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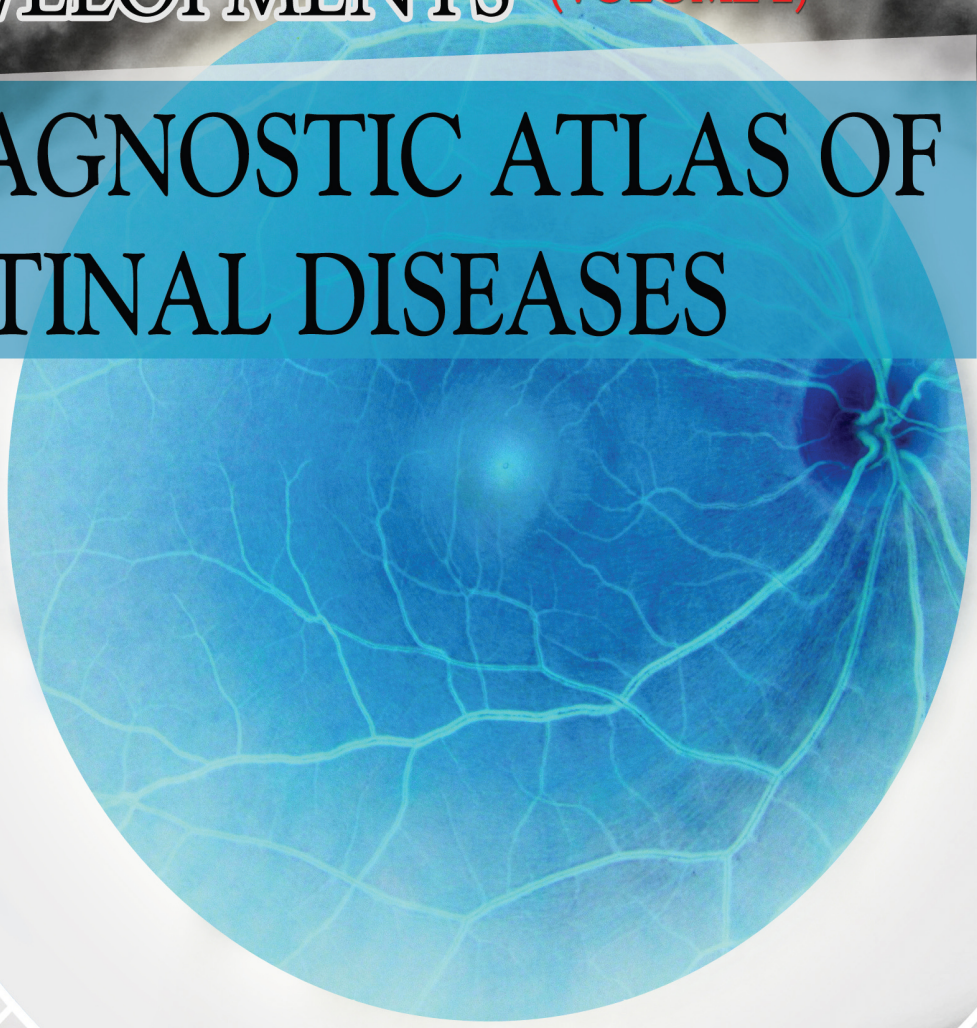
DIAGNOSTIC ATLAS OF RETINAL DISEASES



Editors:
Mitzy E. Torres Soriano
Gerardo García Aguirre
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Bentham Books

Ophthalmology: Current and Future Developments

Diagnostic Atlas of Retinal Diseases

(Volume 2)

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Ophthalmology: Current and Future Developments

Volume # 2

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PREFACE

We are honored to contribute to the information and education of ophthalmology students around the world. We have attempted to distill the current knowledge of medical practice and basic science retina research into a diagnostic atlas of retinal diseases. This is a quick-reference atlas eBook of the retina, edited by specialists in the field, essential to any practicing ophthalmologist or resident who has more than a passing interest in diseases and treatment of the retina.

This e-book includes contributors from Mexico, Venezuela, Argentina, Brazil, United States, Denmark, Spain, Italy, Costa Rica and Peru. It is divided into three volumes: Volume I, retinal vascular diseases, choroidal neovascularization related diseases, vitreomacular interface, and other macular disorders; Volume II, traumatic retinopathies, diseases of vitreous, peripheral degenerations, retinal detachment, pediatric retinal diseases, and retinal dystrophies; and Volume III, posterior uveitis, tumors of the retina and choroid.

This diagnostic atlas eBook of retinal diseases contains full-color, high quality images of the most frequent retinal pathologies with a brief and comprehensive review of retinal diseases. Each chapter includes essentials of diagnosis, differential diagnosis and treatment. The format is concise, well organized, and didactic, without being exhaustive.

We hope and expect that our atlas of retina will facilitate in providing patients with the best pos-sible care.

ACKNOWLEDGEMENTS

We would like to express our gratitude to Judy Soriano, who provided support with english composition and edition.

To our friends and colleagues without whose contribution would not have been possible to realize this project.

We also want to thank the staff of Bentham Science for their help and support and give us the opportunity to publish this eBook.

DEDICATION

This e-book is specially dedicated to Guillermo Manuel Gordon, MD. He inspired us to always work hard and try our best. He was a friend and a recognized ophthalmologist of Rosario-Argentina, who died on May 2nd, 2015.

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CHAPTER 1

Commotio Retinae

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The term commotio retinae describes a whitish or yellowish discoloration of the retina after blunt trauma. It is caused by shock waves that traverse the eye from the site of impact. The mechanism by which the retina acquires this appearance is uncertain, but extracellular edema, glial swelling or disruption of the photoreceptor outer segments have been proposed as potential causes. There is little to no intercellular edema [1, 5, 7].

ESSENTIALS OF DIAGNOSIS

- Decreased vision or asymptomatic.
- History of recent ocular trauma.
- A sheenlike retinal whitening is observed, appearing several hours after injury (confluent area of retinal whitening, gray opacification of the retina) (Fig. **1**).
- Commotio can occur to peripheral retina (most frequently it affects the temporal fundus) or the central macular region; commotio retinae in the posterior pole is also called *Berlin edema* [1 - 9] (Fig. **1**).
- If the macula is involved, a "cherry-red spot" may be seen at the fovea, because the cells involved in the whitening are not present in the fovea (Fig. **1**).
- Retinal blood vessels are unaffected. However, other signs of ocular trauma may be seen, such as intraretinal or vitreous hemorrhage.
- Visual acuity does not always correlate with the degree of commotio retinae [1 - 9].
- Sequelae to more severe commotio may include progressive pigmentary degeneration, choroidal rupture, or macular hole formation [2, 5 - 9].

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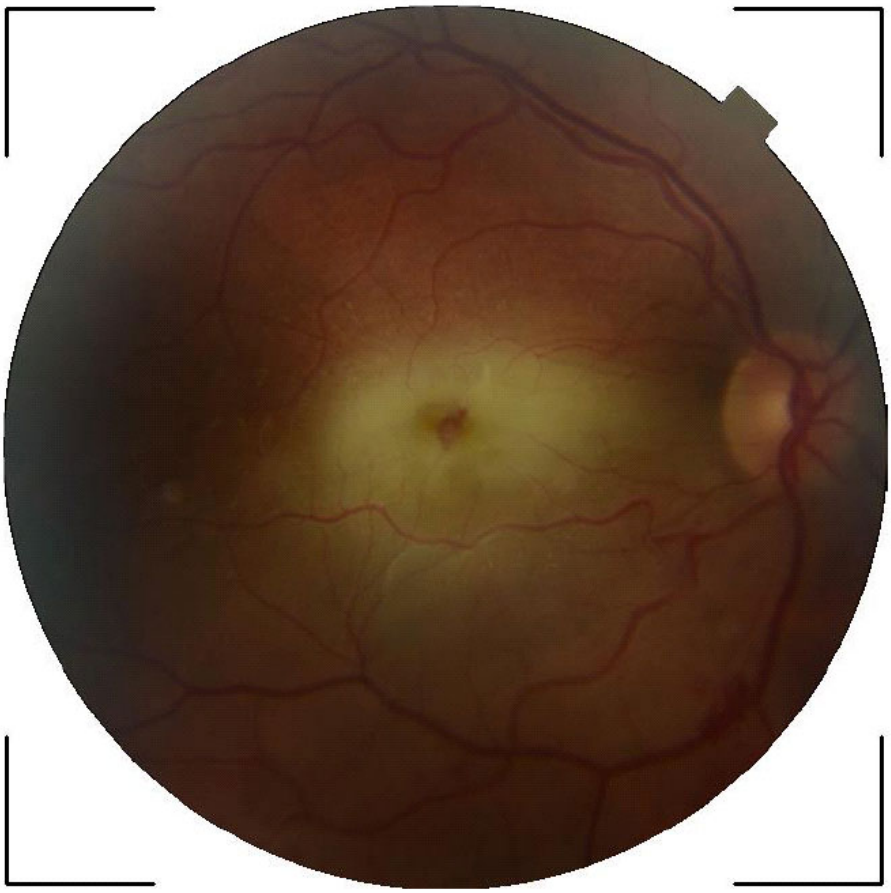

Fig. (1). Color fundus photograph. Commotio retinae.

DIFFERENTIAL DIAGNOSIS

- The patient should also be evaluated for serous retinal detachment, which also diminishes the prognosis for vision recovery.
- Branch retinal artery occlusion (whitening of the retina along the distribution of an artery) should be excluded, even though it rarely follows trauma.
- "White without pressure" (a common peripheral retinal finding) could also present with retinal whitening; it may be associated with a prominent vitreous base.
- Considerable damage to the retinal pigment epithelium can occur, eventually leading to granular pigmentation and bone corpuscular appearance of the

affected retina resembling retinitis pigmentosa.

MANAGEMENT

- Complete ophthalmic evaluation, including dilated fundus examination with scleral depression should be performed (or without scleral depression if a ruptured globe, hyphema, or iritis is present).
- Commotio retinae may decrease visual acuity to as low as 20/200, or even less. Fortunately the prognosis in mild cases, with no associated complications, is good with spontaneous resolution within 3-4 weeks. No treatment is required. Rarely, some patients with foveal involvement may be left with chronic visual impairment secondary to photoreceptor damage.
- Dilated fundus examination is repeated in 1 to 2 weeks. Patients should be educated about the symptoms of retinal detachment and instructed to return sooner if present [1 - 9].

CONFLICT OF INTEREST

The author confirms that author has no conflict of interest to declare for this publication.

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Declared none.

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CHAPTER 2

Choroidal Rupture

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The choroid is the external vascular layer lying between the retina and the sclera [1]. Its thickest part is in the posterior pole (0.22 mm) and it narrows towards the ora serrata to 0.1 mm. The choroid's main function is the vascular supply to the retinal pigment epithelium (RPE) that comes from the internal carotid artery and the ophthalmic artery, and drains into the vortex veins, determining the color of the ocular fundus [2, 3].

The suprachoroidal space is a virtual space. Pathologically, the choroidal rupture is a break in the Bruch membrane and the RPE. Unlike the retina and the sclera, which can resist several impacts thanks to their strength and elasticity, choroidal ruptures occur in 8% of patients who suffer blunt trauma and they are caused by an anteroposterior compression of the globe with expansion in the horizontal plane [3].

ESSENTIALS OF DIAGNOSIS

Initially, a choroidal rupture may be difficult to diagnose because it may be obscured by associated vitreous, intra- or subretinal hemorrhages. Hemorrhages caused by choroidal rupture are characterized by regular, sharply-defined edges, which indicates they are located in the sub retina or the choroid [2].

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Choroidal ruptures can develop in two ways: Indirect ruptures are evidenced at an early stage with choroidal or retinal hemorrhages. After hemorrhages are resolved, the typical crescent-shaped lesions become visible (Fig. **1**), similar to a fundoscopic image of angioid streaks, (Fig. **2**) concentric and concave to the optic disc and, most frequently, in the inter papillo-macular region [4]. In other cases, lesions are located around the optic disc, corresponding to traumatic peripapillary choroidopathy, which can lead to optic atrophy [6]. Direct ruptures are located at the site of trauma, involve hemorrhage and oedema, and, only after hemorrhage is resolved, the atrophic site becomes visible surrounded by pigmentation [4].

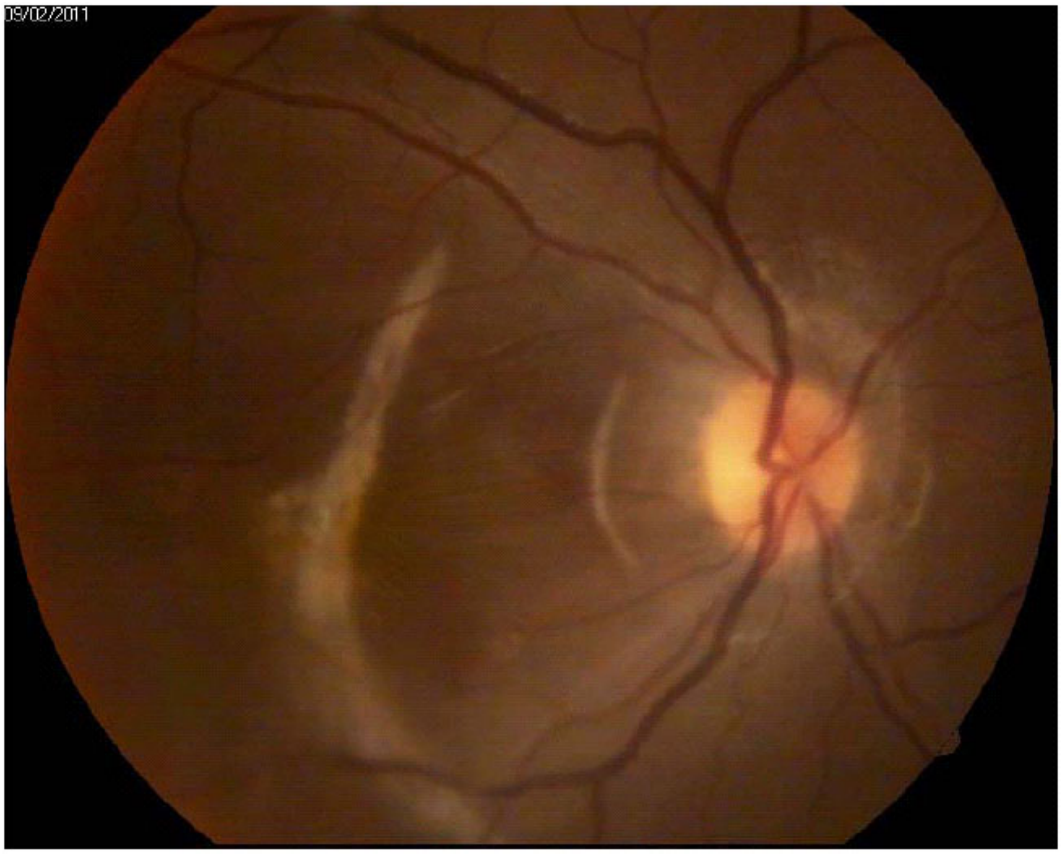

Fig. (1). Colour fundus photograph. Choroidal rupture (Courtesy of Ophthalmology Department, Hospital Central de Maracay, Venezuela).

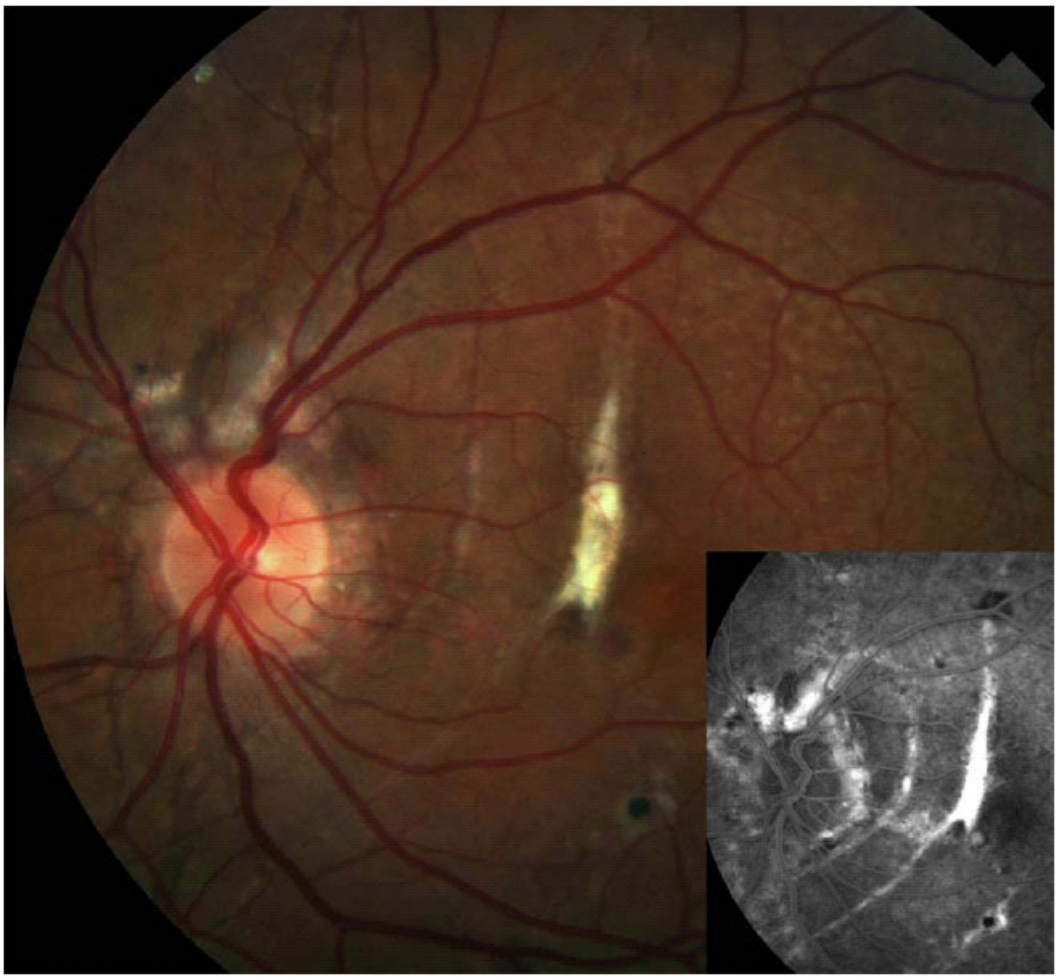

Fig. (2). Angioid streaks, a mixture of brownish streaks, pale atrophic areas, mainly around the margin of the optic disc, curved streaks concentric with the disc that are reminiscent of traumatic choroidal rupture lines (Courtesy of Michael Larsen, MD, Copenhagen, Denmark).

The visual prognosis depends mainly on the location of the injury. The histopathological process of choroidal rupture repair is completed 3 weeks after trauma and is accompanied by the formation of a well-established scar. This tissue process includes fibroblastic activity and RPE hyperplasia at the edges of the lesion. Choroidal neovascularization can develop from choroidal rupture in approximately 10-20% of cases during the scarring process [5].

Diagnosis is made based on clinical findings: clinical record, clinical interview,

routine eye examination, visual acuity (VA) testing. VA may be affected depending on the location and size of the lesion [6]. Vision loss is imminent when the macular area is affected [7]. It is necessary to carry out a timely examination of the ocular fundus, followed by additional tests, such as: an eye ultrasound; an OCT, which will detect a retinal pigment epithelium tear; a fluorescein angiography, which will show hyperfluorescence early and consistently throughout the test, and will also rule out neovascular membrane [8]; and ICG will evidence hypofluorescence in early and late phases [3, 9]. Patients should be recommended to use the Amsler grid for self-assessment [2].

DIFFERENTIAL DIAGNOSIS

Macular degeneration, neovascular membranes, Fuchs' spots, lacquer cracks in myopic eye, angioid streaks (Fig. **2**) and pathological alterations of the RPE are in the differential diagnosis of choroidal rupture.

MANAGEMENT

There is no immediate treatment available. However, the condition is currently being assessed and managed by means of tissue plasminogen activator (tPA) and intravitreal injection of pure C3F8 (0.4 cc) for pneumatic displacement of hemorrhage [10]; vitreous surgery, if clinically necessary [11]; intravitreal administration of anti-angiogenic agents, such as vascular endothelial growth factor (VEGF) inhibitors, for the treatment of post-traumatic choroidal neovascular membrane [12].

CONFLICT OF INTEREST

The author confirms that author has no conflict of interest to declare for this publication.

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CHAPTER 3

Traumatic Macular Hole

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Macular holes secondary to blunt ocular trauma are not an uncommon event and may appear almost immediately after a contusion although they have also been reported after a severe electric shock and accidental laser injury. The true incidence is unknown but traumatic macular holes (TMH) comprise about 10% of all macular holes [1].

ESSENTIALS OF DIAGNOSIS

Clinical characteristics of traumatic macular holes differ somewhat from the idiopathic variety. They tend to be larger (300-1000μ) [2], irregularly shaped and often associated with other pathologic traumatic findings, *i.e.*: commotion retinae, choroidal ruptures, angle recession, hyphema and/or vitreous hemorrhage (Fig. **1**). Visual acuity tends to range from 20/100 to 10/800 [3].

The pathophysiology responsible for macular hole formation is uncertain. Several mechanisms have been proposed including acute antero-posterior vitreous traction, contusional retinal necrosis and tangential traction from the internal limiting membrane. Since posterior vitreous detachment is seldom observed in these patients we believe that the most plausible explanation is that a sudden deformation of the globe during blunt trauma tends to stretch the posterior pole causing a rupture of the fairly inelastic internal limiting membrane producing tangential traction on the thinnest part of the retina [4, 5]. Sometimes the hole

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appears weeks after the traumatic event in which case the initial tear is probably acute but the traction appears later, perhaps associated with epiretinal membrane formation. TMHs, as the idiopathic variety, are seldom associated with large retinal detachments. If a detachment is observed, a peripheral retinal break should be sought.

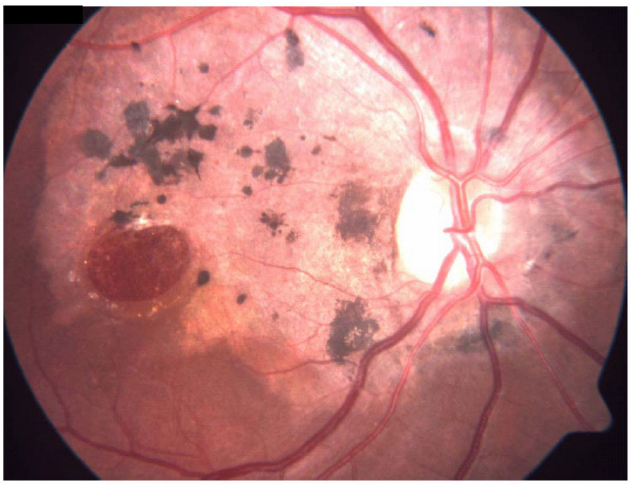

Fig. (1). Colour fundus photograph of a right eye four months after blunt trauma. A large macular hole and severe pigment changes can be observed.

The diagnosis of traumatic macular hole is pretty straightforward most of the times. It can be seen clinically, and easily confirmed by optic coherence tomography (OCT).

DIFFERENTIAL DIAGNOSIS

Differential diagnosis should be made with contusion of the retinal pigment epithelium, submacular hemorrhage, epiretinal membrane with macular pseudohole or lamellar macular hole. An OCT is usually sufficient to make the correct diagnosis.

MANAGEMENT

Management of traumatic macular holes, as of the early 1990's, is surgical. Pars plana vitrectomy with posterior hyaloid removal has proven to be highly beneficial in the majority of patients. Although internal limiting membrane (ILM)

removal is controversial, most authors report better anatomical and visual results [5, 6]. Since most patients tend to be young, some steps in the procedure are not easy. Posterior hyaloid removal is often difficult and requires patience. It is important to avoid iatrogenic retinal trauma on ILM dissection. The use of appropriate forceps and dye to stain it for better visibility is a must. Presently, brilliant blue dye appears to be the colorant of choice although not approved in some countries (Figs. **2**-**4**). Gas tamponade and postoperative positioning at least for a few days appear to improve the anatomical success rate. Often adequate positioning is hampered by associated injuries or physical state. Silicone oil tamponade should be considered in these circumstances. Autologous platelets as an adjunct to ILM peeling in macular hole repair may enhance chronic macular hole closure in patients unable to maintain prone positioning [7]. Anatomical results are good although visual results may be modest, mostly due to associated traumatic eye pathology. We've found that the exception is TMH closely associated with choroidal fractures where the fibrosis associated with the rupture precludes hole closure. This fibrosis is often very hard and involves the retina making it impossible for it to release. A few cases have been reported of spontaneous hole closure [8]. This seems to be a rare occurrence and the possibility should not preclude or delay surgical therapy.

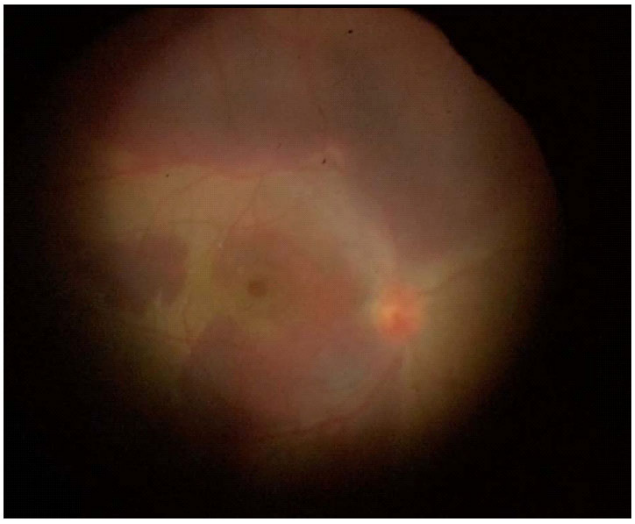

Fig. (2). Still photograph from an intraoperative video showing profuse submacular hemorrhage and a macular hole.

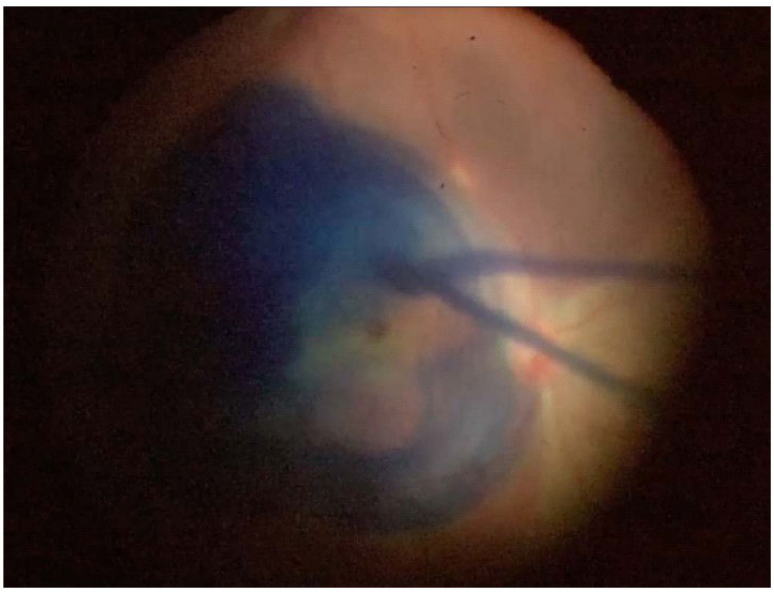

Fig. (3). Still photograph from an intraoperative video showing staining of the internal limiting membrane with brilliant blue G.

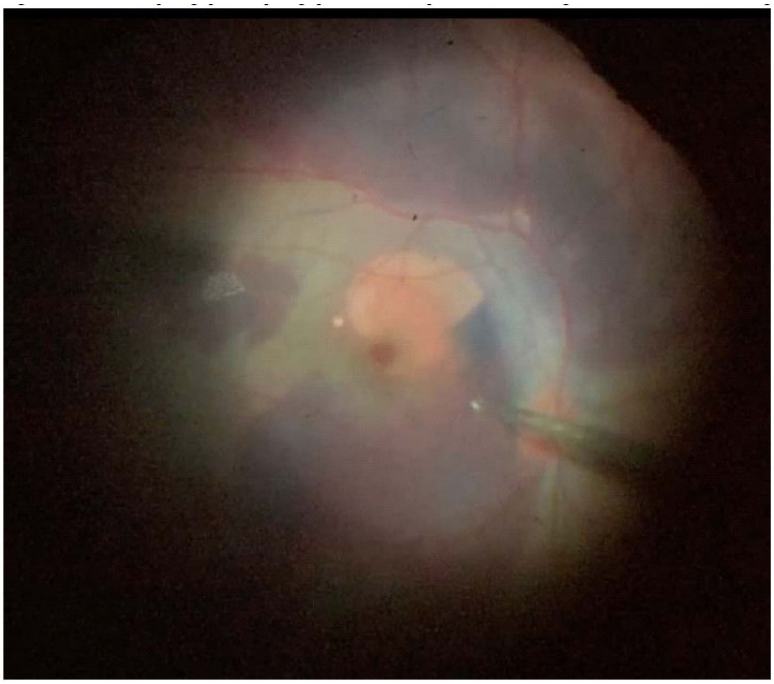

Fig. (4). Still photograph from an intraoperative video showing removal of the internal limiting membrane, previously stained with brilliant blue G.

CONFLICT OF INTEREST

The author confirms that author has no conflict of interest to declare for this publication.

ACKNOWLEDGEMENTS

Declared none.

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CHAPTER 4

Purtscher's Retinopathy

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Purtscher's retinopathy is a retinal vaso-occlusive and hemorrhagic vasculopathy, usually associated with head trauma or thoracic compression.

Even if the real cause is not well understood, the most likely pathogenic process is an embolic obstruction of the precapillary arterioles in the retina [1-4].

ESSENTIALS OF DIAGNOSIS

- Sudden visual loss, hours to days after trauma (variable severity).
- Unilateral or bilateral involvement.
- Patognomonic findings concentrated in the peripapillary area.
- Cotton-wool spots (Fig. **1**).
- Intraretinal hemorrhages and exudates (Fig. **1**).
- Retinal edema.
- "Purtscher flecken", resulting from precapillary arterioles occlusion (50% of cases, pathognomonic).
- Optic atrophy as late finding.

DIFFERENTIAL DIAGNOSIS

- Purtscher's like retinopathy: similar retinal findings, associated to a wide spectrum of systemic diseases, such as acute pancreatitis (Fig. **1**), long bone fracture, amniotic fluid embolism or fat embolism, hemolysis, vasculitic diseases (collagen vascular purpura, lupus) [1, 2].

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- Central retina artery/vein occlusion: fundus findings seem to be the same, but no history of trauma.

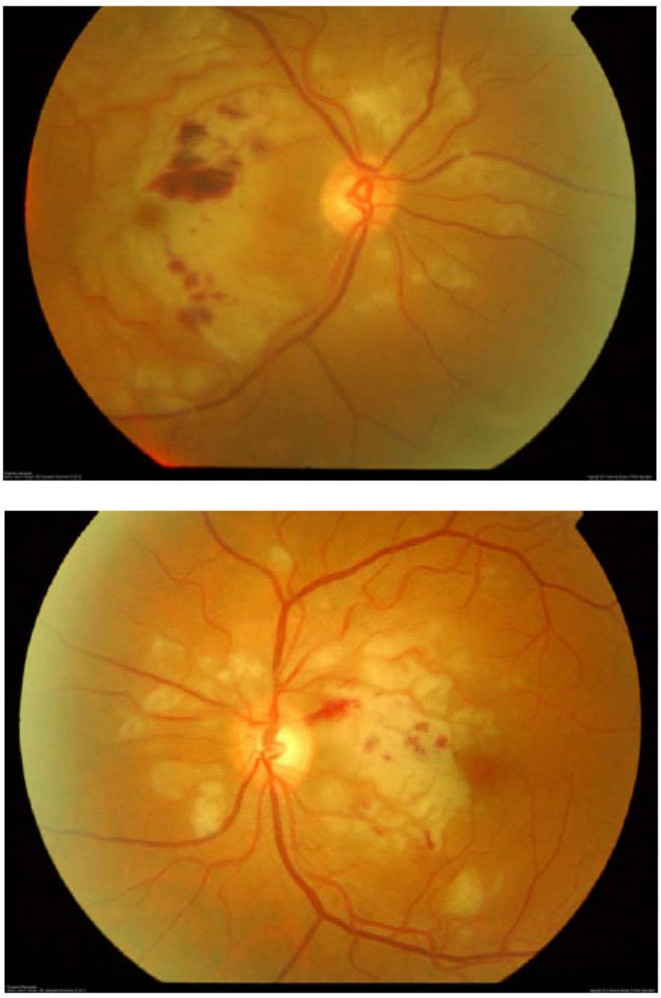

Fig. (1). Fundus photographs (right and left eye) of a 63-year-old male with alcoholic pancreatitis and Purtscher retinopathy (This image was originally published in the ASRS Retina Image Bank. Alex P. Hunyor, MD. Purtscher Retinopathy. Retina Image Bank. 2015; Image Number 2921 and 2922. © the American Society of Retina Specialists).

MANAGEMENT

- Fluorescein angiography: retinal ischemia areas.
- Optical coherence tomography: edema of the nerve fiber layer and subretinal fluid.

- CT imaging of chest and long bones if necessary.
- Permanent visual loss may occur in half of affected eyes; no treatment available [1, 3 - 7].

CONFLICT OF INTEREST

The author confirms that author has no conflict of interest to declare for this publication.

ACKNOWLEDGEMENTS

Declared none.

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CHAPTER 5

Terson Syndrome

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Terson described in 1900 [1] an intraocular hemorrhage in association with subarachnoid bleed or subdural hemorrhage [2]. The syndrome of vitreous hemorrhage in association with any form of intracranial hemorrhage has come to be known as Terson's syndrome. The most common cause of Terson's syndrome is acute subarachnoid hemorrhage resulting from a ruptured intracranial aneurysm [3].

ESSENTIALS OF DIAGNOSIS

Terson's syndrome is more common than usually thought. It has been found to occur in 3% to 8% of individuals with subarachnoid hemorrhage. However, the urgency of managing a serious intracranial hemorrhage usually supersedes fundoscopic examination by a retina specialist.

Bilateral, intraretinal, and subretinal hemorrhages can be observed (Figs. **1** and **2**). Pre-retinal hemorrhage may occur within the temporal vascular arcades, forming a peculiar dome-shaped accumulation of blood [4]. This blood, which has accumulated between the internal limiting membrane and posterior hyaloid face, may disperse into the vitreous. The partially detached posterior hyaloids in some longstanding cases provides a scaffold for cellular proliferation and the development of an elevated epiretinal membrane. A high incidence of macular

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abnormalities, including hemorrhagic cysts and epiretinal membranes, has been reported [3, 4].

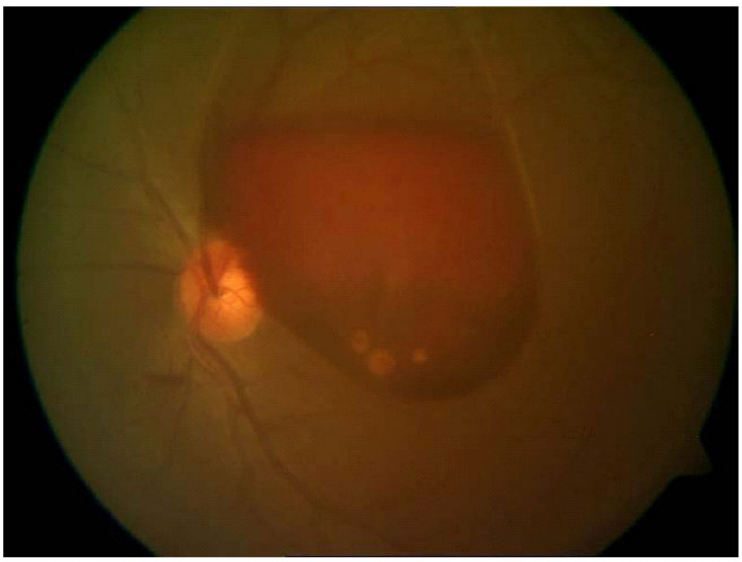

Fig. (1). Fundus photograph of a 31-year-old male with history of recent blunt head trauma, showing media opacities secondary to vitreous hemorrhage, and the presence of a subhyaloid hemorrhage.

The exact pathogenesis of Terson's syndrome is unknown. One report suggested that it was caused by the dissection of blood from the subarachnoid space through the optic nerve sheath and into the eye [5]. However, there is no direct communication between the subarachnoid space and the vitreous cavity in the normal eye, and hemorrhage that is not contiguous with the optic disc can be seen in this condition [4]. A more plausible explanation suggests that an acute rise in intracranial pressure, such as the one that occurs with intracranial hemorrhage, is transmitted down the sub-arachnoid space of the optic nerve, causing venous stasis *via* compression and stretching of the intra-orbital veins. This, in turn, causes a rapid rise in intraocular venous pressure, distention, and rupture of the fine papillary and retinal capillaries and subsequent vitreous hemorrhage.

DIFFERENTIAL DIAGNOSIS

Differential diagnosis should be made with other traumatic retinopathies, such as Purtscher's retinopathy, which is associated to compressive injury to the thorax

and head, causing a characteristic retinopathy with intraretinal hemorrhage and cotton-wool spots, or Valsalva retinopathy, which is caused by a sudden rise in intra-thoracic or intra-abdominal pressure, causing rupture of capillaries in the macula and subsequent hemorrhage beneath the internal limiting membrane. Other differential diagnoses to consider are shaken baby syndrome and anemic retinopathy.

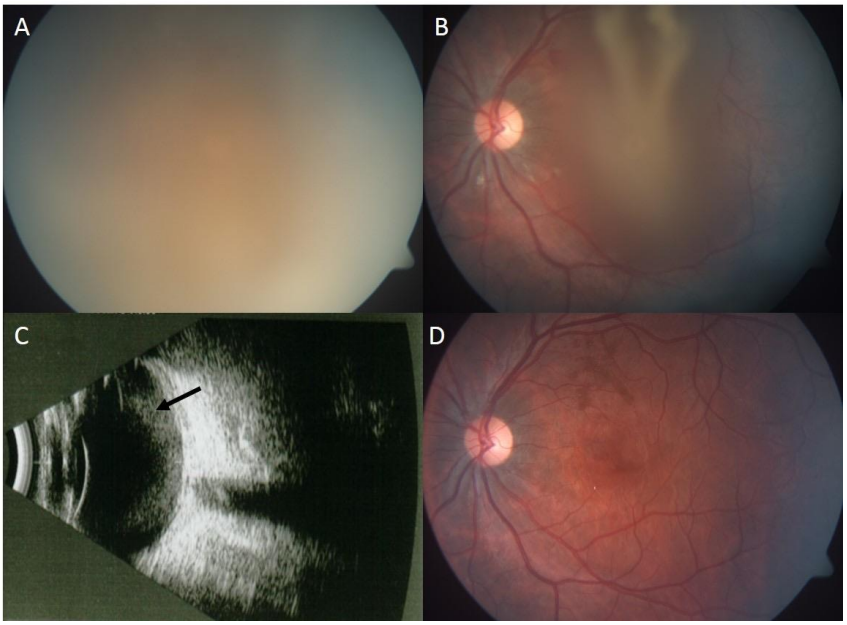

Fig. (2). (**A**). Fundus photograph of the left eye of a 23-year-old male patient with history of blunt head trauma and a subarachnoid hemorrhage showing vitreous hemorrhage. (**B**). Partial reabsorption of the hemorrhage. (**C**). B-scan Ultrasound showing subhyaloid hemorrhage. (**D**). Fundus photograph after pars-plana vitrectomy, showing remnants of subretinal hemorrhage (Images courtesy of Javier Flores-Preciado, MD).

MANAGEMENT

Observation is a management option for vitreous hemorrhage, especially in adults with unilateral involvement. Vitreous hemorrhage in Terson's syndrome usually clears within a year but may take longer [2]. However, surgical intervention is advised to avoid potential complications of persistence of blood in the vitreous such as epiretinal membranes, other macular abnormalities, and retinal detachment, as well as amblyopia and myopia in infants. Several reports have

demonstrated good visual recovery after vitrectomy surgery (Fig. **2**) [6, 7]. Children should be considered for earlier surgery to prevent amblyopia. In patients opting for observation, repeated visual testing and ultrasonography are recommended for early detection of retinal detachment. All patients with intracranial hemorrhage should undergo a dilated funduscopic examination, since the presence of vitreous hemorrhage has implications for the patient's general condition.

CONFLICT OF INTEREST

The author confirms that author has no conflict of interest to declare for this publication.

ACKNOWLEDGEMENTS

Declared none.

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CHAPTER 6

Valsalva Retinopathy

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Valsalva retinopathy is a rare condition that causes a sudden loss of visual acuity. It was first described by Duane in 1972 as a preretinal hemorrhage [1].

ESSENTIALS OF DIAGNOSIS

It may occur as a sudden, dramatic loss of central vision due to the premacular location of the hemorrhage, caused by a rapid increase in intraocular venous pressure as a consequence of valsalva´s maneuver [2]. This maneuver is a forcible exhalation effort against a closed glottis, caused by a sudden rise in intra-thoracic and intra-abdominal pressure, which raises the central venous pressure. There are no valves in the venous rostral system towards the heart, so a rise in the reflux venous pressure may occur in the head and neck region of the body. This unexpected increase in the venous pressure can rupture the perimacular vessels resulting in premacular hemorrhage [3].

The location of the bleeding can differ according to the magnitude of the hemorrhage. The preretinal structures are closely appose to the retinal surface in young adults, although hemorrhage can dissect tissue plane and fill the potential spaces. The most common location is in the subinternal limiting membrane [4]. It can also be present in the subhyaloid or in a combination of both (Figs. **1** and **2**). Vitreous hemorrhage and subretinal hemorrhage have also been described.

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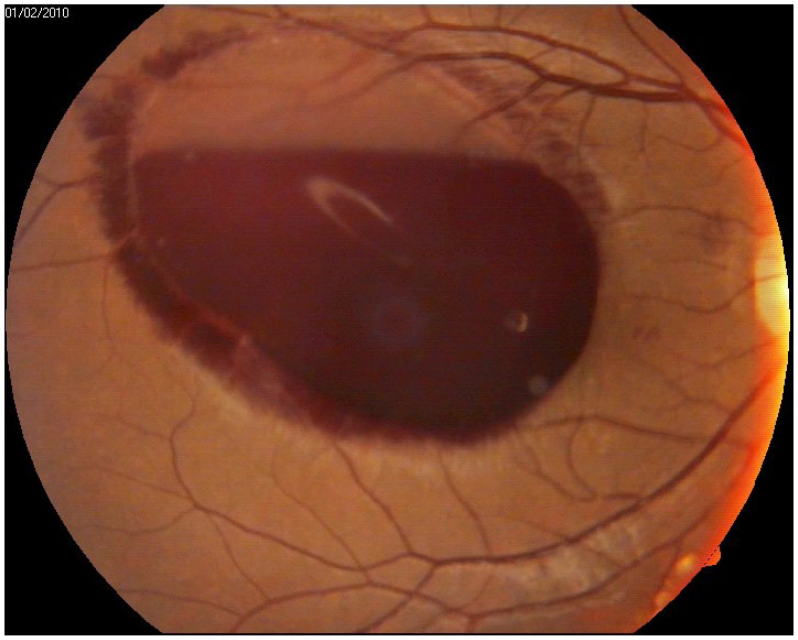
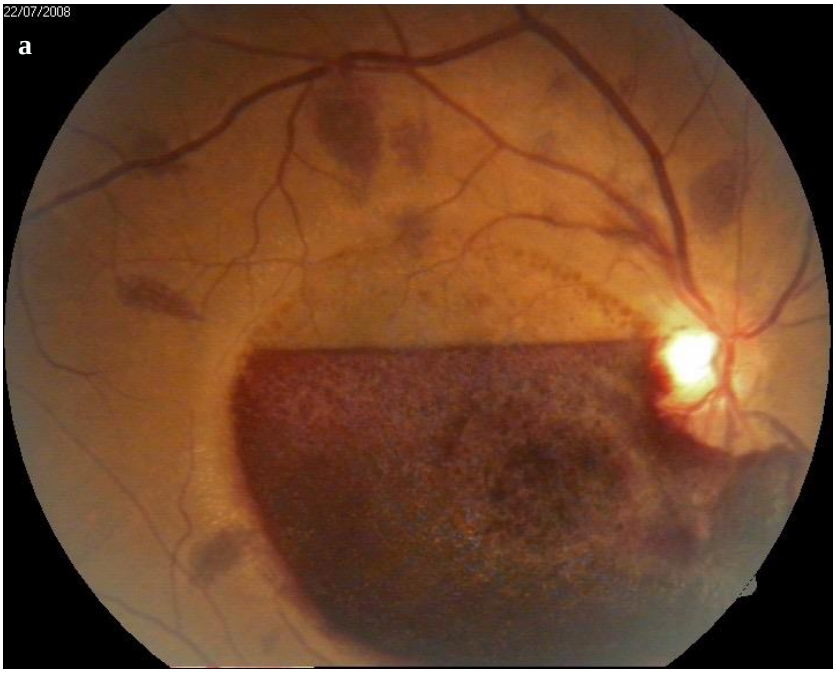


Fig. (1). A 26-year-old male with a sudden loss of visual acuity (HM) in right eye, as a consequence of valsalva´s maneuver. Fundus photograph shows preretinal hemorrhage (Courtesy of Retinal Camera, Ophthalmology Department, Hospital Central de Maracay, Venezuela).



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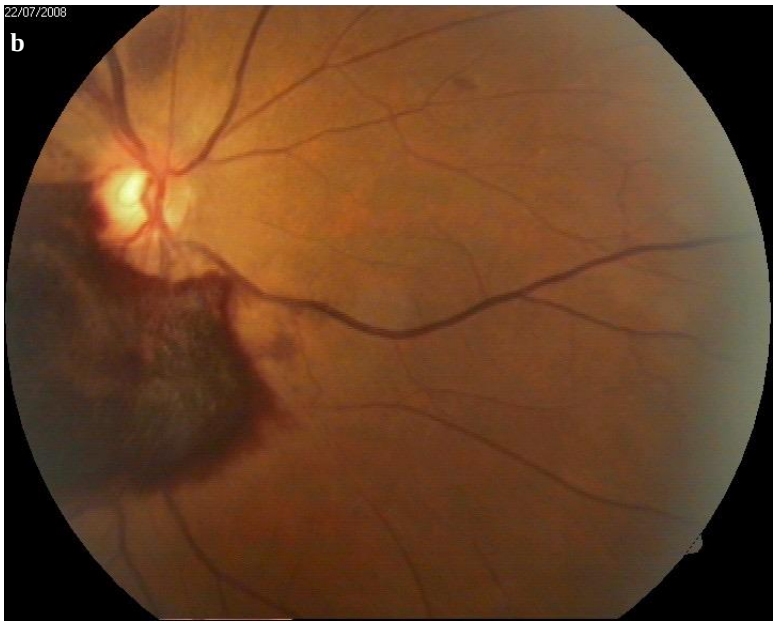

Fig. (2). (**a**) and (**b**) Woman of 45 years old with a massive subinternal limiting membrane hemorrhage in right eye, secondary to valsalva maneuver. Visual acuity: hand motion (Courtesy of Mitzy Torres Soriano, MD).

It often occurs in healthy young male adults as a result of a variety of clinical settings. However, its recurrence is infrequent.

Risk factors that can contribute to this condition:

Intense aerobic exercise, heavy lifting, balloon inflation, straining on the toilet, bout of vomiting (such as in pregnancy or bulimia), bout of coughing [5], thoracoabdominal trauma, vigorous sexual activity [1], choking games, vigorous dancing, and colonoscopy complication [6].

DIFFERENTIAL DIAGNOSIS

It is imperative to exclude systemic disease such as diabetes, hypertension and ocular vein occlusion. Hematological conditions such as sickle cell disease, anemia, coagulopathies, and blood dyscrasias, trauma, infection diseases, degenerations, cancer, rupture retinal macroaneurysm and shaken baby syndrome [7].

MANAGEMENT

Observation: Preretinal hemorrhages secondary to Valsalva retinopathy usually resolve by themselves in a few weeks to a few months (Fig. **3**) [8], so a conservative approach is generally justifiable in hemorrhages smaller than one disk diameter.

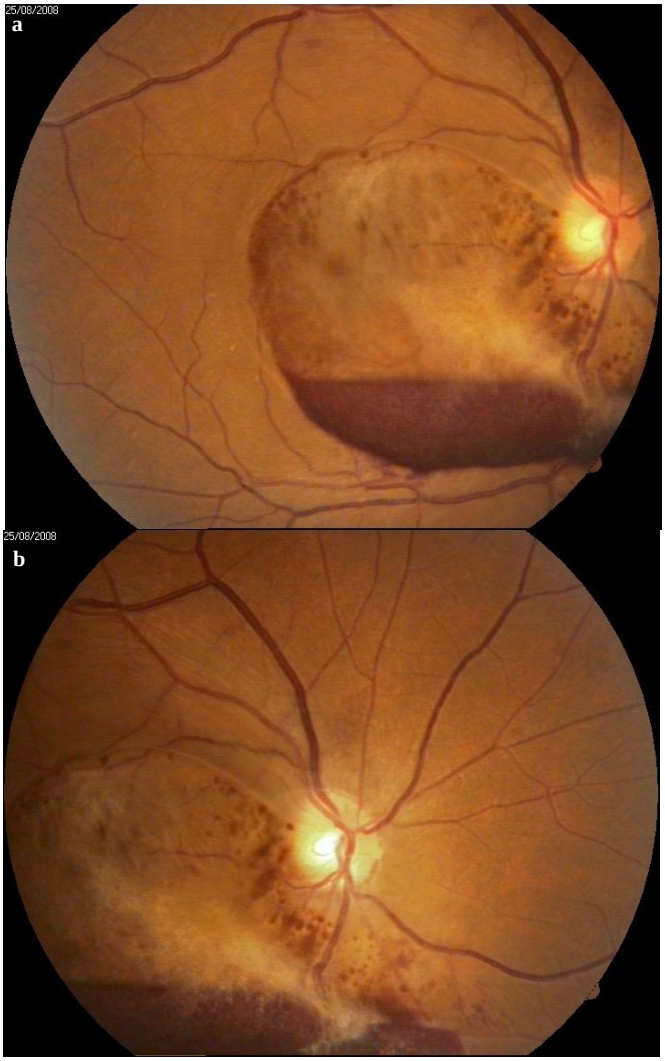

Fig. (3). (**a**) and (**b**) The same patient of Fig. (**2**): Woman of 45 years a month later with a good resolution. Visual acuity: 20/30 (Courtesy of Mitzy Torres Soriano, MD).

