Invited Review

Indocyanine Green Angiography

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Abstract

The choroid plays an important role in the pathophysiology of the eye. Multimodal imaging offers different techniques to examine the choroid. Fundus fluorescein angiography offers limited visualization of the deep layers of the fundus due to the barrier property of the retinal pigment epithelium. Therefore, indocyanine green angiography (ICGA) is widely used in the angiographic examination of the choroidal structure. ICGA is an important component of multimodal imaging in the diagnosis and treatment of many degenerative, tumoral, and inflammatory diseases of the choroid and retina. This review presents the general characteristics of ICGA and a practical approach to its clinical use.

Keywords: Indocyanine green, angiography, choroid, retina, diagnosis, treatment, imaging

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Introduction

While indocyanine green (ICG) dye has long been used in heart and liver function tests, its introduction into ophthalmology as an angiography dye dates back to approximately 40 years ago.[1,2,3]

Its limited leakage from the choroidal vessels and ability to penetrate into the deep layers with little absorption by xanthophyll pigment and the retinal pigment epithelium (RPE) when exposed with infrared light make ICG angiography (ICGA) advantageous in the examination of the choroidal circulation. However, difficulty obtaining quality images because of the low-intensity fluorescence of ICG dye delayed the adoption of this method in ophthalmic diagnosis.

Thanks to the combination of this method with infrared-sensitive high-resolution fundus cameras and scanning laser ophthalmoscopy (SLO), ICGA has taken its place in the diagnosis and monitoring of pathophysiological processes involving the choroidal vasculature.[3,4,5,6] The introduction of wide-angle lenses has also expanded ICGA's area of use.

ICGA is an important component of multimodal imaging in centers performing the diagnosis and treatment of posterior segment diseases. This article aims to provide information about the basic features of ICGA and its role in clinical use.

History

ICG infrared absorption angiography was first used by Kogure and Choromokos[7] in 1969 to examine the pial circulation in dogs. The same study group introduced the fundus infrared absorption angiography technique into ophthalmology by administering the dye intraarterially in monkeys.[8] Using this method, David[9] performed intraarterial ICG infrared absorption choroid angiography in humans for the first time in 1971. Hochheimer[10] obtained a better quality image by administering intravenous ICG to cats and using black and white film instead of infrared-sensitive color film.

As the infrared absorption technique did not provide sufficient choroidal detail, Flower and Hochheimer[2] took advantage of the fluorescent property of ICG and described choroidal ICG fluorescence angiography in 1973. Tokoro et al.[11] enhanced ICG choroid angiography with an infrared-sensitive modified camera and the video angiography technique in 1984. In the following years, Hayashi et al.[12,13,14,15] used this method to detect choroidal blood flow and examine central serous chorioretinopathy (CSCR) and subretinal choroidal neovascular membranes (CNV). In 1989, Scheider and Schroedel[5] performed ICG videoangiography with SLO. The ICG digital videoangiography technique was used in patients with CNV in 1991.[16] Thereafter, ICGA was widely used in the evaluation of retinal and posterior segment diseases, especially cases of occult CNV.[17]

In the following years, ICGA was also used to visualize tumors and inflammatory diseases in the fundus, and images specific to many diseases were published.[18,19,20,21]

Physical and Chemical Properties of ICG

ICG is a tricarbocyanine dye with a molecular weight of 775 g/mol and chemical formula of $C_{43}H_{47}N_2NaO_6S_2$. It differs from sodium fluorescein (NaFl) in two main ways. First is its high rate of plasma protein bonding, which is 98% for ICG compared to 70-90% for NaFl.[22,23] The second important difference is that its maximum absorption is at 805 nm and its maximum fluorescence is at 835 nm, which is in the near-infrared part of the electromagnetic spectrum. For NaFl, these wavelengths are 465 nm and 525 nm, respectively (Table 1).[4]

Unlike NaFl, ICG shows very little leakage from choroidal and pathological vessels due to its high plasma protein binding. Light at its maximum fluorescence wavelength of 835 nm is not absorbed by macular xanthophyll pigments and only 10% is absorbed by the RPE.[24] These features of ICG together with its ability to penetrate into the deep tissues enable visualization of the choroidal vascular structures, especially the submacular area where NaFl is insufficient.

