• Review Article •

Retinal multimodal-imaging and functional tests in a mitochondrial disease with focal and segmental glomerulosclerosis

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Abstract

● The phenotypes of the adenine-to-guanine transition at position 3243 of mitochondrial DNA (m.3243A>G) are highly variable, with different symptoms observed in different patients. These include mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS); maternally inherited diabetes and deafness syndrome (MIDD); other syndromic conditions; or non-syndromic mitochondrial disorders. Renal involvement associated with this mutation generally manifests as subnephrotic proteinuria, progressive deterioration of kidney function, and increased morbidity. The retinopathies linked to the m.3243A>G mutation have heterogeneous presentations, characterized by variable degrees of retinal pigment epithelium (RPE) atrophy and hyperpigmentation at the posterior pole. As a severe phenotype of the m.3243A>G mutation, MELAS combined with focal and segmental glomerulosclerosis (FSGS) is rare. We herein firstly reported in detail the ophthalmic manifestations of a patient with this condition. Additionally, we reviewed the literature on fundus, ophthalmic electrophysiology, and optical coherence tomography (OCT) findings related to the m.3243A>G mutation.

● **KEYWORDS:** mitochondrial retinopathy; MELAS; m.3243A>G; multimodal imaging; ophthalmic electrophysiology; optical coherence tomography
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INTRODUCTION

The acronym of mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS) describes a group of patients with mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes accompanied by seizures, headache, hemiparesis, cortical blindness, hearing disability, and diabetes mellitus[1]. The molecular basis for the disease is the adenine to guanine transition at position 3243 of mitochondrial DNA (m.3243A>G) in the MT-TL1 gene-encoding $tRNA^{LEU(UUR)}$, which is the most frequent cause of MELAS syndrome[1-2]. Renal involvement associated with m.3243A>G generally manifests as subnephrotic proteinuria and progressive deterioration of kidney function and increases morbidity[3-4]. The ocular findings of MELAS include macular dystrophy, external ophthalmoplegia, ptosis, and posterior subcapsular cataract include pigmentary retinopathy, external ophthalmoplegia, ptosis and posterior subcapsular cataract[5]. Retinopathies associated with m.3243A>G have heterogeneous presentations with variable degrees of retinal pigment epithelium (RPE) atrophy and hyperpigmentation[6-7]. As a severe phenotype of m.3243A>G mutation, MELAS combined with focal and segmental glomerulosclerosis (FSGS) is rare. We reported the ophthalmic manifestations of a patient with this condition. We also reviewed the literature on fundus, ophthalmic electrophysiology and optical coherence tomography (OCT) manifestations related to m.3243A>G mutation.

CASE REPORT

Our report was approved by the Ethics Committee of Ruijin Hospital, Shanghai Jiao Tong University School of Medicine (2011No.18). A 28-year-old Chinese female with hereditary nephropathy was referred to our department for ophthalmic examination in 2024. The patient was admitted to hospital because of elevated urine protein and blood creatinine for more than 1y. Kidney biopsy revealed FSGS. Laboratory work-up disclosed elevated lactic acid and the presence of adenine to guanine transition at the position 3243 of mitochondrial DNA (m.3243A>G) in the patient's blood cells. The patient underwent routine hemodialysis (3 times a week). She also

suffered heart failure, hypertension, anemia and sensory neural hearing loss. Oral glucose tolerance test and hemoglobin A1c were within the normal range. She reported no visual symptoms. Her sister confirmed MELAS syndrome by muscle fiber biopsy.

Best-corrected visual acuity was 20/20 with refraction of -3.75/-0.25×100 for the right eye and -2.75/-0.50×78 for the left eye. Anterior segment of the eyeball was normal. Ophthalmoscopy revealed pigmentary abnormality on the fundus and retinal arteriolar attenuation in both eyes. There was stripe hemorrhage beneath the disc of the left eye (Figure 1A-1B). Fundus autofluorescence (FAF) images showing mottled hypofluorescent lesions in the macula and peripapillary region. A small amount of hyperfluorescent spots in the macula region (Figure 1C-1D).