Nd-YAG laser or Green argon laser: It punctures the posterior hyaloids and drains the blood in the vitreous. It is an effective procedure in fresh cases less than 21 days [9]. It achieves rapid resolution of premacular, subhyaloid hemorrhages with restoration of visual function, preventing the need for vitreoretinal surgery [9 - 11].

Pneumatic displacement of the hemorrhage by intravitreal injection of gas, with or without plasminogen activator [12, 13].

Pars plana vitrectomy: Timely surgical intervention is justified when spontaneous resorption is insufficient. Lack of procedure can produce a toxic damage to the retina because of the prolonged contact with hemoglobin and iron on the tissue [14].

Prognosis: In general, the prognosis is good because the hemorrhages are small enough to resolve by themselves. Patients are warned to avoid any valsalva´s maneuver in the future.

CONFLICT OF INTEREST

The author confirms that author has no conflict of interest to declare for this publication.

ACKNOWLEDGEMENTS

Declared none.

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CHAPTER 7

Chorioretinitis Sclopetaria

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Chorioretinitis sclopetaria is a term used to describe a full-thickness retinal and choroidal lesion caused by a high-velocity projectile passing through the orbit without perforating the sclera.

Chorioretinal injury is due to shock waves produced by the missile's passage through the orbit [1 - 3].

ESSENTIALS OF DIAGNOSIS

- Decreased vision (severity depending on region involved).
- History of recent ocular high-velocity penetrating trauma (missile/projectile).
- Subretinal, intraretinal, preretinal hemorrhage, often involving posterior pole.
- Vitreous hemorrhage or vitreous base avulsion, which can lead to peripheral retinal dialysis or retinal tears.
- Choroid and retina ruptures, with underlying bare sclera.
- White fibrous scar and RPE changes, usually in the peripheral retina, when blood is resorbed (Fig. **1**).
- Claw-like break of Bruch membrane [1 - 4].

DIFFERENTIAL DIAGNOSIS

- Ruptured globe: Poor visual acuity, presence of relative afferent pupillary defect (RAPD), subconjunctival hemorrhage and chemosis, irregular pupil, low IOP.

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- Choroidal rupture: Break in the choroid, Bruch membrane, RPE, following a closed globe injury from blunt trauma. Neurosensory retina is not involved. A posterior pole retinal hemorrhage could obscure a choroidal rupture until blood clears after few weeks.
- Optic nerve avulsion: Decreased vision with RAPD, vitreous hemorrhage with hemorrhagic depression or excavation of the optic disc, or retraction of entire nerve if severe. Poor visual prognosis, no treatment.

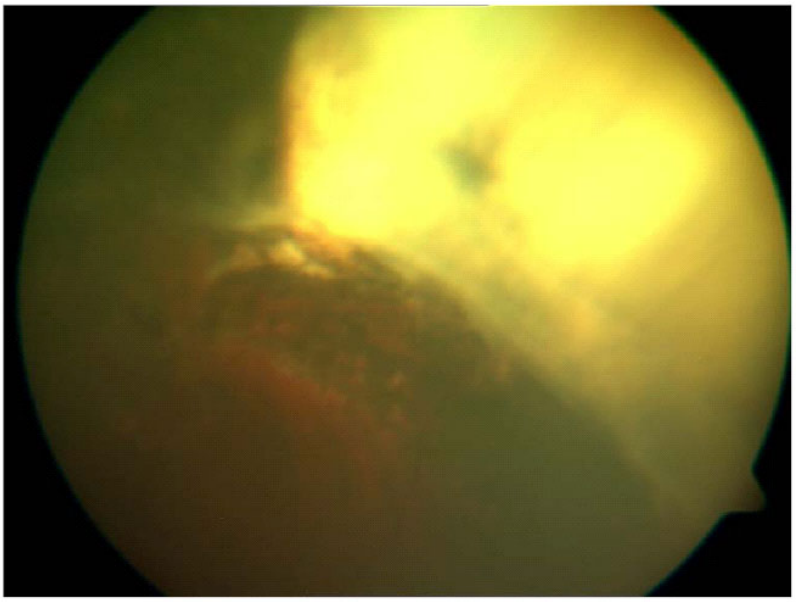

Fig. (1). Chorioretinitis sclopetaria. Fundus photograph showing white fibrous scar and RPE changes in the peripheral retina, one month after blunt trauma with a high pressure water gun (Courtesy of Maximiliano Gordon, MD).

MANAGEMENT

- Complete ophthalmic evaluation, including dilated fundus examination, anterior segment examination, conjunctiva and anterior sclera (check if ruptured globe).
- CT / B-scan or UBM if high risk of intrascleral, intraocular, or intraorbital foreign bodies.
- Follow up examination every 2-4 weeks until blood is resorbed and fibrous changes appear [5 - 7].
- In certain cases, surgery for retinal detachment or nonclearing vitreous hemorrhage may be needed.

CONFLICT OF INTEREST

The author confirms that author has no conflict of interest to declare for this publication.

ACKNOWLEDGEMENTS

Declared none.

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CHAPTER 8

Posterior Vitreous Detachment

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Posterior vitreous detachment (PVD) is a physiological phenomenon in which the posterior vitreous cortex separates from the internal limiting membrane of the retina. Two progressive age-related alterations of the vitreous result in PVD: vitreous liquefaction and weakening of the vitreoretinal adhesion [1]. The detachment occurs between ages of 50 and 70 in general population, but may occur earlier in highly myopic patients [2]. Snead *et al.* [2] report the prevalence of PVD to be 57% in a randomly selected group of normal subjects. In most patients, PVD has no important consequences. However, especially in eyes with abnormally high vitreoretinal adherence, it may lead to symptomatic retinal breaks, and eventually cause a rhegmatogenous retinal detachment (RRD) [3]. The PVD is considered "complete" when the vitreous cortex is not attached to either the fovea or the optic nerve and "incomplete" when is at least partially attached to one of them.

ESSENTIALS OF DIAGNOSIS

Photopsia: Usually more apparent in the dark, as a consequence of vitreous traction exerted over the retina by the vitreous. This phenomena is recognized in the absence of outside light stimulation.

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Floaters: Described as opacities with varying shapes that move with eye movements, due to vitreous condensations, or the presence of a Weiss ring or blood from retinal vessels. Nearly 70% of the patients who reported PVD with a concomitant hemorrhage had at least one break.

These kind of symptoms are all suggestive of retinal breaks. Evaluation should include examination with a corneal contact lens (Goldmann three mirror lens) or slit-lamp indirect biomicroscopy utilizing a 78 or 90 diopter lens. The vitreous cavity may be fully evaluated for the presence of cells by focusing at progressive depths in all quadrants. Careful search should be made for a vitreous face separated from the retinal surface, particularly in the posterior pole of the cavity, and the possible presence of a Weiss ring (Fig. **1**). Peripheral retinal examination should be done with indirect ophthalmoscope and scleral depression. If vitreous hemorrhage precludes adequate retinal examination, B-scan ultrasonography is advisable [4].

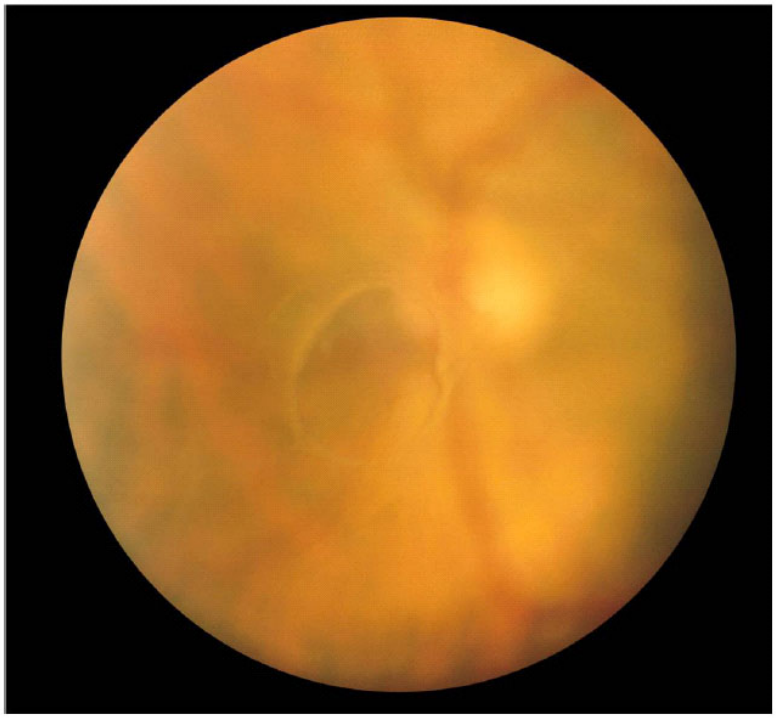

Fig. (1). Posterior vitreous detachment with Weiss ring (Courtesy of Jorge Bar MD, Argentina).

Almost 20% of the patients with symptoms have a retinal break at the moment of examination and there is a direct correlation between the amount of vitreous hemorrhage and the likelihood of a retinal tear [5]. If no retinal breaks are present, but there is vitreous or retinal hemorrhage, a new examination must be considered in the following 3-4 weeks due to a 5% chance of a retinal break. The annual incidence of RRD is approximately 10 to 15 per 100,000 persons [6, 7]. Of these cases, approximately 20% have had cataract surgery and 10% have had ocular trauma [8, 9]. Other risk factors for RRD are myopia and lattice degeneration [3]. Around 80% of eyes that have no breaks at the initial visit, but develop a retinal break during the following weeks, have either a hemorrhage in the vitreous or retina, or new symptoms that required a new evaluation [10].

Classification

PVD may be classified in four stages based on optical coherence tomography or ultrasound imaging using a 10 MHz probe straight to the fovea (Table **1**).

Table 1. Stages of posterior vitreous detachment [3].

Stage 1	Perifoveal separation with adhesion of vitreous to the fovea.
Stage 2	Complete separation of vitreous from the macula.
Stage 3	Extensive vitreous separation with adhesion of vitreous to the disc.
Stage 4	Complete posterior vitreous detachment.

MANAGEMENT

PVD without symptoms: Patient education regarding symptoms of vitreous traction, hemorrhage and retinal detachment. Re-examination annually.

PVD with symptoms (flashes/floaters): Reassurance. Patient education regarding change in nature of symptoms suggesting progression. Re-examination in 4-6 weeks, then 3-4 months, then annually.

PVD with vitreous hemorrhage that precludes retinal examination: B-scan ultrasonography. Clinical examination and B-scan 1 week, then every 1-2 weeks for 6 weeks, then less frequently if no indication of retinal tear or detachment [4].

Retinal cryotherapy and laser photocoagulation are most often employed in prophylactic treatment of tractional retinal breaks, (Table **2**) particularly those associated with symptoms of flashes and floaters, in an effort to create a firm chorioretinal adhesion surrounding the break [4].

Table 2. Management options [3].

Type of Lesion	**Treatment ***
Acute symptomatic horseshoe tears	Treat promptly.
Acute symptomatic operculated holes	Treatment may not be necessary.
Acute symptomatic dialysis	Treat promptly.
Traumatic retinal breaks	Usually treated.
Asymptomatic horseshoe tears (without subclinical RD)	Controversial but treatment usually performed.
Asymptomatic operculated tears	Treatment is rarely recommended.
Asymptomatic atrophic round holes	Treatment is rarely recommended.
Asymptomatic lattice degeneration without holes	Not treated unless PVD causes a horseshoe tear.
Asymptomatic lattice degeneration with holes	Usually does not require treatment.
Asymptomatic dialysis	treatment usually performed.
Eyes with atrophic holes, lattice degeneration, or asymptomatic horseshoe tears where the fellow eye has had a RD.	No consensus on treatment and insufficient evidence to guide management.

* There is insufficient evidence to recommend prophylaxis of asymptomatic retinal breaks for patients undergoing cataract surgery.

In case of retinal detachment and/or persistent vitreous hemorrhage, vitreoretinal surgery is needed.

CONFLICT OF INTEREST

The author confirms that author has no conflict of interest to declare for this publication.

ACKNOWLEDGEMENTS

Declared none.

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CHAPTER 9

Asteroid Hyalosis

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The asteroid hyalosis is a degenerative disease of the vitreous characterized by the presence of multiple birefringent yellowish-white, round particles essentially composed of calcium and phosphate dispersed in the vitreous [1,2]. Its incidence has been estimated at 0.5%. Usually it is unilateral (75%) and observed in patients over 60 years of age. It more commonly affects males than females (3/1) [2-4].

The origin of the asteroid hyalosis remains unknown, but current theories suggest that it is a result of the aging of collagen within the vitreous or depolymerization of hyaluronic acid. There may be a greater prevalence in patients with diabetes, systemic arterial hypertension, hypercholesterolemia, atherosclerotic vascular disease, and hyperopia [3-5].

ESSENTIALS OF DIAGNOSIS

The findings in this disease are very characteristic. It is usually asymptomatic; in severe cases it may slightly affect visual acuity. Floaters are rare.

The biomicroscopic examination is characterized by tiny corpuscles solid, spherical or discoid (white or yellow with little mobility) suspended in an essentially normal vitreous although it may be fibrillar vitreous degeneration. The asteroid bodies are arranged in columns or clusters but more often manifest in the random arrangement [3] (Figs. **1** and **2**).

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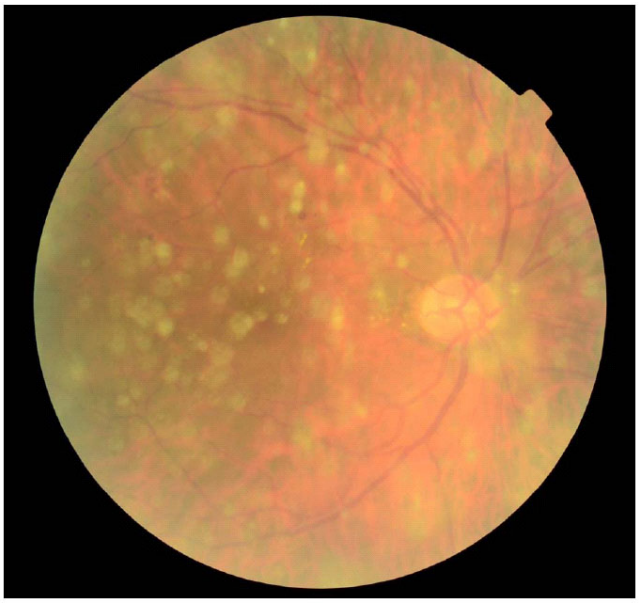

Fig. (1). Asteroid hyalosis: Small, dense, spherical white opacities, fixed in location, attached to vitreous fibrils in the random arrangement.

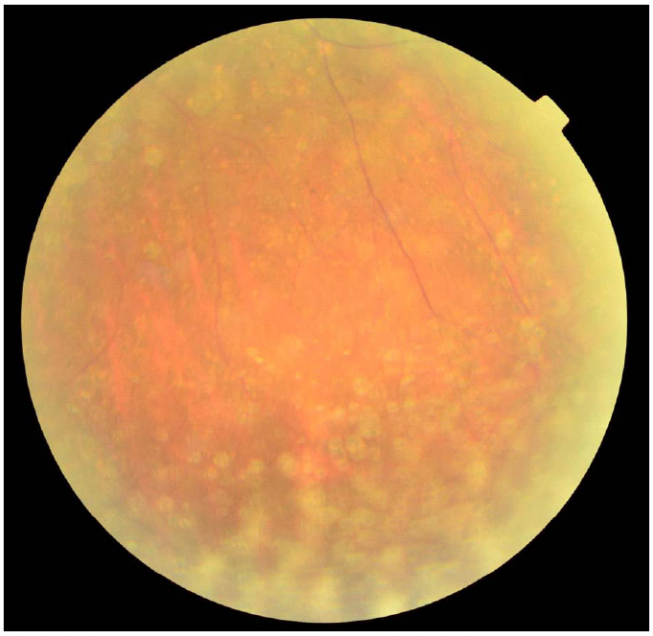

Fig. (2). Left eye of a 64 year-old female with hypertensive retinopathy, vascular occlusion, and asteroid hyalosis. Small white opacities in inferior portion of vitreous cavity.

The ophthalmoscopic examination is characterized by asteroid bodies that reflect light and give a picture as “stars shining in the night sky”. With eye movements have slight mobility but always returning to the original position [1, 3]. Because these opacities cast very short cones of shadow, the patient does not perceive them. They have minimal, if any, effect on vision but by reflecting light back to the observer, they may obscure visualization of the fundus, at times to a severe degree. The use of fluorescein angiography, optical coherence tomography, and ocular ultrasound in these situations may provide extra information about the retinal condition that might not be possible by ophthalmoscopy alone [5] (Fig. **3**).

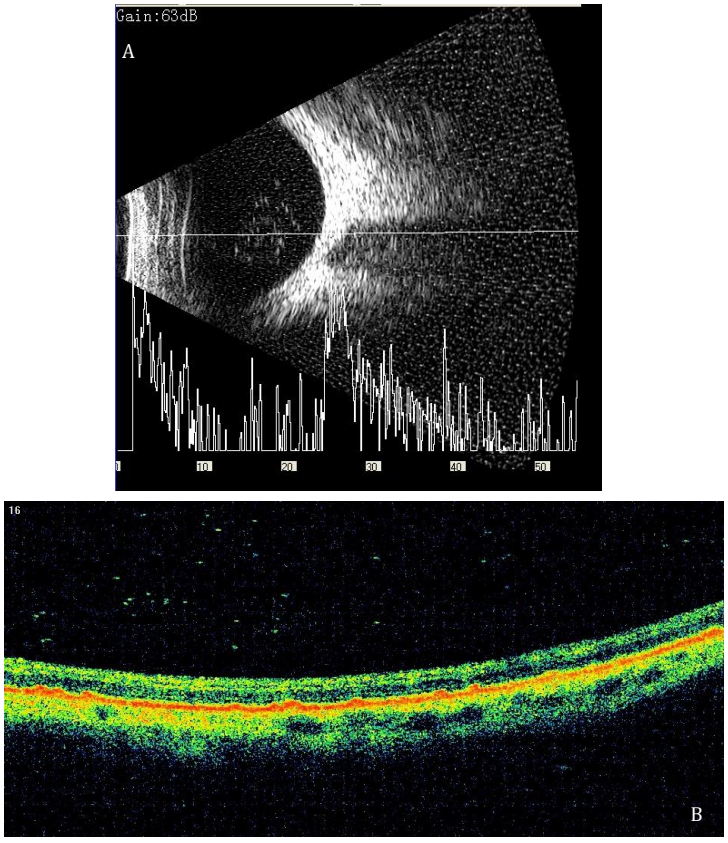

Fig. (3). Studies of the same patient of Fig. (**2**). (**A**). A contact A and B-scan showing hyperechoic dots in vitreous cavity. (**B**). OCT showing some hyperreflective points in the posterior vitreous and severe retinal atrophy.

DIFFERENTIAL DIAGNOSIS

Synchysis scintillans, also called cholesterolosis bulbi, is a relatively rare eye condition that involves the presence of bright opacities formed by cholesterol crystals dispersed in the vitreous humor, where they are free floating. These crystals likely come from leaking retinal vessels. Unlike the asteroid hyalosis particles, cholesterol crystals are flat, highly refractile, move in all directions, and tend to settle at the bottom of liquified vitreous when the eye is at rest due to gravity. They vary in size and number and appear somewhat larger than the bright particles observed in the asteroid hyalosis [5, 6].

The symptoms are also usually mild or absent. Synchysis scintillans is seen most often in the eyes of younger individuals. It occurs secondary to recurrent intraocular inflammation, ocular vitreous hemorrhage, or trauma. In the presence of aphakia or pseudophakia, cholesterol crystals can migrate to the anterior chamber and may cause secondary glaucoma. The condition usually does not require treatment unless the particles clog the drainage of aqueous humor, in this case irrigation of the anterior chamber is needed [6].

Amyloidosis, can result in the deposition of opacities in the vitreous of one or both eyes. Bilateral involvement can be an early manifestation of the dominant form of familial amyloidosis, although rare cases of vitreous involvement in non-familial forms have been reported. The opacities appear in the vitreous adjacent to retinal blood vessels and later in the anterior vitreous. Initially, the opacities are granular with wispy fringes and later take on a “glass wool” appearance. When the opacities form strands, they appear to attach to the retina and the posterior aspect of the lens by thick footplates. Following PVD, the posterior vitreous cortex is observed to have thick, linear opacities that follow the course of the retinal vessels. The opacities seem to aggregate by “seeding” on vitreous fibrils and along the posterior vitreous cortex. In patients with visually significant vitreal amyloidosis, vitrectomy has been used with satisfactory results [4, 6].

MANAGEMENT

It is a benign process, and in very few cases vitrectomy is indicated to improve visual acuity. Vitrectomy is considered if it coexists with diabetic retinopathy or

retinal tear and photocoagulation is necessary. In cases where the asteroid hyalosis is solely responsible for the decrease in visual acuity, subtotal vitrectomy usually improves the vision of patients; however, the visual recovery may be less than expected by the existence or development of concurrent processes [7, 8].

CONFLICT OF INTEREST

The authors confirm that they have no conflict of interest to declare for this publication.

ACKNOWLEDGEMENTS

Declared none.

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CHAPTER 10

Vitreous Hemorrhage

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Vitreous hemorrhage is defined as the presence of red blood cells within the vitreous cavity. It is a frequent cause of visual disturbance, and may be caused by a wide variety of vitreoretinal pathologies [1 - 6].

ESSENTIALS OF DIAGNOSIS

Patients complain of sudden and painless decrease of visual acuity, which is usually unilateral. The intensity of visual loss will depend on the amount of blood present in the vitreous cavity. The patient usually describes the presence of floaters.

Diagnosis is relatively straightforward during ophthalmologic examination, where blood is seen trapped in the vitreous fibers (Figs. **1**, **2**). If hemorrhage is recent, it will be bright red in appearance. If hemorrhage occurred 2-3 months before examination, it may turn yellowish. Fundus details may be obscured, depending on the amount of hemorrhage. In some eyes (especially when diabetic retinopathy is the underlying cause), hemorrhage may become trapped between the detached posterior hyaloid and the retina, causing a so-called subhyaloid hemorrhage (Fig. **3**).

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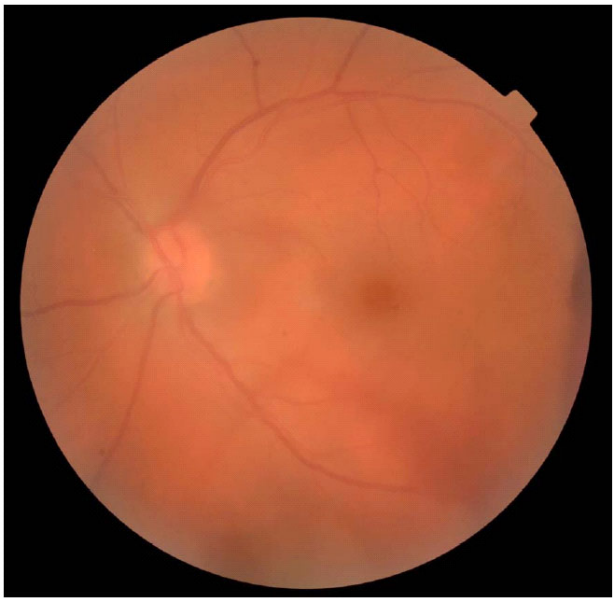

Fig. (1). Vítreous hemorrhage in patient with arterial hypertension (Courtesy of Manuel Torres López, Cagua - Venezuela).

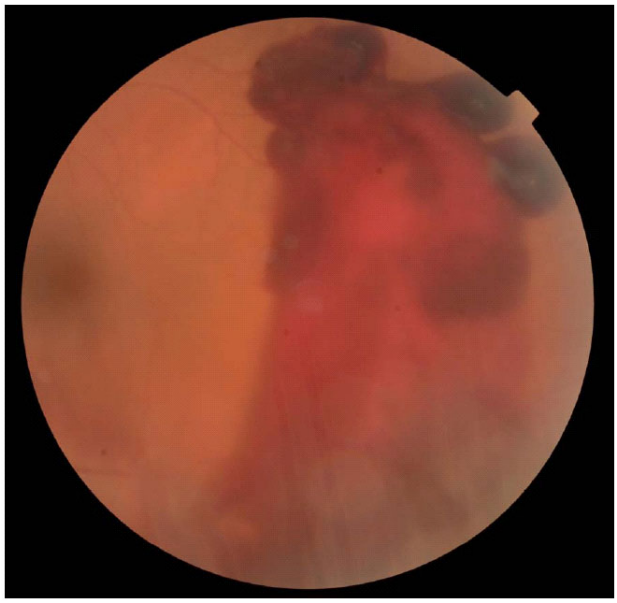

Fig. (2). Same patient as Fig. (**1**) Vítreous, subhyaloid and subretinal hemorrhage in temporal side, probably secondary to arterial macroaneurysm (Courtesy of Manuel Torres López, Cagua - Venezuela).

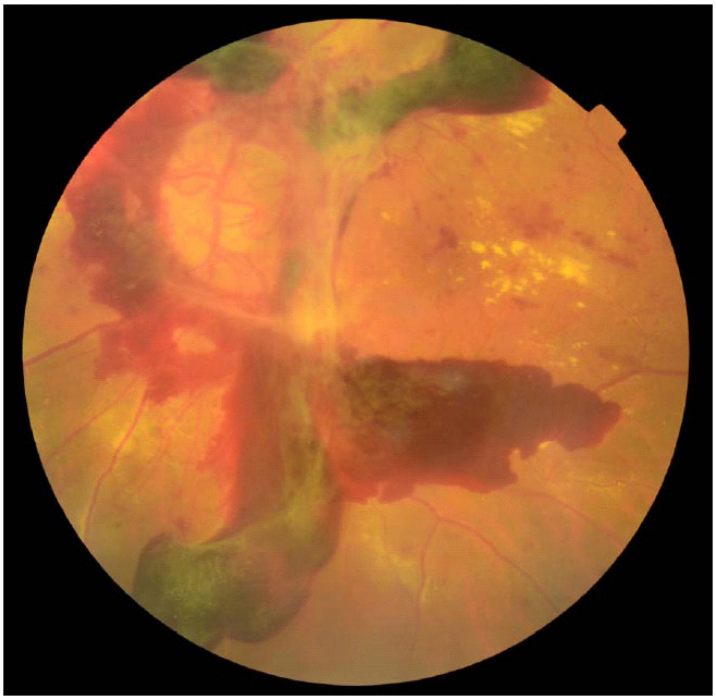

Fig. (3). Subhyaloid hemorrhage secondary to proliferative diabetic retinopathy. It reveals retinal hemorrhages, hard exudates and neovascularization (Courtesy of Manuel Torres López, Cagua - Venezuela).

If the amount of hemorrhage precludes visualization of the fundus, a B-scan ultrasonogram is needed to evaluate the retina and the choroid (Fig. **4**). Examination of the contralateral eye may give valuable clues regarding the etiology of the hemorrhage.

DIFFERENTIAL DIAGNOSIS

The most frequent causes of vitreous hemorrhage in adults are, in order of frequency: Acute posterior vitreous detachment, diabetic retinopathy, retinal vein occlusion, trauma, and breakthrough hemorrhage from a choroidal neovascularization. In children, diseases such as shaken baby syndrome, Coats' disease, pars planitis or familial exudative vitreoretinopathy should be ruled out.

Ophthalmologic examination should be sufficient to make the diagnosis. However, B-scan ultrasound and fluorescein angiogram are valuable tools to elucidate the etiology.

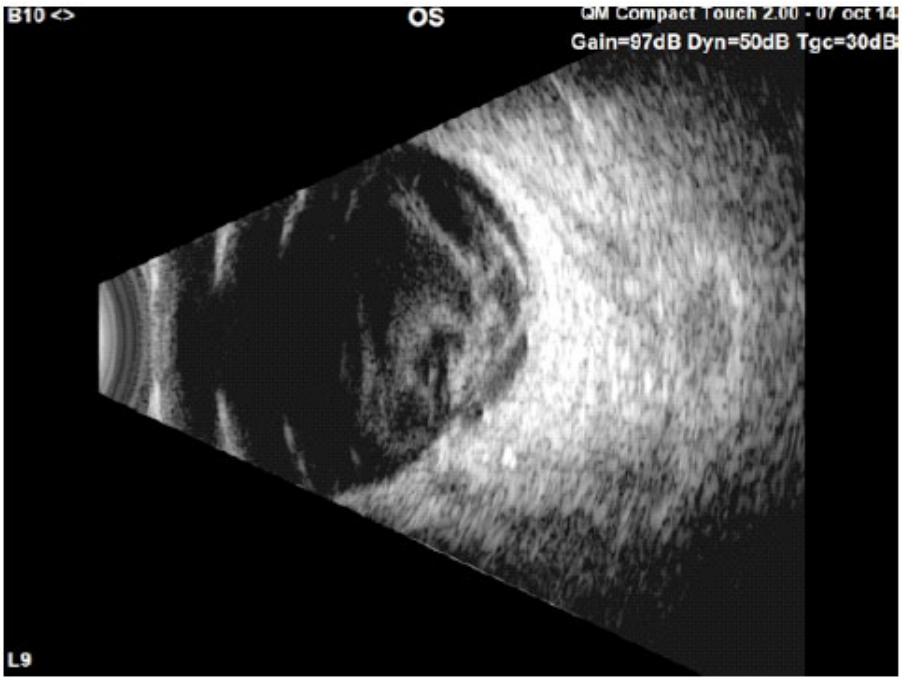

Fig. (4). B-Scan ultrasonogram of an eye with vitreous hemorrhage secondary to diabetic retinopathy. A tractional retinal detachment is also observed.

MANAGEMENT

In around two thirds of patients, vitreous hemorrhage clears during the following weeks without any intervention. If B-scan ultrasound does not show a retinal tear or retinal detachment, patients may be followed every 2-3 weeks until hemorrhage clears. If hemorrhage persists for more than 1-2 months, or if a retinal tear or detachment is observed, three-port pars-plana vitrectomy is advised to clear the hemorrhage and treat the underlying pathology.

CONFLICT OF INTEREST

The authors confirm that they have no conflict of interest to declare for this publication.

ACKNOWLEDGEMENTS

Declared none.

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CHAPTER 11

Retinal Breaks and Peripheral Retinal Degenerations

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These lesions are usually located between the equator and the ora serrata. They have the potential risk of developing retinal breaks and retinal detachment.

ESSENTIALS OF DIAGNOSIS

Diagnosis is made through fundus examination with slit lamp and contact lenses, indirect ophthalmoscopy with scleral indentation or wide field fundus imaging.

Retinal Breaks

These are full thickness holes in the retina. This allows liquefied vitreous to dissect the space between the neuroretina and the pigment epithelium. This produces an imbalance between the adhesion and traction forces that maintain the retina attached, and retinal detachment occurs. The vitreous has normal and abnormal attachments to the retina, some of them are not visible.

Aging of the vitreous include vitreous liquefaction and syneresis. Posterior vitreous detachment may be present in less than 10% of patients under 50 years old, but it increases to 27% of patients above 60 years old and 63% in patients over age 70 [1, 2] (Fig. **1**).

As the posterior vitreous detachment develops, traction is exerted on areas of vitreoretinal adhesion, and retinal breaks may develop [1, 2].

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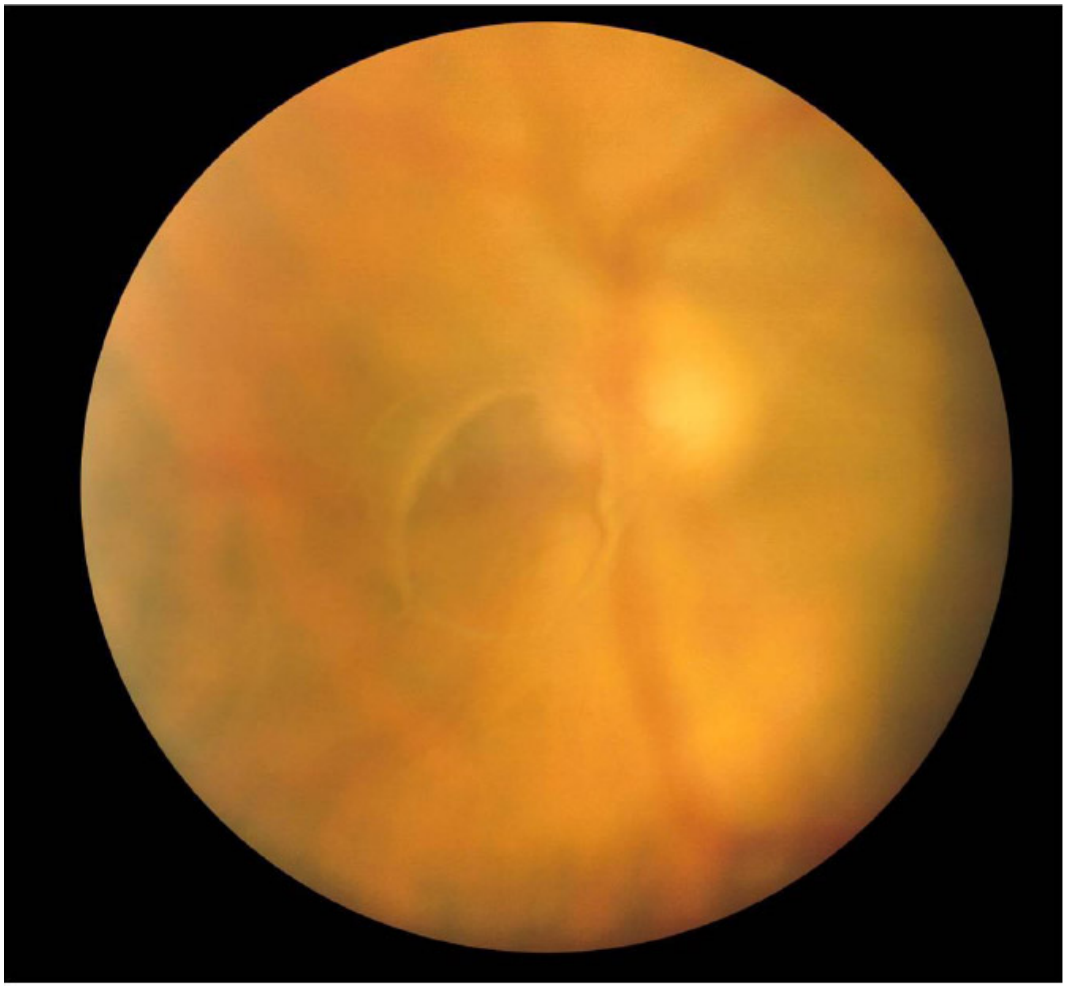

Fig. (1). Posterior vitreous detachment (Courtesy of Jorge Bar MD, Argentina).

The areas of especially firm vitreoretinal adhesion include several vitreoretinal degenerative disorders, meridional folds and complexes, tufts, oral bays, lattice degeneration, and perivascular vitreoretinal attachments. There are other sites of the retina that appear normal before retinal break formation.

Horseshoe Tears

They represent full thickness retinal breaks due to traction of the vitreous that remains attached to the retinal flap (Figs. **2 - 4**) [2].

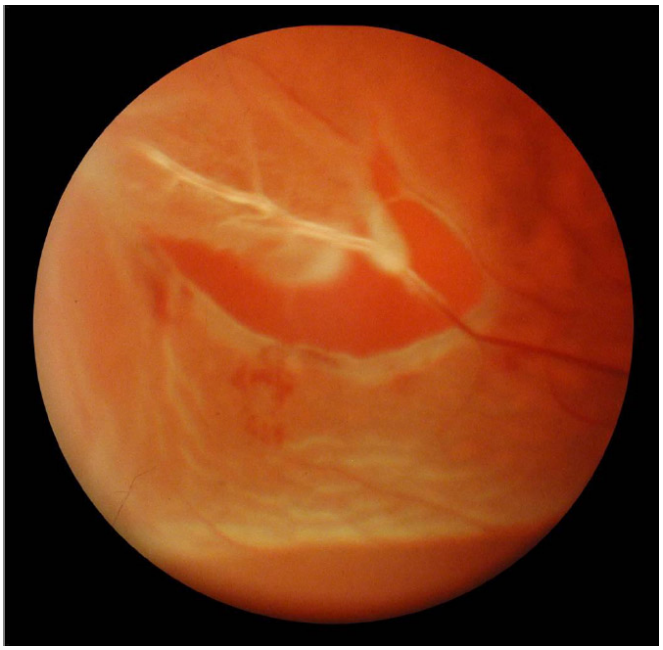

Fig. (2). Horseshoe tear and retinal detachment. Bridging of the overlying retinal vessel (Courtesy of Jorge Bar MD, Argentina).

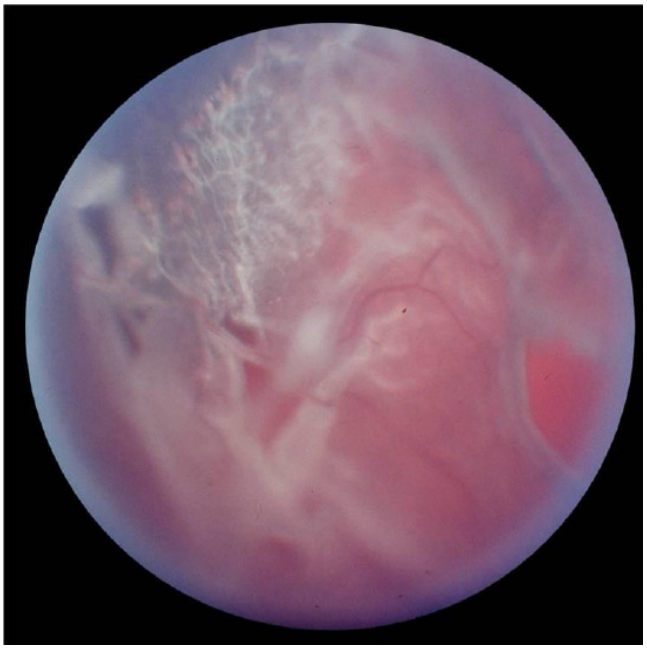

Fig. (3). Horseshoe tear and retinal detachment (Courtesy of Jorge Bar MD, Argentina).

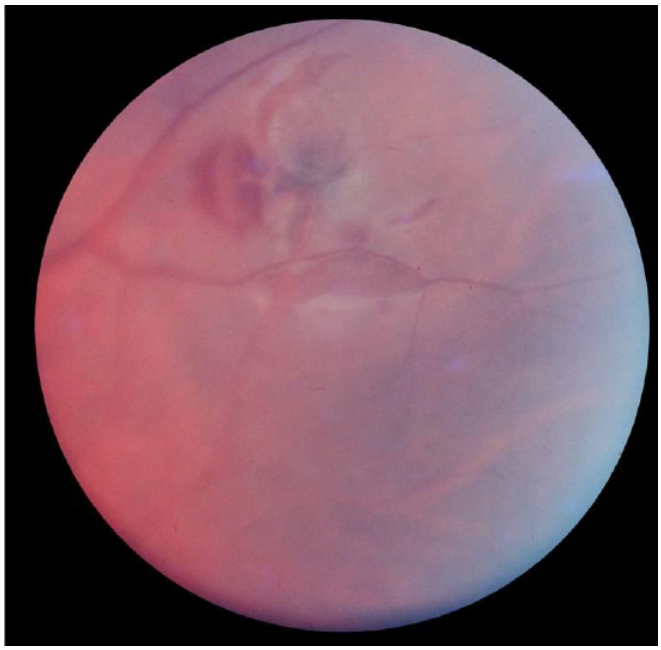

Fig. (4). Retinal tear with hemorrhage (Courtesy of Jorge Bar MD, Argentina).

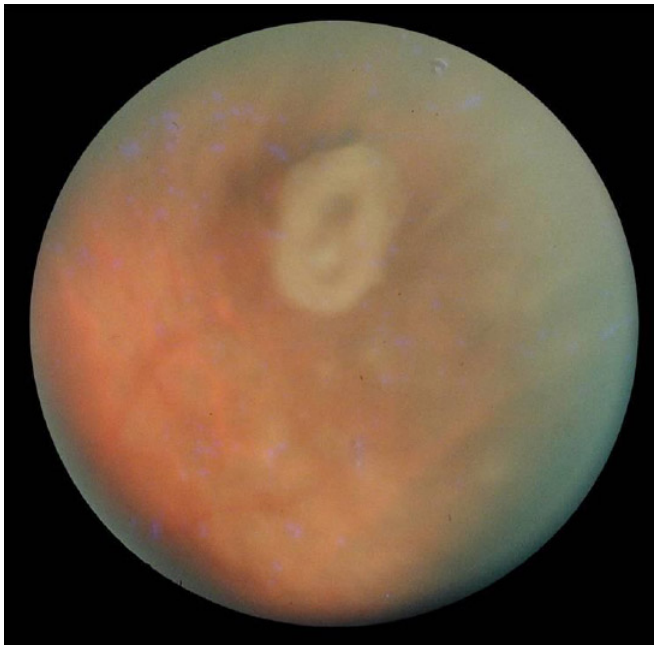

Fig. (5). Round hole with free operculum (Courtesy of Jorge Bar MD, Argentina).

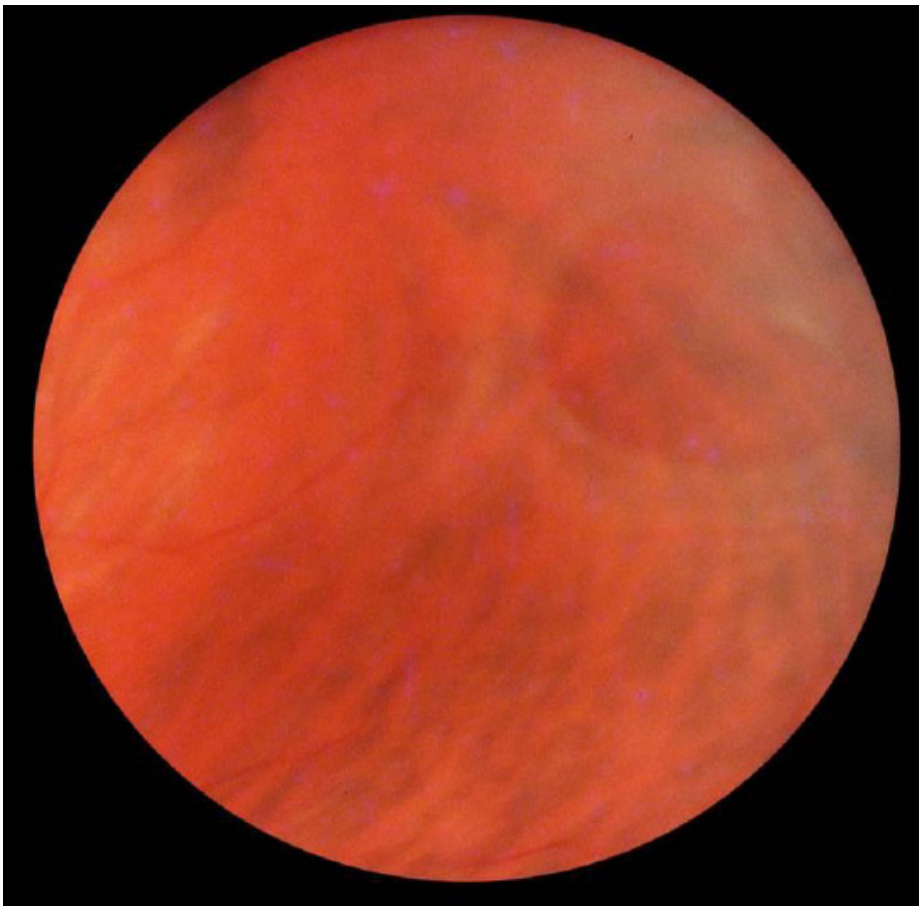

Fig. (6). Round atrophic hole with elevated edges (Courtesy of Jorge Bar MD, Argentina).

Retinal Holes

They are round retinal holes with a free operculum in the vitreous (Fig. **5**).

Round Atrophic Holes (Fig. 6)

Histopathology shows atrophy of the inner layers of the retina. They usually have no traction and rarely develop retinal detachment [2].

Retinal Dyalisis

They represent lineal ruptures along the ora serrata. They can be circumferential and are usually associated with blunt ocular trauma (Fig. **7**).

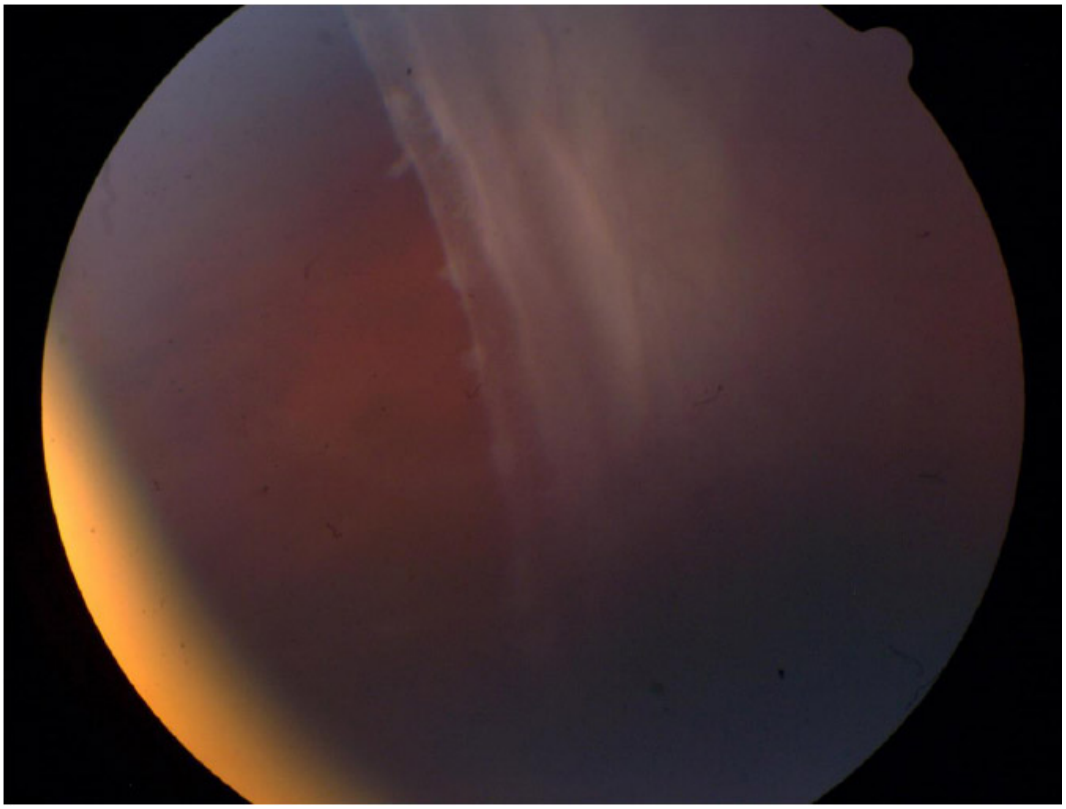

Fig. (7). Retinal dialysis (Courtesy of Mario Saravia MD, Argentina).

Giant Retinal Tears

They are lineal ruptures along the periphery of the retina, have an extension of more than one quadrant or 90 degrees, and are related to traction of the retina.

Lattice Degeneration

Lattice degeneration can be present in 6 to 10% of the normal population. It is bilateral in 4% of the cases and tends to be symmetrical when it is present in both eyes (It is more frequent in myopic eyes).

These are oval areas in the peripheral retina, showing white lines that continue with the retinal vessels. Histopathology shows fibrosis and thickening of the vessel wall. Pigmentary changes occur in 80% of the cases while round atrophic holes are present in 16 to 18% of cases. Vitreous liquefaction is common in the

center of the lesion, and pathological vitreous adhesion is a constant feature at the border of lattice degeneration. Traction in the area produces retinal tears that can be responsible for 20 to 30% of the cases of rhegmatogenous retinal detachment.

Asymptomatic retinal tears are associated with lattice degeneration in 1.5% of the cases.

Radial paravascular lattice degeneration has an atypical equatorial distribution along the retinal vessels and can be associated with some cases of hereditary retinal detachment. (Figs. **8 - 14**) [2 - 5].

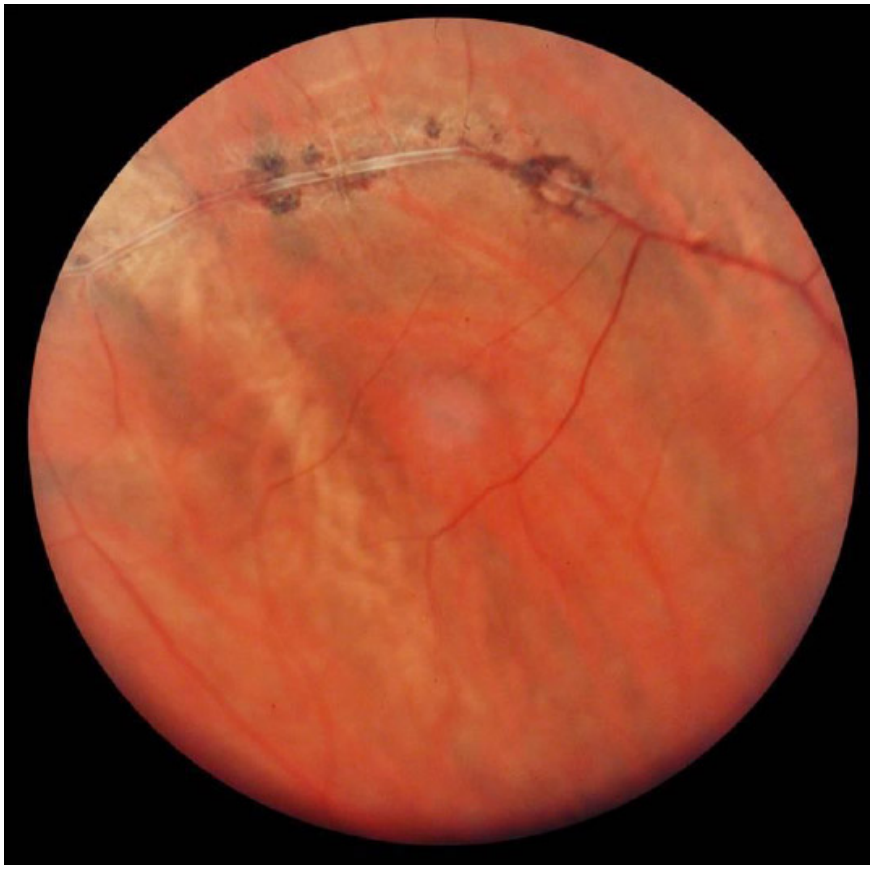

Fig. (8). Lattice degeneration, white lines and pigmentary lesions (Courtesy of Jorge Bar MD, Argentina).

