ICG In Clinical Practice : Where Does It Help?

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Indocyanine green angiography was first used by cardiologists as an indicator of cardiac output. Subsequently it was used by hepatologists to study hepatic blood flow and hepatocellular function.

ICG was first used to image human choroid by Flower and Hochheimer in 1972, however its use was limited due to poor fluorescence and inability to get good quality images on infrared camera.[1] Hayashi and de Laey developed filter combinations with suffi¬cient sensitivity for near-infrared wavelengths.[2] They were also instrumental in the transition from still-frame to dynamic imaging by introducing videoangiography.

In 1992, Guyer et al. intro¬duced the use of a 1024 × 1024-line digital imaging system to produce high-resolution ICGA.[3] Finally, Yannuzzi and coworkers described a system, which had appropriate flash synchronization and image storage capability thus permitting high-resolution and long-duration ICGA.[4]

ICG is a tricarbocyanine dye. Its structural formula is 2,2'-indo-6,7,6',7'-dibenzocarbocyanine sodium salt with a molecular weight of 774.96 Da.ICG absorbs light in the near-infrared wavelength. The maximum absorption is at 790 nm, while the maximum emission occurs at 835 nm.These optical prop¬erties allow penetration through macular pigment, melanin,blood, and pigment.[5]

About 98% of ICG is bound to plasma protein.ICG is excreted mainly by liver.ICG disappears from vascular compartment at the rate of 18–24% per minute, and after 20 minutes less than 4% remains in plasma.

ICG's high molecular weight in combination with the high percentage of dye bound to plasma proteins, reduces the amount of dye that exits from fenestrations in choroidal vessels. This makes it very suitable for studying the choroidal vasculature.

The rate of side-effect is low: 0.15% with mild events (nausea, vomit, sneezing, pruritus), 0.2% with moderate events (urticarial, syncope, pyrexia, nerve palsy), 0.05% with severe events (bronchospasm, laryngospasm, anaphylaxis). However patients with a history of definite iodine allergy should not be given the dye, because of possibility of anaphylaxis.

Food and Drug Administration has classified ICG as a preg¬nancy category C drug, meaning that adequate studies for its safety have not been conducted.

INDOCYANINE GREEN ANGIOGRAPHY INTERPRETATION

Normal Eye

ICGA, one can recognize an early phase when the retinal artery is not yet filled, a midphase when both arteries and veins are filled, and a late or recirculation phase more than 10 minutes after injection. First the haler's layer gets filled followed by satler's layer and then choriocapilaris. One can clearly visualise the vortex veins in widefield angiography.

Exudative Age-related Macular Degeneration

Type 1 Choroidal Neovascularization

The Macular Photocoagulation Study recognized two forms of occult CNV:

(1) a fibrovascular pigment epithelial detachment (PED)

(2) a late-phase leakage of an undeter¬mined source (LLUS).

In case offibrovascular PED, ICGA may delineate the presence of a neovascular network usually located along the edges of the PED (Figure 1). Moreover, dynamic ICGA may reveal a feeder vessel that can be treated with laser photocoagulation if it is located outside the foveal region (Fig.).

In case of LLUS, which may represent 36–78% of occult CNV,dynamic ICGA may differentiate an occult form of CNV from retinal angiomatous proliferation (RAP). Considering that one-fourth of patients with an LLUS have a RAP and that an early diagnosis of these lesions is crucial for the func¬tional prognosis.Yannuzzi et al. found that 39% of lesions classified as poorly demarcated occult lesions by fluorescein angiography were well defined by ICGA.

Type 2 choroidal neovascularization

In classic CNV, ICGA improves visualization of the fine struc¬ture of the neovascular network allowing the choroi¬dal and retinal circulation to be distinguished. This high spatial and temporal resolution permits identification of choroidal vessels that feed into the CNV.

In early phases, ICGA shows a dark rim which corresponds to a whitish ring on infrared imaging and a discrete neovascular network surrounded by a hypocyanescent

margin which is more visible after 15 minutes. Watzke et al. showed that 87% of eyes with classic choroidal neovascular membranes were hypercyanescent with distinct edges.

It has been reported that VEGF inhibitors are more effective in controlling immature vessels, whereas a VEGFinhibitor along with a platelet-derived growth factor (PDGF) inhibitor appeared to show a synergistic effect for controlling the growth of mature vessels.

