Response to comments on: Outer retinal tubulation and inner retinal pseudocysts in a patient with maternally inherited diabetes and deafness evaluated with optical coherence tomography angiogram

Dear Editor:

We sincerely thank Dr. Finsterer[1] for his interest in our work.[2]

1. We fully agree that one of the limitations of our report[2] is that the heteroplasmy rate was not analyzed. Heteroplasmy rate is the proportion of mutated mitochondrial deoxyribonucleic acid (DNA) (mtDNA) to wild type mtDNA.[3] Heteroplasmy rate varies between different cells or tissues of the same patient and between different humans. A specific threshold of mutated mtDNA is needed to cause dysfunction and expression of disease. This effect is well known in different mitochondrially inherited diseases including myoclonic epilepsy and ragged red fibers (MERRF) and mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS). Heteroplasmy rate can be known after mitochondrial whole genome sequencing, which was not done in our index case. Unfortunately, our index patient died in March 2019 from 'respiratory failure, shock, and metabolic encephalopathy with cellulitis of bilateral feet'. She was a known case of coronary artery disease and diabetes mellitus as mentioned in our paper.[2] Thus, mitochondrial whole genome sequencing could not be performed after we received the response from Dr. Finsterer in January 2020.
2. Mother of the index patient denied genetic workup and detailed investigation for multisystemic disease. As mentioned in our paper,[2] she had both diabetes mellitus and hearing loss ('Her mother and maternal aunt had developed diabetes and deafness before the age of 40 years'). As mentioned in the paper, 'The absence of systemic complaints in the siblings and son of the index case may be related to clinical variability due to heteroplasmy. However, they were advised a systemic evaluation for any occult disease'.
3. Various mtDNA mutations have been implicated in the pathogenesis of coronary heart disease/atherosclerotic vascular lesion including G12315A (gene MT-TL2), G15059A (gene MT-CYB), C3256T (gene MT-TL1),[4] and G13513A (gene MT-ND5),[5] and 15910C>T $tRNA^{Thr}$.[6] However, whether the coronary artery disease in our index case was related to some mutation in the mtDNA or was due to diabetes is unknown.
4. However, we do not agree with the comment[1] that 'Overall, this interesting case report has a number of shortcomings that need to be addressed before the conclusions drawn can be adopted.' The family had some members with diabetes mellitus and deafness, which was maternally transmitted. The macular pattern dystrophy was very similar to/typical of maternally inherited diabetes and deafness (MIDD), which was noted in both the index case and her mother. A 3243A-G transition mutation in the MTTL1 gene was demonstrated in the index case. Hence, we believe the conclusion of our work remains unchanged. However, we admit that the limitations of our paper[2] include the absence of whole mitochondrial genome sequencing (not done primarily due to financial constraints) and the nonavailability of a detailed workup for multisystemic disease in the mother of the index case (due to denial of consent by the patient).

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Nil.

Conflicts of interest

There are no conflicts of interest.

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