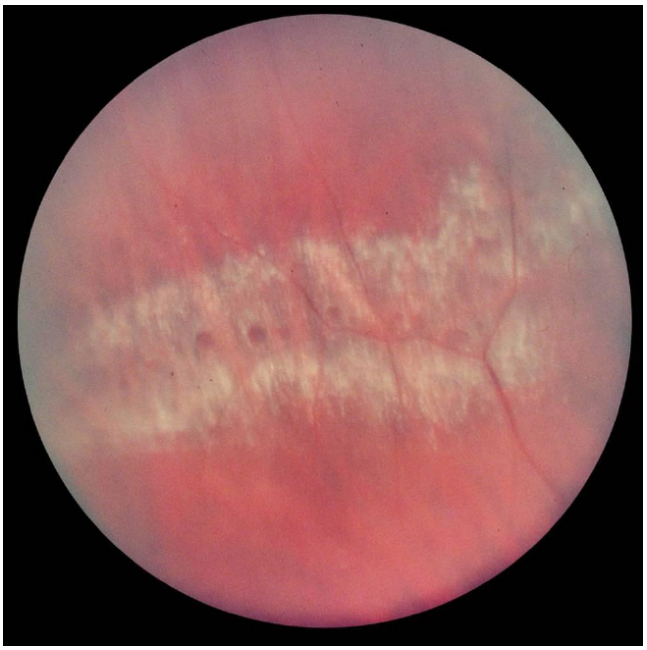

Fig. (9). Lattice degeneration with round atrophy holes (Courtesy of Jorge Bar MD, Argentina).

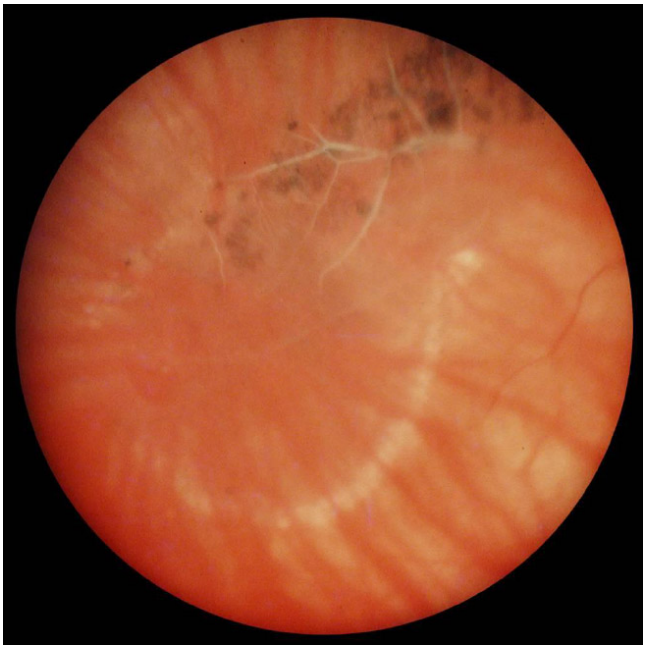

Fig. (10). Lattice degeneration, white lines and pigmentary lesions (Courtesy of Jorge Bar MD, Argentina).

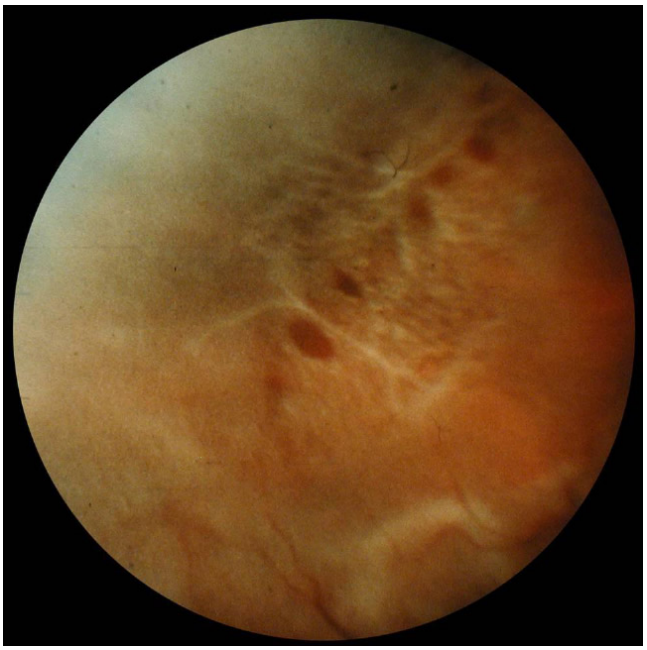

Fig. (11). Lattice degeneration with round atrophy holes (Courtesy of Jorge Bar MD, Argentina).

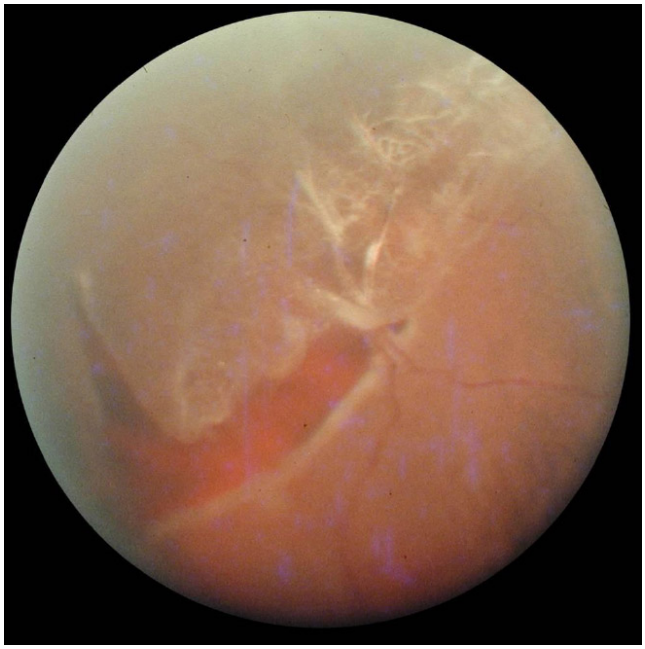

Fig. (12). Horseshoe tear and lattice degeneration (Courtesy of Diego Bar MD, Argentina).

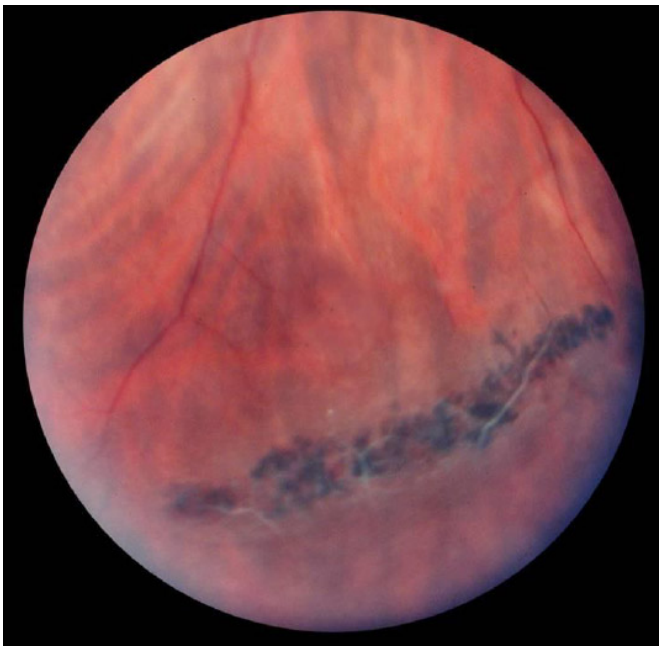

Fig. (13). Lattice degeneration (Courtesy of Jorge Bar MD, Argentina).

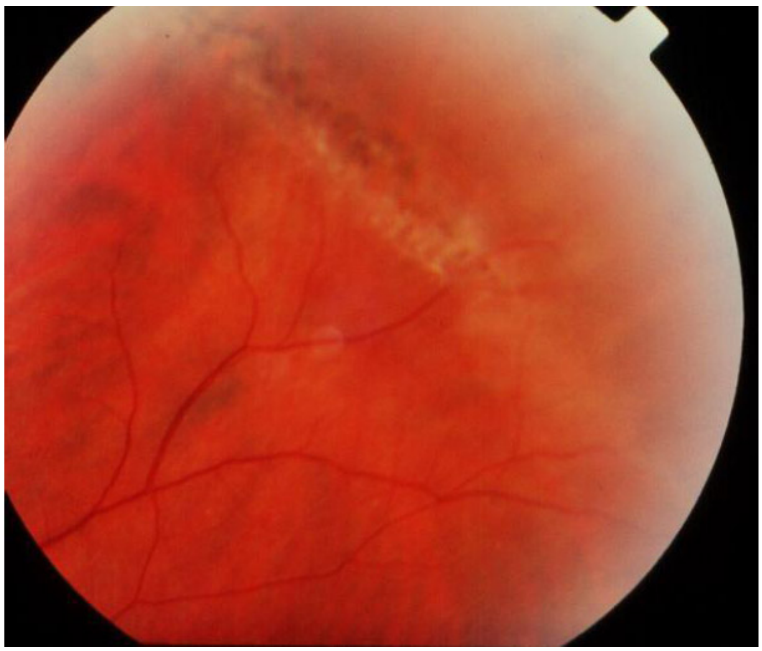

Fig. (14). Lattice degeneration.

Tufts

They are lesions of the peripheral retina that can be precursors of retinal tears. They are small elevations of the peripheral retina with traction. They can be non-cystic, cystic, or zonular tufts.

Non-cystic tufts are composed of glial tissue and abnormal retinal cells; they are not related with retinal tears.

Cystic tufts have a similar component but usually have visible vitreous traction, and they can develop retinal breaks, horseshoe tears or retinal holes with free operculum. Retinal detachment can be present in 10% of the cases.

Zonular traction tufts are anterior projections of the retina adherent to a zonular fiber; they are present at birth [2, 5].

Dentate Processes

They are anterior extensions of the retina in the ora serrata, usually located horizontal and nasally. Histopathology shows thinning of the retina and a firm adhesion to the pigment epithelium and can be associated with peripheral cystic degeneration [2].

Oral Bays

These represent posterior extensions of the pars plana on the retinal side of the ora serrata and can be associated with dentate processes. They can mimic the aspect of a retinal hole, but their color is brown instead of red and the surface of the lesion is granular. They can be present in 4% of the population. When they are associated with a retinal tear, a posterior vitreous detachment is present [2].

Meridional Folds

These are retinal folds localized at the border of the ora serrata. Radial folds are areas of thickened retina and can develop a retinal break due to vitreoretinal traction forces. They are included in the meridional complexes and can be present in 12 to 20% of cases. Their relation with the production of retinal tears is not clear [2].

Paving Stone Degeneration

It is characterized by peripheral areas of outer retinal atrophy that appear as whitish lesions, surrounded by a ring of hyperplasic RPE. In the interior of the lesions choroidal vessels can sometimes be observed. They are found in 20-30% of people older than 20 years old. This number climbs to 40% in patients older than 40 years old. It is bilateral in more than 90% of cases [3, 4].

They are sometimes unique or may appear in groups in a confluent disposition, more frequently in inferior quadrants and not related with retinal breaks or retinal detachment [2]. From the histopathological view they are characterized by the absence of choroicapillarys, loss of RPE and external layers of the retina, and strong adherence between the internal layers and Bruchs membrane [3, 4].

White with or without Pressure

When we look at the fundus with indirect ophtalmoscopy and scleral indentation, the retina is white at the area of indentation that contrasts with the adjacent retina which is redder. White without pressures refers to areas of peripheral retina that look white without scleral indentation. They are present in 15 to 30% of the cases and are not related with retinal tears or retinal detachment [2].

Cystic Degeneration

It is characterized by areas of microcysts in the extreme periphery, near the ora serrata. There are present in almost every adult of more than 20 years old and are bilateral in more than 97% of cases. They look like groups of very small, brilliant intrarretinal vesicles, that tend to coalesce, leaving some areas of intact retina.

Even if sometimes small holes can appear or the cysts may coalesce and a localized retinoschisis may develop, they don't represent a hazard and should not be treated [3, 4].

Retinoschisis

Histopathology shows the splitting of the retina in two layers. The external layer is related to the pigment epithelium, and the inner layer is in contact with the

vitreous body. It can have the appearance of a bulbous localized retinal detachment.

It is bilateral in 50 to 80% of the cases and usually located in the inferior and temporal quadrant.

The Typical Form has a thickened internal wall with an internal limiting membrane, retinal vessels, nerve fiber layer, and an inner plexiform layer. The external wall contains portions of the outer plexiform layer and external nuclear layer. At the edges of the retinoschisis, typical microcystic peripheral degeneration can be seen.

Reticular Retinoschisis is characterized by a more elevated internal wall and complete loss of the pillars between the cystic cavities within the retina [5].

Retinal holes can be observed in the inner wall. The reticular form can present retinal holes in the external wall in 16 to 23% of the cases.

Retinoschisis can be associated with retinal detachment in 2 to 6% of the cases [2, 5].

Retinal Pigment Epithelium Hyperplasia

It generally occurs within vitreous base in the ora serrata. The hyperplasic epithelium appears as a spicule that extends along the surface of the peripheral retina. They have been interpreted as the result of chronic vitreous traction. No treatment is needed for these lesions.

MANAGEMENT

According to the Preferred Practice Patterns of the American Academy of Ophthalmology [6], not all these lesions have to be treated with laser photocoagulation.

In acute symptomatic horseshoe tears, treatment is recommended promptly (Figs. **15, 16**).

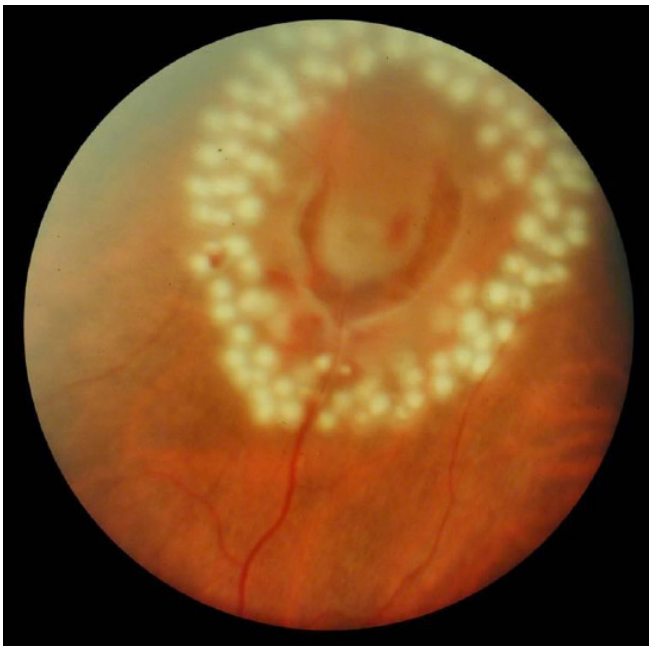

Fig. (15). Horseshoe tear, laser photocoagulation (Courtesy of Jorge Bar MD, Argentina).

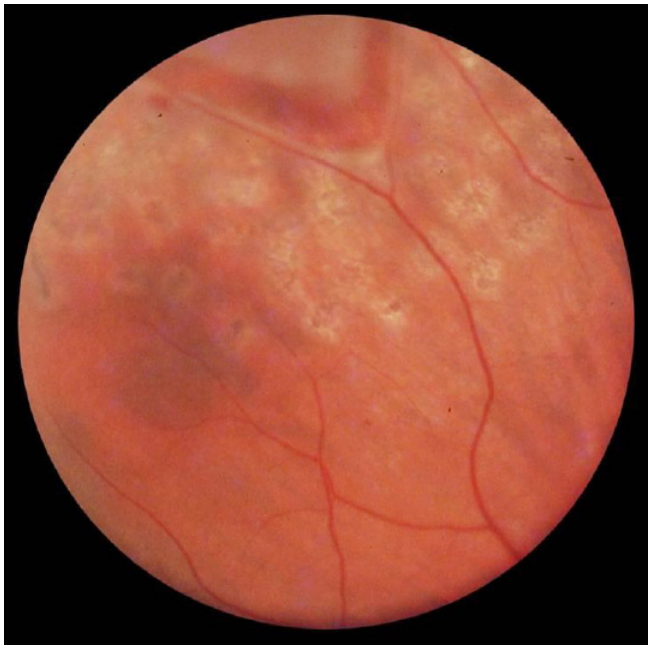

Fig. (16). Retinal tear, laser photocoagulation (Courtesy of Jorge Bar MD, Argentina).

- In acute symptomatic operculated tears, treatment may not be necessary.
- Acute symptomatic dialyses and traumatic retinal breaks are usually treated.
- Asymptomatic horseshoe tears (without subclinical RD) often can be followed without treatment.
- In asymptomatic operculated tears, laser treatment is rarely recommended.
- Asymptomatic atrophic round holes should not be treated.
- Asymptomatic lattice degeneration without holes need does not need to be treated unless posterior vitreous detachment causes a horseshoe tear.
- Asymptomatic lattice degeneration with holes usually does not require treatment.
- There is no consensus in treating asymptomatic dialysis.
- For eyes with atrophic holes, lattice degeneration, or symptomatic horseshoe tears where the fellow eye has had a retinal detachment, there is no consensus on treatment and insufficient evidence to guide management.
- There is insufficient evidence to recommend prophylaxis of asymptomatic retinal breaks for patients undergoing cataract surgery [3].

CONFLICT OF INTEREST

The authors confirm that they have no conflict of interest to declare for this publication.

ACKNOWLEDGEMENTS

Declared none.

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CHAPTER 12

Rhegmatogenous Retinal Detachment

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Rhegmatogenous retinal detachment (RRD) is defined as the separation of the neurosensory retina from the retinal pigment epithelium (RPE), secondary to passage of liquefied vitreous through one or more retinal breaks. These breaks usually originate either from vitreoretinal traction [1] or retinal atrophy [2], and when the amount of fluid entering the subretinal space through these breaks exceeds the amount that can be absorbed by the RPE, the retina becomes detached. It has an estimated incidence in the general population of 1 in 10,000, but the risk is increased in eyes with high myopia (over 6 diopters) or previous cataract surgery [2, 3].

ESSENTIALS OF DIAGNOSIS

Patients usually complain of vitreous floaters (which may correspond to vitreous hemorrhage secondary to a ruptured retinal blood vessel, or vitreous condensations that accompany posterior vitreous detachment) (Fig. **1**), photopsia (due to vitreoretinal traction) and/or a peripheral scotoma (when the retina is detaching).

Diagnosis of RRD is most of the time performed at the clinic. Clinical examination in early stages may reveal predisposing lesions in the periphery, which may take different shapes, such as lattice degeneration (Figs. **2** and **3**) [4], operculated hole (Figs. **3 - 5**) or a horseshoe retinal tear (Fig. **6**). In later stages

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localized subretinal fluid may be observed, which continues to extend and affect wider areas of the retina, which may take different configurations depending on the size and location of the lesion (Figs. **7 - 9**) [5]. Vitreous cells may be observed, either pigment cells know as "tobacco dust" or erythrocytes. If large areas of the retina are detached, the eye may become hypotonous. Chronic retinal detachments might be accompanied by proliferative vitreoretinopathy (Fig. **10**) or pigmentation demarcating the detachment area (Fig. **11**).

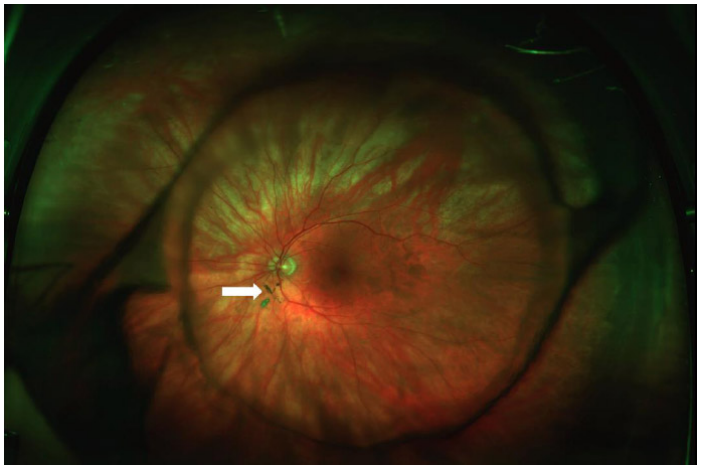

Fig. (1). Ultrawide field fundus photograph of the left eye through an intraocular lens, showing vitreous floaters (arrow).

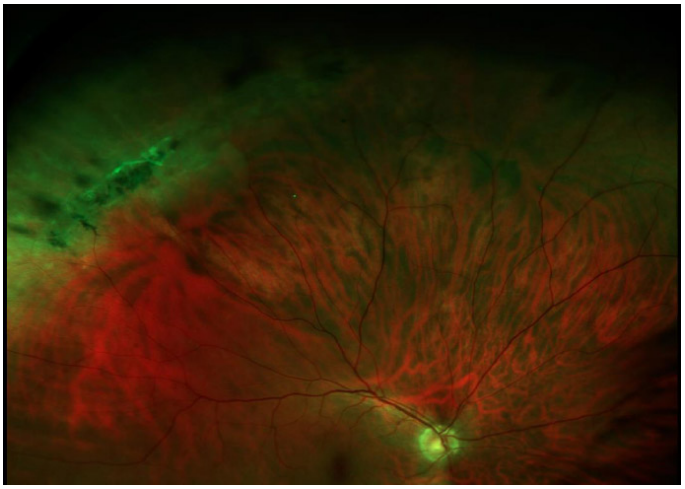

Fig. (2). Ultrawide field fundus photograph of the right eye showing lattice degeneration in the superotemporal periphery.

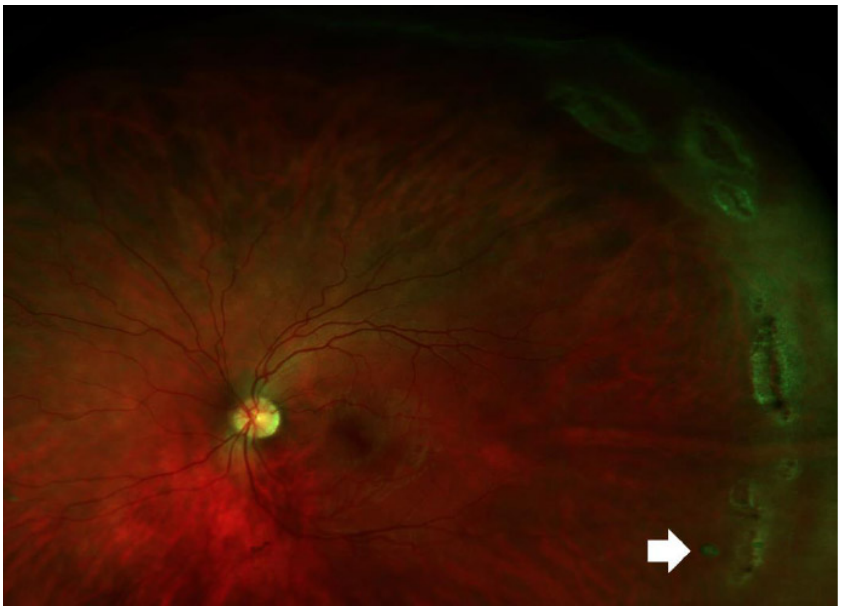

Fig. (3). Ultrawide field fundus photograph of a left eye, showing lattice degeneration in the temporal periphery, and a retinal hole with an associated operculum (arrow).

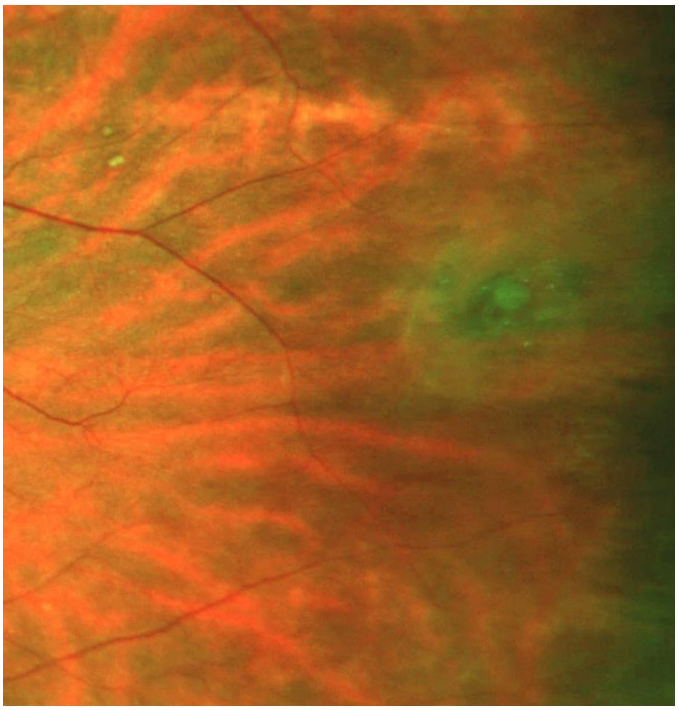

Fig. (4). Operculated retinal hole, with scarce subretinal fluid.

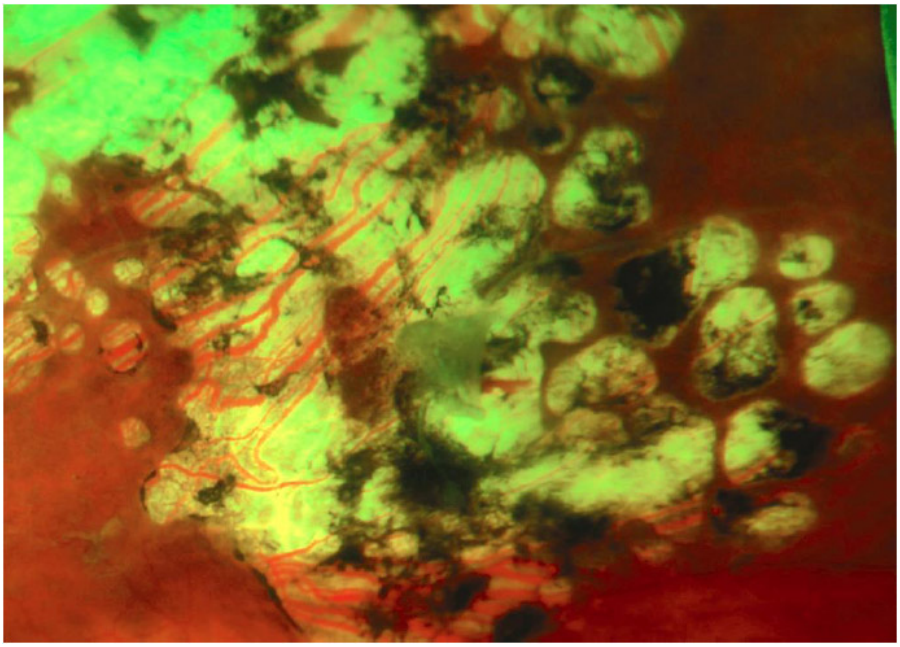

Fig. (5). Operculated retinal hole surrounded by laser photocoagulation scars.

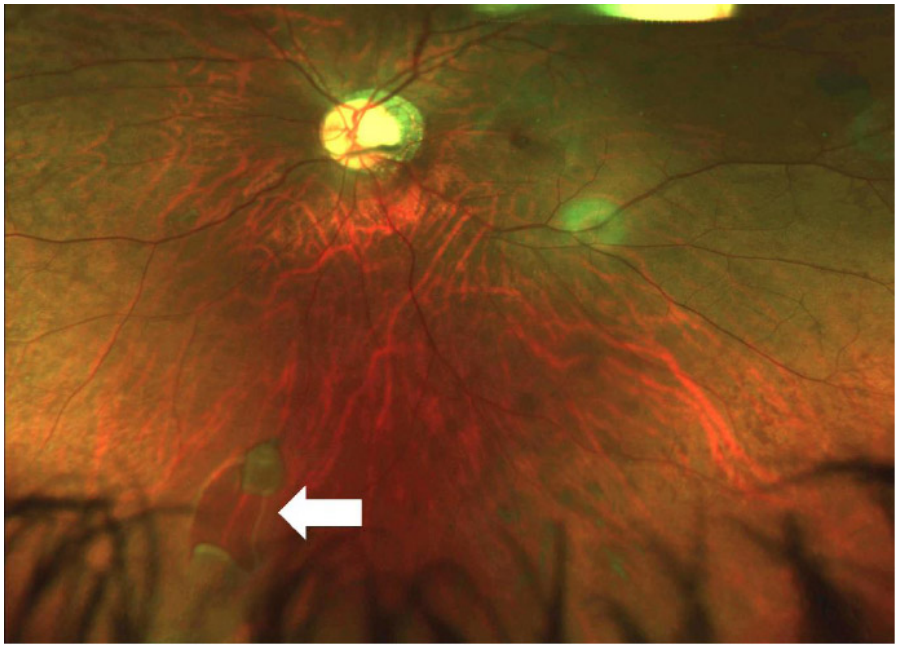

Fig. (6). Ultrawide field fundus photograph of a left eye, showing an inferonasal retinal tear (arrow).

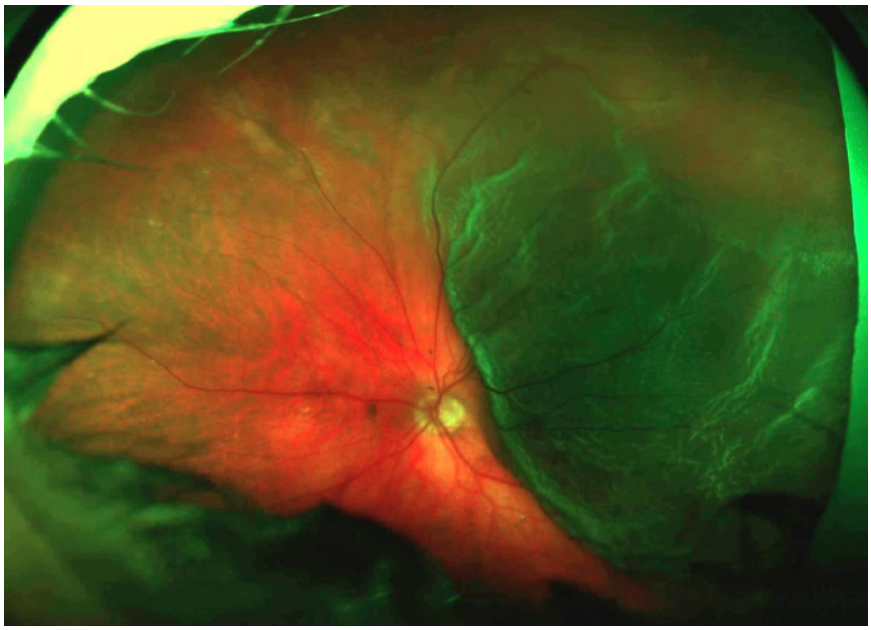

Fig. (7). Ultrawide field fundus photograph of a left eye, which shows a superotemporal retinal detachment. The causative lesion is not visible in the photograph, but should be looked for near the most superior part of the detachment.

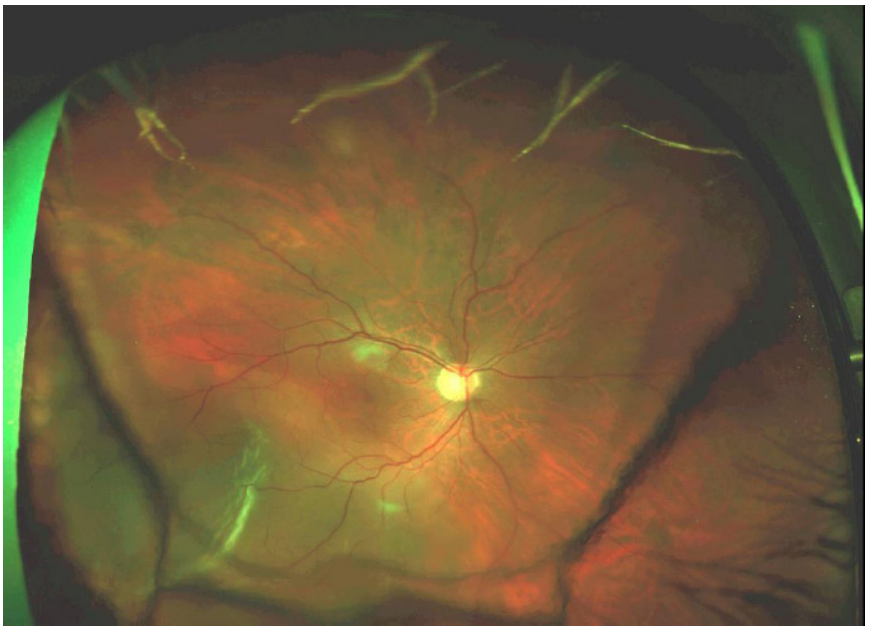

Fig. (8). Ultrawide field fundus photograph of the right eye, showing an inferotemporal retinal detachment.

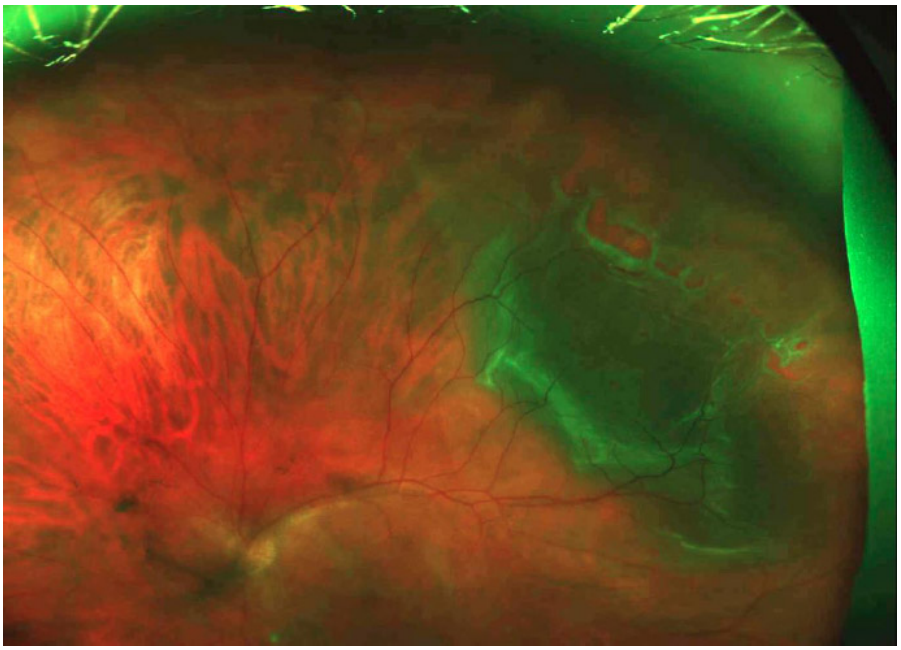

Fig. (9). Ultrawide field fundus photograph of the left eye, displaying a superotemporal retinal detachment, with several retinal tears.

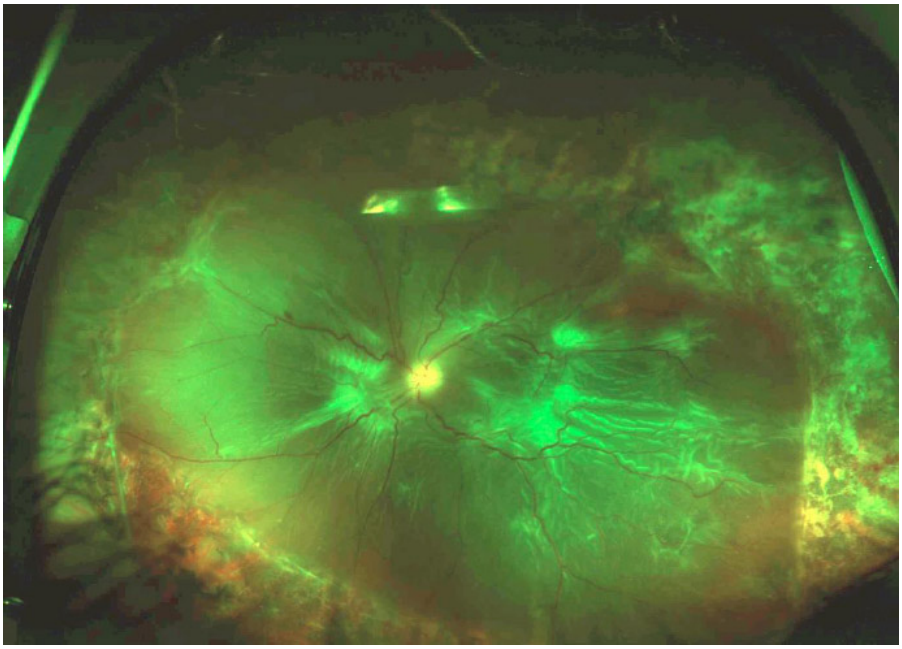

Fig. (10). Total retinal detachment with grade C proliferative vitreoretinopathy.

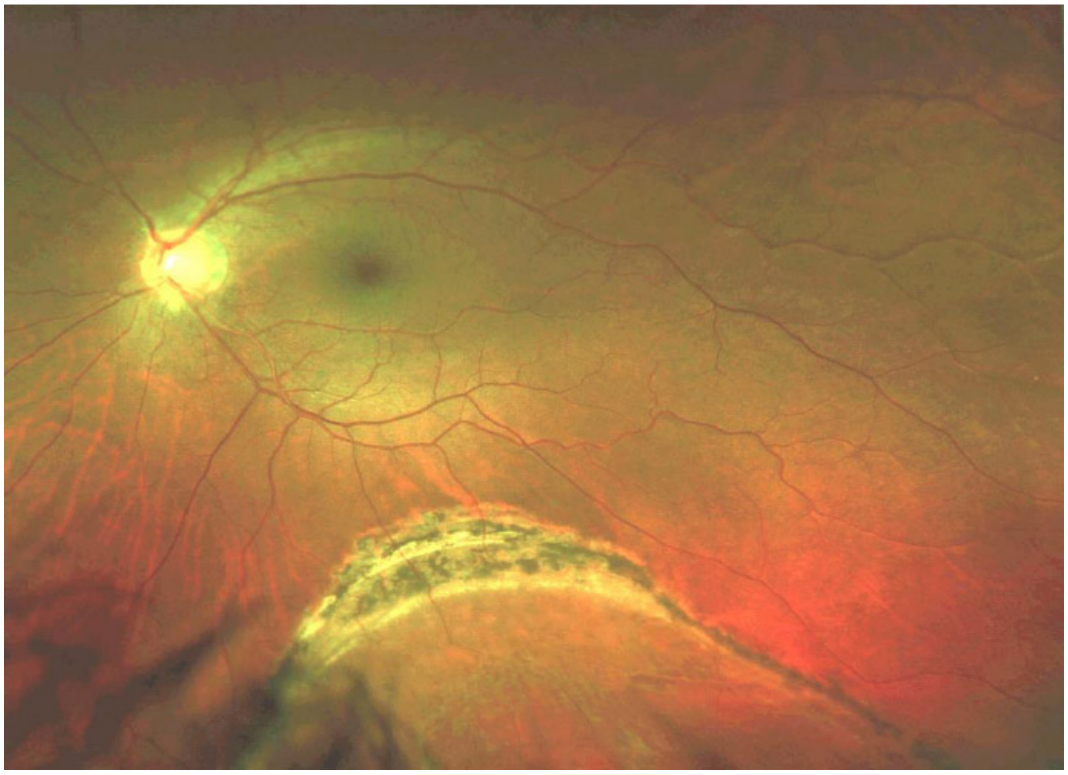

Fig. (11). Inferior self-limited retinal detachment, showing a hyperpigmented demarcation line.

B-scan ultrasound (Fig. **20**) is useful when the vitreous precludes adequate view of the retina, especially in the presence of a dense vitreous hemorrhage or cataract.

DIFFERENTIAL DIAGNOSIS

Differential diagnosis should be made with serous or tractional retinal detachment. Distinction is particularly important in the case of serous detachment, since most of the times the management in these cases is medical, while the management of tractional and rhegmatogenous detachments is surgical.

Serous detachment can have a wide array of causes, ranging from Coats' disease, Vogt-Koyanagi-Harada disease, choroidal hemangioma, choroidal neovascularization, *etc*. Most of the times other clues for the diagnosis (*e.g.* the tumor or neovascularization) are readily seen during clinical examination. In other

cases, a fluorescein or indocyanine green angiography, or a B-scan ultrasound might be needed to clarify the diagnosis.

MANAGEMENT

The management of RRD and its predisposing lesions is surgical.

Retinal holes and tears (especially if they are horseshoe tears) should be treated with laser photocoagulation surrounding the lesion (Fig. **12**) [5]. If a discrete amount of subretinal fluid is present, it should be included within the photocoagulation area [6, 7].

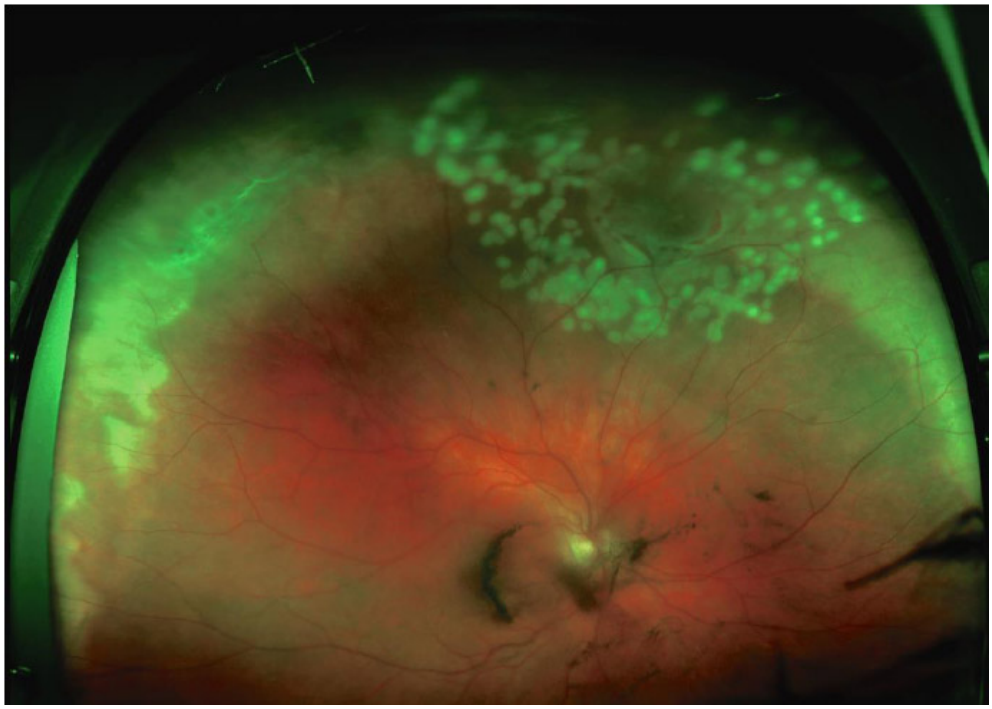

Fig. (12). Ultrawide field fundus photograph of a right eye with a superonasal retinal tear surrounded by laser photocoagulation burns. A superotemporal lattice degeneration can be observed.

Detachments that are in the far periphery may be "walled off" with photocoagulation, providing that the detachment area is not anterior to the equator (Figs. **13** and **14**). Care must be taken to insure that photocoagulation extends to the ora serrata, to adequately confine the detachment area.

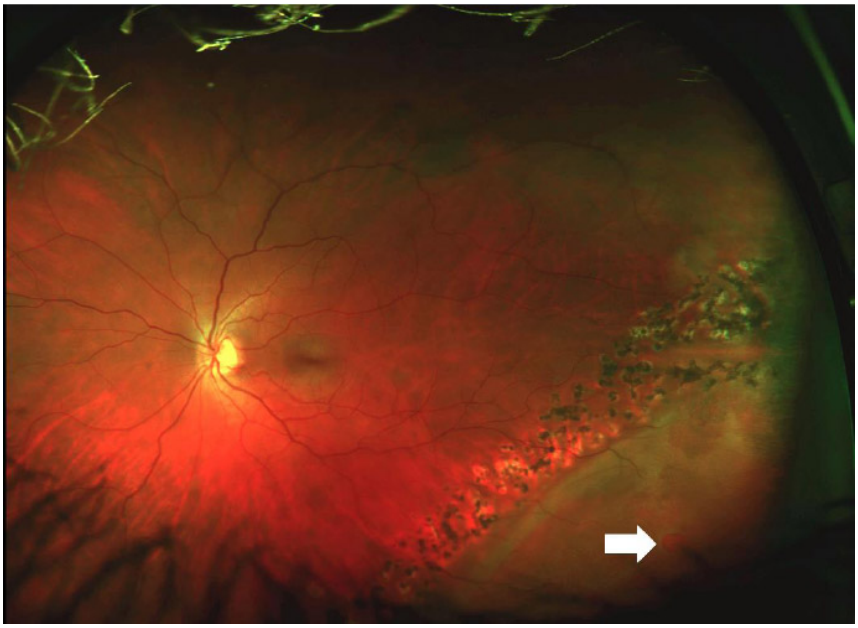

Fig. (13). Ultrawide field fundus photograph of a left eye, displaying an inferotemporal retinal detachment that has been walled off by laser photocoagulation scars. A round hole can be observed (arrow).

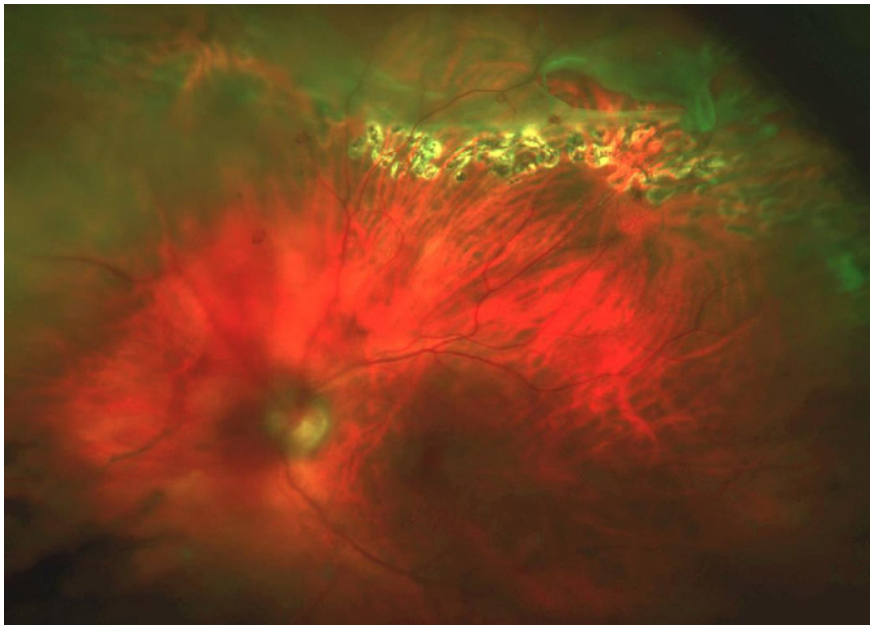

Fig. (14). Ultrawide field fundus photograph of a left eye, showing a superior retinal detachment with a visible retinal tear, walled off by laser photocoagulation scars.

Detachments that are larger than the ones described above may be treated in different fashions. The common objectives of the different treatments are to block the retinal hole using a tamponade agent, promote subretinal fluid reabsorption, and create an adhesion of the neurosensory retina to the RPE by means of laser photocoagulation or cryotherapy. The available techniques are the following [6 - 8]:

Pneumatic Retinopexy, which involves injecting 0.2-0.4 cc of gas (either sulphur hexafluoride SF_6, perfluoroethane C_2F_6, or perfluoropropane C_3F_8) in the vitreous cavity (Fig. **15**). The bubble is injected in an expansible concentration, and the head of the patient is positioned in order for the bubble to block the retinal tear. When the retina has reattached, cryotherapy or laser photocoagulation is applied surrounding the retinal tear. It has the advantage of being an office-based procedure, but the success rate is lower compared to other procedures.

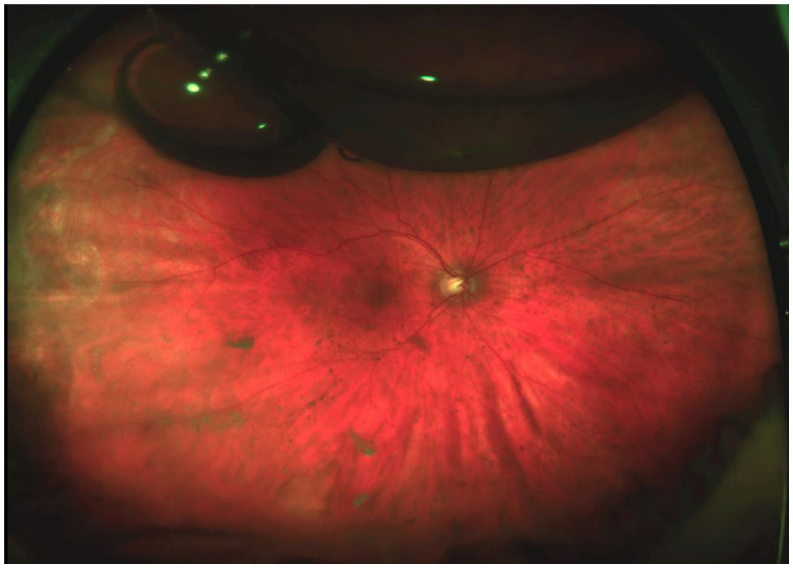

Fig. (15). Ultrawide field fundus photograph of an eye that underwent pneumatic retinopexy, showing two gas bubbles in the superior vitreous cavity. The retina has already attached.

Scleral Buckling, which involves placing an implant (usually made of silicone) that causes indentation in the sclera, thus approaching the RPE to the retinal tear, blocking passage of fluid to the subretinal space (Fig. **16**). During the procedure, cryotherapy or laser photocoagulation is applied surrounding the tear.

