



Case report

A case study of choroideremia carrier – Use of multi-spectral imaging in highlighting clinical features

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ABSTRACT

Purpose: To report the use of non-invasive multi-spectral imaging of a female choroideremia (CHM) carrier with mild visual symptoms and extensive fundus mottling.

Observation: This was an observational case report study. A symptomatic 42-year-old female with a history of binocular CHM presented for routine ocular examination and underwent review of her clinical and photographic records, optical coherence tomography (OCT), intravenous fluorescein angiography (IVFA) and multi-spectral imaging (MSI). Dilated fundus examination and photography revealed similar outcomes of diffuse mottling with normal looking vessels. IVFA showed large irregular and confluent patches of RPE atrophy in the peripapillary and parapapillary areas as well as the midperiphery, corresponding to the OCT findings. The entire range of MSI imaging (520–940 nm) clearly illustrated the anomalies of the fundus including retinal pigment epithelium (RPE) mottling with melanin clumping not readily seen with the other imaging modalities. MSI fundus autofluorescence (MSI-FAF) showed a spotty hypo and hyperautofluorescent appearance of the fundus, consistent with the observations seen on IVFA and OCT images.

Conclusion and Importance: MSI significantly improves visualization of the retinal pigment epithelium in choroideremia. The non-invasive nature of MSI technique is a valuable tool in monitoring the effect of retinal and choroidal presentation in patients with CHM.

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1. Introduction

Choroideremia (CHM) is a recessive X-linked chorioretinal dystrophy caused by mutation in the CHM Xq21 gene which encodes the protein REP-1 [1]. The condition is a progressive, diffuse degeneration of the choroid, retina, retinal pigment epithelium (RPE) and photoreceptors. Symptoms include bilateral nyctopia in childhood followed by annular scotomas leading to concentric visual field loss and impairment of visual acuity, color vision and stereopsis by mid-adulthood, specifically in males. Fundus changes are observed as non-specific pigmentary stippling and focal areas of choroidal atrophy in the mid-periphery. With degenerative changes of the RPE, window defects showing remnants of the choroidal vasculature become apparent in peripapillary areas and

macula. As the disease advances, the sclera becomes visible on fundus examination in the areas of complete choroidal and retinal atrophy.

Differential diagnosis includes retinitis pigmentosa and gyrate atrophy. In the former there is a greater amount of pigment migration and in the later there is elevated plasma concentration of ornithine. Non-invasive visualization of the RPE can assist in the differential diagnosis.

Female carriers of CHM may also show varying degrees of chorioretinopathy, RPE atrophy and granular pigmentary atrophy in the periphery. Severe visual impairment rarely occurs and is typically attributed to skewed X-inactivation [2]. Visual function remains fairly good, with either no symptoms or mild to moderate nyctalopia. Full-field electroretinograms (ERG) vary in female carriers and there is no definitive expected outcome. Most cases are normal or only slightly reduced [3].

Theories on the pathophysiology of CHM include degeneration of rod photoreceptors followed by degeneration of the choroid or primary RPE degeneration [2,4,5]. Advances in ocular imaging have

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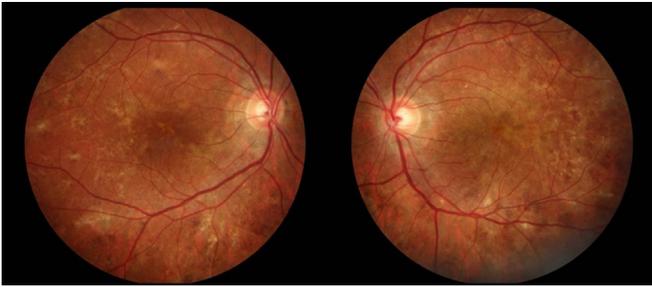


Fig. 1. 50° fundus images of the patient showing discoloration of the retina central and mid-peripherally (right eye < left eye).

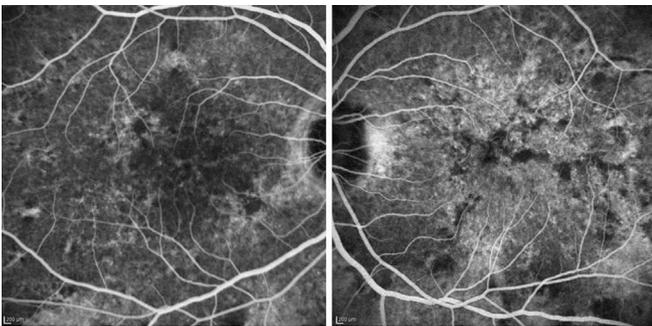


Fig. 2. Intravenous fluorescein angiography (IVFA).

led to better understanding of CHM morphological patterns. Optical coherence tomography (OCT) is used to detect chorocapillaris loss and choroidal neovascularization associated with CHM [6]. An important diagnostic criterion in female carriers is the mottled RPE changes which cause patchy fundus autofluorescence (FAF) irregularities with areas of hypo and hyperautofluorescence [7].

