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LETTER TO THE EDITOR

Reply to Josef Finsterer "MELAS requires broad clinical and genetic work-up"

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We thank Dr Finsterer for his interest in our work [1] and for his precise comments [2]. First of all, we want to emphasize the fact that our paper highlighted a potential useful therapy in treating diabetes in MELAS, so that the clinical neurological environment was duly mentioned but does not represent the main focus of the article.

We agree that the clinical manifestations of MELAS depend on heteroplasmy rates, as in other mitochondrial disorders (MID). In our patient, genetic examination revealed a m.3243 A > G point mutation in heteroplasmy in lymphocytic and urinary epithelial cells, whereas no data are available for other tissues.

At hospitalization, the first diagnostic hypothesis was an inflammatory lesion of the central nervous system (CNS); on the basis of this hypothesis, and before a certain diagnosis of MELAS, a treatment with high-dose glucocorticoids was initiated, considering that it could have some beneficial effect also in some patients with MELAS. The patient remained monitored in the hospital during this treatment, with no relevant detrimental effects on glucose control.

Metformin has been associated with lactic acidosis, even though the specific risk induced by the drug seems to be very low. Metformin treatment does not usually increase lactate levels [3], although mild elevation may occur after physical exercise. There is no evidence that either baseline or post-treatment fasting lactate levels are predictive of metformin-induced lactic acidosis. Therefore, we think that the determination of lactate levels is scarcely useful.

Aseptic pancreatitis can be a manifestation of MID. Anyway, our patient was asymptomatic for pancreatitis and ultrasound abdomen was normal, as well as alpha amylase and lipase levels.

All the items regarding the discrimination of the hyperintense lesion on MRI have been evaluated once the diagnosis of MELAS was suspected. The right parieto-temporal lesion was hyperintense on diffusion-weighted imaging (DWI) sequence and on apparent diffusion coefficient (ADC), and it was not confined to a vascular territory. MRI was performed suspecting an inflammatory disease of the CNS. In such cases, magnetic resonance spectroscopy (MRS) cannot be considered among the first diagnostic tests contrarily to lumbar puncture. MDI is among the differential diagnoses of white matter disorders, but they are much less frequent than inflammatory diseases. In the general population, the prevalence of white matter hyperintensities is 11–21% in adults [4], whereas the prevalence rate for mtDNA mutations is 20 per 100,000 [5].

After genetic result, the diagnosis of MELAS was done. Cerebrospinal fluid's lactate level was determinate by lumbar puncture. Therefore, since magnetic resonance spectroscopy was not strictly necessary for diagnostic criteria, we decided not to repeat MRI.

Genetic testing in first-degrees relatives is currently under way. This will be useful for a better definition of the whole family picture, although it is scarcely relevant for the assessment of mechanisms underlying the response to diabetes treatment.

In conclusion, we appreciate the criticism by Finsterer et al., who appear to be mainly concerned with the definition of the neurological features of the syndrome. The reasons for which we decided to bring this case to the general attention are the unusual response to hypoglycemic treatment, which

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could open new therapeutic perspective for this specific aspect of the syndrome.

Compliance with ethical standards

Conflict of interest The author(s) declare that they have no conflicts of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent The patient signed the informed consent.

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