Acta Scientific Ophthalmology (ISSN: 2582-3191)

Volume 4 Issue 6 June 2021

Mini Review

Evolving Evidence about the Role of Choriocapillaris in Pathogenesis of Uveitis

Hashim Ali Khan[1,2]* and Smaha Jahangir[2]

[1]*SEHHAT Foundation Hospital, Gilgit, Pakistan*

[2]*School of Optometry, The University of Faisalabad, Pakistan*

***Corresponding Author:** Hashim Ali Khan, SEHHAT Foundation Hospital, Main KKH, Danyore, Gilgit, Pakistan.

Received: March 22, 2021

Published: May 11, 2021

Abstract

Choriocapillaris and retinal pigment epithelium maintain as mutualistic metabolic relationship. Insult to either tissue affects the other in number of chorioretinal diseases. Many uveitides have their main activity around retinal pigment epithelium and surrounding tissue. Optical coherence tomography angiographic (OCTA) studies have demonstrated the involvement of choriocapillaris in acute phases and subsequent disruption and formation of irregular capillaries in multiple studies. OCTA has expanded our abilities to study choriocapillaris with greater detail. This short review summarizes the changes in choriocapillaris in choriocapillaropathies and other uveitides.

Keywords: Retinal Pigment Epithelium (RPE); Choriocapillaris (CC); Indocyanine Green Angiography (ICGA); Fundus Fluorescein Angiography (FFA)

Introduction

The outer retinal layers and retinal pigment epithelium of the eye derive nutrition from a dense vascular network of fine capillaries situated between the Bruch's membrane and the Sattler layer of choroid. This 10 - 30 µm thick layer is termed as choriocapillaris and consists of flat capillaries lying in a single plane [1,2]. The presence of Retinal Pigment Epithelium (RPE) poses a challenge to directly analyze the complex vascular network of the underlying choriocapillaris (CC). Conventionally, it has been examined indirectly using dye-based angiography techniques and Indocyanine Green Angiography (ICGA) has been considered a standard method to evaluate the choroid in the past. Fundus Fluorescein Angiography (FFA) is considered a gold standard for examining the vascular network of the ocular tissue, however it can only be used to investigate the outer and inner retinal structures. Additionally, leakage of fluorescein dye may conceal the underlying structures resulting in poor estimation of lesion depth [3]. The choriocapillaris appear as a grey haze in the early phase of the angiogram because the small size of fluorescein dye molecule results in its leakage from the fenestrated capillary bed leading to a diffuse choroidal fluorescence [1]. In contrast, ICGA operates at a longer wavelength of light which makes it possible to image the deeper retinal vessels and provides a higher signal to noise ratio, thus rendering this technique more suitable to visualize choriocapillaris as compared to FFA [4]. Although, dye-based angiography techniques help imaging the choriocapillaris, they still remain limited due to low resolution [1].

The Swept Source Optical Coherence Tomography (SS-OCT) allows deeper penetration through the RPE, higher acquisition speed and lower sensitivity roll-off which enables more accurate imaging

of the underlying choriocapillaris [5]. The Optical Coherence Tomography Angiography (OCTA) is a newer imaging modality that provides high resolution en-face images of retinal and choroidal vessels in a time efficient and non-invasive manner and allows the clinician to view each vascular plexus separately. In contrast to FFA and ICGA, the OCTA can be repeated, does not require dye injections, has virtually no side effects and images the details of retina and choroidal vessels without being affected by the leakage and pooling of dye as seen with dye-based angiography techniques [3].

OCTA delivers better evaluation of choriocapillaris which appears as a fine texture of capillaries evenly distributed across the normal scan on OCTA [3,6]. The multimodal imaging, in particular, the use of OCTA has made possible to comprehend the underlying mechanism of various retinal and choroidal disorders and role of choriocapillaris in the pathology of various uveitides. For instance, APMPPE was thought to involve the RPE by Gass but current evidence suggests that it arises from the choriocapillaris [6].