In this case report, a female carrier of CHM was imaged with traditional technologies as well as with multi-spectral imaging (MSI). MSI has the capability of highlighting the detailed structure of RPE, particularly melanin for early morphologic changes that are not generally visible clinically or with traditional fundus imaging modalities in routine practice [8]. Given the important role of the RPE in the pathogenesis of CHM and other retinal pathologies, examination of this layer with MSI may prove highly valuable for noninvasive differential diagnosis from RP and for monitoring progression.

2. Case report

A 42-year old female presented to the retinal clinic for her annual eye examination, as directed by her physician. She was a known carrier of choroideremia having been diagnosed in her teens and had a positive family history of CHM, with a brother exhibiting the disease. Best-corrected visual acuities (BCVA) were 20/20 in each eye with a refraction of +3.00–0.50 × 090 OD and +2.50–0.75 × 115 OS. The patient had full confrontational visual fields in each eye and refused to have an automated visual field test. Her past medical history was unremarkable with no history of smoking. Her family history of systemic and ocular conditions included heart diseases, arthritis, glaucoma and cataracts. The patient was not on any medications and was allergic to Codeine and Omeprazole. She complained of blurry vision at distance initially, due to under-corrected refractive error, but had no symptoms of CHM including nyctalopia. She refused an electroretinogram (ERG) or specific genetic testing for further assessment of her condition.

Her ocular anterior segment examination was unremarkable. Dilated fundus examination revealed diffuse mottling with normal vasculature. There was some peripapillary atrophy OU. Fundus photography images (Canon CF-1 OIS version 11.4.0) revealed diffuse mottling and scattered changes in fundus coloration centrally and in the mid-periphery (Fig. 1). The intravenous fluorescein angiography (IVFA) images showed large irregular and confluent patches of RPE atrophy (Fig. 2). The patient was further imaged with the spectral domain optical coherence tomography (SD-OCT; Spectralis, Heidelberg Engineering, Germany) where shortening of the photoreceptor inner and outer segments in areas corresponding to RPE atrophy were observed. Additionally, changes in the RPE thickness were seen corresponding to the hypo-reflective regions on the scanning laser ophthalmoscope (SLO) scans. The remaining laminations, however, appeared to be normal in both eyes (Fig. 3).

The patient was imaged on the FDA approved, RHA™ Multi-Spectral Imaging Device (Annidis Corporation, Ottawa, Canada). The system uses twelve specific individual, non-overlapping, narrow-band LED light sources in a range from 520 nm to 940 nm to create en-face spectral images throughout the posterior segment from internal limiting membrane (ILM) to the choroid. The short-wavelength images (MSI-580 nm and MSI-590 nm), which increase the visibility of the anterior retinal layers, showed healthy looking vasculature OU but hyper-reflective white anomalies were seen in the mid-periphery of both eyes (Fig. 4A and B). With the use of longer-wavelength images (MSI-620 nm – MSI-850 nm)

