/Asian (2), and White/Other Pacific Islander (2).

Diagnosis

- Data indicate that most XLMTM diagnoses were initially made with muscle biopsy and confirmed using genetic testing (Table 1).
- Patients surviving beyond 18 months were older at XLMTM diagnosis than those currently ≤18 months old or deceased before 18 months (Table 1).
- From 1996-2000 (the first 4 years after discovery of *MTM1*) to 2011-2014, mean age at genetic diagnosis declined from 35.1 months to 4.4 months.

Genotype

- *MTM1* mutation data were available for 106 unrelated probands, representing 112 affected individuals.
- 105 of 106 *MTM1* sequence variants were predicted to be "disease causing" and were distributed among all 15 exons.
  - 9 were large multi-exonic deletions, duplications or rearrangements; the remaining were single nucleotide variants and small indels of ≤7 nucleotides.
  - 64 were predicted null variants. Frameshift insertions or deletions, and splice site variants or stopgain variants accounted for 56 (88%). 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.
  - Predicted or potential hypomorphic alleles included 37 missense variants and 1 small in-frame deletion, with a further 4 multi-exon in-frame duplications or deletions of unknown consequence.

Respiratory and Ventilator Support

Respiratory support at birth was nearly universal (90%). In the first 24 hours after birth, 88% required respiratory support. Overall, 48% were ventilator-dependent 24 hours per day and 60% underwent tracheostomy.

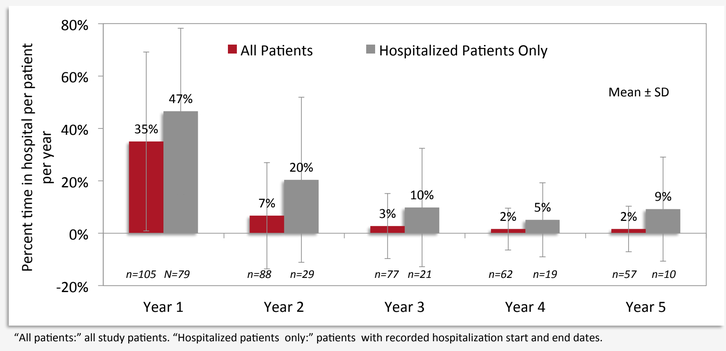
Table 2	Age ≤18 months n=38	Age >18 months n=70	All Patients n=108
Respiratory support required at birth, n (%)	n=38	n=70	n=108
Yes	37 (97)	60 (86)	97 (90)
No	1 (3)	4 (6)	5 (5)
Not documented	0	6 (9)	6 (6)
Type of respiratory support in first 24 hours after birth, n (%)	n=37	n=66	n=103
IPPV/SIMV/Pressure 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[a], 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 hours/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)
Number 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.
[a] Patients may have more than one type of respiratory support.

Hospital and Surgical Burden

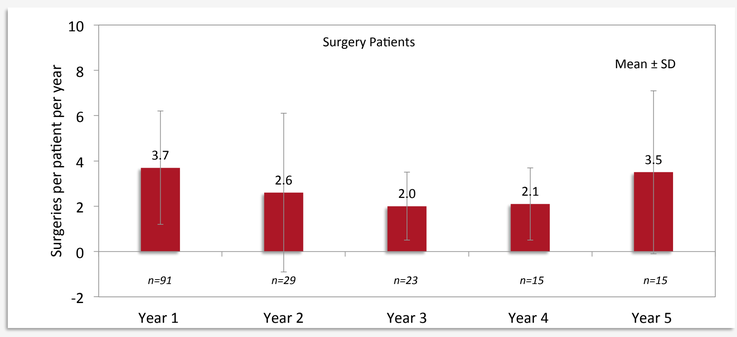
Patients were hospitalized a mean 35% of the first year of life and underwent a mean 3.7 surgeries in that first year.

Figure 1. Annual Percentage Time in the Hospital per Patient



"All patients:" all study patients. "Hospitalized patients only:" patients with recorded hospitalization start and end dates.

Figure 2. Annual Number of Surgeries per Patient



"Surgery patients:" patients with surgical data and known dates for their surgical procedures.

Gestational Characteristics

Decreased fetal movement and polyhydramnios were reported in half of patients. Hypotonia at birth was nearly universal (95%).

Table 3	
Decreased fetal movement:	▪ 53% of patients ▪ Observed at mean 29.2 (4.0) weeks' gestation (among the 13 patients with timing data reported)
Premature delivery (i.e., before 36 weeks):	▪ 31% of births ▪ Among premature births (n=34), delivery occurred at a mean 32.4 (2.3) weeks' gestation
Polyhydramnios:	▪ 52% of patients ▪ Observed at mean 31.2 (5.2) weeks' gestation (among the 27 patients with timing data reported)
Most common form of delivery:	▪ Cesarean section 59% of births (among 110 patients with method of delivery reported)
Apgar scores, mean (SD):	▪ 1-minute: 2.7 (1.9) ▪ 5-minute: 4.8 (2.2)
Hypotonia at birth:	▪ 105/111 (95%)* *101 cases were reported in the June 16, 2016 data cut; since then, the database has been updated to reflect 4 additional patients who were hypotonic at birth.

Conclusions

The RECENSUS study has more completely defined the disease burden and current medical management of XLMTM. The findings reinforce earlier studies showing 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 is a significant unmet medical need for this population.

References:

1. Laporte J, et al. *Nat Genet*. 1996;13(2):175-82.
2. Pierson CR, et al. J *Neuropathol Exp Neurol*. 2005 Jul;64(7):555-64.
3. Biancalana V, et al. *Eur J Hum Genet*. 2012;20(10).
4. Jungbluth H, et al. *Orphanet J Rare Dis*. 2008;3:26.
5. McEntagart M, et al. *Neuromuscul Disord*. 2002;12(10):939-46.
6. Herman GE, et al. *Hum Mutat*. 2002;19(2):114-21.
7. Das S, et al. X-Linked Centronuclear Myopathy. In: Pagon RA AM, Ardinger HH, et al., editor. *GeneReviews®* [Internet]. Seattle (WA): University of Washington, Seattle; 2011.

Acknowledgements:
The RECENSUS study was funded by Audentes Therapeutics. We would like to thank the patients and families with XLMTM who allowed their data to be collected for the RECENSUS study; the Clinical Operations team at Audentes Therapeutics and IND2Results for assistance with data acquisition; Martin Childers and Mike O'Callaghan for their advice on inclusion of key data elements; and Laurie LaRusso of Chestnut Medical Communications for medical writing support funded by Audentes Therapeutics. Support for subject ascertainment, enrollment and data acquisition was provided by National Institutes of Health grant R01 AR044345 and Muscular Disease Association (USA) grant MDA383249. We are grateful for support from the XLMTM patient advocacy community: The Joshua Frase Foundation; MTM-CNM Family Connection; The Myotubular Trust; Where There's a Will There's A Cure Foundation for Myotubular Myopathy; and ZNM – Zusammen Stark!

SCAN TO REQUEST REPRINT