The term Uveitis includes a wide spectrum of inflammatory disorders which makes it crucial to recognize the pathological process and its consequences for the accurate diagnosis and treatment of various entities. The clinical picture of posterior uveitis and various white dot syndromes can be rather similar, though, their treatment and the affected anatomical landmarks vary, making each entity unique. The use of multimodal imaging has made possible to not only localize the origin of the disease and establish a diagnosis but also to monitor the course of the disease and formation of CNV which may develop in the later stages of some disorders [6,7]. In this review, we discuss how the use of newer imaging modalities has changed the understanding of pathological mechanisms involved in various forms of uveitides including intermediate and posterior uveitis by opening the doors to access the better evaluation of choriocapillaris.

Multiple evanescent white dot syndrome

Multiple Evanescent White Dot Syndrome (MEWDS) typically presents with multifocal yellow white spots at the posterior pole in females of age 20 - 25 years [8]. These lesions appear hyperfluorescent located at the level of middle retinal layers on FFA while they appear hypocyanescent and comparatively more numerous on ICGA. Structural OCT shows disrupted ellipsoid zone with hyper-reflective spots at the level of RPE that extend towards Outer Nuclear Layer [7]. The en-face SD-OCT shows hyporeflective areas at the level of RPE-photoreceptor complex which correspond with the hypocyanescent spots evident on ICGA [4]. It was previously assumed that the origin of MEWDS was the hypoperfusion of choroid owing to the hypocyanescence of the lesions on ICGA [9]. However, in later studies OCTA revealed normal architecture of choriocapillaris, superficial and deep retinal plexus at the areas corresponding with the hypocyanescent spots on ICGA which suggested that the origin of the disease lies at the level of RPE-photoreceptor complex [4]. The decreased a-wave amplitude on Electroretinography (ERG) also implied that the disease originates at the level of RPE and outer retinal layers [9].

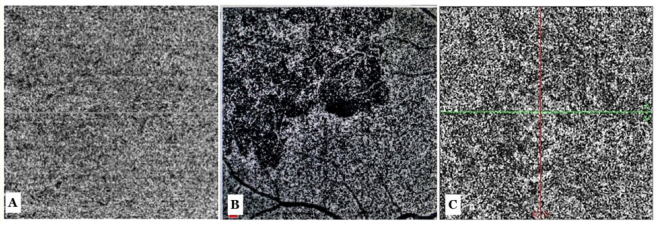

Figure 1: OCTA shows normal choriocapillaris (A), CC hypoperfusion in active serpiginous choroiditis (B) and mild residual hypoperfusion and heterogeneity of choriocapillaris in a resolved case of APMPPE (C).

Acute posterior multifocal placoid pigment epitheliopathy

Acute posterior multifocal placoid pigment epitheliopathy (APMPPE) usually presents bilaterally with a quiet anterior chamber and multifocal lesions at the posterior pole situated at the outer retina, RPE and choriocapillaris [8]. FFA reveals hypofluorescent spots in early phase which stain in the late phase of the angiogram. ICGA shows hypocyanescent spots which are characteristically more numerous as compared to those seen clinically in acute phase of the disease. OCTA in APMPPE shows low flow areas at the level of choriocapillaris which correspond well with the hypofluorescent spots seen in ICGA and early phase of FFA, thus confirming that the hypoperfused areas seen on OCTA are not projection artifacts. With the control of inflammation, the CC low flow zones tend to improve or completely resolve, however, the CC alterations may persist in some cases even after the complete resolution of the inflammation.

These findings help understand the origin of disease and support the hypothesis of APMPPE being an occlusive vasculitis that arises at the level of choriocapillaris [6,7,10].

Serpiginous choroiditis

Serpiginous Choroiditis (SC) is a bilateral inflammatory disorder characterized by multifocal yellow-white lesions appearing around the optic disc which later extend towards the posterior pole. On FFA, the active disease presents as multifocal areas of hypofluorescence which stain in the later phases of angiogram, however, the lesions stay hypocyanescent in all phases of ICGA. The inactive lesions hypofluoresce in early and intermediate phases of FFA and may show hyperfluorescence to a variable degree [11]. The FA is considered particularly useful in evaluation of disease progression as inactive lesions act hypoautofluorescent while active lesions appear hyperautofluorescent. Low flow areas at the level of choriocapillaris are seen on OCTA in acute phase of the disease which accurately correlate with the hypocyanescent areas seen on ICGA.

