American Journal of Ophthalmology Case Reports 26 (2022) 101411

Contents lists available at ScienceDirect

American Journal of Ophthalmology Case Reports

journal homepage: www.ajocasereports.com/

Multimodal retinal imaging of m.3243A>G associated retinopathy

Francesco Romano *, Mariano Cozzi, Giovanni Staurenghi, Anna Paola Salvetti

Eye Clinic, Department of Biomedical and Clinical Science, Luigi Sacco Hospital, University of Milan, Milan, Italy

ARTICLE INFO

Keywords:
Mitochondrial retinopathy
Multimodal imaging
MELAS
Mitochondrial myopathy
Encephalopathy
Lactic acidosis and stroke-like episodes syndrome
Chorio-retinal atrophy
m.3243A>G
Retro-mode illumination
MTTL1 gene

ABSTRACT

Retro-mode illumination imaging can provide good visualization of chorio-retinal atrophy and of the retinal pigment epithelial alterations occurring in m.3243A > G associated retinopathy.

1. Case report

A 55-year-old Caucasian lady was referred to our clinic for bilateral progressive reading disability and visual loss. She had history of diabetes mellitus, hearing loss, mild cognitive impairment and muscle fatigue. Her past ophthalmic history was otherwise silent.

Her best-corrected visual acuity was 20/63 and 20/32 Snellen in the right and left eye respectively, while anterior segment assessment revealed bilateral initial posterior sub-capsular cataract. Multimodal imaging showed a well-demarcated area of chorio-retinal atrophy with partial foveal sparing in both eyes, surrounded by yellow subretinal lesions with peripapillary involvement (Fig. 1). Optical coherence tomography (OCT) documented outer retinal tubulations in correspondence of the atrophic areas with thickening of the residual foveal ellipsoid zone (Fig. 2). Of notice, retro-mode illumination images highlighted numerous irregularities of the retinal pigment epithelium (RPE, Fig. 1) surrounding the atrophic regions and corresponding to the granular pattern on autofluorescence and to the yellow subretinal lesions on structural OCT. NIR-AF images showed diffuse loss of RPE-derived autofluorescence in areas characterized by atrophy and by granular RPE alterations with unmasking of the underlying dark choroidal vessels (Fig. 1).

Considering the ocular and systemic scenario, the patient was referred for genetic testing that revealed a 3243A > G point mutation in the mitochondrial *MTTL1* gene with 75% blood level of heteroplasmy. Muscle histology and elevated serum levels of lactic acid confirmed the diagnosis of mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes (MELAS) syndrome. Upon further questioning, the patient mentioned that her son was recently diagnosed with insulin-dependent diabetes mellitus.

2. Discussion

MELAS syndrome is one of the most frequent maternally-inherited mitochondrial disorders.[1] Typical clinical manifestations include encephalomyopathy, lactic acidosis, stroke-like episodes, dementia, diabetes, sensorineural hearing loss, retinopathy and short stature.[1] Due to the high prevalence of diabetes and hearing loss in the general population, the distinct retinal phenotype often plays an important role in unveiling the underlying mitochondrial etiology.

The 3243A > G mutation in *MTTL1* gene represents the most frequent point mutation among patients affected by MELAS and has

Abbreviations: OCT, optical coherence tomography; RPE, retinal pigment epithelium; NIR-AF, near-infrared autofluorescence; MELAS, mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes.

* Corresponding author. Eye Clinic, Department of Biomedical and Clinical Sciences, Luigi Sacco Hospital, University of Milan, Via G.B. Grassi, 74 – 20157, Milan, Italy.

E-mail address: francesco.romano@unimi.it (F. Romano).

https://doi.org/10.1016/j.ajoc.2022.101411
Received 21 July 2021; Received in revised form 29 January 2022; Accepted 7 February 2022
Available online 3 March 2022

