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Liver involvement in myotubular and centronuclear myopathy: data from the MTM & CNM Patient Registry

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The Myotubular and Centronuclear Myopathy Patient Registry

Registry Publication in NMD Feb 2024

Visit the Registry

The John Walton Muscular Dystrophy Research Centre Biobank

Newcastle University

The Newcastle upon Tyne Hospitals NHS Foundation Trust

Introduction

X-linked myotubular and other centronuclear myopathies (XLMTM and CNM) have historically been viewed exclusively as muscle diseases, with severe respiratory muscle weakness and thus a strong emphasis on respiratory care for effective management. There is however an evolving awareness of liver-related pathology associated with XLMTM and CNM, including treatment-related adverse hepatic events in the first two clinical trials for these conditions, most notably four deaths related to cholestatic liver failure in a gene therapy trial. Definitive understanding of the causes, or potential correlation of underlying pre-existing liver dysfunction with treatment-related adverse events is essential. To address this need, two patient organisations, MTM-CNM Family Connection and the Myotubular Trust, co-created the international, multidisciplinary MTM-CNM Liver Collaborative Working Group (the Liver Collaborative) and designed a questionnaire for permanent implementation in the MTM & CNM Patient Registry.

MTM & CNM Patient Registry Objectives

- International, disease-specific, longitudinal, open-ended research database.
- Demographic, genetic, and clinical data reported by the patient or caregiver and their nominated clinician.
- Inclusion criteria: Living or deceased individuals diagnosed with XLMTM or CNM.
- 509 participants (439 living individuals, 70 deceased individuals).
- To collect patient-reported real-world data through the MTM & CNM Patient Registry to expedite understanding of liver-related pathology associated with XLMTM and CNM, across all programmes and the patient and clinical community.
- To improve clinical care and mitigate risks of liver issues in therapeutic development.
- To make liver data available through the registry to support future research.

Methodology & Analysis

The questionnaire was co-designed by the Liver Collaborative and the Patient Registry through iterative discussions and review at monthly virtual meetings, and finalized through a consensual approach

Multidisciplinary partnership with patient advocates ensured the validity, relevance, and usability of the questionnaire. Collecting data through the existing independent patient registry ensures appropriate and ongoing availability of the data to all stakeholders to support research.

Liver data are collected directly from patients or carers through the online registry portal, and registrations are verified by review of genetic reports where available. We present a cross-sectional analysis of **163** liver questionnaire responses. Of the 163, genetic reports were available for **125** (114 of 146 living individuals and 11 of 17 deceased individuals). Aggregate data are reported from participants' most recent entries and response rates are shown by the denominator in figure titles.

Results

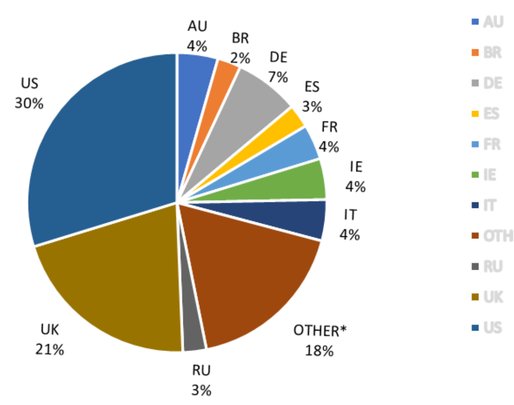
Data is taken over 10 month period between 22 April 2023 (questionnaire launch) to 1 March 2024 (data cut), **163** registry participants completed or partially completed the new liver questionnaire. Fig 1 shows the breakdown of respondents by country. Presently, the main registry questionnaire is available in 10 languages; English, Brazilian Portuguese, Polish, Dutch, Italian, Hindi, French, Spanish, German and Arabic*

*Liver questionnaire not yet available in Arabic

Demographic characteristics of 163 respondents:

- 146 living individuals (87 male, 59 female), 17 deceased patients (all male).
- Of the 146 living individuals, 43 have CNM (17 female, 26 male) and 103 have XLMTM (42 female, 61 male).
- Individual with XLMTM is defined as anyone with a mutation in the *MTM1* gene. Individual with CNM is defined as anyone with a recognised genetic basis of CNM other than the *MTM1* gene. The category 'XLMTM Female' contains a combination of individuals who consider themselves symptomatic or asymptomatic.
- Of the 17 deceased patients; all had XLMTM.
- Mean age (± SD) of living individuals at data cut: 28.3± 22.0 years (range 0-86 years).