It is suggested that the disease process alters choroidal vasculature before the RPE because hypoperfusion areas on FFA and ICGA are reportedly larger than the RPE disruption presented on FA [4]. This hypothesis is further supported by the findings of CC on OCTA in SC by Pakzad., *et al*. who reported that the CC low flow zones co-localized with the ICGA lesions and increased in size with the flare up of inflammation while reduced in size with steroid therapy. Additionally, the low flow areas caused by infiltrates at the level of CC tend to cause signal attenuation to underlying structures while the flow voids observed in SC did not disrupt the signal penetration [12]. Khan and Shahzad reported disrupted homogeneity of choriocapillaris on OCTA in SC after the resolution of inflammation and suggested that the alterations of this vascular bed might be a cause of choroidal neovascularization formation arising in the later stages of the disease [11]. In another study, Khan., *et al*. reported that flow voids in inactive SC and APMPPE, when compared, were found to be larger and more severe in SC. Since the incidence of CNV development is higher in SC, they presumed that a direct relationship between risk of CNV formation and CC alterations severity might exist, though, the assumption needs further evaluation [10].

Multifocal choroiditis and panuveitis

Owing to the characteristic yellow gray lesions appearing at the level of RPE and choroid, Multifocal Choroiditis and Panuveitis (MPC) is included in the white dot spectrum. Typically presenting bilaterally, MCP is a panuveitis with a predilection for females of age 20 to 60 years [8,13]. FFA demonstrates hypofluoresence in the early while hyperfluoresence in the late phase with window defects at the sites of choroidal atrophy patches. On ICGA, the lesions manifest as hypocyanescent spots when in acute phase and may be more in number than ophthalmoscopically visible [4]. Areas of low flow at CC are visible in MPC on OCTA which co-localize well with the hypocyanescent spots on ICGA [4]. CNV is a common complication of MCP and may be difficult to evaluate by using dye based angiography methods only, however, OCTA when used as an adjunct imaging modality may help in distinguishing inflammatory CNV from myopic CNV [13].

Punctate inner choroidopathy

Punctate Inner Choroidopathy (PIC) typically presents with a quiet anterior chamber and multifocal yellow white lesions ranging from 100 to 300 µm in size located at the level of RPE and choroid spreading across the posterior pole. OCTA has been found particularly useful in the detection of inflammatory CNV associated with PIC when other imaging modalities including dye based angiography methods failed [9]. FFA illustrates hypofluorescent spots with late staining while ICGA reveals hypercyanescent spots at the level of choriocapillaris in the acute phase of the disease. A lacy hyperfluorescent formation reveals the CNV on FFA. CNV has been reported to develop in inactive PIC lesions with OCTA demonstrating the choroidal neovascular network [4]. Levison., *et al*. reported active inflammatory CNV in MPC and PIC as hyper-reflective organized network of vessels in the CC slab extending anteriorly into the outer retina [14].

Birdshot chorioretinopathy

Birdshot Chorioretinopathy (BSCR) is a rare, chronic posterior uveitis with a slight predilection for females with characteristic pale yellow lesions dispersed across the whole fundus [8,13]. FFA in BSCR is considered to follow the macular edema as the lesions characteristic of the disease are not displayed by the fluorescence angiogram, although, the circulation time tends to be reduced and quenching phenomenon has been observed. In contrast, the lesions are well illustrated by ICGA and appear hypocyanescent in the early and middle phases of the angiogram. A recent study has also demonstrated that ICGA may reveal lesions in BSCR before they become ophthalmoscopically visible [7]. OCTA has demonstrated a

larger FAZ at the level of SVP than was observed using FFA and DCP also shows areas of hypoperfusion. The deeper choroidal vessels also show reduced flow which is observed to be greater than that in CC. In acute phase, the flow voids are seen at the level of deeper choroidal vessels sparing the CC while in chronic phase, the hypoperfusion defects tend to spread through the complete thickness of choroid and involve the CC as well [13].

