Multimodal Imaging for Retinal Disorders

Dr. Devesh Kumawat MD, **Dr. Vinod Kumar** MS

Dr. Rajendra Prasad Centre for Ophthalmic Sciences, AIIMS, New Delhi, India

Retinal imaging technologies are evolving continuously and have thrown light on several aspects of various retinal disorders. The diagnosis and optimal management of various optic disc and retinal disorders depends on the functional and morphological assessment provided by different imaging techniques. These investigations when used individually may have certain diagnostic benefits as well as limitations for a given disease/disorder. When combined, multiple investigations can cover up the limitations/ lacunae of each other, complement each other and provide better diagnostic accuracy. This has been referred to as 'multimodal imaging'. The concept of multimodal imaging (MMI) is not new and has been long used in other fields of medicine such as radiology, cardiology and oncology. The MMI has been defined as "the combination of imaging modalities to provide improved preclinical assessment, diagnostics, and therapeutic monitoring" or "the efficient integration of two or more methods of imaging to improve the ability to diagnose, guide therapy, or predict outcomes"[1].

The commonly used retinal imaging modalities include color photography, optical coherence tomography (OCT), short-wave and near infrared autofluorescence (AF), fluorescein angiography (FA), indocyanine green angiography (ICGA), confocal scanning laser ophthalmoscopy (cSLO) and OCT angiography (OCTA). Recently the MMI concept has also been extended to the use of digital color disc photography and cSLO for the detection of early optic disc damage in glaucoma[2].

MMI can either be performed over a single machine with available multiple technological systems or over multiple machines with different systems. MMI can be performed concurrently or within a short time frame to obtain accurate cross-sectional information at a given time.

Various kinds of filters (red, blue and green) have been used historically to highlight different tissue characteristics (Figure 1)[3]. Red-free green filters (540-570nm) allow green monochromatic light to enter with minimal scatter and excellent contrast. Retinal hemorrhage, vessel, retinal nerve fibre defects, and drusen are better identified on red-free imaging. Green free imaging is sometimes used for visualisation of retinal pathologies such as angioid streaks. Blue filter is used for assessment of inner retinal surface and dissociated optic nerve fibre layer (DONFL) is seen best on this imaging modality (Figure 2)[4].

Color fundus photography has improved over time to the current digital state which provides good quality en-face images (Figure 3a). However, it still is limited by its resolution, lack of cross-sectional image, and lack of quantitative and functional assessment. The cSLO based systems use pinhole apertures and longer single wavelength to obtain high resolution retinal images, especially AF and ICG. However, cSLO based cameras provide only black and white or pseudo-color images (Figure 4)