Mature, larger choroidal vessels may be readily differentiated from immature choroidal capillaries on ICGA. Thus, in patients with chronic AMD or those who do not benefit from previous treatments with anti-VEGF, ICGA helps to delineate a more mature stage of CNV. This has potential implications for therapeutic decision-making.[7]

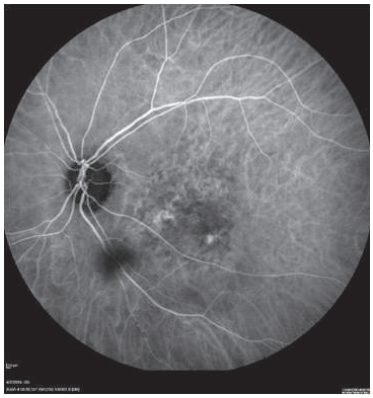

Figure 1 : Case of CNVM showing abnormal branching Vasculature over posterior pole with feeder vessel.

Type 3 Choroidal Neovascularization

Dynamic-ICGA takes up to 12 frames per second and captures progressive filling of the lesion thus allowing detec¬tion of very small and recent-onset cases of RAP.

Polypoidal Choroidal Vasculopathy

This disorder is associated with dilated tortuous choroidal vasculature with polyp like sacculations at the end. It manifests with multiple, recurrent, serosan¬guineous detachments of the RPE and neurosensory retina sec¬ondary to leakage and bleeding from the abnormal choroidal vasculature.

The early phase of the ICG angiogram shows a distinct network of vessels within the choroid (Figure 2). Larger choroidal[5] vessels of the PCV network begin to fill before retinal vessels, and PCV network fills also at a slower rate than retinal vessels. Shortly after the network can be identified by the ICG angiogram, small hypercyanescent "polyps" become visible.In dynamic angiography pulsation may also be noted in these polyps. They appear to leak slowly as the surrounding area becomes increasingly hypercyanescent. In the later phase of the angiogram there is uniform disappearance of dye ("washout") from the polypoidal lesions (Figure 3). ICGA guided Photocoagulation of these polyps has been shown to be helpful in regression of disease (Figure 4). ICG is also used to measure the greatest linear dimension of lesion and perform a guided photodynamic therapy.

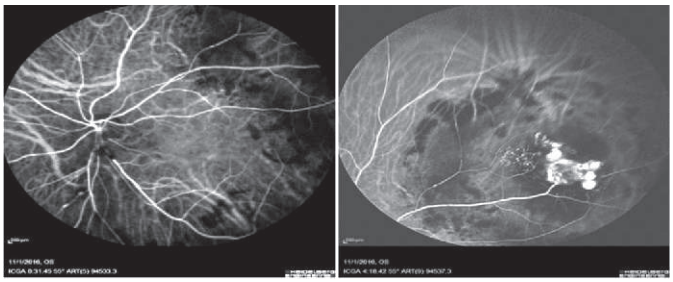

Figure 2 : Case of PCV showing extramacular blocked cyanescence with hypercyanescent polyps.

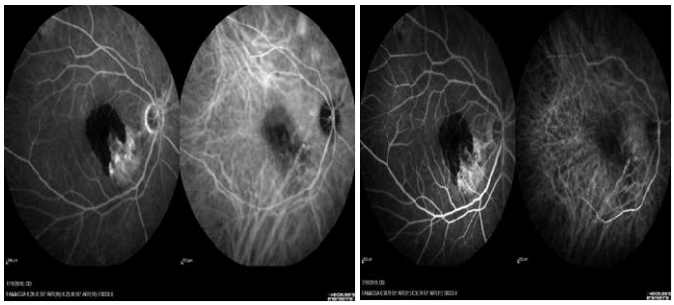

Figure 3 : Simultaneous FFA and ICG of a patient of PCV with subretinal haemorrhage showing blocked flourescence on FFA and clearly deleniating abnormal vasculature on ICGA with knobbed polyp like ending.

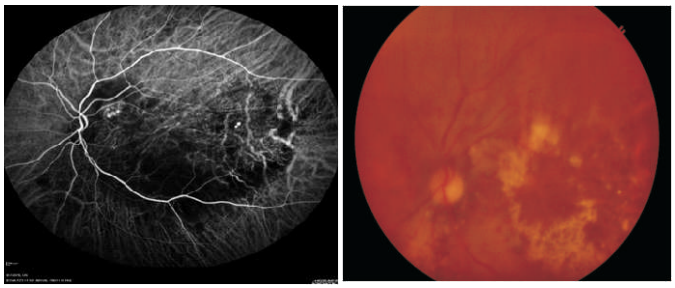

Figure 4 : Case of PCV showing ICG with hypercyanescent polyps which were extramacular and then focal laser was done

Central Serous Chorioretinopathy

CSCR is characterized by multifocal areas of choroidal hyperper¬meability which is visible on ICGA in the mid and late phases (Figure 5). Zones of choroidal hyperpermeability tend to persist in cases of severe and chronic CSC. ICG helps to localise these areas of hyperpermeability and carry out guided treatment with verteporfin photodynamic therapy or laser photocoagulation.[8] Other findings in CSC using ICGA include multiple "occult" serous PED, punctate hyperfluorescent spots, delays in arte¬rial filling of the choroidal arteries and choriocapillaris and venous congestion. ICGA is also useful in differentiating CSC from Pachy choroid vasculopathy.