OCT (Cirrus high-definition OCT 5000 AngioPlex, Carl Zeiss Meditec, Dublin, CA, USA) revealed inhomogeneous signal between the RPE and ellipsoid zone (Figure 2A-2B). The macular thickness, measured from inner limiting membrane (ILM) to RPE (ILM-RPE), was decreased in most ETDRS subfields (Figure 2C-2D). Optical coherence tomography angiography (OCTA) images demonstrated normal macular superficial capillary perfusion (Figure 2E-2F). The thickness for the sum of the ganglion cell layer (GCL) and inner plexiform layer (IPL; GCL-IPL) was significantly decreased (Figure 2I-2J). Retinal nerve fiber layer (RNFL) thickness was normal in all quadrants (Figure 2K).

Full-field electroretinography (ffERG; RETeval™, LKC Techno, USA) showed attenuation of photopic b-wave, 30 Hz flicker, scotopic a-wave and b-wave amplitudes in both eyes. No implicit time delay. In ffERG examination, we used Troland-based stimuli which have constant retinal illuminance and were described by the Troland unit (Td). The stimulus of 85 Td·s with a 850 Td background equals the stimulus of 3 cd·s/m^2 white flash with a 30 cd/m^2 white background described in the ISCEV ERG standard. Pattern visual evoked potential (P-VEP; MGIT-100, LKC, USA) examination showed the latency and amplitude were within the normal range (Figure 3).

No abnormalities were detected using the Humphrey Field Analyzer 30-2 program.

DISCUSSION

The phenotypes of m.3243A>G are highly variable, with different symptoms in different patients，including MELAS, maternally inherited diabetes and deafness syndrome (MIDD), chronic progressive external ophthalmoplegia, other syndromes or non-syndromic mitochondrial disorders, such as hypertrophic cardiomyopathy, enteromyopathy, and cluster headaches[8]. A cohort study including 136 m.3243A>G MIDD patients observed the following comorbidity: hearing loss (85.71%), central nervous system diseases (29.19%), myopathy (22.98%), oculopathy (23.60%), cardiac disease (23.60%), nephropathy (13.66%) and underweight (41.58%)[9]. The complex and variation of phenotype of m.3243A>G are partly depending on the distribution and level of m.3243A>G heteroplasmy across tissues and cells[10-11]. Diagnosis suspicion of MELAS or MIDD in a context of maternal inheritance relies on the systemic abnormalities. Mitochondrial forms of FSGS involved in MELAS and MIDD are associated with retinal atrophy and inherited retinal degeneration[3].

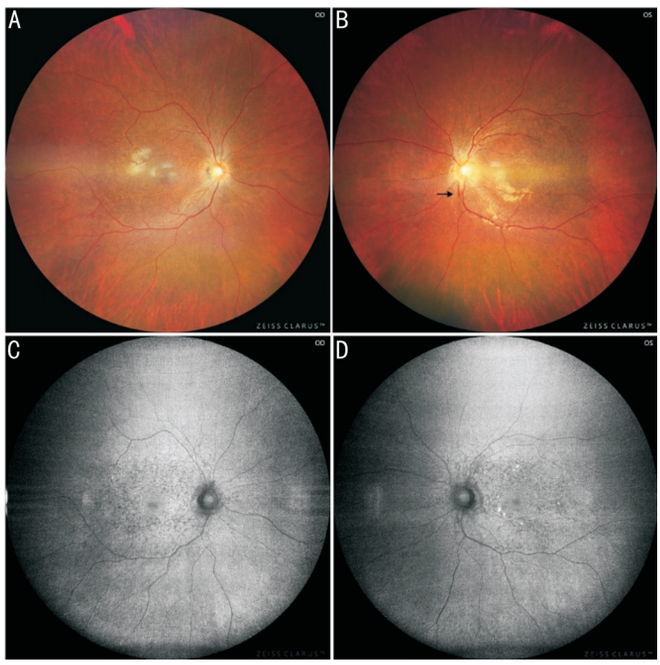

Figure 1 Confocal scanning laser ophthalmoscopy color fundus photograph showed pigmentary abnormality on the fundus and retinal arteriolar attenuation in both eyes The disk was normal (A, B), except stripe bleeding below the optic disc in the left eye (black arrow). FAF showing mottled hypofluorescent lesions and hyperfluorescent spots in the macula and peripapillary regions (C, D). Hyperfluorescent spots were relatively obvious in the left eye (D). FAF: Fundus autofluorescense; OD: Right eye; OS: Left eye.

