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

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Introduction

X-linked myotubular and other centronuclear myopathies (XLMTM and CNM) have historically been viewed as muscle diseases, with severe respiratory muscle weakness and thus a strong emphasis on respiratory care for successful management. There is however an evolving awareness of liver-related pathology associated with XLMTM and CNM, including treatment-related adverse events in liver function 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 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

- 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.
- 472 participants (407 living individuals, 65 deceased individuals).

Objectives

- 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 discussion and review at monthly virtual meetings, and finalised through consensus. 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 report where available. We present a cross-sectional analysis of 110 liver questionnaire responses. Of the 110, genetic reports were available for 80 (74 of 100 living individuals and 6 of 10 deceased individuals). Aggregate data are reported from participants' most recent entries and response rates are shown by the denominator in figure titles.

Results

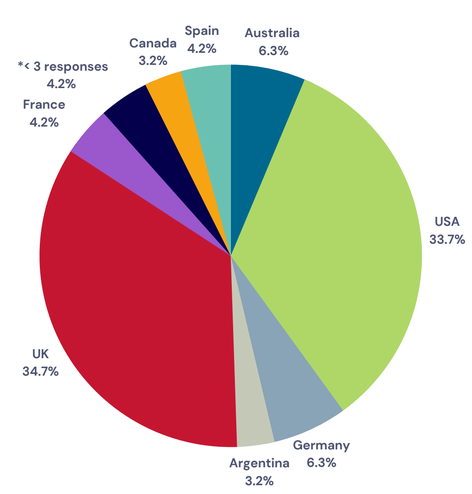
In the 3 months from 22 April (questionnaire launch) to 21 July 2023 (data cut), **110** registry participants completed or partially completed the new liver questionnaire. Fig 1 shows the breakdown of respondents by country. Presently, the main registry questionnaire is available in 10 translations; English, Brazilian Portuguese, Polish, Dutch, Italian, Hindi, French, Spanish, German and Arabic*.

*Liver questionnaire not yet available in Arabic

Demographic characteristics of 110 respondents:

- 100 living individuals (55 male, 45 female), 10 deceased patients (all male).
- Of the 100 living individuals, 31 have CNM (11 female, 20 male) and 69 have XLMTM (34 female, 35 male).
- Individual with XLMTM is defined as anyone with a mutation in the *MTM1* gene. Individual with CNM is defined as anyone with a genetic basis outside of the *MTM1* gene. The category 'XLMTM Female' contains a combination of individuals who consider themselves symptomatic or asymptomatic.
- Of the 10 deceased patients; all had XLMTM.
- Mean age (± SD) of living individuals at data cut: 32.2 ± 22.3 years (range 0-86 years).

Fig 1. Number of respondents by country of residence



*Chile, Israel, Italy, Lithuania, Malaysia, Netherlands, New Zealand, Poland, Portugal, Russia, Slovakia, South Africa, Sweden, Turkey

Fig. 2. Ever diagnosed with a liver condition (n=105)

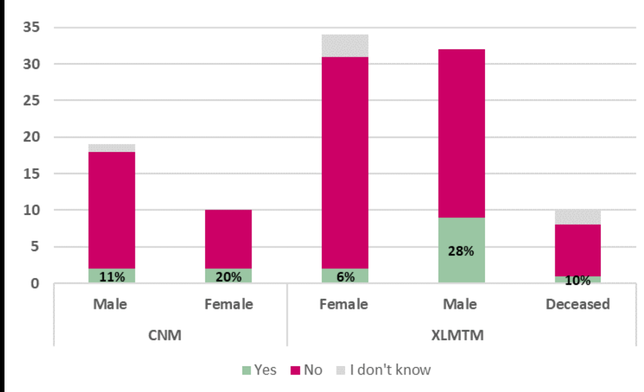


Fig. 3. Treated for high bilirubin/jaundice as a newborn (n=105)

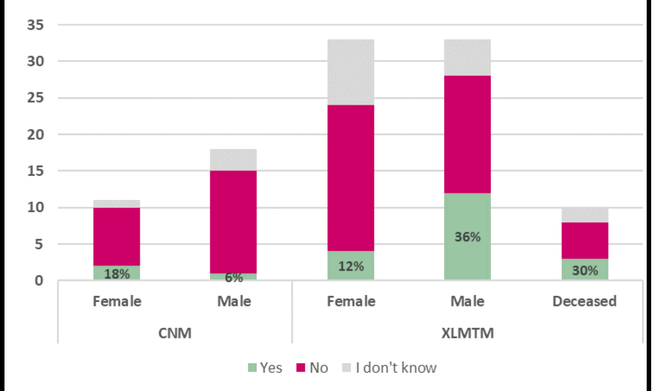


Fig. 4. Ever experienced liver-related symptoms (n=110)

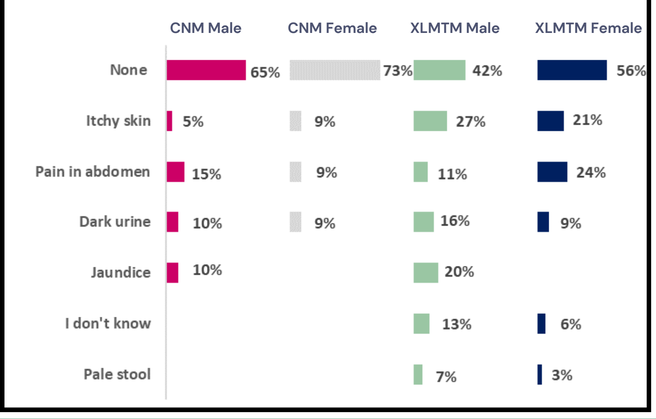


Fig. 5. Review of liver health (n=101)