Fig 1. Number of respondents by country of residence



*18 counties have <3 registered patients ; Afghanistan, Belarus, Chile, Columbia, Hungary, Israel, Lithuania, Malaysia,, Mexico, Netherlands, New Zealand, Poland, Portugal, Slovakia, South Africa, Sweden, Switzerland, Turkey

Fig. 2. Ever diagnosed with a liver condition (n=161)

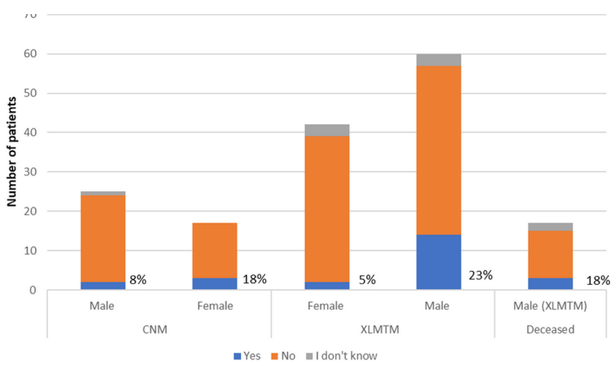


Fig. 3. Treated for high bilirubin/jaundice as a newborn (n=158)

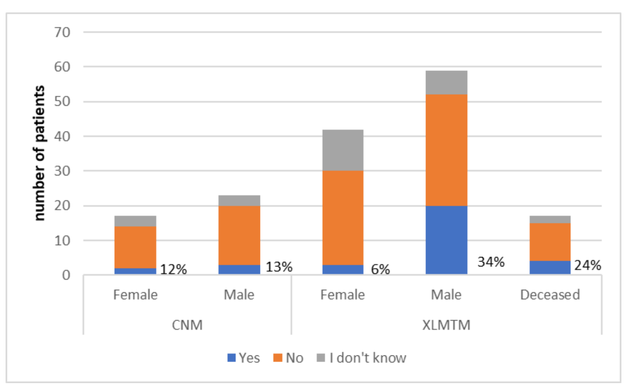


Fig. 4. Ever experienced liver-related symptoms (n=146)

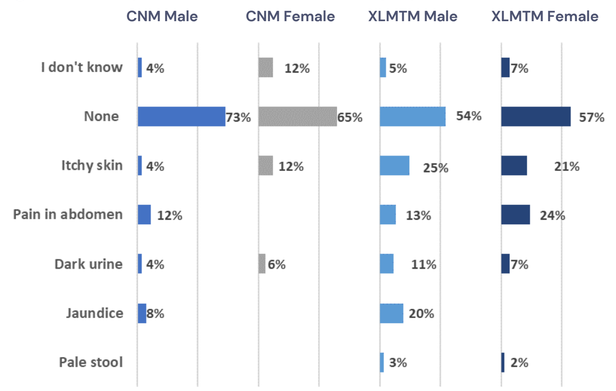


Fig. 5. Review of liver health (n=163)

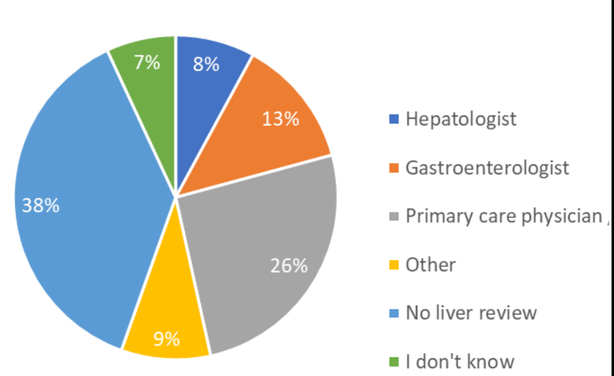


Fig. 6. Liver follow-up frequency (n=131)

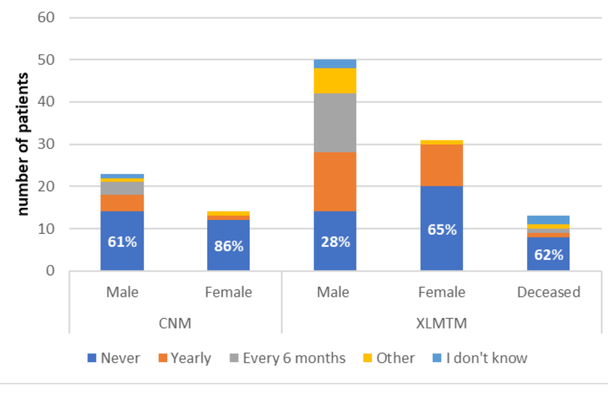


Fig. 7. Frequency of blood tests for liver function (n=149)

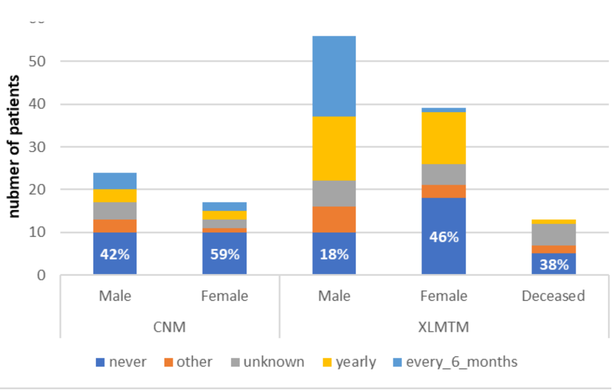


Fig. 8. Abnormal lab test values (n=144)