Mitochondria are essential for cellular function and survival as they mediate processes such as energy production, metabolism control, and apoptosis[12]. The mutation of m.3243A>G causes an electron transport chain defect chiefly due to a deficiency of complex I, subsequent malfunction in ATP production[13] and elevated reactive oxygen species (ROS) production[14-15]. The photoreceptors and the RPE function in a highly oxidative micro-environment. They are under constant attack from ROS, of which the mitochondria are a major endogenous source.

Fundus Changes Associated with m.3243A>G Mutation

The degree of RPE changes was significantly different among patients of m.3243A>G variant, from fine pigment abnormalities to profound chorioretinal atrophy[2,16-17]. There may be granular, “salt and pepper” appearance of RPE that was most marked on the posterior[18]. Multifocal faint white-

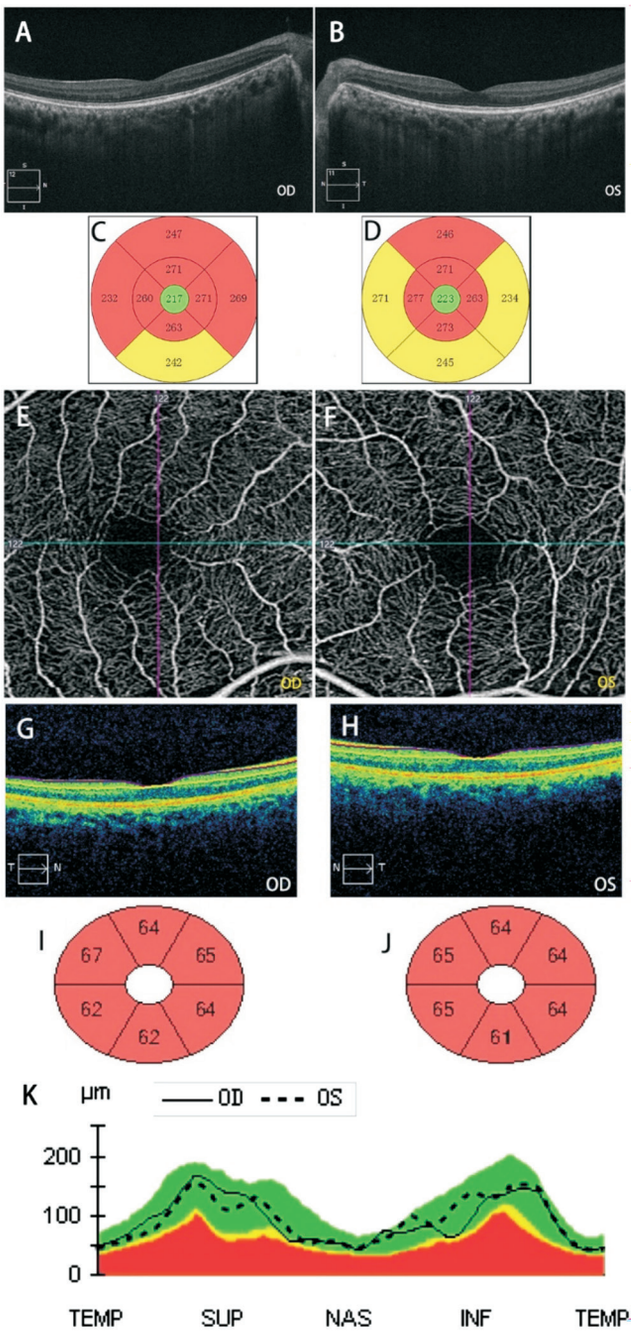

Figure 2 Manifestations on optical coherence tomography (OCT) A-B: OCT revealed inhomogeneous signal between the RPE and ellipsoid zone. C-D: The retina thickness was decreased in most Early Treatment Diabetic Retinopathy Study (ETDRS) subfields (green: normal; yellow: thinned; red: very thinned; ETDRS grid is a division of the macula, by which the macula is divided into 9 subfields). E-F: OCT angiography (OCTA) 3×3 mm images demonstrated normal macular superficial capillary perfusion. G-H: OCT structural B-scan overlaid with the boundaries of the GCL and IPL (GCL+IPL). The purple line represents the inner boundary of GCL. The yellow line represents the outer boundary of IPL. I-J: Sectorial map of thickness measurements showed significant decrease of GCL+IPL thickness. K: Retinal nerve fiber layer (RNFL) thickness analysis was normal in all quadrants. TEMP: Temporal quadrant; SUP: Superior quadrant; NAS: Nasal quadrant; INF: Inferior quadrant; GCL: Ganglion cell layer; IPL: Inner plexiform layer; OD: Right eye; OS: Left eye.

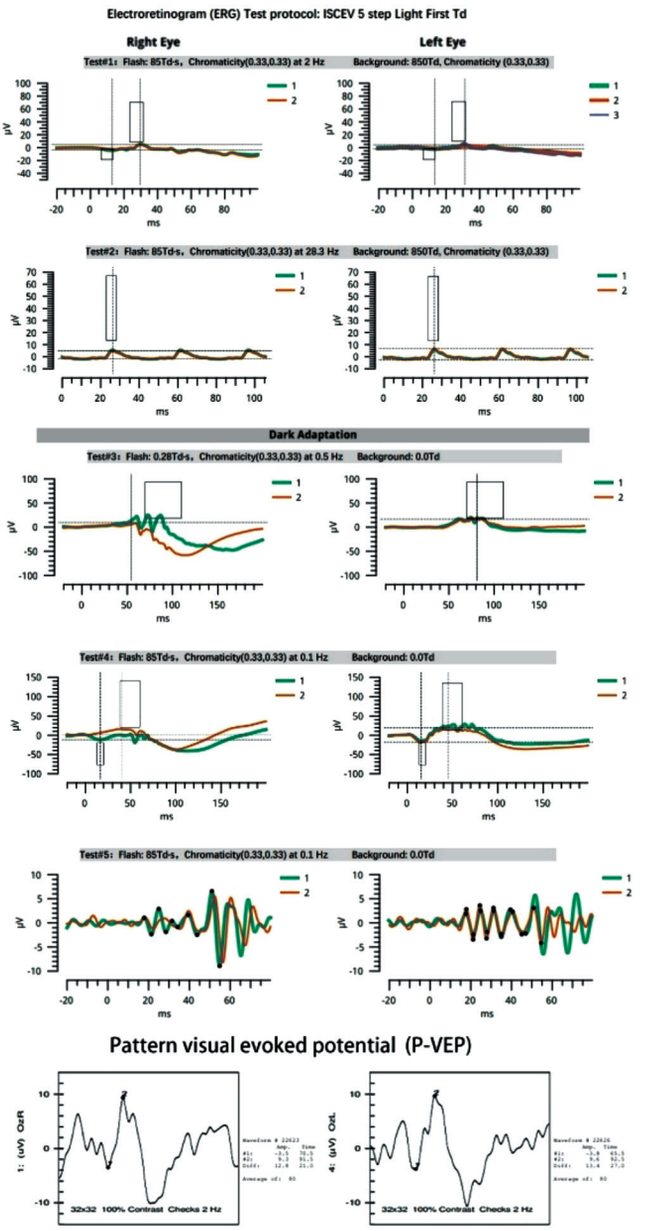

Figure 3 ffERG and P-VEP ffERG showed attenuation of photopic b-wave, 30 Hz flicker, scotopic a-wave and b-wave amplitudes in both eyes. No implicit time delay. P-VEP examination showed the latency and amplitude were within the normal range. ffERG: Full-field electroretinography; P-VEP: Pattern visual evoked potential.

