Multimodal imaging of the carriers of choroideremia and X-linked retinitis pigmentosa

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Dear Editor,

We are Dr. Zhi-Qing Li and Dr. Jin Yang, from the Neuro-ophthalmology and Medical Retinal Department of Tianjin Medical University Eye Hospital, Tianjin, China. We here present two cases of X-linked inheritable retinal diseases with genetic confirmation of the multimodal imaging findings of the patients, especially the female carriers. This study was approved by the institutional review board of Tianjin Medical University Eye Hospital, and the protocols adhered to the tenets of the Declaration of Helsinki. This letter mainly describes a novel imaging modality, multispectral imaging (MSI), which appeared to be sensitive in detecting the pattern of chorioretinal degeneration and the tapetal-like reflex.

X-linked inheritable retinal diseases have a characteristic family pedigree; specifically, the patients usually have sexual differences, and the carriers have no symptoms. Besides retinoschisis, choroideremia (CHM) and X-linked retinitis pigmentosa (RP) are two of the most common X-linked inheritable retinal diseases. These diseases share several common clinical features, including the same family pedigree, night blindness, constriction of the visual field, gradually reduced visual acuity, and retinal degeneration, which may lead to difficulties in the differential diagnosis and may even cause diagnostic confusion, especially in the absence of a typical fundus appearance[1].

The pedigree of X-linked retinal disease is one of the most important factors in making a diagnosis. Thus, identifying the retinal indicators of carriers with limited symptoms would be very useful, especially because some carriers have no symptoms or have mild degeneration. The present paper will focus on characterizing the multimodal imaging findings for X-linked retinal disease and the carries, especially the findings of MSI, a novel imaging modality. The MSI images of 12 specific individuals were obtained using nonoverlapping, narrow-band light sources from light emitting diodes with a range of wavelengths from 520 nm through 940 nm. MSI provided en-face images throughout the posterior pole of the eye to visualize the different retinal and choroidal layers; this information was used to detect unusual retinal and choroidal variations and distributions.

A 44-year-old man was referred with hereditary dystrophy characterized by the onset of night blindness at 20 years of age. The patient had visual acuity of 20/50 in the right eye, finger count capability in the left eye, and extensive atrophy of the choroid and retinal pigment epithelium (RPE) in both eyes (Figure 1A, 1B). For both the patient’s mother and sister, wide-field and fundus autofluorescences (FAF) imaging showing widespread “salt and pepper” changes with normal visual acuity (Figure 1C-1F). Peripheral pigmentary mottling of the RPE was observed corresponding to hypoauflorescence in wide-field FAF imaging (Figure 11-1L). Spectral domain optical coherence tomography (SD-OCT) of the patient demonstrated very severe retinal and choroid atrophy (Figure 2A, 2B). The enlarged inset images show peripheral disruption of the inner and outer segments (IS/OS) junction for the patient’s mother (Figure 2C, 2D, Enlarged inset images). OCT angiography (OCT-A) images showed that the superficial inner retinal angiogram of one of the CHM carrier, patient’s mother, has less retinal vessel density comparing with normal. Smaller and irregular foveal avascular zone (FAZ) was also observed by OCT-A images (Figure 2I-2J).

More than 12 years ago, the choroidal plexus in the fovea was visualized by optical coherence tomography (OCT) to have a retinal island-like structure. MSI demonstrated very severe retinal and choroid atrophy (Figure 2A, 2B). The enlarged inset images show peripheral disruption of the inner and outer segments (IS/OS) junction for the patient’s mother (Figure 2C, 2D, Enlarged inset images). OCT angiography (OCT-A) images showed that the superficial inner retinal angiogram of one of the CHM carrier, patient’s mother, has less retinal vessel density comparing with normal. Smaller and irregular foveal avascular zone (FAZ) was also observed by OCT-A images (Figure 2I-2J).

