Autosomal Recessive Mitochondrial Myopathy due to MICU-1 Variants

We read with interest the article by Mukherjee *et al*.[1] on a 17-year-old male with chorea, myopathy, and skeletal deformities caused by the homozygous variant c1072-1G>C in the mitochondrial calcium uptake-1 (MICU-1) gene.[1] It was concluded that the index patient expanded the phenotypic spectrum of MICU-1 variants. The study is compelling but has limitations that should be discussed.

A limitation of the study is that no muscle biopsy was performed.[1] Since the patient was presented phenotypically with proximal myopathy and since MICU-1 regulates mitochondrial cristae structure,[2] it is to be expected that morphological, immune-histological, and ultrastructural abnormalities can be documented in the muscle biopsy. According to a recent report, hematoxylin-eosin staining revealed slight fiber size variation, scattered round and angular atrophic fibers, clusters of necrotic or degenerative/regenerative fibers, internalized nuclei, and rarely myophagocytosis.[3] Histochemical ATPase reactions showed type-1 fibers predominance.[3] Immunohistochemical staining of sarcolemmal proteins with monoclonal antibodies against dystrophin, α and γ sarcoglycans, dysferlin, merosin, and beta spectrin showed labeling of almost all fibers, suggesting mild myopathic atrophy with few dispersed or small groups of degenerative/regenerative fibers.[3] In another study, muscle biopsy revealed dystrophic features, neurogenic atrophy, severe mitochondrial perturbation, altered Golgi structure, vacuoles, and altered lipid homeostasis.[4]

Another limitation is that the patient was not systematically evaluated for involvement of organs other than the brain, muscle, and bones.[1] It has been reported that MICU-1

variants also manifest phenotypically with hypertrophic cardiomyopathy.[5] Assessing cardiac involvement is critical because it can greatly impact the outcome of MICU-1 carriers.

Another limitation of the study is that the pathogenicity of the MICU-1 variant was only tested using in silico methods. In order to confirm pathogenicity, it is crucial that functional and biochemical tests are performed to confirm that this particular variant is truly responsible for the phenotype.

A fourth limitation is that alternative causes of the phenotype have not been adequately ruled out. In particular, a multisystem mitochondrial disorder due to mtDNA variants should be ruled out. We should know if nerve conduction studies point to polyneuropathy, especially given the conspicuous foot deformity. It is also not mentioned with which genetic method the variant was detected.

Another limitation is that first-degree relatives, particularly the parents, have not been genetically tested. Knowing the genetic status is crucial in assessing whether the mutation was sporadic or inherited. In this regard, we should know if a parent has manifested phenotypically with the disease.

About 50 patients with MICU-1-related myopathy have been reported to date.[6] In some of these patients, serum creatine-kinase was excessively high.[6] Some patients were also presented with seizures, microcephaly, ataxia, hypotonia, ptosis, ophthalmoparesis, and neuropathy.[6] Has the index patient manifested with any of these additional phenotypic traits? Have epileptiform discharges been recorded on EEG?

Overall, the interesting study has limitations that put the results and their interpretation into perspective. Addressing these issues would strengthen the conclusions and could improve the status of the study. Before the MICU-1 variant c.1072-1G>C is held responsible for chorea, myopathy, and bone deformities, the pathogenicity of the variant must be convincingly substantiated.

Author contribution (1. Research project: A. Conception, B. Organization, C. Execution; 2. Statistical analysis

A. Design, B. Execution, C. Review and Critique; 3. Manuscript: A. Writing of the first draft, B. Review and Critique): author JF: 1A, 1b, 1C, 3A, 3B;

Data access statement

All data are available from the corresponding author.

Ethical compliance statement

The authors confirm that the approval of an institutional review board or patient consent was not required for this work. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

Financial disclosures: the authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Josef Finsterer

Department of Neurological, Neurology and Neurophysiology Center, Vienna, Austria

Address for correspondence: Dr. Josef Finsterer, Postfach 20, 1180 Vienna, Austria.
E-mail: fifigs1@yahoo.de

References

1. Mukherjee D, Mukherjee A, Gupta S, Dubey S, Pandit A. Mitochondrial calcium uptake 1 (MICU1) gene-related myopathy with extrapyramidal signs: A clinico-radiological case report from India. Ann Indian Acad Neurol 2023;26:73-5.
2. Tomar D, Thomas M, Garbincius JF, Kolmetzky DW, Salik O, Jadiya P, *et al*. MICU1 regulates mitochondrial cristae structure and function independently of the mitochondrial Ca^{2+} uniporter channel. Sci Signal 2023;16:eabi8948. doi: 10.1126/scisignal.abi8948.
3. Mojbafan M, Nojehdeh ST, Rahiminejad F, Nilipour Y, Tonekaboni SH, Zeinali S. Reporting a rare form of myopathy, myopathy with extrapyramidal signs, in an Iranian family using next generation sequencing: A case report. BMC Med Genet 2020;21:77. doi: 10.1186/s12881-020-01016-y.
4. Kohlschmidt N, Elbracht M, Czech A, Häusler M, Phan V, Töpf A, *et al*. Molecular pathophysiology of human MICU1 deficiency. Neuropathol Appl Neurobiol 2021;47:840-55.
5. Yang Y, Du J, Xu R, Shen Y, Yang D, Li D, *et al*. Melatonin alleviates angiotensin-II-induced cardiac hypertrophy via activating MICU1 pathway. Aging (Albany NY) 2020;13:493-515.
6. Sharova M, Skoblov M, Dadali E, Demina N, Shchagina O, Konovalov F, *et al*. Case report: Unusual episodic myopathy in a patient with novel homozygous deletion of first coding exon of *MICU1* gene. Front Neurol 2022;13:1008937. doi: 10.3389/fneur.2022.1008937.

Submitted: 02-May-2023 **Accepted:** 12-Jun-2023
Published: 08-Aug-2023

DOI: 10.4103/aian.aian_383_23