yellowish or hyperpigmented subretinal deposits and pigment changes were reported[17]. Fundus examination may reveal hyperpigmented lesions surrounding the macula and the optic disc, associated with depigmentation areas of the RPE, or several circumferential perifoveal islands of atrophy and adjacent pale deposits[19]. The peripheral retina, optic disc, and retinal vessels were normal[16]. FAF imaging revealed a decreased FAF signal in areas of RPE atrophy and irregular increased FAF signal adjacent to and between the areas of RPE atrophy, the latter may forming a ring-shaped pattern dystrophy at the posterior pole[2,20]. The characteristics of FAF associated with the A3243G mtDNA mutation are distinct. There is

no widespread speckled FAF in the m.3243A>G related retinopathy compared with the majority of other macular dystrophies, such as the Stargardt macular dystrophy, pattern dystrophy and geographic atrophy due to age-related macular degeneration[21]. The area of abnormal FAF is significantly larger than would be expected from the funduscopic appearance.

de Laat *et al*[2] described in detail 4 grades of fundus changes. Grade 1: discrete pigmentary abnormalities in the central fundus; Grade 2: isolated or multifocal faint white-yellowish or hyperpigmented subretinal deposits in the posterior pole; Grade 3: one or more areas of well-delineated, profound chorioretinal atrophy outside of the fovea, atrophic zones may encircle the fovea but do not involve the central fovea; Grade 4: the central fovea was affected by profound chorioretinal atrophy. According to existing studies, whether the various fundus findings associated m.3243A>G mutation are different evolutive stages or correspond to distinct phenotypes is not fully understood. Pathological studies of the retina showed degeneration of photoreceptor outer segments in the macula, hyperpigmentation and atrophy of the RPE of the macula in MELAS and MIDD patients[22]. In a study, all 10 patients with mild RPE abnormalities were positive for m.3243A>G mutation, suggesting that the perimacular dystrophy/atrophy may be a reliable clinical indicator of this mutation in a significant proportion of maternal relatives[7].

Ophthalmic Electrophysiology Presentations in Patients Harboring m.3243A>G Mutation

ffERG presentations in patients harboring m.3243A>G mutation The ffERG or Ganzfeld ERG[23] is a measure of electrical currents elicited by flashes that stimulate the entire retina. This typically consists of a negative component, the a-wave, which largely reflects the hyperpolarisation of the photoreceptors, followed by a positive component, the b-wave, which arises from the inner retina, predominantly the bipolar cells with a contribution from Müller cells[24]. The oscillatory potentials are thought to be generated by post-receptor dopamine pathways with a presumed significant contribution from amacrine cells[25-26]. The electrical activity of retinal ganglion cells (RGCs) usually can't be observed on the ffERG. The macula contributes minimally to ffERG. Patients who have focal macular disorders do not have abnormalities of ffERG amplitude, nor do patients who have diseases of the inner retina, optic nerve, or cortical conditions. Photopic and maximum ERG have input from both rod and cone systems.

As the fundus changes associated with the m.3243A>G variant usually remain limited to the posterior pole, it makes sense that the ffERG results are usually normal. De Laat *et al*[2] described this retinal dystrophy and classified them into 4 grades according to the ophthalmoscopy and FAF imagings. They reported normal ffERG results in 3 patients with advanced grade 3 disease[2]. The normal ffERG results were observed in reports from Vialettes *et al*[18], Massin *et al*[16], Daruich *et al*[19] and Birtel *et al*[17]. However, abnormal ERG had also been reported. Latvala *et al*[27] performed ffERG on 8 patients with m.3243A>G-related pigmentary retinopathy and found mild to moderate attenuation in rod or cone amplitudes or lengthened latencies in 7 patients. Latkany *et al*[28] reported reduction of photopic and scotopic electroretinogram b-wave amplitudes a MELAS patient. Smith *et al*[6] found that abnormal ERG findings were in 4 of 12 subjects diagnosed with MIDD (including one patient had retinal photocoagulation due to diabetic retinopathy), not mentioning other systemic involvements. Oh *et al*[22] reported decreased maximum b-wave and 30 Hz flicker amplitudes in 3 MIDD patients, in one of them with 30 Hz flicker implicit time delay. These abnormal ffERG results suggested that the m.3243A>G related retinopathy may not limit to the posterior pole, as seen on fundus photographs, and that the effect of this mutation on the retina may be extensive. The conflicting results of these reports may be due to the phenotypic heterogeneity of m.3243A>G mutation, which was controlled and affected by heteroplasmy, environmental factors, and variations in mtDNA repair and maintenance[29]. Besides, the small sample size in each study may be an explanation.

