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Authors' response

The issue raised by Finsterer J[1] is valid and well noted. Our study being a pilot study, was conducted with limited resources, therefore, only common mutation and large deletions were looked into. Mitochondrial sequencing results in peripheral blood DNA may not rule out mitochondrial disorders as the involvement may be tissue specific and this is the major limitation to confirm mitochondrial disorders. Another valid point was that dynamic lactate levels were not done. This again would have increased the period of stay in the hospital which was an additional financial burden for which most patients did not comply. The concern is justified and will be taken into consideration in future studies. The CPK levels were in the normal range in all except in one whom it was 201 U/l (normal up to 200).

The concern to include lipid storage disease which requires muscle biopsy is valid but as mentioned muscle biopsy is an invasive method for which Ethics Committee approval was not taken and hence not done.

The author's concern about considering lysosomal storage disease (LSD) as a differential was considered though not mentioned. It is to be noted that none of the patients had muscle weakness or hypotonia which are usual presentations along with or without organomegaly in lysosomal storage disease. Since there were no specific signs or symptoms warranting to cardiac and brain imaging hence it was not done, however, as rightly pointed out by the author, this should be considered in patient work up.

Though family history taking was not mentioned in the article, none of the participants had a family history of muscle problem or exercise intolerance to the best of our knowledge. Following the correspondence by the author[1], sequencing for mitochondrial genome was undertaken in 10 patients. Most of the variants found on further sequencing in these 10 patients till date are reported as polymorphisms in the database[2]. One variant 3920 C>T was found to be homoplasmic. It is conserved across the species, and involves NADH-ubiquinone oxidoreductase chain 1 protein (ND1) region with amino acid change Ser205Phe (Serine to Phenylalanine at codon250)[2]. A nearby variant 3919 T>C leading to the same amino acid change Serine205Proline has been found to segregate with the disease of Leber Hereditary Optic Neuropathy (LHON)[3]. However, our patient did not have eye symptoms till date and does not fit into the phenotype and the variant, therefore remains to be of uncertain significance. Moreover, the percentage of homoplasmy could not be ascertained, but presumed to be >80 per cent. Next generation sequencing would probably give the accurate percentage of homoplasmy due to better accuracy[4]. Functional studies may further clarify the pathogenicity of the variant. Further studies are planned and would help in clarifying the issues further. The genetics of mitochondrial disorders is complex and a better designed study with a large sample size is indicated.

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