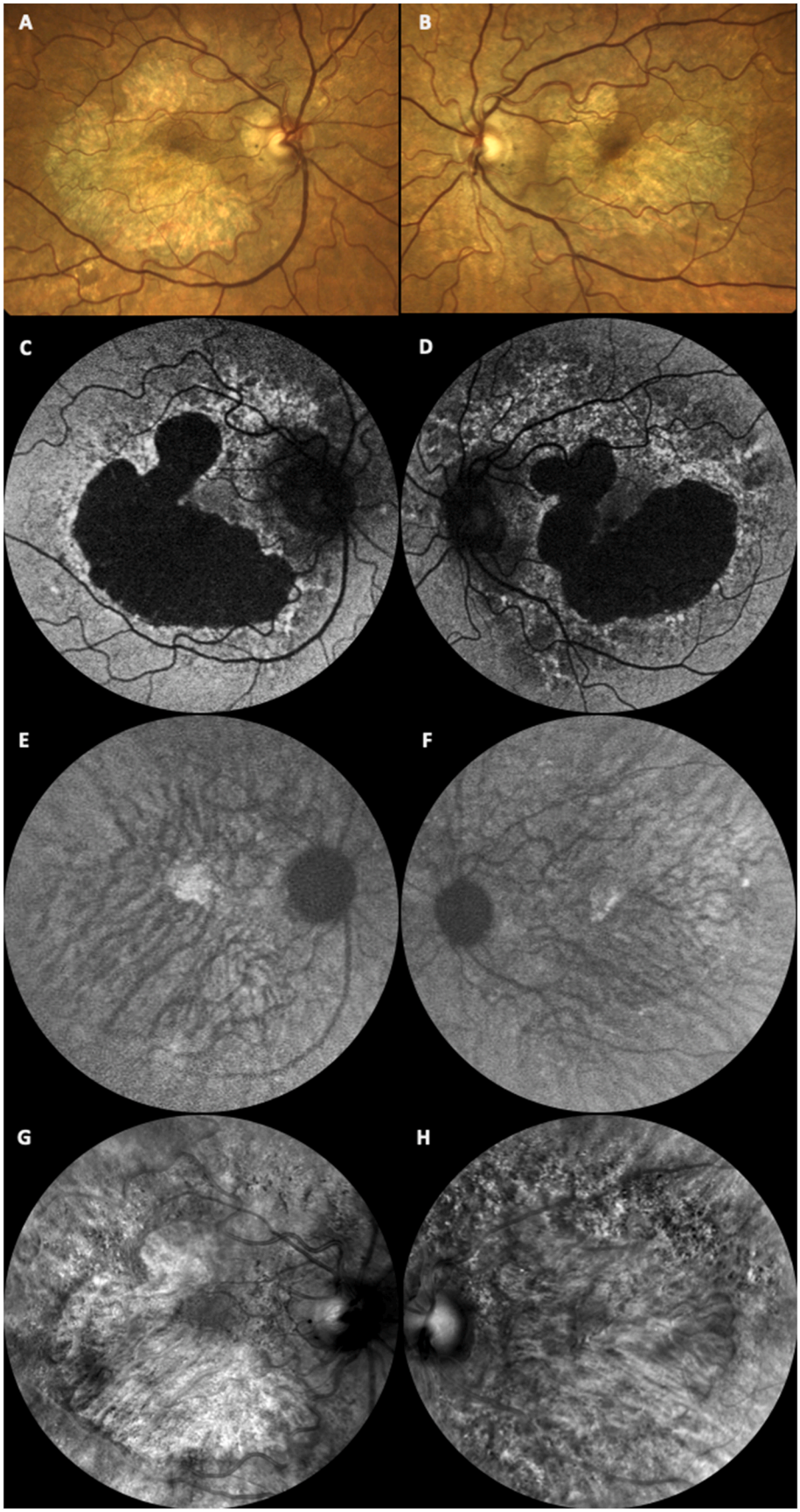

Fig. 1. Multimodal retinal imaging of m.3243A > G associated retinopathy.
A–
B: Color fundus photographs (Eidon; CenterVue, Padua, Italy) show large areas of chorio-retinal atrophy with minimal foveal sparing, bordered by numerous yellowish sub-retinal lesions that extend to the nasal peripapillary area.
C–
D: The widefield fundus autofluorescence images (55° × 55°, Spectralis HRA2; Heidelberg Engineering GmbH, Heidelberg, Germany) confirms the presence of retinal pigment epithelium (RPE) atrophy surrounded by a granular pattern of hypo- and hyper-autofluorescence.E–
F: Near-infrared autofluorescence signal appears similarly decreased in the atrophic areas and the surrounding RPE alterations with a better visualization of the underlying hypo-autofluorescent choroidal vessels; interestingly, the foveal hyper-autofluorescent spot results partially preserved in both eyes.
G–
H: Retro-mode illumination imaging (Mirante; Nidek co. Ltd, Gamagori, Japan) further refines the RPE irregularities around the macular atrophy, corresponding to the sub-retinal deposits.

