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Review on imaging methods in non-infectious posterior uveitis, principles, relevance, and practical clinical applications to disease entities

Carl P. Herbort Jr, MD, PD, FEBO; **Ioannis Papasavvas,** MD FEBO

Retinal and Inflammatory Eye Disorders, Centre for Ophthalmic Specialised Care (COS)

Lausanne (Switzerland)

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The work-up and diagnosis of posterior uveitis rely heavily on multiple imaging methods that have become available beyond the mere photographic imaging and fluorescein angiography (FA) used to image uveitis in the past. Global assessment and precise follow-up of posterior uveitis were achieved with the development of indocyanine green angiography (ICGA) since the mid-1990ties that, together with FA, made it possible to perform dual FA and ICGA giving information on both the retina and the choroidal compartment. Further non-invasive imaging methods were developed subsequently that contributed to additional valuable information completing the dual FA/ICGA basic appraisal of uveitis, including (1) optical coherence tomography (OCT) giving a quasi-histological morphology of retinal structures of the posterior pole, (2) enhanced-depth imaging OCT (EDI-OCT) allowing to image the choroidal compartment and (3) blue light fundus autofluorescence (BAF) showing the integrity or damage of the retinal pigment epithelium, the photoreceptors and the outer retina. OCT-angiography (OCT-A) became available more recently and presented the advantage to image the retinal and choroidal circulations without needing dye injections, necessary for dual FA/ICGA. This review article will illustrate the principles, relevance and practical applications of these different imaging methods used in uveitis by examining the main categories of non-infectious posterior uveitis entities including (1) retinal inflammatory disorders, inflammatory diseases of the outer retina and of the choriocapillaris (choriocapillaritis) and stromal choroiditis.

Introduction

Appraisal and work-up of uveitis rely on clinical examination, patient history and laboratory investigations. However, since the development of performing methods, imaging plays a central role in the diagnosis and management especially of posterior uveitis. Imaging of posterior uveitis was limited to fundus photography until Novotny and Alvis developed the revolutionary technique of fluorescein angiography (FA) in the early 1960s allowing to evaluate retinal inflammation (vasculitis) in posterior uveitis [1]. This was followed by the ground-breaking development of indocyanine green angiography (ICGA) in the mid-1990ties that made it possible to evaluate inflammation in the choroidal compartment thanks to a schematic interpretation of angiographic signs [2]. Constant progress occurred with the advent of ever new modalities that had the advantage to be non-invasive, starting with optical coherence tomography (OCT) and enhanced depth imaging OCT (EDI-OCT), followed by blue light fundus autofluorescence (BAF), and finally OCT-angiography (OCT-A) that allowed the examination of retinal and choroidal circulation without the need of dye injection.

1. Imaging methods for posterior uveitis: principles, interpretation, and relevance

1.1. Dual fluorescein (FA) and indocyanine green angiography (ICGA)

Dual FA/ICGA represents the mainstay of posterior uveitis imaging. It allows global and precise evaluation and follow-up of posterior uveitis and should be performed for all posterior uveitis cases at presentation as long as there is a substantial degree of inflammation for which angiography is deemed necessary. [3,4,5] For many decades the standard of care was to perform FA in case of posterior uveitis with information limited to the superficial structures of the fundus that was later completed with ICGA giving access to the previously occult compartment of the choroid. (Figure 1)

The different structures identified by dual FA/ICGA are schematically shown in figure 2. (Figure 2)

The two types of angiographies distinguish themselves through the physicochemical properties of the dyes used. (Figure 1)

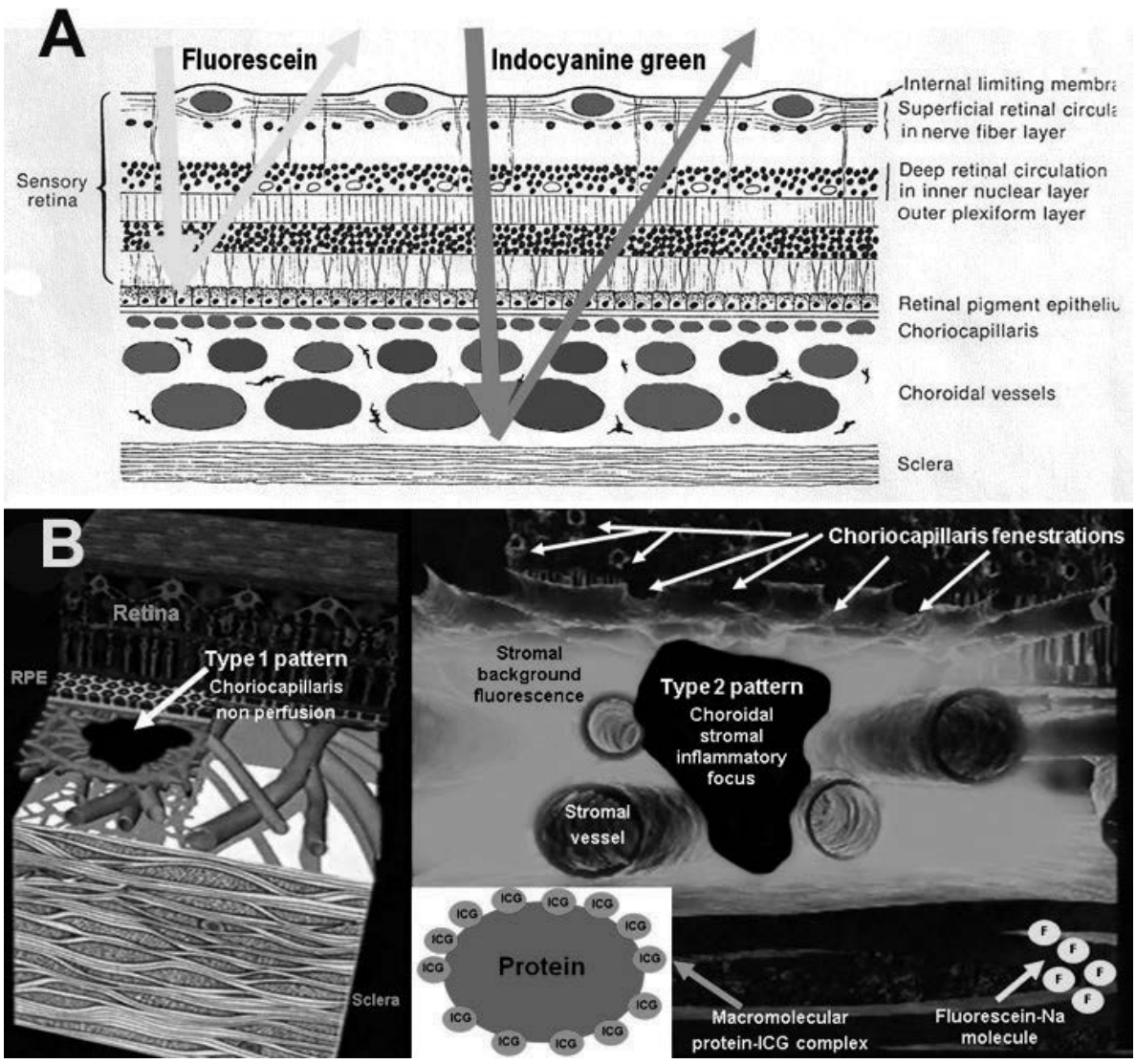

Figure 1. Principles of dual FA/ICGA angiography. Top image (A) illustrates the different impacts and structures analysed by FA (yellow ray, superficial fundus structures) and ICGA (green ray, choroidal structures). Bottom composite picture (B) explains the principles of ICGA. The ICG-protein complex egresses physiologically from the choriocapillaris (white arrows, top right) and impregnates the choroidal stroma and has a slow wash-out because of the size of the macromolecule (red-green insert). In case of stromal foci (black structure), the dye diffusion is impaired and lesions appear as hypofluorescent dark dots (HDDs, type 2 pattern). On the left side the cartoon shows choriocapillaris non perfusion (type 1 pattern hypofluorescent areas).

Fluorescein angiography (FA)

Fluorescein sodium (FNa) is a small molecule with a molecular weight of 332 Daltons (d) that fluoresces in the spectrum of visible light. Therefore, fluorescence emitted from the choroidal compartment is blocked by the retinal pigment epithelium (RPE) and, except for the first 60 seconds, only fluorescence from superficial fundus structures is recorded including the retina and optic disc. Because of the small size of the FNa molecule, it can egress from even slightly inflamed retinal vessels. The relevance and the main pathologies shown by FA are exposed in figures 3a and 3b. (Figures 3a & 3b) They include retinal vasculitis, optic disc inflammation, retinal dye impregnation occurring in the acute phase of HLA-A29 birdshot retinochoroiditis (BRC), cystoid macular oedema (CMO), exudative retinal detachments (ERD) in acute Vogt-Koyanagi-Harada disease (VKH), retinal neovascularization, choriocapillaris non-perfusion on early angiographic frames and cicatricial RPE damage. A schematic analysis of FA hyper and hypofluorescence towards a differential diagnosis is represented in diagram 1.

Indocyanine green angiography (ICGA)

The ICG molecule has two specificities that are at the base of the particularity of ICGA. For one, the molecule (775 d) is not much larger than the FNa molecule, but it is close to 98% linked to plasma proteins which results in a macromolecular complex with a molecular weight of around 70’000 d. (Figure 1B) This means that it does not egress from even substantially inflamed retinal vessels. However, the ICG molecular complex egresses freely and

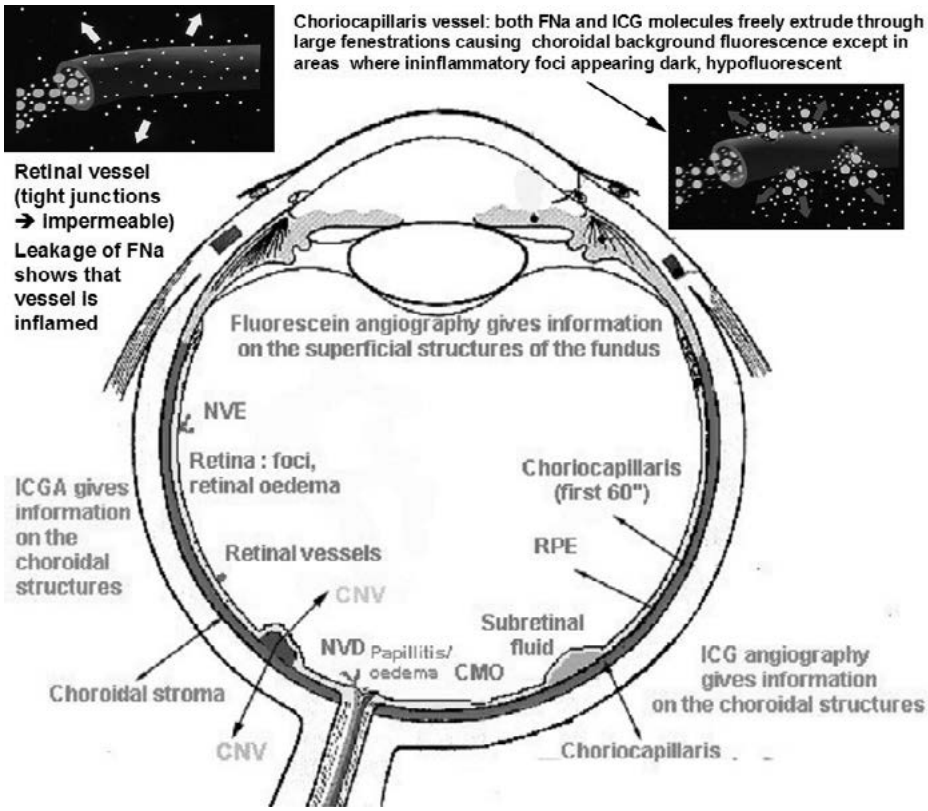

Figure 2. Principles of dual FA/ICGA angiography. Schematic representation of posterior segment structures respectively identified by FA and ICGA. FA gives information on retinal vessels (vasculitis or occlusion), on the retina (foci and/or dye impregnation), on retinal neovascularisation, on optic disc inflammation (hyperfluorescence), on subretinal fluid pooling and on cystoid macular oedema (CMO). In the early angiographic sequence (60'') FA gives also information on the filling of the choriocapillaris. ICGA gives information on the choroidal structures including choriocapillaris, choroidal stroma and choroidal neovascularization. The inserts show the different behaviour of the FNa and ICG molecules in retinal (top left) and choriocapillaris (top right)

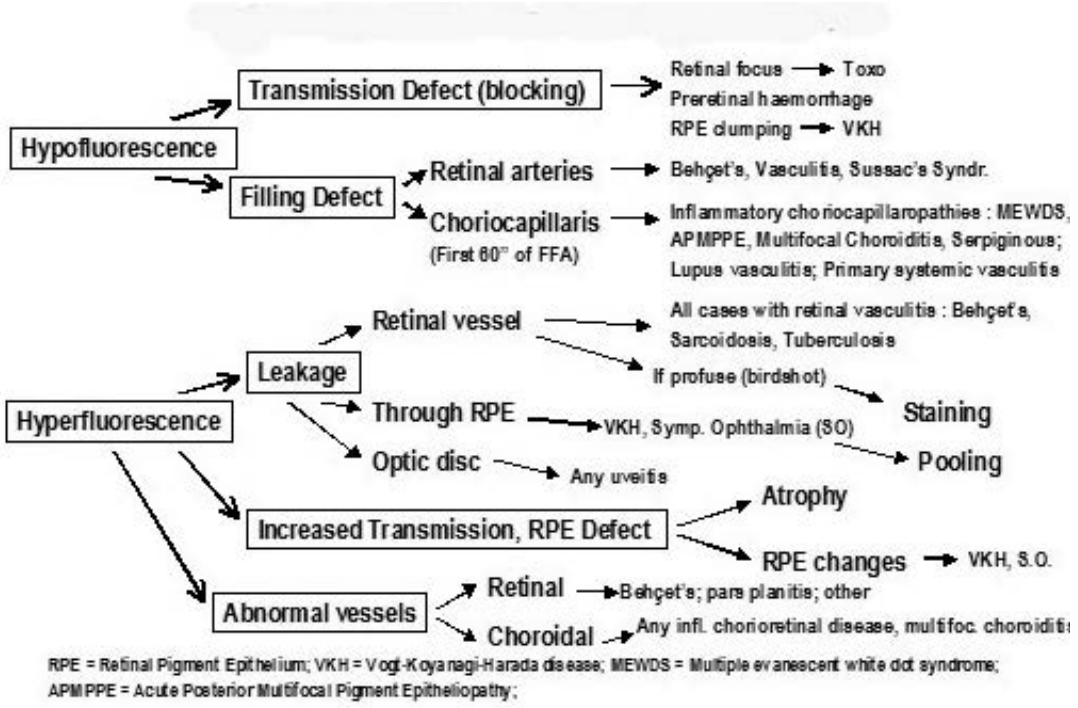

Diagram 1. Flow-chart interpretation of FA hyper and hypofluorescence for main posterior uveitis pathologies.