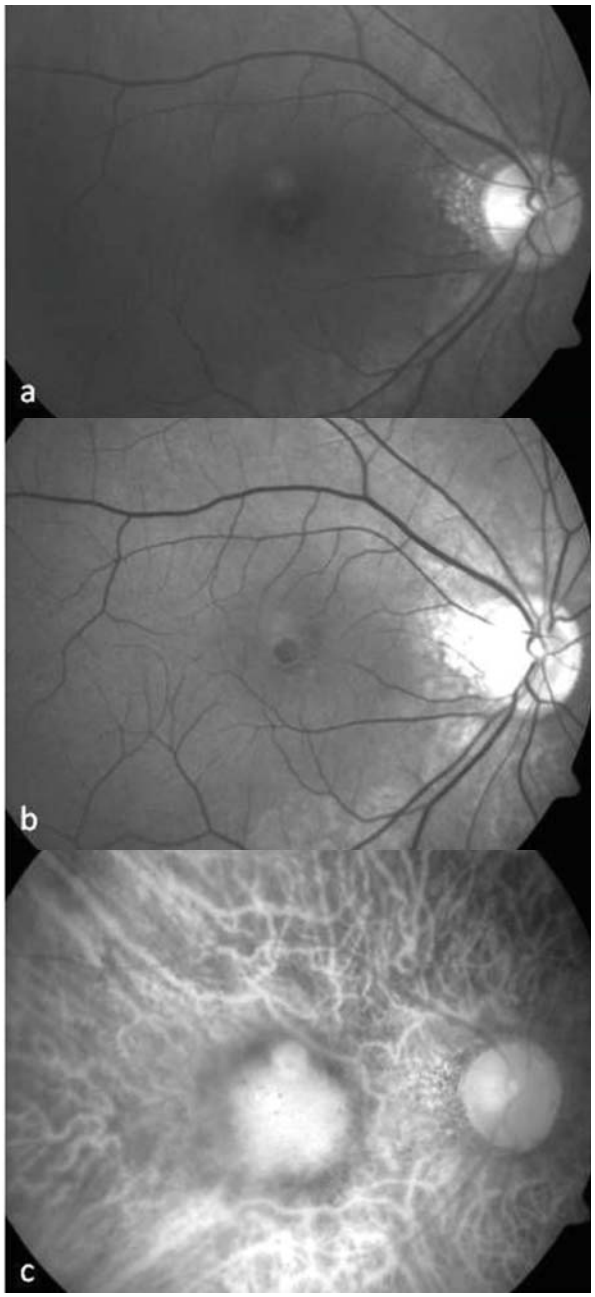

Figure 1: *Fundus photographs of the right eye of a patient with circumscribed choroidal hemangioma with overlying full-thickness macular hole using different filters.* ***(a):*** *shows the images using blue filter. The retinal surface and the arcuate nerve fibres are better visible.* ***(b):*** *shows the image using green filter. The retinal vessels and the macular hole are clearly visible.* ***(c):*** *shows the image using red filter. The choroidal vessels and the hemangioma are visible using the red filter only.*

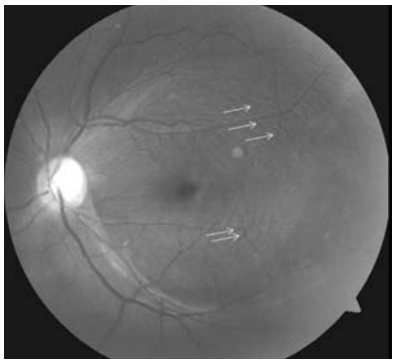

Figure 2: *Blue filter fundus photograph of left eye of a patient who underwent epiretinal membrane peeling and internal limiting membrane peeling for full thickness macular hole with epiretinal membrane. Slightly dark straie can be noted at the posterior pole along the course of nerve fibre layer (white arrows), also known as Dissociated optic nerve fibre layer appearance.*

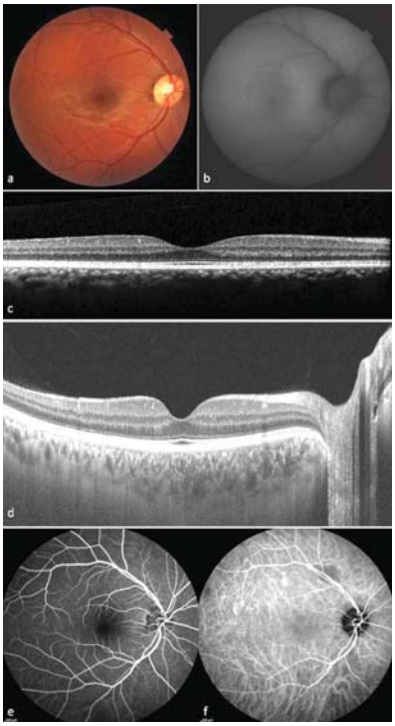

Figure 3: *Multimodal imaging of the right eye of a healthy male.* ***(a):*** *shows the standard color fundus image.* ***(b):*** *shows the blue-wave autofluorescence image with bright areas having more lipofuschin laden RPE cells and dark areas being devoid or having less lipofuschin.* ***(c):*** *shows the spectral domain optical coherence tomography of the macular area with normal foveal architecture. Note that the choroidal details are not better visible.* ***(d):*** *shows the swept source optical coherence tomography with better delineation of the choroidal layers and the choroido-scleral junction.* ***(e):*** *shows the fundus fluorescein angiogram at 2 minutes with normal retinal vasculature. Note that the choroidal vasculature is not appreciated.* ***(f):*** *shows the indocyanine green angiogram at 2 minutes showing both the retinal and the choroidal vasculature.*

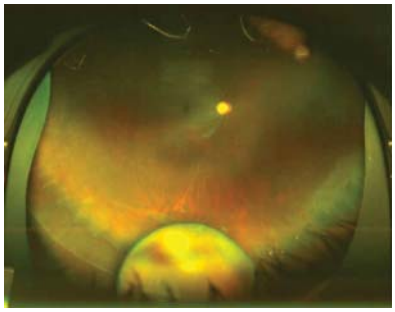

Figure 4: *Ultra-wide field pseudocolor image (Optos cSLO imaging system) of the right eye of a child with posterior dislocation of crystalline lens. Note that the use of separate single wavelength green and red SLO provides a false colored image where the retina appears bright orange and certain details of retinal pathologies may be obscured.*