ICG Metabolism

ICG is excreted from the body exclusively by the liver. In people with normal liver function, the half-life of ICG in the circulation is approximately 2.6 minutes. Its rapid elimination from the circulation allows angiography to be repeated after a short time when needed.[25]

ICGA Procedure

After dissolving crystallized ICG in 5 mL of solvent, a bolus of 25-50 mg or 1-2 mg/kg is administered via the antecubital vein. Some researchers follow this with an injection of 5 mL of sterile saline solution.

The early phase is very short, so even if no dye is observed in the fundus at 10 seconds after ICG administration, serial images should be obtained and the light level should be kept as low as possible during imaging. This reduces the "blooming artifact" (i.e., a white field that obscures detail) which occurs due to choroidal fluorescence in the first few seconds after the dye reaches the choroid. Dark images can be improved by adjusting the light and contrast during the angiography analysis phase. Immediately after the first early phase images are obtained in one eye, imaging of the fellow eye should be started. Afterwards, ICGA images should be acquired at 1-minute intervals until minute 5 and then typically at 5-minute intervals from minute 10 to 20. These intervals can be adjusted according to the characteristics of each case. Pseudostereoscopic imaging may be helpful in the analysis.

Some devices allow fluorescein angiography (FA) and ICGA to be performed simultaneously. Although this may be advantageous when interpreting the angiograms, it is rarely done in practice. A disadvantage of this method is the difficulty of revealing the exact cause of a side effect after injecting two different dyes at the same time.

ICGA recordings can also be obtained as video, which enables the determination of circulation times and a dynamic examination of the vasculature.[25] This allows the feeding vessels of vascular anomalies to be identified more easily, and can also demonstrate the pulsation feature of lesions such as polypoidal choroidal vasculopathy (PCV).

Side Effects of ICGA

ICGA has a safer side effect profile compared to FA. Moderate side effects have been reported at a rate of 1:63, serious side effects at a rate of 1:1900, and death at a rate of 1:222000 after FA.[26]

Adverse effects after the use of ICG are rare. Rates of mild, moderate, and severe reactions have been reported as 0.15%, 0.02%, and 0.05-0.07%, respectively.[27,28]

ICG dye contains up to 5% sodium iodide as an additive to prevent recrystallization. Therefore, caution should be exercised considering the potential side effects in patients with thyroid hyperfunction. Thyroid function tests performed after ICGA give inaccurate results. On the other hand, it is argued that since iodine is naturally found in the human body, there can be no risk of antibody formation or the development of an immune-mediated allergic reaction against it.[29] The allergies that develop after consuming shellfish and other seafood are attributed to the proteins in the food, not the iodine.[30]

The cause of side effects following ICGA has not been fully explained. Non-allergic histamine release due to iodine or ICG, IgE-mediated hypersensitivity, complement system activation, or the release of other inflammation mediators are suggested mechanisms.[31]

Moreover, although very rare, adequate preparation is necessary in the event of anaphylactic shock after ICG injection.[32]

Table 1. Absorption, fluorescence, and protein binding properties of indocyanine green and sodium fluorescein

	ICG	NaFl
Maximum absorption (nm)	805	465
Maximum fluorescence (nm)	835	525
Protein binding (%)	98	70-90

ICG: Indocyanine green, NaFl: Sodium fluorescein

ICG dye can also be prepared without the addition of iodine, but severe side effects have also been reported after iodine-free ICGA.[33]

As ICG separates bilirubin from protein in *in vitro* studies, it should not be administered to preterm infants and neonates who require transfusion due to hyperbilirubinemia. The indication should also be reviewed in patients with uremia, severe liver failure, or a history of severe multiple allergy (Table 2).[3]

It has been reported that ICG shows minimal passage across the placenta and that the placenta has a protective effect against its passage to the fetus.[34] Although there is no proven teratogenic effect, its indication for use in pregnancy should be carefully discussed.

Non-specific side effects following angiographic dye delivery are usually recorded as allergic reactions. This leads to the restriction of new angiographic examinations needed in the future. For this reason, it is important to reevaluate a patient's history of post-angiography side effects and other possible factors in detail.

ICGA Phases

Early phase: Filling of the choroidal arteries, choriocapillaris, and choroidal veins. It includes the few seconds after the ICG dye reaches the choroidal circulation.

Middle phase: Late venous phase, lasting up to minute 10. In this phase, contrast differences between the choroidal vessels and background fluorescence decrease slowly.