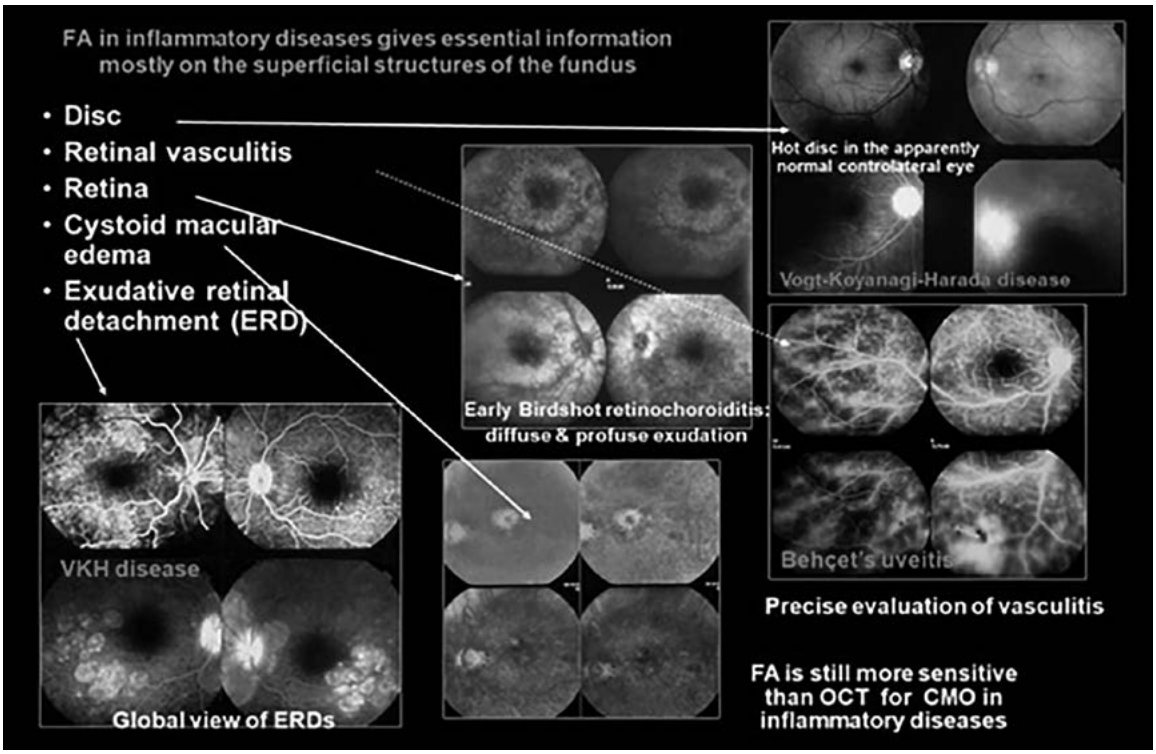

Figure 3a. Relevance and main pathologies disclosed by FA

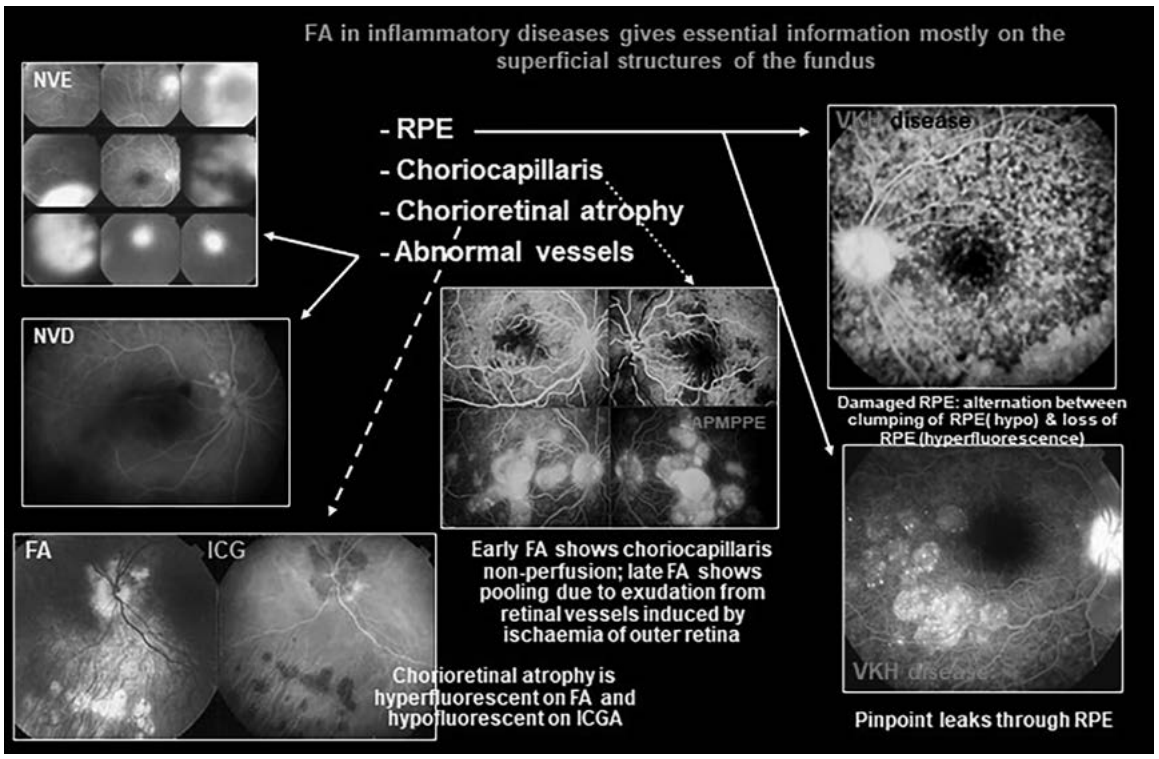

Figure 3b. Relevance and main pathologies illustrated by FA

physiologically into the choroid from the large fenestrations of the choriocapillaris. (Figure 1B) It can also diffuse pathologically from inflamed choroidal vessels. While the wash-out time is very rapid for the small FNa molecule, it is slow for the large ICG-protein complex that remains for a longer time in the choroid. The main pathologies determined by ICGA are either hypofluorescent areas due to choriocapillaris non-perfusion (choriocapillaritis) or hypofluorescent dark dots (HDDs) due to impaired diffusion because of the presence of choroidal foci (stromal choroiditis). In case of severe choroiditis there is also increased leakage from inflamed choroidal vessels producing ICGA

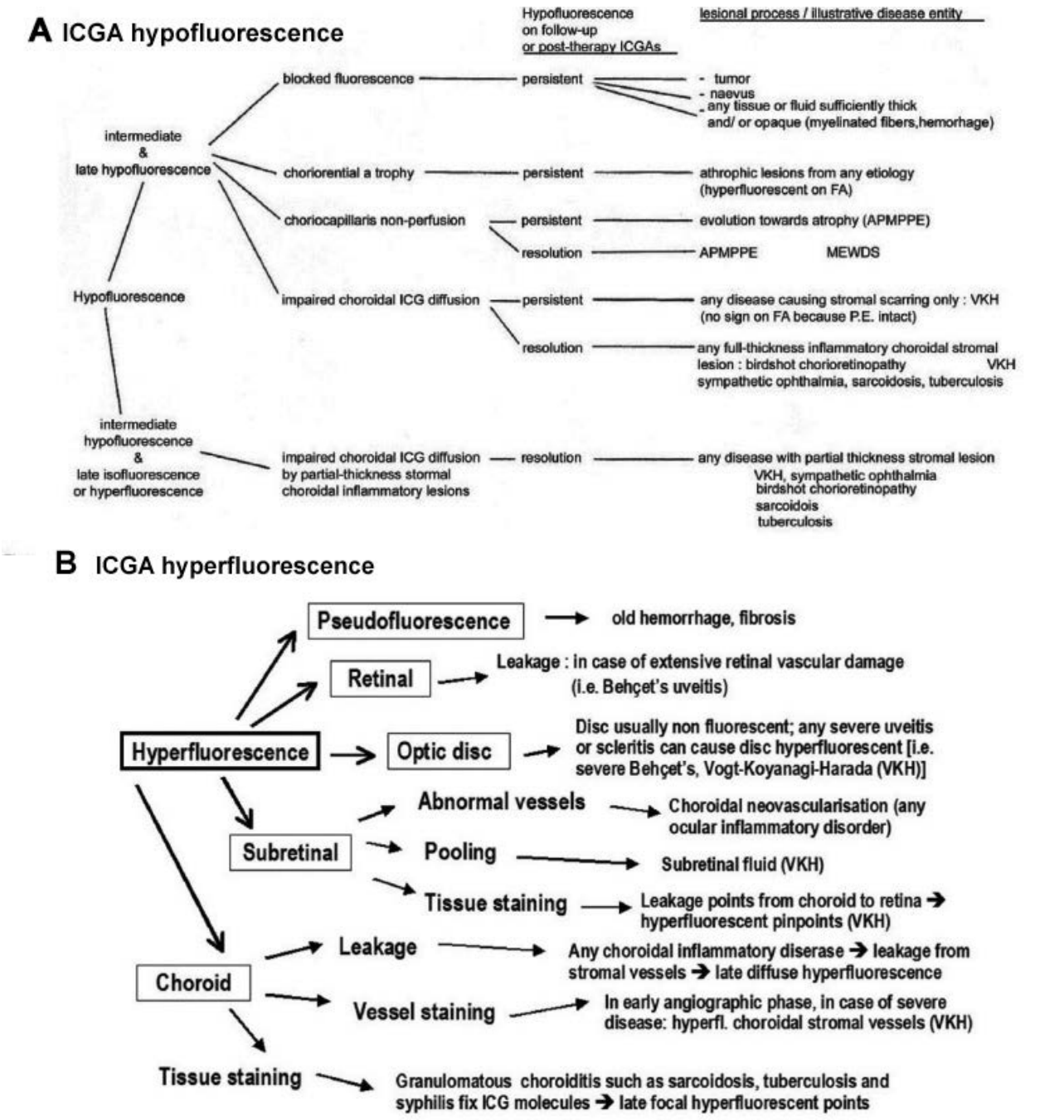

Diagram 2. Flow chart interpretation of ICGA hypofluorescence (A) and hyperfluorescence (B) for posterior uveitis.

hyperfluorescence. The second crucial specificity of the ICG molecule is that it fluoresces in the infrared spectrum which can be detected through the RPE. The main pathologies analysed by ICGA are choriocapillaritis entities such as multiple evanescent white dot syndrome (MEWDS) and others, and stromal choroiditis such as HLA-A29 birdshot retinochoroiditis (BRC), VKH, sympathetic ophthalmia (SO) and granulomatous posterior uveitis caused by sarcoidosis or of tubercular origin. The relevance and the main pathologies shown by ICGA are represented in diagram 2.

Thanks to dual FA/ICGA, both retinal and choroidal inflammation could thus be evaluated in current uveitis practice. [6] Moreover, dual FA/ICGA allowed the clinicians to quantitatively establish the degree of inflammation independently in both the retinal and the choroidal compartments thanks to a numerical angiographic score at presentation and during follow-up. [7] This represented a considerable advantage over classical "standardization of uveitis nomenclature (SUN)" that promoted merely qualitative and inadequate vitreous haze estimation as the sole measurement of posterior uveitis. Dual FA/ICGA has

increasingly been used in clinical uveitis trials. [8, 9] The major drawback of FA/ICGA is the fact that injection of dyes is necessary, limiting the frequency at which the procedure can be performed.

1.2. Optical coherence tomography (OCT) and enhanced depth OCT (EDI-OCT)

OCT uses rays of low-coherence light to obtain cross-sectional images of the retina. It provides information of quasi histological quality on the different layers of the retina of the posterior pole. A very detailed article traces the development and the immense impact it had on ophthalmological practice. [10] Whether of the spectral-domain type (SD-OCT) or the swept-source type (SS-OCT), it is an imaging modality of crucial importance in everyday clinical practice for two main reasons. It is an instrument easily commercially available to clinical centres for routine use and is a non-invasive easily performed procedure. Therefore, when taking care of an incoming patient, it is the first imaging performed before all other imaging modalities, whether being OCT or EDI-OCT (see below) and determines the type of patient management. The main use of OCT is to detect changes and damage to the retino-choroidal architecture being especially useful in the detection and follow-up of macular oedema whether being diffuse or cystoid (CMO) with a significant advantage over FA as it is a non-invasive imaging method and can be easily repeated not being invasive which means better follow-up and fine-tuning of therapy [11]. (Figure 4) At present in practice, the standard of care for the assessment of retinal inflammation including CMO is a baseline FA and OCT. Posterior pole pathologies can then further be assessed closely and non-invasively by follow-up OCTs. Besides the morphological information on the inner retina, OCT is furnishing detailed information on the ellipsoid zone and especially on outer retinal ischaemic disruption, secondary to inflammatory choriocapillaris non-perfusion, in choriocapillaritis entities including acute posterior multifocal placoid pigment epitheliopathy (APMPPE), MEWDS, idiopathic multifocal choroiditis (MFC) and serpiginous choroiditis (SC). [12, 13, 14] In the same area of pathology, OCT also delineates outer retinal lesions in primary inflammatory photoreceptoritis such as acute zonal outer occult retinopathy (AZOOR) [15].

Until 2008 high-resolution cross-sectional images were limited to the retina as the near-infrared light source used in many traditional OCT systems was scattered by the photoreceptor and retinal pigment epithelium layer, limiting its capability to visualize the underlying choroidal structures precisely. To overcome this limitation, some modification in collecting OCT images was applied to develop EDI-OCT [16], which provided more information on the choroidal compartment and allowed to measure its thickness a feature available in most OCT instruments. Fluctuation of choroidal thickness on EDI-OCT occurs in case of stromal choroiditis such as VKH and HLA-A29-BRC. (Figure 5) Due to its non-invasive nature, repeated EDI-OCT imaging makes it possible to follow these conditions more closely and frequently, an advantage which ICGA, despite being the gold standard exam for such situations, does not possess. [17] Moreover, EDI-OCT, contrary to ICGA can provide accurate 3-dimensional images of the choroidal layers with precise measurement of the depth and morphology of the lesions. The drawback of the method is that it is still limited to the posterior pole for most easily commercially available devices with mostly only research instruments going beyond into peripheral areas.

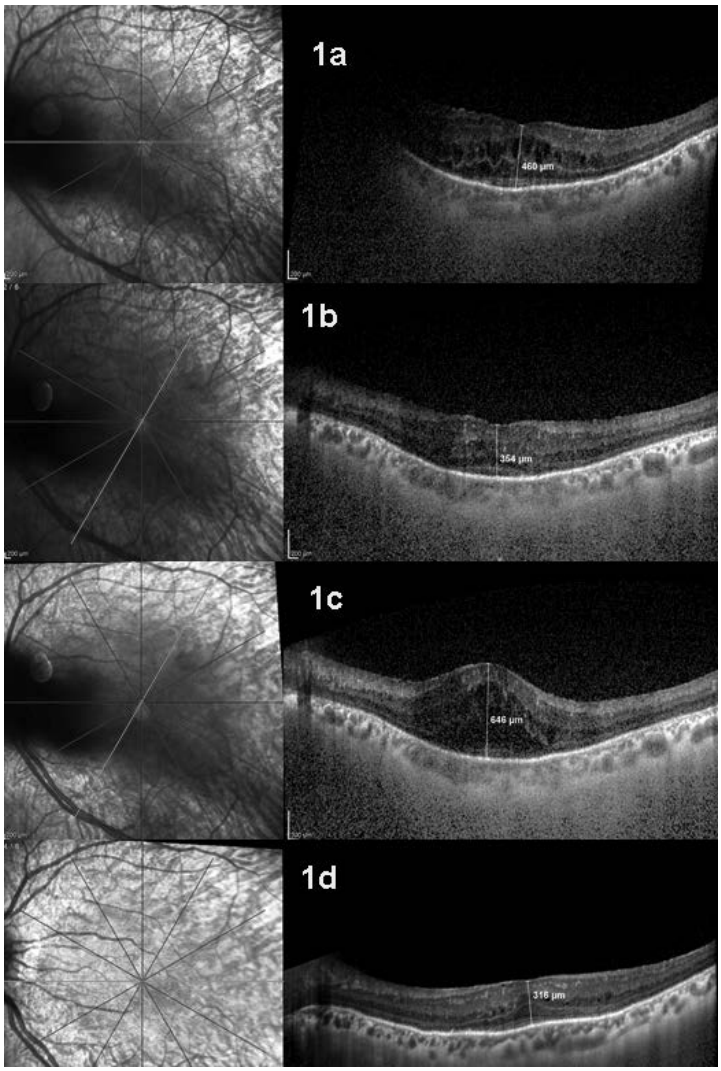

Figure 4. Example of OCT use in posterior uveitis: a case of CMO after cataract operation in a retinitis pigmentosa patient. Evolution of retinal foveal thickness (RFT) during the followed by OCT. (a) 10 days after surgery showing CMO; (b) 1 week after sub-Tenon's triamcinolone acetonide injection, decrease of CMO; (c) 1 month after surgery showing recurrence of CMO; (d) 6 months after vitrectomy. Further decrease of RFT.

