Faculty of Medicine

A Study of

INTRAVITREAL TRIAMCINOLONE ACETONIDE IN THE MANAGEMENT OF CENTRAL SEROUS RETINOPATHY

An Essay Submitted For Partial Fulfillment Of The Master Degree In Ophthalmology

By

Eman Shokry Abada

MBBCH

Supervised By

Prof. Dr. Sherif Zaky Mansour

Professor Of Ophthalmology

Ain Shams University

Dr. Mohammad Abdel Hakim Zaki

Lecturer Of Ophthalmology

Ain Shams University

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EMAN SHOKRY ABADA
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Prof. Dr. SHERIF ZAKY MANSOUR
Professor of Ophthalmology
Ain Shams University

Dr. MOHAMMAD ABDELHAKIM ZAKI
Lecturer of Ophthalmology
Ain Shams University

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ANATOMY OF THE MACULA

Clinically the macula is regarded as the area within the temporal vascular arcades (fig.1). Histologically, it is the region with more than one layer of ganglion cell nuclei (Fagman & Fine 1977).

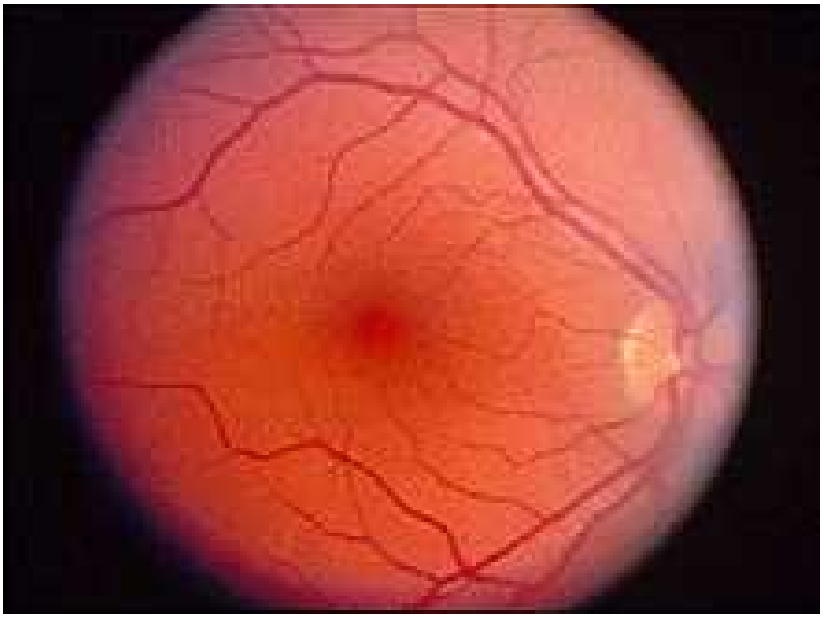


Fig.1. Color photograph of posterior pole (AOIH 2007).

The name macula lutea (yellow spot) derives from the yellow colour of the central retina in dissected cadaver eyes; this colour is due to the presence of carotenoid pigments chiefly located in Henle's layer.

Two major pigments have been identified: zeaxanthin and lutein, whose proportions vary with distance from the fovea; the lutein to zeaxanthin ratio is 1: 2.4 in the central area (0.25 mm from the fovea) and greater than 2:1 in the periphery (2.2 – 8.7 mm from

the fovea). This variation in pigment ratio corresponds to the rod to cone ratio. Lutein is more concentrated in rod-dense areas of retina and zeaxanthin is more concentrated in cone-dense areas. Lipofuscin, the yellow age pigment, has been observed in the cytoplasm of the perifoveal ganglion cells by electron microscopy (Fernandez et al. 1988).

The masking of choroidal fluorescence observed in the macula during fundus fluorescence angiography (FFA) is caused partly by xanthophyll pigment and partly by the higher melanin pigment content of the foveal retinal pigment epithelium (RPE).

The fovea is a concave central retinal depression approximately 1.5 mm in diameter; it is comparable in size to the optic nerve head. Its margins are clinically indistinct, but in younger subjects the fovea is evident ophthalmoscopically as an elliptical light reflex that arises from the slope of the thickened internal limiting membrane of the retina (Weale & Bird 1974).