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Figure 1 Ultrawide-field images of patient 1 and carriers  A, B: Pseudocolour panoramic imaging showed the retina and choroid atrophy in the patient; C-F: Widespread “salt and pepper” morphology in the patient’s sister and mother; G, H: Ultrawide-field FAF in patient 1 showing the bright fluorescence from the sclera caused by the severe fundus atrophy. Atrophy of the choroid and RPE leading to bright fluorescence from the sclera. Preservation of some of the RPE island was detected (arrow); I-L: Peripheral RPE and photoreceptor FAF changes in CHM carriers.

Figure 2 Segmentation of the SD-OCT horizontal scan through the fovea of the patients and carriers  A, B, E, F: SD-OCT of patients demonstrated very severe retinal and choroid atrophy on both of the patients; C, D, G, H: Enlarged inset images show peripheral disruption of the ellipsoid zone of both of the patients’ mothers. OCT-A images: I, M: The superficial inner retinal angiogram of complement factor H carrier shows less retinal vessel density comparing with the normal. Smaller and irregular foveal avascular zone was also observed by OCT-A images; J, N: The deep inner retina angiogram; K, O: En face OCT angiogram of the outer retina after application of the projection artifact removal algorithm showed residual patches of nonvascular flow signal; L, P: The choriocapillaris angiogram.
by the folds, which is a new characteristic of CHM determined by MSI that had not been detected with traditional fundus photo imaging. A choroidal oxy-deoxy map, used to detect variations in the distribution of choroidal blood, revealed more obvious hyperreflective large choroidal blood vessels than other imaging systems while also providing information about the inner retina. The genetic test results showed that exon 1 of the CHM gene was absent in this patient.

The second case involved a 5-year-old boy with negative RP gene panel test results whose parents discovered that he had night blindness symptoms and was referred by other doctors. The patient had visual acuity of 20/100 in both eyes. The best corrected vision was -3.75DS-2.00DC×20=20/25 in the right eye and -2.25DS-2.00DC×180=20/25 in the left eye. Ultrawide-field imaging showed a dim retina with widespread yellow-white dots (Figure 4A, 4B). Pigment migration in the peripheral area in the left eye was detected. A hyperautofluorescent ring in the macula was found by ultrawide-field autofluorescence (UWAF) imaging (Figure 4G, 4H). SD-OCT images showed obvious thinning of out retina segment with preserved fovea area (Figure 2E, 2F). The enlarged inset images showed the same peripheral disruption of the ellipsoid zone for the patient 2’s carrier (Figure 2G, 2H, and enlarged inset images). For the patient’s mother and sister, fundus images showed similar phenotype from each other (Figure 4C-4F). Ultrawide-field imaging showed a widespread yellow-red tiny point reflex. A radial hyper autofluorescence pattern that spread to the distant peripheral retinal area was detected by UWAF in both eyes (Figure 4I-4L). A tapetal-like reflex sign (TLR) was observed as a hyperreflective radial pattern in 488-R and near-infrared reflectance (NIR-R) images at the posterior pole (Figure 4M, 4N).

At earlier stages of RP, it is difficult to detect the characteristics of RP in regular images since the pigment migration is not clearly observable; in contrast, detection of the choroidal layer at a shorter than usual wavelength may be one of MSI characteristics of RP. The characteristics of retinitis pigmentosa GTPase regulator (RPGR) carriers’ short-wavelength MIS images were similar to those of 488-R images showing a typical tapetal-like reflex (580 nm, Figure 4O-4R). Note that the radial pattern in the anterior layer can travel deeper than the nerve fibre layer and was even present in the bottom row of longer wavelength MSI images (810 nm, Figure 4S). The radio pattern reflex sign became a tiny point reflex as the wavelength became longer (Figure 4S, arrow) and this feature wasn’t detected by other imaging methods.

Although the RP panel test was negative at the beginning, based on the family pedigree and the characteristics of the patient’s fundus, we suspected an X-linked RP with RPGR mutation, which accounts for 70%-90% of its causes[2-3]. A genetic retest targeting on the RPGR gene confirmed the diagnosis and was performed instead of a test of the entire inheritable retinal diseases panel. The genetic test result was as follows: NM_001034853.1:c.3027_3028delGG (p.Glu1010GlyfsTer68), Homo. The patient’s mother and sister are RPGR gene mutation carriers.