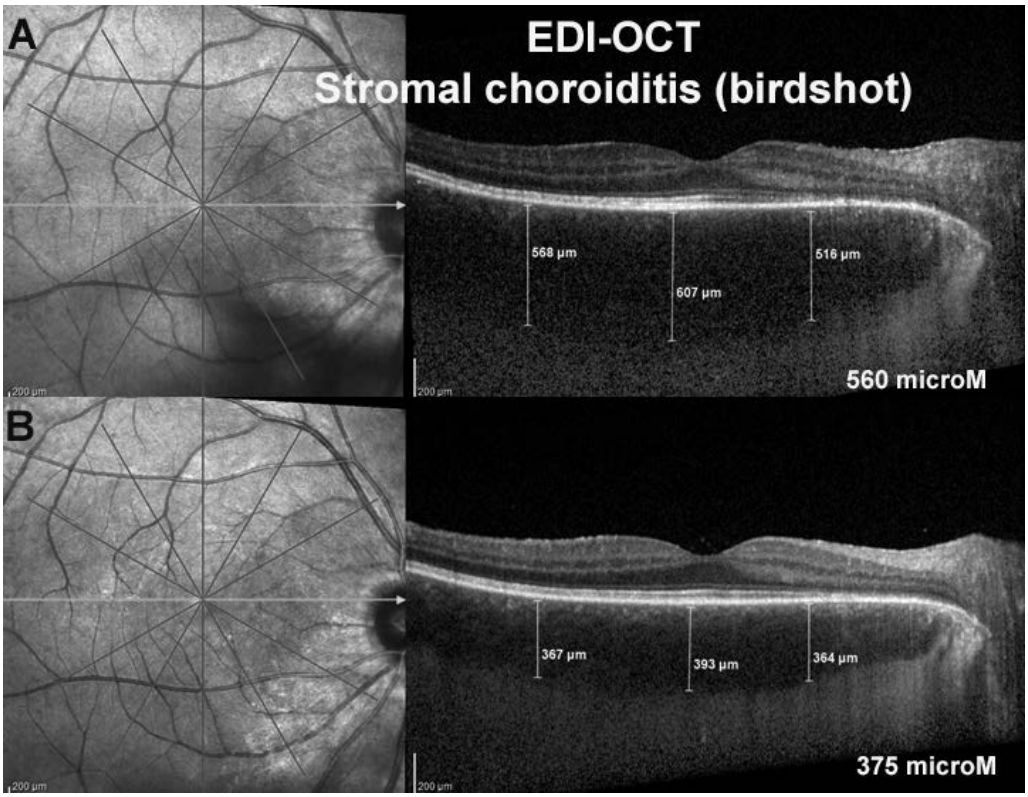

Figure 5. EDI.OCT. Case of HLA-A29-BRC imaged by EDI-OCT showing a substantially thickened choroid at presentation (top, 560 microns). After 4 months of triple immunosuppression (bottom) the choroidal thickness has substantially diminished (375 microns).

1.3. Blue light fundus autofluorescence (BAF)

BAF is increasingly used in clinical practice as it does not require the injection of a dye in order to image the fundus. It is recording, thanks to a specific filter, the (auto) fluorescent properties of lipofuscin contained within the RPE and gives information on pathologic changes leading to modification of natural (auto)fluorescence. [18] BAF can provide information on the RPE and the outer retina and in some cases, can replace the dye exams in the follow up of certain uveitis entities such as MEWDS and MFC. Hypoautofluorescence indicates loss of RPE due to atrophy or scarring. Hyperautofluorescence (1) can indicate damage to the RPE cells unable to eliminate fluorophores that accumulate unduly, or (2) indicates a frequent cause of hyperautofluorescence, namely the damage to photoreceptor outer segments, a layer that functions as a screen to normally auto-fluorescent RPE lipofuscin. [19] (Figure 6) The ocular inflammatory disease that can present simultaneously all 3 situations of altered autofluorescence is APMPPE. [20] (Figure 7)

BAF is especially useful in choriocapillaritis entities including MEWDS, APMPPE, MFC, SC, whether TB associated or not, and acute syphilitic posterior placoid chorioretinitis (ASPPC), as well as primary photoreceptoritis cases such as AZOOR [21]. Although less global, BAF (in combination with OCT) is almost as performing as ICGA in the diagnosis and follow-up of conditions such

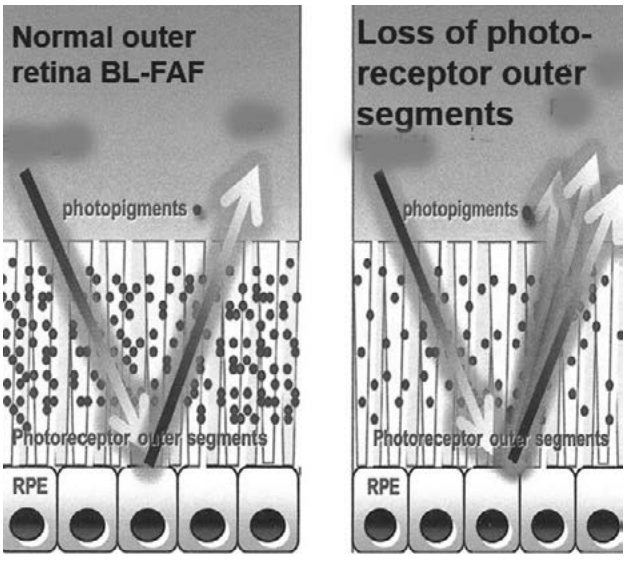

Figure 6. Mechanism of hyperautofluorescence in choriocapillaritis and primary diseases of the photoreceptors (AZOOR). On the left side the photoreceptors are preserved with a normal aspect and act as screen to the normal RPE autofluorescence. On the right side, photoreceptors are damaged with loss of photopigment, loss of the natural screen and better visualization of the normal RPE autofluorescence

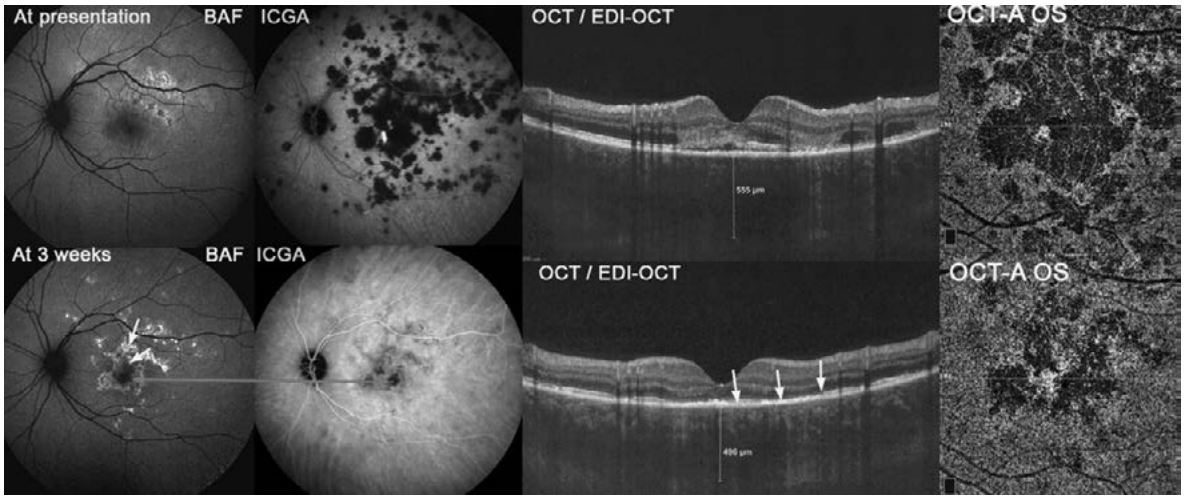

Figure 7. Multimodal imaging in APMPPE combining BAF, ICGA and OCT/EDI-OCT. This combination of invasive (ICGA) and non-invasive methods (BAF & OCT/EDI-OCT) gives a precise appraisal of the condition. BAF at presentation (top left) still shows minimal changes despite extensive choriocapillary non perfusion shown on ICGA (top middle) because the overlying RPE and outer retina are still at an oedematous stage as shown on OCT/EDI-OCT (top right). Three weeks later after partial re-perfusion seen on ICGA (bottom middle), the damaged areas are visible on BAF (bottom left). In the centre there is hypo-autofluorescence corresponding to remaining non perfusion on ICGA (crimson arrow). The bright hyperautofluorescent areas correspond to both suffering RPE cells with accumulated fluorophores and to loss of photoreceptor outer segments as shown on OCT/EDI-OCT (bottom right) (yellow arrows). OCT-A did not yield additional information, showing the same non perfusion areas as seen on ICGA (choriocapillary drop out) limited to the central macular area, but was useful in the follow-up of these central damaged areas (see figure 3). (Far-right) OCT-A images at presentation (top right) and after 3 weeks (bottom right)

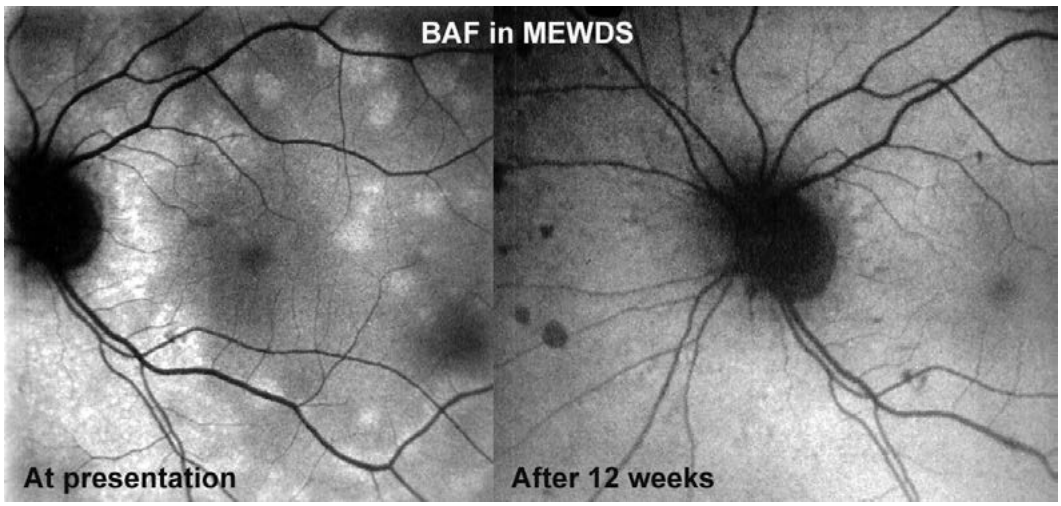

Figure 8. BAF in choriocapillaritis. BAF is of comparable value to ICGA to follow choriocapillaritis entities such as MEWDS or MFC. This patient was diagnosed and followed as MEWDS thanks to BAF. At presentation, numerous areas of hyperautofluorescence (left) that disappeared 12 weeks later without treatment (right). However, after resolution of hyperautofluorescence areas, scars (dark dots nasal to disc on right) were noted compatible with MFC. Indeed, the patient developed a recurrence 2 years later and the diagnosis was reverted to MFC.

as MEWDS and MFC avoiding repeated dye injections. (Figure 8)

1.4. Optical coherence tomography angiography (OCT-A)

OCT-A enables to picture the retinal and choroidal circulations without the need for dye injections. We give a brief account of the method without going into details, which has been done in many comprehensive articles. [22, 23], OCT-A is an evolution of OCT technology. It uses multiple scans per second to detect differences between the images and especially the movement of red blood cells in order to provide anatomic information on vessels in the scanned area [22]. Hence, there has to be a minimal degree of flow in order to detect vessels by OCT-A which is not the case in end-choriocapillary vessels. In MEWDS non-perfusion occurs precisely in the end-capillaries which cannot be imaged by OCT-A and therefore non-perfusion cannot be evidenced by OCT-A but is only shown

by ICGA. The limited field of view in commercially available instruments is a major disadvantage, as is the case for OCT, when compared to dye exams. The presentation of the retinal vasculature and choriocapillaris without the use of a dye was a revolution which led to theories that OCT-A could replace the dye exams which is absolutely not the case [24, 25], but nevertheless stimulated the publication of articles attempting to oppose the two methodologies [26, 27]. Indeed, OCT-A is of limited practical value in everyday routine clinical practice with limited value-added information after other multimodal investigations have been performed [28]. In contrast to OCT or EDI-OCT where findings are immediately relevant, there is a lack of standardization of data obtained by OCT-A. As already indicated the contributions of OCT-A in current practice are marginal [28]. It can bring adjunct elements such as monitoring the choriocapillary drop-out lesions in APMPPE, reducing the need for dye angiography. (Figure 9). The main situations where OCT-A was of determining utility in everyday practice reported in the literature included the rare inability to use fluorescein dye and the even rarer inability to use ICG because of allergic reactions. OCT-A was shown to be useful and a help in the detection of choroidal neovascularization (CNV) such as in MFC/PIC and other choriocapillaritis entities as well as its follow-up during anti-VEGF treatment but none of the articles recommended it as an exclusive use. [29-34] One report indicated that OCT-A could possibly better identify new vessels obscured by retinal haemorrhage [35]. OCT-A has been reported to be useful to distinguish CNV from active uveitic lesions [36]. In predominantly retinal diseases such as Behçet's uveitis, OCT-A cannot be considered as essential in the diagnosis but analysis of macular microcirculation and its monitoring have shown to be sometimes useful to the clinician, although no standardization has been put together so far. [37] However, as indicated previously, the most useful application of OCT-A concerns the group of choriocapillaritis diseases including APMPPE, MFC and SC for which it is mainly useful in the close follow-up it allows as no dye injection is needed. [38, 39] (Figure 9) As far as MEWDS is concerned OCT-A is useless as the end-capillary low flow circulation is not identified by OCT-A. This was at the origin of the erroneous thinking that there was absence of choriocapillaris non perfusion, and, hence, it was alleged that the choriocapillaris was intact and that MEWDS was supposedly a primary photoreceptoritis [40]. Finally, among the anecdotal descriptions of cases that benefited from OCT-A, we would like to mention the report of suspected retinal granulomas in a sarcoidosis case. [41] This indicates that despite the limited practical use of OCT-A, it is worthwhile to perform the non-invasive test as such unexpected findings can occur.

