• Comment and Response •

Retinopathy and focal segmental glomerulosclerosis are not uncommon phenotypic features in m.3243A>G carriers

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Dear Editor,

We read with interest the article by Liu *et al*[1] on a 28-year-old woman with mitochondrial encephalopathy, lactic acidosis syndrome, and stroke-like syndrome (MELAS) due to the m.3243A>G variant confirmed in blood lymphocytes. The *MT-TL1* variant manifested clinically with focal segmental glomerulosclerosis (FSGS), which required hemodialysis, heart failure, arterial hypertension, and hearing impairment[1]. Although the patient reported no visual symptoms, ophthalmological examination revealed changes in the perimacular and peripapillary retinal pigment epithelium (RPE)[1]. The study is noteworthy, but some points require discussion.

The first point is that we disagree with the diagnosis of MELAS in the index patient[1]. MELAS is usually diagnosed according to the Hirano or Japanese criteria, but the index patient did not meet either the Hirano or Japanese criteria.

The second point is that we disagree with the view that the index case is the first case of retinal atrophy and FSGS to be reported[1]. MELAS patients with retinal atrophy and FSGS have also been described by Deva *et al*[2] and Doleris *et al*[3]. Deva *et al*[2] reported on a 46-year-old woman with MELAS who presented with a stroke-like episode, FSGS, hypoacusis, hypertrophic cardiomyopathy, and diabetes. The patient had also suffered from deterioration of night vision and reduced visual acuity for four years. Fundoscopy revealed bilateral depigmented areas consistent with pigment epithelial atrophy, which was confirmed by optical coherence tomography[2]. One of the four MELAS patients described by Doleris *et al*[3] had FSGS and bilateral macular dystrophy on fluorescence angiography.

The third point is that no heteroplasmy rates have been reported for clinically affected and unaffected tissues[1]. Since heteroplasmy rates are one of the determinants of the phenotype, it would be helpful to know the heteroplasmy rates, especially of affected organs such as the kidneys. Heteroplasmy rates are also crucial for the prognosis of the disease course and for genetic counseling.

The fourth point is that no family history was provided[1]. Since the m.3243A>G variant is inherited through the maternal line in 75% of cases[4], it would have been essential to test at least the mother and other first-degree relatives for the presence of the variant to determine whether it was inherited or occurred sporadically.

The fifth point is that retinopathy is a common feature in carriers of m.3243A>G[5]. In a study of 29 carriers of the m.3243A>G mutation, 35 (86%) had retinal abnormalities[5]. Six patients had grade 1 retinal dystrophy with fine pigment abnormalities that were clearly visible on fluorescein angiography. Eleven patients had grade 2 abnormalities characterized by yellowish or slightly pigmented deposits in the early stages. Six patients had grade 3 disease, with marked chorioretinal atrophy outside the fovea. Two patients had grade 4 disease, with atrophy affecting the fovea and marked loss of visual acuity[5].

In summary, retinopathy is common in m.3243A>G carriers but is rarely associated with FSGS. Since retinopathy in m.3243A>G carriers can be subclinical, these patients should be prospectively examined for ocular and renal involvement.

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Availability of Data and Materials: All data are available from the corresponding author.

Conflicts of Interest: Finsterer J, None.

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Author Reply to the Editor:

Dear Editor,

We attach great importance to the several points made by Josef Finsterer. The following is our reply.

The diagnosis in this case was made after discussion between the neurology and nephrology physicians. We accepted the diagnostic information provided by them. However, we missed the following neurological symptoms: The patient occasionally had headaches and her magnetic resonance imaging (MRI) from another hospital indicated intracranial abnormalities. We apologize for this negligence.

The case by Deva *et al*[2] was reported earlier than ours for sure. However, this is the first time for such case been reported in multiple aspects of ophthalmology, such as autofluorescence photography, electrophysiology and visual field. Meanwhile, we don't mind removing the word "first" either.

This patient underwent subsequent genetic and variability analyses. Since she was only referred to us for eye examination. These data are not publicly available to us. Detailed genetic and heterogeneity analysis would indeed be of great help to in-depth disease analysis. This is also our regret.

The purpose of this article is to draw attention to the retinal examinations of such patients. Some abnormalities in the retina may require special examinations to be revealed. As an extension of the nervous system, abnormalities in the retina may sometimes indicate abnormalities in the nervous system.

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