Around the fovea is the parafovea, 0.5 mm wide (fig.2), where the Ganglion cell layer (GCL), the Inner nuclear layer (INL), and the Outer plexiform layer (OPL) are thickest; surrounding this zone is the most peripheral region of the macula, the perifovea which is 1.5 mm wide.

The foveola is a central depression within the fovea, located approximately 4.0 mm temporal and 0.8 mm inferior to the center of the optic disc. It is approximately 0.35 mm across and 0.10 mm in thickness at its center (fig.2).

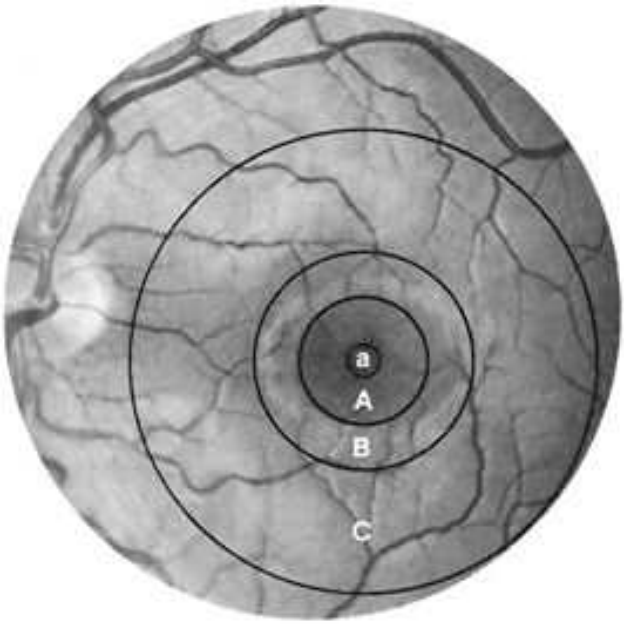
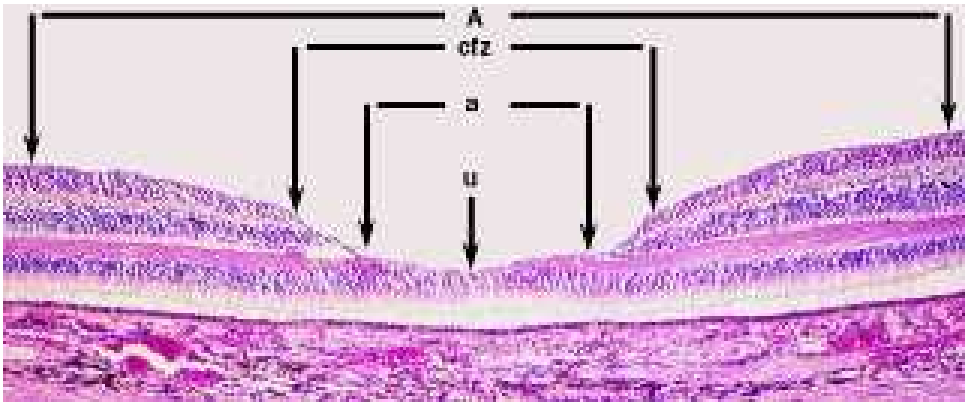


Fig.2. Above: fundus view. Below: histological cross section of macula. **A**, Fovea containing the foveola (a), capillary-free zone (FAZ), and umbo (u). **B**, Parafovea. **C**, Perifovea (Gass 1999).