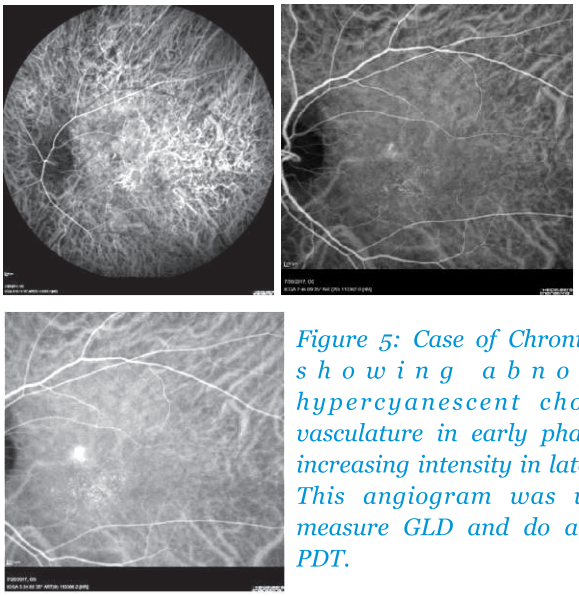

Figure 5: Case of Chronic CSCR showing abnormal hypercyanescent choroidal vasculature in early phase with increasing intensity in late phase. This angiogram was used to measure GLD and do a guided PDT.

Choroidal Tumors

Choroidal *hemangioma*

ICGA is the most useful study for demonstrating the intrinsic vascular pattern of circumscribed choroidal hemangioma. The advan¬tage of ICG dye over sodium fluorescein dye is that it diffuses very slowly out of fenestrated small choroidal vessels as compared to sodium fluorescein. Within 30 seconds of injection of the ICG dye, the tumor's intrinsic vascular pattern becomes apparent. By 1 minute, choroidal hemangiomas completely fill with the dye, showing brilliant hyperfluorescence which is diagnostic of this tumor.Thetumor vasculature has low resistance and high flow property so it allows rapid flow in and out of tumor. The result¬ing final effect is that the tumor empties faster than the normal surrounding choroid and thus appears hypofluorescent in late phase compared to surrounding choroid. This washout sign is very helpful in differentiating cho¬roidal hemangiomas from amelanotic malignant melanoma and choroidal metastases.

Choroidal *melanoma*

ICGA is capable of identifying tumor vessels which are usually irregularly tortu¬ous, with anarchic branching, dilated and have a parallel course. ICGA is superior to fluorescein angiography to clearly delineate these vessels.

Multiple Evanescent White-dot Syndrome

Multiple evanescent white-dot syndrome is a unilateral acute disease that affects young women, presenting with a transient, self-limiting visual loss. The disease involves the choroid and the outer retina. ICGA shows a pattern of multiplehypofluorescent areas at the posterior pole and peripheral retina due to slow movement of dye through the inflamed vessels. These spots become visible in the mid to late phases, range in size between 50 and 1000 µm and are more appar¬ent in ICGA images than by fundus examination and fluorescein angiography.

In addition, ICGA may show hypofluorescence surrounding the disc area. The hypofluorescent spots disappear at the recovery stage of the disease.

Multifocal Choroiditis

In multifocal choroiditis the active lesions are visualized as hypo¬fluorescent spots in ICGA images. These lesions may be followed up with ICGA and used as measure of response to treatment. A reduction in size and number of hypofluorescent spots is observed after successful treatment. Other finding visible on ICGA is a large hypofluorescent area surrounding the optic nerve (Figure 6).

