Indicators of mitochondrial disease

Indicadores de doença mitocondrial

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Dear Editor,

We read with great interest the article published by Silva et al. entitled "Steatosis of indeterminate cause in pediatric group: is it a primary mitochondrial hepatopathy?".[1] In the article, the authors hypothesize that hepatosteatosis with unknown etiology presented by group of pediatric patients may be mitochondrial disease. They attribute their idea to mitochondrial structural abnormalities detected through electron microscopy examination. They indicate that they have not found any significant difference in mitochondrial density between the control and other groups. To explain this situation, they suggest that the normal distribution of cytosol becomes altered because of the existence of lipid vacuoles in hepatocytes.

We would like to comment on their findings. First of all, in mitochondrial disease, mitochondrial proliferation almost always occurs because of mitochondrial dysfunction. Absence of increased mitochondrial density is not compatible with mitochondrial disease. Furthermore, the most reliable indicator of mitochondrial density is the level of citrate synthase activity in the tissue.[2] Secondly, mitochondrial structural alterations do not provide strong enough evidence to indicate mitochondrial disease in the absence of other evidence, because many reasons other than mitochondrial disease can cause mitochondrial structural abnormalities.[3,4] Thirdly, indicators for mitochondrial disease, such as lactic acid levels in blood, muscle histochemistry or mitochondrial enzyme activity were not evaluated in the article by Silva et al.[1] At least mitochondrial deoxyribonucleic acid (mtDNA) alterations should be analyzed, because almost all mitochondrial disease involves mtDNA deletion, mtDNA depletion, mtDNA point mutation or nuclear deoxyribonucleic acid (nDNA) alterations.[5] So, in our opinion, the evidence is not strong enough to hypothesize that this group of patients might have a mild form of primary mitochondrial hepatopathy.

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RESPONSE TO LETTER TO THE EDITOR

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We have carefully analyzed the remarks directed towards the original article "Steatosis of indeterminate cause in a pediatric group: is it a primary mitochondrial hepatopathy?".[1] Firstly, we would point out that the aim of our study was to evaluate and characterize "pure" steatosis in the pediatric group by means of morphological and morphometric analysis. This aim focused mainly on diagnostic characterization of the group of patients studied and not on elucidating the molecular mechanisms of the disease.

Some authors[2-5] have taken the view that increased mitochondrial density, which may confer an oncocytic appearance on hepatocytes, is a major characteristic of microvesicular steatosis in nonalcoholic fatty liver disease (NAFLD). It is a possibility that increased mitochondrial density is an important causal factor of mitochondrial disease. Another indication of mitochondrial impairment is the frequent observation of megamitochondria, often showing crystalline inclusions. More recently, this has been indirectly correlated with oxidative stress in NAFLD.[6]

We agree that complementary analyses, such as determination of serum lactic acid and studies on mtDNA, make it possible to obtain more conclusive results. However, our study was retrospective, with material originating from biopsy files, which made it impossible to perform complementary analyses. Despite these limitations, we believe that the results support our conclusions, especially in relation to better characterization of mitochondrial morphological changes that are present in cases of fatty liver in children, for which causes such as metabolic diseases, obesity, undernutrition, infections and others were investigated and ruled out.

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