British Medical Bulletin, 2014, **111**:77–88
doi: 10.1093/bmb/ldu022
Advance Access Publication Date: 18 August 2014

Ophthalmic imaging

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Accepted 14 July 2014

Abstract

Introduction or background: The last two decades have seen a revolution in ophthalmic imaging. In this review we present an overview of the breadth of ophthalmic imaging modalities in use today and describe how the role of ophthalmic imaging has changed from documenting abnormalities visible on clinical examination to the detection of clinically silent abnormalities which can lead to an earlier and more precise diagnosis.

Sources of data: This review is based on published literature in the fields of ophthalmic imaging and with focus on most commonly used imaging modalities.

Areas of agreement: New imaging techniques enable non-invasive evaluation of ocular structures at a resolution of a few micrometres. This has led to a re-evaluation of diagnostic criteria for ocular disease, which were previously defined by clinical findings without significant reference to imaging.

Areas of controversy: Lack of formal training and clinical guidelines regarding use of new imaging techniques in diagnosing and monitoring various ocular conditions. Lack of large normative databases and interchangeability issues between different commercial machines can hinder the detection of disease progression.

Growing points: Imaging devices are being constantly refined with improved image capture and image analysis tools.

Areas timely for developing research: Clinical applications of new techniques and devices have yet to be determined using systematic scientific research methods.

Key words: ophthalmic imaging, optical coherence tomography, fundus autofluorescence, fluorescein angiography, indocyanine green angiography, scanning laser ophthalmoscope

Introduction

Since the first photograph of human retina in 1886 until today, there have been huge advances in ophthalmic imaging. Until the last decade of the 20th century, knowledge and techniques have advanced in a linear progression. However, the arrival of scanning laser ophthalmoscope (SLO) imaging first described in 1981[1] and optical coherence tomography (OCT) imaging 10 years later[2] have heralded a golden age in ophthalmic imaging with a near exponential rise in peer review publications relating to clinical applications of these new imaging modalities. Historically, some of the techniques including ultrasound and MRI were adopted from other fields of medicine, while others were first introduced as ophthalmic imaging modalities and were later adopted by other fields of medicine. For example, OCT imaging is used in dermatology, gastroenterology, cardiology, odontology and even beyond medical applications to analyse layers and structure of ancient paintings.

Ophthalmic imaging has advanced so much that its role has shifted from simple photographic documentation of the condition to a powerful and advanced investigation method enabling clinicians to make objective measurements and assessments of the structures and details of the eye unavailable to conventional clinical examination using ophthalmoscopy.

Very quickly the progress in imaging techniques has been translated into a better understanding of the eye in health and disease, revealing new, previously undiagnosed conditions, a more detailed description of disease phenotype and providing an objective tool to evaluate the efficacy and safety of treatments.

In this review we will discuss the most commonly used ophthlamic imaging modalities with an emphasis on recent developments in imaging techniques and clinical applications.

Colour fundus photography

Thirty-five mm film photography had been a gold standard for ophthalmic photography for many decades until digital image capturing systems replaced film cameras over the last 15 years (Figs 1 and 2). However, camera optics and principles remained mainly unchanged. Using traditional techniques fundus photography requires pupil dilation with short-acting mydriatic eye drops which can cause temporary ocular discomfort for patients. Non-mydriatic cameras have been developed during the last 10 years and may be particularly useful in retinal screening programs where a large number of patients have to be imaged without the need to dilate the pupils. Although they may improve patient experience of fundus photography, they are susceptible to media opacity (such as cataract) and mydriatic cameras remain the instrument of choice especially if peripheral retina requires imaging.

Fluorescein and indocyanine green angiography

Another important field of use of fundus cameras is for fluorescein angiography (FA) and indocyanine green (ICG) angiography. With the use of different barrier and excitation filters, the retinal and choroidal circulations can be imaged both as still images and videos. For FA intravenous sodium fluorescein of 10–20% is generally used. Fluorescein as a smaller molecule is suitable for imaging of retinal circulation but does not allow detailed choroidal imaging due to profound leakage of dye from fenestrated blood vessels in the choroid (including the choriocapillaris). Indocyanine green as a larger molecule does not leave the choriocapillaris and with the use of infrared camera imaging allows visualization of the choroidal circulation. Both fluorescein and indocyanine green are generally safe and well tolerated with nausea or vomiting as the main adverse event (in 5–10% of cases). Fluorescein is excreted via kidney and can colour the urine for a few hours; however, kidney insufficiency or dialysis is not a contraindication. Indocyanine green is excreted via the liver and should not be used in patients with terminal liver failure.