2. Classification of the main categories of posterior uveitis

Non-infectious uveitis can be classified into different categories depending on which ocular structure is predominantly involved which also determines the imaging modalities recommended for diagnosis and follow-up. Three main categories can be determined whether the retina, the choriocapillaris/outer retina or the choroidal stroma are predominantly involved. Some entities involve more than

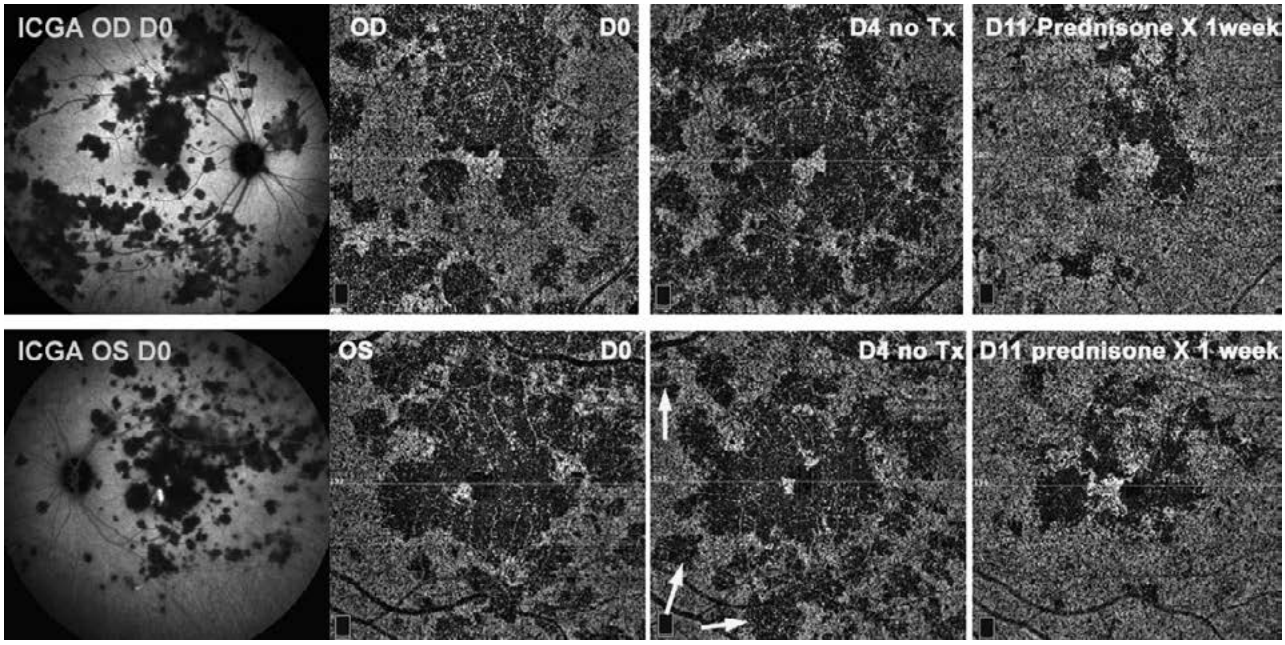

Figure 9. OCT-A follow-up of APMPPE. Example of practical usefulness of OCT-A in a patient with APMPPE (same patient as figure 1). At presentation ICGA frames clearly establish the global involvement of the fundus. To monitor the evolution of lesions and the impact of therapy, OCT-A allowed a close follow-up, although only of the central lesions (6 frames to the right). Yellow arrows show new areas of drop-out before regression of lesions following introduction of corticosteroids (frames at the extreme right)

one structure and will be listed under the heading of the different categories in which significant inflammation occurs. The list of disease entities is not exhaustive and is limited to the more common conditions.

2.1. Predominantly retinal inflammation

The main disease entities with preponderant retinal inflammation include (1) Behçet's uveitis, (2) intermediate uveitis, whether idiopathic or of the pars planitis type, vasculitis linked to collagen diseases and rare conditions such as Susac syndrome. A stromal choroiditis that also causes significant retinal vasculitis is HLA-A29 BRC with both structures (retina and choroid) being equally but independently involved. Sarcoidosis uveitis or tubercular uveitis are two stromal choroiditis entities that very often also involve the retina and in rare cases the retina can be involved exclusively. Obviously, the imaging modality of choice for diseases with predominantly retinal inflammation is FA giving global information, as well as OCT to monitor the evolution and/or the response to treatment of the posterior pole.

2.2 Choriocapillaritis and diseases of the outer retina

Choriocapillaritis is caused by inflammatory non-perfusion of the choriocapillaris, the main entities being MEWDS, MFC, APMPPE and SC. Damage is limited to the outer retina in mild cases such as MEWDS and in mild cases of MFC and APMPPE, while the RPE is involved in severe cases of APMPPE, MFC and in SC which can also evolve to chorioretinal atrophy. The photoreceptor layer can also be involved primarily in case of photoreceptoritis such as AZOOR. The relevant imaging modality for choriocapillaritis is ICGA showing choriocapillary non-perfusion as hypofluorescent areas not filled with ICG.. For AZOOR the ICGA is normal as the choriocapillaris is not involved. The damage to the photoreceptor layer is shown by OCT for choriocapillaritis and primary photoreceptoritis. BAF shows hyperautofluorescence in MEWDS, mild cases of MFC APMPPE and AZOOR and is a reliable modality to follow the disease evolution. In severe disease (APMPPE, MFC and SC), additionally in severely affected areas, ICGA shows hypofluorescence and BAF shows hypoautofluorescence because of loss of RPE cells and/or atrophy.

2.3 Predominantly stromal choroiditis

VKH is an example of pure stromal choroiditis, as inflammation starts exclusively in the choroidal stroma. Retinal inflammation is only secondary to choroidal inflammation. In contrast, HLA-A29-BRC is characterised by dual parallel but independent involvement of the choroidal stroma and the retina. Both sarcoidosis and tuberculosis related uveitis can involve the choroid exclusively, both retina and choroid or retina exclusively. The gold standard imaging of stromal choroiditis is ICGA. For follow-up EDI-OCT measuring choroidal thickness is useful in VKH and HLA-A29-BRC and allows to reduce the frequency of ICGA.

3. Practical clinical applications of ocular imaging methods in non-infectious uveitis

Only a few cases in each category will be presented in order to illustrate the flow-chart of imaging investigations of non-infectious posterior uveitis. (diagram 3)

3.1. Cases of predominantly retinal inflammation

3.1.1. Intermediate uveitis of the pars planitis type

This 14-year-old girl had been given methotrexate 3 months prior to coming to our centre which had caused a total hair loss. At presentation, she was still under 5 mg of prednisone. Visual acuity was 0.9-1.0 in both eyes. There was a slight flare bilaterally. Laser flare photometry values amounted to 15.6 photons/milliseconds (ph/ms) OD and 17.9 ph/ms OS (normal values 4-6 ph/ms). We noted 1-2+ cells in the anterior vitreous. Fundus examination showed snowbanks in the periphery and vitreous opacities bilaterally and crowded slightly elevated discs. Octopus bilateral visual fields were normal. OCT showed slightly thickened foveas bilaterally. (Figure 10a & 10b)

ICGA did not show any choroidal involvement. FA showed retinal vasculitis and an angiographic oedema bilaterally but no neovascularization. (Figure 11) Prednisone was tapered to zero within 3 months.

It was decided to follow the patient without treatment, paying attention, to both clinical examination and to the evolution of laser flare photometry inflammation values, OCT analysis of foveal thickness and degree of vasculitis using FA. After 2 years and 9 months, visual acuity, visual field, laser flare photometry values, OCT foveal thickness and retinal vasculitis remained stable. (Figures 10a, 10b, & 11) The appraisal and follow-up of intermediate uveitis is best achieved by a combination of FA and OCT

3.1.2. Behçet's uveitis

This patient was followed for several years for Behçet's uveitis with FA monitoring of the degree of vasculitis. As shown in figure 12, FA, the most appropriate imaging modality in Behçet's uveitis, was useful to monitor therapeutic intervention showing decrease of vasculitis after strengthening of treatment, (Figure 12)

3.1.3. HLA-A29 birdshot retinochoroiditis (retinal involvement)

HLA-A29-BRC is a stromal choroiditis which presents in parallel concomitant retinal and disc inflammation which occurs independently from the choroidal inflammation. [42] The most relevant imaging modalities for retinal involvement are FA and OCT. As both the retinal and choroidal compartments are involved, ICGA and EDI-OCT should also be performed (see below). Figure 13 shows the substantial vasculitis that some cases can present associated with disc hyperfluorescence and macular oedema (cystoid in the left eye). (Figure 13) OCT allows to follow the evolution of retinal involvement starting with a substantial oedema during the early exudative phase of HLA-A29-BRC followed by a mix of oedematous and atrophic retina. Thereafter, if proper treatment is not applied the retina evolves towards atrophy and presence of an epiretinal membrane (ERM). (Figure 14 - see cover page 2) OCT

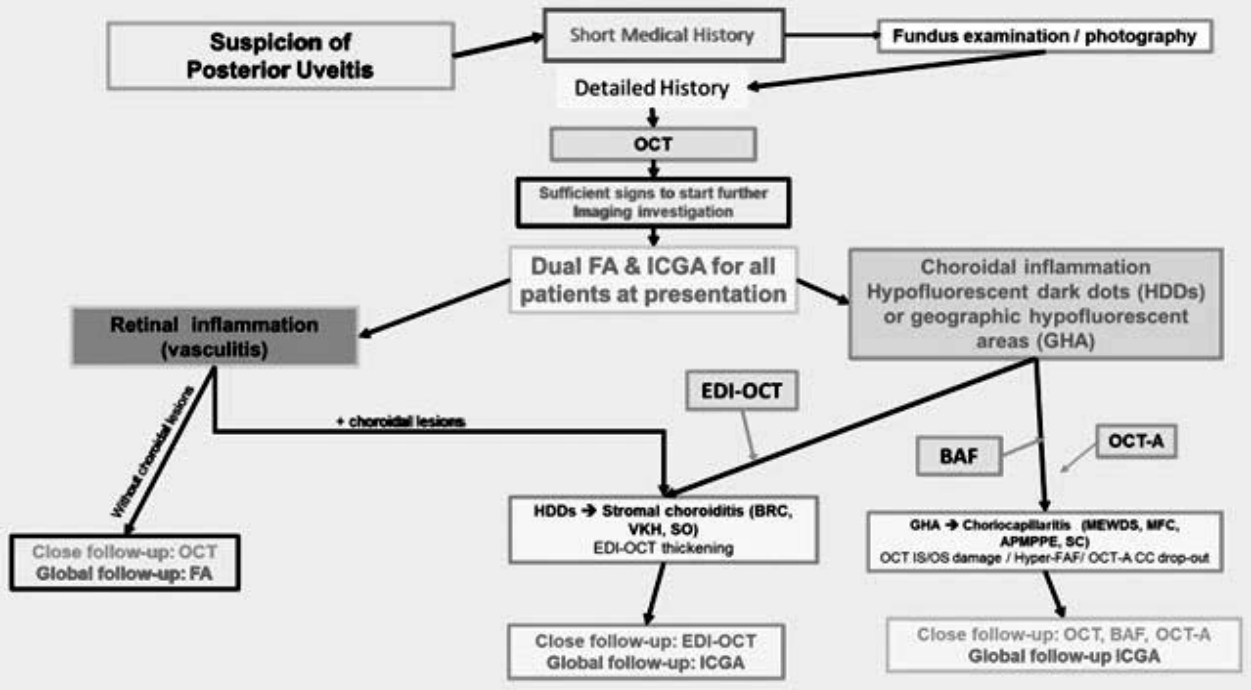

Diagram 3. Suggested flow-chart of imaging investigations in non-infectious posterior uveitis. OCT: optical coherence tomography FA: Fluoresceine angiography ICGA: indocyanine green angiography EDI-OCT : enhanced depth imaging-OCT BAF: blue-light autofluorescence OCT-A: OCT-angiography HDDs: hypofluorescent dark dots BRC: birdshot retinochoroiditis VKH : Vogt-Koyanagi-Harada disease SO: sympathetic ophthalmia GHA: Geographic hypofluorescent area MEWDS: multiple evanescent white dot syndrome MFC: multifocal choroiditis APMPPE: acute posterior multifocal placoid pigment epitheliopathy SC: serpiginous choroiditis.

is an important adjunct imaging modality that allows to precisely follow the retinal inflammation in HLA-A29-BRC.

3.2. Choriocapillaritis and diseases of the outer retina

3.2.1. Multiple evanescent white dot syndrome (MEWDS)

MEWDS is a typical mild choriocapillaritis [40]. Some authors falsely asserted that the disease was a primary photoreceptoritis which is not the case. The mechanism in MEWDS is indeed an inflammatory choriocapillaris non-perfusion. However, the vessels occluded are end-choriocapillary vessels with quasi no flow or very reduced flow that, by definition, cannot be detected by OCT-A and, hence, some clinicians deduced that the choriocapillaris was intact, which is not the case. The only modality that can show non-perfusion of end-capillary

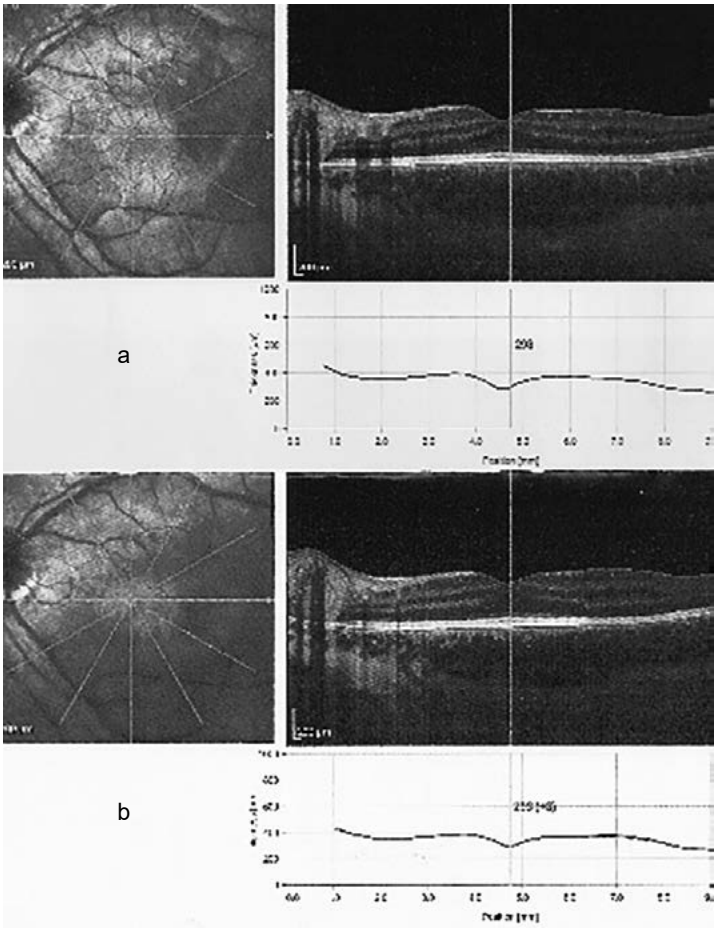

Figure 10a. OCT of the right eye at presentation (top) and after 2 years and 9 months evolution (bottom) without treatment. No increase if foveal thickness.

Figure 10b. OCT of the left eye at presentation (top) and after 2 years and 9 months evolution (bottom) without treatment. No increase if foveal thickness.