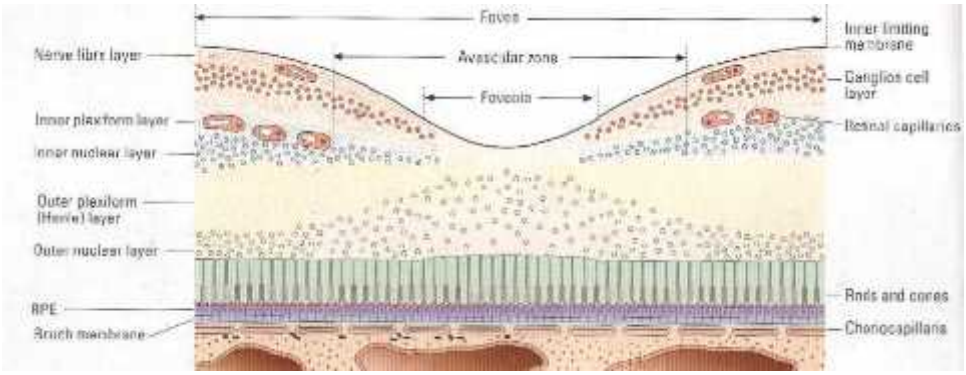


Fig.3. Cross- section of the fovea (kanski 2003)

The borders of the foveola merge imperceptibly with the fovea (fig.3). The nuclei of the photoreceptor cells in the region of the foveola bow forward towards the internal limiting membrane (ILM) to form the fovea external. Usual only photoreceptors, Muller cells, and other glial cells are present in this area. Occasionally light microscopy reveals ganglion cell nuclei just below the ILM (Weale & Bird 1974).

The photoreceptor layer of the foveola is made up entirely of cones whose close packing accounts for the high visual acuity of this small area. The foveal cones are shaped like rods; they possess all the cytological characteristics of extramacular cones. The outer segments are oriented parallel to the visual axis and perpendicular to the plane of the RPE. In contrast, the peripheral photoreceptor cell outer segments are tilted towards the entrance pupil.

The foveal avascular zone (FAZ) or capillary-free zone (fig.2) is an important clinical landmark in the treatment of subretinal neovascular membranes by laser photocoagulation.

The location of the FAZ is approximately that of the foveola. The diameter of the FAZ varies from 250 to 600 um or more; often,

a truly avascular or capillary-free zone cannot be identified (Weale & Bird 1974).

RECEPTOR DISTRIBUTION

Cone density is maximum at the fovea, which contains about 10% of all retina cones. Cone density decreases drastically across the macula beyond the border of which density is relatively constant but asymmetric with higher densities nasally than temporally.

Approximately the central 0.75 mm of foveal region is free of capillaries. It is nourished by choriocapillaris circulation.

Rods are also distributed unevenly across the retina; there are no rod receptors within approximately the central 0.57 mm of fovea.

Beyond this rod-free zone, rods increase rapidly in density with eccentricity and reach maximum density about 18 degrees temporal and 23 degrees nasal to fovea (Yanoff 1979).

VASCULAR SUPPLY OF THE MACULA

The macula has a double vascular supply: the very rich network of choriocapillaris supplying the outer layers of RPE and photoreceptors while the inner retinal layers are fed via the capillary network derived from central retinal artery (CRA). The CRA temporal branches arch over and under the macula and send twigs to the horizontal meridian.

The choriocapillaris is thicker over the posterior pole than the periphery and is thicker over macular area than in any other part (Gass 1977).

The structures of fenestrated choroidal capillaries is different form the retinal capillaries and is identical to those of renal glomeruli, the thyroid, ciliary process and other organs concerned with selective permeability.

In about 15 to 20% of individuals, a variable portion of papillomacular bundle is supplied by one or more cilioretinal arteries derived from ciliary circulation. The existence of macular supply from ciliary origin constitutes a beneficial anomaly in case of CRA occlusion (Bonnet 1976).

The peripheral macular region is richly vascularized by three arcades or layers of capillaries all situated within inner half of the retina.

A deep capillary net lying at the outer boundary of the INL, and two superficial nets are entirely in the nerve fiber layer (NFL) and the outer at the inner boundary of the INL. This is in contrast with the remainder of the retina that is supplied by two layers of capillaries except for the periphery that is supplied by only a single layer.

The different capillary nets are not, however, independent as anastomotic capillaries from one layer to the other and the same capillary may run from part of its course in one layer and the change to another (Wolff 1976).