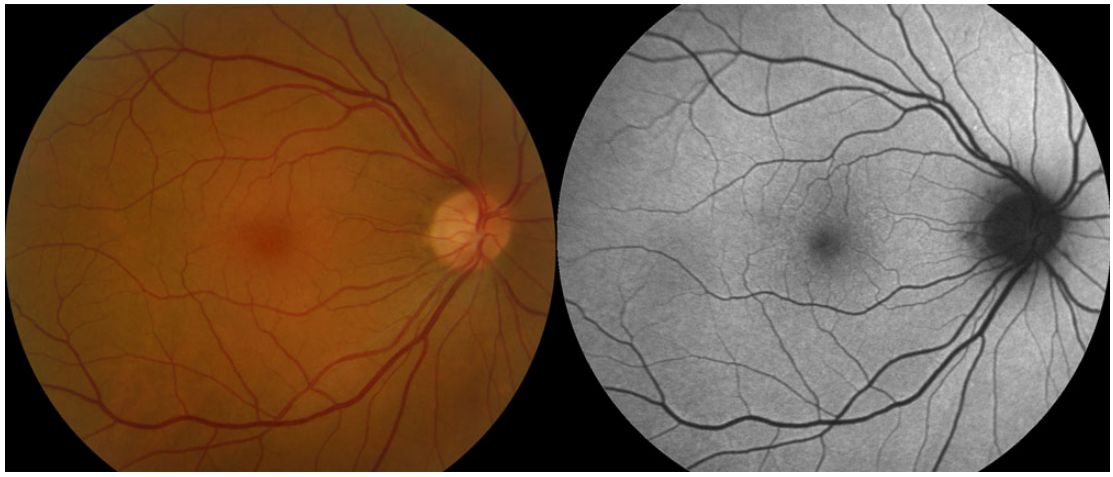

Fig. 1 Left: colour fundus photography of healthy fundus. Right: corresponding fundus autofluorescence image of healthy fundus.

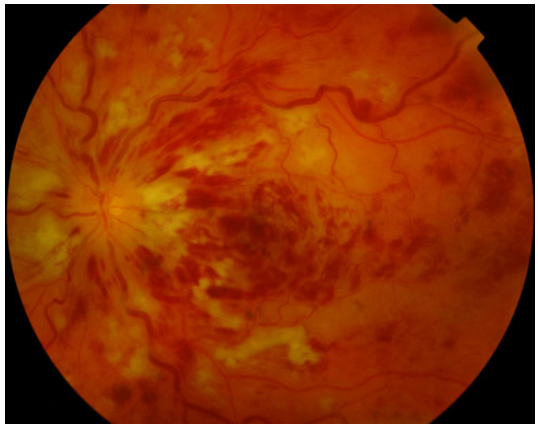

Fig. 2 Typical fundus appearance with retinal haemorrhages in all four quadrants in a case of central retinal vein occlusion.

Paediatric fundus imaging

In paediatric practice, fundus photography is useful for documenting of retinopathy of prematurity (ROP), intraocular tumours, vascular abnormalities, optic nerve head status and also anterior segment pathology. For diseases affecting the paediatric retina, the most widely used camera for imaging is a contact digital imaging system RetCam (Clarity Medical Systems, Inc., Pleasanton, CA, USA). Non-contact narrow angle hand-held cameras (e.g. Nidek NM200-D) exist and had been used in some studies. RetCam interchangeable lenses offer a wide spectrum of imaging options ranging from high-magnification and high-contrast view of the optic disc and macula to wide angle photos and fluorescein angiogram up to the anterior retinal border (the ora serrata) and even anterior chamber angle imaging. The major clinical applications include ROP screening and monitoring especially in remote areas,[3,4] documentation of paediatric fundus abnormalities, treatment results and intra-operative fundus photography. The anterior chamber angle can be assessed using the same device with a special lens. An agreement between slit lamp gonioscopy and RetCam imaging detecting closed angles has been shown to be good.[5]

