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Management of Mitochondrial Disorders Should not be Limited to Specialised Centres, As the Number of Patients Now Exceeds Their Capacities

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LETTER TO THE EDITOR

We read with interest the review article by Heath *et al*. on the diagnosis and treatment of mitochondrial disorders (MIDs) in pediatric patients [Heath, O. *et al*., 2024]. It was pointed out that recent advances in next-generation sequencing and -omics technologies have laid the foundation for precision mitochondrial medicine through improved diagnostic accuracy and better insight into their pathophysiology, which promises the development of targeted treatments for MID patients [Heath, O. *et al*., 2024]. It has also been highlighted that curative treatment is currently lacking, but that the establishment of mitochondrial centers of expertise could provide the logistics for appropriate genomic testing and the basis for an integrated multidisciplinary approach to treating MID patients [Heath, O. *et al*., 2024]. The review is noteworthy, but some points should be discussed.

The first point is that excellent centers are not required to suspect, diagnose and treat MID in either children or adults. Adult neurologists and pediatricians are now sensitized enough to suspect MID based on clinical presentation and basic laboratory, imaging and functional testing. Genomic testing can be self-organized by any physician treating MID patients. Several specialized commercial and government genetic laboratories offer karyotyping, mtDNA and nDNA analysis of exomes and introns, copy number variant (CNV) analysis, and perform variant interpretation and ACMG classification. Another argument against the need for mitochondrial centers of expertise is that the number of MID patients is now too large for a single center to meet the current need for diagnostic and therapeutic management of MID patients.

The second point is that MID is usually a multisystem disease that either appears at the onset of the disease or becomes a multisystem disease as the disease progresses. Therefore, MID patients must be prospectively screened for subclinical or mildly manifesting involvement of organs commonly involved in MID. These include not only the muscles, brain, heart and endocrine organs, but also the eyes, ears, gastrointestinal tract, kidneys, skin, bone marrow, cartilage, immune system, bones and skin. The earlier the involvement of one of these organs or systems is detected, the earlier symptomatic treatment can be offered.

The third point is that cardiac involvement has not been specifically mentioned as a risk factor for mortality in MIDs [Heath, O. *et al*., 2024]. In addition to brain involvement, respiratory muscle involvement, and lactic acidosis, cardiac involvement is one of the most common causes of death in MID patients (e.g. intractable heart failure, sudden cardiac death). Cardiac impairment in MID includes dilated cardiomyopathy, hypertrophic cardiomyopathy, left ventricular hypertrabeculation (non-compaction), arterial hypertension, myocardial fibrosis, late gadolinium enhancement, sinus tachycardia, atrial fibrillation, non-sustained ventricular tachycardia, Wolf-Parkinson-White syndrome, left or right bundle branch block or sudden cardiac death [Seitun, S. *et al*., 2016; Finsterer, J. *et al*., 2020]. Therefore, all MID patients should undergo a cardiac examination using echocardiography, long-term ECG recording and possibly a cardiac MRI as well as an endomyocardial biopsy. This is important as the heart may be the first or sometimes the only organ affected in MID [Kalantari, S. *et al*., 2025].

The fourth point is that the treatment of stroke-like episodes (SLE) has not been discussed in detail [Heath, O. *et al*., 2024]. SLE are the hallmark of MELAS, but can also occur in other syndromic and non-syndromic MIDs [Yamashita, S. *et al*., 2008]. SLE are not always caused by seizures and can even occur without epilepsy. Therefore, the recommendation to treat SLEs with aggressive seizure management is not relevant for every

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patient. Since some antiepileptic drugs (ASDs) can be mitochondrial toxic [Finsterer, J, 2017], whether patients with SLE need AEDs or not should be considered very carefully. Only SLEs that manifest with seizures should be treated with ASDs.

Finally, in a review of the treatment of MIDs, it should be mentioned that lactic acidosis can be successfully reduced by hemodialysis or even peritoneal dialysis [Sari, N. Y. *et al*., 2024; Parapiboon, W. *et al*., 2025].

In summary, this interesting review has limitations that put the results and their interpretation into perspective. Removing these limitations could strengthen the conclusions and reinforce the message of the study. All outstanding questions must be clarified before readers uncritically accept the study's conclusions. The management of MIDs should not be limited to specialized centers as the number of patients now exceeds their capacity. Treatment of MIDs should be individualized and tailored to the specific needs of each patient.

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