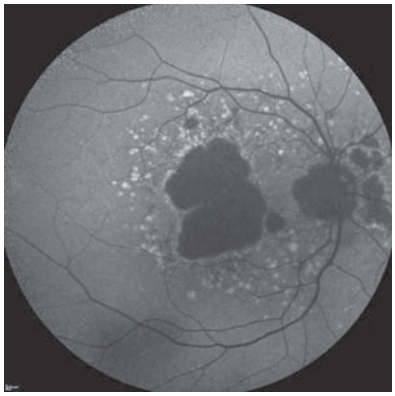

Figure 5: *Blue or short-wave autofluorescence image of the right eye of a patient with non-exudative age related macular degeneration. A central well defined area of hypoautofluorescence is seen suggesting an area of geographic atrophy with total loss of retinal pigment epithelium (RPE). Surrounding hyper-auto fluorescent areas correspond to the drusen.*

and are susceptible to motion artefacts.

The traditional methods to image vessel flow and structure such as FA and ICG (Figure '3e' and '3f') have their own limitations other than being invasive and prone to hypersensitivity reactions[5]. FA determines the retinal vessel flow and leakage, thereby is useful for detection of retinal capillary non-perfusion and neovascularisation in disorders such as diabetic retinopathy, vasculitis sequalae, vascular occlusion etc. Due to its physiochemical properties, fluorescein normally leaks from the choroidal vasculature and is thereby of limited usage in diagnosis and management of choroidal abnormalities. However, ICG stays within choroidal vasculature (more protein bound and high molecular weight) and because of longer absorption (790 to 805µm) and emission spectrum (770 to 880 µm), ICGA allows much-improved evaluation of the choroid. FA and ICG however do not provide depth wise resolution of retinal and choroidal layers and leakage of dye may obscure details thereby preventing precise evaluation.

AF non-invasively maps the fluorophores lipofuschin and melanin present in retinal pigment epithelium (RPE) and provides topographic information about the RPE health but lacks information about vessel flow[6]. Short-wave AF uses the fluorescent properties of lipofuschin, which is a photoreceptor degradation product present within the RPE. The lipofuschin absorbs light with peak excitation wavelength of 470nm and yellow-green light at wavelength of 600-610nm. On the other hand, near-infrared AF uses a longer exciting wavelength (790nm) for the fluorophores melanin present in the RPE and choroid. A spatial distribution of lipofuschin/melanin decides the pattern of AF. The dark areas correspond to low intensities of emission and bright areas correspond to high intensities of emission (Figure 3b). Topographic mapping of lipofuschin/melanin and indirectly the RPE health is of utmost importance in diagnosis, prognosis and management of age-related macular degeneration (Figure 5), white dot syndromes and various retinal and RPE dystrophies. However, background noise, poor image quality and interference from the crystalline lens are the major drawbacks of AF.

Infrared or near infrared reflectance (NIR) imaging is a new modality with increasing popularity of cSLO based cameras[7]. Due to a longer wavelength (>800nm) of the light used from IR source and strong reflectance from melanin, subretinal changes such as reticular drusen are visible better. Also, it easily penetrates through lenticular opacities and vitreous hemorrhage. Choroidal hamartomas in neurofibromatosis are seen best on NIR imaging (Figure 6).

OCT allows high resolution cross-sectional analysis and measurements of various interface and layers such as vitreo-retinal interface, outer retinal bands, RPE-Bruch's complex, choroidal layers and sclera-choroidal junction (Figure '3c' and '3d'). Again OCT lacks the retinal and choroidal flow details. While conventional longitudinal OCT scanning provides a cross-sectional retinal image, en-face OCT provides a transverse image at a particular depth (Figure 7)[8]. En-face