Scanning laser ophthalmoscopy

The SLO was first described in 1981 and uses a monochromatic, low-powered laser light and a confocal raster scanning technique to produce images of the retina and optic nerve head. Images taken with SLO systems show similarities to images taken from monochromatic fundus photos but with improved image quality particularly in patients with cataract. Combining different wavelength lasers allows capture of a pseudo-colour fundus image, near IR reflectance image, fundus autofluorescence (FAF) images and the capability of performing FA and ICG

angiography. Another application of SLO imaging is for wide field retinal imaging as in the Optos camera system (Optos plc, Scotland, UK) which is capable of a range of imaging modalities including pseudo-colour imaging, FAF imaging and FA angiography. Optos camera systems utilize SLO technology to focus a low-powered laser on to the retina using a large dome-shaped mirror to image far peripheral retina in up to 200°. A wide field technique is particularly useful in detecting peripheral vascular pathology in diabetic retinopathy, retinal vein occlusions, uveitis, vitreo-retinal disorders and peripheral tumours. This allows the visualization of previously difficult-to-image peripheral parts of the retina and may contribute to better understanding of retinal vascular pathology in different conditions.

Other SLO imaging systems such as the Heidelberg Retinal Analyser II (HRA II; Heidelberg Engineering, Heidelberg, Germany) have additional hardware with retinal tracking capability permitting repeated imaging of identical points on the retina. This allows for greater precision when identifying clinical change between follow-up visits as the same retinal points are being imaged. SLO-based imaging is also used to image and analyse changes at the optic nerve head (Heidelberg Retinal Tomograph; Heidelberg Engineering, Heidelberg, Germany). SLO images are usually processed by built-in software allowing optic nerve head analysis and help in the diagnosis of glaucoma. The strength of HRT analysis, however, is to recognize progressive neuroretinal rim loss in patients suspected of glaucoma or undergoing treatment. For this reason, it remains the commonest imaging device for monitoring progression but may be replaced by OCT when the progression software improves. Another advantage of real-time eye tracking is the ability to superimpose and average images, thereby increasing the signal-to-noise ratio in images. In the case of SLO-based FA, this means that smaller doses of intravenous contrast need to be used to obtain images compared with conventional flash photography-based fundus cameras.

The scanning laser polarimeter—GDx (Carl Zeiss Meditec, Inc., Dublin, CA, USA) uses a similar technique to the SLO but instead of measuring scattered and reflected light from the retina, measures change in polarization state of the light as it passes through the retinal nerve fibre layer (RNFL) and calculates retardance which corresponds to status of the RNFL in a band concentric to the optic disc. GDx can be used to detect glaucoma and monitor disease progression; however, its diagnostic value remains unclear. Vessani *et al.*[6] have reported that GDx ability to detect glaucoma was better than general ophthalmologists assessing stereo photographs of optic nerve disc but not greater than that of glaucoma experts. There is also conflicting data whether RNFL thickness measured by OCT or retardance measured by GDx occurs earlier in disease progression.[7] GDx can be helpful in assessing and monitoring glaucoma progression in patients with atypical discs (ex. high myopia, tilted disc, optic disc drusen etc.). Improved OCTs are likely to compete with GDx for retinal nerve fibre layer imaging and have the benefit of wider applications within ophthalmology.

Optical coherence tomography

OCT imaging is the optical analogue of ultrasound and uses light in the near-infrared region to determine the optical reflectivity profile of tissue (e.g. the retina). This is a non-invasive, painless imaging modality, which produces three-dimensional images of the retina in a few seconds. Since the first description of the technology[2] in 1991, OCT imaging has undergone a rapid commercialization with improvements in technology leading to faster imaging with improved resolution. The axial resolution of modern OCT systems is 4–7 μm with a transverse resolution of 15–20 μm. Since the first description of OCT imaging >20 years ago, there have been several improvements in OCT technology. There has been a shift from older time-domain OCT technology to newer spectral-domain systems which have fewer moving parts leading to a 50–100 times faster imaging speed. The increased speed of imaging has resulted in a shorter time required to perform a scan and less artefacts related to eye movements or blinks.