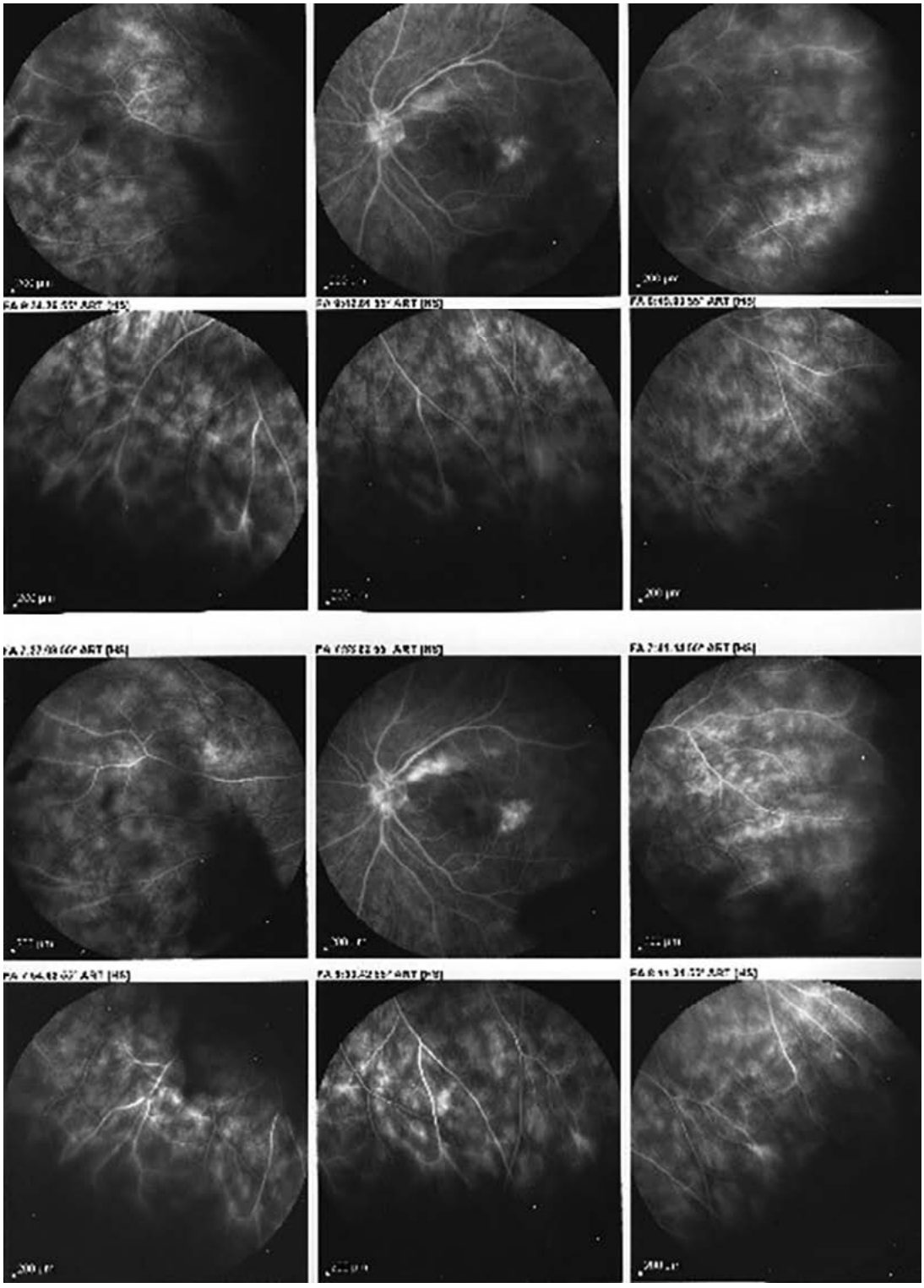

Figure 11. FA of the left eye at presentation (top six frames) and after 2 years and 9 months of evolution (bottom six frames) without treatment. Vasculitis is stable and absence of neovessels.

vessels is ICGA which is the crucial imaging of choice for MEWDS. Because there are numerous small areas of non-perfusion, there are many skipped areas of loss of photoreceptor outer segments, well visible on OCT. As a consequence, these areas are well identified on BAF images as the loss of photopigment unveils the normally present autofluorescence in the RPE cells. (Figure 15) BAF, together with OCT, in the special case of MEWDS are as performing, if not more, than ICGA to detect and follow lesions. Usually, MEWDS is unilateral and self-limited, does not necessitate treatment and does not recur. If there is a recurrence, the diagnosis that has to be considered is MFC

3.2.2. Multifocal choroiditis (MFC)

Idiopathic multifocal choroiditis regroups several entities that have been described in the past as separate conditions such as punctate inner choroiditis (PIC) or pseudo-ocular histoplasmosis syndrome (POHS) and others [43]. The first episode can resemble MEWDS and can be mistaken for it. However, the diagnosis must often be reoriented to MFC when recurrences occur. In contrast to MEWDS, MFC is often bilateral, recurrent, at the origin of small chorioretinal scars, needs aggressive immunosuppressive treatment and is complicated in around 30% by inflammatory CNV [14]. ICGA is an essential modality as it is the only way to identify occult lesions indicative of active disease which means introduction or maintenance of immunosuppressive treatment. (Figure16 - see cover page 2).

3.2.3. Acute posterior multifocal placoid pigment epitheliopathy (APMPPE)

APMPPE can present as a large spectrum of severity going from mild forms with limited lesions involving small areas of outer retina damage that can resolve without treatment, to very extensive areas of profound ischaemia leading to scars needing high-dose corticosteroid treatment [12]. Multimodal imaging is

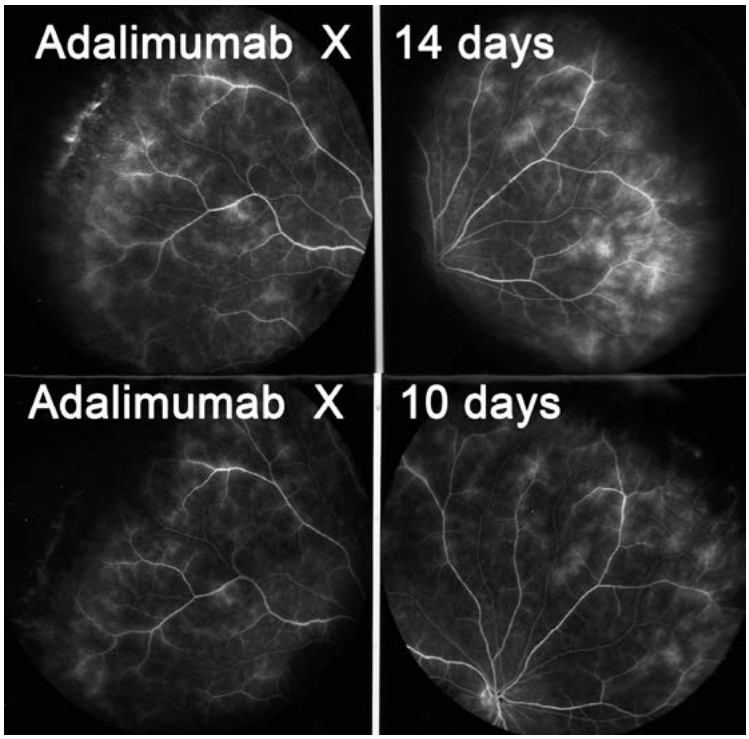

Figure 12. Behçet's uveitis. FA of the right eye shows substantial vasculitis under the treatment of adalimumab once every two weeks (top two frames), which improved after increase of treatment to once every 10 days

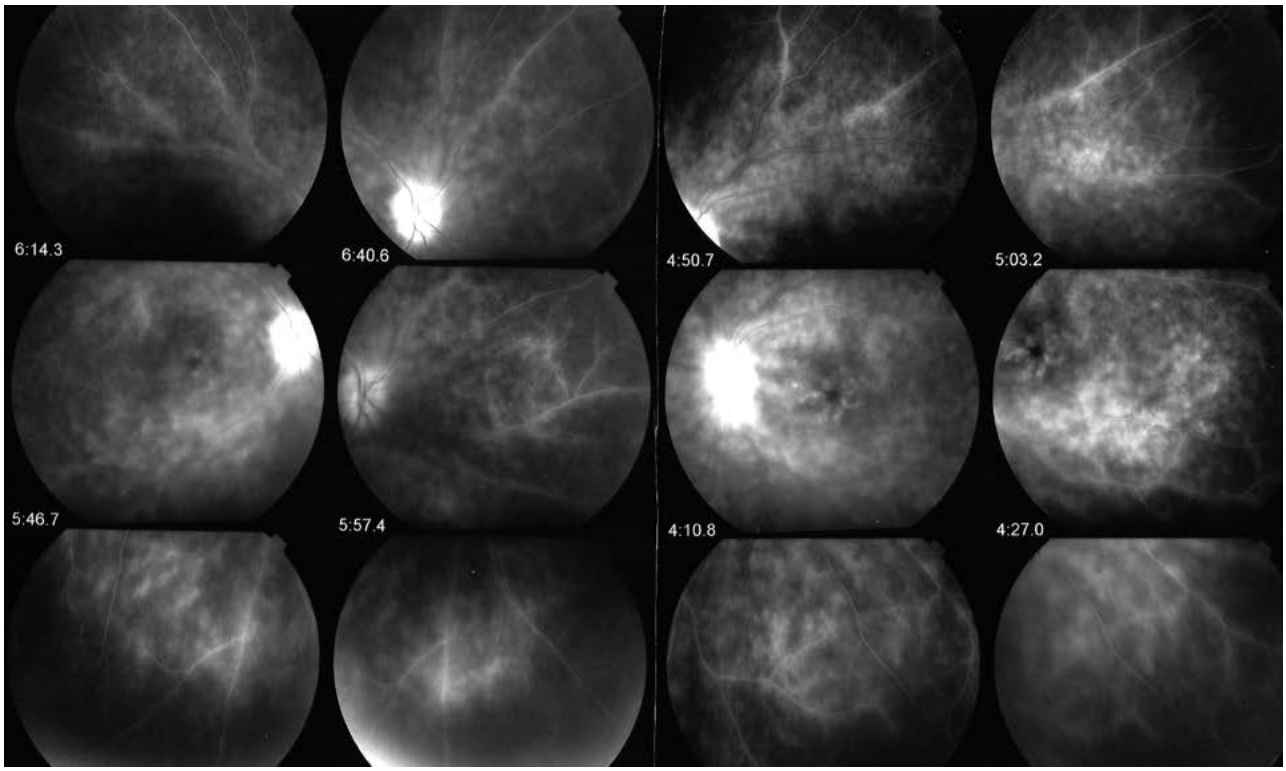

Figure 13. Retinal involvement in HLA-A29 birdshot retinochoroiditis. This case of HLA-A29-BRC presents substantial vasculitis and optic disc inflammation (hyperfluorescence)

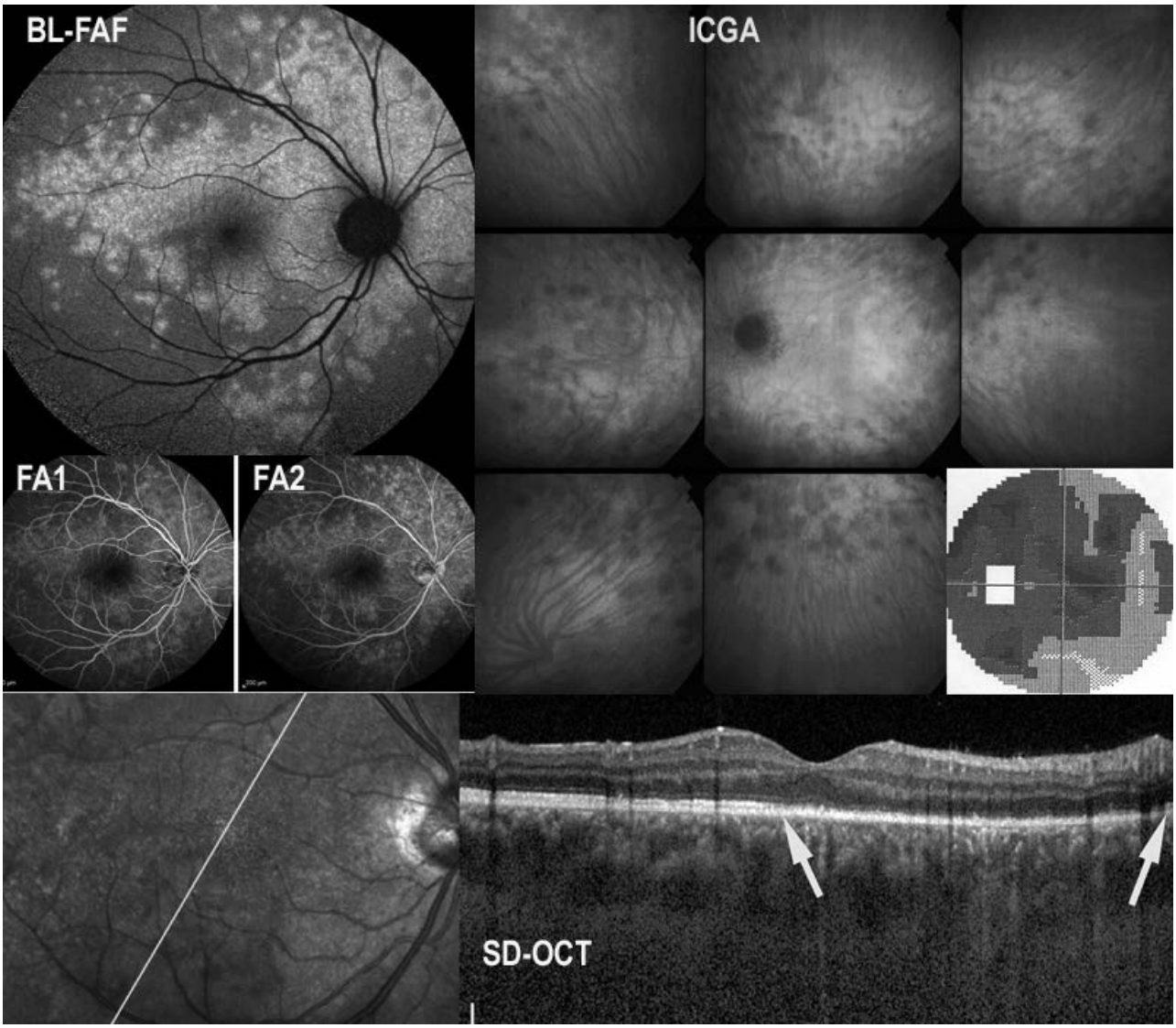

Figure 15. Multimodal imaging signs in MEWDS. BL-FAF (top left) showing geographic area of hyperautofluorescence indicating active lesions. ICGA (top right, different patient) showing patchy areas of hypofluorescent with peripapillary hypofluorescence causing severe visual field loss (insert). FA (middle left) faint hyperfluorescence on early (FA1) and late (FA2) frames. SD-OCT (bottom) showing loss of photoreceptor outer segments (between yellow arrows)

necessary to depict the range of lesions in APMPPE. ICGA is needed to have a global overview of lesions precisely showing the extent of choriocapillaris non-perfusion. (Figure 7) OCT shows lesions to the RPE and outer retina. BAF shows 3 types of lesions, hyperautofluorescence in case of loss of photoreceptor outer segments, more bright hyperautofluorescence in damaged RPE cells or hypoautofluorescence in case of loss of RPE cells. (Figure 7) OCT-A is useful in the close follow-up of posterior pole lesions avoiding to repeat ICGA. (Figure 9).

