

## Letter to Editor

# Severity of Diabetes in MELAS and MERRF May Rather Reflect Genotype and Comorbidities than Histology of Islet Cells

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### Abstract:

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## LETTER TO THE EDITOR

With interest we read the article by Norose, T. *et al.*, 2020 about the histological and immune-histological findings of islet cells in two patients with mitochondrial diabetes (Norose, T. *et al.*, 2020). One patient was diagnosed with mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) syndrome due to the variant m.3243A>G (patient-1) and the second patient was diagnosed with myoclonic epilepsy with ragged-red fibers (MERRF) syndrome due to the variant m.8344A>G (Norose, T. *et al.*, 2020). Patient-1 required insulin, whereas patient-2 did not require any anti-diabetic treatment (Norose, T. *et al.*, 2020). It was concluded that the severity of diabetes correlates with the severity of the histological and immune-histological findings on autopsy (Norose, T. *et al.*, 2020). We have the following comments and concerns.

We do not agree with the conclusions that the different histological findings in the two patients correlate with the severity of diabetes. First, MELAS and MERRF are completely different disorders, why simply the genotype can explain the difference between the two patients. Second, phenotypic expression of mtDNA variants strongly depends on heteroplasmy rates, mtDNA copy number, and the haplotype (Scholle, L. M. *et al.*, 2020). Thus, it would be interesting to know if heteroplasmy rates and mtDNA copy numbers were different in islet cells or other clinically affected tissues between the two patients. We should also know if the two patients carried the same haplotype or not. Furthermore, we should know if there were alterations in the nuclear background and if the two patients had variable co-morbidities. Third, differences in histology and immune-histology could be also due to previous pancreatitis in either patient. Pancreatitis has been repeatedly reported as a clinical manifestation of mitochondrial disorder (MIDs) (Duran, G. P. *et al.*, 2011), why we should know if the previous history was positive for acute or chronic pancreatitis in either patient or if post-mortem histological findings on autopsy were indicative of previous pancreatitis. Fourth, we should know if there were any indications for affection of the cellular immune system in either patient, which has been previously reported (Finsterer, J., & Zarrouk-Mahjoub, S. 2017), and if titers of antibodies against islet cells or mitochondria were different between the two patients.

Furthermore, we do not agree that atrophy of islet cells necessarily means reduced production of insulin. Morphology not necessarily correlates with function. Thus, we should be informed about serum insulin levels and serum levels of the C-peptide to assess if islet cell function was truly reduced or not.

Since both MELAS and MERRF syndrome are multisystem diseases, potentially affecting liver and frequently the muscle (Ban, S. *et al.*, 1992), we should know if elevated blood glucose was due at least partially due to increased solution of liver or muscle glycogen or if gluconeogenesis was increased.

Since patient-2 had an HbA1c value of 6.9% (n, 4.6-6.2%) and diabetes was diagnosed, we should know why no anti-diabetic drugs or insulin were given. Was blood glucose well-controlled simply by diet?

Missing are the current blood chemical findings and the medication the two patients were taking at the time of decease. From various drugs it is known that they are potentially pancreato-toxic (e.g. valproic acid). Serum lactate may influence blood glucose levels as well and may have been different between the two patients.

Overall, the interesting, valuable study has some shortcomings which should be addressed before drawing final conclusions. Particularly, we need to know more about the genetic background, the current medication, and about the comorbidities of both patients before attributing different severity of diabetes only to different morphology of islet cells.

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