A further development has been to modify existing OCT imaging to image the choroid (the blood rich layer of tissue below the retina) with greater resolution. One approach is that of enhanced depth

imaging (EDI) which involves using existing spectral-domain OCT but bringing the choroid closer to the most sensitive part of the scan window. Another approach is to use a light source with improved depth penetration (swept-source OCT). The first commercially available swept-source OCT was the deep range imager (DRI) OCT produced by Topcon, Inc. (Topcon, Tokyo, Japan). Swept-source posterior segment OCT uses a tunable frequency swept laser light source with faster imaging and better depth resolution than spectral-domain OCT.[8] As the resolution is only marginally improved (3 μm compared with 4–6 μm) the main advantage of the technology is a much deeper tissue penetration and wider imaging depth allowing high-quality imaging of the choroid and sclera, at least 4-fold faster collection rate (100000 scans/s) and much improved penetration through opaque media when compared with spectral-domain OCT.

OCT imaging produces quantitative information about macular or retinal thickness as well as qualitative information relating to abnormalities of retinal or subretinal morphology. OCT imaging techniques have excellent intra-session reproducibility and repeatability of corneal thickness,[9] macular thickness[10,11] and RNFLthickness[12] measurements (within a few per cent) however, measurements may not be interchangeable between different machines.[11] The use of OCT is not limited to imaging of retinal diseases but is also widely used by neuro-ophthalmologists, glaucoma and anterior segment specialists.

Clinical applications of posterior segment OCT

OCT imaging is now an essential part of the evaluation of the patient with symptoms or signs of macular disease. The technology has been widely adopted in eye units in the UK and there has also been significant adoption of this ophthalmic imaging technology by high-street optometrists. In hospital settings, OCT imaging of the retina is used to diagnose macular or retinal conditions, monitor disease activity and assess the efficacy of any treatment. Undoubtedly, the biggest patient group to benefit from OCT imaging are those with age-related macular degeneration (AMD) followed by diabetic retinopathy or maculopathy (Fig. 3), retinal vascular occlusions (particularly branch and central retinal vein occlusion) and inflammatory conditions of the retina and choroid.

Age-related macular degeneration

Though dry AMD characterized by atrophy of the macula (photoreceptors, retinal pigment epithelium (RPE) and choriocapillaris) is more common than wet AMD (bloodvessel leak due to choroidal neovacularization), it is the wet form of the condition which can result in rapid loss of vision. As there are now effective treatments for wet AMD which block the action of vascular endothelial growth factor (anti-VEGF agents), there is a need to identify patients at an early stage in the disease and offer treatment. Established cases of wet AMD usually have clear biomicroscopic markers such as haemorrhages, exudates, pigment epithelium detachments or obvious oedema evident on clinical examination; however, in early stages of the disease the distinction between wet and dry AMD requires OCT imaging and FA. The typical AMD findings on OCT had been described elsewhere[13] and summarized recently.[14]

Although FA is helpful in confirming and charactering wet AMD, when monitoring disease activity and response to treatment, OCT imaging has shown excellent sensitivity[15,16] to detect disease activity and almost completely replaced FA in busy daily clinical practice for monitoring the success of treatment and indicating the need for further anti-VEGF treatment. Hyporeflective spaces within or below the neurosensory retina on OCT imaging are common features of disease activity and may indicate the need for ongoing treatment with anti-VEGF agents.

When anti-VEGF agents were first licensed for use, the initial clinical trials used fixed monthly intravitreous injections. More recently, OCT-guided treatment (in combination with vision assessment and biomicroscopy) of wet AMD has been proved to be an alternative approach to treatment, thereby reducing the injection burden for patients.[17,18]

An ageing population with increasing numbers of patients presenting with wet AMD and other

