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Letter to Editor

Alternative Causes must be Ruled out Before Single mtDNA Deletions are Made Responsible for Macrocytosis

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Letter to the Editor

We read with interest the article by Almarzooqi et al. on a 60-years-old female with a mitochondrial disorder (MID) due to a single mtDNA deletion with a heteroplasmy rate of 40% in muscle that manifested phenotypically with Chronic Progressive External Ophthalmoplegia (CPEO), macrocytosis without anemia, and hypersegmented neutrophils [1]. Alternative etiologies of macrocytosis, such as hyper-homocysteinemia, vitamin-B12 deficiency, hepatic disease, hypothyroidism, myelodysplastic syndrome, medication effect, Chronic Obstructive Pulmonary Disease (COPD), and alcohol misuse were ruled out [1]. Additionally, 16 patients with a single mtDNA deletion but without macrocytosis were compared to 10 patients with an mtDNA deletion and macrocytosis [1]. The study is excellent but raises concerns that should be discussed.

A limitation of the study is that it remained unclear whether the single mtDNA deletion in the index patient was inherited from the mother or occurred sporadically. Four percent of single mtDNA deletions follow a maternal trait of inheritance [2]. Knowing whether the mtDNA deletion was inherited or due to a sporadic mutation is crucial not only for genetic counselling but also for assessing if heteroplasmy increased between generations and therefore contributed to the phenotypic expression and heterogeneity. We also should know in this regard, whether the mother underwent a clinical exam or was prospectively investigated for mild or subclinical manifestations of a MID.

A second limitation is that it was not reported what drugs the index patient was regularly taking and if these medications were tolerated without side effects. Of particular interest is whether the index patient and the 10 patients with mtDNA deletions plus macrocytosis were ever undergoing chemotherapy, had epilepsy, or had an autoimmune disease. Because, mtDNA deletions can go along with epilepsy, it is crucial to know whether any of the included patients was on a regular Anti-Seizure Drug (ASD) therapy. Drugs known to cause macrocytosis include sulfasalazine, hydroxyurea, methotrexate, azathioprine, zidovudine, antiretroviral agents, trimethoprim, valproic acid, carbamazepine, and phenytoin [3].

A third limitation is that several causes of macrocytosis were not ruled out. Causes of macrocytosis not considered in the study were reticulocytosis, hemodialysis, pregnancy, and anaplastic anemia. We should know whether any of these conditions were found in the index patient or any of the 10 patients previously diagnosed with macrocytosis. We should know whether any of the included female patients was pregnant. Vitamin-B12 deficiency can be due to Addissonian anemia, after gastrectomy or ileum resection, bacterial overgrowth, or parasitic infestation, HIV, diet, or pernicious anemia. Folate deficiency can be due to dietary deficiency, malabsorbtion, increased demand due to hemodialysis, leukemia, rapid cell turn-over, third trimenon of pregnancy, or increased urinary excretion. Was the history positive for any of these conditions?

A fourth limitation is that neither the index patient nor the other 26 patients with an mtDNA deletion were investigated for biochemical abnormalities in clinically affected tissues to assess which respiratory chain complexes exhibited a reduced activity. Of particular interest is whether the mtDNA deletion resulted in a single or multiple respiratory chain complex deficiency(ies).

Because heteroplasmy rate was 40% in skeletal muscle we should know whether the index patient also manifested with myopathy, particularly if there was weakness of skeletal muscles other than the extra-ocular muscles. In this regard, we should also know whether the index patient complained about easy fatigability, exercise intolerance, muscle cramps, myalgia, sore muscles, or easy fatigability.

Overall, the interesting study has limitations that call the results and their interpretation into question. Clarifying these weaknesses would strengthen the conclusions and could improve the study. Before blaming single mtDNA deletions for macrocytosis, alternative causes should be ruled out.

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that could be construed as a potential conflict of interest.

Compliance with Ethics 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.

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