Late phase: Between 10 and 20 minutes. The fundus is dominated by homogeneous fluorescence (i.e., isofluorescence). Hypofluorescent silhouettes of the large choroidal veins are observed on this background. This phase is also called the inversion phase due to the reversal of the contrast pattern.[35]

ICGA Interpretation

The logic of ICGA and FA interpretation is similar. However, because the infrared excitation light used in ICGA penetrates beneath the RPE and ICG shows less leakage due to high plasma protein binding, the images appear more "whitish" in the early phase compared to FA in normal eyes. The contrast between the vascular structures and the background is low. ICGA interpretation should be made in conjunction with color fundus photographs and FA images from the same eye. In eyes that have undergone multimodal imaging, these data should also be considered when interpreting ICGA.

Hypofluorescence: Appears as dark or black areas caused by filling defects and blockage. Filling defects (i.e., failure of the ICG dye to reach the vessel) is mostly seen in pathologies that directly affect the circulation of the choriocapillaris. Blocked hypofluorescence is the result of a formation that prevents tissue fluorescence from reaching the imaging device. A pigmented lesion in the fundus (e.g., choroidal nevus), thick subretinal hemorrhage, or infiltrations in the choroidal stroma are the most common causes.

Hyperfluorescence: Appears as a white area. Window defect often causes the underlying vascular structures to appear brighter after thinning or atrophy of the RPE or choriocapillaris. The best example of this is that in age-related macular degeneration (AMD), large choroidal veins in atrophic areas show more hyperfluorescence than the choroidal vessels observed in other areas of the macula. Leakage can be observed in severe stromal choroiditis, although it is considerably less with ICG compared to FA. Another cause of hyperfluorescence is abnormal vessel formations, such as choroidal hemangioma or nodular formations in PCV.

Table 2. Contraindications of indocyanine green angiography

1. Thyroid gland hyperfunction
2. History of previous or suspected severe allergy
3. Severe liver failure, uremia
4. Hyperbilirubinemia
5. Pregnancy and breastfeeding

ICGA in Clinical Practice

1. Neovascular Age-Related Macular Degeneration

ICGA was used extensively in the mid-90s to visualize occult CNVs. Hyperfluorescent lesions (generally referred to as "hot spots") that appear in the middle phase and are smaller than one disc diameter were considered to be the active part of occult CNV. A larger "plaque" type lesion seen in the late phase was considered the silent or less active component of the occult CNV.[36,37] Another application area, dynamic ICGA, enabled visualization of CNV feeder vessels.[38] However, after the results of laser photocoagulation to both hot spots and feeder vessels demonstrated its limited effectiveness and the superiority of photodynamic therapy to laser photocoagulation, the use of ICGA in neovascular AMD declined.

ICGA has an important place in the differential diagnosis of neovascular AMD subgroups. ICGA can demonstrate nodular hyperfluorescent lesions in PCV and the accompanying abnormal vascular network (Figure 1).[39]

In type 3 CNV or retinal angiomatous proliferation lesions, the retinochoroidal vascular anomaly can be visualized more clearly with ICGA than FA due to the low leakage.[40]

In recent years, the causal relationship between pachychoroid (thick choroid) and neovascular AMD has been intensively studied. ICGA plays an important role in visualizing the choroidal vasculature in the macula.[41]

2. Central Serous Chorioretinopathy

Although the pathogenesis is not completely understood, exudation resulting from permeability of the choroidal vasculature in CSCR causes RPE detachment and serous retinal detachment. Areas of leakage in the choroid can be visualized in more detail with ICGA compared to FA (Figure 2). The hyperfluorescent areas detected on ICGA reveal targets for the application of photodynamic therapy. Due to their choroidal thickening, ICGA plays a central role in the differentiation of CSCR, PCV, and other pachychoroidal entities.[41,42]