3.2.4. Serpiginous choroiditis (SC)

SC is situated at the severe end of choriocapillaritis entities due to larger vessel choriocapillaris non-perfusion. It is usually bilateral and progressing if triple to quadruple immunosuppression is not given. In case SC is related to latent or active tuberculosis, antitubercular antibiotic has to be added. Multimodal imaging is the best way to investigate SC. ICGA is essential as it delineates exactly in dark hypofluorescence the atrophic areas on one side and the active perilesional hyperfluorescent areas. (Figure 17 - see cover page 3) Similar to MFC, the propensity of SC to develop choroidal neovascularization is high and such a case is shown in figure 18.

3.2.5 AZOOR

Multimodal imaging analysis of AZOOR identified the outer retina as the structure primarily involved, as already hinted by Gass who, adequately, spoke of outer retinopathy. [21] There is damage and loss of photoreceptor outer segments in the posterior pole and beyond (with sparing of the central foveal area), clearly shown on SD-OCT. (Figure 19, top right - see cover page 3) This process causes the following imaging characteristics: (1) a faint discoloured halo around the fovea on fundus photography (Figure 19, top left - see cover page 3); (2) a slight halo of late discreet

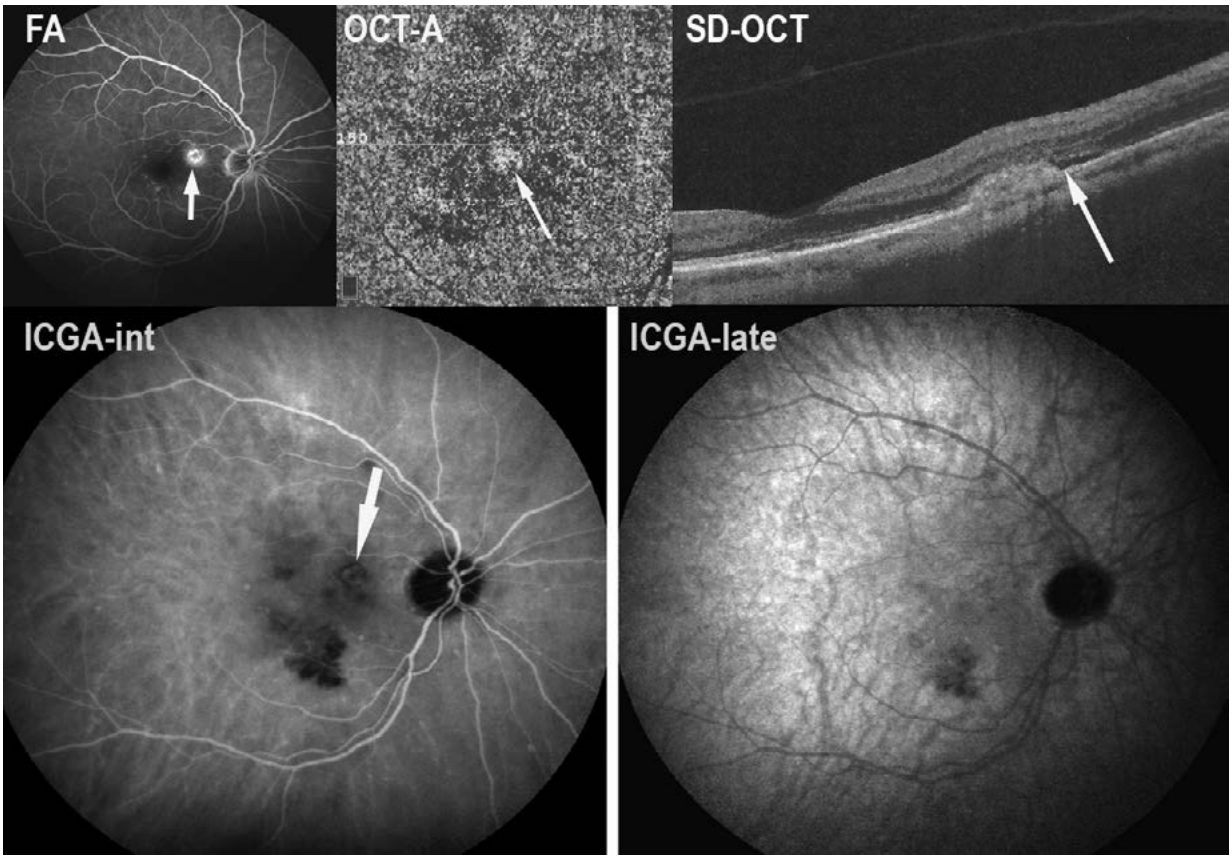

Figure 18. Serpiginous choroiditis: CNV OD. 7 years after introduction of immunosuppression, hypofluorescence is still kept under control, especially in ICGA late frames (ICGA-late). However, parafoveolar CNV is detected: yellow arrow on FA, ICGA, OCT-A, and SD-OCT (with fluid), which responded well to one intravitreal injection of anti-VEGF agent (not shown)

FA hyperfluorescence around the fovea (Figure 19 bottom left); (3) a conserved ICGA fluorescence being hyperfluorescent in the area of photoreceptor loss (Figure 19, bottom middle); (5) FAF hyperautofluorescence in the area of SD-OCT photoreceptor loss (Figure 19, bottom right). When the lesions progress, chorioretinal atrophy develops (arrows in the three bottom pictures of Figure 19), hyperfluorescent on FA (window effect), dark/hypofluorescent on ICGA (choriocapillaris drop-out) and dark on FAF (loss of RPE cells).

OCT-A did not contribute significant additional information. It simply showed integrity of the choriocapillaris (no drop-out), which was already demonstrated on ICGA.

3.3 Predominantly stromal choroiditis

Stromal choroiditis is characterized by inflammatory foci occupying the stromal choroidal space and so impairing the diffusion of ICG dye in these areas which appear as dark hypofluorescent dots, clearly identifying the foci. Indeed, ICGA is the imaging modality of choice with EDI-OCT being helpful in the early stages of the disease but giving limited posterior pole information that is less precise than ICGA [17]. There are two patterns of lesions with regular size diffuse HDDs in the group of disease where the pathological process starts within the choroidal stroma such as VKH, HLA-A29-BRC and SO which are called primary stromal choroiditis. In cases like sarcoidosis and tuberculosis related chorioretinitis, also called secondary stromal choroiditis, the lesions are of diverse size and have an irregular distribution, as the choroid is a chance location of systemic diseases.

3.3.1. HLA-A29-Birdshot retinochoroiditis (HLA-A29-BRC)

As indicated earlier, HLA-A29-BRC is particular among primary stromal choroiditis entities because there is an independent retinal involvement in addition to choroiditis (see above). The disease is always bilateral. Global precise information is obtained from ICGA which is also essential for follow-up purposes (Figure 20). In the early stages of the disease EDI-OCT is another modality that shows thickened choroid progressively diminishing under immunosuppressive therapy (Figure 5). For the long-term follow-up EDI-OCT is useful to monitor choroidal atrophy, as thickness tends to decrease if treatment is insufficient [44]. Evolution of lesions and response to treatment are best monitored by ICGA. OCT-A and BAF are of little help in the choroidal disease of HLA-A-29-BRC as the structures they depict (choriocapillaris and outer retina) are only secondarily and inconsistently involved.

For HLA-A29-BRC, ICGA is specially recommend because it enables a diagnosis before photographic fundus

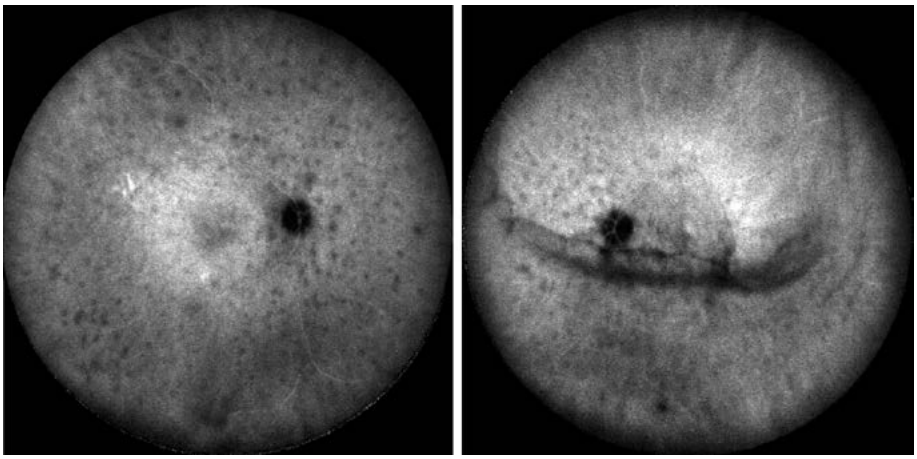

Figure 20. Choroidal involvement in HLA-A29 birdshot retinochoroiditis depicted by ICGA. Precise global information is obtained by ICGA showing numerous HDDs in both eyes. Note also the vitreous opacities, a frequent feature in HLA-A29-BRC

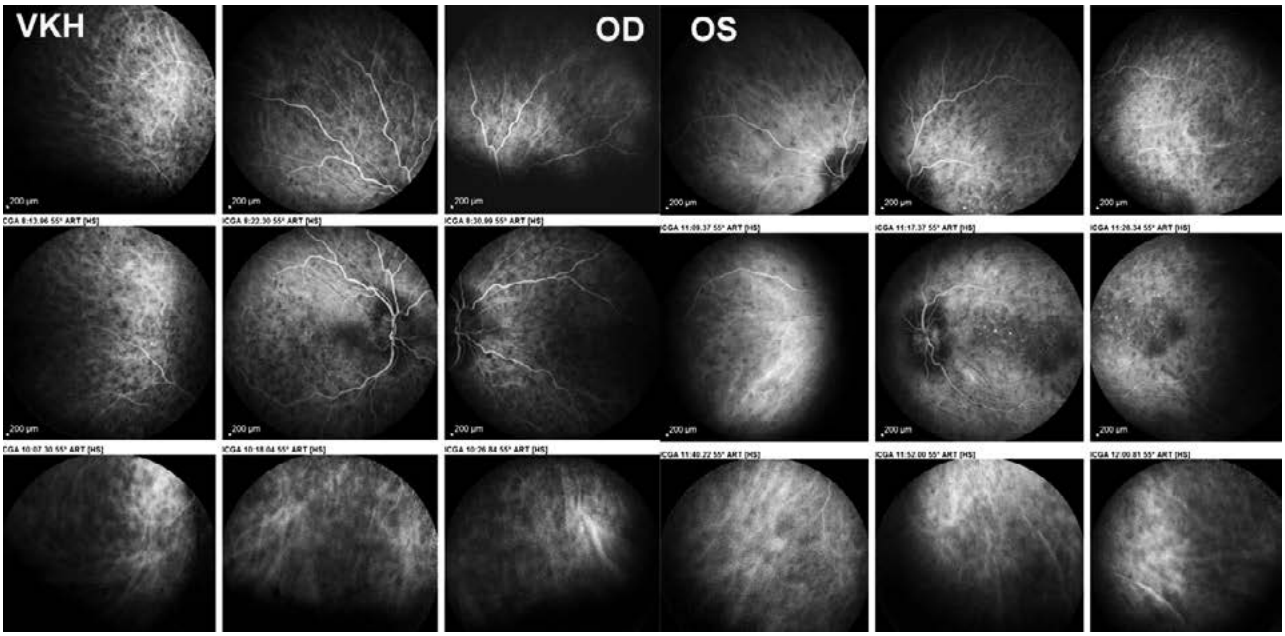

Figure 21. ICGA of VKH. Numerous bilateral HDDs at presentation. Note also disc hyperfluorescence bilaterally due to severe inflammation; usually, disc is not hyperfluorescent on ICGA.

lesions become apparent and so allows to start early treatment. [45]

3.3.2. Vogt-Koyanagi-Harada disease (VKH)

VKH is purely stromal choroiditis. Retinal inflammation such as ERD (see figure 3a) and optic disc inflammation is secondary to choroiditis. ICGA is the gold standard for the appraisal, follow-up and monitoring of therapy [46]. As for HLA-A29-BRC, EDI-OCT can be useful at the early stage of disease, accounting for the decrease of choroidal thickness after introduction of immunosuppressive therapy and has some utility to detect recurrences. However, ICGA is much more sensitive for a precise follow-up and for fine-tuning therapy [47].

The 4 main ICGA angiographic signs in stromal choroiditis such as VKH, include HDDs, early hyperfluorescent choroidal vessels, late fuzzy vessels and disc hyperfluorescence (in super-acute disease). (Figure 22)

The crucial importance of ICGA is the fact that it allows early diagnosis and early treatment. If steroidal and non-steroidal immunosuppression is not introduced early enough and the therapeutic window of opportunity is missed, the disease will have a chronic evolution [48].

3.3.3. Sarcoidosis chorioretinitis

Sarcoidosis (and tuberculosis) chorioretinitis have very similar imaging presentations, The choroid is the principal structure involved but very often there is both retinal and choroidal inflammation. In contrast to primary stromal choroiditis, inflammation does not originate from within the eye, The choroid (and retina) are just chance locations of a systemic disease. Therefore, size and location of lesions are variable and distribution is irregular. As both retina and choroid can be involved the most appropriate imaging approach is dual FA/ICGA. Thanks to a semi-quantitative angiographic scoring system the proportion of inflammatory involvement in both structures can be calculated. [7, 26] The proportion of respective involvement can be very different from one case to another as shown in figures 24 and 25. (Figures 24 & 25) As both retina and

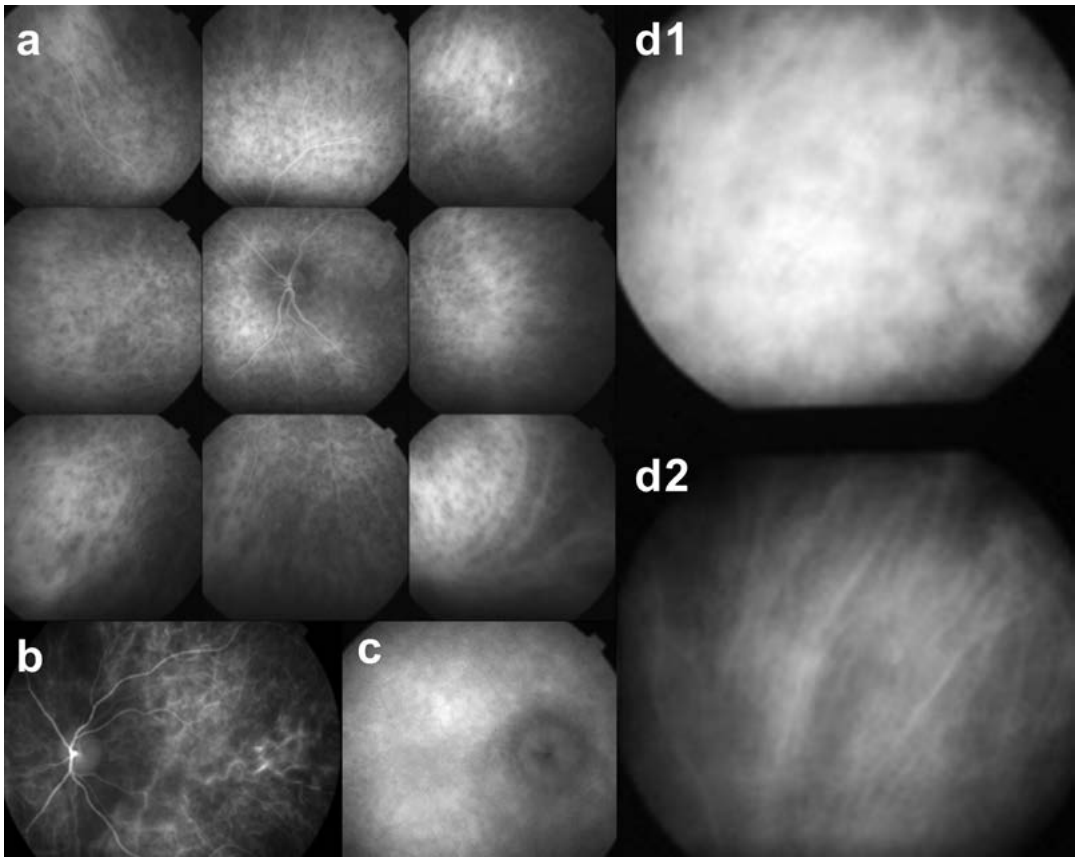

Figure 22. Four main ICGA signs in acute initial onset VKH disease. Numerous regularly distributed over the whole fundus and evenly sized hypofluorescent dark dots (HDDs) is the most demonstrative and quantifiable ICGA sign (top left, a). Early hyperfluorescent vessels (b) and hyperfluorescent disc (c) (usually hypofluorescent on ICGA) indicate very severe inflammation. Fuzzy indistinct choroidal vessels represent the 4th ICGA sign (d1, top right). After 3 days of intravenous methylprednisolone, the course and structure of choroidal vessels are again distinctly visible (d2).