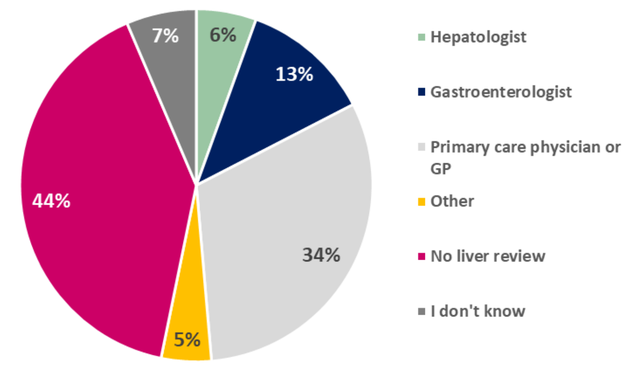


Fig. 6. Liver follow-up frequency (n=87)

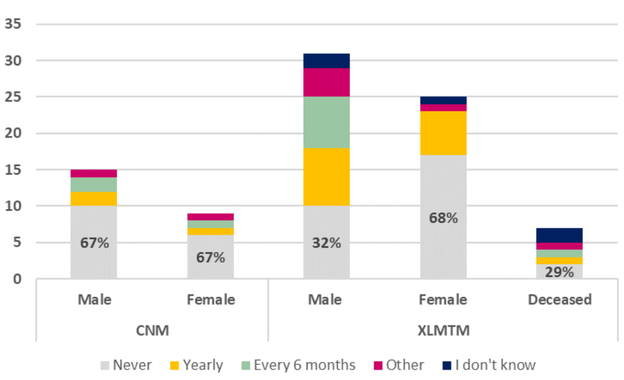


Fig. 7. Frequency of blood tests for liver function (n=98)

Fig. 8. Abnormal lab test values (n=110)

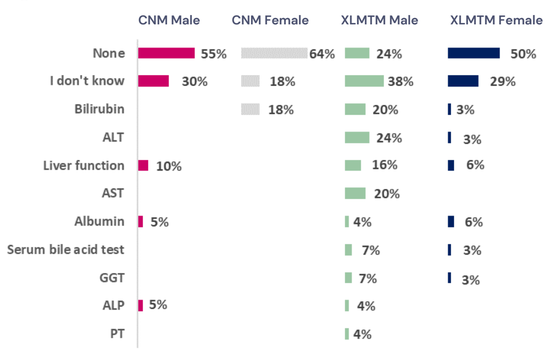


Fig. 10. Ever taken medication for liver issues (n=98)

Data labels correspond to % of subgroup/category size

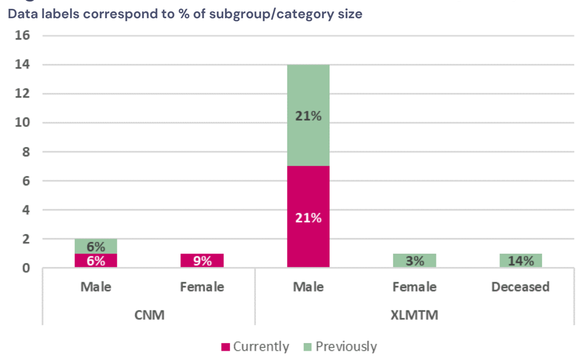


Fig 9. Ever hospitalised due to lab test values (n=102)

Data labels correspond to % of admissions that were emergency

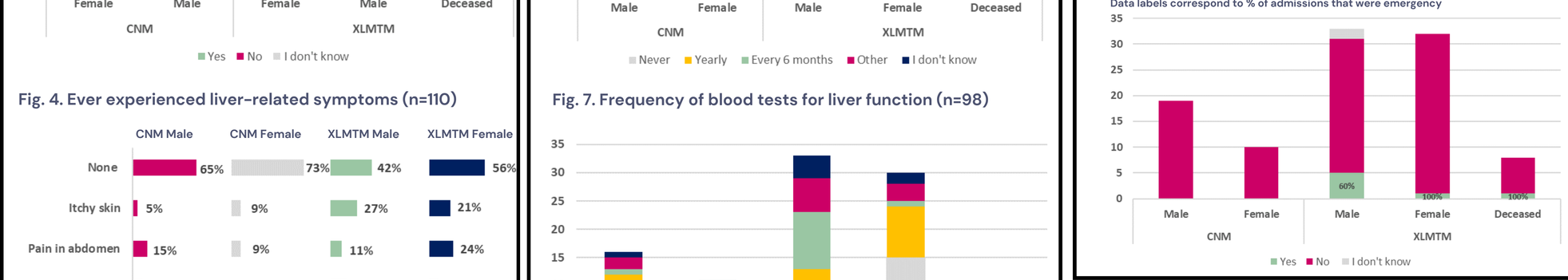


Fig. 11. How liver issues affect/ed the patient's health (n=84)

Fig 12. Liver imaging scan performed (n=42)

Imaging type	CNM		XLMTM		
	Male	Female	Male	Female	Deceased
Ultrasound	1	1	23	2	2
CT	0	0	4	0	1
MRI	0	0	4	1	1
Fibroscan	1	0	1	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, and can 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 are 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 in only a 3 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

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