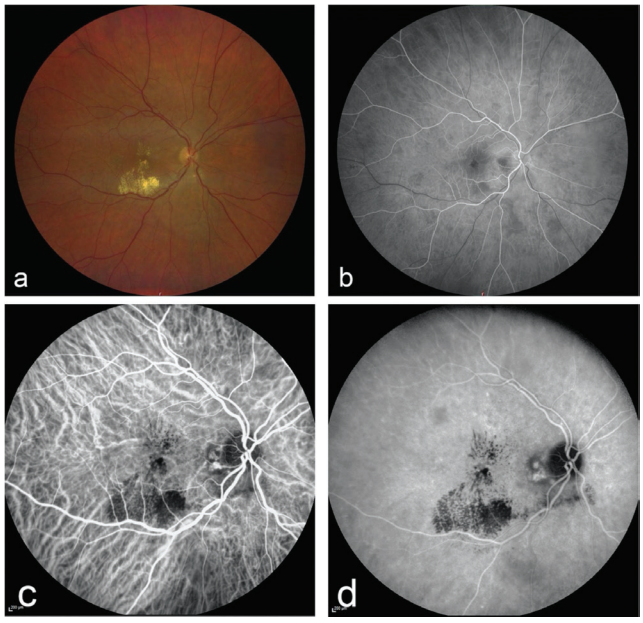

Figure 1. Polypoidal choroidal vasculopathy. (a) Color fundus photograph of the right eye posterior pole shows perifoveal lipid deposition. (b) Early-phase fluorescein shows hypofluorescence temporal to the optic disc and an arc of hyperfluorescence temporal to this lesion. (c) Mid-phase indocyanine green angiography (ICGA) (1.5 minutes) shows hyperfluorescent lesions with a nodular appearance (polypoidal lesions) temporal to the optic disc and perifoveal hypofluorescence (masking due to lipid deposition). (d) Late-phase ICGA (18 minutes) shows persistence of the temporal juxtapapillary hyperfluorescence and macular hypofluorescence

In cases of neovascular AMD that do not respond to treatment with anti-vascular endothelial growth factors, ICGA imaging is also used for the differential diagnosis of possible PCV, CSCR, or secondary CNV associated with CSCR.

3. Choroidal Inflammation

Due to the limited blocking effect of the RPE layer, ICGA plays an important role in the evaluation of inflammatory events in the choroid.[43] Diseases affecting the choriocapillary structure, such as acute posterior multifocal posterior pigment epitheliopathy (APMPPE) or multiple evanescent white dot syndrome (MEWDS), cause reduced choriocapillaris perfusion that manifests as filling defect and hypofluorescence (Figures 3, 4). Diseases that cause infiltration and granuloma formation in the choroidal stroma, such as birdshot retinochoroidopathy (Figure 5) and Vogt-Koyanagi-Harada disease (VKH), also present with hypofluorescent lesions due to blocked fluorescence. The number, shape, size, location, and laterality of hypofluorescence lesions are important in the evaluation of ICGA. Inflammations that involve the choroidal stroma and follow an aggressive course (e.g., VKH disease) may cause leakage from the large choroidal veins, resulting in diffuse hyperfluorescence and vessel staining in the choroid. If in cases of multiple white dot diseases ICGA does not yield pathognomonic features, then findings in other organ systems, retinal involvement, multimodal imaging methods (especially FA, optical coherence tomography, and autofluorescence) and demographic characteristics should also be evaluated.