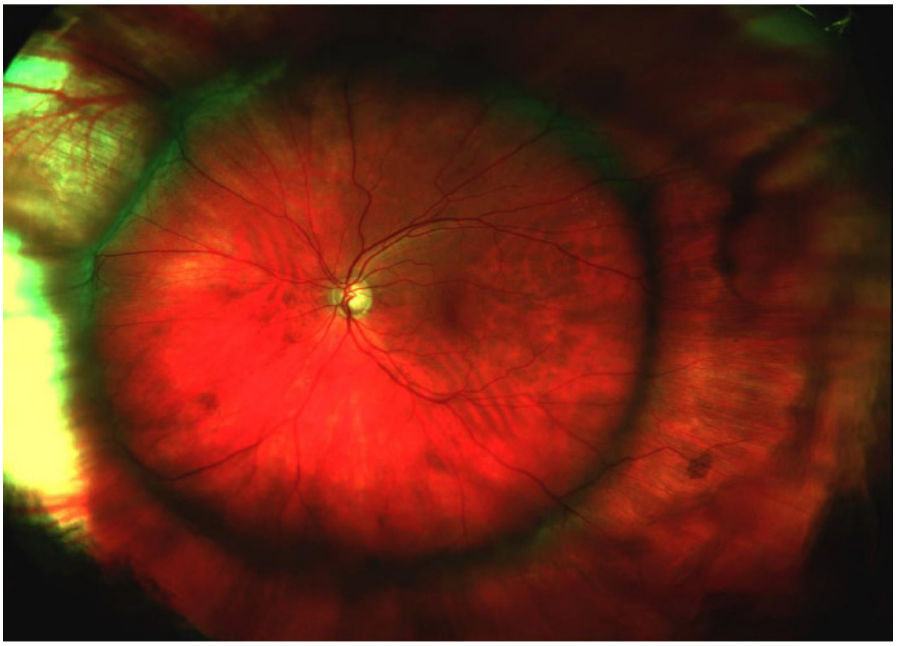

Fig. (16). Ultrawide field fundus photograph of an eye that underwent scleral buckle, showing broad indentation of the equatorial retina.

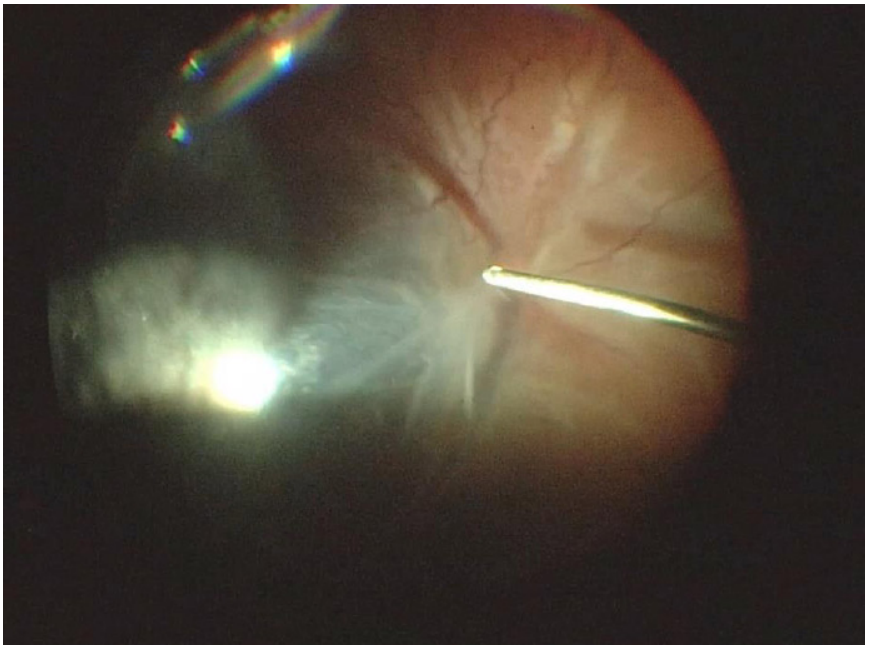

Fig. (17). Intraoperative view of a pars-plana vitrectomy in an eye with rhegmatogenous retinal detachment.

Pars Plana Vitrectomy, consists of extracting the vitreous using a cut-suction probe (Fig. **17**), draining the subretinal fluid while filling the vitreous cavity with air, applying laser photocoagulation surrounding the tear (Fig. **18**), and leaving gas (SF_6, C_2F_6 or C_3F_8) or silicone oil as a tamponade agent (Fig. **19**).

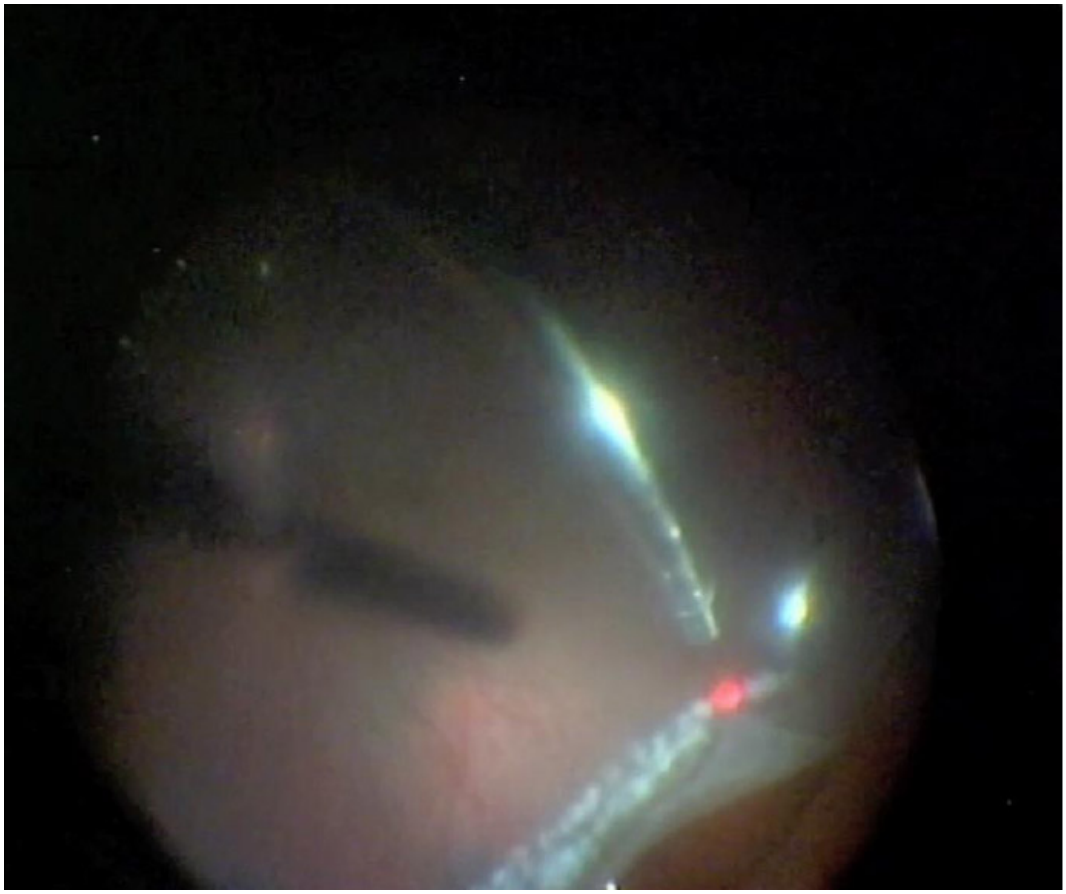

Fig. (18). Intraoperative view of laser endophotocoagulation surrounding a retinal tear.

A combination of scleral buckling and pars-plana vitrectomy, usually performed on more complicated cases.

Visual prognosis, regardless of the procedure performed, depends on whether the macula becomes affected and on the duration of the detachment. Prompt surgical repair in uncomplicated detachments yields success rates superior to 95% with a single procedure [7, 8].

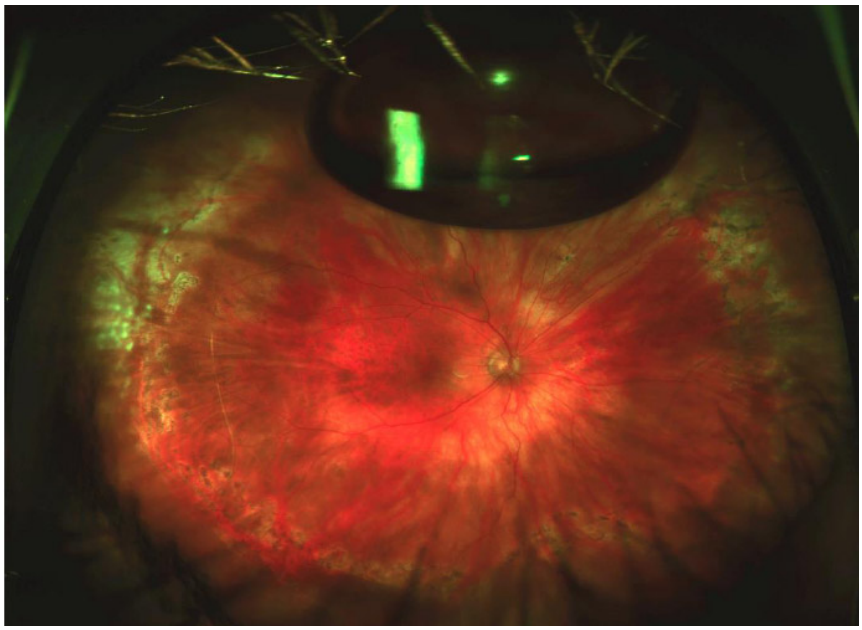

Fig. (19). Ultrawide field fundus photograph of an eye that underwent a pars plana vitrectomy for rhegmatogenous retinal detachment. Some remaining gas is observed in the superior vitreous cavity. Laser photocoagulation scars are observed in the retinal periphery.

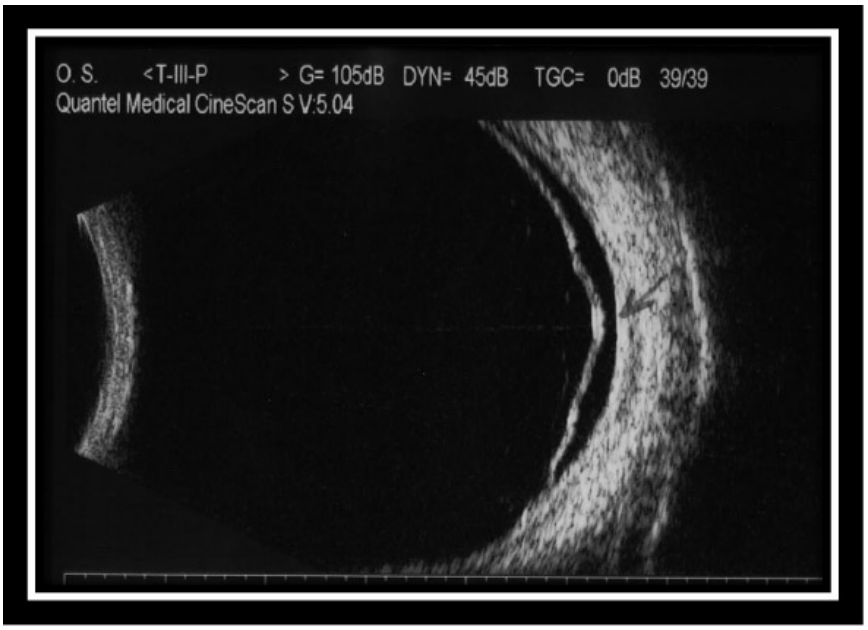

Fig. (20). B-scan ocular ultrasound of retinal detachment (Courtesy of Mitzy Torres Soriano MD).

CONFLICT OF INTEREST

The authors confirm that they have no conflict of interest to declare for this publication.

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Declared none.

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CHAPTER 13

Proliferative Vitreoretinopathy

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The retinal tear occurs without having an anatomical support that enables autofill the solution of continuity. Therefore, the retinal tear gives rise to the repair process producing a cell growth of the retinal pigment epithelium, glia or other cell types [1]. These cell types migrate over the internal and external surface of the retina and the anterior segment of the vitreous producing membranes called proliferative vitreoretinopathy (PVR).

ESSENTIALS OF DIAGNOSIS

PVR is the most frequent cause for lack of repair of the retinal detachment (around 10%). The PVR is an amplified healing process. Today there are multiple lines of research to elucidate the process and improve outcomes techniques.

The contraction of these membranes produces fixed retinal folds, equatorial traction, non-pigmented retinal detachment of the pars plana, and widespread retinal contraction.

Although some treatments such as low molecular weight heparin, cytostatics, and corticosteroids are used aiming to reduce the impact of PVR, their results do not change the incidence rate. As a consequence, the causal retinal ruptures may re-open, triggering new ruptures or a tractional retinal detachment.

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The risk factors [2] are:

- Long time between the retinal detachment diagnosis and its surgical repair.
- Hemorrhage in the vitreous due to the rupture of retinal vessels.
- Giant tears.
- Multiple surgeries.
- Ocular damage mainly punctures.
- Young patients.
- Aphakia.
- Uveitis.
- Choroidal detachments.
- Excessive cryocoagulation.
- Postsurgical infection and inflammation.

PVR Classification

Grade A: Represents the presence of pigment in the vitreous space and on the surface of the retina (Fig. **1**).

Grade B: Fine folds on the surface of the retina. Proliferation in the vitreous tissue causes reduced retinal mobility in the vitreous cavity (Figs. **2** and **4**).

Grade C: Fixed retinal folds. They can be in the posterior or anterior segment, with an imaginary boundary in the equatorial part of the eyeball (PC – AC) (PC = posterior chamber; AC = anterior chamber) (Fig. **3**).

It is divided into 5 different degrees of contraction:

C1, Posterior focal star folds (Figs. **3a** and **5**).

C2, Posterior confluent irregular folds. Poor visualization of the optic disc (Figs. **3b** and **6**).

C3, Anterior and posterior subretinal annular strand close to the disc; linear strands with or without pigmentation; sheets with a moth-eaten appearance (Fig. **3c**).

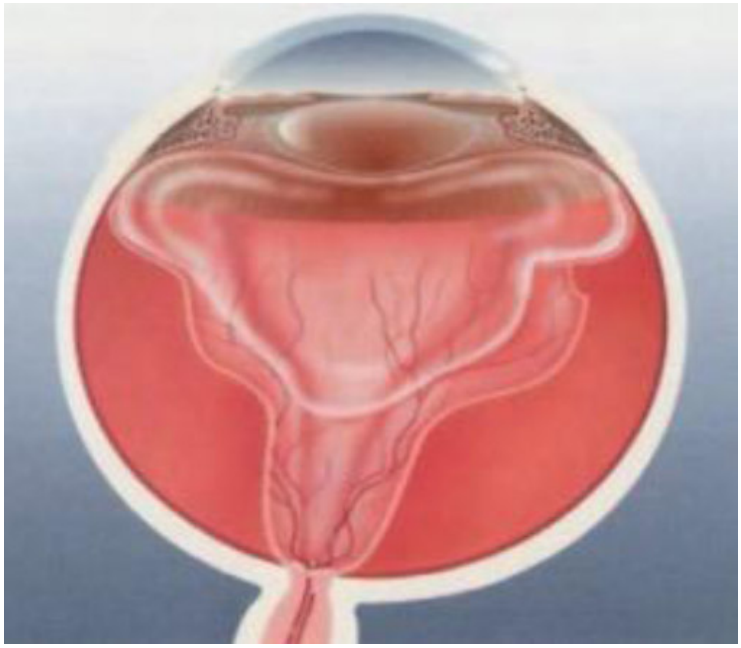

Fig. (1). PVR grade A.

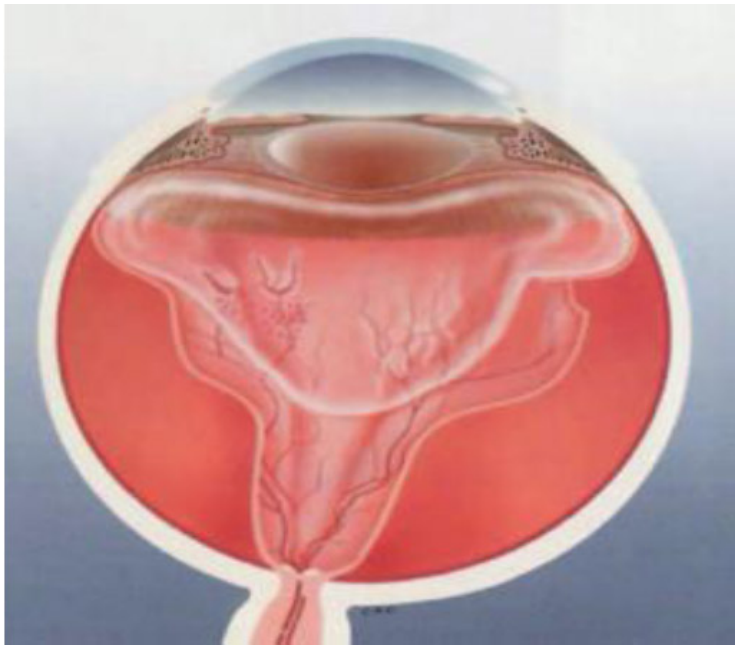

Fig. (2). PVR grade B.

C4, Anterior circumferential contraction along posterior margin of vitreous base with central displacement of the retina and stretching of the peripheral retina; posterior retina in radial folds (Fig. **3d**).

C5, Anterior displacement, anterior pull on the vitreous base; trough of varying width is present in the peripheral retina; ciliary processes may be stretched and covered by membranes; possible iris retraction [3] (Fig. **3e**).

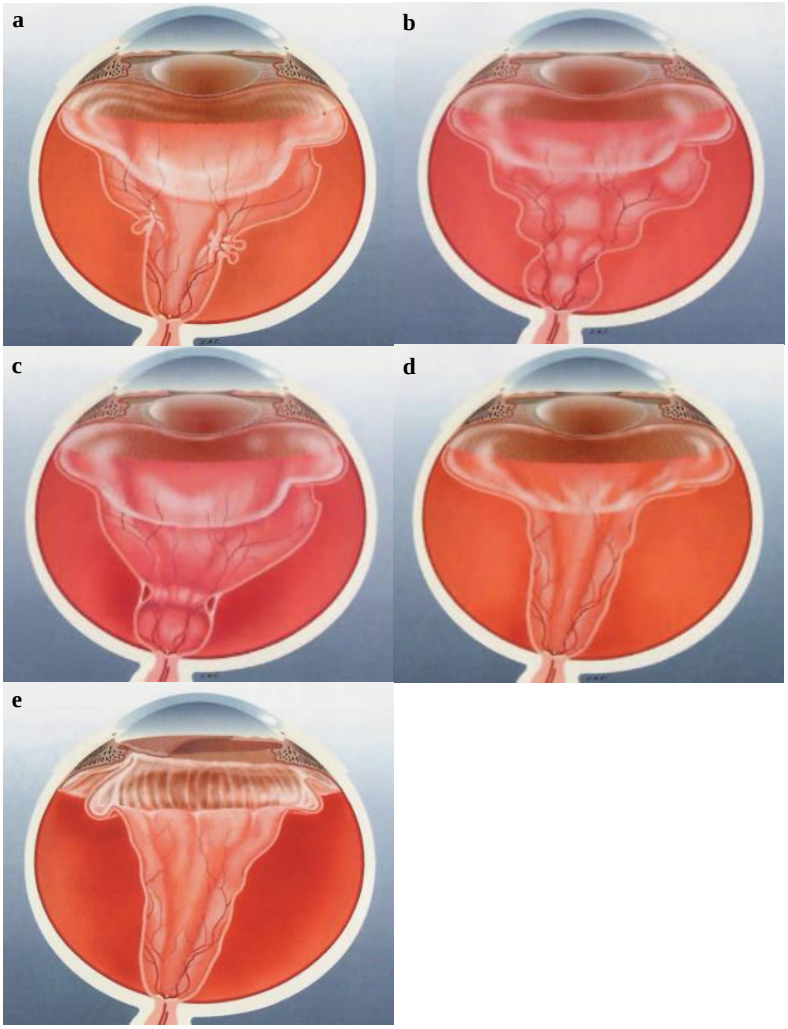

Fig. (3). PVR grade C.

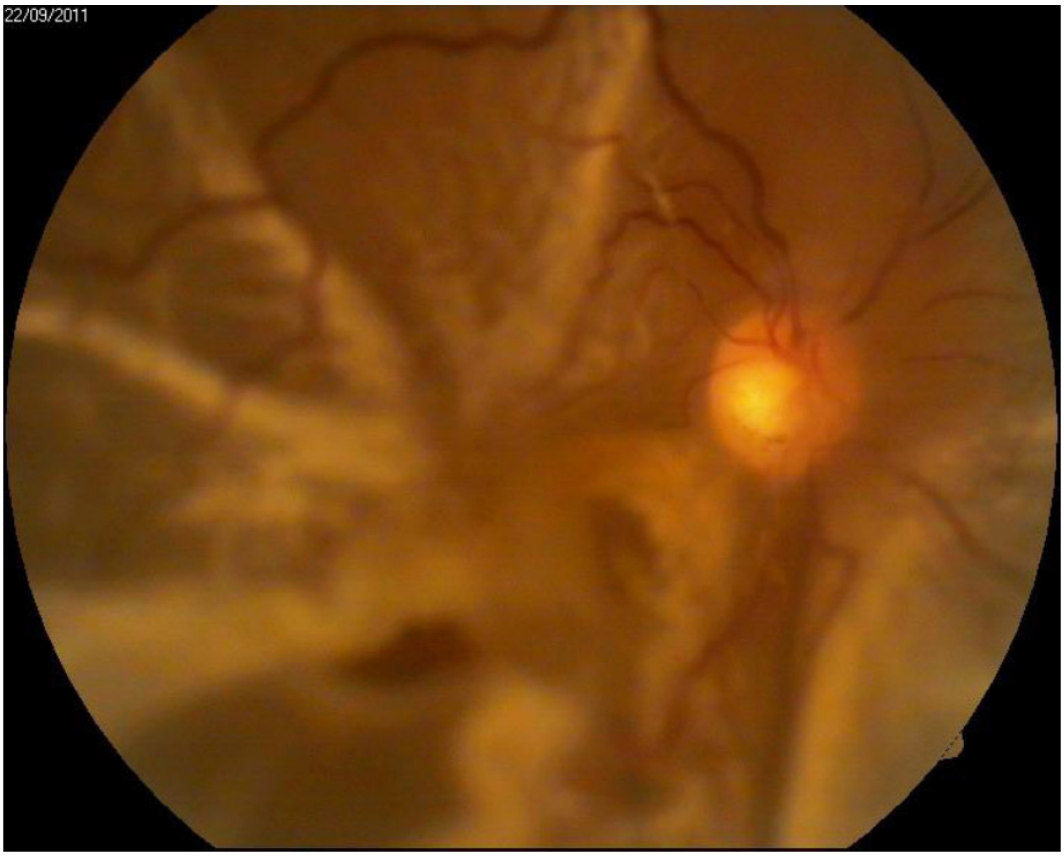

Fig. (4). Retinal detachment with PVR grade B (Courtesy of Retinal Camera of Hospital Central de Maracay, Maracay-Venezuela).

DIFFERENTIAL DIAGNOSIS

The main differential diagnosis is proliferative diabetic retinopathy with tractional retinal detachment. The main difference between the PVR and the diabetes membranes is that the former membranes are avascular while the latter are vascular.

MANAGEMENT

- Scleral surgery.
- Vitrectomy.
- Retinotomies and retinectomy [4].
- Epiretinal dissection [5].

- Perfluorocarbon helps to reposition the retina and extract the epiretinal membranes [6]. Currently, the best tamponade system is prolonged gas inside the eye [7].

In some cases, this treatment is insufficient and silicon oil must be used [8].

Pharmacological agents: 5-fluorouracil (5FU) and low-molecular-weight heparin (LMWH) have not shown consistent evidence to prevent PVR following retinal reattachment surgery and did not lead to a relevant increase of the success rate of vitreoretinal surgery in patients with established PVR [9 - 11].

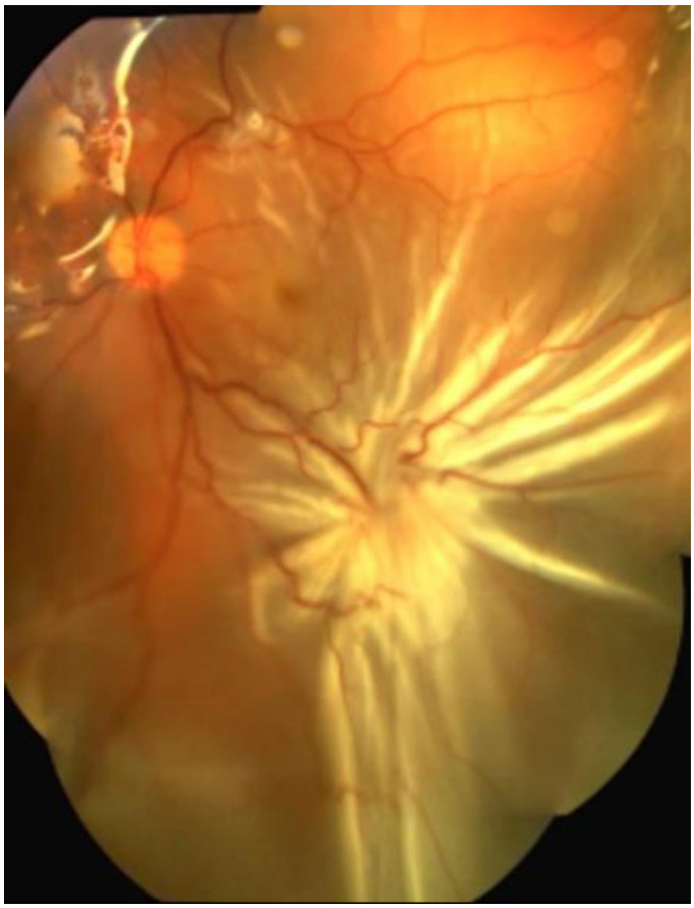

Fig. (5). Proliferative Vitreoretinopathy grade C1 (This image was originally published in the ASRS Retina Image Bank. Thomas A. Ciulla, MD MBA. Starfold in Proliferative Vitreoretinopathy. Retina Image Bank. 2014; Image Number 19588. © the American Society of Retina Specialists).

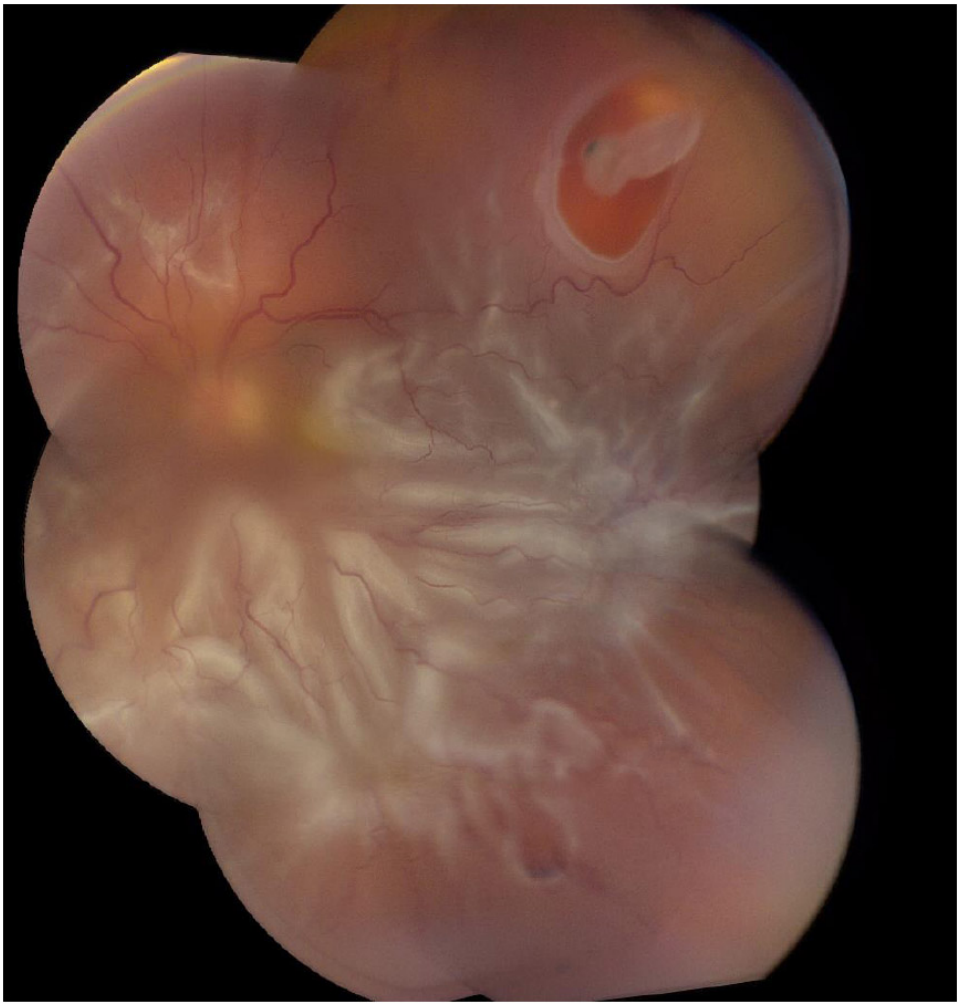

Fig. (6). 63-year-old pseudophakic male with hand motion vision in the left eye due to a total retinal detachment with severe proliferative vitreoretinopathy (This image was originally published in the ASRS Retina Image Bank. Darin R. Golman, MD. Total Rhegmatogenous Retinal Detachment with Severe PVR. Retina Image Bank. 2014; Image Number 25035. © the American Society of Retina Specialists).

CONFLICT OF INTEREST

The authors confirm that they have no conflict of interest to declare for this publication.

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Declared none.

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CHAPTER 14

Retinopathy of Prematurity

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Retinopathy of prematurity (ROP) is a vasoproliferative disorder of the developing retina. It is one of the main causes of childhood blindness in developing countries [1]. Although prematurity and low birth weight are the greatest risk factors for developing ROP, there are a multitude of factors that have been implicated in the disease progression.

ESSENTIALS OF DIAGNOSIS

The International Classification of Retinopathy of Prematurity (ICROP) was developed to describe the early levels of severity of ROP based on zone, stage, extent of stage and presence of plus disease [1, 2].

The **zone** of ROP refers to I-III regions that describes the affected retinal area (Figs. **1 - 3**).

The **stage** of ROP defines the clinical appearance of the retina and the avascular area. There are 5 stages. In stage 1, a demarcation line is apparent (Fig. **4**). In stage 2, there is a prominent ridge and some vitreous traction (Fig. **5**). In stage 3 ROP, there is neovascularization growing onto the vitreous ridge (Fig. **6**). In stage 4, contraction of the fibrovascular proliferation causes traction on the retina leading to a partial retinal detachment, 4A without macular involvement and 4B with macular involvement (Fig. **7**). Stage 5 ROP is a total retinal detachment and is described as closed funnel when the retina is adherent to itself or open when

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it is not (Fig. **8**). There is an anterior displacement of iris-lens diaphragm because of the retinal detachment and contraction of anterior vitreous fibers [3 - 5] (Fig. **9**).

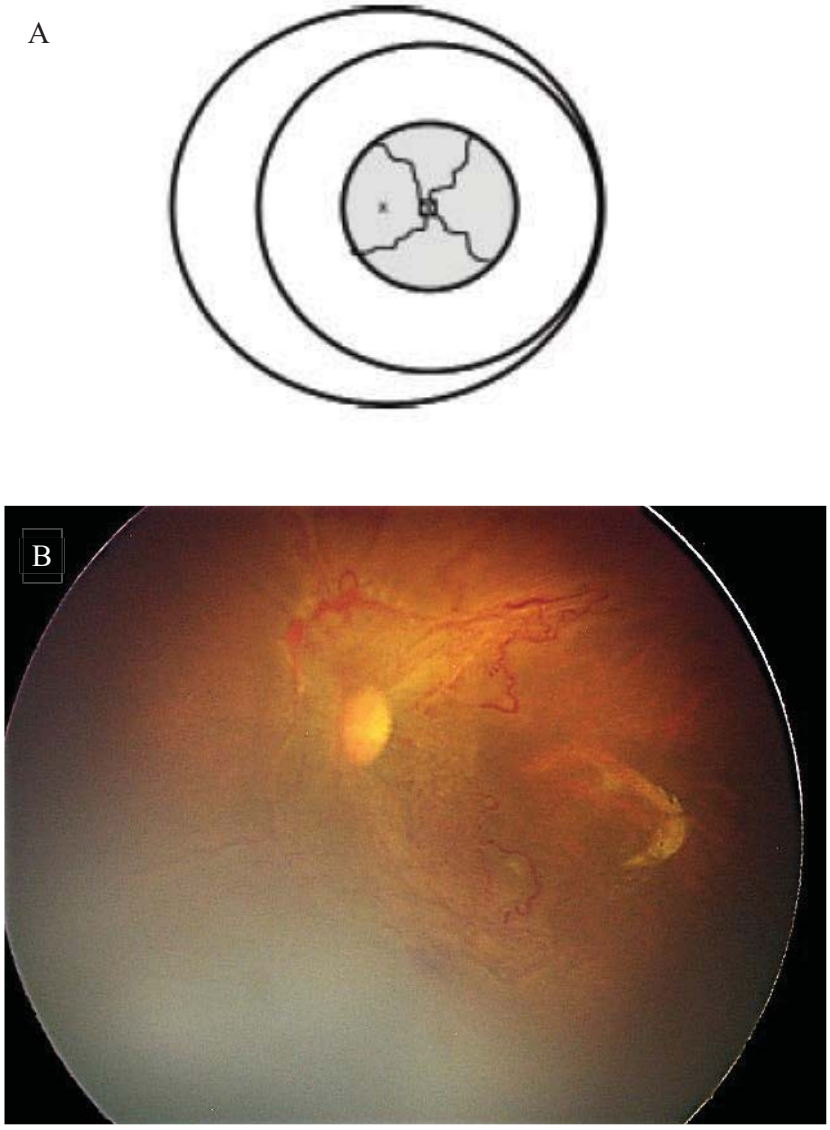

Fig. (1). (**A**). Diagram illustrating zone I, defined as a circle, the center of which is the disc, and the radius of which is twice the distance of the disc to the fovea. (**B**). Clinical photograph of a patient with zone I involvement.

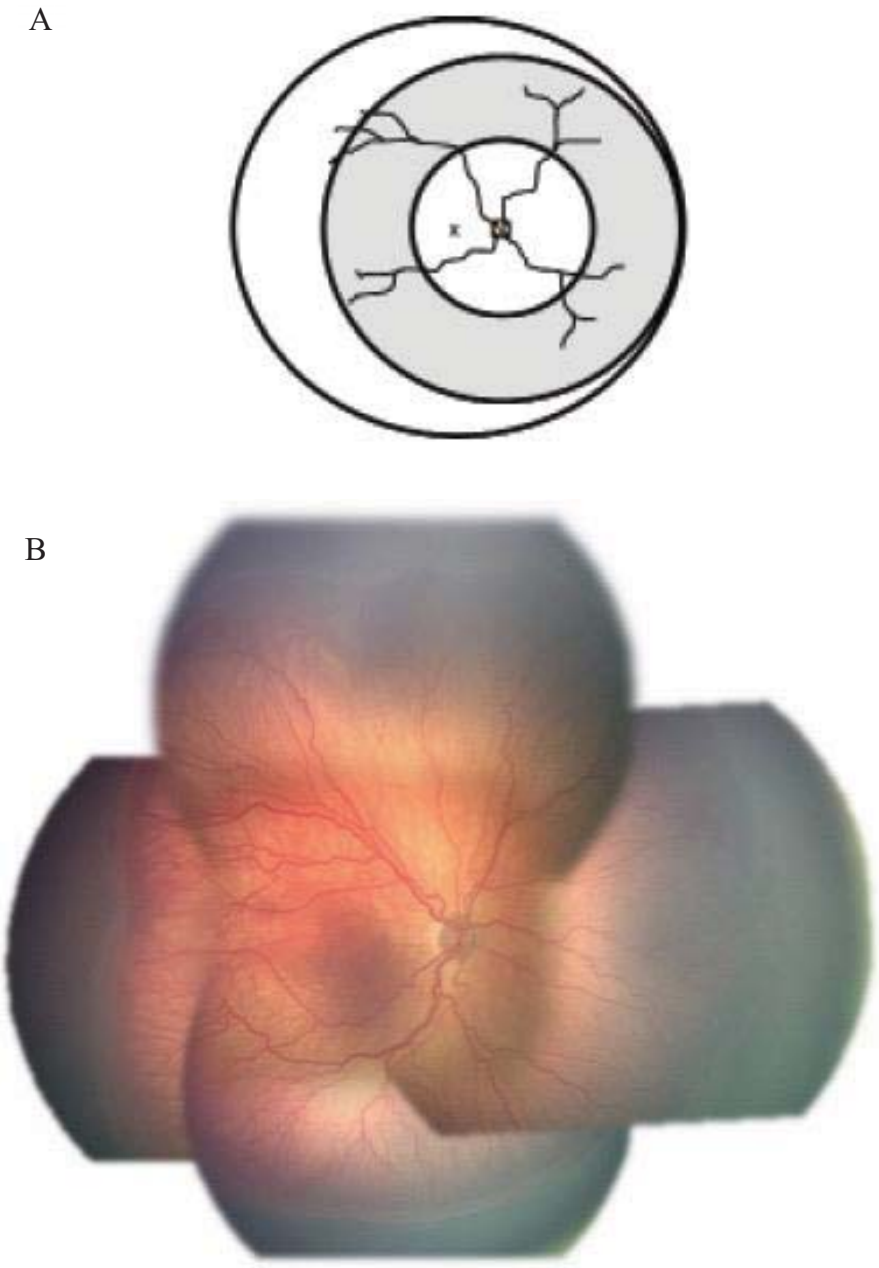

Fig. (2). (**A**). Diagram describing zone 2, which extends from the anterior border of zone I to within one disc-diameter of the ora serrata nasally and to the anatomic equator temporally. (**B**). Photograph composition of a patient that shows zone II involvement.

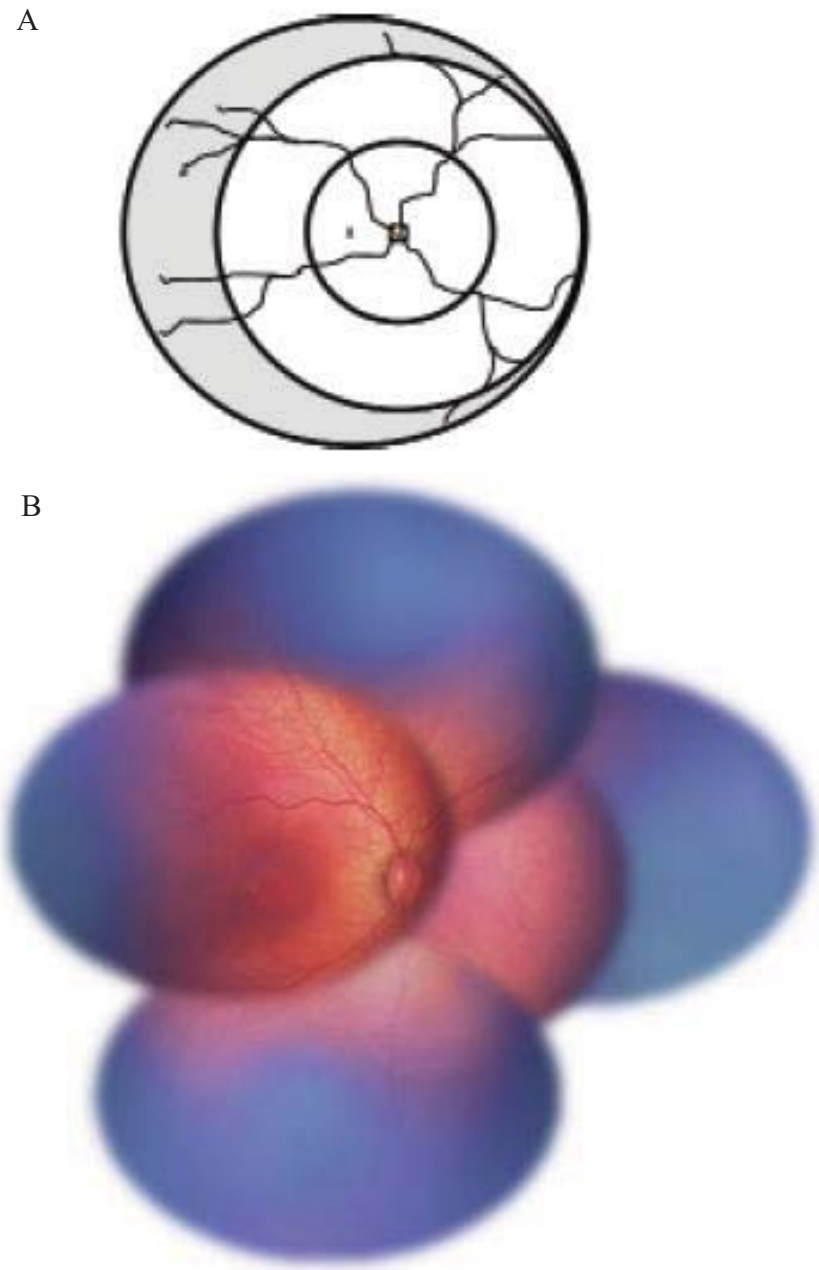

Fig. (3). (**A**). Diagram showing zone III, which encompasses the residual temporal retina. (**B**). Clinical composition that shows zone III involvement.

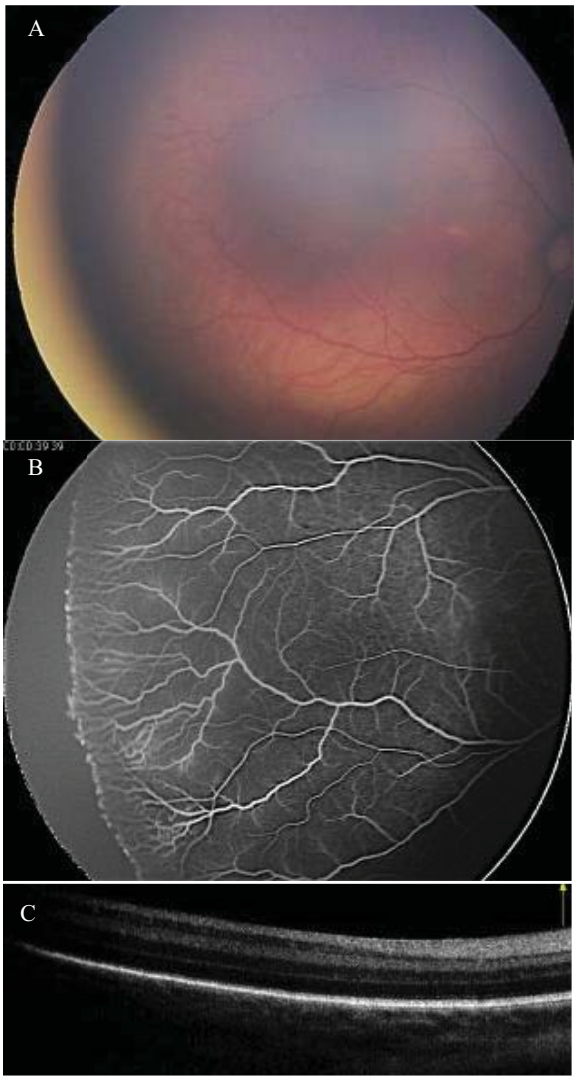

Fig. (4). (**A**). Clinical photo of a patient with stage 1 ROP; the arrows show the flat demarcation line. (**B**). Fluorangiography shows in the area that joins vascular and avascular retina some rounded hyperfluorescent images in the end of the vessels; these structures are the vascular "sprout" or the sac that will form a neovessel that will vascularize the avascular area. Next to the demarcation line in the vascularized area, the vessels have an abnormal dichotomizing pattern due to active vascular remodeling. This means that these vessels are immature; some will persist and some will disappear once the metabolic demands of the developing retina are reached. Immaturity of these vessels leads to a parietal leakage pattern; as the vessels are still under remodeling they are not fully covered by pericytes allowing leakage of fluorescein. (**C**). The SD-OCT image of the demarcation line shows a difference in the thickness of the internal layers of the retina and some degree of disorganization of the retinal layers.

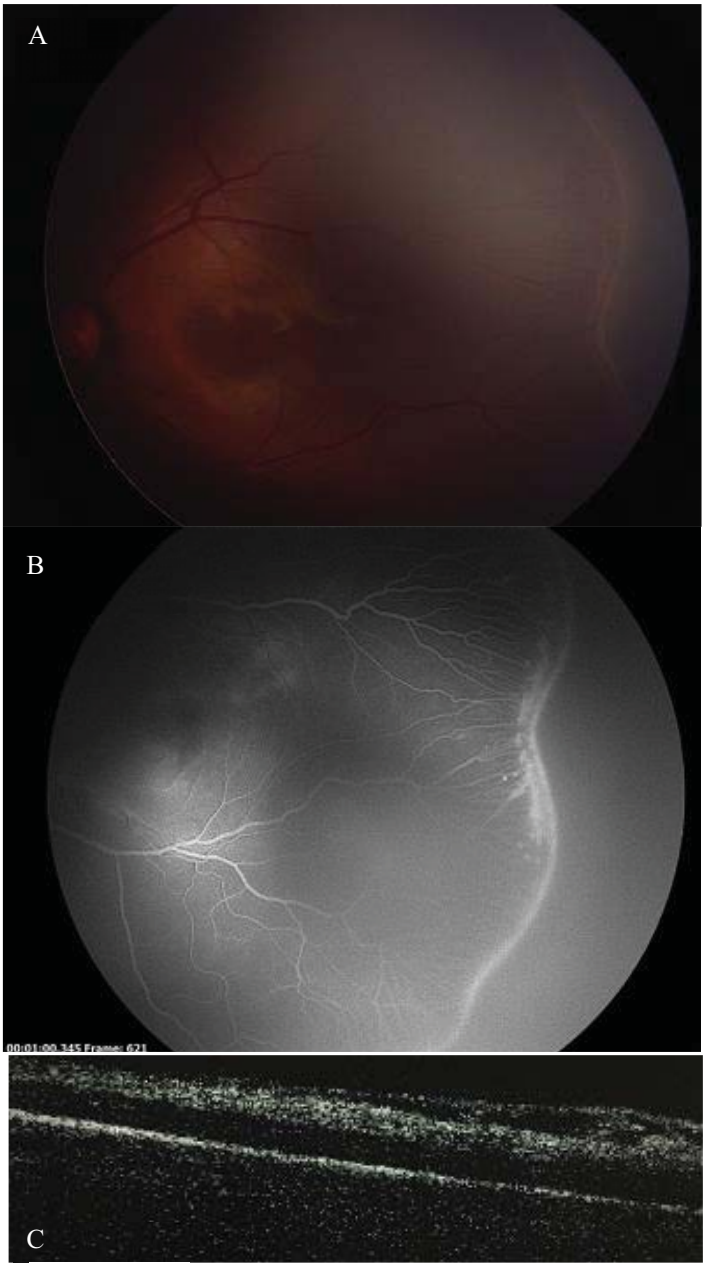

Fig. (5). (**A**). Clinical image of stage 2 zone II with an elevated ridge. (**B**). Hyperfluorescent demarcation line that does not leak even in late phases of the study. There are other structural changes such as arterio-venous joints, capillary unions, and irregular branching. (**C**). In the OCT performed on the demarcation line, there is a clear disorganization of the retina layers with retinoschisis-like pattern due to the traction of the vitreous.

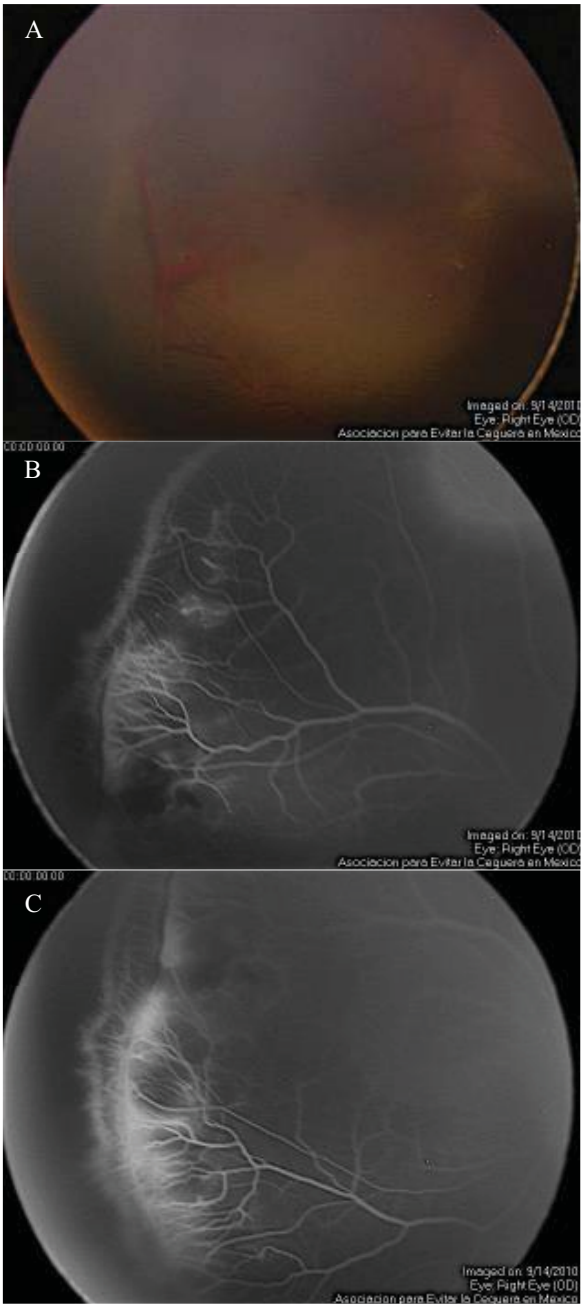

Fig. (6). (**A**). Color fundus photograph of stage 3 zone II with vitreous hemorrhage due to neovascularization on the ridge. (**B**). Fluorangiography showing leakage over the ridge. (**C**). Leakage increases in late phase of fluorangiography.

