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Liver involvement in Myotubular and Centronuclear Myopathy: Review of one year's data collected by the MTM & CNM Patient Registry

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Study Background

Myotubular and Centronuclear Myopathy Patient Registry:

- A patient-initiated, clinically-supported international platform collecting data Myotubular Myopathy (MTM) & Centronuclear Myopathy (CNM) patients.
- **534** participants from **56** countries (462 living and 72 deceased)
- Available in **ten** languages.
- **In partnership with patients and professional leaders** to accelerate disease enquires, expand clinical knowledge, and support evolving research.

Liver Health in Myotubular & Centronuclear Myopathy

- **Growing awareness of liver-related dysfunction** related to MTM-CNM.
- Liver dysfunction can be naturally-occurring or treatment-related.
- Four liver failure deaths recorded in X-linked MTM in the adeno-associated virus (AAV)-based gene therapy clinical trial

MTM-CNM Liver Collaborative:

- **Patient organisations** MTM-CNM Family Connection (US) and Myotubular Trust (UK) recognized the **urgent need to better understand liver-related dysfunction.**
- This **patient-driven** initiative brought together experts from clinical research, patient advocacy, and pharmaceutical industry groups to create MTM-CNM Liver Collaborative in 08/21.

Methodology

Two new questionnaires were co-designed by the *Liver Collaborative* and the *Registry* through regular virtual meetings. The working group adopted a **consensus-building approach** driven by **patient leaders** prioritizing real-world experiences of liver, nutrition and diet health.

- Data is collected directly from patients or carers, through registry platform to ensure quality and availability to stakeholders.
- Registrations verified by **review of genetic reports** where available.
- New questions promoted by *Registry*, *MTM-CNM Family Connection* and *Myotubular Trust.*
- Aggregate data reported from participants' most recent entries and response rates shown by denominator in figure titles.

Liver Collaborative Questionnaires

Liver Health Questionnaire

- Liver Health questionnaire was added in 04/23 to improve knowledge around patient liver health and assess liver screening prevalence.
- We present a cross-sectional analysis of 187 **Liver Health** responses from data collected (04/23 – 08/ 24).

Diet and Nutrition Questionnaire

- In response to research from the *Dowling Lab (Myology 2024)* discussing relationship between liver health and diet, the *Liver Collaborative* and the *Registry* created a new questionnaire on **Diet and Nutrition** (08/24).
- Focuses on **what, how** and **when** people eat to understand nutritional practices and specialised diets
- We present early findings from **56 responses** collected in first two weeks of implementation of Diet and Nutrition section.

Key Observations & Further Research Questions

Those who indicated using invasive ventilation had higher incidences of liver abnormalities.

- Are both ventilatory and liver manifestations indicators of underlying increased severity?
- Is this higher incidence unique to MTM/CNM patients?

Of living patients who indicated liver abnormalities, only half have been diagnosed with a liver condition.

- Are liver diagnoses being underreported?
- Is there a need for increased awareness/surveillance and expanding considerations of potential underlying liver disease?

Ultrasound indicated as most common form of liver imaging in respondents with liver diagnosis.

- Is ultrasound the best liver imaging modality for MTM/CNM?
- Do considerations in MTM/CNM (tracheostomies or surgical hardware) *hinder use of imaging modalities that may be more optimal for liver imaging?*

Takeaways

This unique patient-driven initiative emphasizes the value of collaboration between patients and stakeholders, resulting in clinically relevant evidence told directly from the patient perspective.

- *Registry* and *Liver Collaborative* demonstrated ability to respond to evolving research needs, mobilize stakeholders, and **prioritize real-world data**.
- **High response rates** to questionnaires in short timeframes suggests an **engaged patient cohort.**
- Collaborative effort enhances understanding of comorbidities and may guide future drug development initiatives
- Further investigation can be **aided by the *Registry***.

Liver Questionnaire Results

187 participants responded to the Liver Health questionnaire (70% increase since WMS 2023 poster)

- 167 living participants (99 male and 68 female)
- 20 deceased male patients (19 had XLMTM, 1 had RYR1 genetic mutation)*
- Mean age (±SD) of living individuals at data cut was 28.3 ± 21.9 years (range 0-87 years)
- Genetic confirmations received from 73% of respondents

Individuals with **MTM are defined as anyone with a mutation in the **MTM1 gene**. Individuals with **CNM** are defined as anyone with a recognised genetic basis of CNM, which includes mutations in **BIN1, DNM2, RYR-1, TTN**. The category **'MTM Female'** is defined as women with a mutation in the MTM1 gene and is a combination of individuals who consider themselves symptomatic or asymptomatic.*

