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Letter to the Editor

Mitochondrial Myopathy can Occur in Isolation or be part of a Multisystem Mitochondrial Disorder

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We read with interest Beecher *et al.*'s article on a retrospective chart review of 94 adult patients with mitochondrial myopathy diagnosed at the Mayo Clinic between 2005 and 2021 [1]. Ten patients had a single mtDNA deletion, 38 patients an mtDNA point mutation, 12 patients had multiple mtDNA deletions or mtDNA depletion, and 29 had a nuclear defect [1]. The most frequently mutated genes were *POLG1* and *MT-TL1* [1]. The most common phenotypes included non-syndromic multisystem disease, MELAS, limb myopathy, CPEO, and CPEO plus [1]. Isolated myopathy was found in 27%, CNS involvement in 69%, and cardiac involvement in 21% of patients [1]. Thirty patients died at an average age of 55 years and cardiac involvement was associated with increased mortality [1]. The study is excellent, but some points need discussion.

The first point is the discrepancy between the objectives and the results of the study [1]. The aim was to describe the genotypic and phenotypic spectrum of 94 patients with mitochondrial myopathy, but only 27% of these patients had isolated myopathy [1]. It would have been less ambiguous to talk about mitochondrial disorders in general rather than mitochondrial myopathies specifically.

The second point is that we do not agree with the statement in the abstract that mitochondrial myopathies are often overlooked in adulthood [1]. On the contrary, adult patients provide more commonly detailed information about their muscular symptoms and can often describe them in more detail than pediatric patients. In addition, paediatric patients with mitochondrial myopathy often suffer from a multisystem mitochondrial disorder that involves the brain and leads to developmental delays and cognitive impairment, making it impossible to obtain a detailed and comprehensive medical history.

A third point is that five patients had multiple mtDNA deletions or mtDNA depletion, but no nuclear DNA variant [1]. However, there is no mention of which genes were examined. Multiple DNA deletions or mtDNA depletion are most commonly associated with mutations in *POLG1*, *POLG2*, *ANT*, *SLC25A4*, *PEO1*, or *twinkle* [2]. Have these five patients undergo panel testing for these genes or whole exome sequencing (WES) to determine the underlying cause?

A fourth point is that only 42 patients had a muscle biopsy [1]. We should know what criteria were used to diagnose mitochondrial myopathy in the remaining 52 patients. Diagnosis of mitochondrial myopathy based on clinical presentation, blood tests, and needle electromyography alone could be misleading because mitochondrial myopathy, especially when not associated with multisystem involvement, may mimic myopathy due to other causes. Did the 52 patients without a muscle biopsy have CPEO or carry a variant known to be associated with mitochondrial myopathy?

A fifth point is that the cause of rhabdomyolysis was not described in detail in the 6 patients who suffered from it according to table 1. Was the history of these patients positive for seizures, medications known to cause muscle necrosis, mechanical trauma, intoxication, infectious diseases, muscle ischemia, electrolyte imbalances, or was rhabdomyolysis attributed to the underlying metabolic defect [2]?

A sixth point is that it is not mentioned how many of the 94 patients included had axial or respiratory muscle involvement [1]. Since respiratory muscle impairment can greatly influence the outcome of these patients [3] and may be associated with the question of whether these patients should be on long-term mechanical ventilation or not, it is important to know how many of them had respiratory dysfunction due to muscle impairment. Were there any patients who required full respiratory support? How many had nightly or 24h CPAP ventilation?

A seventh point is that intestinal pseudo-obstruction, which is common in MNGIE, MELAS, and Leigh syndrome, has not been considered and discussed as a cause of poor prognosis. Since, according to table 1 [1], one third of the included patients had gastrointestinal involvement, it should be specified which type of gastrointestinal involvement these 30 patients suffered from. The extent to which gastrointestinal involvement contributed to mortality in the entire cohort should also be reported.

An eighth point is that measurement of serum lactate and pyruvate during light exercise was not mentioned as a tool for screening patients with suspected mitochondrial myopathy. Lactate stress has proven to be a valuable and simple tool to decide whether patients with suspected mitochondrial myopathy should be further and more invasively evaluated [4].

In summary, the excellent study has limitations that male the results difficult to interpret. Removing these limitations could strengthen and support the study's message.

Declarations

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