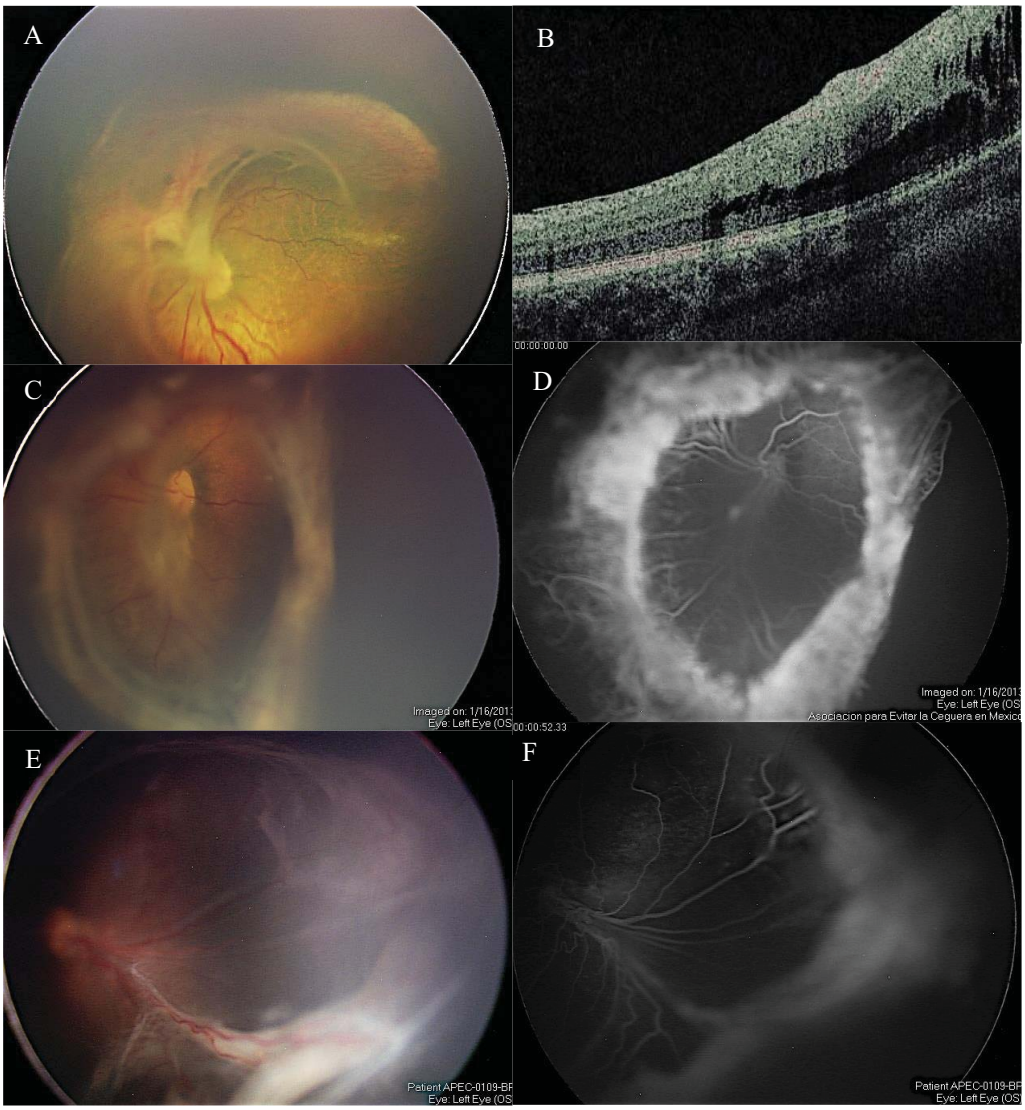

Fig. (7). (**A**). Color photograph that shows fibrovascular proliferation with retinal traction without macular involvement. (**B**). OCT that shows detachment of the retinal layers. (**C**). Color fundus photograph of clinical stage 4B, with macular detachment. (**D**). Fluorangiography of figure C that shows a hyperfluorescent traction ring. (**E**). Color fundus photograph with macular detachment and fibrovascular proliferation. (**F**). Fluorangiography of figure E that shows a hyperfluorescent fibrovascular proliferation.

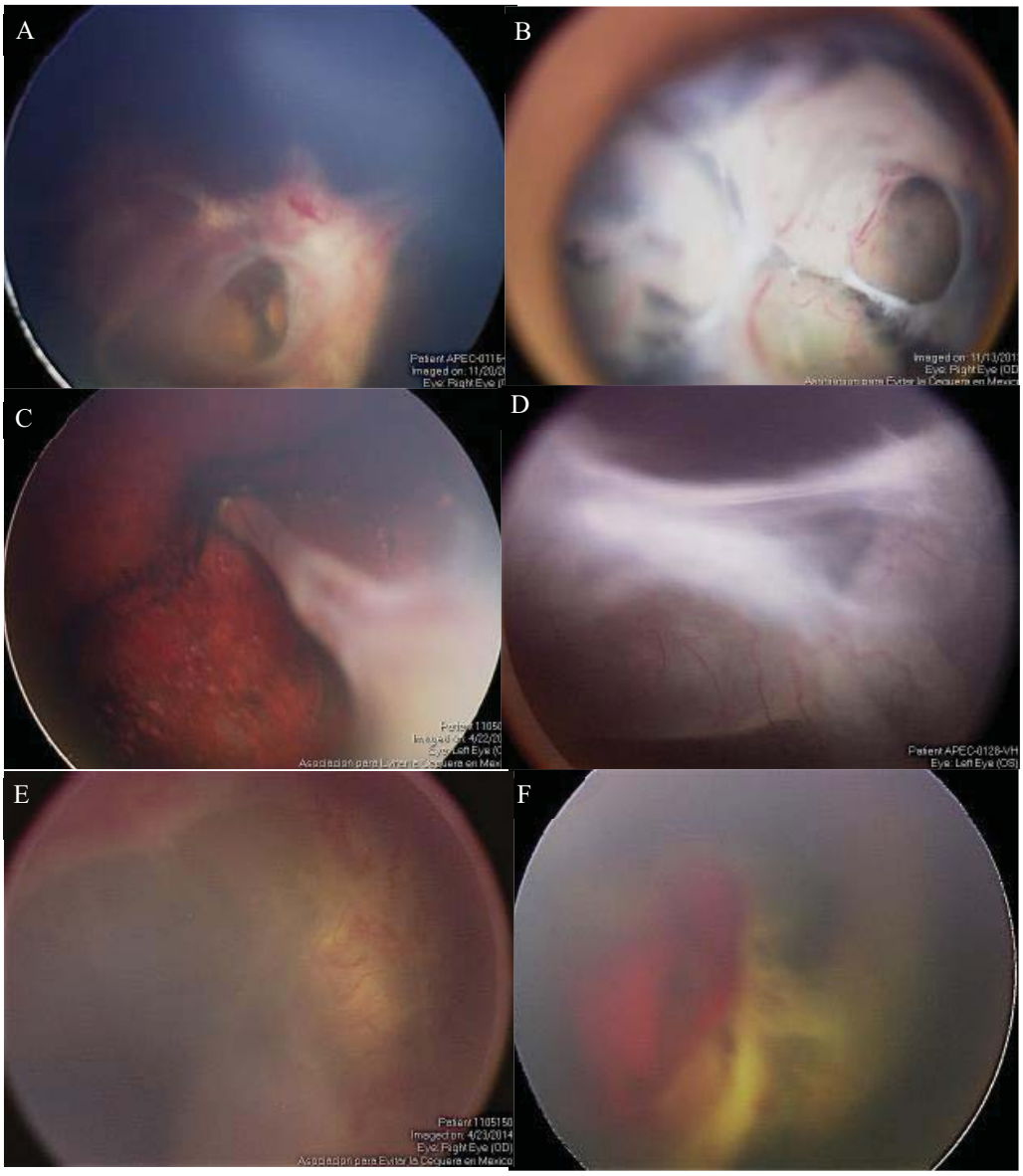

Fig. (8). (**A**). and (**B**). Opened funnel retinal detachment. (**C**). Closed funnel retinal detachment attached to posterior lens capsule with exposed choroid. (**D**). Anterior vitreous fibers that traction the retina. (**E**). Open-funnel retinal detachment. (**F**). Closed -funnel retinal detachment with anterior hemorrhage.

The extent of ROP refers to the dilation and tortuosity of the retinal arterioles and veins in the posterior pole (number of clock-hours involved) and is based on a

standard photograph published in the multicenter trial of cryotherapy for retinopathy of prematurity (CRYO-ROP) (Fig. **9**). Based on the CRYO-ROP Study [2], threshold ROP is defined as the level of severity of ROP at which the risk of an unfavorable anatomic outcome approached 50%, and is diagnosed as 5 contiguous or 8 non contiguous clock hours of stage 3 ROP in zones I or II, with plus disease (Fig. **10**).

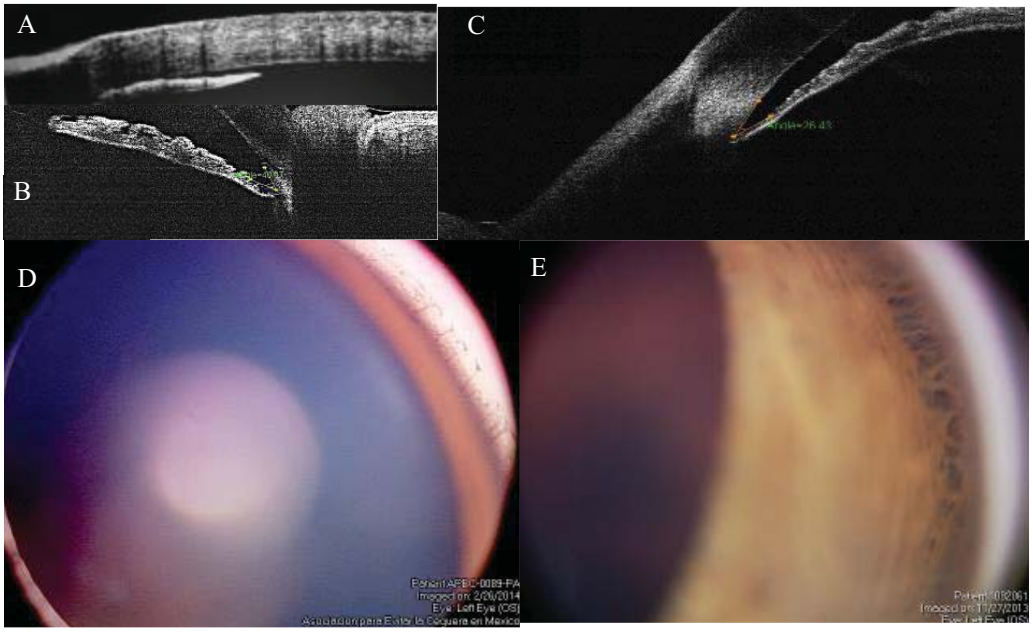

Fig. (9). (**A**). In the OCT performed on the angle, there is evident contact of the anterior portion of the iris and the corneal endothelium. (**B**), (**C**). In these OCT photographs, there is anterior displacement of the iris resulting in a narrow angle. (**D**), (**E**). Open angle with long ciliary processes.

Plus disease refers to the presence of marked venous dilation and arterial tortuosity in the posterior pole [2, 3, 5] (Figs. **11** and **12**).

DIFFERENTIAL DIAGNOSIS

Familial exudative vitreoretinopathy (FEVR) [5 - 9] is a developmental anomaly of the retinal vasculature characterized by a failure of peripheral retinal vascularization. Diagnosis of FEVR can be made based on the presence of peripheral retinal avascularity with exudates in the nearly full-term infant with

somewhat lower than average birth weight and no history of supplemental oxygen. It may present with more subtle changes, including subretinal fluid, exudates, telangiectasias, and aneurysms [8]. Unlike ROP, FEVR does not follow a predictable timeline of progression, and neovascular, tractional, or exudative activity may occur throughout childhood and adulthood.

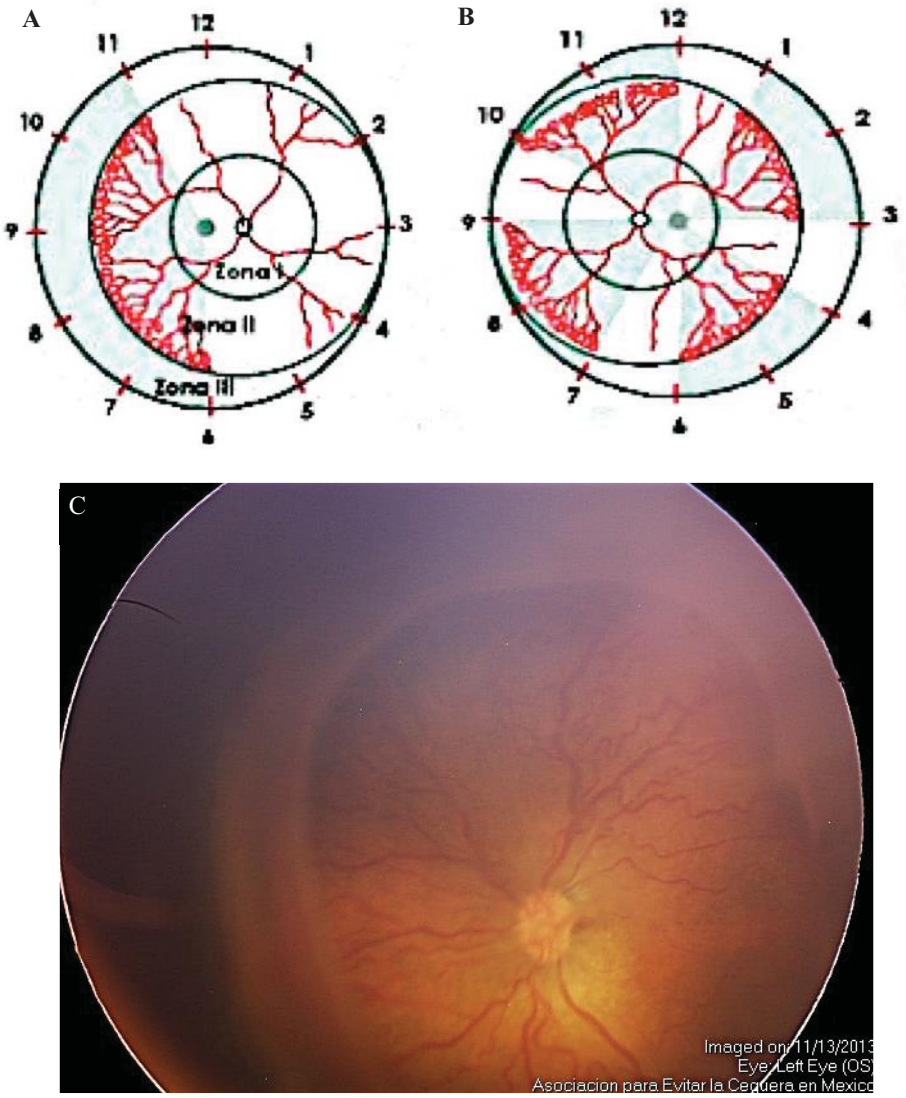

Fig. (10). (**A**). Diagram of threshold ROP with five contiguous clock hours. (**B**). Diagram of threshold ROP with eight discontinuous clock hours. (**C**). Clinical photograph of threshold ROP.

In oxygen-induced retinopathy (OIR) [10] there is obliteration of blood vessels in previously formed retinal vessels in a centripetal fashion toward the optic disc. First, there is a non-proliferative phase; then, with the increased metabolic demand of the retinal cells, there is a rise in the synthesis of pro-angiogenic factors resulting in a vasoproliferative second phase. The complexity of the diagnosis relies on the fact that it is hard to clinically distinguish OIR from ROP. Performing a fluorescein angiography makes it possible to differentiate both entities.

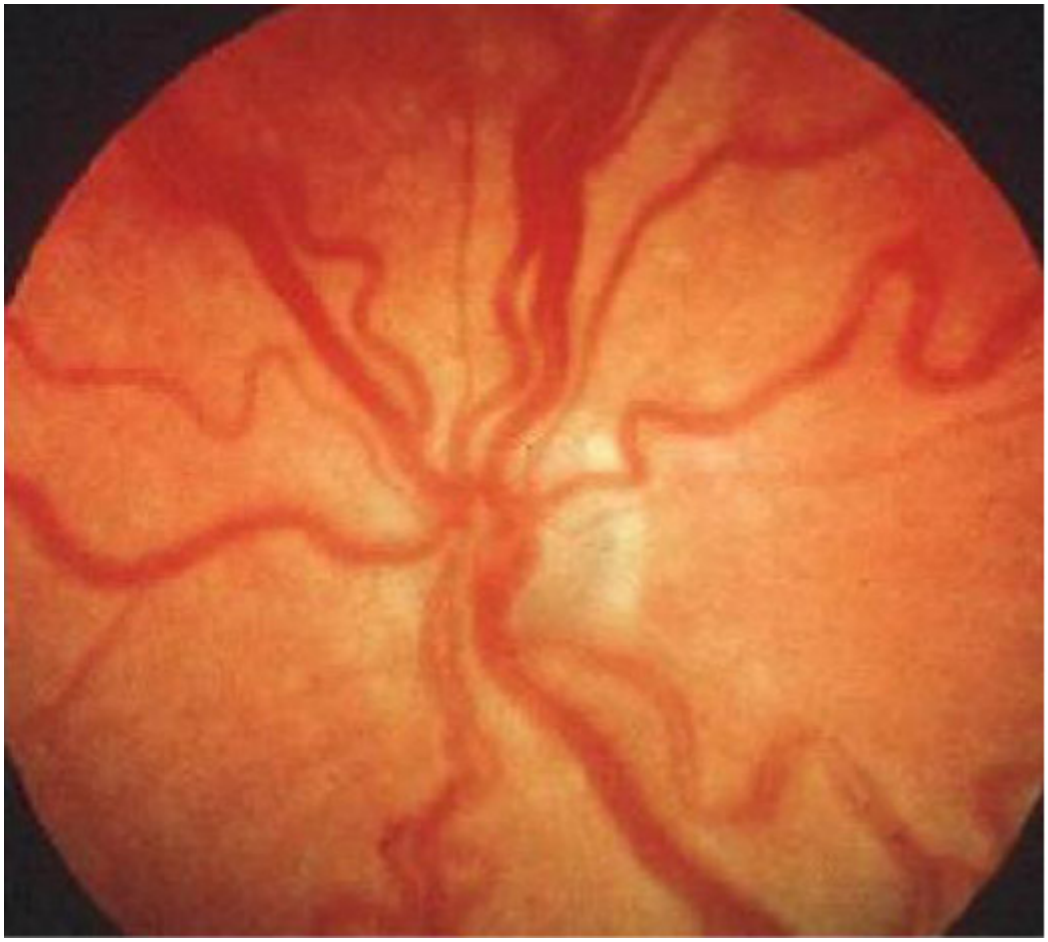

Fig. (11). Clinical photograph showing dilatation and tortuosity of the retinal vessels.

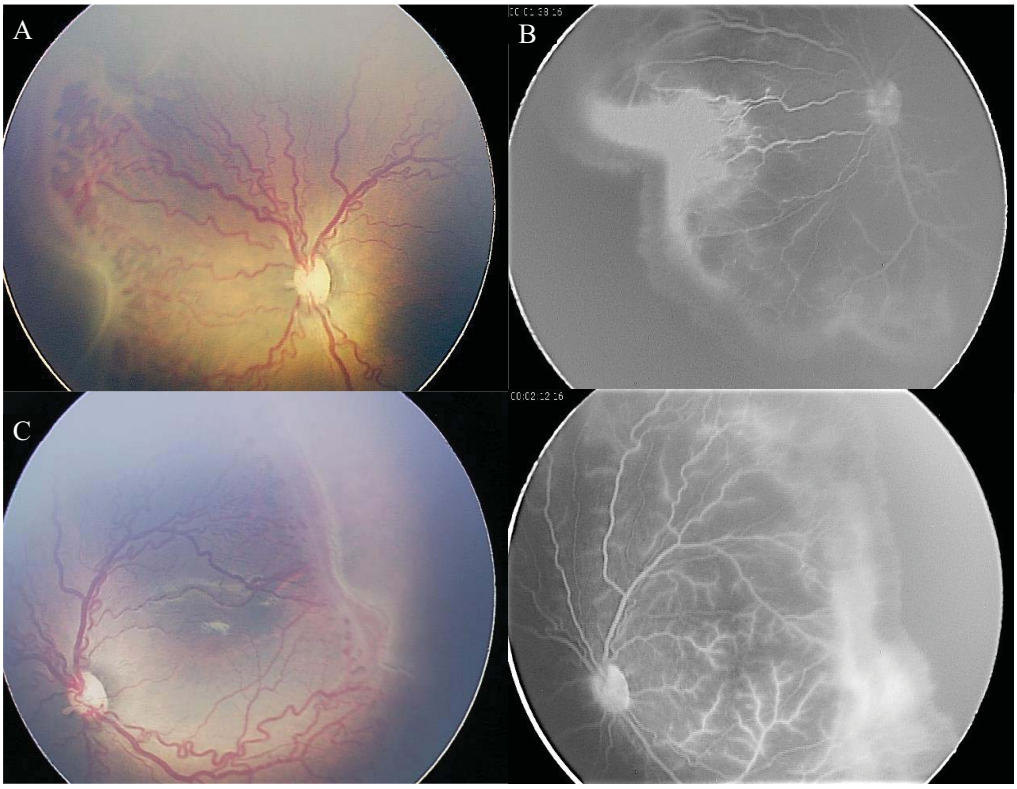

Fig. (12). (**A**). Color fundus photograph of stage 2 zone I with plus disease. (**B**). Fluorangiography that shows hyperfluorescence between the vascular and avascular zones. (**C**). Color fundus photograph of stage 3 zone II with plus disease. (**D**). Fluorangiography of figure C.

Retinoblastoma [10, 11] is the most common intraocular malignancy of childhood. Retinoblastoma occurs in hereditary and nonhereditary forms. The patient may present with unilateral or bilateral leukocoria or strabismus. Small tumors are whitish, with foci of calcification. Medium-sized tumors are larger and have blood vessels that penetrate the tumor (Fig. **13**).

Coats Disease [10, 12 - 14] is a retinal disease of unknown etiology that is characterized by the presence of telangiectasias in the retinal vasculature that cause significant exudation. It causes an exudative retinal detachment which is not seen in eyes with ROP.

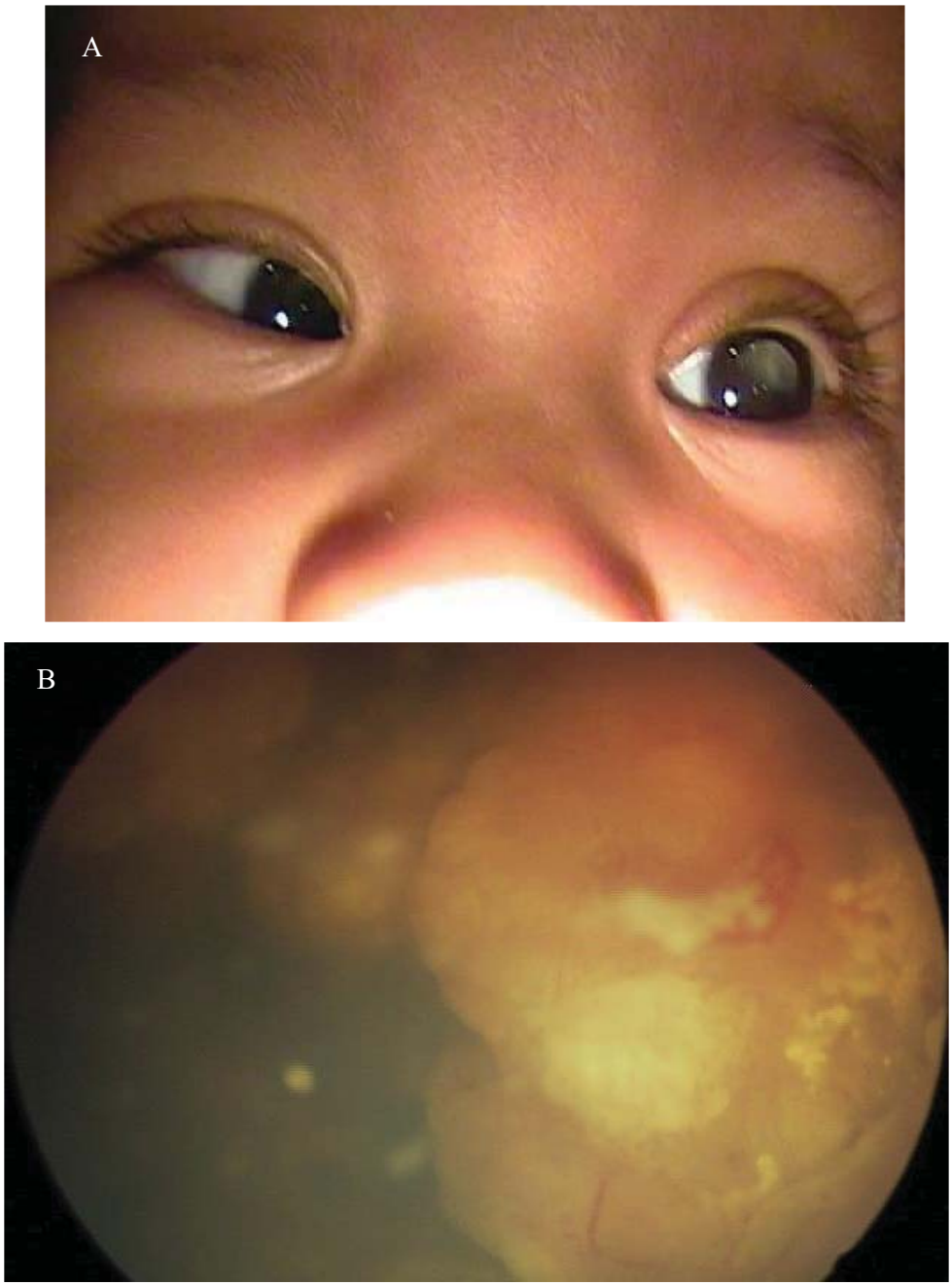

Fig. (13). (**A**). Left eye leukocoria. (**B**). Color fondus photograph with an endophytic retinoblastoma with vitreous seed.

Incontinentia pigmenti is an X-linked dominant disease that is present only in females, manifesting as an avascular peripheral retina that may progress to a proliferative retinopathy (Fig. **17**) [10, 12, 15]. Patients have a history of hyperpigmented lesions in the skin since birth, that fade during the first years of life.

Persistent fetal vasculature (PFV) [6, 16] presents as vascularized tissue covering part or all of the posterior aspect of the lens, and with elongated ciliary processes. PFV usually presents with unilateral leukocoria; bilateral PFV is rare. Bilaterality, history of prematurity and typical retinal vasculopathy of ROP can be used to exclude PFV as the primary disorder [16].

A very useful tool to aid in differential diagnosis is the RetCamII Camera [17, 18]. Using coupling gel, the contact retinal camera is placed on the cornea and images the retina with a choice of 5 lenses (130°, 120°, 80°, 30° and Portrait). The wide-field image is captured instantly and made into a digital, high-resolution color photograph (side-by-side image). Fluorescein angiography (FA) allows more objective assessment of disease stage and zone, shows vessel changes in detail (Figs. **14 - 18**). It is ideal for the monitoring of regression or recurrence after anti-VEGF treatment.

MANAGEMENT [20]

Timing of the initial examination is based on both postmenstrual age (PMA) and chronological age (CA), and is undertaken to detect 99% of infants at risk of a poor visual outcome. The first examination is conducted between four and nine weeks' CA, depending on PMA at birth. Acute phase ROP screening may stop when the risk of developing severe ROP is no longer present. It was found that 99% of prethreshold ROP develops by 45 weeks' PMA. Retinal examinations in preterm infants should be performed by ophthalmologists skilled in the identification of ROP including location and staging as described in the International Classification of Retinopathy of Prematurity revisited [19].

Treatment for ROP should be initiated under any of the following circumstances:

- Zone I, any ROP with plus disease (Fig. **12**),

- Zone I, stage 3 without plus disease,
- Zone II, stage 2 or 3 with plus disease (Fig. **12**).

Treatment of ROP aims to prevent retinal detachment or scarring, therefore avoiding an unfavorable visual outcome.

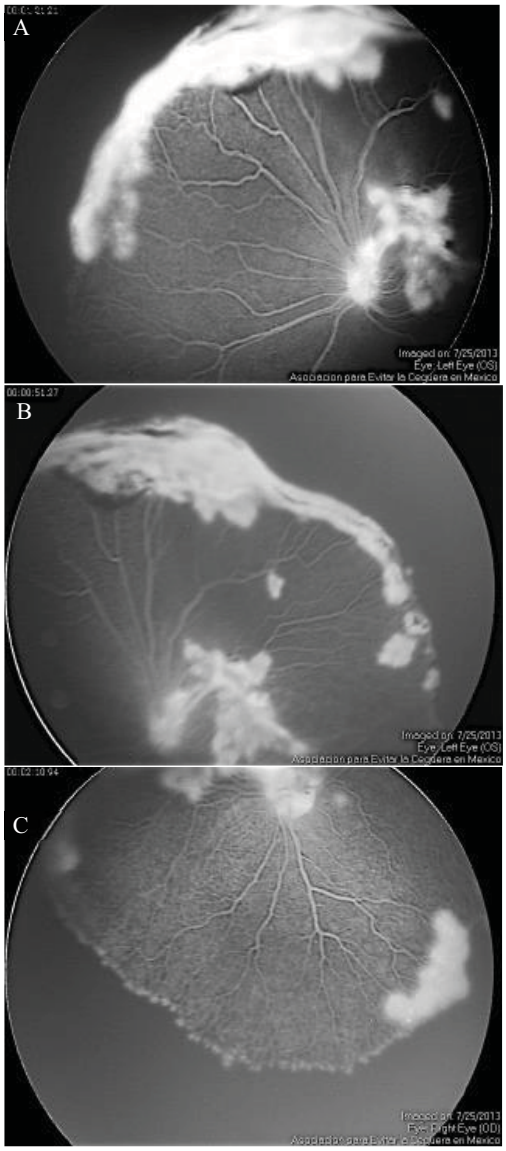

Fig. (14). (**A**), (**B**), (**C**). Photographs showing hyperfluorescence of fibrovascular proliferation between vascular and avascular regions.

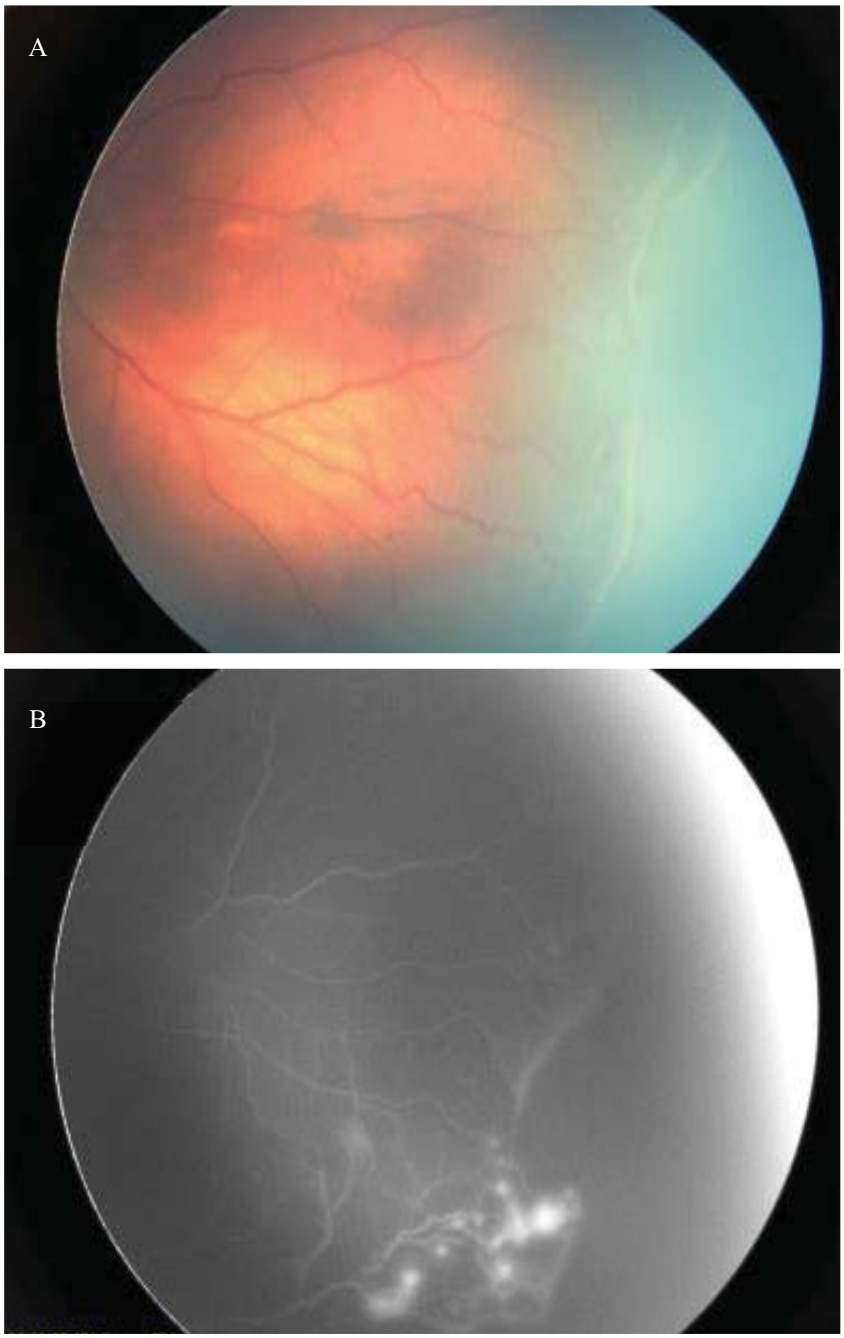

Fig. (15). (**A**). Color fundus photograph of stage 2 with vascular changes near the inferior ridge. (**B**). Fluorangiography that shows hyperfluorescence that corresponds to new vessels in preformed retina.

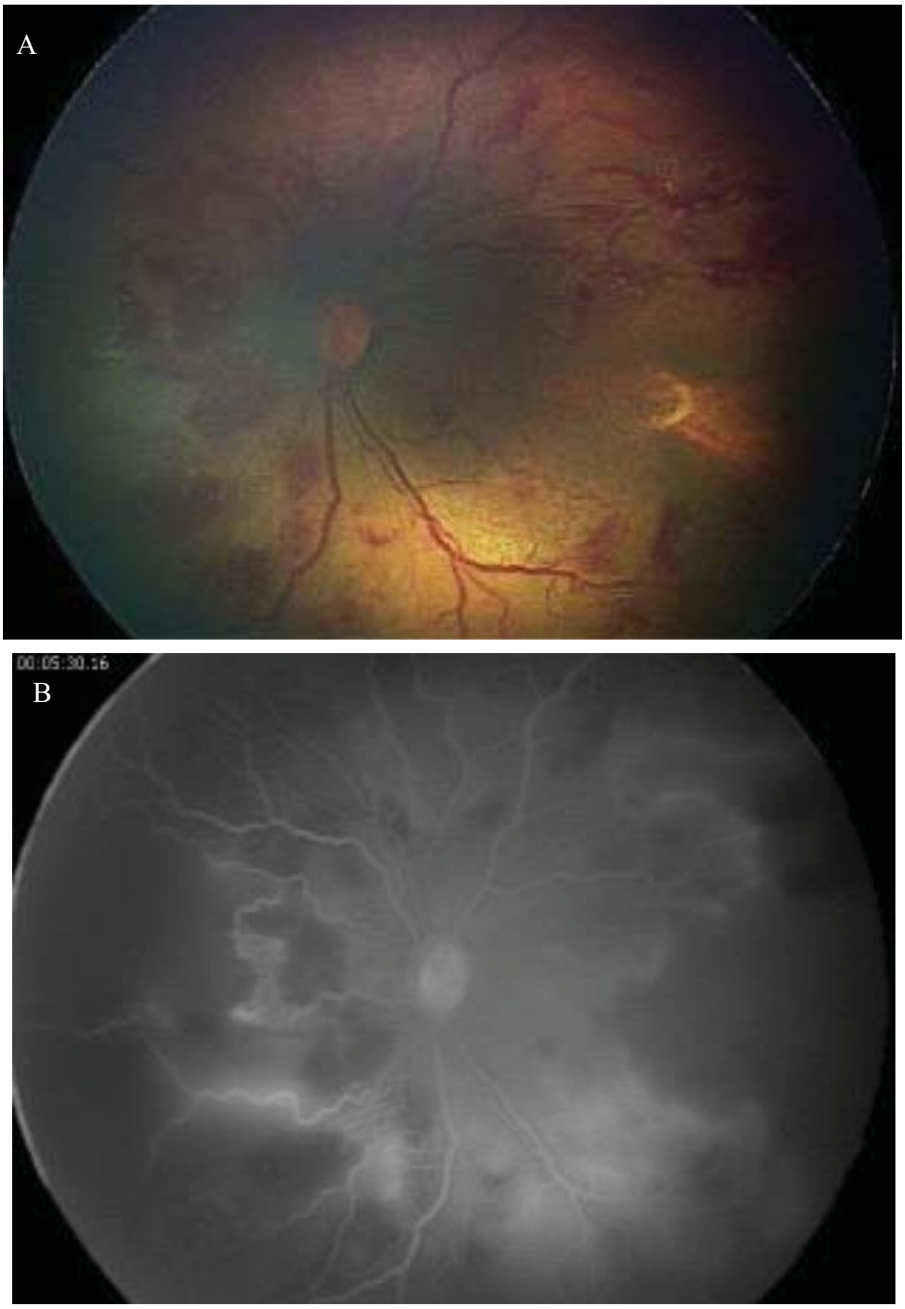

Fig. (16). (**A**). Color fondus photograph that shows vascular tortuosity with multiple retinal hemorrhages and temporal RPE atrophy. (**B**). Fluorangiography with hypofluorescent zones that correspond to the hemorrhages in the clinical photograph.

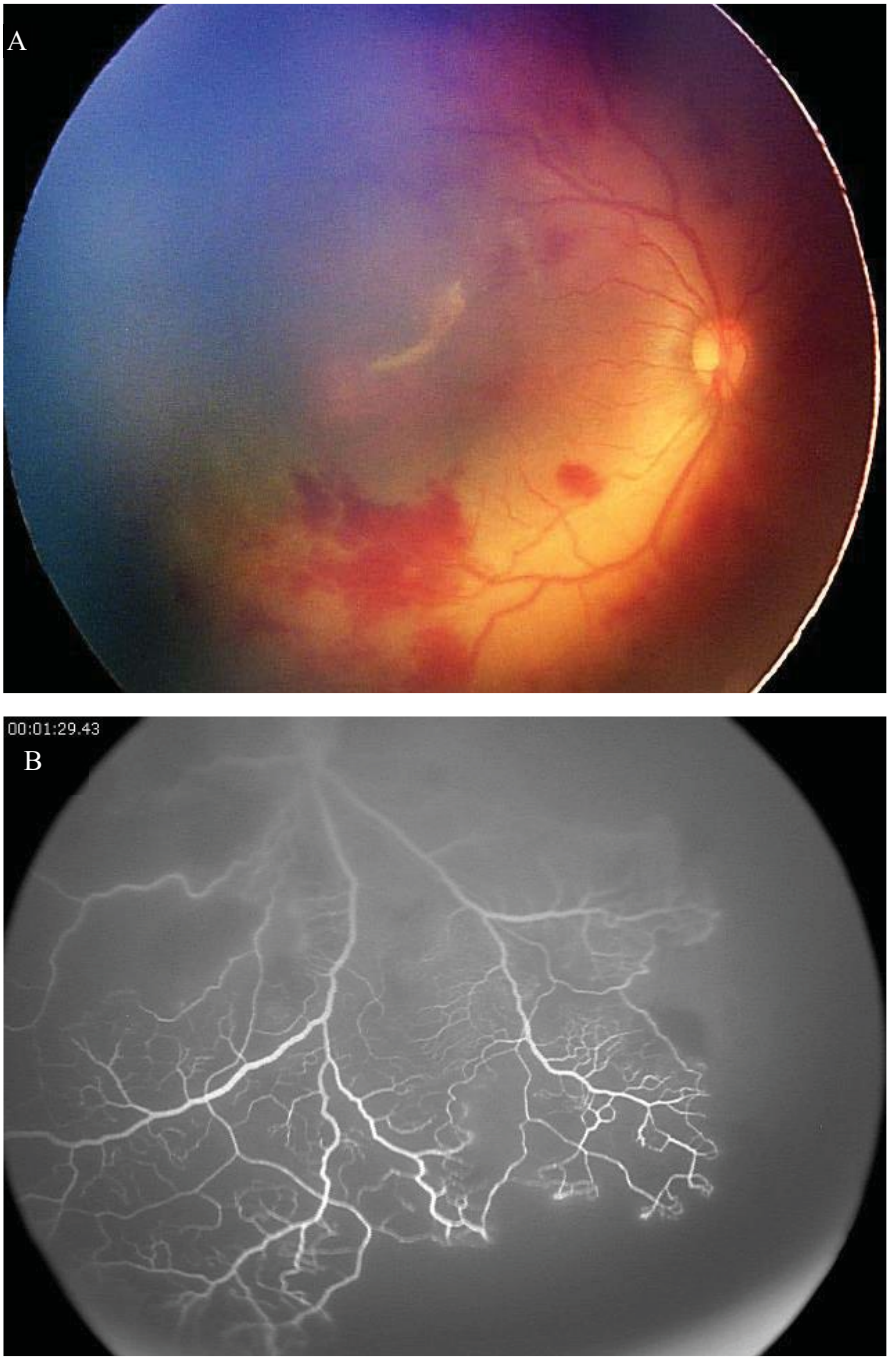

Fig. (17). (**A**). Color fundus photograph with multiple retinal hemorrhages in the posterior pole. (**B**). Fluorangiography that shows capillary closure and non-perfused zones.

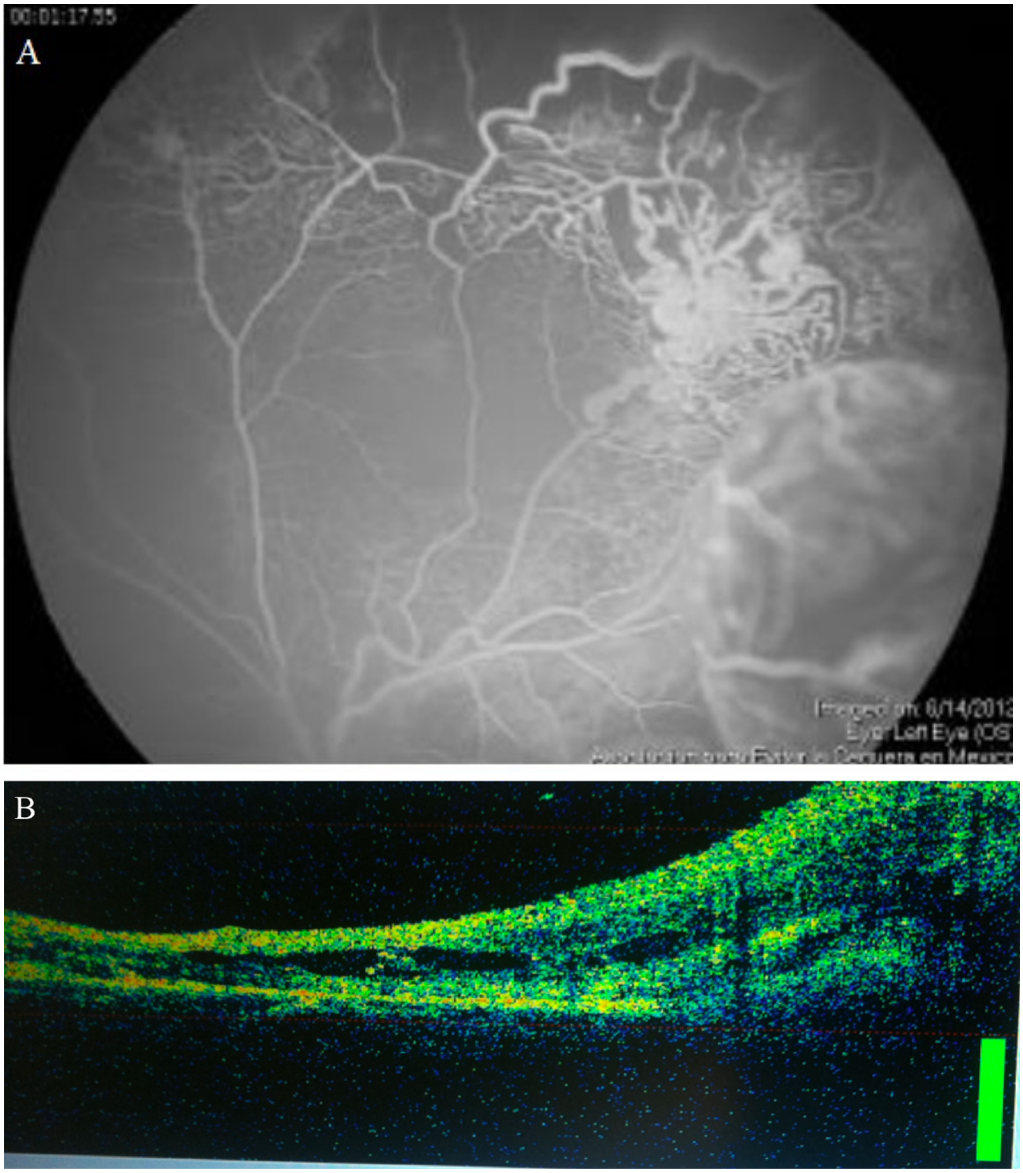

Fig. (18). (**A**). Fluorangiography with vascular dilations and non-perfused capillary zones. There is a retinal detachment in the right lower quadrant of the picture. (**B**). OCT with hyporeflective zones between retinal layers that can correspond to effusion.

Treatment Options [2 - 4, 18]

Laser photocoagulation: Transpupillary laser therapy delivered by an indirect

ophthalmoscope is the first line therapy for ROP. Either argon green laser or diode laser may be used, but diode laser offers the advantages of greater portability, being easier to use, and lower rate of cataract formation, especially if there is persistence of the tunica vasculosa lentis. Treatment is directed to the avascular retina, with near-confluent (0.5-1 burn-width) burns. Although ablation of the peripheral retina with laser reduced the progression and incidence of the disease in the Early Treatment for Retinopathy of Prematurity (ETROP) study, patients still had poor visual outcomes after treatment, especially for zone I ROP (Fig. **19**).

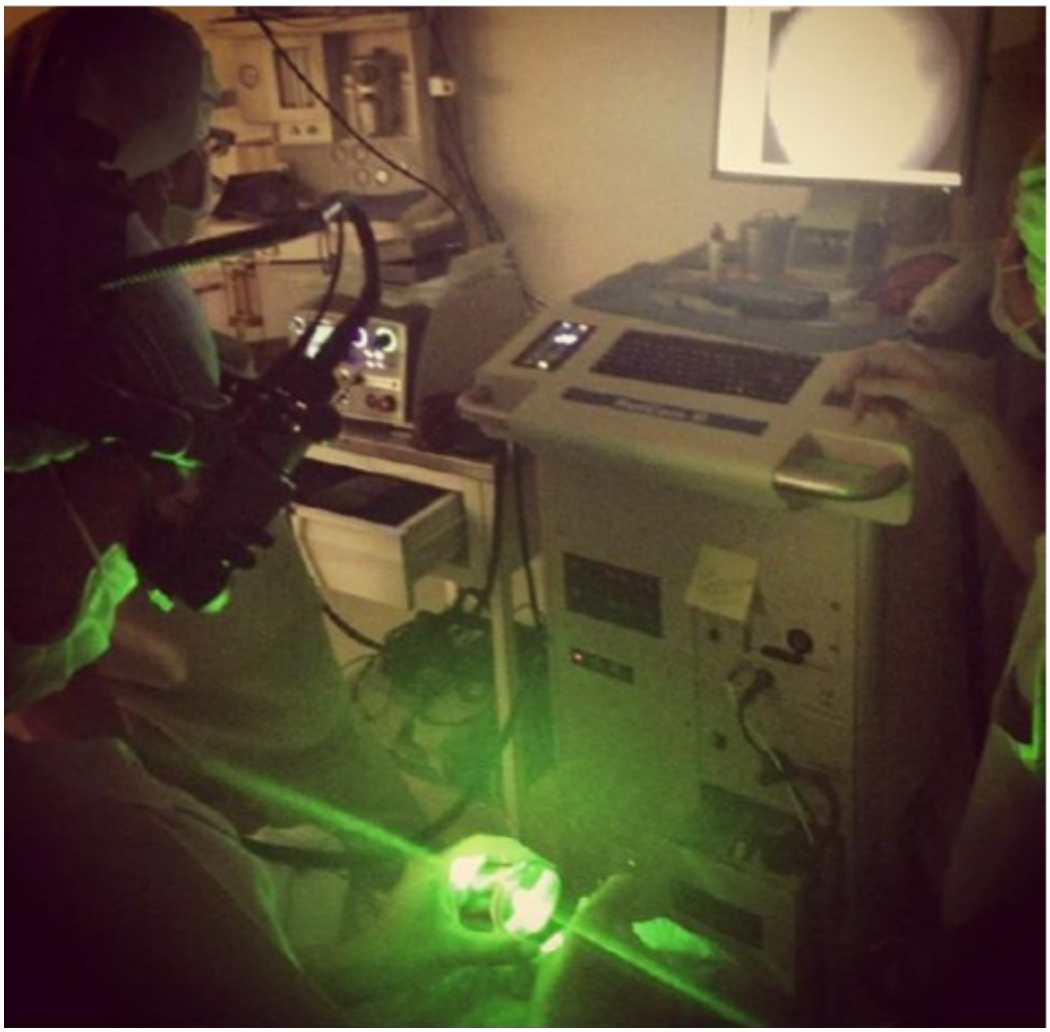

Fig. (19). Laser photocoagulation in the NICU.

Angiogenesis Inhibitors: Vascular endothelial growth factor (VEGF) is a potent mitogen for vascular endothelial cells that promotes both physiological and pathological angiogenesis. VEGF blockage induces regression of neovascularization in eyes with ROP. The use of anti-VEGF therapy seems an efficacious treatment for severe ROP, but correct injection timing might be an important limitation for its use. If anti-VEGF drugs are given late in the course or in cases with retinal detachment, increased concentrations of TGF-β may contribute to a tractional retinal detachment due to accelerated fibrosis and contraction of fibrous membranes. Another important consideration is the potential risk of local and systemic complications.

Future Therapeutic Strategies: New pharmacological treatment concepts such as systemic propranolol, gene therapy, supplementation with omega-3 fatty acids, or IGF-1 also represent interesting pharmacological approaches to the management of ROP.

Telemedicine [20, 21]. Availability of retinal imaging devices such as the RetCamII and the ease to share information digitally makes ROP a very good scenario to implement a telemedicine strategy, in order to identify patients that need urgent attention of a specialist that is able to manage these patients. This imaging device has proven to have a 95% sensitivity for the presence of plus disease, which is a very reliable sign that the patient needs treatment [20]. Telemedicine has the potential to improve the quality, delivery, and accessibility of care for infants with ROP and for patients with other ophthalmic and medical diseases [21].

