

LETTER TO THE EDITOR**Liability of sepsis is hardly determined by the COXI variant m.6459T>C**

With interest we read the article by Shen et al about seven members of a three-generation Han Chinese family in which four members carried the mtDNA variant m.6459T>C in the COXI gene.¹ The other three members of the family did not carry the mutation.¹ Interestingly, all four mutation carriers had a history of sepsis,¹ which was fatal for three of the mutation carriers.¹ Mononuclear cells (B-lymphocytes, T-lymphocytes, monocytes) were infected with EBV. Afterwards, T-lymphocytes and monocytes were inhibited and B-lymphocytes stimulated to proliferate.¹ Measurement of reactive oxygen species (ROS), the mitochondrial membrane potential, the apoptosis status, and the mitochondrial ATP level revealed that mutation carriers had increased ROS and apoptosis and decreased mitochondrial membrane potential and ATP-levels compared to non-mutation carriers.¹ The authors concluded that m.6459T>C mutation carriers are prone to experience sepsis. We have the following comments and concerns.

We should be informed at which time point of the history blood was taken from the seven probands. Since three of the mutation carriers had died already, blood from these three subjects must have been drawn for the investigation prior to death. Was blood drawn during the infection in all four patients experiencing sepsis or was it taken during a period of healthiness? The time point at which blood was drawn is crucial as lymphocytes may have different potentials to react during infection and during health.²

As the pedigree are small and the three affected males (II-1, II-2, II-4) did not have children the occurrence of sepsis in the mutation group could have followed also an autosomal dominant trait of inheritance. Thus, also other hereditary immunodeficiency syndromes need to be excluded, such as immunodeficiency due to TWEAK mutations³ or hyperimmunoglobulin E syndrome. Were the levels of immunoglobulins normal prior to sepsis in the four mutation carriers? Was the status of the cellular immune system normal prior to the infection?

A further shortcoming of the study is the low number of subjects in the mutation and non-mutation group.¹ Only four patients constituted the mutation group and only three patients the non-mutation group.¹ The low number of patients represents a strong limitation for statistical comparisons, as both groups are heavily underpowered.

Though we agree that immune cells may be affected in patients with a mitochondrial disorder (MID),^{4,5} MIDs usually manifest as a multiorgan syndrome, affecting the brain, muscles, peripheral nerves,

eyes, ears, endocrine organs, the myocardium, the gastrointestinal tract, the lungs, the kidneys, the blood cells, the cartilage, and the skin in addition to the immune cells.⁶ Thus, it is important to prospectively investigate carriers of mtDNA mutations for clinical or subclinical involvement of the other organs. We also should be informed if biochemical investigations of the muscle or of skin fibroblasts or immunohistochemistry revealed COX-deficiency, respectively, reduced activity of the complex four of the respiratory chain.

Since phenotypic manifestations of mtDNA variants strongly depend on the mutation load of the variant (heteroplasmy rate), we should be informed about differences of the mutation loads between the four mutation carriers. Heteroplasmy rates not only in lymphocytes but also in hair follicles, buccal mucosa cells, skin fibroblasts, muscle, and urinary epithelial cells should be compared. Differences of ROS, apoptosis frequency, membrane potential, and ATP levels between mutation carriers and controls can be reliably assessed only if heteroplasmy rates are determined and compared between the included subjects.

As MIDs frequently manifest with lactic acidosis, it would be interesting to know if there were any differences between the mutation and non-mutation group with regard to lactate concentrations in the serum and brain.

Overall, we doubt that the m.6459T>C variant was responsible for sepsis in the four mutation carriers described. Arguments against the speculation that the variant is responsible for the liability to infections are that the pathogenicity of the variant was not confirmed, that heteroplasmy rates were not considered, and that manifestations in organs other than immune cells were not described.

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