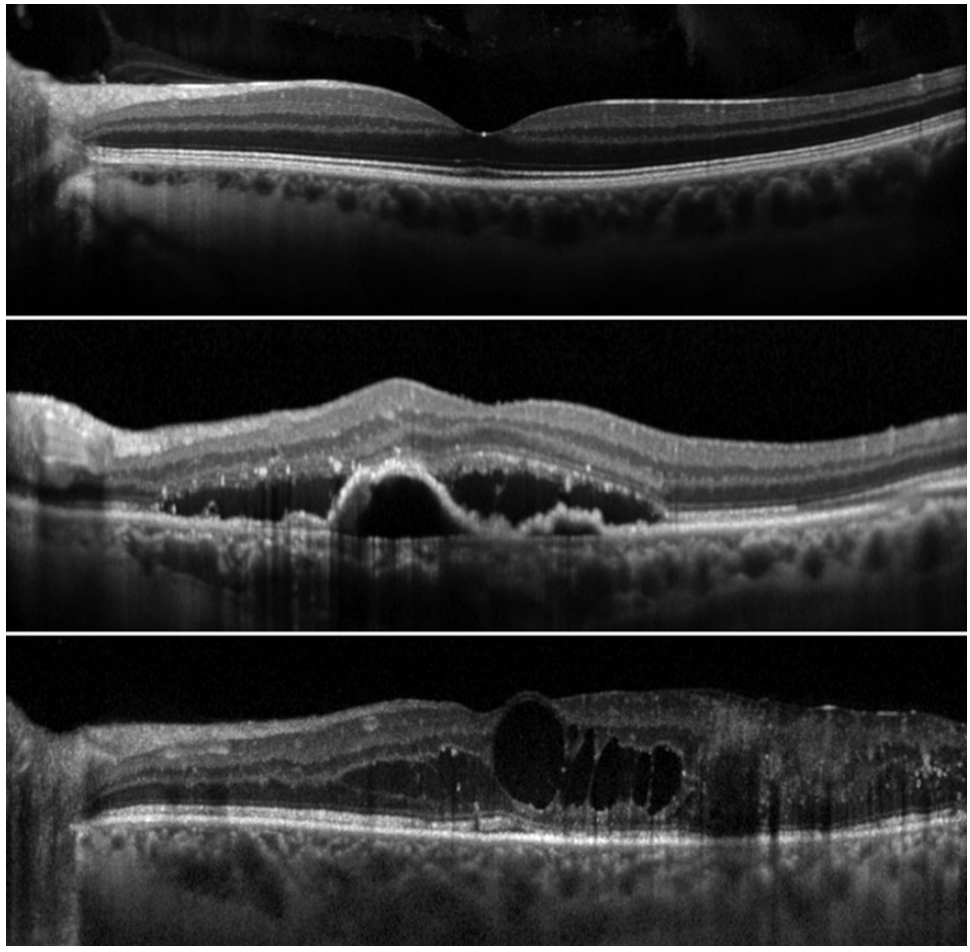

Fig. 3 Top: OCT line scan through healthy macula with normal central foveal depression. Middle: OCT of a patient with wet AMD showing hyporeflective areas below neurosensory retina and RPE (subretinal and sub-RPE fluid). Bottom: OCT of a patient with DMO showing hyporeflective change in the retina (retinal fluid) and diffuse retinal thickening.

treatable macular disease has the potential to put significant strain on hospital eye clinic resources as these patients need to attend for regular monthly or bimonthly review. The improvements in OCT and other ophthalmic imaging modalities open up the possibility of running 'virtual' clinics when patients can be imaged on 1 day and a doctor (potentially in a different location) can review the images and vision measurements on another day. It should be noted that OCT imaging alone (without colour photograph) despite being easily able to pick up most characteristic features of wet AMD[19] is not sensitive enough to always identify activity of wet AMD lesions[20] and further research is needed to evaluate the feasibility of using OCT imaging in such new models of care delivery.

OCT software advance enables automated retinal layer segmentation, retinal thickness and volumetric measurements of the macula and facilitates longitudinal monitoring of disease activity and response to treatment; however, segmentation errors does not always allow to completely rely on automatic measurements without human interpretation of the data.[21]

Despite OCT having its biggest value in wet AMD management, it is also useful in the diagnosis of dry AMD. Different types of drusen are being

identified,[22–24] progression of geographic atrophy can be assessed[25] and now more attention is paid to the detection of early markers of disease progression.[26]

Diabetic macular oedema

OCT imaging is also widely used for assessing and monitoring diabetic retinal disease.[27] Traditionally, plain or stereo colour photographs together with FA were used to investigate and screen for diabetic retinopathy. Recently, OCT imaging has proved to be a powerful adjunct to colour fundus photographs in diabetic screening to detect diabetic macular oedema (DMO)[28] by significantly reducing false-positive referrals for DMO from photographic screening services to ophthalmology clinics.