CONFLICT OF INTEREST

The authors confirm that they have no conflict of interest to declare for this publication.

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Declared none.

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CHAPTER 15

Coats` Disease

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Coats' disease is a retinal disease of unknown etiology, described by George Coats in 1908 [1] that is characterized by the presence of telangiectasias in the retinal vasculature that cause significant exudation [2].

Although the pathophysiology is unknown, a gene named NDP that codes for a protein known as norrin has been implicated in this and other diseases that involve retinal vasculogenesis [3]. Although syndromes such as Hallerman Streif or Senior Loken have been associated to Coats' disease, most patients present just with the retinal findings without a systemic association [4, 5].

Histologically, retinal vessels of eyes with Coats' disease have a significant reduction in the number of pericytes, which in turn leads to the vascular malformations and abnormal vascular permeability that are characteristic of this disease [6, 7].

ESSENTIALS OF DIAGNOSIS

Patients with Coats' disease present during the late first or early second decades of life [1], although there is an adult form of the disease [8, 9]. Around three quarters of patients are male, and in most of them, only one eye is affected [1].

Expression of the disease is variable: some patients may have very mild exudation and therefore be asymptomatic, while other patients with more significant exudation may present with leukocoria, strabismus or decreased visual acuity [10]. In adults, strabismus is less frequent as a presenting symptom [11].

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Fundus examination of an eye with Coats' disease usually shows a significant amount of subretinal yellow exudates (Fig. **1**) that is associated to vascular malformations such as aneurysms or telangiectasias that are located in the retinal periphery and affect mainly the temporal retina.

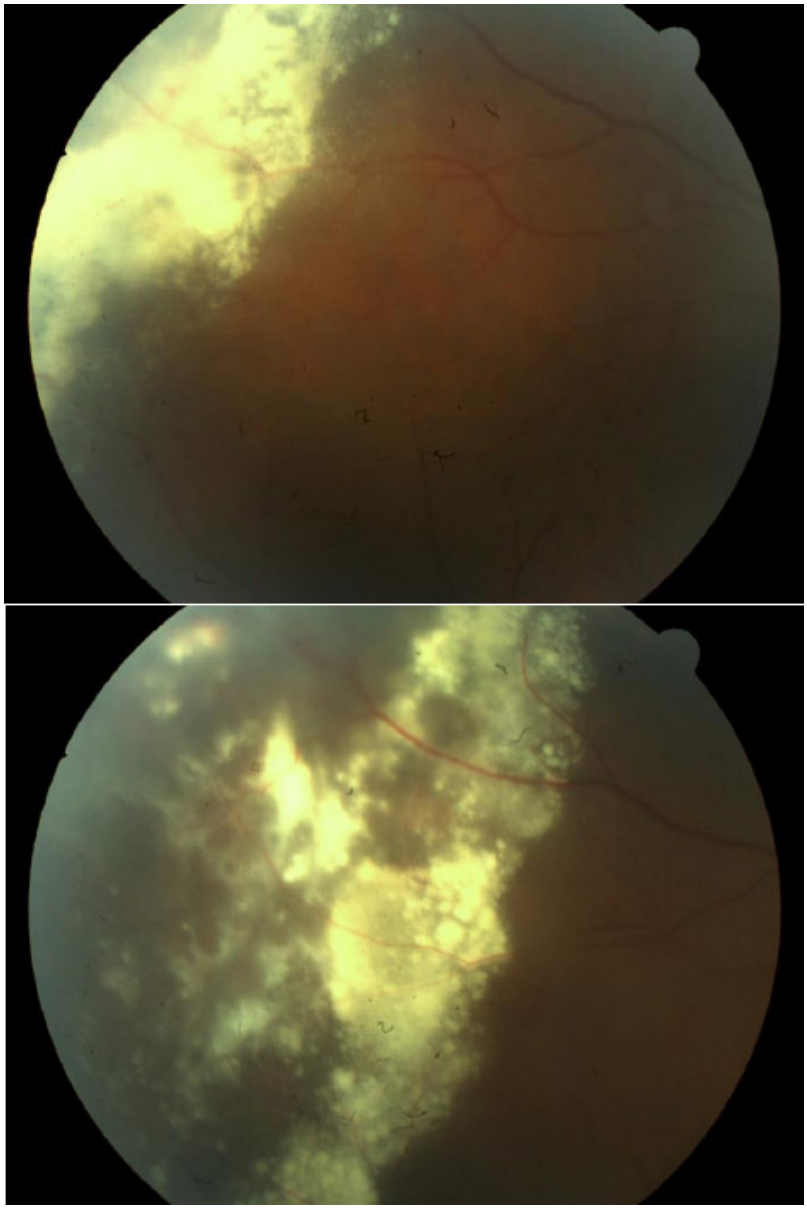

Fig. (1). Fundus photograph of 55-year-old man with Coats' disease. It shows peripheral exudation.

Clinical course of the disease may be variable but is generally progressive. Acute exacerbations of the disease may be separate in time by more quiescent stages [11]. Spontaneous remission has been reported but is really uncommon [12]. Subretinal exudation tends to increase in time, causing a serous retinal detachment that may progress until the affected retina becomes visible behind the lens. Eventually, neovascular glaucoma may develop and lead to phthisis bulbi in severe cases [11].

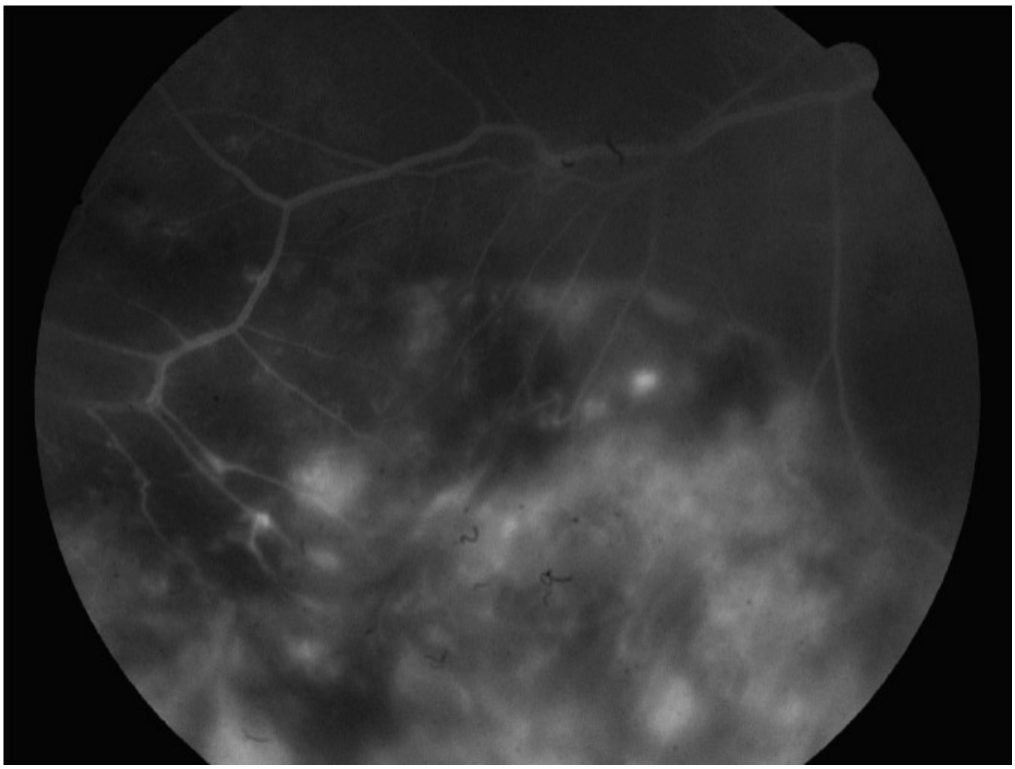

Fig. (2). Fluorescein angiogram of the same patient of Fig. (**1**) reveals several areas of hyperfluorescence from leaking retinal telangiectasia, giving a typical 'light bulb' appearance.

Fluorescein angiography shows retinal telangiectasia giving a typical "light bulb appearance", aneurysms, beading of vessels walls, and arteriovenous shunts are seen in the larger vessels involved (Fig. **2**). These vessels show early and persistent leakage. Areas of capillary non-perfusion or macular edema may appear [11]. Optical coherence tomography [13], is a very valuable tool to monitor response to treatment, especially in the macular area [13 - 15]. In advanced cases

that have high amounts of subretinal fluid, ultrasonography may be useful to identify cholesterol crystals in the subretinal space, which are characteristic of this disease [16]. CT and MRI may also have some utility in atypical cases to identify calcification or enhancement that may be indicative of retinoblastoma.

Classification

In 2000, a classification scheme for Coats' disease was proposed that correlates the stages of the disease with known indicators of long-term prognosis [17]. This system utilizes five stages, representing the spectrum from isolated telangiectasia to end-stage neovascular glaucoma with phthisis. Stage 1 disease consists of telangiectasia only; stage 2 indicates that both telangiectasia and exudation are present (2A, extrafoveal exudation; 2B, foveal exudation); stage 3 indicates retinal detachment (3A, subtotal retinal detachment; 3B, total retinal detachment); stage 4 consists of total retinal detachment and secondary glaucoma; and stage 5 indicates end-stage disease approaching phthisis [17].

DIFFERENTIAL DIAGNOSIS

The most important distinction that must be made is between Coats' disease and retinoblastoma. Both can present with extensive effusive retinal detachment that does not allow direct visualization of underlying tumors and some of the classic signs of Coats' described above. Several pearls for distinguishing between the two are: (1) The subretinal fluid in Coats' disease is comprised of proteinaceous and lipid exudation. This makes the subretinal fluid yellowish in color. Retinoblastoma on the other hand usually presents with clear subretinal fluid. (2) Fluorescein angiography is useful in identifying the abnormal retinal vasculature in Coats' disease, while retinal vasculature remains relatively normal in retinoblastoma. Also, retinal vessels can abruptly enter a retinoblastoma, which is not seen in Coats' disease. (3) Vitreous and subretinal seeding is seen in retinoblastoma, but not in Coats' disease. (4) Examination of the fellow eye may reveal subclinical tumors suggestive of hereditary retinoblastoma. (5) B-scan ultrasonography will allow visualization of underlying tumors in retinoblastoma. Other differential diagnoses include persistent fetal vasculature; retinopathy of prematurity; familial exudative vitreoretinopathy; retinal capillary hemangioma;

retinal cavernous hemangioma; incontinentia pigmenti; Norrie's disease; and toxocariasis. A “Coats-like reaction” consisting of vascular abnormalities and varying degrees of exudation has been described in retinitis pigmentosa, branch retinal vein occlusion, toxoplasmosis and systemic conditions such as muscular dystrophy, Turner syndrome, Alport syndrome and others [18].

MANAGEMENT

Treatment options for Coats' disease are best tailored to disease severity. Observation may be appropriate in some patients with stage 1 Coats' disease (telangiectasia without exudates), but treatment should generally be applied at the first signs of exudation, given that stage 2 disease will often progress if untreated. Scatter laser photocoagulation to the area of telangiectasia with direct treatment to the abnormal vessels and moderately intense retinal burns in between is preferred if the retina is attached. For stage 3 disease, cryotherapy is useful for treating the detached retina. Overly aggressive treatment may worsen the retinal detachment, and repeat treatments should generally be spaced at least three months apart. This also allows adequate time for the resorption of subretinal fluid and provides a more accurate assessment of treatment efficacy [17]. Limited cases reports support the beneficial role of anti-VEGF therapy as an adjuvant therapy, combined with laser or cryotherapy [19, 20].

Patients with extensive retinal detachment may benefit from scleral buckling, vitrectomy or both [21, 22]. Patients with stage 4 or stage 5 disease, particularly those with neovascular glaucoma or phthisis bulbi, may require enucleation.

Prognosis: Poor visual outcome (20/200 or worse) is uncommon in stage 1 disease, but occurs in half of patients with stage 2 disease and nearly 75 percent of those with stage 3 disease, even when those patients receive aggressive treatment. Patients with stage 4 or stage 5 disease invariably have a poor visual prognosis [17].

CONFLICT OF INTEREST

The author confirms that author has no conflict of interest to declare for this publication.

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Declared none.

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CHAPTER 16

Ocular Toxocariasis

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Toxocariasis is a very frequent helminthic infection, caused by the larval stages of the ascarids *Toxocara canis* and *catis*, the common roundworm of dogs and cats respectively. Egg and larval forms of *Toxocara* have difficulty surviving at temperatures below 50°F (10°C), which is why the disease is more prevalent in warmer climates [1]. Playgrounds and sandboxes are common sources of contamination because they are regularly frequented by dogs, cats and children (higher risk population) who ingest dirt because of their play habits and hygiene standards [1 - 4] (Fig. **1**).

Toxocara infection in humans originates with ingestion of infectious *Toxocara* eggs, and can have three distinct clinical pictures: visceral larva migrans, ocular larva migrans, and covert toxocariasis. Visceral larva migrans occurs when *Toxocara* larvae reach major internal organs through the bloodstream, causing a variety of symptoms, such as eosinophilia, headache, abdominal pain, pneumonitis, or hepatitis. Ocular larva migrans occurs when larvae migrate into the eye [3 - 5] (Fig. **2**). Contrary to visceral larva migrans, patients with ocular affection do not develop eosinophilia, leukocytosis and have normal serum IgE

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levels [3 - 6]. Covert toxocariasis, on the other hand, represents a diagnostic challenge since symptoms are nonspecific (coughing, wheezing) accompanied by eosinophilia [3 - 6].

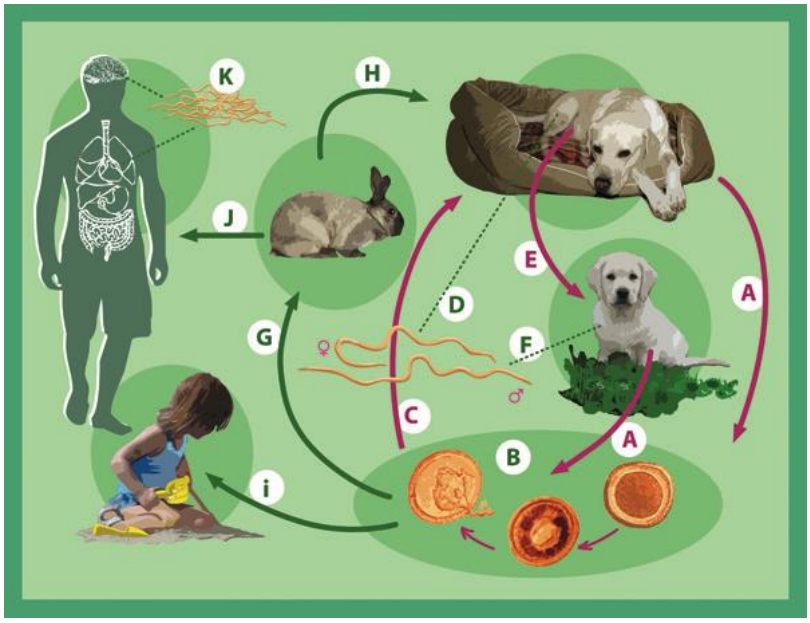

Fig. (1). *Toxocara* life cycle. (**A**) *Toxocara canis* accomplishes its life cycle in dogs, with humans acquiring the infection as accidental hosts. (**B**) Unembryonated eggs are shed in the feces of the definitive host. Eggs embryonate and become infective in the environment. (**C-D**) Following ingestion by dogs, the infective eggs hatch and larvae penetrate the gut wall. In younger dogs, the larvae migrate through the lungs, bronchial tree, and esophagus; adult worms develop and oviposit in the small intestine. (**E-F**) In older dogs, patent infections can also occur, but larval encystment in tissues is more common. Encysted stages are reactivated in female dogs during late pregnancy and infect by the transplacental and transmammary routes the puppies, in whose small intestine adult worms become established. Puppies are a major source of environmental egg contamination. (**G**) *Toxocara canis* can also be transmitted through ingestion of paratenic hosts: eggs ingested by small mammals (*e.g.* rabbits) hatch and larvae penetrate the gut wall and migrate into various tissues where they encyst. (**H**) The life cycle is completed when dogs eat these hosts and the larvae develop into egg-laying adult worms in the small intestine. (**I-J**) Humans are accidental hosts who become infected by ingesting infective eggs in contaminated soil or infected paratenic hosts. (**K**) After ingestion, the eggs hatch and larvae penetrate the intestinal wall and are carried by the circulation to a wide variety of tissues (liver, heart, lungs, brain, muscle, eyes). While the larvae do not undergo any further development in these sites, they can cause severe local reactions that are the basis of toxocariasis. The two main clinical presentations of toxocariasis are visceral larva migrans and ocular larva migrans. Diagnosis is usually made by serology or the finding of larvae in biopsy or autopsy specimens. (Garcia *et al.*) With permission from SLACKS inc. In Arevalo JF, Espinoza JV, Arevalo FA. Ocular Toxocariasis. J Pediatr Ophthalmol Strabismus 2013;50(2):76-86.

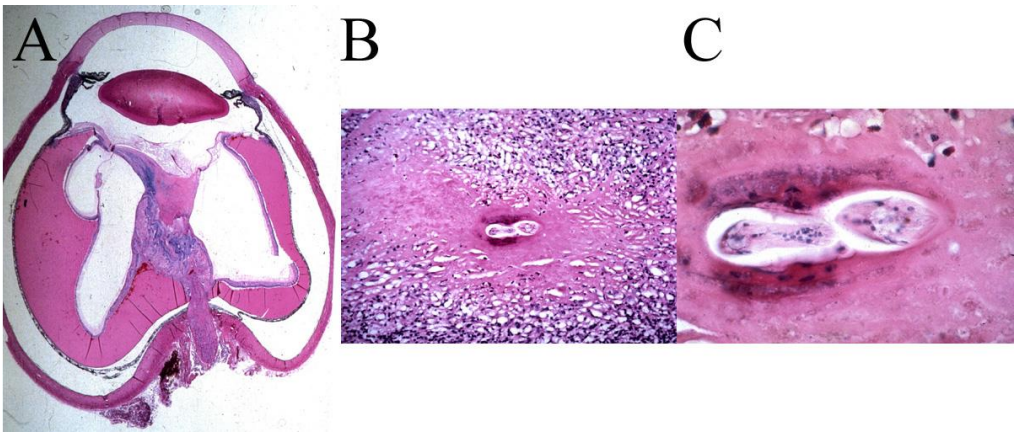

Fig. (2). A histopathology of the enucleated eye showing: (**A**) Retrolental intravitreal fibroinflammatory mass with retinal detachment. (**B**) Intravitreal mass composed of fibroinflammatory cells with plasma cells, eosinophils and fibrous tissue surrounding a nematode of *Toxocara canis*. (**C**) Partially well preserved nematode of *Toxocara canis*. (Garcia *et al.*) With permission from SLACKS inc. In Arevalo JF, Espinoza JV, Arevalo FA. Ocular Toxocariasis. J Pediatr Ophthalmol Strabismus 2013;50(2):76-86.

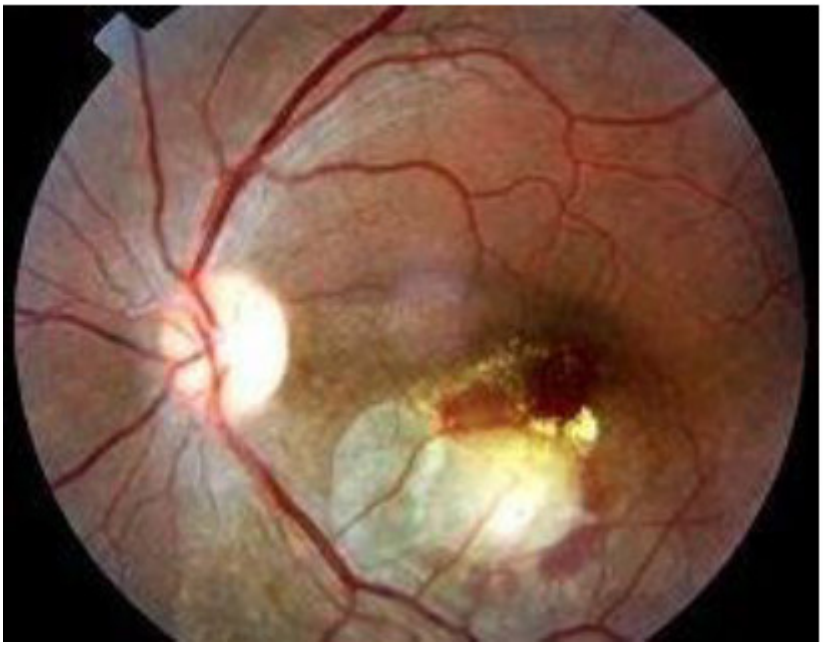

Fig. (3). Fundus photograph: Posterior pole granuloma due to *Toxocara canis*. There is secondary exudation into the fovea, perilesional hemorrhages and submacular fluid (Garcia *et al.*).

ESSENTIALS OF DIAGNOSIS

Ocular toxocariasis is typically unilateral. Patients usually show unilateral decrease in visual acuity, strabismus, or leukocoria [7]. Ocular toxocariasis usually presents in one of three different clinical pictures: a posterior pole granuloma (Figs. **3** and **4**), a peripheral granuloma (Figs. **5** and **6**) or chronic endophthalmitis. Other clinical presentations, such as granulomas in the optic nerve or iris, presence of larvae in the cornea, vitreous or retina, or scleritis [7 - 10].

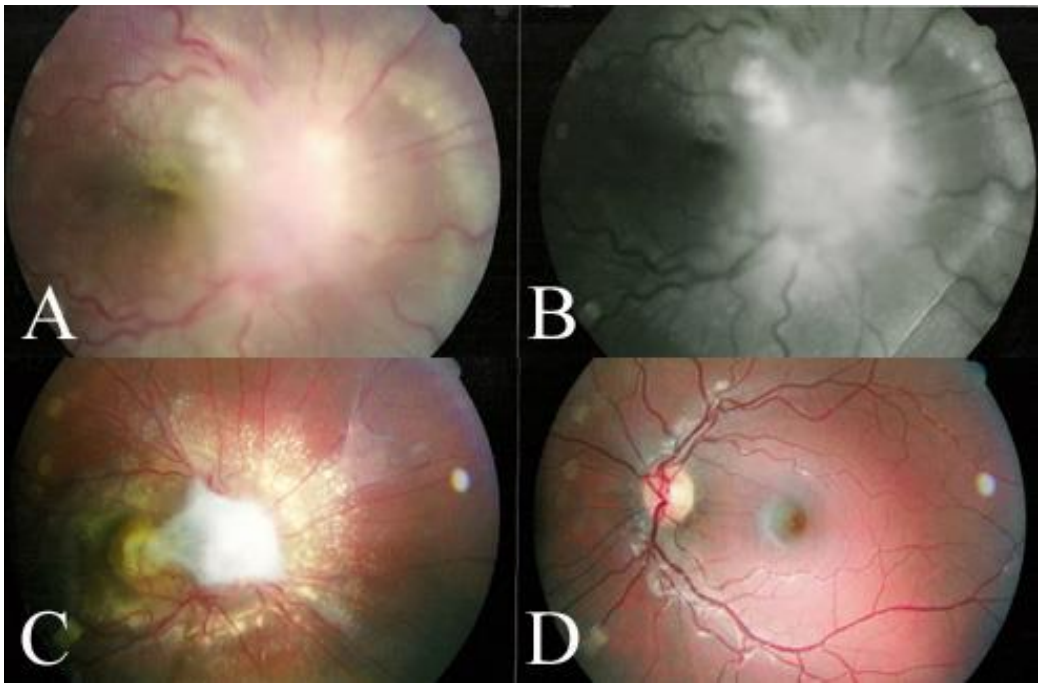

Fig. (4). Fundus photograph: (**A-B**) Color (**A**) and red free (**B**) images of a patient with an active inflammatory granuloma over the optic disk with vitritis, perilesional exudation and subretinal fluid. (**C**) After the resolution of the active phase there is a fibrotic granuloma over the disk with secondary fibrocellular membranes extending into the fovea. Note there is no more subretinal fluid but persistent perilesional exudation. (**D**) Normal left eye (Garcia *et al.*).

Ocular toxocariasis is diagnosed by ocular clinical signs supported by testing for an antibody to the *Toxocara* parasite. The recommended test for toxocariasis is a specific enzyme-linked immunosorbent assay (ELISA), which has sensitivity of

73% and a specificity of 90% at a titer of 1:32 [11]. Some authors have reported serum titers of 1:8 or less when there are signs and symptoms compatible with the disease [12 - 14]. ELISA titers can remain elevated for years; therefore, positive serology does not always indicate active infection. A negative serology is strongly suggestive that *Toxocara* is not the cause of ocular disease [12 - 14]. ELISA testing aqueous or vitreous humor, if samples are available, can be of great aid to make the diagnosis [12 - 14]. Testing for eosinophilia is rarely done because it is neither sensitive nor specific for diagnosing ocular *Toxocara* infection [15]. Stool examination for egg or larval forms has not proven useful since in human larvae do not mature into adult worms and therefore no eggs are shed.

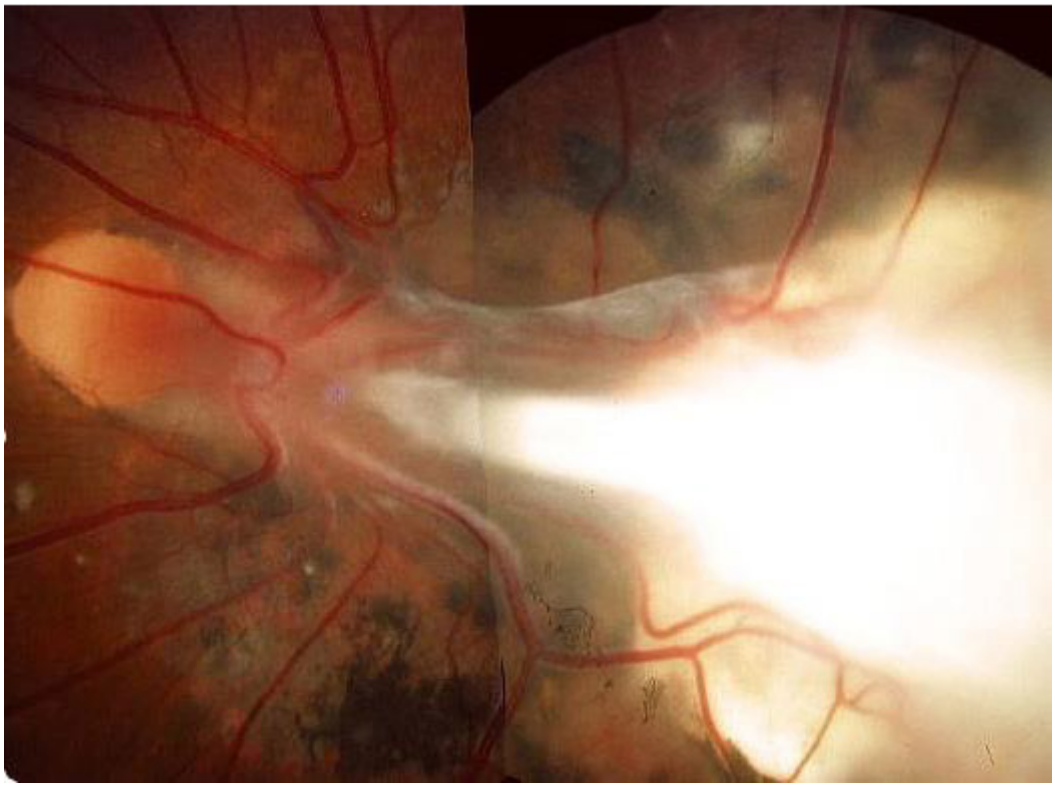

Fig. (5). Fundus photograph of peripheral granuloma due to *Toxocara canis* (Garcia *et al.*).

DIFFERENTIAL DIAGNOSIS

Retinoblastoma, delayed onset infectious endophthalmitis, active toxoplasmic retinochoroiditis, retinopathy of prematurity, familial exudative vitreoretinopathy,

persistent fetal vasculature, Coats' disease and Combined hamartoma of the retina and retinal pigment epithelium have to be included in the differential diagnosis [3, 4, 14].

Fig. (6). Fundus Photograph. Tractional retinal detachment due to peripheral granuloma in a patient with Toxocariasis. There is a thick subretinal fibrotic band extending into the optic disk. There are also some pre-retinal membranes due to inflammatory PVR (Garcia *et al.*).

MANAGEMENT

When active vitritis is present, treatment with periocular (trans-septal betamethasone injection) and systemic (0.5-1 mg prednisone) steroids should be initiated. There is widespread belief that administering anthelmintic therapy might cause severe intraocular inflammation due to a hypersensitivity reaction to dead larva. However, this has been proven wrong clinically and experimentally [10, 14, 16, 21].

The ultimate utility of antihelmintic therapy remains controversial [15]. The most common used antihelmintic drugs are Thiabendazole (25 mg/kg twice daily for 5 days with a maximum of 3 g per day), Albendazole (800 mg twice daily for 6 days), or Mebendazole (100 to 200 mg twice daily for 5 days) [3 - 6, 14 - 16].

Most patients respond well to anti-inflammatory therapy, although a granuloma or fibrotic scar may remain, which may be associated with poor visual acuity if the macula is affected. Some patients may require surgical management, in case of vitreous opacities that do not respond to treatment, retinal detachment (Fig. **6**) or epiretinal membrane that causes traction to the macula or the optic nerve. Surgery has been shown to result in satisfactory anatomic results and may even help to preserve visual acuity in cases where the fovea is not yet affected [17 - 21].

CONFLICT OF INTEREST

The authors confirm that they have no conflict of interest to declare for this publication.

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Declared none.

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CHAPTER 17

Familial Exudative Vitreoretinopathy

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Familial exudative vitreoretinopathy (FEVR) is a hereditary anomaly of retinal vascular development caused by *Wnt* signaling genetic defects [1].

ESSENTIALS OF DIAGNOSIS

The clinical presentation is highly variable, from subtle asymptomatic peripheral vascular changes to dragging of retinal vessels and severe tractional retinal detachments [2, 3]. Widefield fluorescein angiography with imaging systems such as the RetCam (Clarity Medical Systems, Pleansanton, CA, USA) for younger children and Optos (Optos, Marlborough, MA, USA) for older children and adults, greatly enhance the ability to diagnose and manage patients with FEVR.

FEVR staging is based on clinical and angiographic findings [4]. Stage 1 FEVR is characterized by peripheral nonperfusion with abnormally pruned distal retinal vasculature, such as bulb-like endings, telangiectatic vessels, supernumerary branching, and circumferential vascular loops (Fig. **1**). Extraretinal neovascularization characterizes stage 2, usually observed at the junction of vascular and avascular retina (Fig. **2**). Stage 3 and 4 are macula-sparing and macula-involving tractional retinal detachment, respectively (Fig. **3**). Total retinal detachment is

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denoted as stage 5, which can have open or closed funnel configurations.

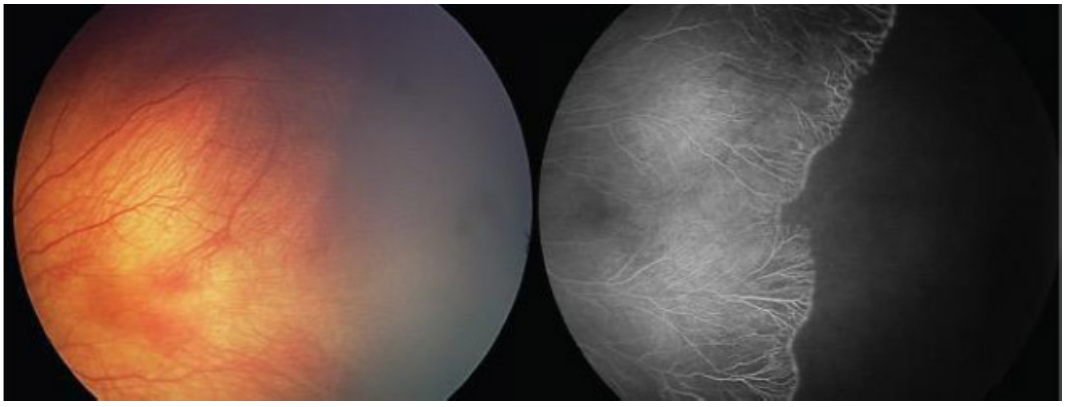

Fig. (1). Stage 1 Familial exudative vitreoretinopathy (FEVR). Stage 1 FEVR is characterized by peripheral nonperfusion with abnormal vascular endings. In this example, the clinical examination shows that there is peripheral nonperfusion (left), and RetCam widefield fluorescein angiography reveals that there is supernumerary branching and pruning of the vascular tips with extensive distal nonperfusion (right).

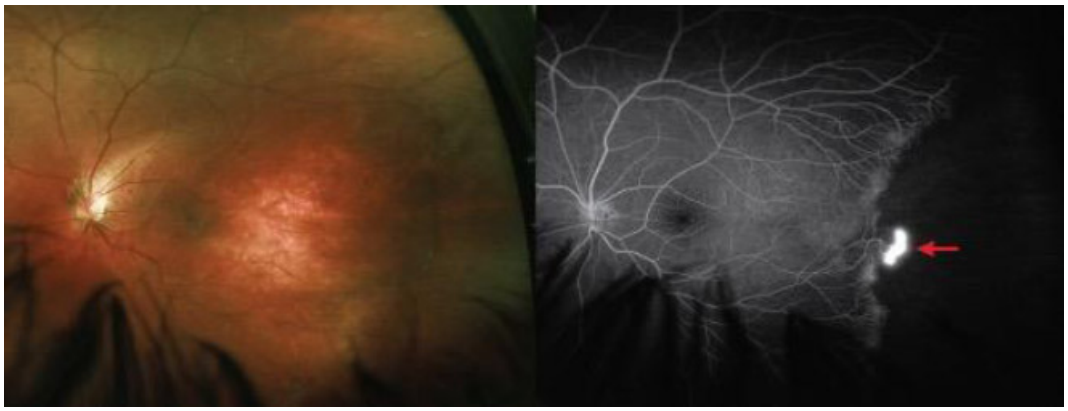

Fig. (2). Stage 2 Familial exudative vitreoretinopathy (FEVR). Stage 2 FEVR is characterized by retinal neovascularization, which is seen at the junction between vascular and avascular retina. Optos widefield fluorescein angiography in this example (right) shows a frond of retinal neovascularization seen as intense focal leakage of dye. Also note the abnormal vascular endings and the distal nonperfusion.

Diagnostic pearls for FEVR in order to distinguish it from other pediatric vitreoretinopathies are: (1) Careful inspection of the fellow eye. FEVR typically has bilateral findings, and identifying peripheral vascular changes in the less involved eye can help secure a diagnosis. (2) Examining family members for findings suggestive of FEVR – the majority of asymptomatic family members will

have clinical or angiographic findings [5]. (3) Genetic testing for mutations in *FZD4*, *NDP*, *TSPAN12*, and *LRP5*, are confirmatory. Although approximately only half of patients with FEVR will have detectable mutations, it is helpful when the clinical presentation is not typical [5].

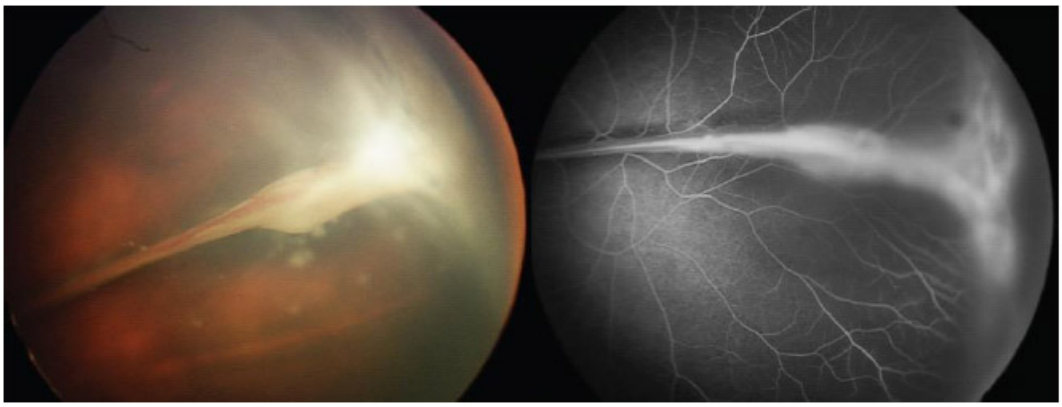

Fig. (3). Stage 4 Familial exudative vitreoretinopathy (FEVR). Macula-sparing tractional retinal detachment is considered stage 3 FEVR, macular-involving is stage 4, and total detachment is stage 5. In this example, there is a radial retinal fold involving the macula (stage 4), which is pulled up to the posterior lens surface.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of FEVR depends on the stage of disease [6, 7]. Several pediatric retinopathies may mimic stages 1-2. Retinopathy of prematurity (ROP) that spontaneously regressed or treated with anti-VEGF agents may present with similar peripheral vascular findings. Inquiring about birth history is therefore important for all suspected FEVR patients. In addition, ridges of previous arterial-venous shunting will often characterize regressed ROP, which is not seen in FEVR. Incontinentia pigmenti (IP) can usually be differentiated by the characteristic dermatologic findings and X-linked dominant inheritance pattern. The vascular anomalies in Coats' disease tend to be more sectorial with prominence of telangiectasias, bulb-like capillary endings, and extensive exudation. Of note, Coats' disease is not a vitreoretinopathy; hyaloid contraction will not be seen in Coats,' but it is a key element in FEVR, especially in advanced disease. Sickle cell retinopathy, Eales' disease, and diabetic retinopathy should also be considered, depending on the demographics and medical history.

Stages 3-4 with retinovascular dragging may have overlapping clinical appearances with toxocariasis. Identification of the granulomas characteristic of toxocariasis, and widefield angiography to reveal the vascular changes of FEVR will help distinguish the two, as well as toxocara antibody titers. Stage 5 FEVR with retrolental plaques are challenging to distinguish from Norrie disease, persistent fetal vasculature (PFV), and stage 5 ROP. Norrie disease is X-linked and associated with hearing loss and developmental delay. The vitreoretinopathy is aggressive and of early onset, and the retina is more dysplastic than in FEVR. The phenotype of PFV is highly variable, and the hyaloid architecture may not be easily appreciated in advanced disease. Microphthalmia and anteriorly displaced ciliary processes are the classic signs of advanced PFV, but these findings can be seen in FEVR also. ROP, as mentioned above, can be distinguished by birth history. However, stage 5 ROP can also occur in larger infants born close to term if unregulated oxygen was administered. This phenomenon may occur in some neonatal ICUs of developing countries.

MANAGEMENT

Stage 1 FEVR without leakage or exudation is generally observed. If there is leakage or exudation, laser photocoagulation of the avascular peripheral retina should be considered. Stages 2, 3, and 4 are also treated with laser. For stages 3, 4, and 5, surgical intervention to release active and progressive tractional forces can improve visual and anatomic outcomes [8]. Focal anterior traction can be addressed with encircling buckles and/or radial elements, but vitrectomy with membrane dissection may be recommended for diffuse pathology, posterior disease, or if lensectomy is required. Surgical intervention for radial folds can be beneficial if there is vascular activity and/or progressive traction. Follow-up schedules depend on the severity and activity of disease, but examinations are generally recommended at least every 6-12 months. FEVR is a life-long disease because reactivation can occur later in life [6].

CONFLICT OF INTEREST

The authors confirm that they have no conflict of interest to declare for this publication.

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Declared none.

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CHAPTER 18

Persistent Fetal Vasculature

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Persistent fetal vasculature (PFV), also known as persistent hyperplastic primary vitreous, is a congenital developmental disorder of the hyaloid system. Hyaloid vasculature reaches peak prominence during the 8th to 12th weeks of gestation in the human embryo, after which it normally regresses gradually to establish a clear visual axis [1]. PFV occurs when the hyaloid system fails to regress, and the remnants of embryonic tissues cause varying degrees of pathology.

ESSENTIALS OF DIAGNOSIS

PFV is classically described in a smaller eye with elongated ciliary processes and a posterior lenticular opacity connected to a stalk emanating from the optic disc. However, the phenotypic spectrum is very broad: the mildest forms of PFV are the Mittendorf dot on the lens capsule and Bergmeister's papilla on the optic disc, while advanced forms present with dense leukocoria and underlying complex tractional retinal detachment (Figs. **1 - 3**).

An understanding of developmental anatomy facilitates accurate diagnosis [2]. There are two components to fetal vasculature: the tunica vasculosa lentis, and the hyaloid system (primary vitreous). Anteriorly, the tunica vasculosa lentis encompasses the lens and extends to the pupillary margins. Posteriorly, it envelops the

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posterior surface of the lens and extends to the ciliary processes. The posterior tunica connects with the hyaloid vessel that emanates from the optic disc. It is important to remember that hyaloid vasculature is not just the central hyaloid vessel as commonly drawn in figures; depending on the patient, it can fill the entire vitreous cavity with multiple tractional attachments to the retina. There can be variable degrees of retinal dysplasia in PFV also, which can limit visual potential despite optimal management. The disease itself is usually not progressive, but as the eye grows, the traction will also increase, and hypotony from ciliary body traction may occur [3].

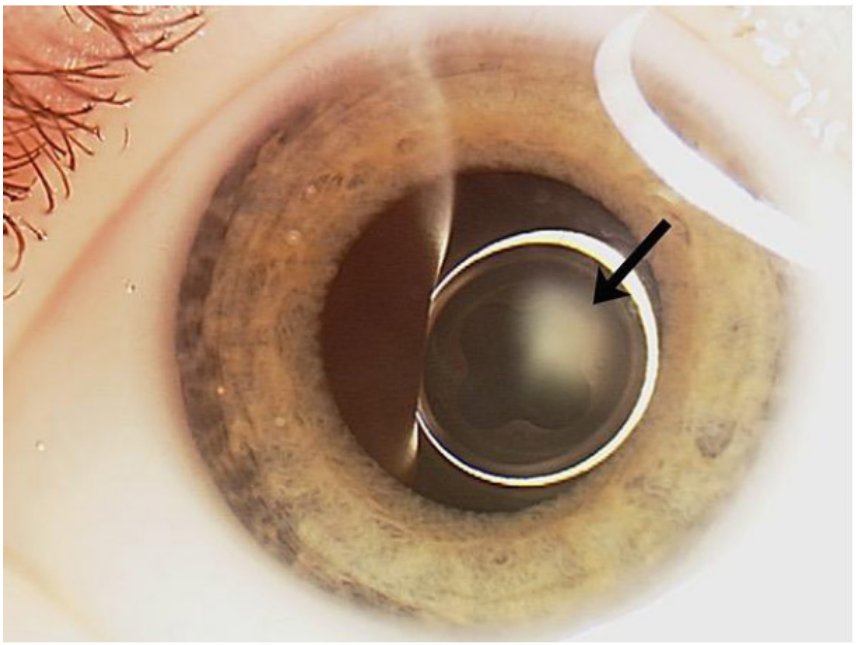

Fig. (1). Persistent fetal vasculature. This is an anterior segment photograph of a 6-month-old boy who presented with unilateral leukocoria. There is a white opacity attached to the posterior aspect of the crystalline lens (arrow).

A rare form of PFV is associated with posterior lenticonus and coloboma, a syndrome named microcornea, posterior megalolenticonus, PFV, and coloboma (MPPC) [4]. Like most syndromes, the presentation will vary and certain components of the syndrome will predominate the clinical picture. The megalolenticonus protrudes posteriorly, and the lens may even occupy the majority of the vitreous cavity.

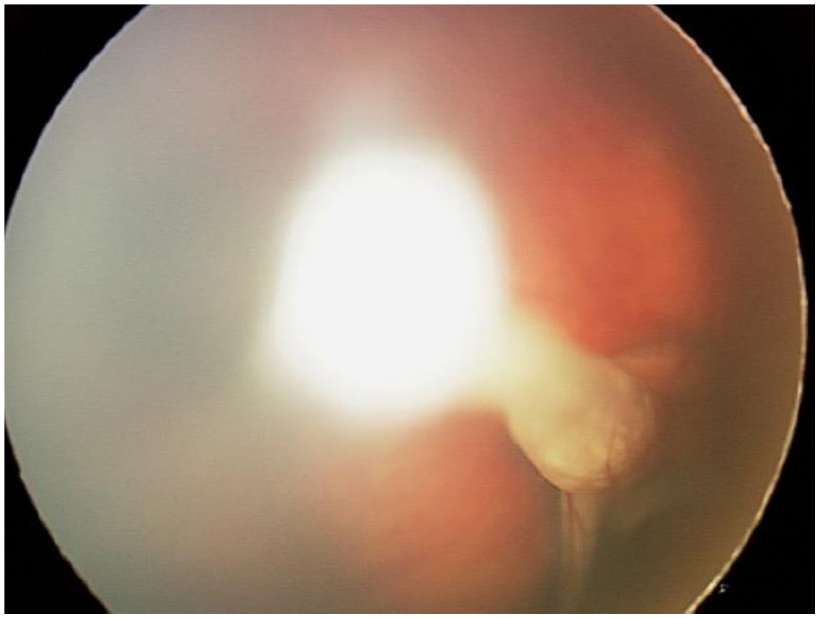

Fig. (2). Persistent fetal vasculature. A dilated fundus examination in the same patient as Fig. (**1**) showed a vascular stalk that was connected to the optic disc. Retinal tissue and vasculature are also pulled up and incorporated into the base of the stalk.

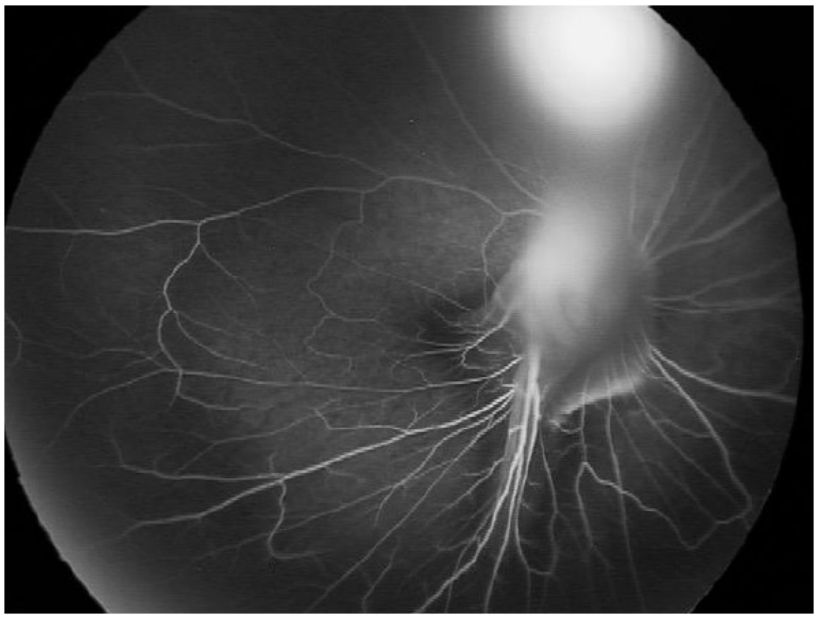

Fig. (3). Persistent fetal vasculature. Widefield fluorescein angiography shows the traction on the retina and an ill-defined macula.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of PFV depends on the extent of disease [2]. The most important disease to rule out when a child presents with leukocoria is retinoblastoma. If the posterior view is challenging, ultrasonography and/or CT/MRI can aid in the diagnosis to detect a mass with calcifications for retinoblastoma. Other anatomic clues such as microphthalmia and elongated ciliary processes will help to distinguish PFV from retinoblastoma also. Advanced tractional retinal detachment from other pediatric vitreoretinopathies should be considered in the differential, such as Norrie disease, familial exudative vitreoretinopathy, incontinentia pigmenti, and retinopathy of prematurity.

MANAGEMENT

The typical child with PFV will present with unilateral leukocoria noted shortly after birth. After retinoblastoma is ruled out, surgical intervention should be considered for visually significant disease. Two- or three-port vitrectomy with stalk transection is performed if a clear stalk presents itself [5 - 7]. Anterior involvement with central stalk insertion will require lensectomy also. In PFV, the stalk tissue is usually integrated into the posterior capsule. If the stalk is inserted eccentrically off the visual axis, the lens may be spared [8].

Once the stalk is clearly visualized, the stalk can be diathermized and intraocular pressure elevated. The stalk is transected either with the vitreous cutter or intraocular scissors. There should be no movement of the stalk during transection, because it can create clefts in the posterior lens. Care must also be taken to avoid severing retinal tissue. This can be at times challenging, because the peripapillary retina can be dragged and wrapped around the stalk tissue, and intrinsic retinal vessels may be mistaken for hyaloid vasculature. For uncomplicated stalk transections, only a limited vitrectomy around the stalk is necessary. Choroidal neovascularization may accompany PFV, which can be treated with anti-vascular endothelial growth factor agents [9]. Visual outcomes will depend on the extent of retinal dysplasia, anatomic success, and postoperative amblyopia care.

CONFLICT OF INTEREST

The authors confirm that they have no conflict of interest to declare for this publication.

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Declared none.

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CHAPTER 19

X-Linked Juvenile Retinoschisis

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X-linked juvenile retinoschisis (XLRS) is a degenerative retinal disease that affects males and usually presents early in life. It is relatively common and characteristically presents with mild to severe loss of central vision, radiating foveal streaks, splitting of the inner retinal layers, most prominently in the retinal periphery, and marked reduction of the b-wave amplitude which results in a negative electroretinogram (ERG) [1, 2]. Disease progression is variable even in families with the same mutation. Visual loss can be worsened by complications such as retinal detachment and vitreous hemorrhage. Minor retinal abnormalities can be found in asymptomatic female carriers [3].

XLRS is a disease of the photoreceptors and bipolar cells. It is caused by mutations in the RS1 gene that encodes a 24kDa discoidin-domain containing protein that is secreted as a homo-oligomeric complex. This complex binds to the surface of photoreceptor and bipolar cells where it helps to maintain cellular organization and the structure of the photoreceptor-bipolar cell synapse [4, 5].

More than 190 mutations in the RS1 gene are known to cause XLRS. The extents to which the different mutations affect the structure and function of retinoschisin have enabled further understanding of its importance to retinal function and pathology [4 - 7].

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Its prevalence ranges from 1:5,000 to 1:20,000, which makes it one of the more common inherited retinal disorders affecting the macula [1]. Presentation at an early age is usually associated with bilateral reduced visual acuity. Acute loss of vision is associated with complications such as hemorrhage or retinal detachment [6, 7].