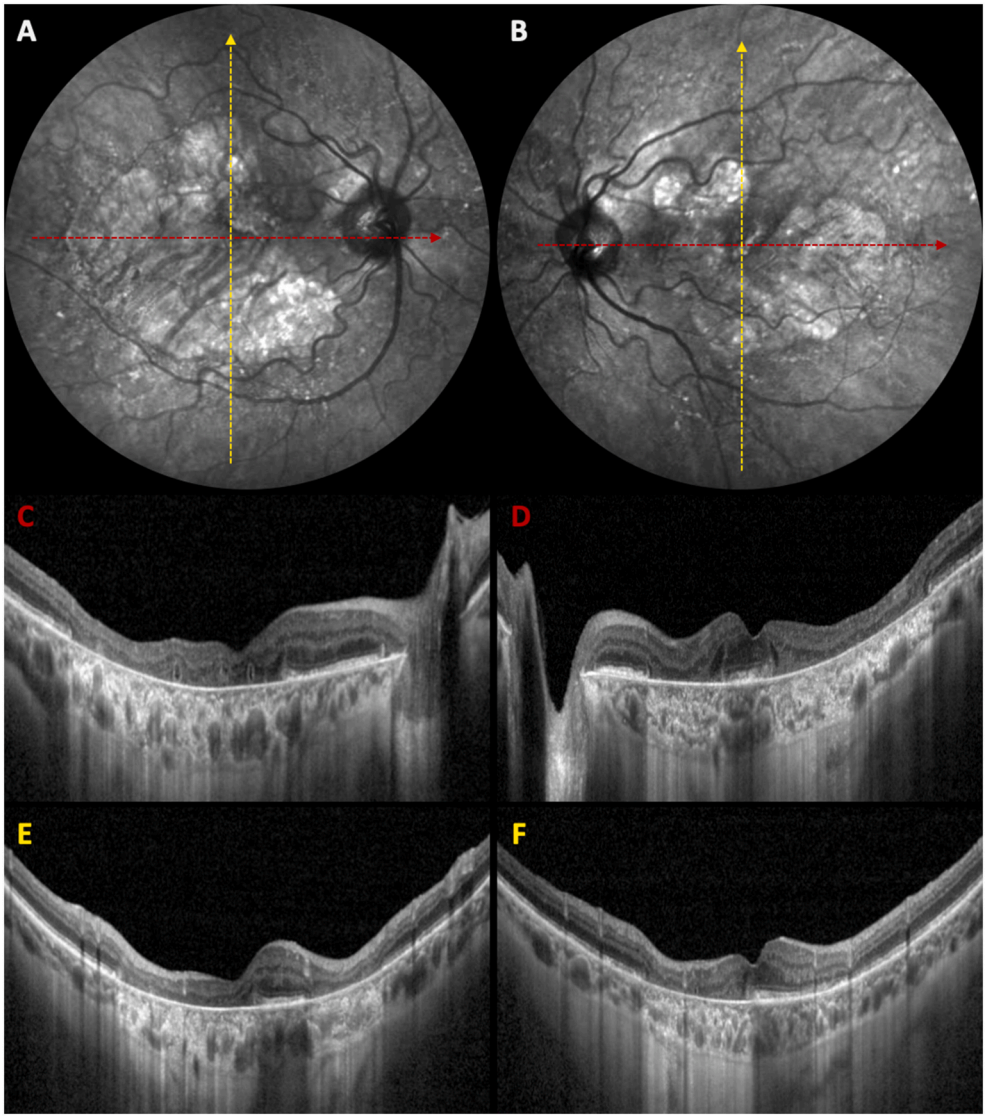

Fig. 2. Near-infrared reflectance images (A–B) and optical coherence tomography (OCT, C–F).
Structural OCT shows extensive and well-demarcated retinal pigment epithelium atrophy with numerous outer retinal tubulations lying above the Bruch's membrane in horizontal scans (C,D). The foveal ellipsoid and interdigitation zones appear significantly thickened in the preserved areas (D,E). Subretinal flecks/spots can be better appreciated in vertical OCT scans (E,F).

been associated to variable degrees of macular dystrophy, from a mild salt-and-pepper retinopathy to more severe atrophic changes.[2] The preferential foveal sparing until late in the course of the disease has been attributed either to the protective role of macular pigments on red and green cones or to a primary effect of mitochondrial dysfunction on rods.[2,3] Possible differential diagnoses include age-related macular degeneration, late-onset Stargardt disease, central areolar choroidal atrophy and pentosan polysulfate maculopathy.[1]

We presented a case of advanced m.3243A > G associated retinopathy (grade 4 according to de Laat) highlighting the most prominent clinical and multimodal features. Of notice, this represents the first description of retro-mode illumination characteristics in this retinal condition. Albeit not widely used in clinical practice, this imaging technique is able to accurately detect the extent of atrophy and the diffuse RPE alterations occurring in our patient.

3. Conclusions

Ophthalmologists keep playing an important and underestimated role in suspecting mitochondrial pathologies. Retro-mode imaging allows for good characterization of the RPE modifications in m.3243A > G associated retinopathy.

Patient consent

The patient consented to the publication signing a written informed consent.

Funding

None.

Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

Declaration of competing interest

MC has the following disclosures: Bayer (recipient), Nidek (recipient). FR and APS have no financial disclosures. GS is consultant for Heidelberg Engineering, Optos, OptoVue, CenterVue, Allergan, Bayer, Genetech, Novartis, Quantel Medical, Carl Zeiss Meditec, Boheringer, Topcon, Roche.

Acknowledgments

none.

References

1. Coussa RG, Parikh S, Traboulsi EI. Mitochondrial DNA A3243G variant-associated retinopathy: current perspectives and clinical implications. *Surv Ophthalmol*. 2021;66(5):838–855. https://doi.org/10.1016/j.survophthal.2021.02.008.PMID:33610586.
2. de Laat P, Smeitink JAM, Janssen MCH, et al. Mitochondrial retinal dystrophy associated with the m.3243A>G mutation. *Ophthalmology*. 2013;120(12):2684–2696. https://doi.org/10.1016/j.ophtha.2013.05.013.PMID:23806424.
3. Birtel J, von Landenberg C, Gliem M, et al. Mitochondrial retinopathy. *Ophthalmol Retina*. 2021. https://doi.org/10.1016/j.oret.2021.02.017. S2468-6530(21)00071-3, PMID: 34257060.