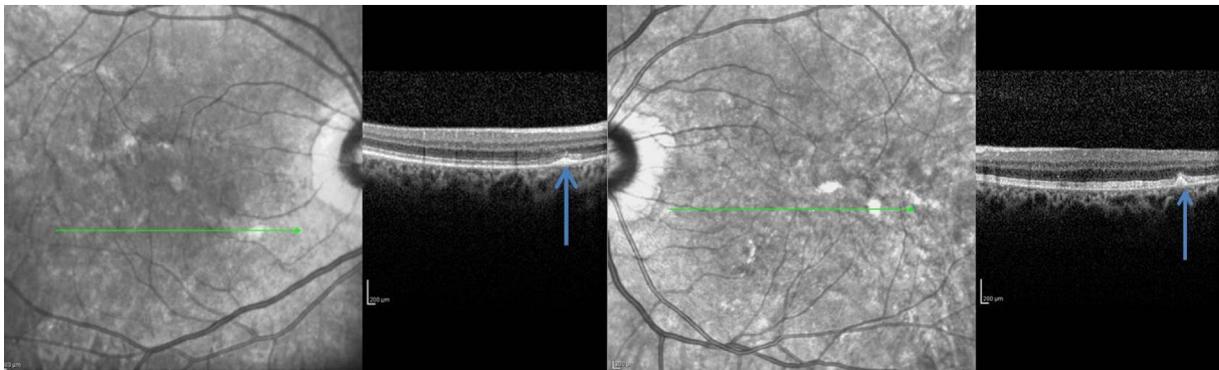


Fig. 3. Optical coherence tomography (OCT) scans of patients eyes. The blue arrows indicate areas of irregularities of the retinal pigment epithelium in both eyes in the OCT en-face thickness scan corresponding to hypo-reflective spots in the per-macular area (see green lines through the area of irregularity).

visualization of the RPE and the anterior surface of the choroid were possible and the images showed hypo-reflective areas as well as defined melanin pigment clumps, not seen with the other modalities and likely associated with the loss of the inner segment/outer segment junction. (Fig. 4C and D).

The retinal oxy/deoxy maps (MSI-OH1) are the combination of the 580 nm and 590 nm wavelength images used to enhance the differential contrast of the retinal vasculature based on hemoglobin oxygenation level in the vessels and the retina. Arteries appear bright while deoxygenated veins appear dark. These images strongly resemble IVFA with respect to pooling of fluid but are non-invasive to obtain. The black spots seen in this case are melanin clumps obscuring the view of the underlying choroidal structure. They correlate directly with the spots observed with the long wavelength MSI images (Fig. 5). The oxy/deoxy feature plays a significant role in the detection of vascular disorders such as early diabetic and hypertensive retinopathies. It may help with the differential diagnosis of CHM from RP where vessel attenuation is generally observed.

MSI-FAF is generated by an absorption and reemission process in which the retina is illuminated with an average wavelength of 600 nm and re-emitted at a wavelength greater than 660 nm. For this patient, the MSI-FAF showed a primarily hypoautofluorescent fundus with some actively degenerating hyperautofluorescent areas (Fig. 6A). Such appearance is typically described as irregular mosaic of low to high density FAF. Mottled irregularities were seen on both sides of the vessel arcades. Multiple small flecks of reduced and single flecks of increased autofluorescence were also visible.

The MSI-940 images (clinical research only) of this patient are shown in Fig. 6B. The RHA™ can capture transmission images of the choroid by projecting 940 nm light to the back of the eye by way of the sclera, which acts as a wave guide. Backscatter provides a high-resolution image of the choroidal vasculature without the use of invasive dyes. The MSI-940 images, which resemble indocyanine green angiography (ICGA), also revealed melanin stacking in the area of RPE disruption.

3. Discussion

Choroideremia is a progressive, recessive X-linked disease that primarily affects males. Although, female carriers are often asymptomatic, the fundus may show the presence of pigmentary mottling. These clinical signs rarely lead to the visual dysfunction and fundus manifestations experienced by males.

Although functional tests such as ERG have shown abnormal retinal function in CHM patients [9], ERG can still be normal in the early stages of the disease. Rod amplitude responses have been found to be generally reduced in affected males with minimally prolonged rod implicit times while cone amplitudes are initially normal or reduced [10]. In female carriers, ERG amplitudes have been found to be abnormal in only 15% of cases [9] and therefore must be used in combination with other diagnostic techniques. In a report on a case of CHM carrier with unilateral central vision loss, multifocal ERG (mfERG) showed severely reduced amplitudes associated with a band of retinal pigment epithelial and choroidal atrophy in the macula [11]. Reports on visual field results in carriers of CHM have mainly suggested normal outcomes with possibility of blind spot enlargement in some cases in an older study [12]. This corresponds to the peripapillary atrophy seen in this case. Grover S et al. [13] reported normal visual field results in 6 CHM carriers who had fundus abnormalities. Another study showed a dense central scotoma on Humphrey visual fields testing in a case of a CHM carrier with severe unilateral central vision loss [11]. In our case, the patient refused additional procedures including ERG, visual fields and genetic testing for further

assessment of her condition as it was diagnosed over 20 years previously. MSI with FAF and a thorough clarification of family history are readily available primary care tools to assist in the diagnosis of the CHM state in carriers.