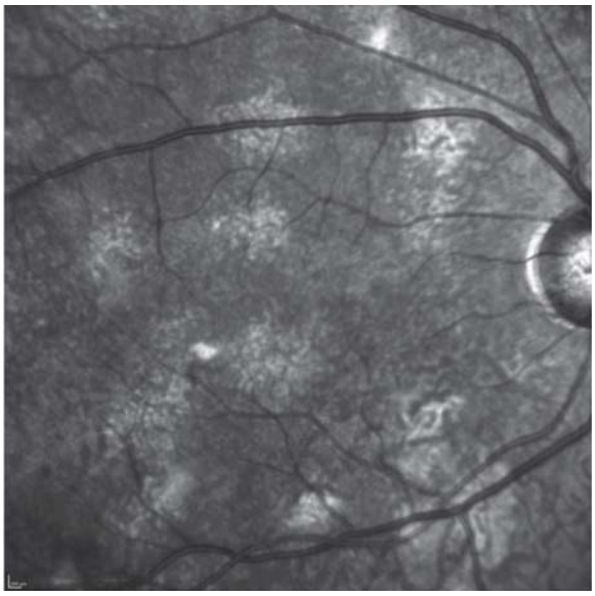

Figure 6: *Near infra-red reflectance (NIR) image of the right of a patient with neurofibromatosis. Choroidal hamartomas appear as bright patches on NIR.*

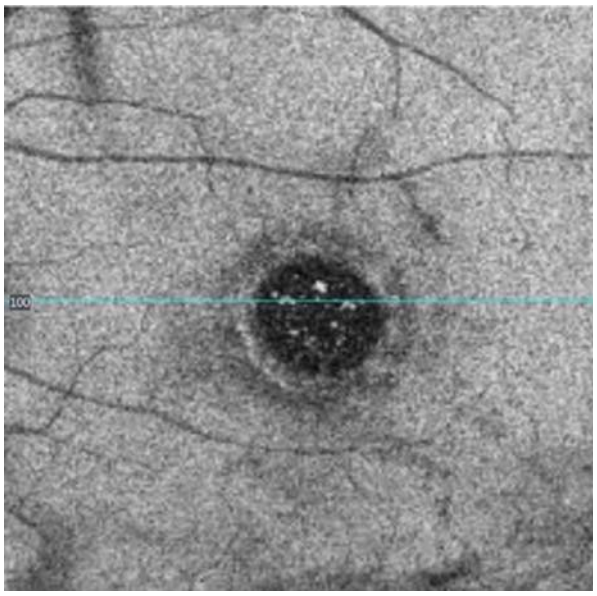

Figure 7: *En-face optical coherence tomography of the left eye of an adult patient with a full thickness macular hole. The transverse image provides a better topographic delineation of the pathology.*

OCT not only provides a view similar to that in fundus photography, it also helps in better overview and delineation of pathological changes in a single image at a particular level within the retina or choroid. En-face OCT has provided us with high resolution transverse images and better understanding of diabetic macular edema, reticular pseudo-drusen, and choroidal neo-vascular membrane.

OCTA is a non-invasive imaging that provides both retinal and choroidal vascular structural details (Figure 8)[9]. It even images the radial peripapillary and deep retinal capillary networks that are not clearly visible on FA. Limitations of OCTA include inability to show leakage and tendency for numerous image artefacts. Clearly none of the above mentioned modality in itself provides complete structural and functional information of the fundus and a holistic approach is to use the modalities in combination to arrive at a conclusion.

To better understand the concept of MI, a clinical case is being discussed. A 25 year-old male patient presented with complaint of metamorphopsia in the left eye for the past two months. Clinical fundus photography shows a deep excavation in the temporal half of optic disc suggestive of juxta-papillary excavation (Figure 9a). The foveal reflex was blunted and neurosensory elevation could be noted at the macula. However the extent and level of abnormality could not be gauged form the clinical photograph. OCT scan was able to confirm and measure the neurosensory detachment at the macula which did not have a connection with the excavation area (Figure 9b). The differentials included juxta-papillary excavation with resulting maculopathy or coexistent serous choroidopathy. However, FA showed a characteristic smoke stack leakage which confirmed the diagnosis of central serous choroidopathy (CSC) (Figure '9c' and '9d'). In addition the choroid was thickened on OCT assessment. A multimodal approach helped in attaining an accurate diagnosis of juxta-papillary excavation with CSC which needed conservative approach and counselling, whereas a misdiagnosis and surgical treatment in line of juxta-papillary excavation with maculopathy could have been futile and troublesome for the patient.

