

LETTER TO THE EDITOR

LIVER PATHOLOGY IN HEPATO-CEREBRAL MITOCHONDRIAL DEPLETION SYNDROMES DUE TO *POLG1*, *DGUOK*, OR *MPV17* VARIANTS

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With interest we read the article by Pronicki *et al.* about a histopathological study of liver specimens (biopsy $n = 5$, autopsy $n = 8$) from 13 children with the hepato-cerebral form of mitochondrial depletion syndrome due to pathological variants in *POLG1*, *DGUOK*, and *MPV17* [1]. The authors found depletion of mtDNA in the liver, ranging from 0.01 to 11% [1]. Five of the 13 patients had epilepsy [1]. All patients died from liver failure [1]. We have the following comments and concerns.

We do not agree with the notion that mitochondrial depletion syndromes exclusively follow an autosomal recessive (AR) trait of inheritance as mentioned in the introduction [1]. Particularly mitochondrial depletion syndrome due to *RRM2B* mutations may be inherited in an autosomal dominant (AD) way [2]. Also transmission of mutations in *TWINKLE* may follow an AD trait of inheritance [3].

Since mitochondrial depletion syndrome may go along with reduced activity of a single or multiple respiratory chain complexes [4], we should be informed about the results of biochemical investigations of the presented liver or muscle specimens of the included patients. Which of the respiratory complexes were reduced in activity? Was there reduction of single or multiple complex activity?

Ultrastructural investigations of mitochondria in mtDNA depletion syndromes show that mitochondria may be abnormal in number, size, structure, and dynamics [5]. Thus, we should be informed about the ultrastructural findings in the 13 included patients. It would be also helpful to know the results

of the Gomori trichrome stain, and of the NADH-, SDH-, and COX stainings.

Since blood, muscle, and liver were used for genetic analysis, we should be informed if the amount of mitochondrial DNA (mtDNA) depletion was different between these tissues. Particularly we would like to know if there was depletion also in clinically non-affected tissues.

Since five patients had epilepsy we should be informed about the antiepileptic drugs these patients received. Particularly from valproic acid, phenytoin, carbamazepine, and phenobarbital it is known that they are potentially mitochondrion-toxic [6]. Was deterioration of the phenotype in these five patients associated with the antiepileptic drug therapy? Since epilepsy in mitochondrial depletion syndrome may also respond to ketogenic diet, we should know how many of the included patient received it.

Overall, this interesting study could be more meaningful if depletion rates from the liver were compared with depletion rates from other tissues, if detailed information about the antiepileptic regimen were provided, if results of immune-histochemical investigations of the specimens were provided, and if electron microscopy findings were presented.

References

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