Using MSI, clinical signs such as peripapillary atrophy, RPE mottling in the macular region, RPE melanin clumping, flecks of atrophy in the periphery and hypoautofluorescence in areas of RPE atrophy with some mottled hyper and hypoautofluorescence can be found in CHM carriers [7,14]. Mottled irregularities seen in FAF imaging are helpful in identifying female CHM carriers and a

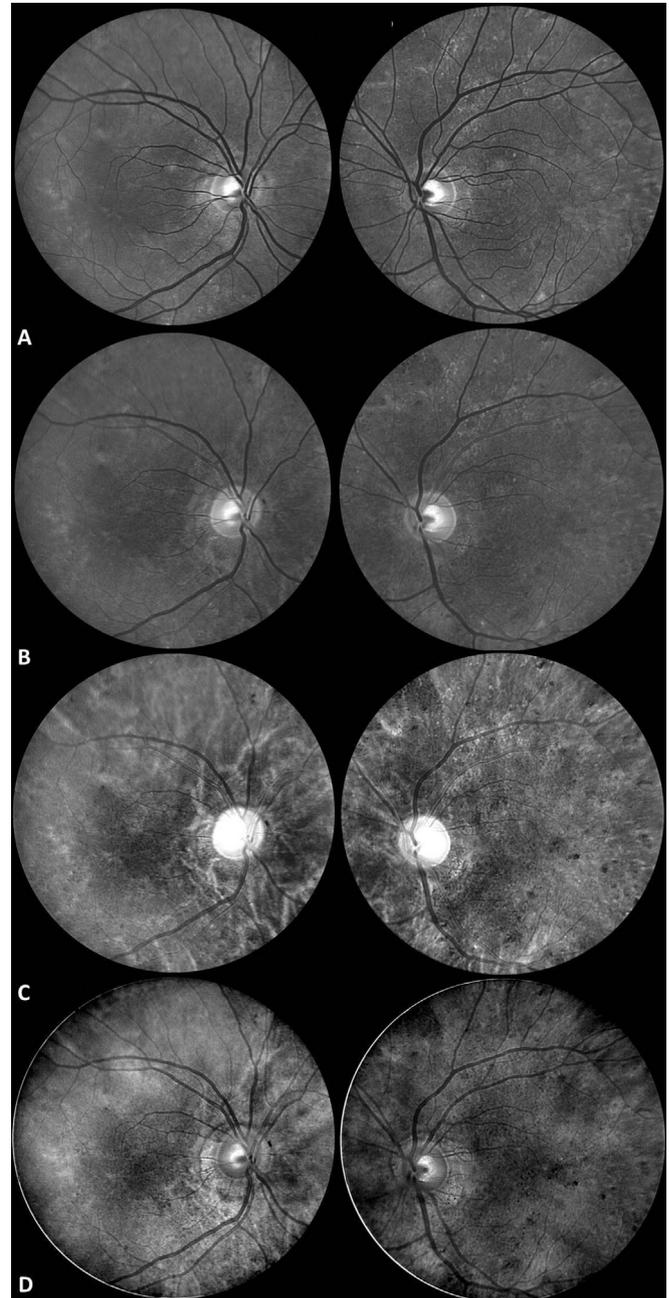


Fig. 4. Multi-spectral imaging (MSI) imaging - MSI-580 (A) and MSI-590 (B) images of the patient's eyes showing a healthy looking vasculature in both eyes and some scattered hyper-reflective deposits superiorly in the left eye. MSI-620 (C), MSI-660 (D) images of the eyes showing increased visibility of the pigment mottling and retinal pigment epithelium disruption with an increase in wavelength and depth penetration.

valuable diagnostic factor that facilitates specific genetic testing [9]. OCT studies in female CHM carriers have demonstrated only subtle RPE irregularities with attenuation more prominent outside the macular region [15].

To the best of our knowledge, this is the first report of a fundus appearance of CHM carrier using MSI. Details of this technique have been described and published previously [16]. Conventional fundus imaging provides minimal diagnostic value because of the poor view of the RPE. Fundus images are useful in the documentation of certain features, but identification of pathologies at early stages is limited due to color over-saturation and the impact of media opacities such as cataracts. This limitation is even more evident with deeper structures of the retina. With the use of MSI and the specific selection of spectral bands, the sub-retinal structures and metabolic features of the retina and choroid can be visualized in finer details. This makes MSI a valuable tool for diagnosing and monitoring the effect of retinal and choroidal preservation of patients with CHM in combination with en-face high-resolution OCT.