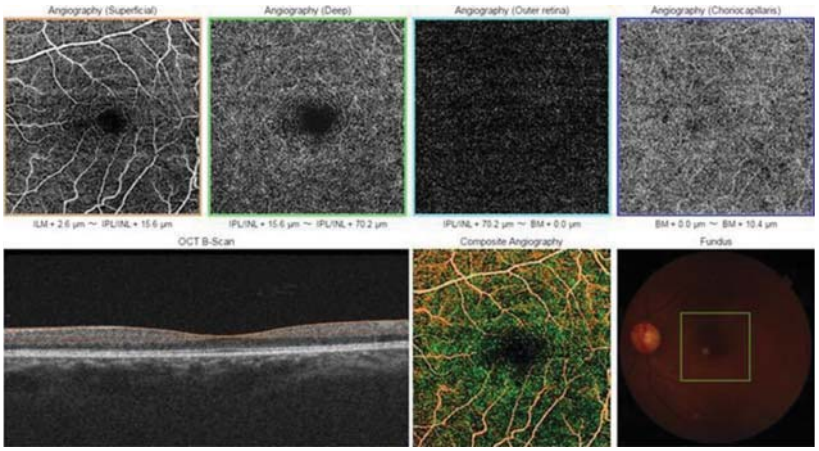

Figure 8: *Optical coherence tomography angiography of the left eye of a healthy adult male. Other than the OCT B scan and color fundus photograph, it provides with fine details of the superficial and deep retinal vasculature. Any abnormal vasculature at the level of the outer retina and the choriocapillaris can be picked up.*

There is no doubt that MI is a boon for the ophthalmologists, but the clinical information provided by multiple modalities may be similar and thereby redundant. The availability of advanced imaging modalities have a possibility of increased misuse through futile studies that contribute little to diagnosis and management other than increased healthcare expenditure. The type of investigations ordered should be such that maximum information is achieved with minimum number of investigations performed in a reasonable time frame with minimum overall cost as well. Currently the use of MI needs to be

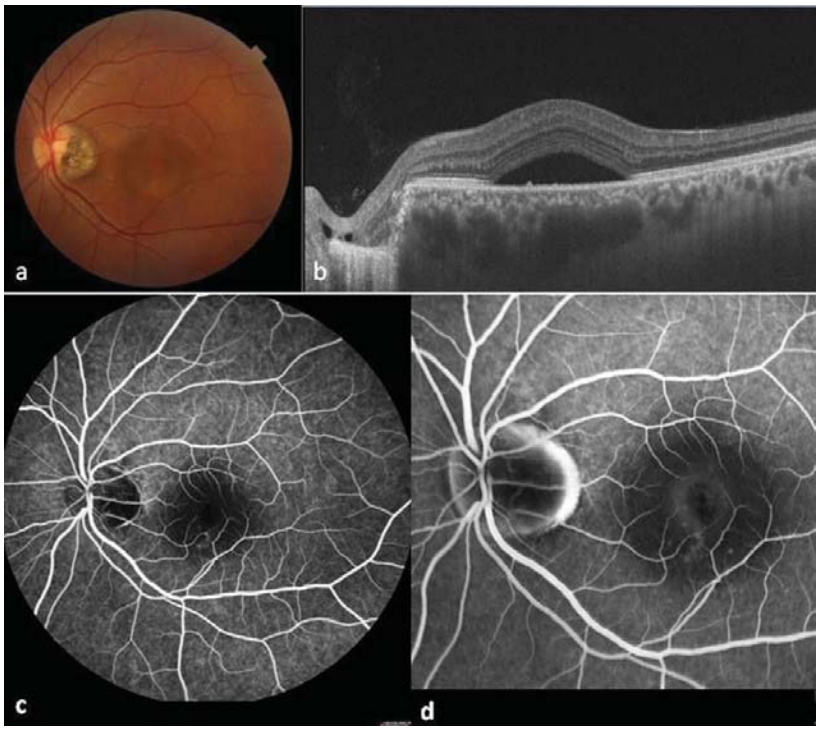

Figure 9: *Color fundus photograph of left eye of an adult shows a temporal excavated area adjacent to the optic disc and a neurosensory elevation centred on the macula* ***(a)****. The macular OCT line scan through the lesion and macula confirms the juxta-papillary excavation and neurosensory detachment at the macula* ***(b)****. Fundus fluorescein angiography shows pint point multiple leaks* ***(c)*** *at the macula in early phase. One of the leaks turns into pooling into the subretinal space in the form of a 'smoke-stack' in the late phase* ***(d)****.*

guided by a preceding detailed clinical examination and then standardized to obtain greater efficiency and efficacy of patient care.

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Correspondence to:
Dr. Devesh Kumawat
Dr. Rajendra Prasad Centre for Ophthalmic Sciences, AIIMS, New Delhi, India