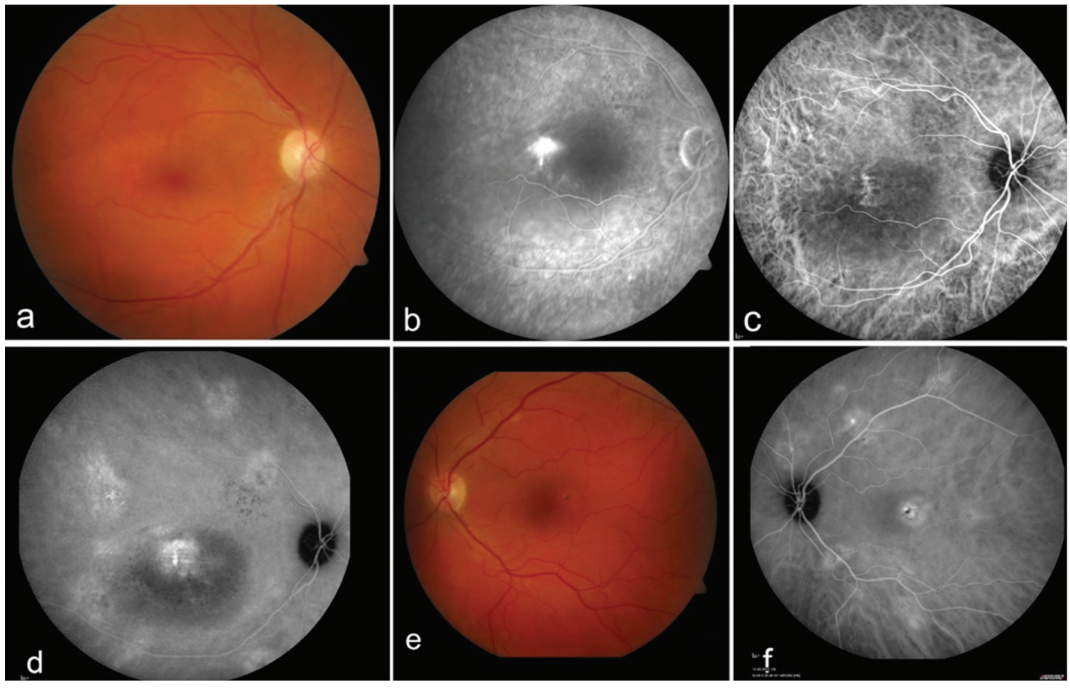

Figure 2. Central serous chorioretinopathy. (a) Color fundus image of the right eye posterior pole shows altered reflex temporal and inferior to the fovea. (b) Late-phase fluorescein angiography shows hyperfluorescence temporal to the fovea (consistent with the umbrella-like leakage of central serous chorioretinopathy). (c) Mid-phase indocyanine green angiography (ICGA) (2 minutes) shows a thick, hyperfluorescent choroidal vascular structure temporal to the fovea and an arc of hypofluorescence inferior to the macula (consistent with a possible neurosensory retinal detachment). (d) Late-phase ICGA (12 minutes) reveals multiple hyperfluorescent lesions in the posterior pole. (e) Color fundus photograph of the left eye posterior pole. (f) Mid-phase ICGA (6 minutes) reveals multiple hyperfluorescent lesions around the fovea and the major vascular arcades. This case is a good example of ICGA revealing occult lesions in an asymptomatic eye

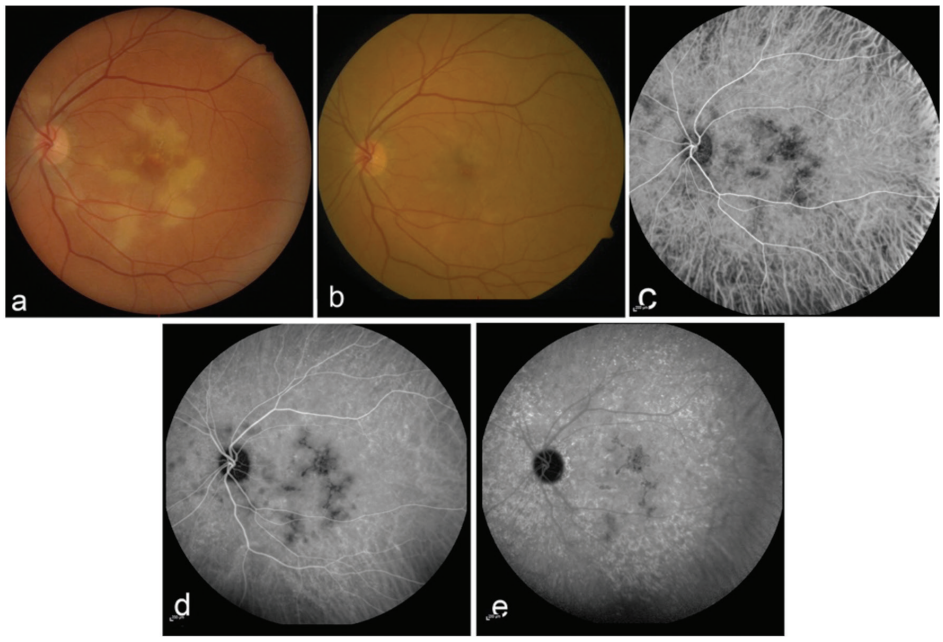

Figure 3. Acute posterior multifocal placoid pigment epitheliopathy. (a) At initial presentation, color fundus photograph of the posterior pole (left eye) showed granular pigment epithelial changes in the fovea and multiple white/cream-colored lesions in the deeper retinal layers in the perimacular and parapapillary areas. (b) After 6 weeks, color fundus photograph of the posterior pole demonstrated changes in the fovea and perifoveal granular pigment epithelium. The cream-colored lesions were not observed. (c) Early-phase indocyanine green angiography (ICGA) (11 seconds) performed at 6 weeks showed multiple macular and peripapillary hypofluorescent lesions (hypofluorescence consistent with filling defects due to choriocapillary ischemia). (d) In mid-phase ICGA (4 minutes), an increased number of hypofluorescent lesions were observed as a result of the difference in contrast from the background isofluorescence. (e) In late-phase ICGA (14 minutes), the hypofluorescent lesions decreased in number and size (likely due to reperfusion from the intact choriocapillary tissue surrounding the lesions)