OCT imaging provides detailed information about retinal structure and abnormalities of retinal morphology. This is leading to an OCT-based reclassification of DMO and this work is ongoing with different research groups describing different OCT patterns of DMO.[29–31] Other researchers have highlighted the ability of OCT imaging to detect abnormalities at the interface between the vitreous and the macula in association with DMO. These changes may influence choice of treatment and prognosis.[32]

Retinal vascular occlusions

Arterial occlusion

Retinal arterial vascular occlusions usually cause profound and irreversible visual loss. In severe cases the diagnosis can easily be made through clinical examination of the fundus by identifying cloudy, pale swelling of retina and in the case of central retinal artery occlusion—the pathognomonic 'cherry-red' spot. In patients with milder or very early phase of the disease ophthalmoscopic findings may be subtle and hard to detect. Even in the early stage of arterial occlusion, OCT imaging shows increased reflectivity of inner retina and increased retinal thickening which is finally replaced by inner retinal atrophy in corresponding areas.

Venous occlusion

In retinal vein occlusions, OCT findings include prominent retinal oedema with large cystic spaces and not uncommonly localized serous retinal detachment. If retinal haemorrhages are prominent, inner retinal reflectivity on OCT imaging increases in corresponding areas. When retinal oedema resolves, inner retinal atrophy may develop in severe cases. There may also be potential to use abnormalities detected on OCT imaging to correlate with the level of retinal ischaemia and help predict vision outcome.[33]

Although OCT can detect retinal thickening or optic nerve head swelling in vascular occlusions, it cannot for example differentiate between arteritic and non-arteritic anterior ischaemic optic neuropathies. Other ophthalmic imaging techniques such as FA and ICG angiography can be used to evaluate the extent of retinal and choroidal ischaemia may help in trying to differentiate between arteritic and non-arteritic causes of anterior ischaemic optic neuropathy.

Vitreo-retinal interface abnormalities

OCT has shed a new light on to abnormalities of the vitreo-macular interface which previously had been difficult to assess by ophthalmoscopy or ultrasound (Fig. 4). OCT imaging helps to differentiate between lamellar holes and macular pseudohole (due to the epriretinal membrane)[34] and OCT imaging is helping to guide a reclassification of vitreo-macular interface disease.[35] Precise staging of vitreo-macular traction syndrome becomes particularly important in

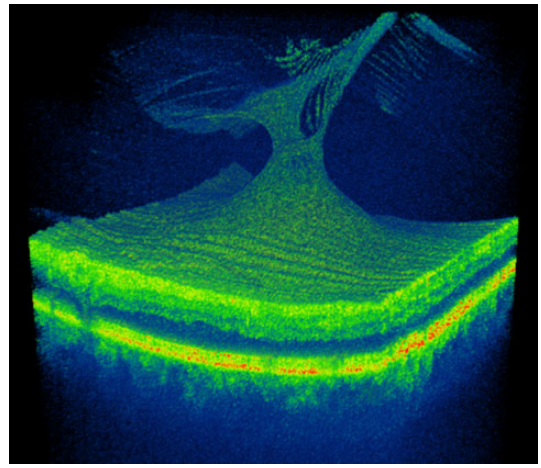

Fig. 4 3D reconstruction from 128 OCT horizontal line scans through the macula of a patient with vitreo-macular traction.

selecting patients for pharmacological vitreolysis with intravitreous ocriplasmin (Jetrea; Thrombogenics Inc, USA, Alcon/Novartis EU). Intra-operative OCT imaging has also recently been described and may be a useful adjunctive tool during vitreo-retinal surgery.

Other posterior segment OCT applications

OCT is an essential imaging tool in many other retinal conditions enabling the detection of subtle, ophthalmoscopically almost undetectable changes and allowing a better understanding of retinal and choroidal structural changes. The ability of OCT imaging to detect subretinal fluid, abnormally increased choroidal thickness and signs of structural change in the outer retina is particularly useful in conditions such as central serous chorioretinopathy in which increased permeability of the choriocapillaris and/or the RPE leads to the collection of macular fluid.

OCT imaging is also used in uveitis clinics to detect cystoid macular oedema due to inflammatory causes, monitoring anti-inflammatory treatment effectiveness and identifying secondary CNV development. As the technology improves further there may also be a role of OCT imaging in the assessment of the choroid in patients with posterior uveitis.

OCT has become a part of routine practice in clinics assessing patients with inherited retinal and macular dystrophies. When combined with FAF imaging, OCT imaging can be used to assess disease progression by identifying abnormalities of retinal morphology. As OCT imaging technology continues to improve and advance, new features of retinal disease are being identified with each iteration of the technology.