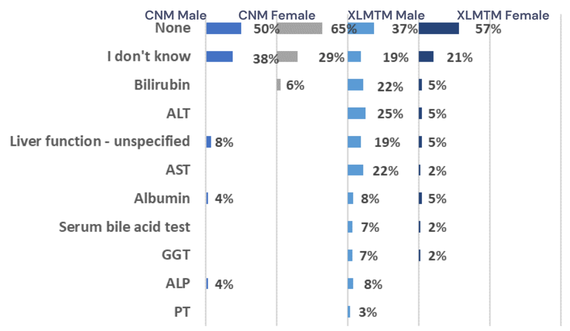


Fig 9. Ever hospitalised due to lab test values (n=146)

Data labels correspond to % of admissions that were emergency

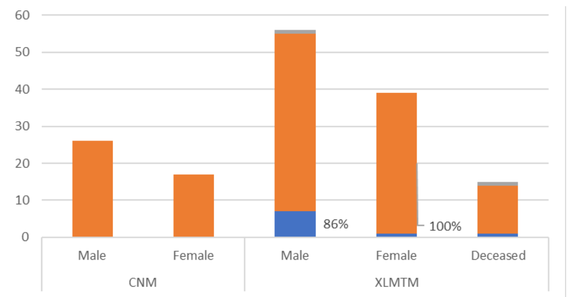


Fig. 10. Ever taken medication for liver issues (n=150)

Data labels correspond to % of subgroup/category size

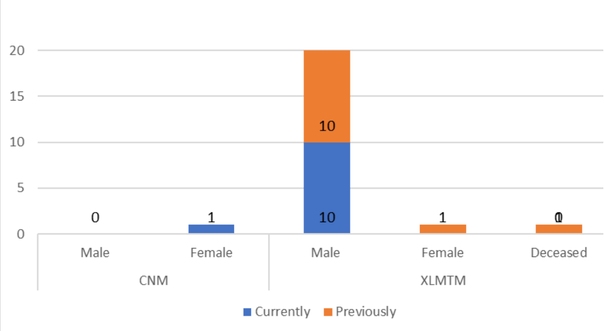


Fig. 11. How liver issues affect/ed the patient's health (n=84)

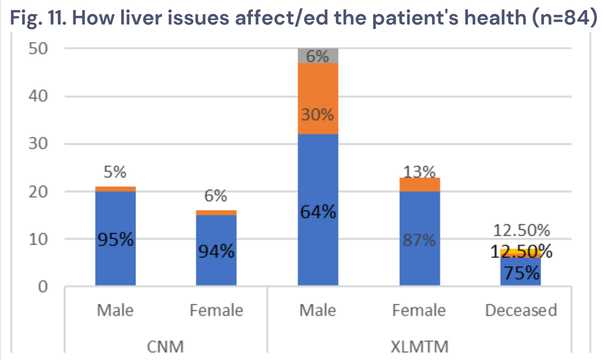


Fig 12. Liver imaging scan performed (n=158)

Imaging type	CNM		XLMTM		
	Male	Female	Male	Female	Deceased
Ultrasound	5	1	40	5	3
CT	0	0	6	2	2
MRI	1	0	6	1	1
Fibroscan	1	0	2	0	0

% of scans that were abnormal
76-100%
51-75%
26-50%
0-25%

Discussion & conclusion

The MTM & CNM Patient Registry provides a unique opportunity for stakeholders to examine real-world data in patients with these conditions, with the ability to respond rapidly to evolving data needs of the research community. The natural history data collected through this questionnaire will accelerate future research of liver related issues and inform clinical care and therapy development in XLMTM and CNM.

The liver questionnaire will remain open indefinitely as part of the main registry case report form and the data is available for third party enquiries.

Limitations of the data presented include possible reporting errors due to the element of self-selection and recall bias. Additionally, the cohort for this analysis is predominately comprised of individuals from English-speaking countries. This may introduce bias, particularly regarding socioeconomic status and healthcare equity/availability.

Key Takeaways:

- Self-reported liver abnormalities in people with CNM and XLMTM appear to be common (fig 2, 3, 4, 8, 11)
- Liver management appears to be highly variable, and patients would likely benefit from more standardised follow-up (fig 5, 6, 7)
- Healthcare utilisation indicated by lab testing, hospitalisations, imaging scans, and medications is substantial (fig 7, 8, 9, 10, 12)
- Lack of historical screening and emerging awareness of liver pathologies in this population could point to possible under reporting of liver issues (fig 5, 6, 7)
- The quantity of data collected over a 10 month period further highlights the importance of an international disease specific registry to facilitate and centralise research efforts
- This patient-driven initiative demonstrates the power of collaboration between patients and multiple stakeholders resulting in meaningful and clinically relevant evidence told directly from the patient perspective

Ref 1 - PubMed PMID 37977713 : Safety and efficacy of gene replacement therapy for X-linked myotubular myopathy (ASPIRO): a multinational, open-label, dose-escalation trial

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