Summarizing these two cases, the sign of the carrier’s retinal fundus can be detected by the different imaging systems. The Optos fundus camera (Optos PLC, Dunfermline, Scotland) is a Cslo-based system with an ellipsoid mirror that permits visualization of up to 200° (wide-field imaging), which can provide images of the peripheral area very clearly and easily[4]. The “salt and paper” characteristics in the peripheral area in
CHM carriers were more obvious in ultrawide-field colour images. The tapetal-like reflex in X-linked RP carriers can be detected well using UWAF; this UWAF finding has never been published previously. The characteristics of the TLR were determined using the short-wavelength (488-nm excitation) or the near-infrared (820-nm excitation), FAF previously; these capabilities are available with a Heidelberg HRA cSLO[5]. Compared with the UWAF, 488-R and 820 near-infrared provided better visualization of the reflex, but with UWAF, the reflex had a more widespread location and a more diffuse appearance.

MSI is an emerging technology that is being developed in a solitary device; this technology will continue to evolve because new metabolic diagnostics are required for enhanced patient care[6]. The factors differentiating MSI from digital fundus imaging are multifaceted; one factor is the monochromatic spectral slicing. Since the CHM gene mutation occurs in one gene that will be studied in a clinical trial[7], details of the retinal anatomy are becoming more important for follow-up treatments. In case 1, choroidal plexus in the fovea was observed directly by MSI; this feature cannot be detected by other model imaging systems. The choroidal oxy-deoxy
map, which was used to detect variations in the distribution of choroidal blood, more clearly showed the hyperreflective large choroidal blood vessels. In case 2, the radial pattern found in the short wavelength range became a tiny point reflex in the longer wavelength range, providing a new indicator for RPGR patients. More cases should be evaluated to confirm this phenotype. Access to both in vivo dissections on SD-OCT and topographic spectral slices on MSI generates a wealth of information that can help a managing clinician more accurately diagnose an occult pathology such as retinal degeneration disease. MSI is a novel non-invasive tool for retinal imaging. In patients with RP, the hyperautofluorescence ring (also called the Robson Holder ring) in the posterior area is one of the characteristics of RP[8]. For case 2, there was an obvious binocular symmetric high fluorescence ring, but this feature was not detected in CHM patients. At present, preliminary studies have shown that the hyperautofluorescence ring may be caused by the increase in oxidative stress and the accumulation of lipofuscin that occurring during the process of disease development. The specific pathogenesis remains to be studied[9]. However, the size of the Robson Holder ring in patients with RP can be an important indirect sign to evaluate during follow-up[10]. SD-OCT showed that the changes in photoreceptor cell layer thinning and the Robson Holder ring are features that should be considered in an optimal protocol for clinicians to identify the disease progress. The density of retinal vessel and the characters of FAZ in X-linked retinal disease showed by OCT-A need to be confirmed by more cases in the future.

Multimodal imaging can help identify the target gene that should be tested. The patient in case 2 previously had a negative RP panel genetic test result. Negative genetic test results generally have several possible explanations: 1) the mutation gene is located in a specific area that is easy to miss or undetectable using the general detection methods; 2) important genetic information is missed, the wrong disease panel is selected, or the genetic test panel covers a limited range; 3) the mutation is novel, requiring evaluation of the full exon or genome-wide genetic testing. Whenever a negative genetic test result is found, the guidelines of gene sequencing recommend a whole exome genetic test. However, for this case, although the initial gene report was negative, multimodal imaging detected a tapetal-like reflex sign, which is part of the phenotype of an RP carrier. Thus, a single genetic test was performed rather than the whole exosome gene test, benefiting both the patients and the genetic counsellor. In conclusion, using non-invasive techniques to characterize the phenotype of X-linked inheritable retinal disease patients and carriers is useful for targeted genetic tests and genetic counselling of affected family members. The limitation of this letter is the small number of cases. Additional related cases are needed to identify new characteristics. Subsequently, all new characteristics identified using the new technology must be elucidated in the future and may help inform management decisions.

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