Neuro-ophthalmology also exploits OCT imaging to detect and monitor axonal loss in demyelinating, compressive, inflammatory, ischaemic optic nerve disease and retrograde trans-synaptic degeneration has been successfully demonstrated by OCT.[36]

Glaucoma

Glaucoma specialists are mostly interested in inner retina and optic disc architecture and changes. Traditionally, peripapillary RNFL thinning was considered to be associated with glaucoma progression but recently focus has expanded and macular ganglion cell layer and inner plexiform layer thinning has been noticed in glaucomatous eyes.[37,38] Most OCT devices have software that allows the RNFL to be identified. RNFL thickness maps of the posterior pole graphically demonstrate defects which may confirm the clinical suspicion of a diagnosis of glaucoma. Glaucoma detection and progression analysis algorithms differ slightly from machine to machine and also depend on retinal layer segmentation success performed by built-in software. However, despite differences between different OCT machines the ability to discriminate between normal and glaucomatous eyes is similar.[39] It is important though, that different machines should not to be used interchangeably for glaucoma progression analysis. Progression analysis algorithms are in their infancy and further long-term studies confirming their benefit are awaited. Deep penetration of swept source OCT allows *in vivo* analysis of the structure and anatomy of optic disc and lamina cribrosa in glaucoma patients.[40]

FAF imaging

FAF is a non-invasive imaging modality of the ocular fundus which makes the use of the property of autofluorescence. Autofluorescence of fundus structures (optic disc drusen, hard exudates) was previously noted in FA imaging before the injection of fluorescein dye. However, it was often difficult to detect autofluorescence in the ocular fundus with conventional digital fundus imaging techniques. The arrival of SLO-based imaging systems has resulted in improved detection of autofluorescence from the ocular fundus with the confocal optics (used in HRA II and Optos imaging systems) and eye tracking (used in HRA II and Spectralis imaging systems). The predominant source of autofluorescence from the ocular fundus is from lipofuscin which builds up in RPE cells (Figs 1 and 5). Increased FAF may arise in conditions in which there is an excess of lipofuscin in RPE cells such as Best's inherited macular dystrophy or in a range of other diseases (including

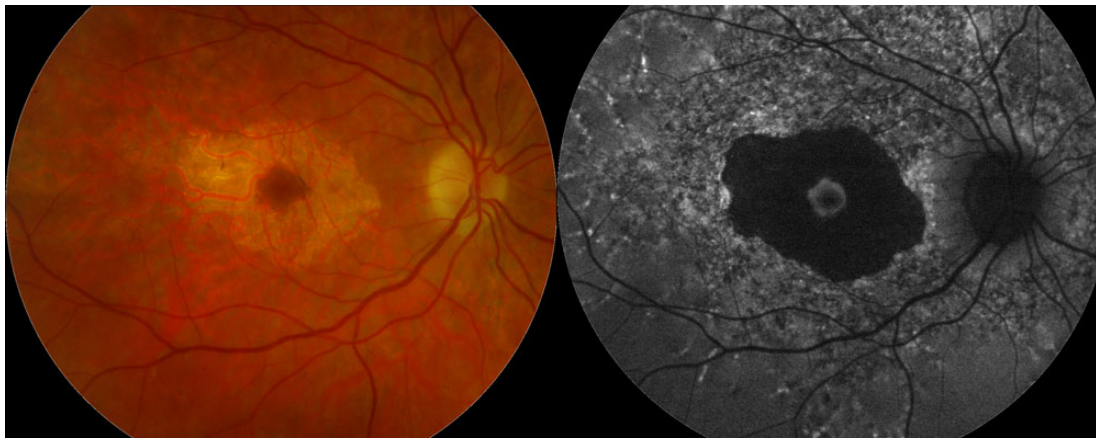

Fig. 5 Right eye colour fundus photograph to the left and corresponding autofluorescensce image to the right of 61 years old woman with autosomal recessive macular dystrophy—fovea sparing Stargardt's disease. On autofluorescence image hypofluorescent (black) areas represents the absence of RPE and hyperfluorescent (bright) areas represent areas of pathologically affected RPE.