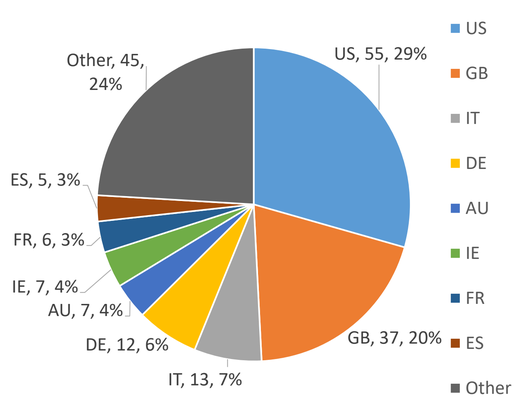

Figure 1: Country (code) of residence of Liver Health questionnaire respondents *(N=187) 'Other' includes patients from countries <5 respondents - BR, CA, RU, AR, NL, AT, CH, CL, PL, PT, SE, TR, AF, BE, BY, HU, IL, LT, MX, MY, NZ, RO, SK, ZA*

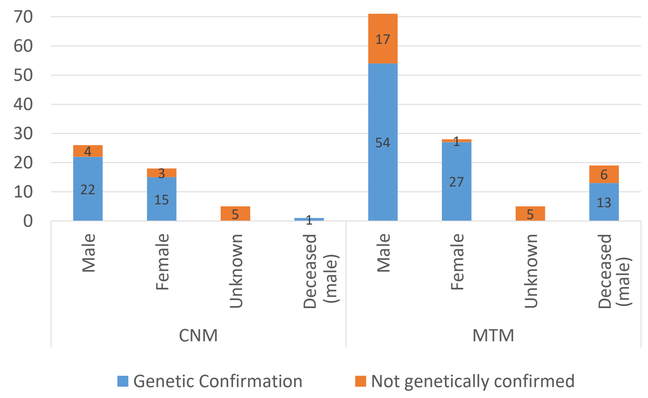

Figure 2: Neuromuscular diagnosis of the Liver Health questionnaire respondents (N=187)

Liver Health questionnaire respondents were asked about their **liver symptoms**, **labs** and **diagnosis**. Some patients reported abnormal liver lab values, among other symptoms. This includes abnormal lab values for one or more of the following: ***Serum bile acid, PT, GGT, AST, albumin, bilirubin, ALP*** and ***ALT*.**

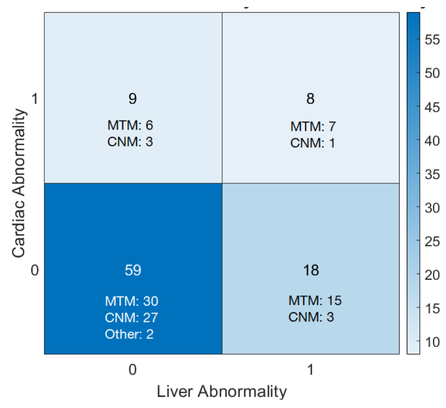

Figure 3: Correlation between abnormal liver lab values and abnormal cardiac values (*abnormal ECG and/or echocardiogram) for living, genetically confirmed patients (N=94)*

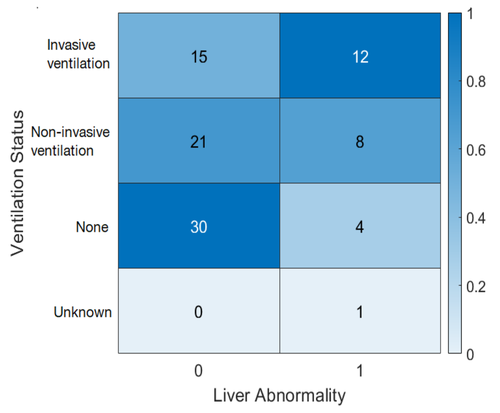

Figure 4: Correlation between abnormal liver lab values and required ventilation for living, genetically confirmed patients *(normalised by column) (N=91)*

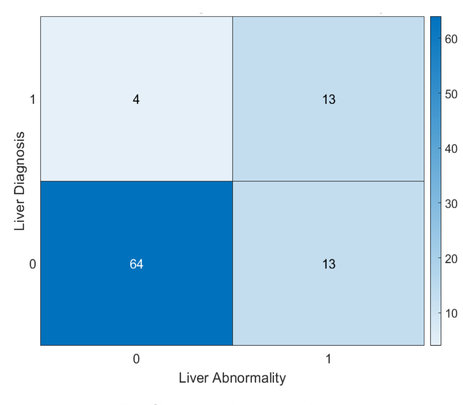

Figure 5: Correlation between abnormal liver lab values and a diagnosed liver condition *for living, genetically confirmed patients (N=94)*

Of the **187** liver questionnaire respondents, **29** patients reported a **diagnosis** of one or more **liver conditions**.