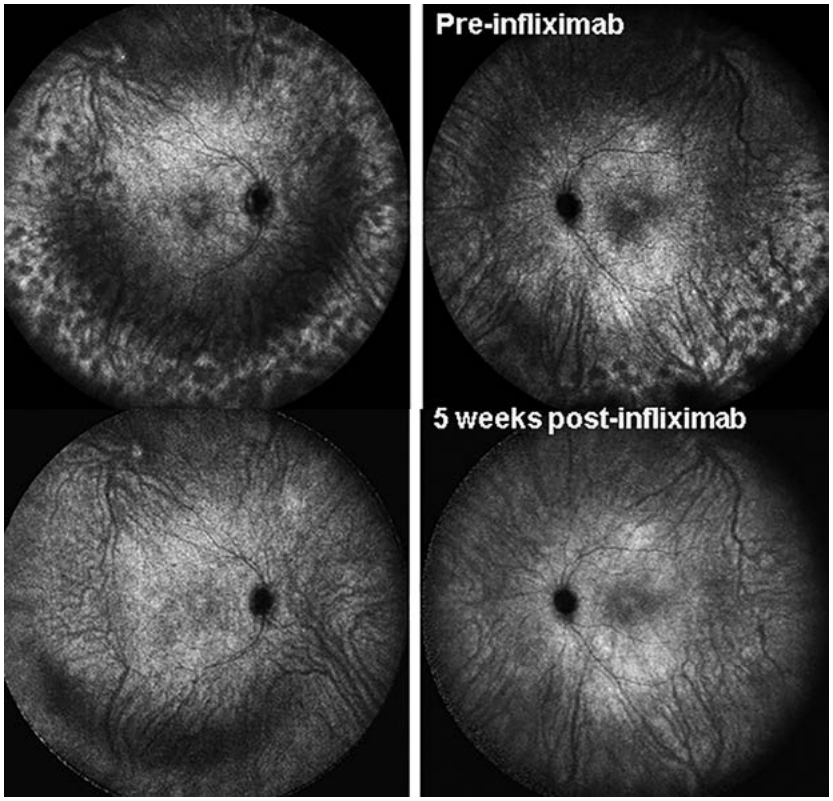

Figure 23. Extreme sensitivity and global information on whole fundus involvement given by ICGA. Case of VKH disease responsive to initial highly dosed corticosteroids with peripheral recurrence under mycophenolic acid (Myfortic ®) and cyclosporine (CsA) characterized by numerous HDDs (top pictures). After introduction of infliximab, complete resolution of choroiditis within 5 weeks (bottom pictures), establishing infliximab as the therapy of choice in this case to which this VKH patient was responsive. Posterior pole involvement was minimal and choroidal OCT did not reflect the spectacular improvement of choroiditis. ICGA assisted monitoring of choroidal inflammation is crucial to promptly establish inefficiency or efficiency of immunosuppressive treatment for each individual case.

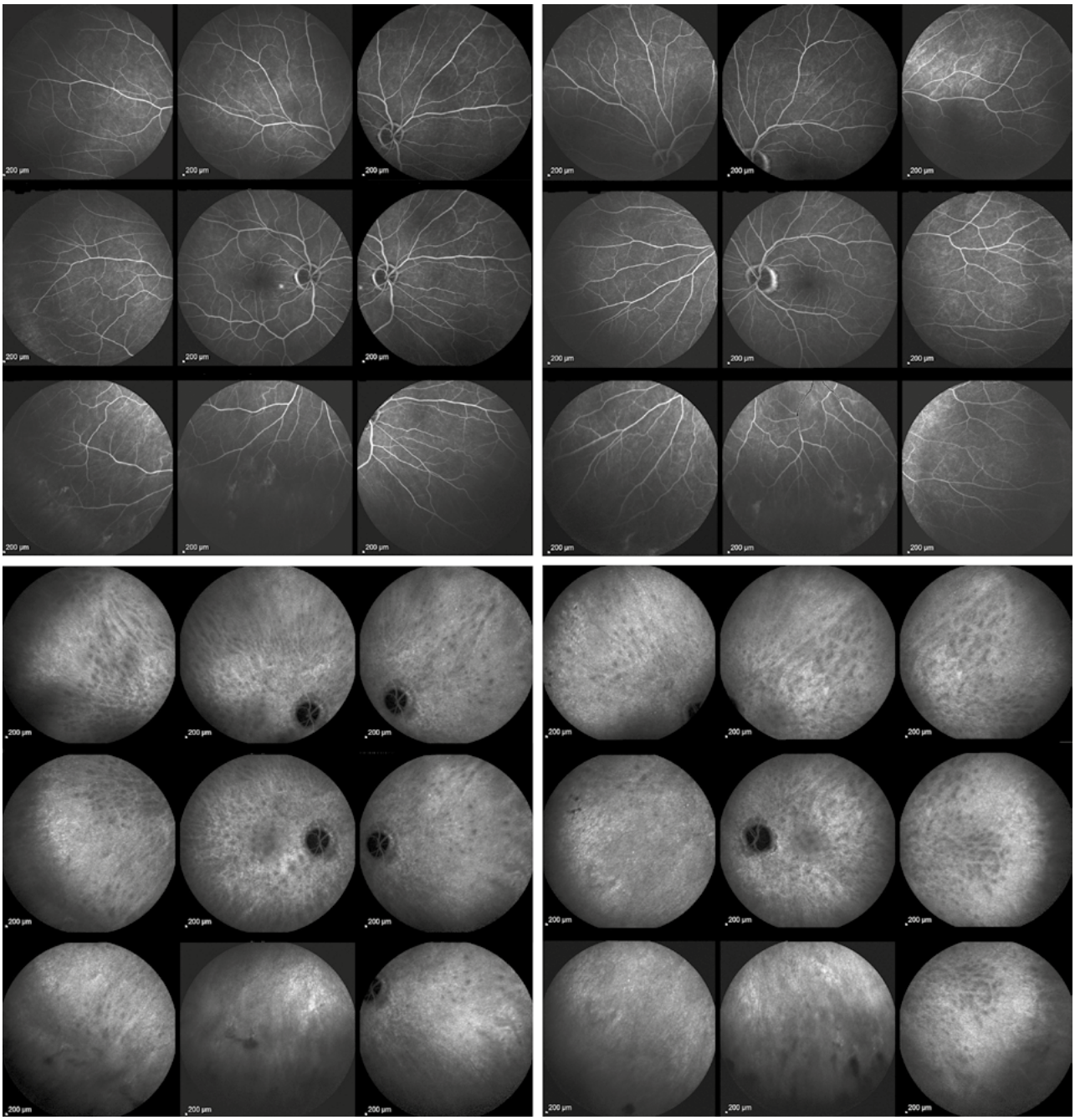

Figure 24. FA / ICGA in sarcoidosis chorioretinitis. Patient with ocular sarcoidosis showing predominant choroidal involvement. FA (intermediate angiographic phase - top frames) showing macroaneurysms in the right eye (top left) with ocular sarcoidosis and appearing normal in the left eye (top right). The FA score was 1 in the right eye and 0 in the left eye. ICGA (late phase – bottom frames) of both eyes (bottom right and left) had numerous HDDs, indicating presence of occult granulomas that cannot be seen on fundus imaging and FA. The ICGA score was 20 in both eyes.

choroid are involved in the inflammatory process, OCT and EDI-OCT should be performed for complementary information.

Conclusion

The different imaging modalities available presently to the clinician for posterior uveitis allow a precise work-up of most the cases. The mainstay of imaging investigation is dual FA/ICGA with additional more fine analysis of certain structures with non-invasive methods including OCT, EDI-OCT and BAF that are sometimes also suited for the follow-up allowing to reduce the number of invasive dye angiographies. Although OCT-A is of high-grade technology and has allowed significant progress in research, its contribution to practical everyday clinical management of clinical cases is of limited value.

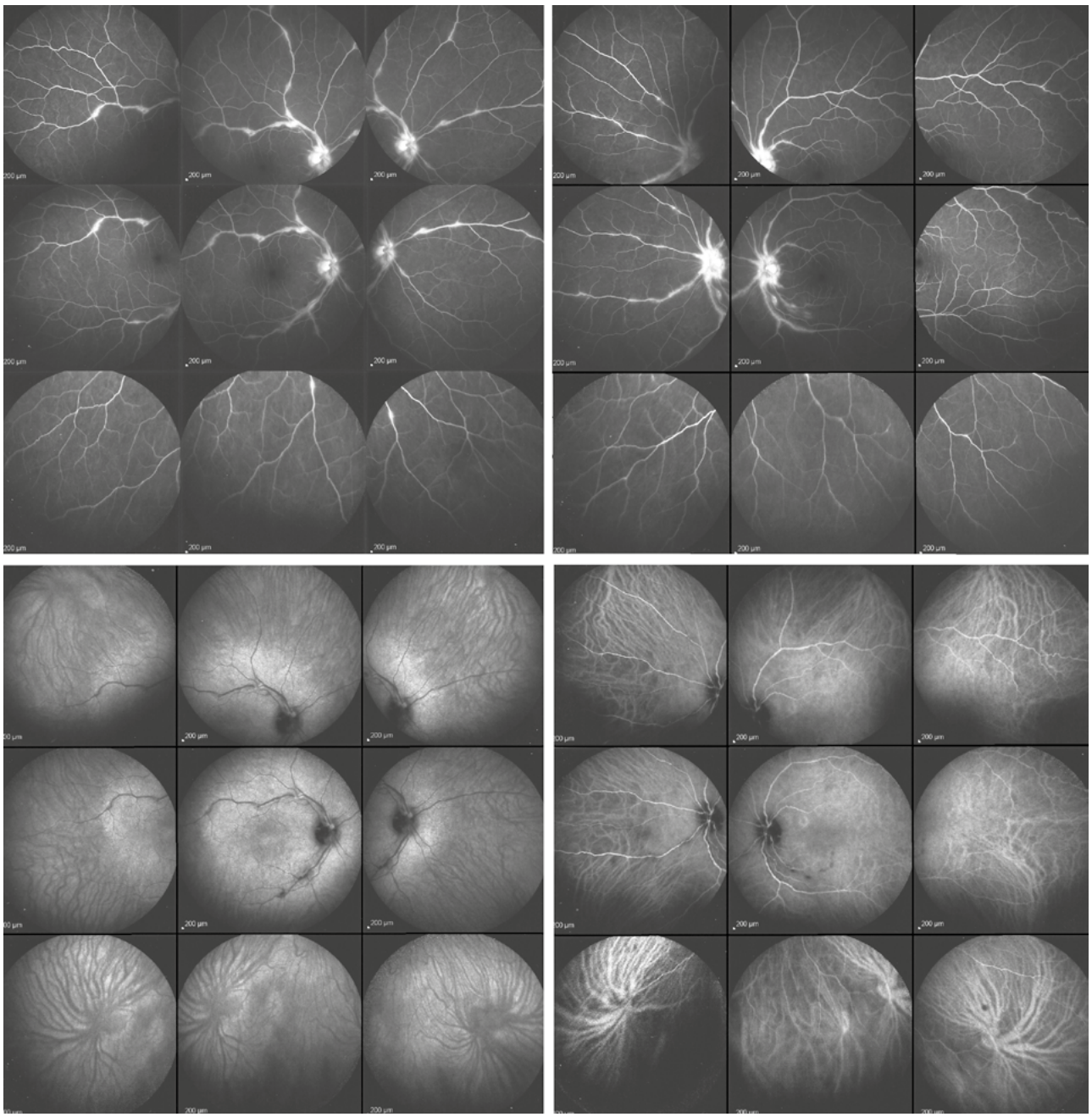

Figure 25. FA / ICGA in sarcoidosis chorioretinitis. images of a woman with ocular sarcoidosis showing predominant retinal involvement. FA (intermediate angiographic phase) showing optic disc hyperfluorescence and retinal vascular staining and leakage in both eyes (top right and left). The FA angiographic score was 7 in the right eye and 6.5 in the left eye. ICGA (late phase) showing both eyes (bottom right and left) had small hypofluorescent dark areas along the retinal vessel producing a mask effect. The ICGA score was 2 in both eyes.

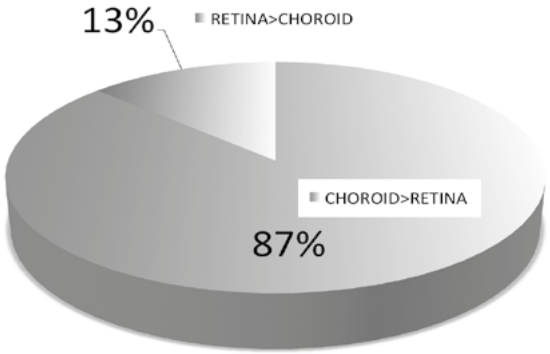

Figure 26. Pattern of involvement of each eye in sarcoidosis - related chorioretinitis. 40 (87%) of the 46 eyes had more choroidal than retinal lesions, and 6 (13%) of the 46 eyes had more retinal than choroidal lesions.

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Disclosures

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Corresponding author: *Carl P. Herbort Jr – cph@herbortuveitis.ch*

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Abbreviations: *APMPPE – Acute Posterior Multifocal Placoid Pigment Epitheliopathy; AZOOR – Acute Zonal Occult Outer Retinopathy; BAF – Blue Light Auto Fluorescence; CMO – Cystoid Macular Oedema; CNV – Choroidal Neovascularisation; EDI-OCT – Enhanced Depth Imaging Optical Coherence Tomography; ERD – Exudative Retinal Detachment; ERM – Epiretinal Membrane; FA – Fluorescein Angiography; FNa – Fluorescein Sodium; HDD – Hypofluorescent Dark Dot; HLA-A29-BRC – Human Leukocyte Antigen A29 Birdshot Retinochoroiditis; ICG – Indocyanine Green; ICGA – Indocyanine Green Angiography; MEWDS – Multiple Evanescent White Dot Syndrome; MFC – Idiopathic Multifocal Choroiditis; OCT – Optical Coherence Tomography; OCT-A – Optical Coherence Tomography Angiography; PIC – Punctate Inner Choroidopathy; POHS – Pseudo Ocular Histoplasmosis Syndrome; RFT – Retinal Foveal Thickness;*

RPE – Retinal Pigment Epithelium; SC – Serpiginous Choroiditis; SD-OCT – Spectral Domain Optical Coherence Tomography; SS-OCT – Swept Source Optical Coherence Tomography; SO – Sympathetic Ophthalmia; SUN – Standardization Uveitis Nomenclature; (anti-) VEGF – anti Vascular Endothelial Growth Factor; VKH – Vogt-Koyanagi-Harada disease.