ESSENTIALS OF DIAGNOSIS

Ophthalmoscopic evaluation reveals the presence of a spoke wheel pattern in the macula in males under the age of 30 (Fig. **1**). Older patients can present with unspecific retinal abnormalities [8]. Fifty percent or fewer patients may present with peripheral retinoschisis (Figs. **2 - 4**). Other findings such as the Mizuo phenomenon or white flecks have also been described [9, 10].

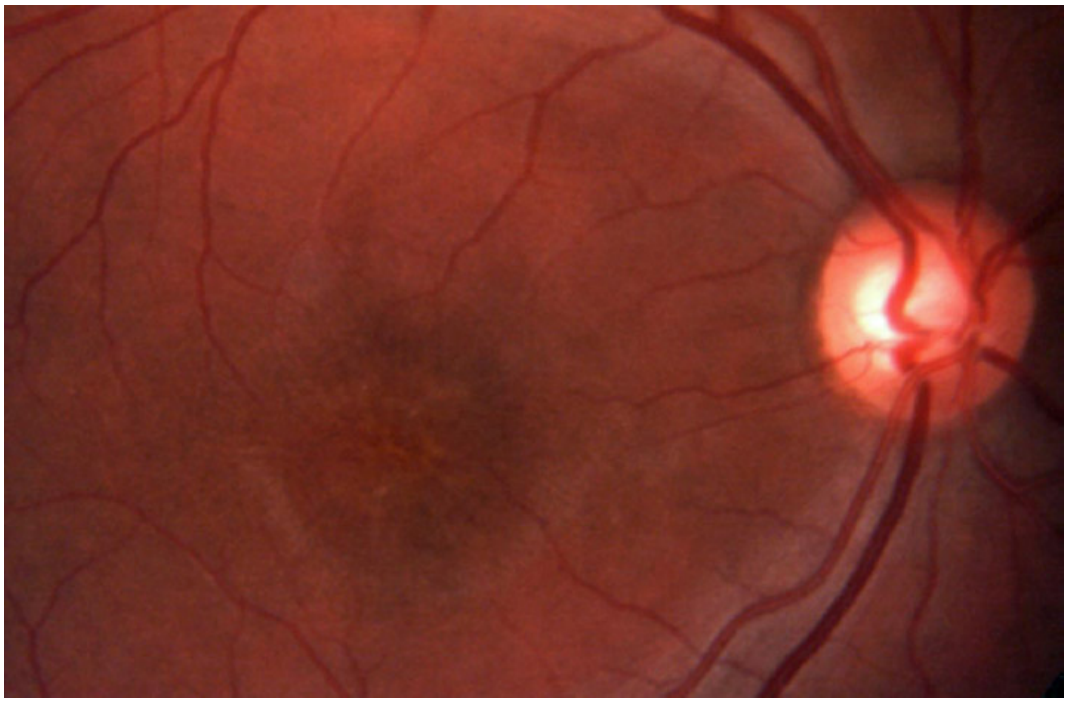

Fig. (1). Color fundus photograph of a 20-year-old male showing the hallmark foveal spoke wheel pattern.

The advent of optical coherence tomography (OCT) has changed the way XLRS is studied and diagnosed, and spectral domain OCT (SD-OCT) has become the mainstay for diagnosis of this disease [11 - 13]. It is relatively easy to obtain even

in young patients, and the tomographic features are very specific to XLRS in pediatric male patients presenting with visual loss (Fig. **5**) [14]. SD-OCT has shown that the area of schisis goes beyond the area observed on ophthalmoscopy and can extend beyond the vascular arcades [15 - 17]. OCT has provided insight into the accurate location of the histologic location of retinal splitting. Cystoid changes involve any retinal layer, mainly the deeper retina (*i.e.*, inner nuclear layer and outer nuclear layer) [18, 19]. Thinning of the nerve fiber layer has also been described. Progressive thinning and epiretinal membrane formation are features of XLRS in older patients that can make the differentiation from other macular dystrophies difficult [20, 21].

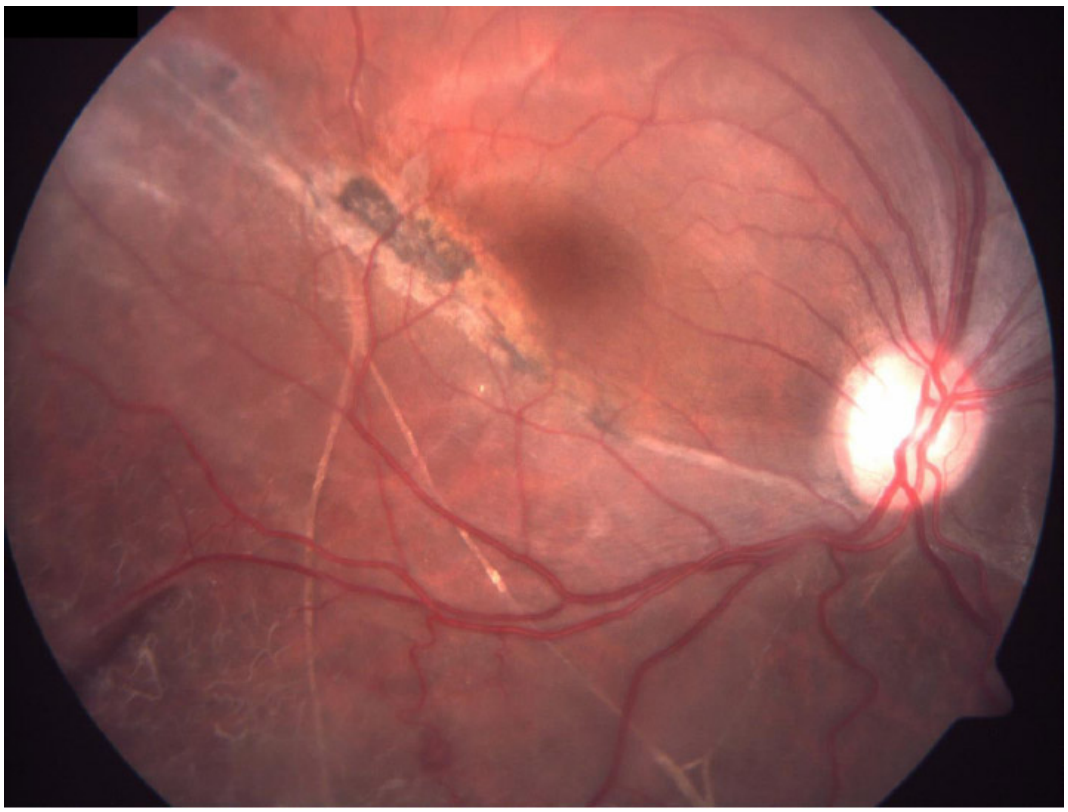

Fig. (2). Color fundus photograph of a 18-year-old male showing inferior retinal schisis that involves the macula. Some intralamellar fibrosis is observed.

Before OCT was available, ERG was the mainstay diagnostic technique for XLRS. A characteristic “negative” ERG pattern observed on dark-adapted retinas

in which the a-wave is greater than the b-wave as compared to the normal pattern is an indicator (Fig. **6**). Light adapted responses show reduced amplitude as well. Khan *et al.* showed disruption of the ON- and OFF-pathways at the level of the bipolar cells as the origin of the retinal dysfunction [22]. Multifocal ERG (mfERG) has demonstrated widespread cone dysfunction as well [23]. Even though OCT has diminished the diagnostic role of ERG in XLRS, ERG still has great value to the differential diagnosis in older patients with unexplained visual loss [24].

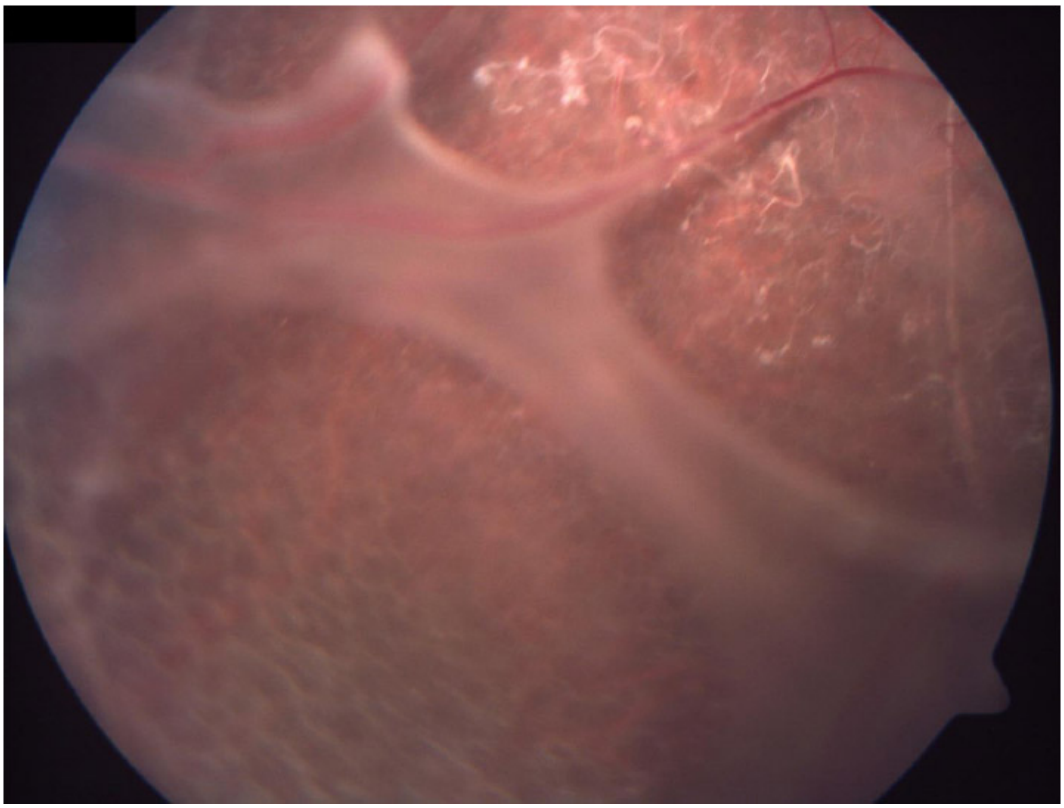

Fig. (3). Color fundus photograph of the same eye as Fig. (**2**), showing the inferior retina with some remnants of the internal lamella, predominantly along the course of major blood vessels.

DIFFERENTIAL DIAGNOSIS

Retinal disorders that present with early onset retinal detachment must be considered in the differential diagnosis of XLRS. These include X-linked Norrie syndrome (NS) and familial exudative vitreoretinopathy (FEVR) both in its x-

linked and autosomal dominant varieties [25, 26]. NS presents with complete retinal detachment at birth and null visual function. FEVR can present with variable retinal abnormalities that may lead to retinal detachment; these findings are distinct from those observed in XLRS.

Other forms of macular dystrophies can be ruled out using SD-OCT.

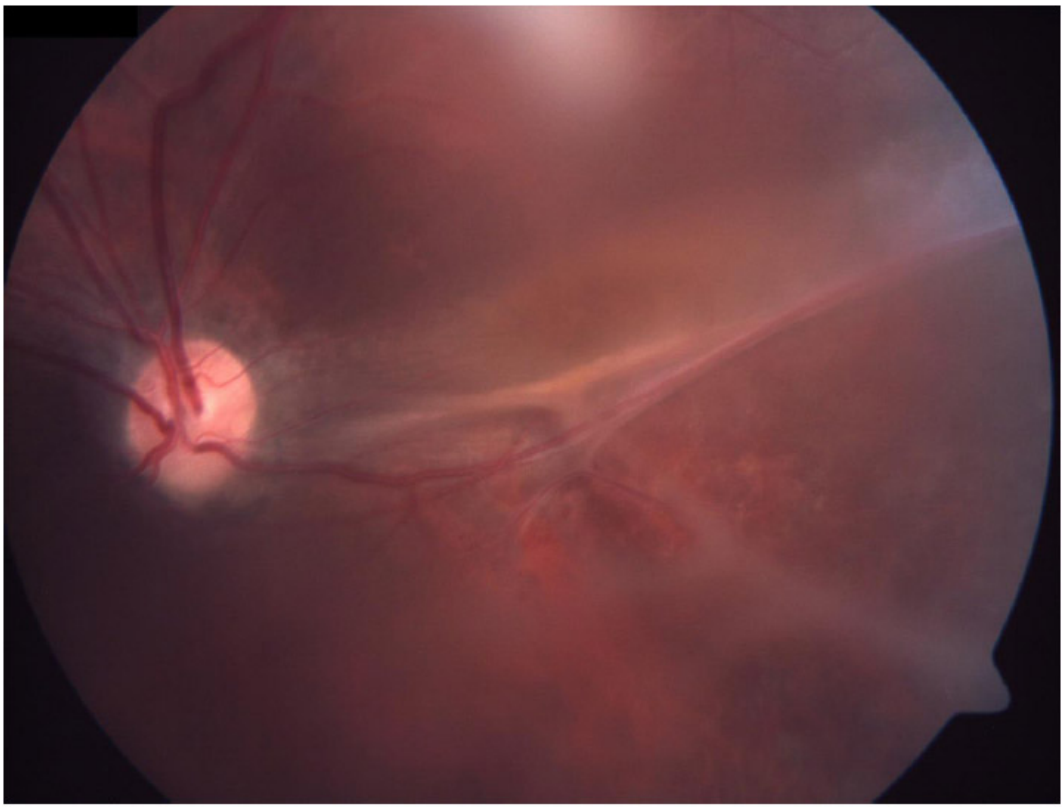

Fig. (4). Color fundus photograph of the contralateral eye of the same patient as Figs. (**2**, **3**), showing inferior schisis and macular dragging.

MANAGEMENT

Treatment of XLRS is mostly limited to the use of vision aids. The use of 2% dorzolamide has shown marked reduction of retinoschisis in select cases [27, 28].

Pars plana vitrectomy is indicated in cases of vitreous hemorrhage and retinal detachment [29, 30].

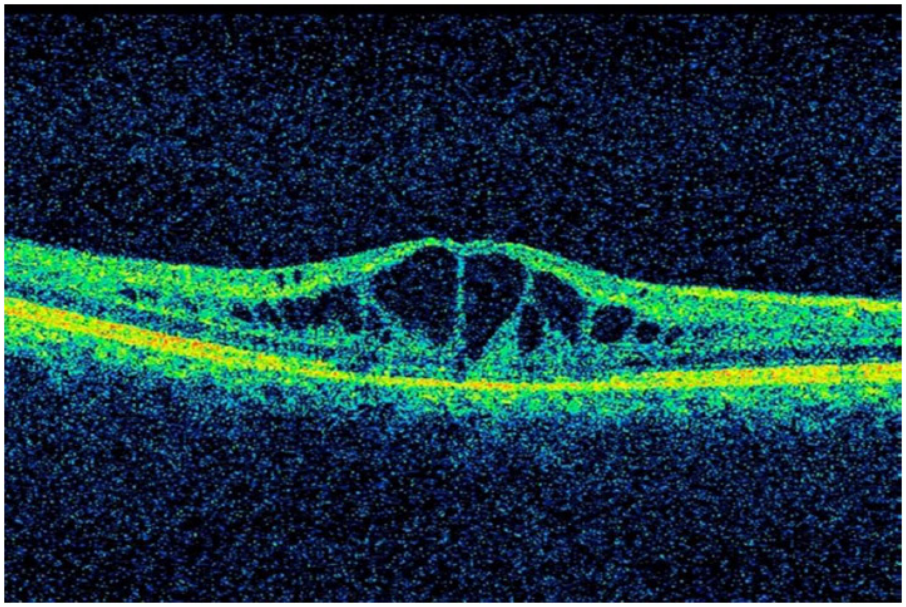

Fig. (5). Foveal SD-OCT shows cystic changes involving all retinal layers in a 20-year-old male.

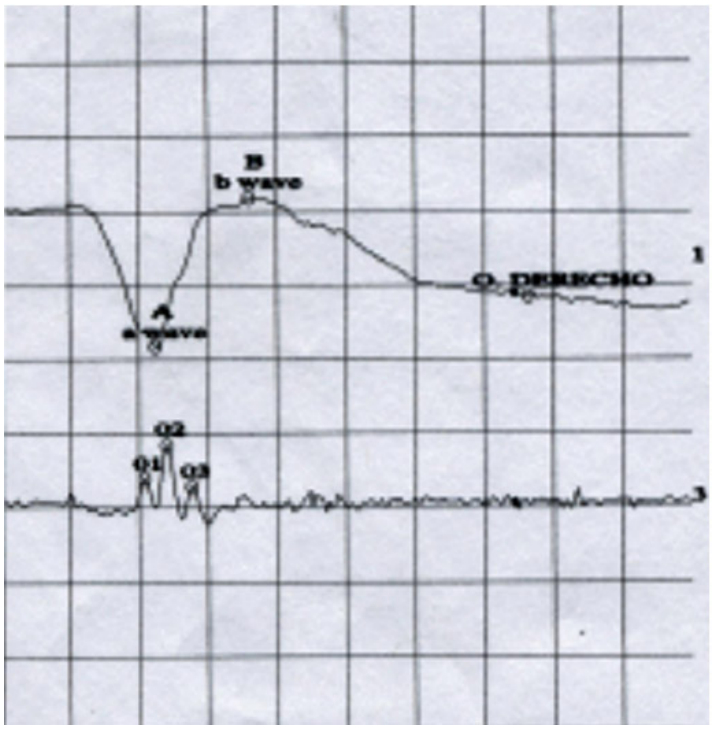

Fig. (6). Characteristic “negative” ERG pattern with a very prominent a-wave and a flat b-wave.

CONFLICT OF INTEREST

The authors confirm that they have no conflict of interest to declare for this publication.

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CHAPTER 20

Incontinentia Pigmenti

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Incontinentia Pigmenti (IP), or Bloch-Sulzberger syndrome, is a rare X-linked dominant syndrome lethal in males characterized by dermatological, ocular, dental, and neurological features [1 - 4]. It is caused by mutations in the NEMO gene located on the q28 portion of X chromosome [5, 6]. This gene is involved in the activation of NFkB, a transcription factor for inflammatory and apoptotic pathway required for many physiological and pathological functions [7 - 9]. The prevalence is 0.7/100,000 [10] and 50-97% of cases have a positive family history [11].

ESSENTIALS OF DIAGNOSIS

IP has four cutaneous stages: Stage 1 is known as vesicular and is characterized by vesiculobullous skin lesions following the lines of Blaschko (Fig. **6**); it presents at birth in 50% of patients (Figs. **10, 11**); stage 2 is reported in 70% of patients with IP and is marked by verrucous lesions appearing between 2 and 6 months of age; stage 3 is characterized by linear brownish pigmentation (Fig. **4**) and atrophy most common in extremities; stage 4 represents the sequelae of IP, characterized by areas of hypopigmentation (Figs. **5, 9**) and alopecia (Fig. **7**) [3, 5, 9].

Histopathology in the early stage shows intraepithelial cleft with eosinophils; the verrucous stage is characterized by hyperkeratosis and acanthosis; and later stages

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show the typical macrophages containing melanin in the sub-epithelial connective tissue (Fig. **3**) [2].

Ophthalmologic manifestations are present in 35%, and approximately 20% will develop vision threatening disease [1, 4, 10] including strabismus, nystagmus, microphthalmia, iris hypoplasia, cataracts, glaucoma, and optic atrophy [1]. Retinal complications are the most severe and arise as a result of peripheral ischemia with microvasculature abnormalities and neovascularization (Figs. **1, 2, 5, 12**). The presence of retrolental mass with detachment or dysplastic retina is typical [7, 9]. Neurologic manifestations are present in one third of patients with IP, from seizure episodes to severe motor and intellectual impairment [5, 10].

A B C

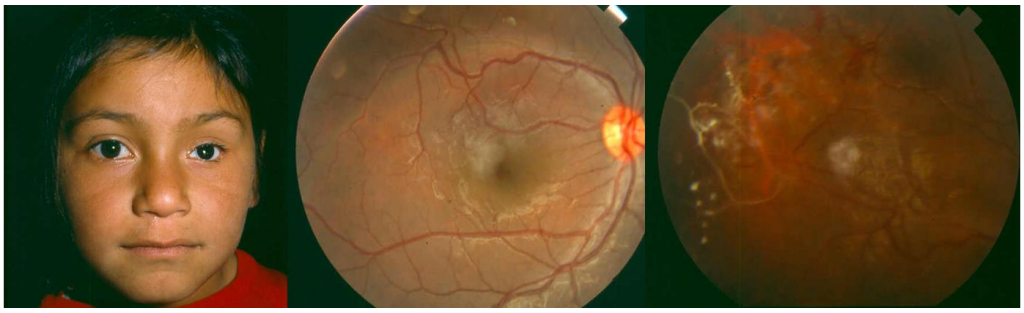

Fig. (1). (**A**). Patient 1, a 12-year-old patient with prosthesis on the left eye. (**B-C**). Fundoscopy of right eye showing peripheral non-perfusion and vasculature anomalies.

A B

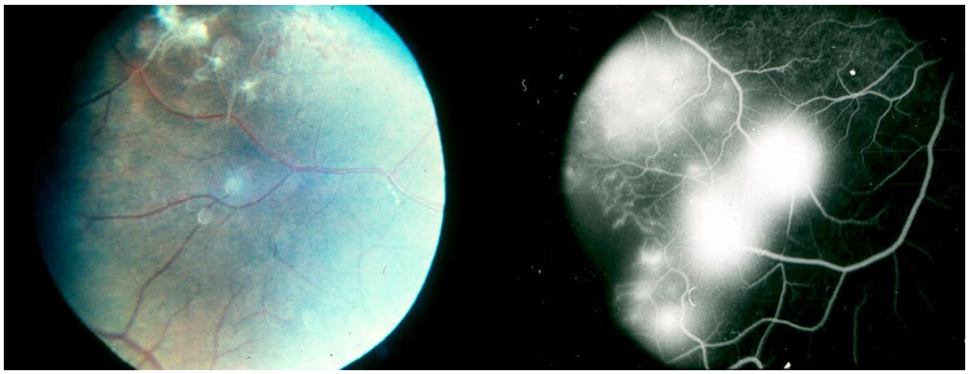

Fig. (2). (**A-B**). Fundoscopy and fluorescein angiography of patient 1 showing peripheral non-perfusion and neovascularization with leaking vessels.

Other alterations include alopecia, scoliosis, spina bifida, syndactyly, ear defects, short stature, oligodontia, anodontia, deformities of teeth (Fig. **8**), soft palate hypoplasia, and prominent chin and facial asymmetry [6, 11].

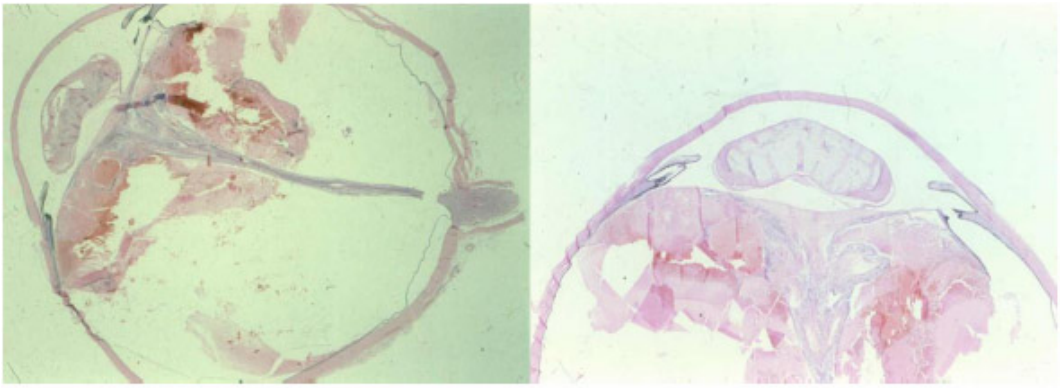

Fig. (3). Histopathology of enucleated left eye of patient 1 showing eosinophilic infiltration, iris hypoplasia, atrophic retina, and retrolental fibroplasia (Courtesy of Gomez Leal MD, Mexico).

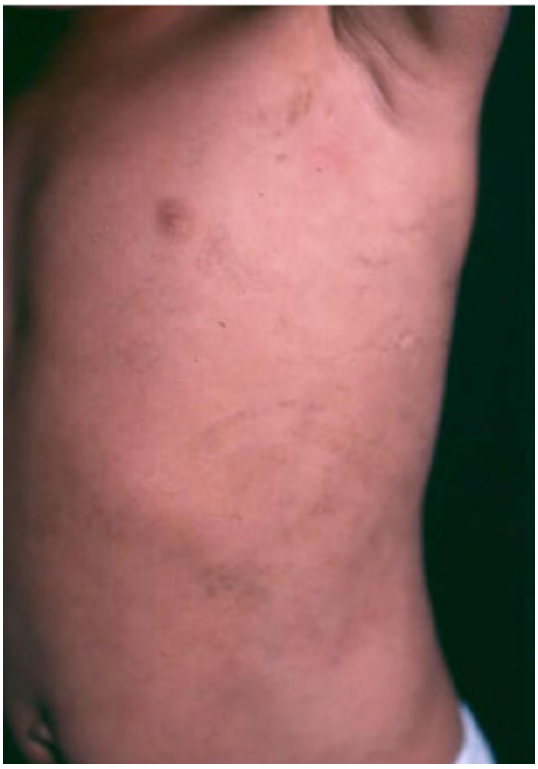

Fig. (4). Patient 1 with areas of linear skin hyperpigmentation lesions.

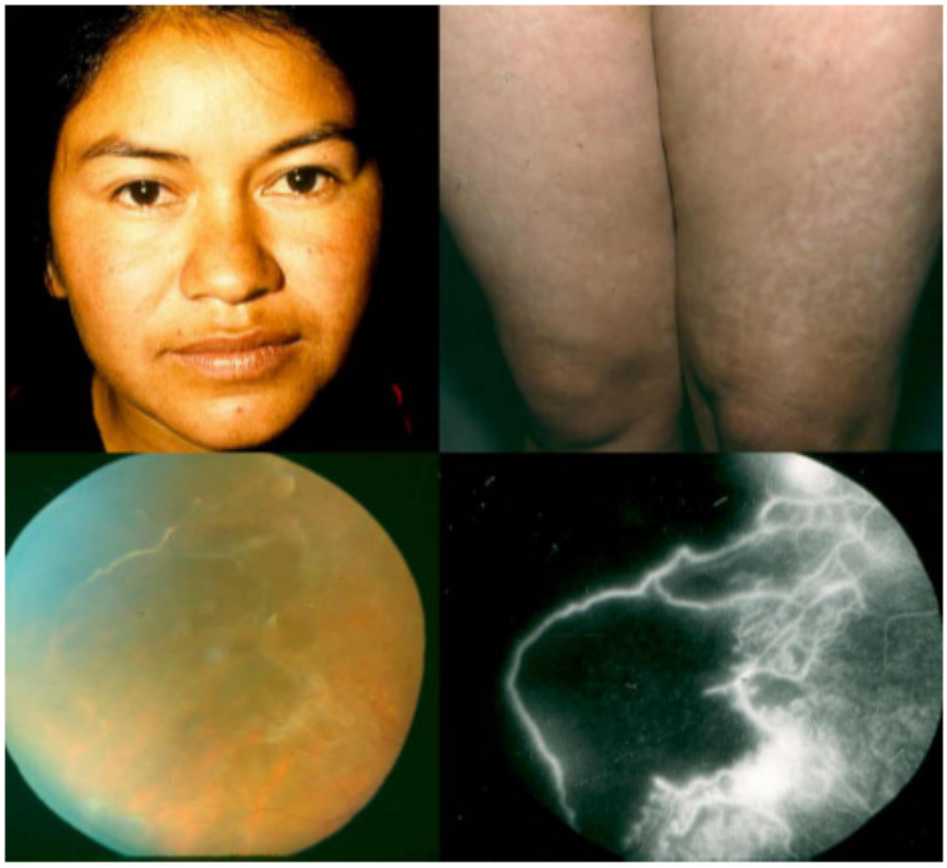

Fig. (5). Patient 2. Mother of patient 1 with incontinentia pigmenti (IP) showing ocular asymmetry, hypopigmentation and absence of hair in lower extremities. Fundoscopy and fluorescein angiography showing extended areas of non perfuse retina.

The diagnosis can be made by molecular study or biopsy [7]. Clinical diagnosis is based on Landy and Donnai criteria [3, 4]. Major criteria include typical neonatal vesicular rash with eosinophilia, hyperpigmentation on the trunk that disappears in adolescence and lineal, atrophic lesions with absence of hair. Minor criteria include dental anomalies, alopecia, wooly hair, abnormal nails, ocular anomalies, history of multiple miscarriages of male child, and typical features on cutaneous histology [8]. If there is no family history of IP and NEMO mutations are unknown, at least 2 major criteria or 1 major and 1 minor criteria are required for the diagnosis. If there is family history of IP and NEMO mutations are unknown, one major criteria or 2 minor criteria are required for the diagnosis; on the other

hand, if NEMO mutations have been confirmed, any major or minor criteria make the diagnosis [3, 8].

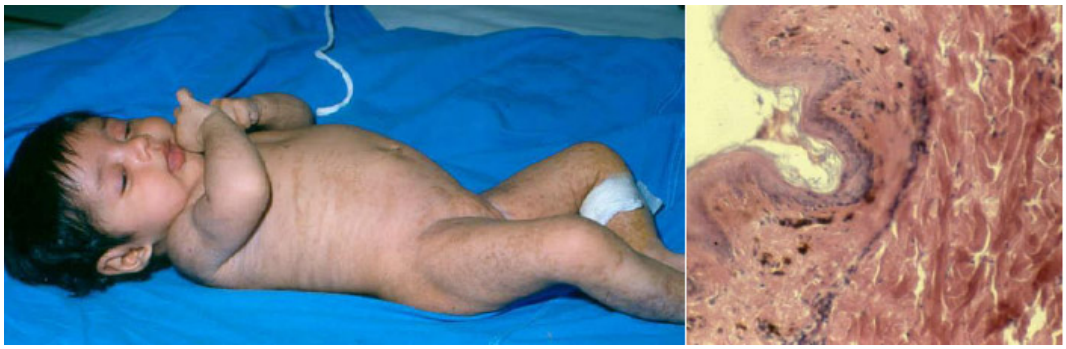

Fig. (6). Patient 3 showing papular and erythematous skin lesions along Blaschko lines. Skin biopsy was performed on left leg.

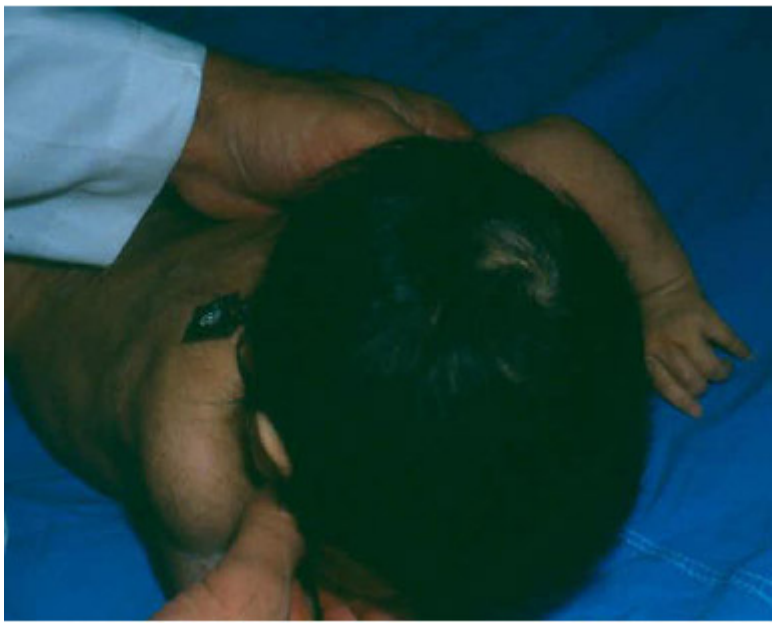

Fig. (7). Patient 3 showing alopecia, a typical finding in IP patients.

DIFFERENTIAL DIAGNOSIS

Vesicular and pustular lesions in children are challenging and include a variety of pathologies such as herpes simplex virus, impetigo, lichen striatus, linear lichen planus, linear psoriasis, inflammatory linear verrucous epidermal nevus,

incontinentia pigmenti, phytophotodermatitis, and allergic contact dermatitis [3, 12]. Dental anomalies in IP may be mistaken with congenital syphilis or ectodermal dysplasia [5]. Other vascular diseases that should be considered include retinopathy of prematurity, sickle cell disease, and Eales disease.

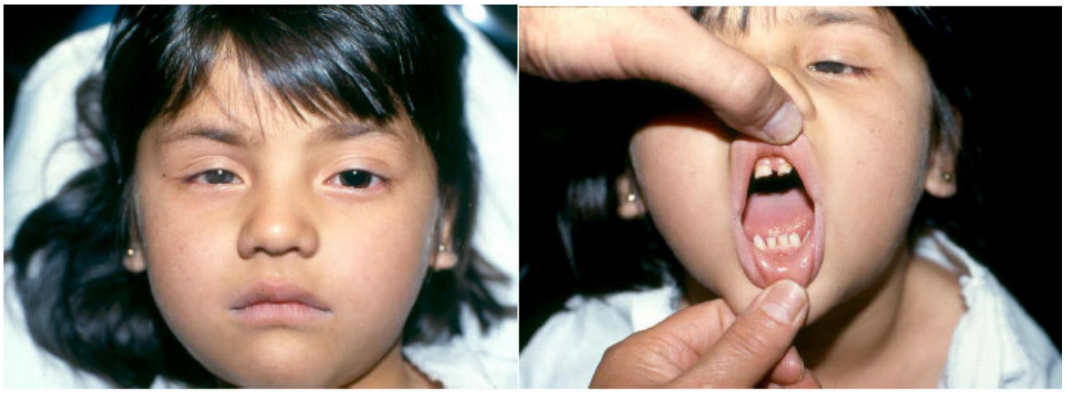

Fig. (8). Patient 3 followed years later showing ocular asymmetry with oral anomalies that include malformed anterior teeth and dental agenesis.

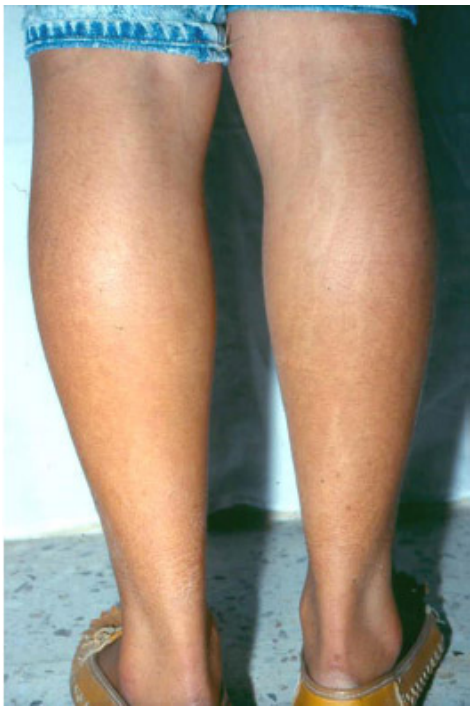

Fig. (9). Patient 3 showing linear hypopigmentation lesions in lower extremities.

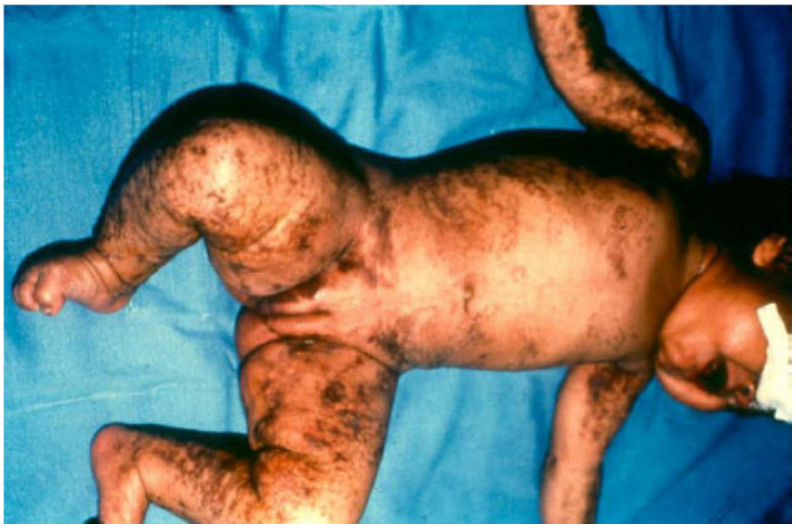

Fig. (10). Newborn patient with vesiculobullous and verrucous lesions in the skin along the Blaschko lines.

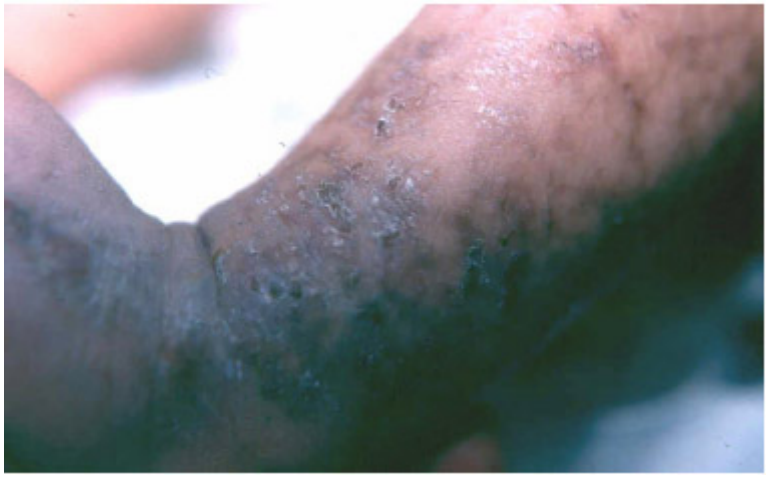

Fig. (11). Left arm of newborn patient with typical IP skin lesions.

MANAGEMENT

Cutaneous manifestations do not require specific treatment. Ophthalmologic alterations may progress to retinal detachment, so the recommendation is to examine patients at birth and regularity during childhood [3]. Peripheral non-perfused retina can be treated with photocoagulation or cryotherapy; new therapy with anti-vascular endothelial growth factor have been used in some case reports [1, 13].

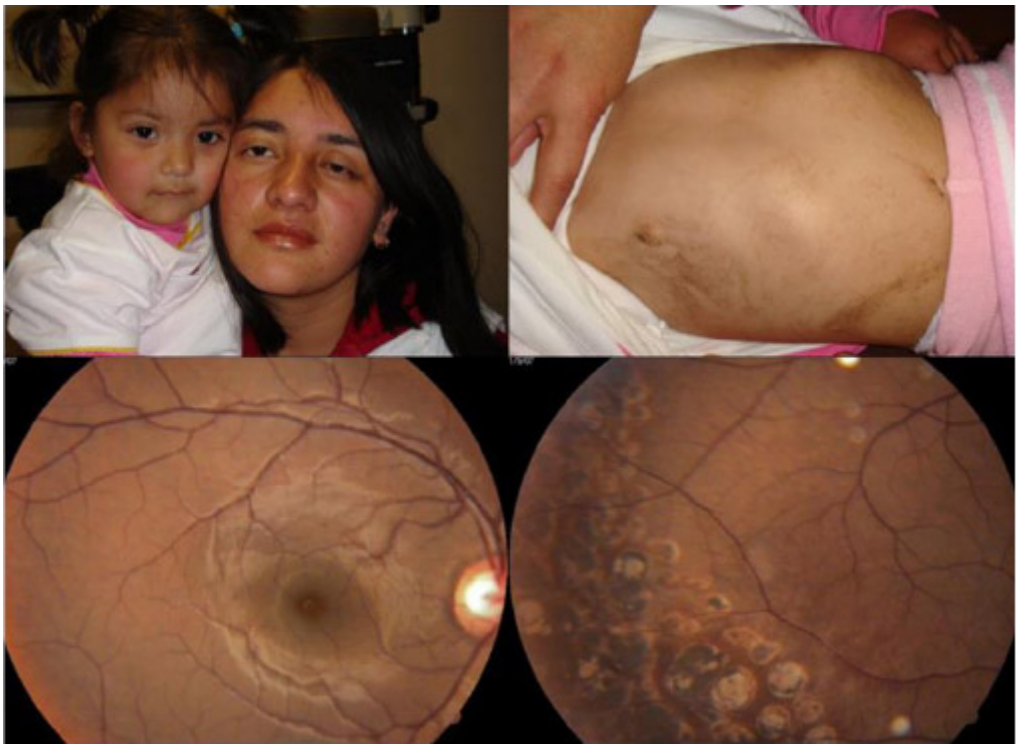

Fig. (12). Family history of IP in mother and daughter. Trunk of daughter shows lineal hyperpigmentation following Blaschko lines with no ocular involvement. Fundoscopy of mother without alterations (right eye) and peripheral retinal photocoagulation (left eye).

CONFLICT OF INTEREST

The authors confirm that they have no conflict of interest to declare for this publication.

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Declared none.

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CHAPTER 21

Congenital Prepapillary Vascular Loop

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A prepapillary vascular loop is a very rare congenital malformation of the vasculature that emerges from the optic nerve. Its incidence is low, ranging from 1 in 2000 to 1 in 9000, and are mostly unilateral. Bilateral loops occur in 9-17% of cases. They are most often asymptomatic and detected in routine ophthalmologic examinations. However, they have been associated with retinal vascular occlusive disease, vitreous hemorrhage, and complications during vitrectomy [1]. Prepapillary optic nerve head loops may be arterial (arteriole), or less commonly, venous (venule). They may occur in and around the optic nerve head, particularly the arteriole, and may bleed into the vitreous [1 - 4].

ESSENTIALS OF DIAGNOSIS

Clinical features: The condition is usually asymptomatic, unless it is complicated with sudden vascular obstruction or bleed [2, 3]. Occlusive events may be facilitated by hemodynamic or intravascular changes associated with exercise and complicated by ischemic events by twisting or thrombosis of the loop [4]. Patients with these complications present with a history of sudden blurred vision, amaurosis fugax, or visual field defect in their eyes [2].

Signs: Loops may take different shapes (hairpin, figure-eight, or corkscrew). They usually emerge from the optic disc, protruding into the vitreous cavity (Fig. **1**). The loops often exhibit movement within the vitreous and cast a shadow on the surrounding fundus. They may be pulsatile. The pathogenesis of the vitreous hemorrhage occurring in and around these loops is uncertain but is probably

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caused by rupture of small vessels near the base of the loop caused by its movement when pulled by the vitreous. Loops are also associated with branch retinal artery occlusion. Two different mechanisms are thought to be the cause of occlusion: twisting of the loop or thrombosis or following a Valsalva-like mechanism [5 - 7]. The length of the loop is thought to be a key predisposing factor since the twisting of the vessel and turbulent flow encourage thrombus formation [8].

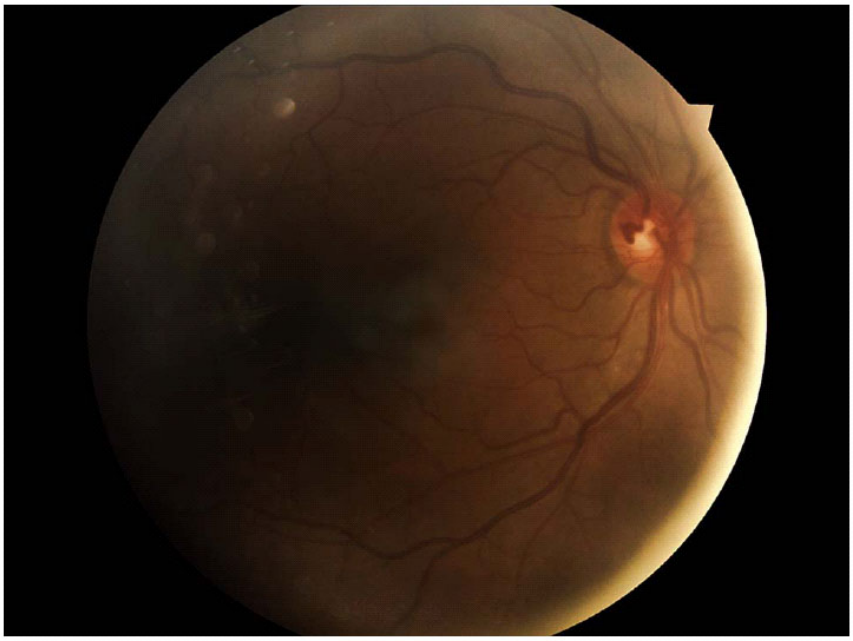

Fig. (1). Color fundus photograph of right optic disk showing prepapillary loop (Image courtesy of Gerardo Garcia-Aguirre, MD).

DIFFERENTIAL DIAGNOSIS

Arterial loops are much more common than venous loops. Fluorescein angiography is the diagnostic method of choice to distinguish between them [8]. Congenital venous vascular loops should be differentiated from acquired dilated venous collateral channels (optocilliary vessels) caused by retinal venous obstruction and meningioma of the optic nerve. Associations between prepapillary vascular loop and persistent fetal vasculature [1] and macroaneurysm [9] have been reported.

MANAGEMENT

Congenital prepapillary vascular loops are usually asymptomatic and do not require treatment. Possible complications are vitreous hemorrhage and venous or arterial thrombosis. When present, vitreous hemorrhage may be treated with pars-plana vitrectomy [3]. Care must be taken to minimize vitreous traction when performing the procedure to avoid breakage of the loop and subsequent intraoperative bleeding, which sometimes may be difficult to control.

CONFLICT OF INTEREST

The author confirms that author has no conflict of interest to declare for this publication.

ACKNOWLEDGEMENTS

Declared none.

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CHAPTER 22

Chorioretinal Coloboma

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Colobomas occur due to an incomplete closure of the embryonic fissure of the eye, which is supposed to occur during the sixth and seventh weeks of gestation [1], which results in a lack of tissue in the chorid, retina, or both [1]. It is of congenital nature, and may affect other tissues, such as the eyelid, iris, ciliary body and optic nerve [2]. It has an incidence of 0.14% in the general population, and it is associated with a very high risk (up to 40%) of retinal detachment [3].

Colobomas may appear as an isolated finding, or be associated to other conditions, such as neurological disorders, chromosomal disorders, and other syndromes (such as the CHARGE association or Goldenhar syndrome) [4 - 7].

ESSENTIALS OF DIAGNOSIS

Chorioretinal colobomas are in many instances asymptomatic. Symptoms vary according to the ocular structures affected. Complications are frequent and may profoundly affect visual acuity, especially if the macula or the optic disc are involved. Visual field defects are rarely perceived by the patient due to the

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congenital nature of this condition. However, choroidal neovascularization or retinal detachment are common complications that can cause further reduction of visual acuity later in life.

Most colobomas are readily apparent in ophthalmologic examination. They appear as a yellowish lesion with well-defined circular borders, almost always in the inferior part of the globe, where there is a trace of hypoplastic retinal tissue (known as *intercalary membrane*), and no retinal pigment epithelium or choroid. The sclera is thin, usually producing a staphyloma (Figs. **1**-**3**, **5**).

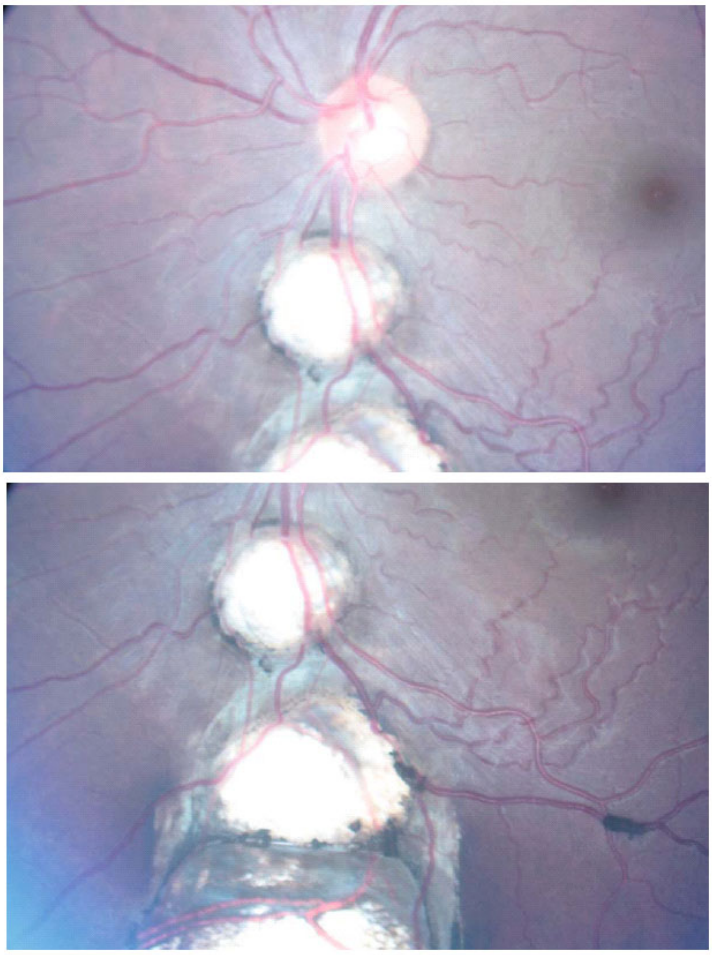

Fig. (1). Fundus photographs: Small multiple chorioretinal coloboma inferior to optic nerve (Courtesy of Alejandra Scaraffia, Mendoza, Argentina).