In all of these studies, some studies did not report systemic involvements beyond the eyes and hearing, and none mentioned kidney conditions. Smith *et al*[6] reported that abnormal ERG findings were more frequent in patients over 40 years of age and in those with diabetes duration longer than 5y. It is generally accepted that longer diabetes duration means higher risk of kidney damage. Association of retinopathy with chronic kidney disease (CKD) have already been reported[30-32]. In a study of chronic renal failure patients, decreased b-wave amplitude of maximal combined response and delayed implicit time of oscillatory potentials 1, and 2 were significantly different from those in hypertensive control patients[33]. The findings suggest that anemia and uremia may aggravate retinal damage. To the best of our knowledge, there are almost no reports on ERG in patients with FSGS, let alone that in patients with MELAS and FSGS. The patient herein we reported was only 28 years old without diabetes, but with renal failure. Her mild pigmentary abnormalities on fundus can be classified into grade 1 m.3243A>G retinopathy according de Laat *et al*[2]. However, her ERG outcomes significantly altered. MELAS combined with FSGS itself was a severe clinical phenotype of m.3243A>G mutation. Renal failure due to FSGS may further aggravated retinal dysfunction in this case.

Patten-ERG and multifocal ERG presentations in patients with m.3243A>G mutation Patten-ERG (PERGs) were recorded to an alternating checkerboard. Since the PERG (in contrast to the ffERG) is a focal response summed from the retinal area covered by the stimulus image, the P50 component can be used as a sensitive indicator of cone system function within the macular region and P50 reduction and/or delay can represent macular cone system dysfunction[34]. The PERG may also complement the ffERG in distinguishing between generalized retinal dysfunction and macular cone dysfunction. There are very few reports on PERG in patients harboring m.3243A>G mutation. Sue ever reported 11 such patients with normal PERG[35].

Multifocal electroretinography (mfERG) responses to a scaled array of 61 or 103 stimulus hexagons usually covering the central 40–50° of the retina under light-adapted conditions. The mfERG technique allows recording of electrical signals from multiple discrete areas across the posterior pole, enabling the topographic representation and localization of retinal activity[36]. mfERG may disclose subtle central changes that can't be detected by PERG. In the study from Bellmann *et al*[20], abnormalities were revealed in 3 of 10 eyes (2 of 5 subjects) by ffERG, while amplitudes reduction were observed in 5 of 10 eyes by PERG (3 of 5 subjects) and in all eyes by mfERG (total 4 subjects). Abnormalities in mfERG also observed by Daruich *et al*[19] in patients harboring m.3243A>G mutation, whose ffERG results were normal. For m.3243A>G related retinopathy, lesions usually localized to the central retina, mfERG is more likely to detect abnormalities and thereby, a more suitable measurement for this disease.

Other ophthalmic electrophysiological examinations in patients with m.3243A>G mutation Electrooculography (EOG) records the standing electrical potential generated by the RPE. The Arden ratio provides a measure of the generalized function of the RPE/photoreceptor[37] complex. Smith *et al*[6] reported subnormal EOG responses in approximately 4 of 9 patients with m.3243A>G-related pigmentary retinopathy. de Laat *et al*[2] found slight decreased Arden ratio on EOG in 3 patients with grade 3 3243A>G-related retinopathy. While Daruich *et al*[19] reported normal EOG results in 2 m.3243A>G patients, whose mfERG was abnormal.