Histologically, the retinal capillaries consist of two distinct cell types: the endothelial cells and the pericytes. The endothelial cell encircles the lumen of the capillary and in turn is encircled by a basement membrane. They are closely bound together about the lumen by intercellular junctions of zonula occludentes. These junctions normally prohibit a free flow of fluid and solute from vascular lumen into retinal interstitium, thus creating the inner blood retinal barrier. The absence of flourescein leakage from these

vessels is an evidence of this barrier. The maintenance of dry extracellular spaces in the retina is the result of the physiological RPE pump.

The pericytes form a layer around the outer aspects of endothelial basement membrane. The pericytes themselves also elaborates a basement membrane around the outer circumference of capillary wall. Normally the endothelial cells and pericytes are present in a one to one ratio in young individuals. However, as age increases there is gradual decrease in number of endothelial cells. On the other hand, various diseases (most notably diabetes) cause relative decrease in number of pericytes (Gass 1977).

CENTRAL SEROUS CHORIORETINOPATHY

Central serous chorioretinopathy (CSCR) was first described by Von Graefe and termed it "idiopathic detachment of the macula" in the year 1866 (Von Graefe 1866).

It is a common idiopathic dysfunction of the posterior pole affecting the sensory retina, RPE, and choroid (fig.4). Hallmarks of this condition include mild to moderate central visual loss not related to optic nerve dysfunction. It usually resolves spontaneously with possible recurrences (Maguire 1994).

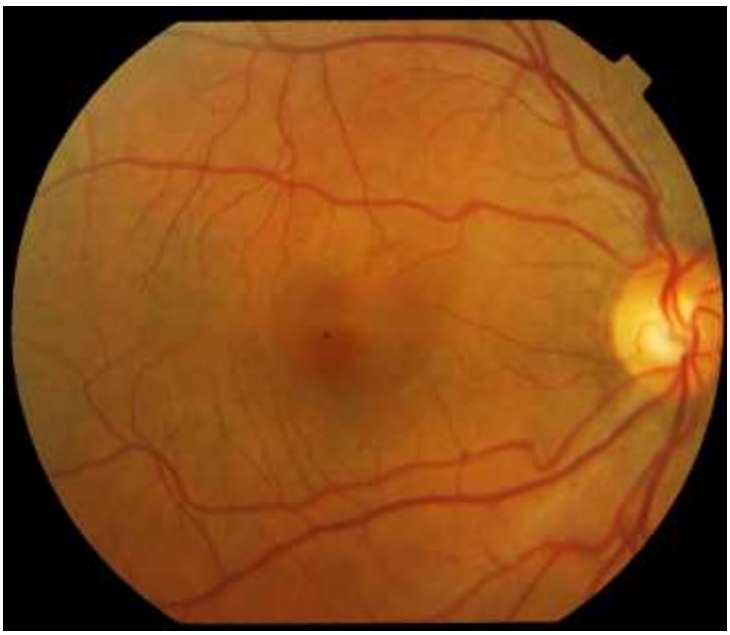


Fig.4. A color photograph of CSCR (AOIH 2007)

A chronic variant of this condition may be associated with persistent subretinal exudation, extensive RPE atrophy, cystoid macular degeneration, choroidal neovascularization, and consequent sever visual decline (Yannuzzi et al. 1984; Jalkh et al. 1984a; Gass 1987; Levine et al. 1989; Loo et al. 2002).

EPIDEMIOLOGY

CSCR typically affects males in the age range of 20-50 years. No case has been reported under the age of 20 years. In patients older than 50 years, CSCR does occur but can be difficult to distinguish from age related macular degeneration (ARMD). An increased frequency may exist in intelligent individuals engaged in visually demanding work who display type 'A' personality traits or who are experiencing physical strains or emotional stress. A history of migraine type headaches may be elicited (Bonnet 1955; Gass 1967a).

It has been also associated with smoking, endogenous hypercortisolism (Bouzas et al. 1993), systemic corticosteroid use (Polak et al. 1995), and vasoconstrictive agents. It can be also produced in animals by repeated intravenous epinephrine injections (Prunte & Flammer 1996).