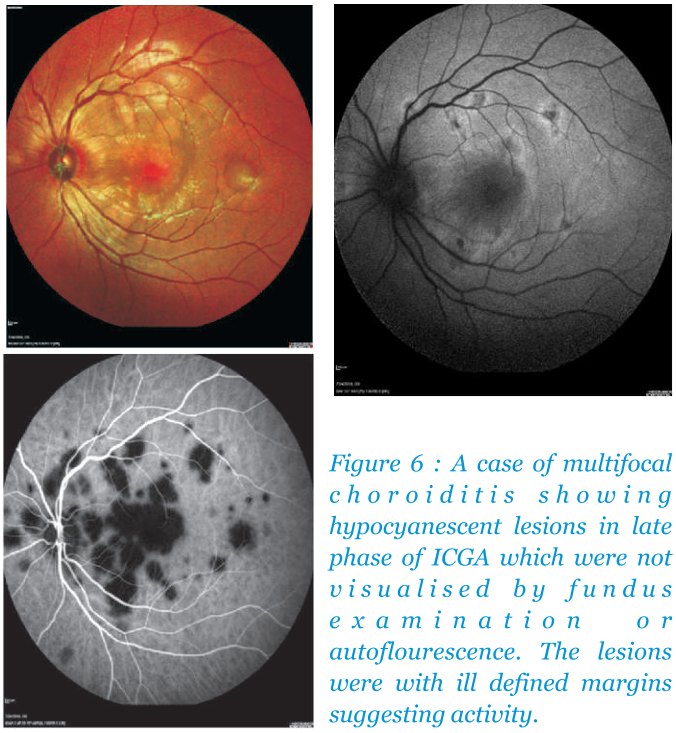

Figure 6 : A case of multifocal choroiditis showing hypocyanescent lesions in late phase of ICGA which were not visualised by fundus examination or autoflourescence. The lesions were with ill defined margins suggesting activity.

Serpiginous Choroidopathy

ICG allows better staging and identification of active lesions in serpiginous chorioretinopathy. The active lesions are characterized by hypofluorescent areas with poorly defined margins the lesions detected on ICGA may preceed the lesions seen on FFA and may also be larger in size and number as compared to FFA.[9]

Acute Multifocal Placoid Pigment Epitheliopathy

ICG of acute posterior multifocal placoid pigment epitheliopa¬thy (AMPPE) shows areas of hypofluorescence in both early and late phases that correlate with the placoid

lesions (Figure 7). These lesions may be caused by choroidal hypoperfusion, secondary to occlu¬sive vasculitis. New, activeand healed, inactive lesions in AMPPE can both be imaged and differentiated using ICGA.

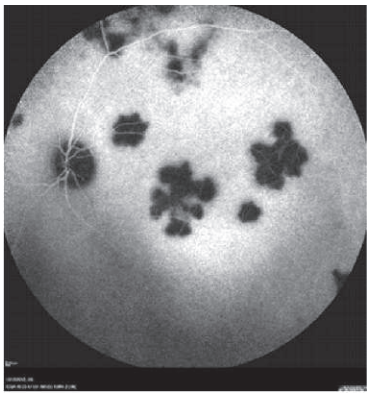

Figure 7 : case of AMPPE showing hypocyanescence corresponding to the placoid lesions.

Punctate Inner Chorioretinopathy

The subretinal lesions observed in punctate inner chorioreti¬nopathy are visualized by ICG as hypofluorescent areas through¬out all the phases of the angiogram. Another finding in ICG images is the presence of hyperfluores¬cent points situated close to the vessel wall, suggestive of vasculitis.

Acute Zonal Occult Outer Retinopathy

In acute zonal occult outer retinopathy, ICGA shows a variety of patterns of presentations. Spaide reported that the peripapil¬lary drusenoid material blocks the choroidal fluorescence in ICG and therefore the involved areas appear hypofluorescent. The secondary atrophy of the choriocapillaris produces hypofluores¬cence as well, which does not affect the fluorescence from the underlying larger choroidal vessels. In some cases, thoughICG may show an increase in fluorescence from the affected areas, due to the lack of photoreceptor outer segments and the minor blocking effect from this layer.

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JOURNAL ABSTRACT

New Stains For Anterior Capsule Surgery

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ABSTRACT:

Purpose: To investigate whether new dyes and dye combinations can give equivalent or better staining in anterior capsule surgery than existing dyes with a low degree of toxicity on relevant cells.

Setting: University laboratory of Jacobs University Bremen, Germany.

Design: Laboratory experimental study.

Methods: Pig eyes were collected post mortem. Cataract was induced by microwave irradiation. Access to the lens capsule was through open-sky surgery. Staining was performed and results were documented by photography. The toxicity of the dyes was evaluated in 3 different cell lines immediately after exposure and with a delay of 24 hours, with exposure in the dark or subsequent strong illumination.

Results: A new cyanine dye, BIP (2-[5-[3,3-dimethyl-1-(4-sulfobutyl)-1,3-dihydro-indol-2-ylidene]-penta-1,3-dienyl]-3,3-dimethyl-1-(4-sulfobutyl)-3H-indolium sodium), was found to lead to green staining, with reduced toxicity on corneal endothelial cells. Staining could be further enhanced by combining it with trypan blue. Methylene blue was very toxic, whereas its combination with trypan blue was much less toxic.

Conclusions: With BIP alone or in combination with trypan blue, safe staining of the capsule can be achieved, resulting in a green color.