The unique location of the RPE, between the photoreceptors and choroid, makes it a vital feature in mediating the transport of nutrients and oxygen to photoreceptors. A progressive accumulation of oxidative stress, that is an imbalance between the production of reactive oxygen species (free radicals) and antioxidant defenses due to pathological factors, is a fundamental mechanism involved in RPE cell death. Previous research has shown that photoreceptor degeneration in both humans and animal models of hereditary retinal degenerative disease corresponds with a progressive reduction of the retinal circulation [17,18]. To-date no known studies have shown alteration of retinal and choroidal oxygenation in a case of choroideremia. Loss of the choriocapillaris and the RPE are suggested to contribute to photoreceptor degeneration in choroideremia and the RPE is suggested as one primary site of degeneration in patients with choroideremia [4,5]. The MSI-OH1 represents oxy/deoxyhemoglobin contrast maps which can hence identify any disturbance in the retinal circulation and oxygenation due to atrophy or hypoxia. MSI technology allows clinician to detect the extent of RPE and photoreceptor abruptions in pathologies that involve the retinal inner layer and the choroid, including CHM and age related macular degeneration.

Clinical diagnosis of CHM can be confirmed with an immunoblot assay. An examination of the genomic DNA or the mRNA must be performed to identify the molecular cause of CHM. CHM carriers with no detectable fundus signs can be identified only through such molecular analysis [19]. The patient profiled here presented with a positive family history and extensive fundus mottling. With regards to treatment options for CHM patients, gene therapy can potentially improve rod and cone function and ultimately overcome any negative effects of retinal detachment [20]. Non-invasive MSI imaging of the retina and choroid can be very beneficial in clinical

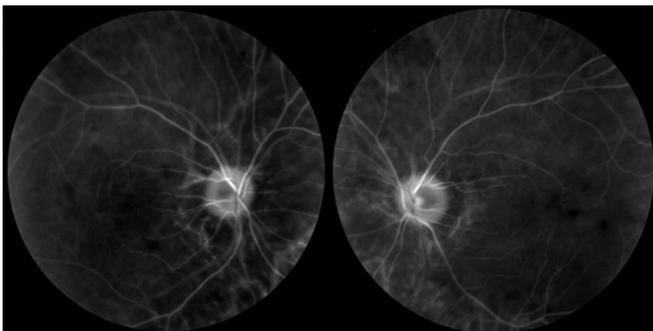


Fig. 5. Multi-spectral imaging (MSI-OH1) retinal oxy-deoxy contrast images.

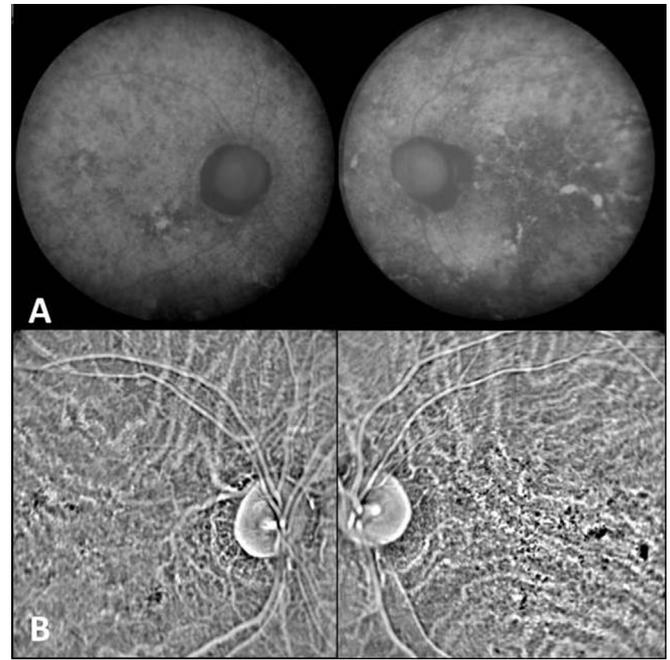


Fig. 6. Multi-spectral imaging (MSI) fundus autofluorescence (MSI-FAF) (A) and MSI-940 (B) [clinical research application only] for right and left eyes.

practice both for diagnosis and monitoring of vision threatening pathologies including CHM. The discrete LEDs and filters used in MSI significantly improve visualization of vital fundus structures, particularly the RPE. Considering the important role of the RPE and choroid in the pathogenesis of retinal pathologies, examination of these layers with MSI may prove highly valuable at every stage of disease in combination with other imaging modalities.

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