Vogt-Koyanagi-Harada (VKH) disease

VKH typically presents bilaterally and is characterized by granulomatous inflammation which may often be accompanied with exudative retinal detachment [7]. Multimodal imaging studies are crucial to diagnose and differentiate VKH from other disorders which may present a similar clinical picture [4]. Multiple hypofluorescent isolated spots are visible in the early phase of FFA while in the later phase numerous areas of hyperfluorescence become visible as the dye leaks and amasses in the subretinal space. On ICGA, the active disease appears as uniformly dispersed multifocal hypocyanescent spots which either stay the same through all phases of ICGA or may become isofluorescent in late phase. OCTA reveals low flow areas with well-defined margins in CC that match with the hypocyanescent spots demonstrated on ICGA [4]. CC ischemia has also been demonstrated by EDI-OCT where it appears to be increased in thickness with pattern loss and hyperreflective spots. The CC flow voids visible on OCTA scans of VKH have also been reported to reduce in size upon treatment. The patients in which the flow voids did not improve upon treatment had a recurrence of the disease [15].

Intermediate uveitis

The inflammation in Intermediate Uveitis (IU), by definition, is limited to the vitreous and ciliary body and is often associated with peripheral retina vasculitis but recent evidence has revealed CC alterations observed on OCTA in IU. Areas of low flow and hypoperfusion were reported in the CC on central 3 x 3 mm OCTA by Wintergerst., *et al*. who postulated that these vascular alterations might be a result of recurrent episodes of inflammation [16]. Moreover, widefield OCTA (12 x 12 mm scans) also demonstrated CC hypoflow areas in IU regardless of the presence of chorioretinal atrophy [17].

The various forms of uveitis may pose a diagnostic challenge for the clinician owing to the overlapping nature of their presentation.

Disease Entity	Changes seen at the level of CC with OCTA
MEWDS	Normal CC with no areas of flow voids evident.
APMPPE	Disrupted homogeneity with flow voids.
SC	Flow voids in active disease. Flow voids improve with control of inflammation and may or may not resolve completely.
MCP	Low flow areas CNV: A hyperreflective vascular network in the CC slab frequently extending into outer retina.
PIC	CNV: Hyperreflective fine vascular complex in the CC often spreading into outer retina.
BSCR	Acute Phase: Normal CC Chronic Phase: Flow voids in the CC.
VKH	Well-defined flow voids in active disease

Table: Findings seen on optical coherence tomography angiography at the level of choriocapillaris. MEWDS: Multiple Evanescent White Dot Syndrome; APMPPE: Acute Posterior Multifocal Placoid Pigment Epitheliopathy; MCP: Multifocal Choroiditis and Panuveitis; SC: Serpiginous Choroiditis; BSCR: Birdshot Chorioretinopathy; PIC: Punctate Inner Choroidopathy; VKH: Vogt-Koyanagi-Harada disease; CC: Choriocapillaris; OCTA: Optical Coherence Tomography Angiography.

Understanding the nature of disease and its effect on choriocapillaris can help differentiate one from another. For instance, MEWDS and APMPPE present a rather similar clinical picture, however, CC remains normal in MEWDS while CC in APMPPE shows areas of flow voids. It is significant to understand and diagnose each entity as some of the disorders have a self-limited course while other may progress and develop CNV such as PIC, MPC, APMPPE and SC. As the inflammatory CNV often originates at the level of CC and progresses anteriorly towards the outer retina [14], the multimodal imaging of CC remains crucial in the long term management of uveitis to warrant that vision saving treatment is delivered on time. Moreover, the recent development of OCTA has played a vital role by unfolding the role of CC in various forms of uveitides. MEWDS was considered an inflammatory entity of choroidal origin while recent studies have shown that CC and deeper choroidal vessels

remain normal and the disorder arises from RPE-photoreceptor complex. While the origin of APMPPE was thought to be RPE, recent advances in OCTA have shown that CC is the primary site of inflammation.

Conclusion

This short review summarizes the changes in choriocapillaris in choriocapillaropathies and other uveitides.

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