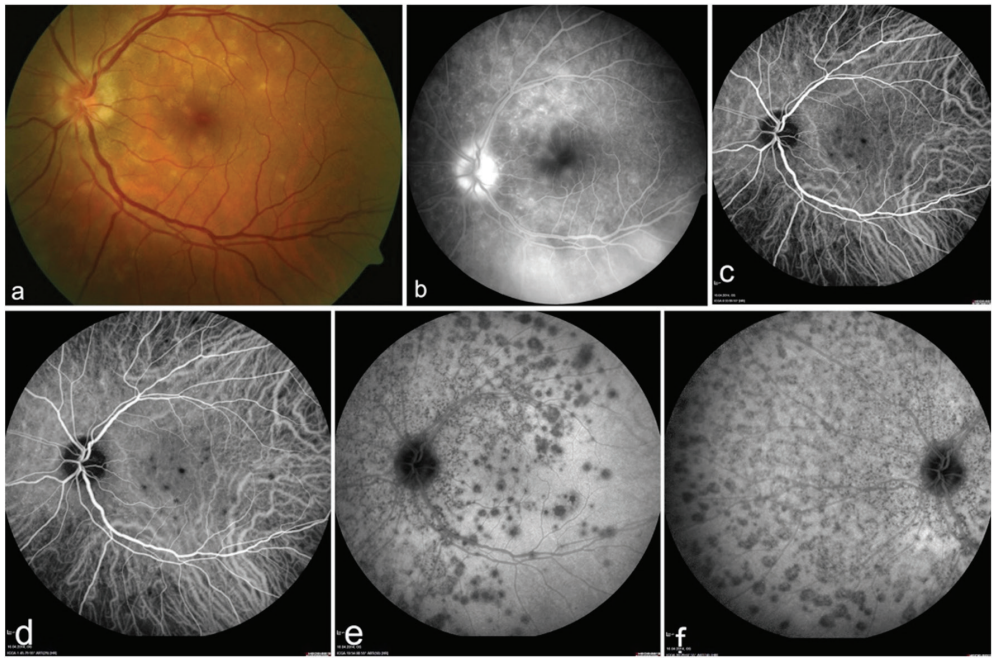

Figure 4. Multiple evanescent white dot syndrome (MEWDS). (a) Color fundus photograph of the posterior pole (left eye) shows numerous hypopigmented lesions. The optic disc margin is ill-defined. (b) Late-phase fluorescein angiography shows optic nerve head staining and diffuse hyperfluorescence in the posterior pole. (c) Early/mid-phase indocyanine green angiography (ICGA) (1 minute) shows small, barely visible hypofluorescent lesions. (d) In mid-phase ICGA (4 minutes), the hypofluorescent lesions in the macula become more evident as a result of increased contrast difference. (e) Late-phase ICGA (14 minutes) reveals numerous small hypofluorescent lesions in the posterior pole that did not appear in previous phases. (f) Late-phase ICGA (14 minutes) also shows numerous small hypofluorescent lesions nasal to the papilla. This case example of MEWDS demonstrates phase-specific differences in findings and the importance of imaging nasal to the papilla (and also in all fundus quadrants)