VEPs are visually evoked potentials extracted from the electroencephalographic activity in the visual cortex recorded from the corresponding scalp. VEPs depend on functional integrity of central vision at all levels of the visual pathway including the eye, retina, the optic nerve, optic radiations and the occipital cortex[38]. P100 amplitude and implicit time are commonly used metrics in VEP. Sue *et al*[35] reported in 11 patients (MELAS patients and their maternally related relatives) with normal PERG, 3 patients had delayed P100 responses to full-field stimulation on VEP and 4 patients had delayed P100 responses after central field stimulation on VEP. Scarcella *et al*[39] described a woman habouring m.3243A>G mutation first presented with ischemic optic neuropathy. Her VEP showed a reduction in amplitude with prolonged P100 in the involved eye. VEP abnormalities were seldom reported in patients with m.3243A>G variant and often indicated abnormalities in the visual pathway.

OCT Presentations in Patients Harboring m.3243A>G Mutation On OCT B-scan of m.3243A>G retinopathy, alterations including no obvious abnormalities, reflectivity changes at the interface between photoreceptor outer segments and RPE, irregular thickening of the line corresponding to the photoreceptor inner/outer segment (ellipsoid) area, attenuated and irregular fading or atrophy of RPE and/or photoreceptors[2,17], outer retinal tubulations (a feature of degenerative retinal diseases, but not specific to mitochondrial retinopathy)[22,40].

RGCs encompass three layers in the retina, each layer corresponding to different part of RGC. IPL is RGC dendrites; GCL is RGC bodies; and RNFL is RGC axons. All three layers, collectively known as the ganglion cell complex (GCC). The declination of GCC thickness had been reported in MELAS patients without retinal/RPE degeneration[41]. There was a negative correlation between GCC thickness and disease duration, which suggested that RGCs degeneration may develop gradually over time in MELAS patients. It was reported that some MELAS patients can experience visual symptoms due to lesions involving the retrochiasmal visual pathways. Posterior brain regions are typically involved in the stroke-like episodes, potentially leading to homonymous visual field defects and detectable thinning of the GCC, as a result of trans-synaptic retrograde degeneration of the RGCs[41]. On the analysis of our case, the exact thinning layer within the GCC was the IPL-GCL. RNFL thickness was normal, although it may gradually become thinner secondary to RGCs scarcity as the disease progresses. GCL-IPL thickness, as well as GCC, is an early and sensitive biomarker for many neurodegenerative diseases. The GCL-IPL thickness thinning may also be caused by renal dysfunction[42]. A cohort study[43] in a large population showed that poorer renal function negatively correlated with GCL-IPL thickness with a mean of 0.15 μm thinner in mild CKD and 0.83 μm thinner in moderate to severe CKD compared with subjects without CKD. Longitudinal analysis showed that the GCL-IPL decreased more rapidly in persons with poorer renal function.

Macular GCL-IPL thickness analysis led us to challenge the previous points on taking RPE and/or the the inner segment/outer segment junction layer (IS/OS) as the primary involved retinal sites in m.3243A>G-related retinopathy. Actually,

the inner retina may also be involved from the early stage of disease, especially in the patients with severe clinical phenotypes. It had been disclosed by multimodal single-cell analysis that m.3243A>G was nonrandomly distributed, being high in neural retina and RPE and lower in the choroidal endothelium[44]. Transmission electron microscopy revealed swollen and hypertrophied mitochondria existing in MELAS neural retina and RPE[44]. However, other early subtle changes in the inner retina could not be detected due to limited detection methods. Macular thickness analysis, rarely reported in MELAS patients or m.3243A>G mutation carriers, may be used as a good tool to monitor and predict retinopathy progression.

CONCLUSION

In summary, the finding of perimacular/peripapillary RPE changes may suggest the possibility of 3243A>G mutation and should prompt a screening for this mutation and multidisciplinary investigations. For patients of MELAS or other phenotypes of the same mitochondrial defect, whose retinal lesions are not obvious, retinal function and macular thickness may have already altered, significantly before the visual acuity and visual field changes. Electrophysiology and OCT examinations, as well as FAF imaging, are essential in early detecting and subsequent monitoring the retinal impairments in patients with m.3243A>G mutation.

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