Journal of Medical Case Reports and Reviews

Received 11 Jan 2021 | Revised 15 Jan 2021 | Accepted 15 Mar 2021 | Published Online 20 Mar 2021

JMCRR 04 (03), 830-831 (2021) ISSN (O) 2589-8655 | (P) 2589-8647

JMCRR

RETINOPATHY IN M.3243A>G CARRIERSFA

Finsterer J, MD, PhD [1]

[1] Klinik Landstrasse, Messerli Institute, Postfach 20, Vienna, Austria.

Key words: mtDNA, m.3243A>G, heteroplasmy, mtDNA copy number, genotype, phenotype

Corresponding author: **Finsterer J, MD, PhD**

Postfach 20 1180 Vienna, Austria,Tel. +43-1-71165-72085,Fax. +43-1-71165E-mail: fifigs1@yahoo.de

Letter to the Editor

With interest we read the review article by Coussa et al. about the current perspectives and clinical implications of retinopathy in m.3243A>G carriers [2]. It was concluded that mitochondrial disorders (MIDs) require a multidisciplinary team approach to ensure effective treatment, regular follow-ups, and accurate genetic counseling. The study is appealing but raises the following comments and concerns.

The phenotypic expression and variability of the m.3243A>G variant may not only depend on heteroplasmy rates but also on mtDNA copy number, the haplotype, and mtDNA polymorphisms. Thus, heteroplasmy predicts the phenotype and outcome only insufficiently. Concerning the genotype phenotype correlation, it has to be stressed that heteroplasmy rates are usually determined in tissues easily accessible to diagnostic work-up and not in tissues predominantly affected (e.g. retina, brain, pancreas, muscle). Thus, the value of heteroplasmy rates is limited and genotype phenotype correlations published should be regarded with caution since they may be completely different in clinically affected tissues.

Pigmentary retinopathy is a hallmark of Kearns Sayre syndrome (KSS) but rare in mitochondrial encephalopathy, lactic acidosis and stroke-like episode (MELAS) or other mitochondrial disorders (MIDs) due to the variant m.3243A>G. Accordingly, we do not agree that pigmentary retinopathy is the most frequent ophthalmologic abnormality in m.3243A>G carriers [2]. More frequent than retinopathy is ptosis, ophthalmoparesis, cataract, or optic atrophy. As with retinopathy, ophthalmoparesis and optic atrophy are often mild or subclinical why they go frequently undetected and remain unrecognised.

Visual impairment in m.3243A>G carriers may not only be due to retinopathy but also due to ptosis, ophthalmoparesis with consecutive double vision [8], cataract [3]. retinal detachment [7], optic atrophy [5], or a stroke-like lesion (SLL), the hallmark of MELAS syndrome [1]. A further pathophysiological factor that should be considered with regard to visual acuity in m.3243A>G carriers is lactic acidosis. The high the lactate levels, the worse the visual acuity [6]. Non-ischemic central retinal vein occlusion (CRVO) should be considered as a rare cause of impaired vision in MELAS patients [4]. Visual impairment may be even due to epileptiform discharges in the occipital cortex [1].

A pathophysiologic factor not sufficiently considered that could explain the specific retinal abnormalities in m.3243A>G carriers is the anti-oxidative capacity of retinal structures. This may be different between the central compared to the peripheral retinal areas.

MELAS patients are in the majority of the cases young. Onset of the disease is frequently before age 10y or at least before age 20y. Thus, ageing does not play a pathophysiological role to explain the retinal abnormalities.

Since m.3243A>G carriers can develop diabetes and diabetic is a frequent complication of badly controlled diabetes, it is crucial that the HbA1c values of m.3243A>c are included in the considerations about affection of the retina in m.3243A>G carriers.

It should be mentioned that the m.3243A>G variant not only manifests as a syndromic MID but more frequently as a non-syndromic MID. Non-syndromic phenotypes do not fit to any of the >50 mitochondrial syndrome so far specified.

It is also crucial to discuss the influence of the current medication and nutrition on the phenotype. For example, there are indications that the ketogenic diet can lower serum and CSF lactate values, can reduce seizure frequency, and can improve the anti-oxidative capacity. It should be also mentioned that NO-precursors may exhibit a beneficial effect on the phenotype, although these compounds and measures have not been investigated in randomised, prospective, and controlled trials in m.3243A>G carriers.

Overall, the article has several limitations, which should be met before drawing final conclusions. Importantly, heteroplasmy rates are not the only factor determining the phenotype, current medication and diet need to be considered when evaluating phenotypic features and outcome, and the anti-oxidative capacity may contribute to the phenotypic heterogeneity in m.3243A>G carriers. We agree that a multidisciplinary approach is required to optimally manage m.3243A>G carriers diagnostically and therapeutically.

References:

1 Cecchini S, Polonara G, Regnicolo L, Sallei M, Cesaroni E, Zamponi N. Atypical Clinical Picture in a Patient with Benign Occipital Epilepsy: Diagnostic Contribution of Morpho-Functional MR. A Case Report. Neuroradiol J. 2007 Feb 28;20(1):43-7. doi: 10.1177/197140090702000107.

2 Coussa RG, Parikh S, Traboulsi EI. Mitochondrial DNA A3243G Variant Associated Retinopathy: Current Perspectives & Clinical Implications. Surv Ophthalmol. 2021 Feb 18:S0039-6257(21)00060-6. doi: 10.1016/j.survophthal.2021.02.008.

3 Hansrote S, Croul S, Selak M, Kalman B, Schwartzman RJ. External ophthalmoplegia with severe progressive multiorgan involvement associated with the mtDNA A3243G mutation. J Neurol Sci. 2002 May 15;197(1-2):63-7. doi: 10.1016/s0022-510x(02)00048-5.

4 Hsieh YT, Yang MT, Peng YJ, Hsu WC. Central retinal vein occlusion as the initial manifestation of LHON / MELAS overlap syndrome with mitochondrial DNA G13513A mutation--case report and literature review. Ophthalmic Genet. 2011 Mar;32(1):31-8. doi: 10.3109/13816810.2010.531880.

5 Modrzejewska M, Chrzanowska M, Modrzejewska A, Romanowska H, Ostrowska I, Giżewska M. Zmiany oczne w przebiegu zespołu MELAS – opis przypadku [Ocular findings in MELAS syndrome – a case report]. Klin Oczna. 2016;118(4):301-7.

6 Ryu S, Oh SK, Son SH, Jeong WJ, You YH, Ham YR. Reversible Acute Blindness in Suspected Metformin-Associated Lactic Acidosis. J Emerg Med. 2019 Nov;57(5):e153-e156. doi: 10.1016/j.jemermed.2019.06.047.

7 Sultan H, Kellogg C, El-Annan J. Retinal detachment and microangiopathy in mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes syndrome. Can J Ophthalmol. 2017 Dec;52(6):e208-e211. doi: 10.1016/j.jcjo.2017.05.007.

8 Zhu CC, Traboulsi EI, Parikh S. Ophthalmological findings in 74 patients with mitochondrial disease. Ophthalmic Genet. 2017 Jan-Feb;38(1):67-69. doi: 10.3109/13816810.2015.1130153.