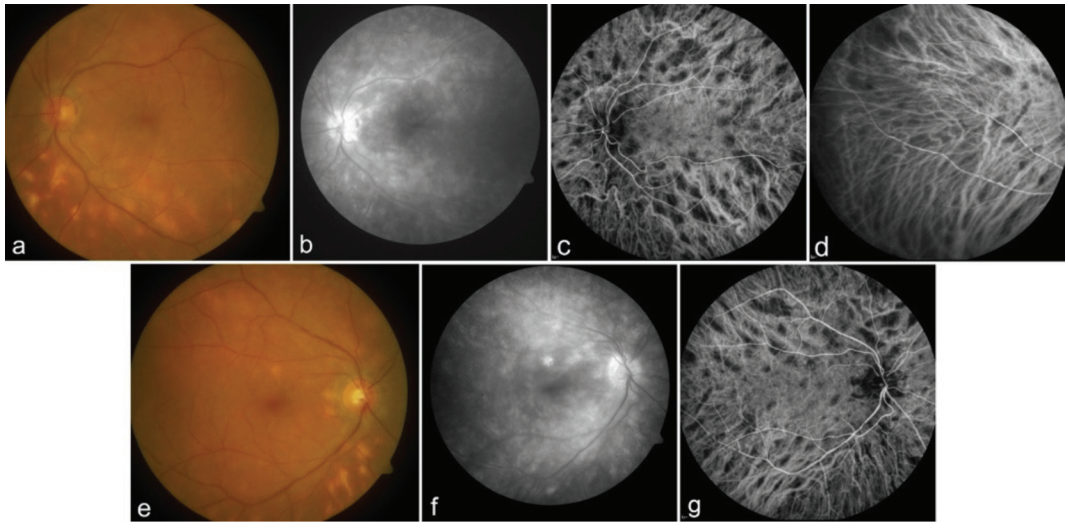

Figure 5. Birdshot chorioretinopathy. (a) Color fundus photograph of the posterior pole (left eye) shows numerous hypopigmented subretinal lesions around the inferior major arcade. (b) Late-phase fluorescein angiography (FA) shows diffuse hyperfluorescence due to leakage in the optic nerve head and posterior pole. (c) Early/mid-phase indocyanine green angiography indocyanine green angiography (ICGA) (30 seconds) reveals numerous oval hypofluorescent lesions resembling rice grains in the macula. (d) Mid-phase ICGA (4 minutes) shows scattered hypofluorescent lesions in the nasal middle periphery. (e) Color fundus photograph of the posterior pole (right eye) shows hypopigmented lesions in the macula and along the major arcades. (f) Late-phase FA shows diffuse hyperfluorescence due to leakage at the optic nerve head margin and the posterior pole. (g) Early/mid-phase ICGA (35 seconds) showed numerous oval hypofluorescent lesions resembling rice grains in the macula. The similarity of ICGA images in both eyes is important for the diagnosis of birdshot chorioretinopathy

4. Intraocular Tumors

The most important contribution of ICGA is in the diagnosis of choroidal hemangiomas. ICGA particularly helpful in the differential diagnosis of thin, amelanotic fundus tumors and choroidal metastases from choroidal hemangioma.[19,44] In the choroidal filling phase, the tumor shows rapid, bright hyperfluorescence. In the late phase, the intensity of hyperfluorescence decreases as the ICG dye leaves the vessels ("wash-out phenomenon"). This feature enables the differentiation of choroidal hemangioma from amelanotic malignant melanoma of the choroid (Figure 6).

In cases where FA is insufficient or cannot be applied, ICGA also facilitates the examination of vascular tumors of the fundus. Due to rapid leakage and masking, FA has limited ability to determine the topographic location and vascular structure of pathologies that present with intense exudation at the papillary margin and retinal thickening. ICGA is advantageous in recognizing lesions because of the deep penetration and low leakage of ICG. Thus, it aids in the differential diagnosis of masses and pathologies around the optic disc, such as juxtapapillary retinal capillary angioma, PCV, and CNV.

5. Hemorrhagic Diseases of the Fundus

Retinal arterial macroaneurysms may cause bleeding in the posterior segment. They may be located in the inferior or superior temporal arcade and can usually be recognized as white-yellowish round formations along the arteries. However, in cases where intense hemorrhage covers the lesion or blocks FA, ICGA can be used to visualize the vascular anomaly despite bleeding. Distinguishing retinal artery macroaneurysms from CNV and PCV in hemorrhages localized to the macula is an important area of use of ICGA.