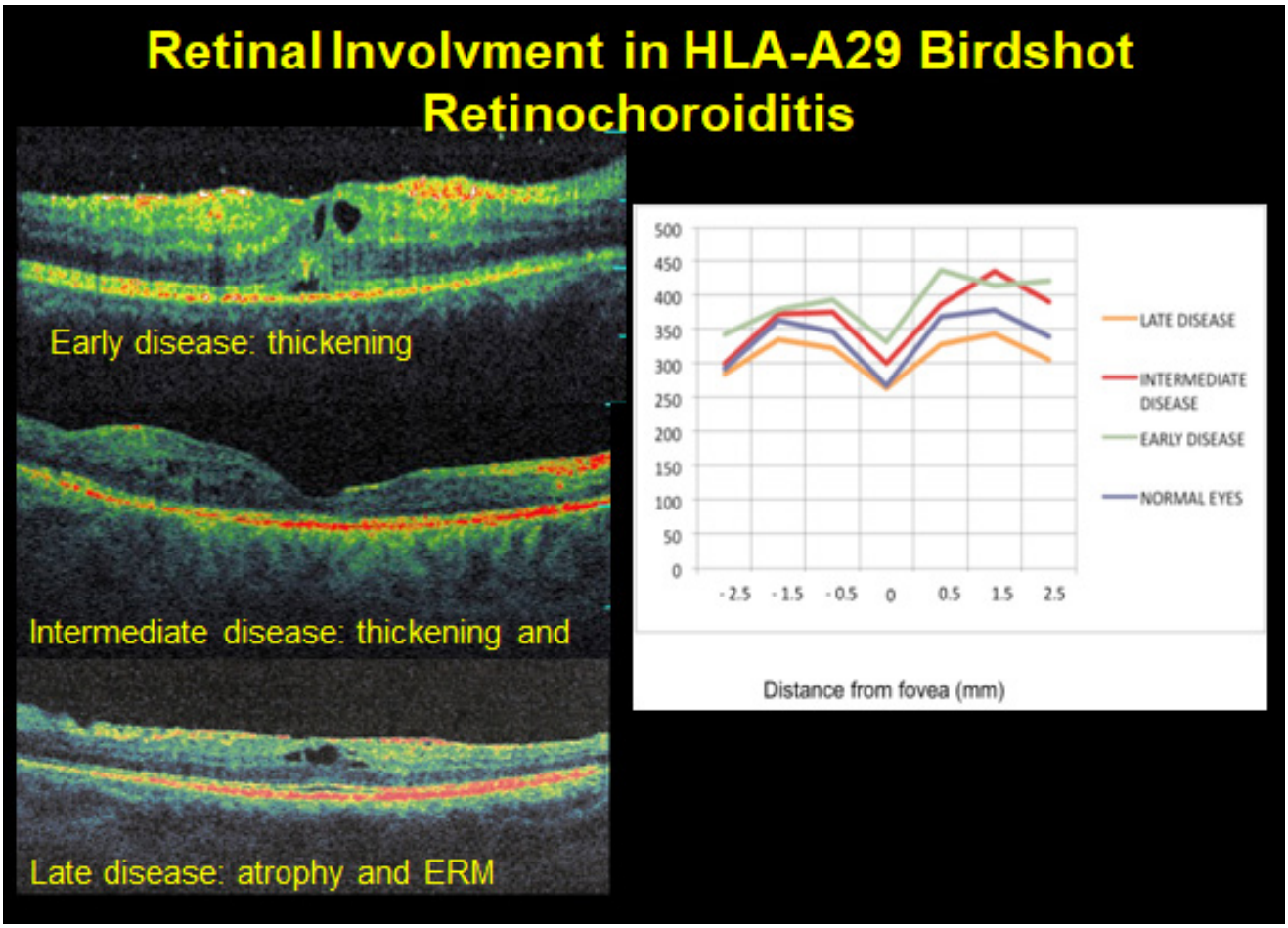

Figure 14. OCT monitoring of Retinal involvement in HLA-A29 birdshot retinochoroiditis. OCT shows a thickened oedematous retina (top left) in the early exudative phase of the disease. In the intermediate phase of the disease if appropriate treatment is not applied, there is a mix of thinned and oedematous retina (middle scan) that can evolve towards atrophy with formation of an epiretinal membrane (ERM).(bottom scan). On the right, the graph shows the evolution of retinal thickness at the level of the fovea and at three points on the nasal and temporal macula.

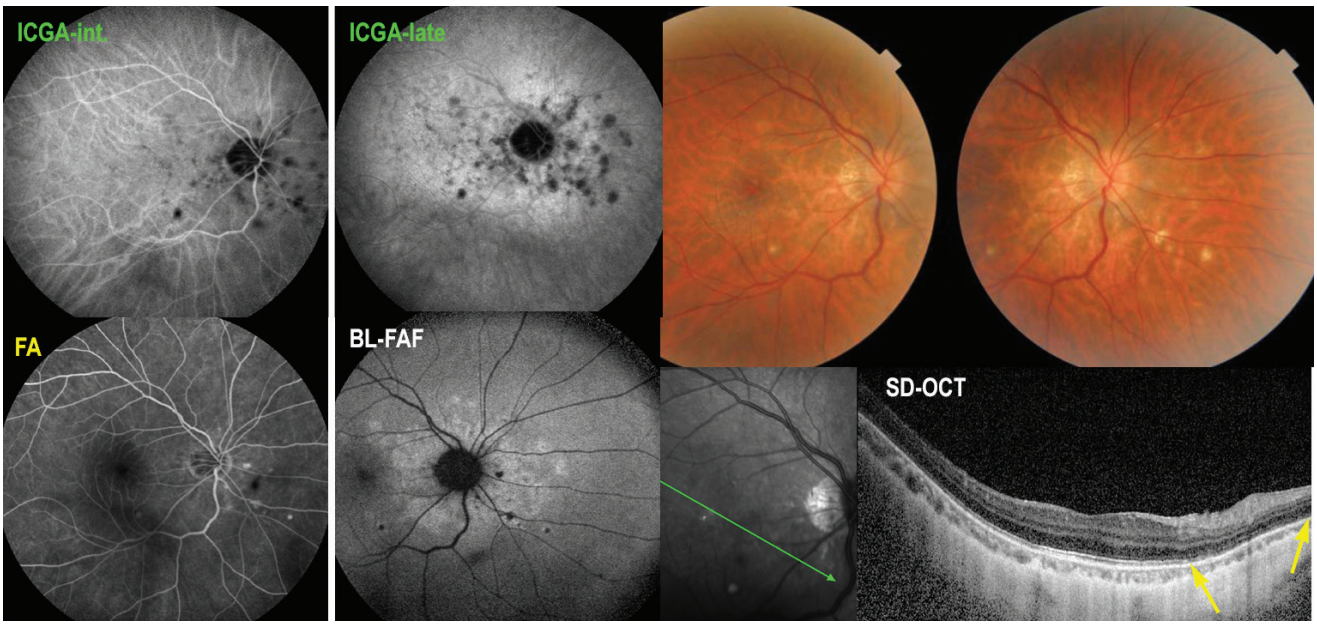

Figure 16. Multimodal imaging signs in MFC. The ICGA top two left frames show numerous hypofluorescent dark dots (HDDs) in the intermediate angiographic phase (top left) but much better visualized in the middle left late phase frame (ICGA-late) . These HDDs correspond both to the cicatricial lesions visible as hyperfluorescent punctiform spots on fluorescein angiography (bottom left). The BL-FAF picture (bottom middle) shows hyperautofluorescent areas corresponding to active lesions characterized by loss of photoreceptor outer segments shown on SD-OCT (bottom right, between two yellow arrows)

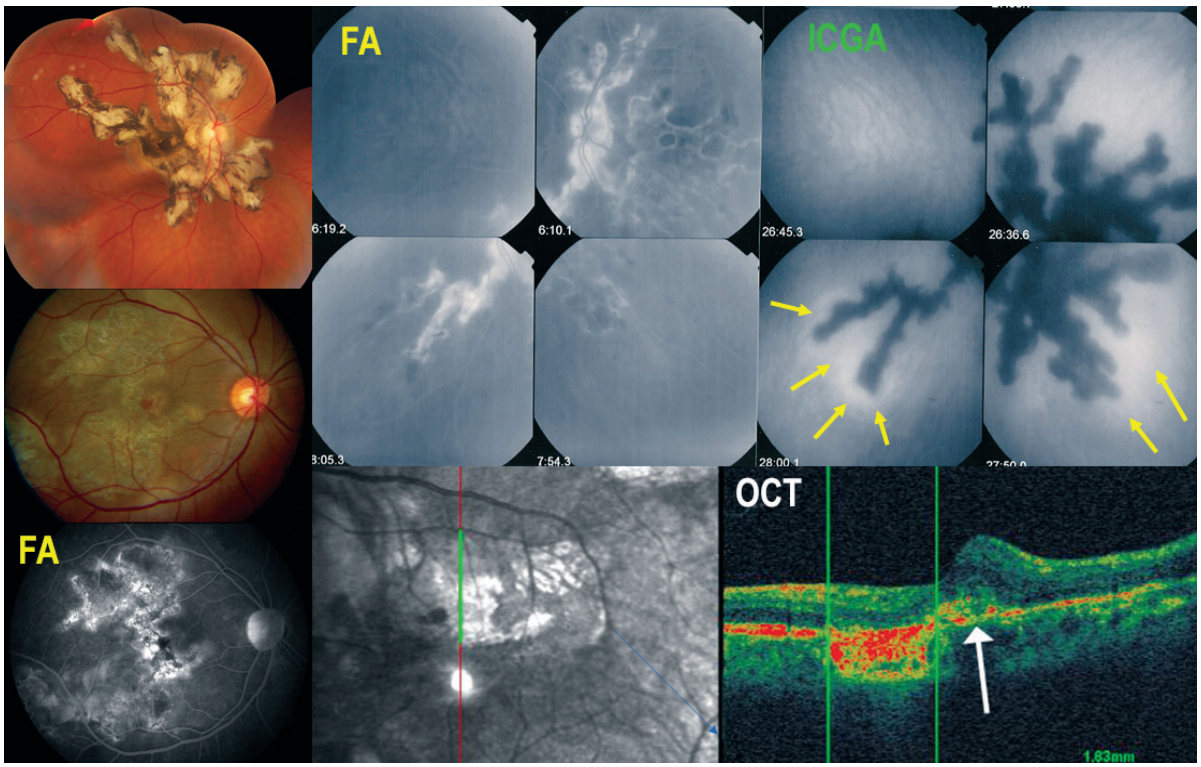

Figure 17. imaging signs in SC. Typical fundus aspect of SC (top left); extensive central atrophy in different case (middle left) with FA hyperfluorescent window effect (bottom right). Comparison of FA (top middle) and ICGA (top right) findings; ICGA hypofluorescence is much more widespread than FA hyperfluorescence as it represents both atrophy and choriocapillaris non-perfusion of new lesions. Perilesional ICGA hyperfluorescent halo (yellow arrows) indicates progression of disease. OCT (bottom right) shows that at the border of atrophy there is retinal oedema and damage to the outer retina (white arrow).

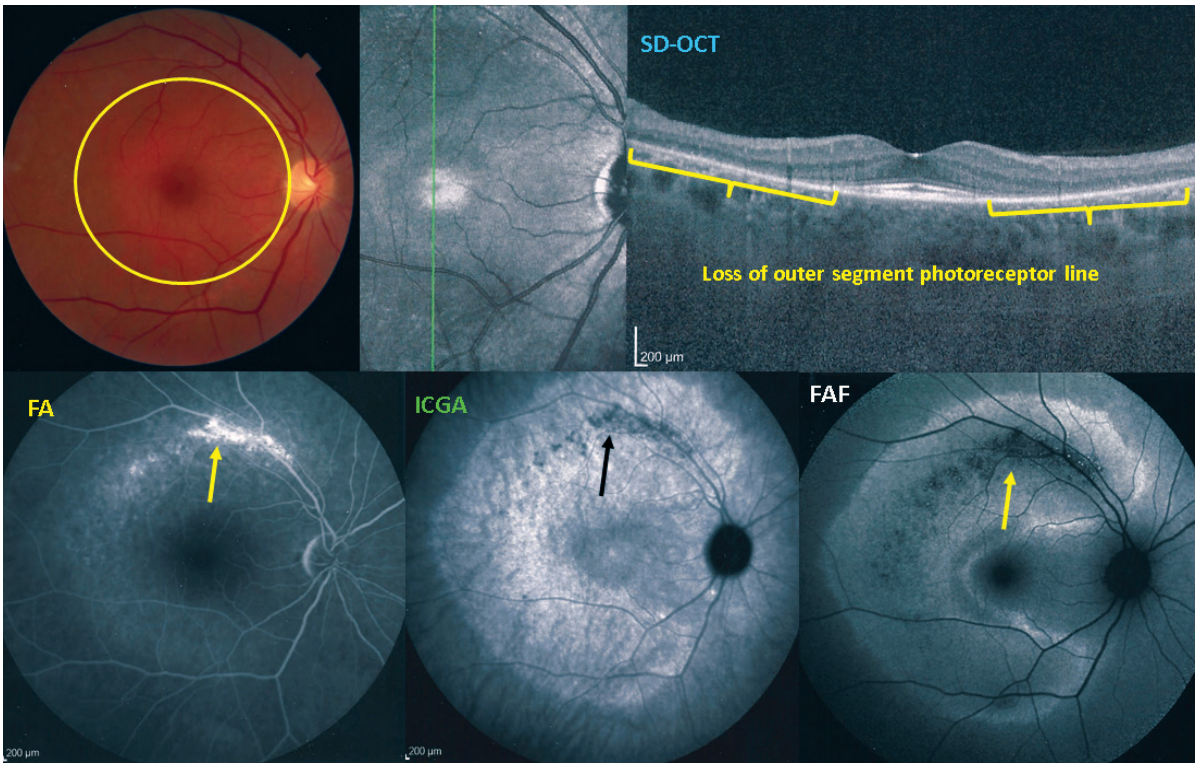

Figure 19. Imaging illustration of the clinicopathology of AZOOR. Fundus shows a pale discoloured halo around the fovea that retains a normal colour (top left, yellow circle) due to loss of photoreceptor photopigment. FA (bottom left picture) shows the same halo of discreet hyperfluorescence due to photopigment loss and an area of bright hyperfluorescence (window effect) along superior temporal arcade due to chorioretinal atrophy (dark on ICGA - bottom middle- and FAF – bottom right). ICGA (bottom middle) shows preserved choriocapillaris (except in the arciform area of chorioretinal atrophy) with increased fluorescence in the area of loss of the screen of photopigments which also explains fundus hyperautofluorescence (bottom right). SD-OCT (top right) shows the loss photoreceptor outer segments.