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Impaired Bone Mineralization in Mitochondrial Disorders

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In a recent article, Gandhi et al. reported about a retrospective study of a cohort of 80 pediatric and adult patients with genetically confirmed mitochondrial disorder (MID) of whom 73% presented with at least one cause of poor bone health [1]. We have the following comments and concerns.

We do not agree with the statement that understanding about bone health predominantly derives from children [1]. There are a number of reports about osteoporosis, osteopenia, endocrine impairment, and renal disease resulting in poor bone health in adult patients with MID [2varanasi99].

Bone health refers also to the presence or absence of malignancy or benign neoplasms, of which the prevalence has been shown to be increased in MIDs [3fi]. Was the history in any of the 80 patients positive for osteosarcoma, osteoma, Ewing sarcoma, chondrosarcoma, or multiple myeloma?

A further cause for poor bone health, not mentioned in the article, is pituitary adenoma. Though only rarely reported, it is fairly frequent in non-specific syndromic MIDs, also known as mitochondrial multiorgan disorder syndrome (MIMODS). Was history in any of the 80 patients positive for pituitary adenoma or were cererbral imaging studies reviewed for pituitary abnormalities?

What were the causes of death in the 11 patients mentioned in table 1 who died during follow-up? Which was the mean duration of the interval between diagnosis and decease?

Among those with a primary mtDNA mutation, was bone health correlated with the heteroplasmy rate? It is conceivable that bone health may be negatively correlated with the mutation load.

Among the patients with a lifetime history of bone fracture, nine were under antiepileptic drugs (AEDs) [1]. AEDs have been shown to impair bone health [4]. Low bone mineral density, osteopenia/osteoporosis, osteomalacia, rickets, altered concentration of bone turnover markers, and fractures were particularly reported with phenobarbital (PB), phenytoin (PHT), carbamazepine (CBZ), valproate (VPA), oxcarbazepine (OXC), levetiracetam (LEV), and lamotrigine (LTG) [5hamed]. Which AEDs were the 9 patients mentioned in table 4 taking?

A quarter of the included patients were wheel-chair bound [1]. It would be helpful to know since when these patients required a wheel chair already. Was bone health among these patients particularly diminished?

We should be informed how many had vitamin-D deficiency and did not receive replacement therapy?

What was the indication for corticosteroids in 8 patients? Steroids may have a detrimental effect in some MIDs, particularly those with Kearns-Sayre syndrome [6fi].

Since primary MIDs are genetic disorders and frequently inherited, we should be informed in how many of the 80 cases the family history was positive for bone health impairment. In how many was the causative mutation regarded as inherited and in how many as sporadic?

Poor bone health in patients with Duchenne muscular dystrophy is not only due to muscle weakness and falls with traumatic fractures but also due to the fact that most of these patients receive steroids usually on from age 10y (e.g. deflazacort).

Overall, this interesting study may be more meaningful if more clinical data were provided, if the heteroplasmy rate of mtDNA mutations would have been correlated with bone health, if AEDs that were taken and the duration of immobility would have been detailed, and if a detailed family would have been provided.

Keywords: mitochondrial, mtDNA, phenotype, genotype, fractures, osteoporosis

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