OCULAR MANIFESTATIONS

Although unilateral metamorphopsia is the classic symptom of CSCR, patients also may present with unilateral blurred vision, micropsia, impaired dark adaptation, colour desaturation, delayed retinal recovery time to bright light, and a relative scotoma. Visual acuity usually ranges from 20/15 (6/5) to 20/200 (6/60), but average 20/30 (6/9). The visual acuity may improve with hyperopic correction. Symptoms typically resolve; only rarely do they persist indefinitely. Permanent sequelae include metamorphopsia, decreased brightness perception and altered colour vision. (Bonnet 1955; Gass 1967a)

CSCR can present as a bullous non-rhegmatogenous peripheral retinal detachment mainly inferiorly. The presence of RPE atrophic tracts from the macular region to the peripheral

retinal detachment reveals the true diagnosis and source of the subretinal fluid. It is best seen by FFA (Yannuzzi et al. 1984).

DIAGNOSIS OF CSCR

The diagnosis of CSCR is clinical and confirmed with FFA. While in most cases the diagnosis can confidently be made without ancillary testing, the information derived from angiography is critical to detect the extent of the retinal abnormalities and to exclude the presence of other pathology. Biomicroscopically, a transparent blister in the posterior pole between the neural retina and the RPE is observed. Signs that suggest the presence of a retina-RPE separation include beam splitting as the light traverses the serous space an increased distance between the retinal vessels and their shadows, and an absent foveal reflex. Shallow detachments may be difficult to demonstrate clinically (Gass 1967a).

Oval yellow-gray elevations beneath the detachment also may be seen. These are generally less than one fourth of a disc diameter in size and are surrounded by a faint grayish halo. Fluorescein angiography (FA) identifies them as RPE detachments and frequently demonstrates the focal RPE leaks responsible for the neural retinal detachment within their borders (Gass 1967a).

Fluorescein angiography plays an important role in the evaluation of CSCR; it is used to exclude the presence of other pathologies that produce neural retinal detachments and also to confirm the diagnosis.

Classically, dye from the choroid leaks through a focal RPE defect and pools in the subretinal space. In over 75% of patients, this pooling occurs within one disc diameter of the fovea (Klein et al. 1974). Less pooling may be observed in older lesions in which the RPE exudate has become inspissated (Gass 1967a).

Fluorescein angiography reveals various types of leakage present in about 95% of all cases of CSCR (Spitznas 1989). In the early phase of angiography, a dot like hyperfluorescent develops due to leakage of the dye from the choroid through the RPE; the dye then ascends from this pinpoint leak, which appears simultaneously with beginning of the arterial phase. The stream of dye reaches the superior limit of the detachment where it spreads in an umbrella shape (fig.5), which is known as the smokestack appearance (Gass 1997).

In the majority of patients however, the point leak that appears in the initial phase slowly and symmetrically spreads to about 1/4th disc diameter (fig.6), and is known as the inkblot type (Yamada et al. 1992).

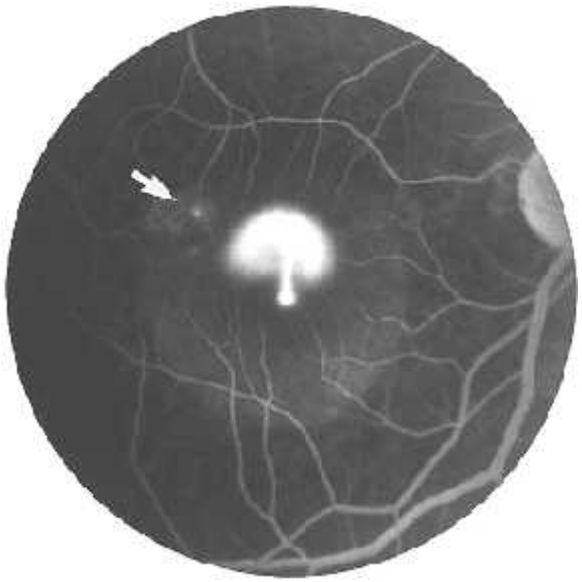


Fig.5. FFA showing smoke stack leakage (Gass 1999).