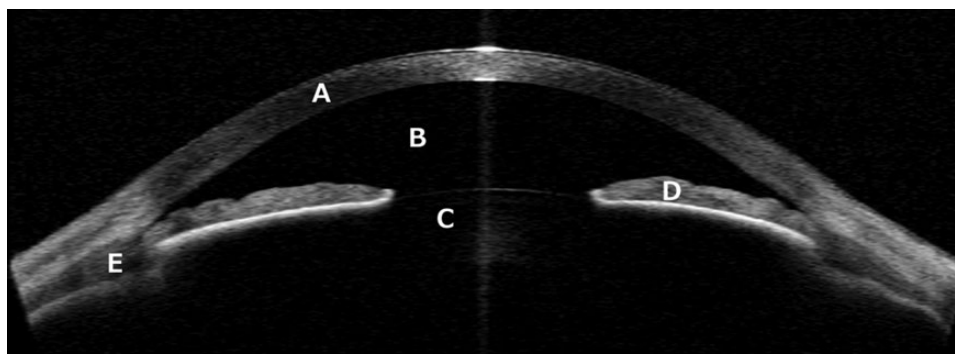

Fig. 6 Anterior segment OCT scan of the eye: A, cornea; B, anterior chamber; C, anterior part of the lens; D, iris; E, ciliary body.

subsets of patients with dry AMD). FAF signal is also increased in optic nerve head drusen which can be confused clinically with optic disc swelling and FAF imaging can help in distinguishing the two conditions.

FAF changes often precede clinically visible abnormalities of the retina. FAF may serve as a monitoring tool for progression of dry AMD and even may predict its progression rate. In inherited retinal dystrophies, FAF is used to document and longitudinally follow progress of the disease. Autofluorescence patterns may change over the course of different diseases; therefore, it is important to repeat OCT to monitor disease progression.

Advance in anterior segment imaging

Anterior segment OCT

An emerging application of OCT is for anterior segment imaging including imaging of the cornea, iris and aqueous drainage angle (Fig. 6). There are devices dedicated only to anterior segment OCT imaging and other OCT devices which are able to take retinal and anterior segment imaging. OCT imaging may also be might be helpful in studying the tear film and evaluating dry eye conditions[41] as well as supplying with biometric measurements of anterior segment including corneal thickness and curvature, anterior chamber depth, thickness of lens and

anterior chamber angle parameters. Most of the structures of the front of the eye (for example conjunctival tumours, corneal dystrophies, surgical incision architecture, filtering blebs) can be imaged using OCT; however, its role in imaging these conditions has yet to be fully evaluated.

Confocal microscopy

Using principals similar to SLO, confocal microscopy allows obtaining depth selective high-resolution *in vivo* optical images of anterior segment of the eye but is most widely used for corneal imaging.[42] Confocal illumination principle allows scanning the whole thickness of cornea layer by layer and then performing 3D reconstruction. With a lateral resolution of ~ 1 μm it allows phenotyping single cells in a scan. Probably, the most acknowledged clinical application is instant and reliable diagnosis of protozoan (acanthamoebal) keratitis. *In vivo* diagnosis and differentiation of corneal fungal infections is another important clinical application of this technique. There is increasing interest and evidence of ability to early diagnose diabetic neuropathy by imaging corneal sub-basal nerve plexus. Other clinical and research applications include imaging of lids, conjunctiva, limbus, tear film, sclera, together with studying various corneal changes during keratitis, keratoconus, pre- and post-refractive surgery.

Conclusions

Ophthalmic imaging has developed and advanced enormously during the last 20 years. This has led to a shift from using imaging merely to document changes in the eye to an advanced set of diagnostic tools which give unprecedented views of ocular disease *in vivo*, enabling objective assessment of disease progression and response to treatment. Intra-operative,[43] hand-held,[44] whole-eye[45] OCT, non-invasive angiography[46] are only a few of bundle of next generation optical imaging tools moving from laboratory development to the clinical environment. Smartphone applications such as PEEK (also presented recently as a TED talk) can become a promising tool in telemedicine and would help to bring eye care to remote and resource-poor societies.[47] We now look forward to the next 20 years in ophthalmic imaging and the potential improvements in patient care advances in imaging may herald in the years to come.

Acknowledgements

The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.

Funding

This work was supported by the National Institute for Health Research (NIHR) Biomedical Research Centre based at Moorfields Eye Hospital NHS Foundation Trust and UCL Institute of Ophthalmology.

Conflict of interest

P.J.P. has lectured for Heidelberg UK and Topcon UK imaging companies.

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