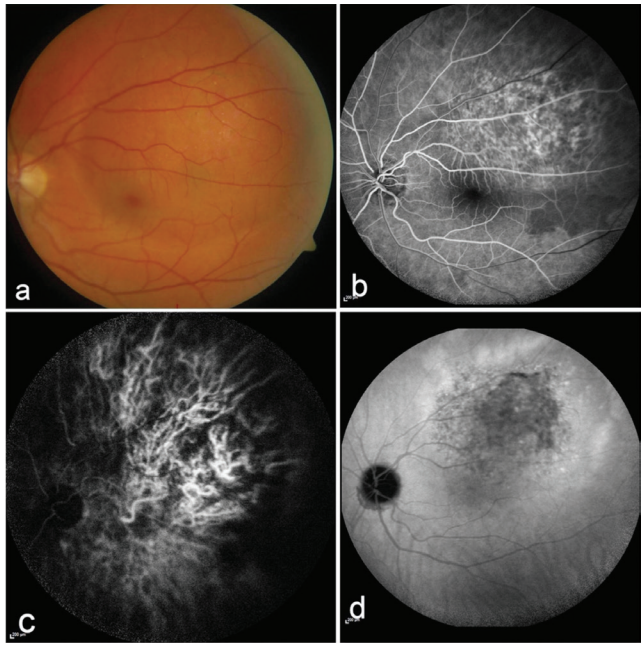

Figure 6. Choroidal hemangioma. (a) Color fundus photograph of the posterior pole (left eye) shows a subretinal red-orange colored lesion in the superior half of the macula. (b) Early-phase fluorescein angiography shows a large number of linear hyperfluorescent lesions in the upper half of the macula and above the superior major arcade (pathological tumor vasculature is observed because of reduced masking due to retinal pigment epithelium atrophy. These lesions could not be observed with a healthy retinal pigment epithelium). c) Early-phase indocyanine green angiography (ICGA) (12 seconds) demonstrates early hyperfluorescence of the pathological tumor vasculature in the superior part of the macula. (d) In late-phase ICGA (15 minutes), the lesion superior to the macula appears as a hypofluorescent area due to the dye leaving the eye (wash-out phenomenon). ICGA is an important diagnostic tool for choroidal hemangioma because of its hyperfluorescent vasculature in the very early phase and wash-out phenomenon in the late phase

ICGA is also used as a diagnostic tool for the differentiation of CNV, PCV, and vasoproliferative retinal tumors in eyes with large hemorrhagic lesions in the peripheral fundus (Figure 7).

6. Unexplained Vision Loss

In patients with unexplained vision loss, ICGA can be performed if choroidal involvement is suspected and other multimodal diagnostic methods are inconclusive.

Conclusion

Despite the important role in the physiopathology of the eye, diagnostic methods that examine the choroidal circulation have not been incorporated in routine ophthalmological diagnosis with the same intensity. This deficiency arose more from limitations of the techniques used rather than a disregard for their function. Although ICGA was introduced to ophthalmology in the 1970s, technical challenges delayed its development. Recently developed devices with high time and space resolution capacity have provided excellent image quality. The need for sophisticated and expensive imaging devices and experienced practitioners constitutes the main barriers to the wider adoption of ICGA in clinical practice. Despite all of these difficulties, the information it provides has made ICGA an important component of multimodal imaging in the examination of the fundus.

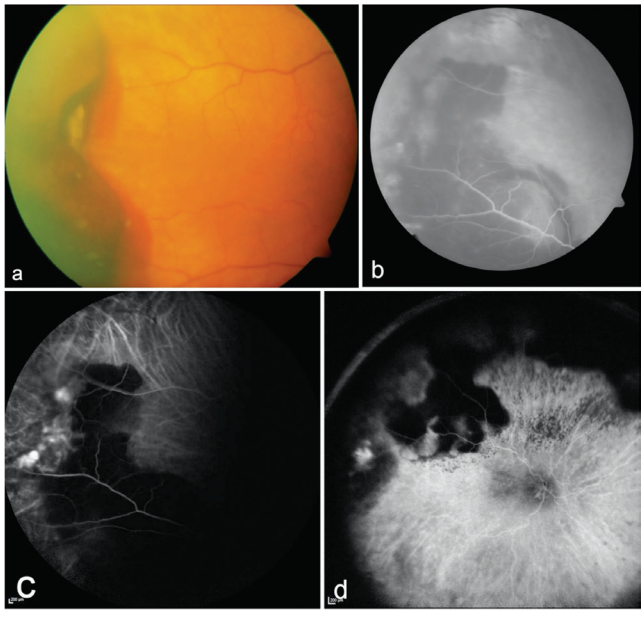

Figure 7. A peripheral hemorrhagic lesion. (a) Color fundus photograph of the temporal mid-periphery (right eye) shows a subretinal hemorrhagic lesion. (b) Late-phase fluorescein angiography shows hypofluorescence due to the hemorrhage and hyperfluorescence with indistinct borders at its periphery. (c) Mid-phase indocyanine green angiography (ICGA) (3 minutes) shows nodular hyperfluorescent lesions at the periphery of the hemorrhagic masking and branching vessels between them. This appearance is consistent with peripheral polypoidal choroidal vasculopathy. (d) A wide-angle image of late-phase ICGA (13 minutes) shows leakage from the temporal lesion and large areas of hypofluorescence due to hemorrhage in the upper peripheral quadrants

Ethics

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