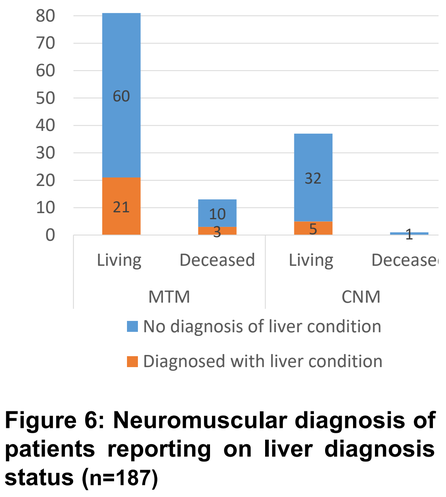

Figure 6: Neuromuscular diagnosis of patients reporting on liver diagnosis status (n=187)

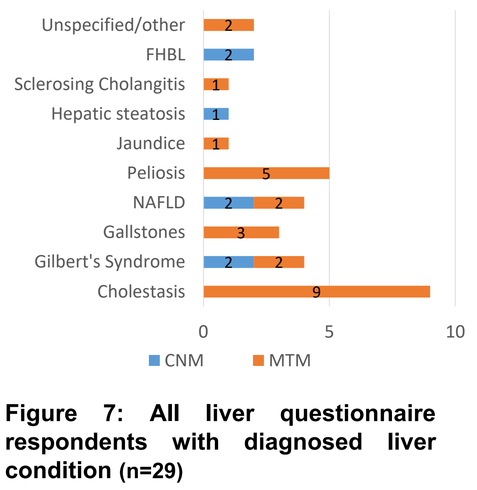

Figure 7: All liver questionnaire respondents with diagnosed liver condition (n=29)

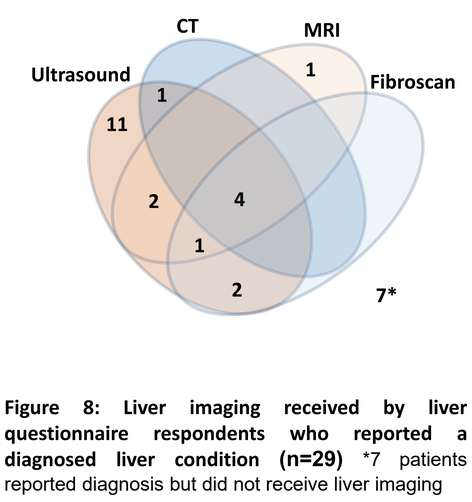

Figure 8: Liver imaging received by liver questionnaire respondents who reported a diagnosed liver condition (n=29) *7 patients reported diagnosis but did not receive liver imaging

Nutrition Questionnaire Results

56 participants responded to the Nutrition and Diet Questionnaire over a two-week period

- 51 living respondents (28 male and 23 female)
- 5 deceased male patients with XLMTM diagnosis
- Genetic confirmations received from 76% of respondents

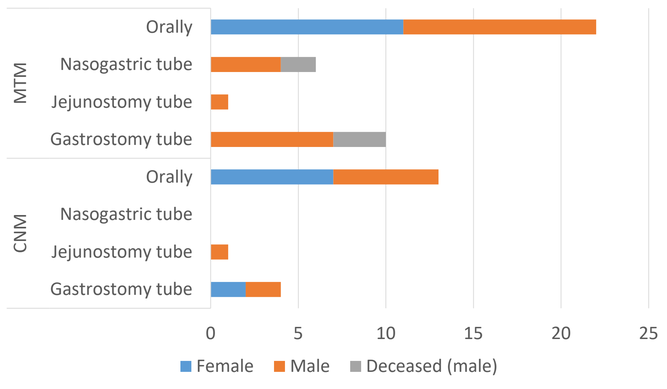

Figure 9: Patients were asked to select all current or typical modes of nutrition (n=56)

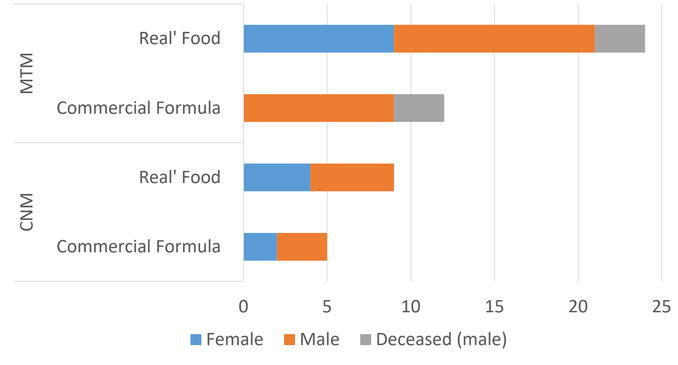

Figure 10: Reported current or typical diet for nutrition questionnaire respondents (n=56). Patients were asked to select all forms of nutrition

We are grateful to (i) registry participants for their involvement in entering data, (ii) the Liver Collaborative Working Group for their enthusiasm, commitment and input into developing the questions (iii) patient organisations MTM-CNM Family Connection and the Myotubular Trust UK for their drive, determination and enthusiasm to learn more, enrich the community and support research (iv) MTM-CNM Steering Group for on-going support and direction of the registry

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