

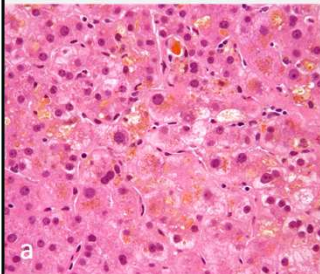
Liver Considerations for Myotubular & Centronuclear Myopathy

MTM-CNM Liver Collaborative Working Group
September 2023

The Purpose of this document

- A resource for individuals with MTM/CNM, their caregivers, and healthcare providers
- To encourage surveillance based on current understanding of potential liver involvement
- To inform community members of how they can be a part of building knowledge related to liver

Known Liver problems in MTM/CNM



Hepatic Cholestasis

- Bile can't flow and is trapped in the liver tissue
- Symptoms include jaundice, itching
- Can lead to liver failure

Hepatic Peliosis

- Blood-filled cavities in the liver
- May have no symptoms
- Potential for sudden life-threatening internal bleeding



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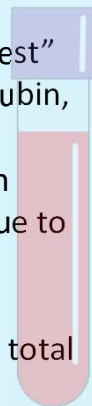
History of Liver and MTM/CNM

- Myotubular and Centronuclear Myopathy (MTM/CNM) have historically been viewed as muscle diseases
- Strong emphasis on managing breathing and other muscle-related functions
- Liver issues have been more subtle, likely underreported historically, but can be significant
- Literature includes documented rare cases of hepatic peliosis, and more commonly elevation of liver enzymes in the blood
- More recently, evolving understanding of hepatic cholestasis as another liver-related issue in MTM/CNM
- In 2 separate clinical trials for MTM/CNM, there were treatment-related adverse events associated with liver function
- 4 deaths from cholestatic liver failure in the AAV gene therapy trial
- Definitive causes, or potential underlying pre-existing liver dysfunction in those cases has not yet been fully determined nor fully understood

Suggestions for Monitoring Liver Health in MTM/CNM

Blood Tests

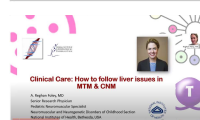
- “Liver function panel” or “liver function test”
- Should include bilirubin, ideally total bilirubin, direct bilirubin, and indirect bilirubin
- In individuals with MTM, there have been observations of total bilirubin elevated due to elevated direct bilirubin, tending toward cholestasis
- Increased understanding that monitoring total serum bile acids may also be important
- Elevation of bile acids, even without other abnormal blood results, may indicate cholestasis
- Cholestasis can get worse during illness, so individuals with MTM and a history of cholestasis should have liver functions carefully monitored during illness
- Ursodiol (ursodeoxycholic acid) medication may be an effective treatment for cholestasis



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Imaging

- To assess an abnormal appearance of the liver
- Careful imaging can assess for potential hepatic peliosis
- Liver ultrasound is usually the first screening
- Unusual or subtle ultrasound findings should be pursued with further imaging (i.e., MRI, CT)
- If ultrasound is normal & liver blood tests are normal, then chance of liver involvement is low
- Repeat ultrasound could be considered, however the exact time interval for repeat imaging is uncertain at this time
- FibroScan/elastography is increasingly used for additional followup and liver assessment
- Note: liver biopsy may have risk of bleeding



For more: watch our webinar,
“Community Conversations: Liver
Issues in MTM and CNM” at
[youtube.com/watch?v=E1WXpZsh0YI](https://www.youtube.com/watch?v=E1WXpZsh0YI)



Liver Considerations for Myotubular & Centronuclear Myopathy, continued

Help build knowledge and accelerate research

- The global MTM and CNM Patient Registry has added a section to the Registry's questionnaires, for liver information from both living and deceased patients: please visit mtmcmregistry.org
- The MTM/CNM community can help accelerate data collection and enable necessary further research on these issues by participating
- ALL affected individuals are invited, even if you have never had liver problems or symptoms, so that the Registry can get a representative sample
- It is hoped to better understand liver issues in MTM/CNM to help with day-to-day care of people with the conditions and to improve future treatment research and development
- Findings will be shared with the community

Important Links & More Info



The Myotubular and Centronuclear Myopathy Patient Registry



mtmcmregistry.org



myotubulartrust.org mtm-cnm.org

Disclaimer

While the understanding of liver involvement in MTM/CNM continues to evolve, increasing evidence of hepatic cholestasis occurrences and more rarely hepatic peliosis within the community has highlighted the importance of promoting awareness of these issues. Suggestions for liver surveillance, testing and imaging included here are based on the information known to date. While further research is necessary and information included here is evolving, the international MTM/CNM community has observed sufficient evidence of liver involvement in MTM/CNM to share suggestions for increased liver surveillance, which will hopefully result in earlier identification of liver involvement and the potential mitigation of hepatic complications. Individuals living with MTM/CNM should communicate directly with their care providers and develop an individualized plan for monitoring of the liver.

Selected Relevant Publications

- Molera, Cristina et al. "Intrahepatic Cholestasis Is a Clinically Significant Feature Associated with Natural History of X-Linked Myotubular Myopathy (XLMTM): A Case Series and Biopsy Report." *Journal of neuromuscular diseases* vol. 9,1 (2022): 73-82. doi:10.3233/JND-210712
- Shimizu, Seiichi et al. "Living-donor liver transplantation for liver hemorrhaging due to peliosis hepatis in X-linked myotubular myopathy: Two cases and a literature review." *American journal of transplantation* vol. 20,9 (2020): 2606-2611. doi:10.1111/ajt.15978
- Karolczak, Sophie et al. "Loss of Mtm1 causes cholestatic liver disease in a model of X-linked myotubular myopathy." *Journal of Clinical Investigation* 2023 (in press). doi:10.1172/JCI166275
- Dowling, James J et al. "INCEPTUS Natural History, Run-in Study for Gene Replacement Clinical Trial in X-Linked Myotubular Myopathy." *Journal of neuromuscular diseases* vol. 9,4 (2022): 503-516. doi:10.3233/JND-210781

This information sheet was developed by the MTM-CNM Liver Collaborative Working Group, a patient-driven initiative that has gathered academic researchers, medical experts, industry partners, and patient advocates in the community to seek a better understanding of liver challenges experienced by individuals living with MTM/CNM, guide the care of individuals living with MTM/CNM today, mitigate risks, and optimize the potential of future therapeutic developments.

*Members include representatives from **MTM-CNM Family Connection, Myotubular Trust, MTM and CNM Patient Registry, Kings College, Boston Children's Hospital, Harvard Medical School, Radboud UMC, National Institutes of Health, Hospital for Sick Kids, Astellas Gene Therapies, Dynacure, Flamingo Therapeutics, and Diverge Translational Science Laboratory***