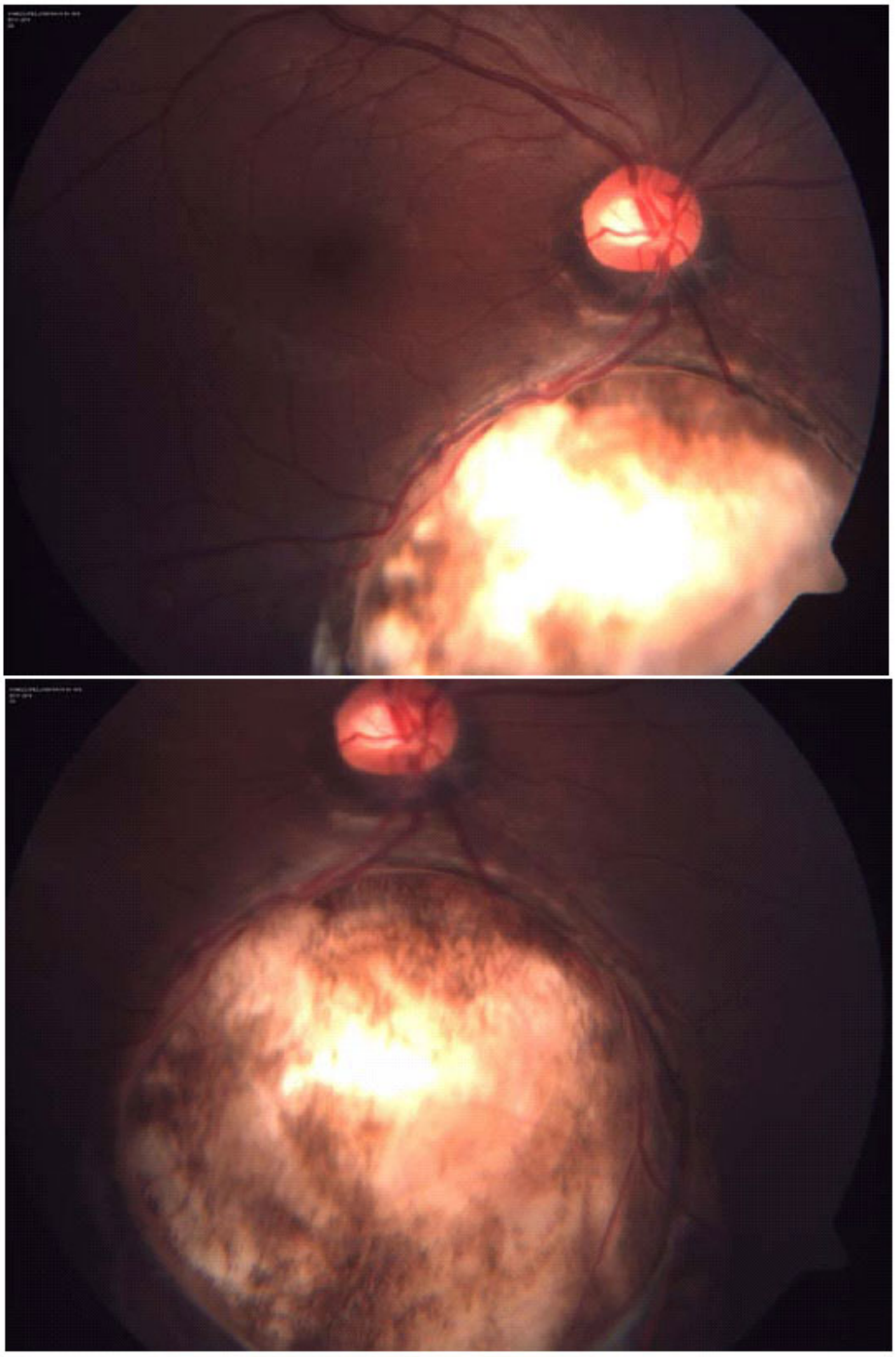

Fig. (2). Fundus photographs of inferonasal chorioretinal coloboma.

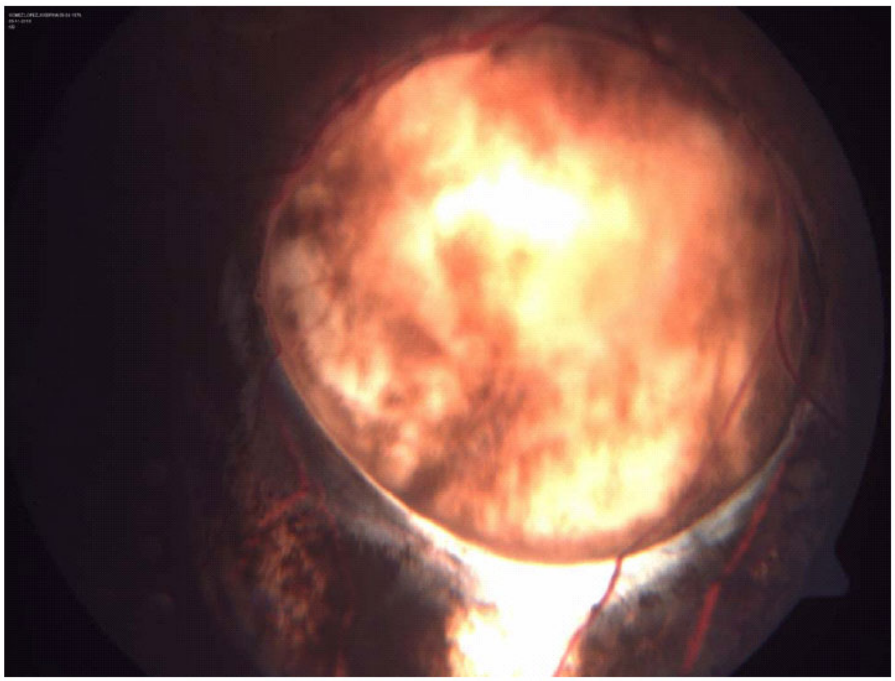

Fig. (3). Fundus photograph: Magnified view of chorioretinal coloboma of the same patient of Fig. (**2**). Yellow-white appearance with hyperpigmented margins.

Sometimes, a chorioretinal coloboma may be accompanied by a coloboma in the iris, which is located inferiorly, rendering the pupil keyhole-shaped (Fig. **4**).

The incidence of retinal detachment is very significant in eyes with chorioretinal colobomas (Fig. **6**). It ranges from 8.1% to 43% in hospital based series [8, 9], and 4% in the general population [10]. Although there are rare cases where spontaneous retinal reattachment has been reported [11, 12], most cases require vitreoretinal surgery, prognosis being relatively poor [13 - 15].

OCT imaging of the margin of the coloboma shows that the union of the normal retina with the intercalary membrane may be gradual or abrupt, and that subclinical retinal detachments are more frequent than previously thought [16].

B-scan ultrasonography may show chorioretinal and optic disc coloboma in case of media opacities and is an adjuvant for the clinical assessment in case of associated retinal detachment before (Fig. **7**) and after surgery.

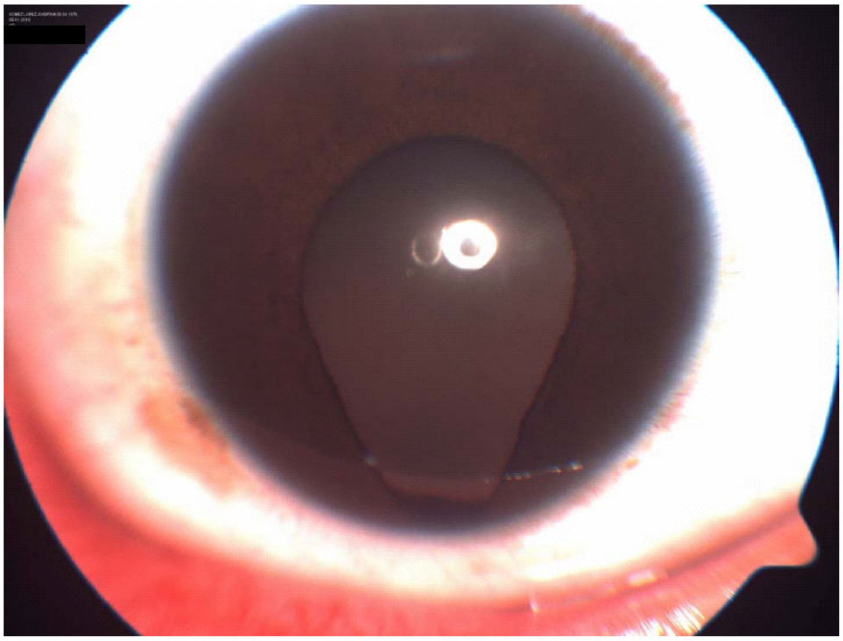

Fig. (4). Anterior segment photography: Coloboma of the iris in the same patient.

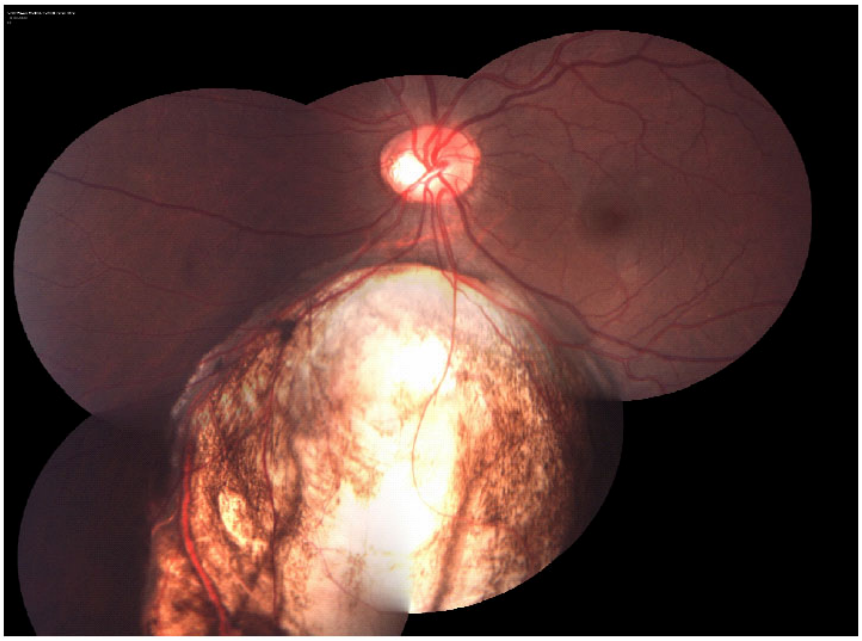

Fig. (5). Colour fundus photograph: Large chorioretinal coloboma in the inferonasal quadrant.

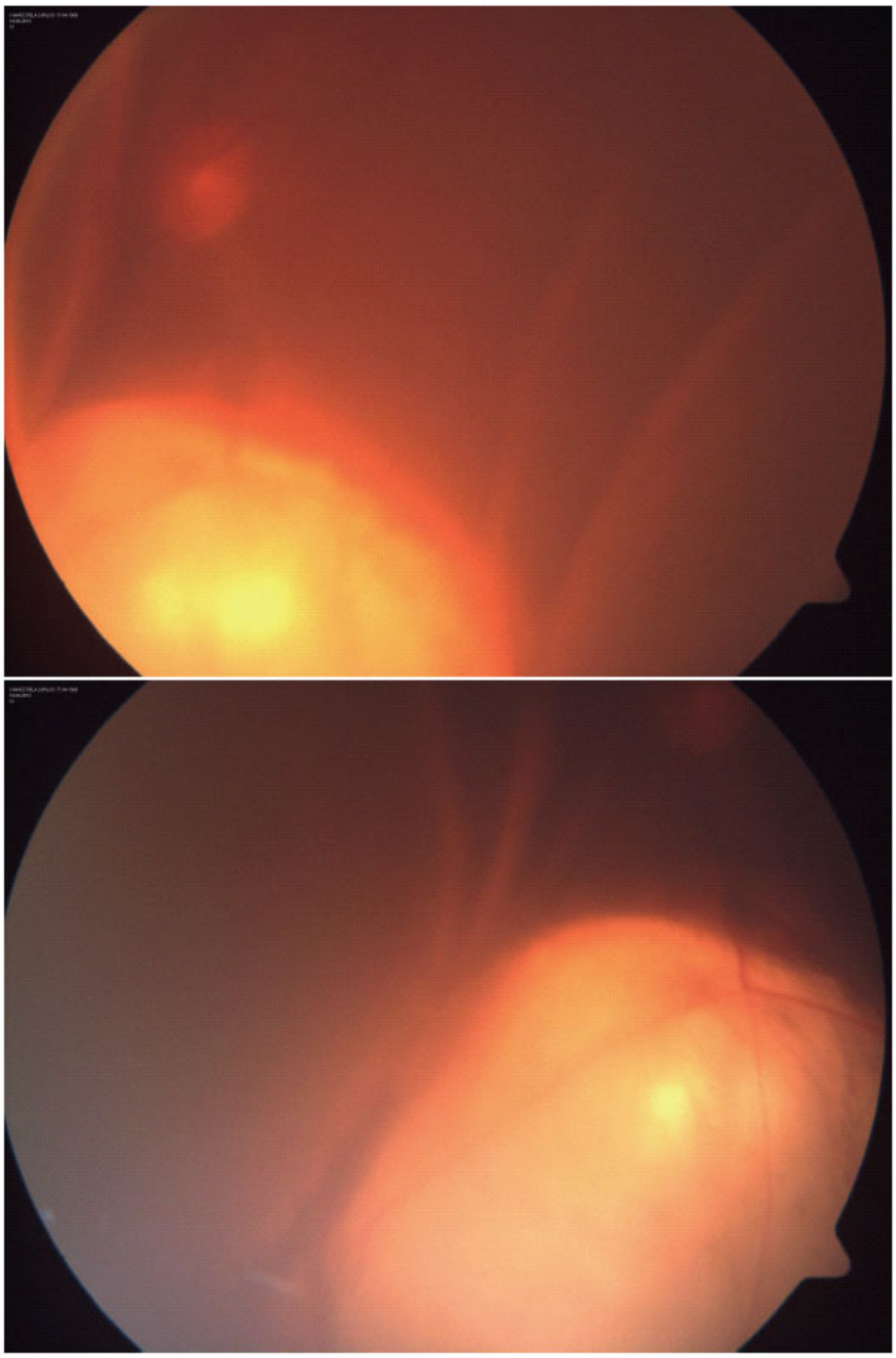

Fig. (6). Colour fundus photograph: Retinal detachment associated with choroidal coloboma.

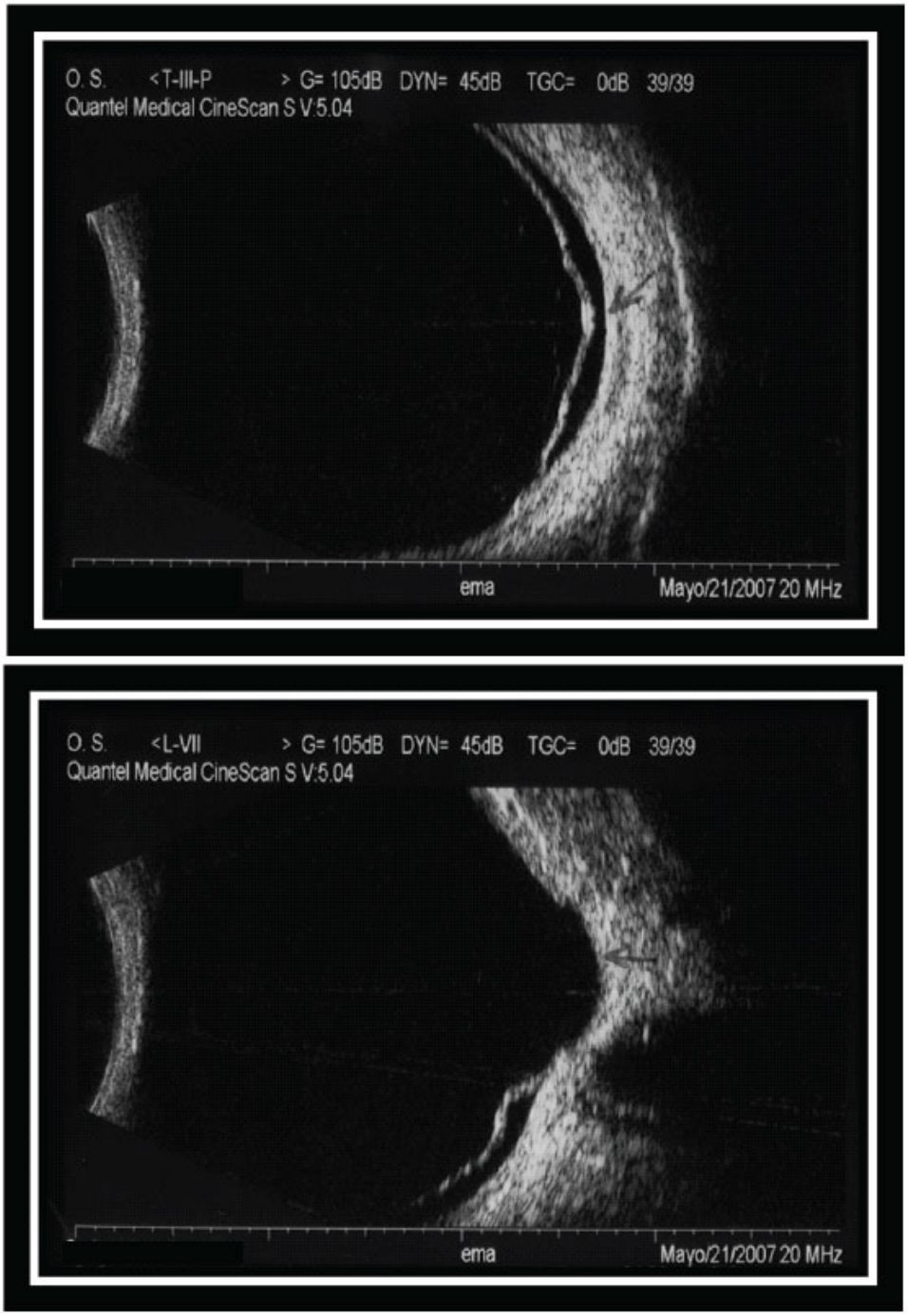

Fig. (7). B-scan ultrasonography shows chorioretinal coloboma with associated retinal detachment.

DIFFERENTIAL DIAGNOSIS

The clinical appearance of colobomas of the retina and choroid is usually so typical, that differential diagnosis is rarely a challenge. Chorioretinal scars secondary to inflammatory or infectious conditions (*e.g.* toxoplasmosis) may resemble a small coloboma. Staphylomas due to other causes (such as high myopia) should also be ruled out.

MANAGEMENT

The single most important factor impacting visual acuity is the preservation of a normal foveal structure [17, 18]. When no complications are present, spectacle correction of refractive errors is advised. Patients should also be referred to a genetics consult [19]. If a choroidal neovascularization develops, treatment with anti-VEGF and follow up with OCT is advised.

Retinal detachments associated with a chorioretinal coloboma pose a therapeutic challenge [20]. Occasionally, detachments may be secondary to a retinal hole outside the coloboma (known as Type I detachments), in which case they are treated conventionally using scleral buckling, vitrectomy, or both. However, detachments may be secondary to breaks within the coloboma (known as Type II detachments). These breaks are harder to identify, since the intercalary membrane is really thin, they are usually posterior to the equator, and there is no retinal pigment epithelium to provide adhesion when treated with cryotherapy or laser photocoagulation. Type II detachments are usually treated with pars plana vitrectomy and silicon oil as tamponade [20].

CONFLICT OF INTEREST

The authors confirm that they have no conflict of interest to declare for this publication.

ACKNOWLEDGEMENTS

Declared none.

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CHAPTER 23

Bergmeister Papilla

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The term "Bergmeister papilla" refers to the presence of fibrous glial tissue just anterior to the optic disc. It is present since birth, and it is a remnant of the fibrous sheath that normally surrounds the hyaloid artery during fetal life as it arises from the optic disc. This tissue is called the central supporting tissue meniscus of Kuhnt [1].

ESSENTIALS OF DIAGNOSIS

Clinical features: Bergmeister's papilla is usually asymptomatic, the visual acuity is unaffected by the abnormality, and systemic associations are generally lacking [1, 2].

Signs: A small mass of glial tissue takes the form of a veil-like membrane overlying the optic disc, it is also referred to as epipapillary membrane (Figs. **1** and **2**). The glial tissue often fills in the optic cup such that the cup is obliterated; a visible white, fibrous remnant that is seen on ophthalmoscopy to overlay the optic disc. The nasal side of the disc is more frequently involved than the temporal side. Absence of physiologic cupping can also be seen in affected eyes [1, 2].

DIFFERENTIAL DIAGNOSIS

Differential diagnosis should be with diseases that can produce peripapillary membranes, such as ischemic retinopathies; however, these membranes are

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accompanied by retinal alterations and the membranes are vascularized. Bergmeister papilla is avascular.

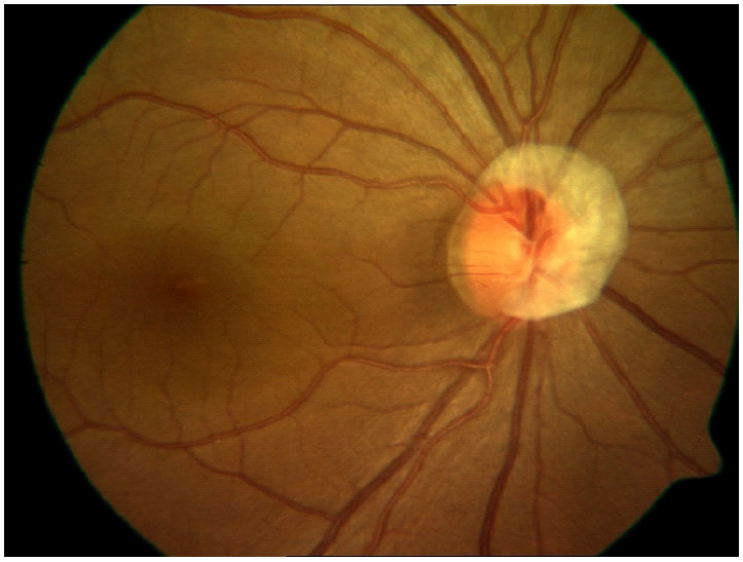

Fig. (1). Bergmeister's papilla. Presence of fibrous tissue anterior to the optic disc (Photograph courtesy of the Pathology Department Image Archive, Asociación para Evitar la Ceguera en México).

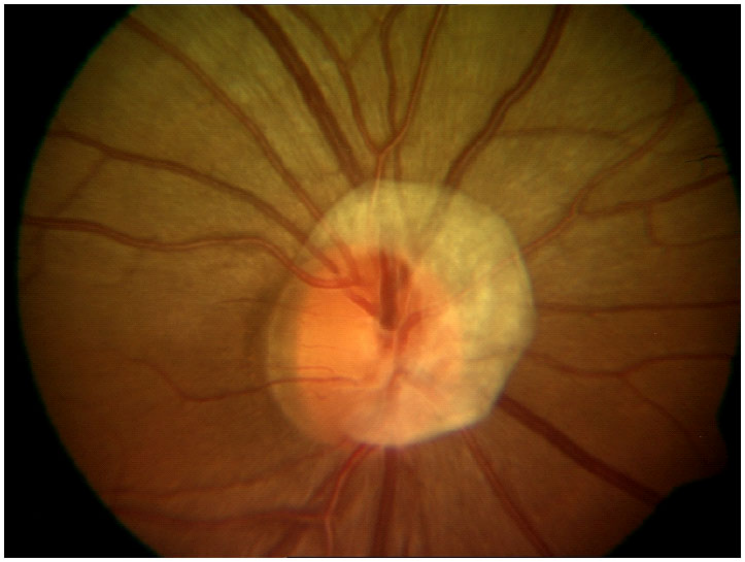

Fig. (2). Close up of Fig. (**1**) , showing a thin veil-like membrane anterior to the optic disc, affecting predominantly the nasal side (Photograph courtesy of the Pathology Department Image Archive, Asociación para Evitar la Ceguera en México).

One publication reports association with aniridia, microcornea, and myopia [3]. Optic Coherence Tomography (OCT) provides non-invasive visualization of the fibrous tissue and its relation with the vitreoretinal interface [4].

MANAGEMENT

Bergmeister's papilla by itself does not require treatment, does not affect visual acuity, and does not produce symptoms.

CONFLICT OF INTEREST

The author confirms that author has no conflict of interest to declare for this publication.

ACKNOWLEDGEMENTS

Declared none.

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CHAPTER 24

Optic Disc Pit

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Optic disc pit (ODP) is a rare, congenital excavation of the optic nerve head, described by Wiethe in 1882 [1]. Usually seen in association with other abnormalities including large optic nerve head size, large inferior colobomas of the optic disc, and retinal colobomas. These associations may suggest a common origin, caused by an incomplete closure of the embryonic fissure [2].

ESSENTIALS OF DIAGNOSIS

A congenital ODP is usually a solitary, whitish depression, usually located in the inferotemporal portion of the optic disc (Fig. **1**). It may be asymptomatic, but may also be associated to serous retinal detachment or cystoid retinal edema in the macular area [3, 4]. Presence of a pit and serous detachment is really uncommon at the nasal margin of the optic disc (Figs. **4**-**7**). It may occur bilaterally in 10 to 15% of cases and may be inherited as an autosomal dominant abnormality [5].

Approximately one-half to two-thirds of optic disc pits are associated with maculopathy, classically, serous retinal detachment. The maculopathy can be discovered on slit-lamp funduscopic examination or with direct or indirect ophthalmoscopy [1 - 3]. Fluorescein angiography and OCT may provide further elucidation [1, 4, 6] (Fig. **2**).

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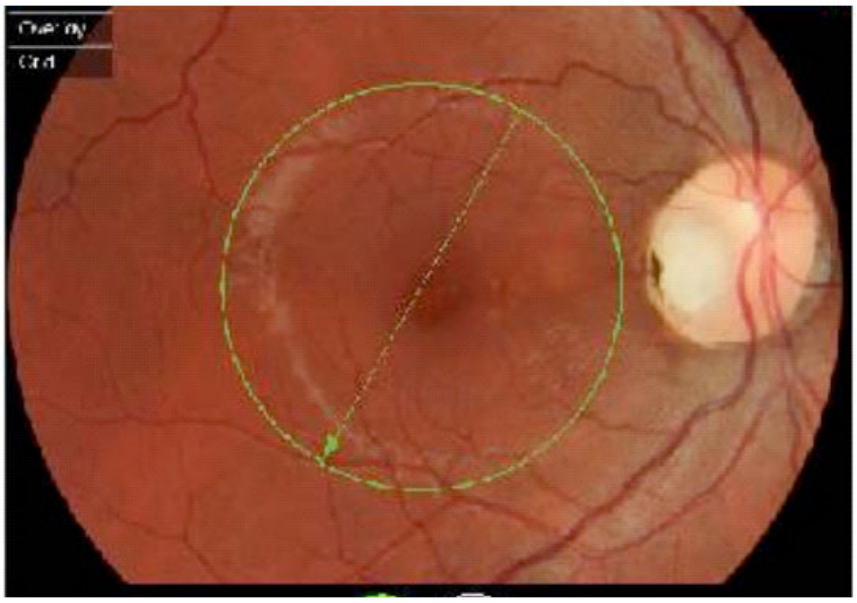

Fig. (1). Color fundus image of a 24-year-old female with congenital optic pit and recent vision loss secondary to optic pit maculopathy.

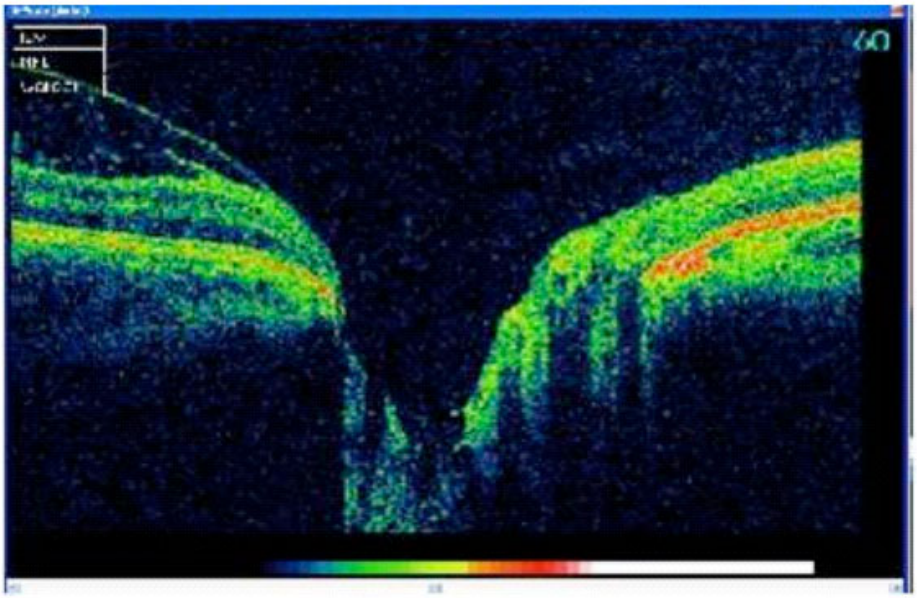

Fig. (2). OCT scan with schisis-like cavity extending from the optic disc to the macula and cystoid macular edema.

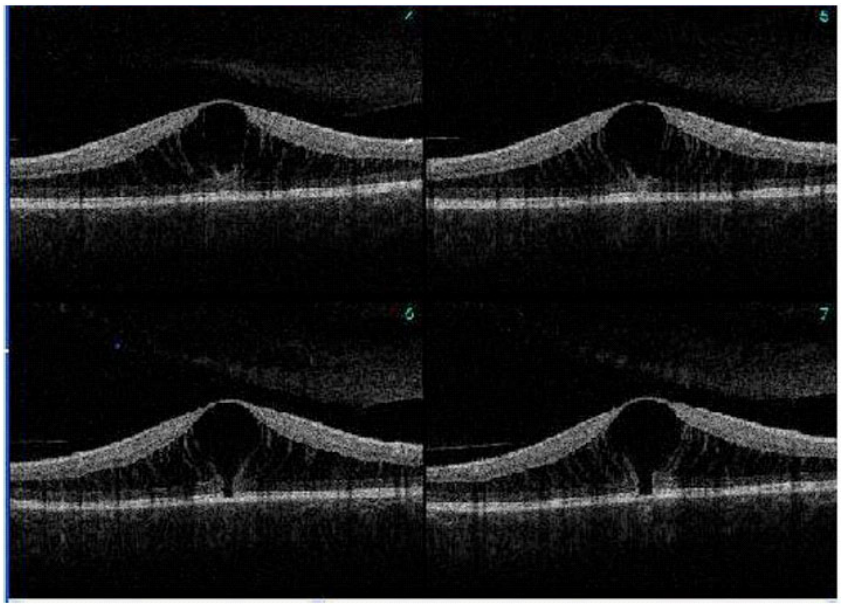

Fig. (3). OCT of the same patient of Fig. (**1**). Intraretinal cyst formation in macular area.

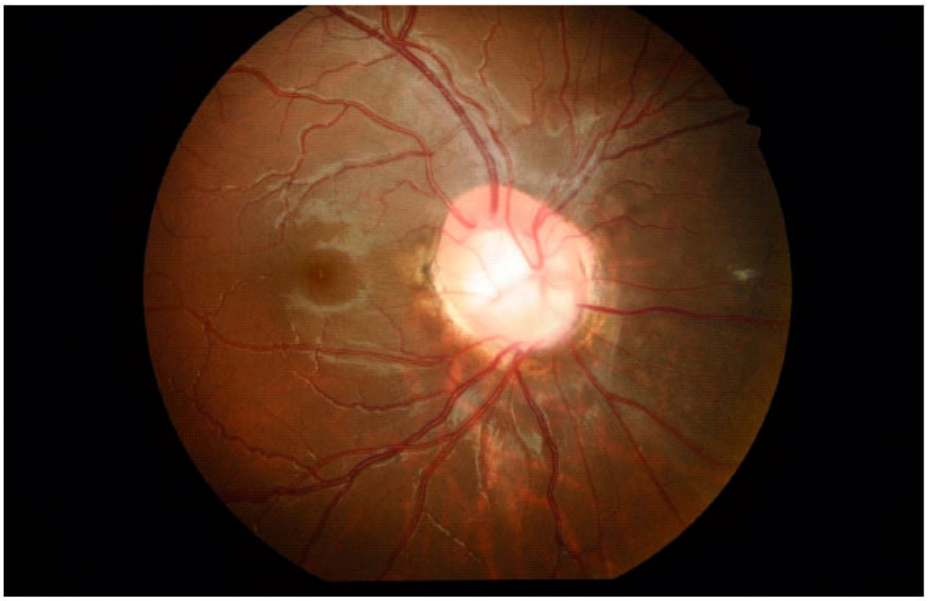

Fig. (4). This 7-year-old, boy complained of blurred vision. Serous retinal detachment extended to nasal retina. Pit in the inferior and nasal margin of the disc. Macula is normal.

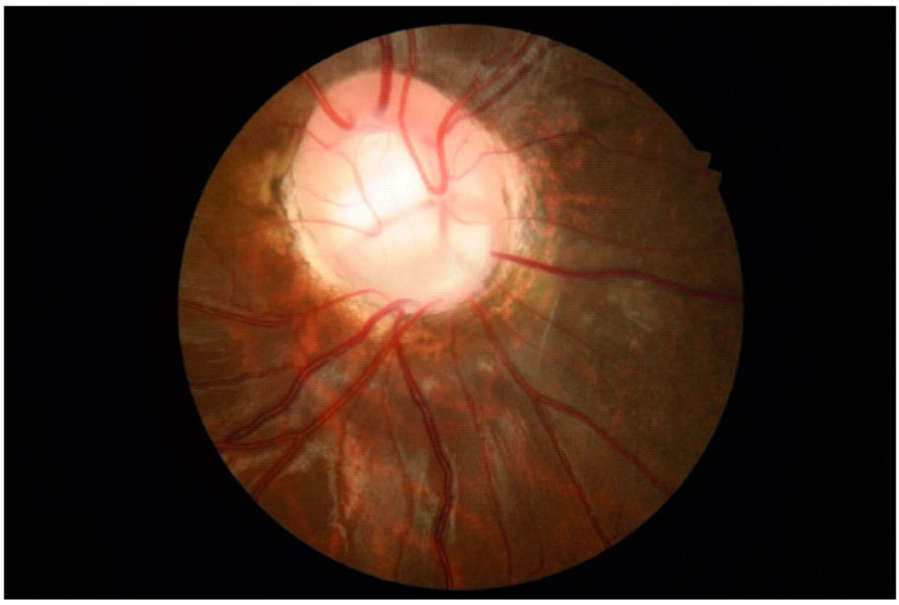

Fig. (5). Colour fundus photograph: Head of the optic nerve. Pit high magnification.

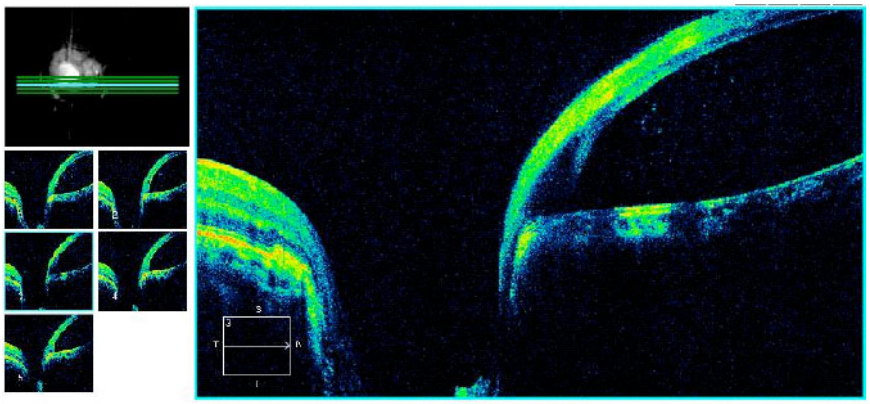

Fig. (6). Horizontal OCT line scans through the optic disc pit show a deep pit in the nasal aspect of the cup. Retinal serous detachment in nasal area (OCT realized by María E. Centeno MD, CECOF).

The mechanism by which fluid accumulates within the retina or in the subretinal space is still unknown. One theory states that fluid flows from the vitreous cavity through the pit into the subretinal space or into the retina [7]. Another theory suggests that cerebrospinal fluid flows from the subarachnoid space into the subretinal space through the pit [8].

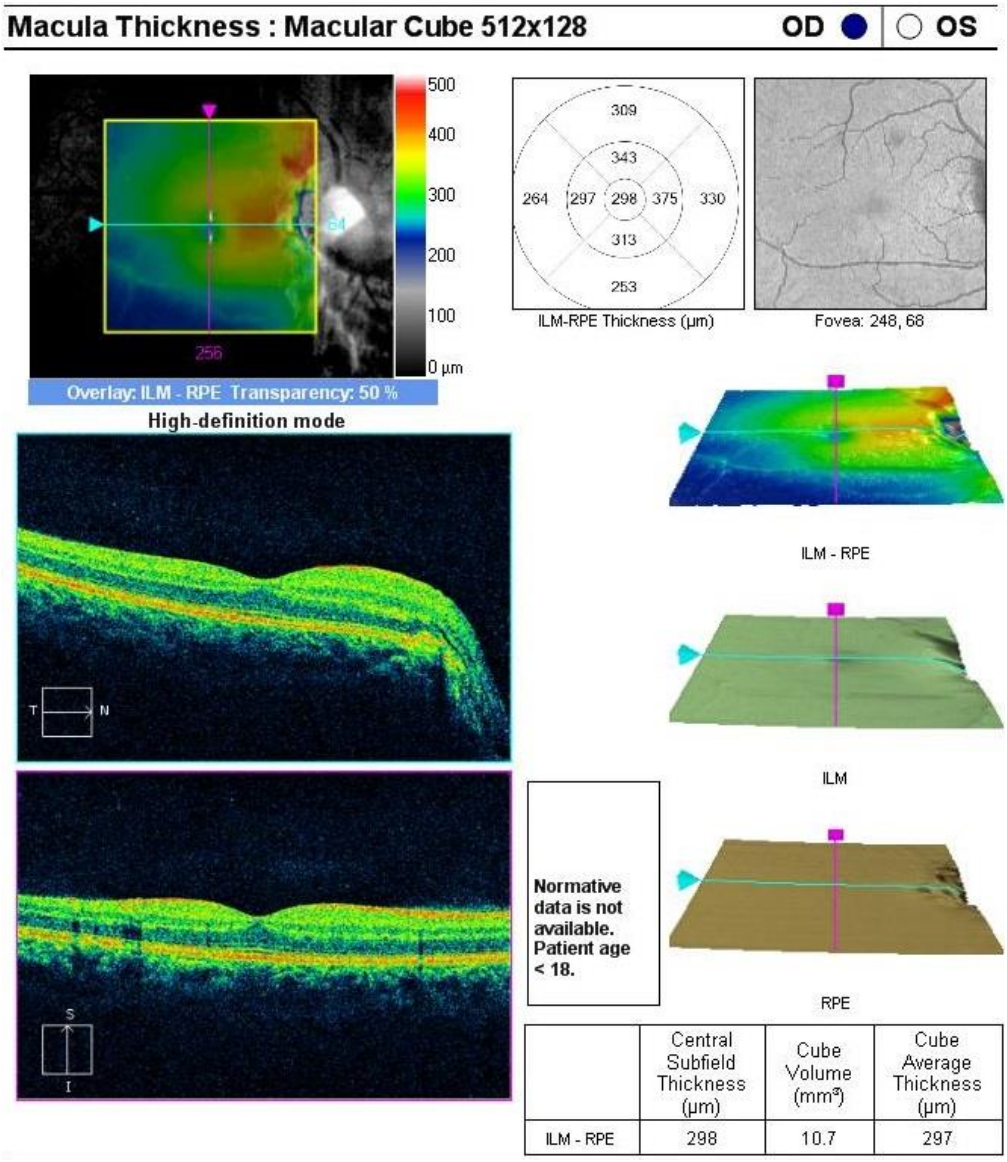

Fig. (7). OCT raster line scan through the macula of the same patient of Figs. (**4**) and (**5**) showing macula is normal (OCT realized by María E. Centeno MD, CECOF).

Optic pits are usually asymptomatic unless complicated by macular lesions. A patient with macular involvement complains of moderate reduction of central visual acuity. Macular complications of an optic pit may manifest as edema,

schisis or serous detachment [9]. Visual field testing may show a relative central scotoma or an enlarged blind spot. These patients may have a greater predisposition to develop normal-tension glaucoma, although sometimes it is unclear if the visual field defects are caused by the optic disc pit or glaucomatous damage [3, 9, 10]. Optical coherence tomography (OCT) is the diagnostic procedure of choice, since it can detect subretinal or intraretinal fluid that is connected to the pit (Figs. **2**, **3**, **6**). It is important that the OCT image extends to the optic nerve in order to see the connection [1, 3]. It may also reveal vitreopapillary traction, which may play a role in the passage of fluid from the vitreous cavity to the subretinal space or into the retina. Fluorescein angiography (FA) is not particularly useful in this entity, although it may be helpful to rule out other differential diagnoses. If a patient has an optic pit and is asymptomatic, an Amsler grid may be useful to monitor for macular involvement [2, 5].

DIFFERENTIAL DIAGNOSIS

A typical optic disc pit is usually readily identifiable in clinical examination. Other congenital anomalies of the optic disc such as optic nerve coloboma, morning glory anomaly, tilted disc staphyloma and hypoplasia of the optic disc must be ruled out. Careful examination of the optic nerve is vital to rule out these diagnoses [6, 10]. The presence of severe glaucomatous cupping of the optic disc may cause an acquired pit or pseudopit, that may develop intra or subretinal fluid.

Other causes of subretinal or intraretinal fluid in the macula, such as central serous chorioretinopathy or choroidal neovascularization must also be ruled out. Fluorescein angiogram tends to be helpful in this regard [1, 5].

Other causes of macular edema must also be ruled out, such as retinal vein occlusion, diabetic macular edema [2], uveitis [11], retinitis pigmentosa, niacin-induced cystoid macular edema and dominant cystoid macular edema [4]. Myopic foveoschisis should also be ruled out, since it may be accompanied by subretinal fluid and retinal schisis in the posterior pole in eyes with posterior staphyloma [12].

MANAGEMENT

While there are, to date, no clinical trials evaluating therapy for congenital optic pit and macular retinal detachment, the disease appears to be visually disabling in the majority of instances. Therapy is aimed at eradicating the associated retinal detachment by closing the communication between the optic pit and subretinal space in the peripapillary region.

Most publications on the topic have supported surgical management, but several case reports have also shown success with expectant management [2, 4, 13, 14]. To remove fluid from the retina, fluid-air exchange, sulfur hexafluoride gas injection, silicone oil injection, perfluoropropane (C3F8) gas injection, perfluoroethane gas injection, and scleral buckling have been used [1, 6, 11, 15, 16].

To prevent reaccumulation of fluid *via* a presumed communication between the optic disc pit and the macula, laser photocoagulation of the temporal peripapillary retina has been performed. Studies using focal laser alone have demonstrated less than satisfactory anatomical results and equivocal visual outcomes [2, 4, 10, 11, 17, 18].

Pars plana vitrectomy in conjunction with laser photocoagulation of the temporal peripapillary retina and gas tamponade has also been used for the treatment of optic pit–associated maculopathy [15]. Internal limiting membrane peeling in addition to removing the posterior hyaloid has also been attempted in order to relieve all possible tractional components [19].

CONFLICT OF INTEREST

The authors confirm that they have no conflict of interest to declare for this publication.

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Declared none.

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CHAPTER 25

Tilted Disc Syndrome

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The tilted disc syndrome is a non-hereditary congenital anomaly arising from an incomplete closure of the fetal fissure [1]. According to a population-based study, the prevalence of tilted discs was found to be associated with astigmatism and the degree of myopia [2]. In this study, the general prevalence of tilted disc was 1.6%. However, the prevalence increased from 0.1% when the astigmatism was ≤ 1 D to 17.9% when the astigmatism was ≥ 5 D. Myopia was present in 66.2% of eyes with tilted disc compared to 12.4% of eyes with a normal disc appearance.

ESSENTIALS OF DIAGNOSIS

The diagnosis of a tilted disc is a clinical one and is made with ophthalmoscopy. The superotemporal optic disc is elevated, whereas the inferonasal portion of the disc is displaced posteriorly. This leads to an oval appearing disc with its long axis in an oblique orientation. The retinal vessels exit the nerve nasally rather than temporally (situs inversus). An inferior or inferonasal crescent is often present as well. An inferonasal staphyloma characterized by RPE and choroidal thinning is also present (Figs. **1**, **2** and **3**).

DIFFERENTIAL DIAGNOSIS

- Optic Nerve Hypoplasia
- Chiasmal Syndrome

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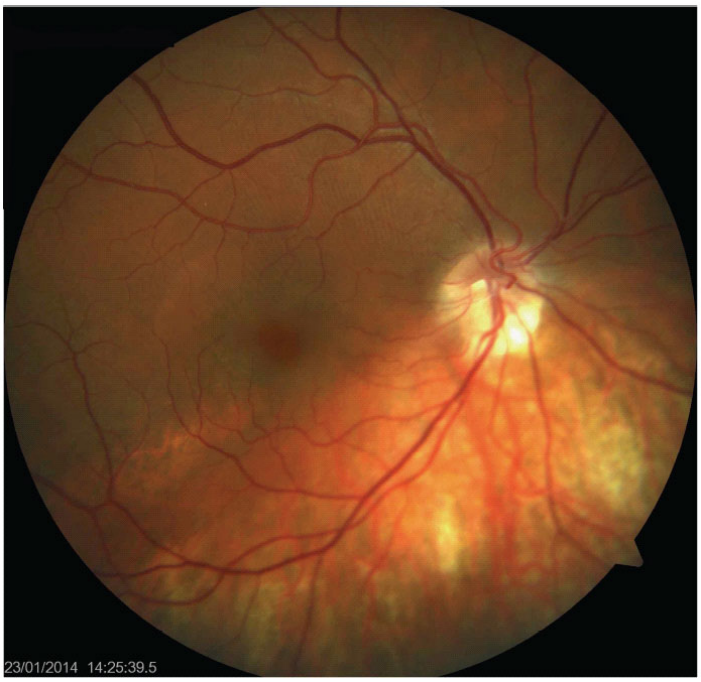

Fig. (1). Colour fundus photograph of a right eye with a tilted disc. The retinal vessels exit the nerve nasally rather than temporally (situs inversus). Notice the staphyloma in the inferior macula.

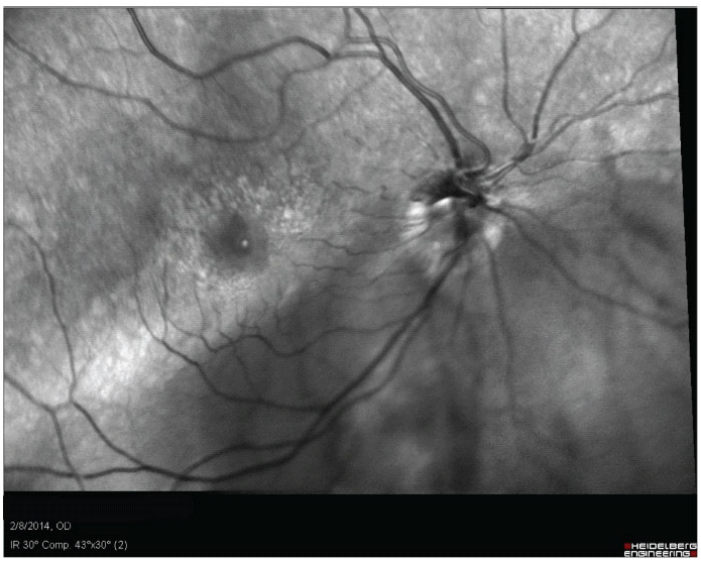

Fig. (2). Infrared reflectance image of the same eye as in Fig. (**1**). Notice that the area of the staphyloma is slightly out of focus.

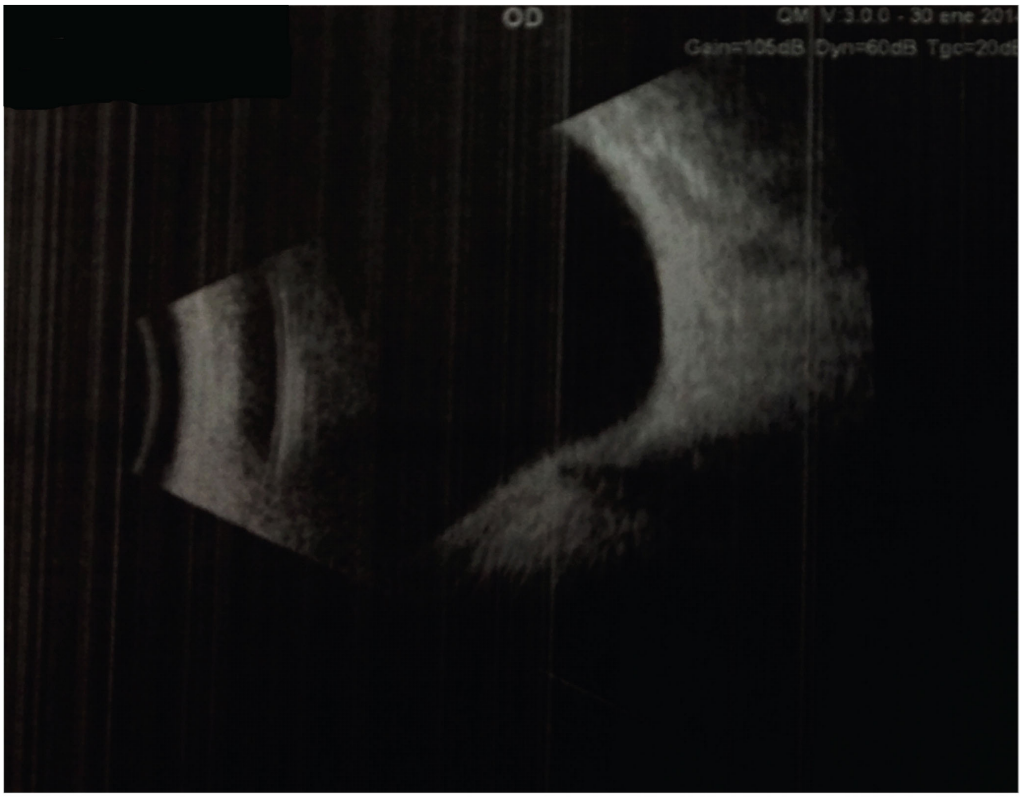

Fig. (3). B Scan ultrasound of the same eye as in Figs. (**1** and **2**). This demonstrates that there is no retinal detachment and an inferior staphyloma is present.

MANAGEMENT

The management of the tilted disc syndrome is directed towards differentiating it from a chiasmal syndrome. Unlike compressive lesions of the chiasm, the visual field defects in the tilted disc syndrome do not progress nor respect the vertical midline. In some cases, the visual field defect may improve or even disappear by increasing the myopic correction [3]. In equivocal cases neuroimaging is indicated.

Eyes with tilted disc syndrome often have macular complications when the inferior staphyloma crosses the macula [4]. Choroidal neovascularization (CNV), serous retinal detachment (SRD), RPE atrophy, and polypoidal choroidal vasculopathy (PCV) have all been reported [4]. It is speculated that the different radii of curvature between the globe and the staphyloma lead to tractional forces

and hemodynamic changes that produce these complications [4]. SD-OCT has shown that the subfoveal choroidal thickness is relatively thin in these eyes, and the underlying sclera is thick. A thick sclera may cause choroidal thinning and an abnormal circulation in the fovea leading to RPE atrophy [5] (Fig. **4**). RPE atrophy could cause breakdown of the outer blood retinal barrier and subsequent SRD (Fig. **5**). No effective treatment is known.

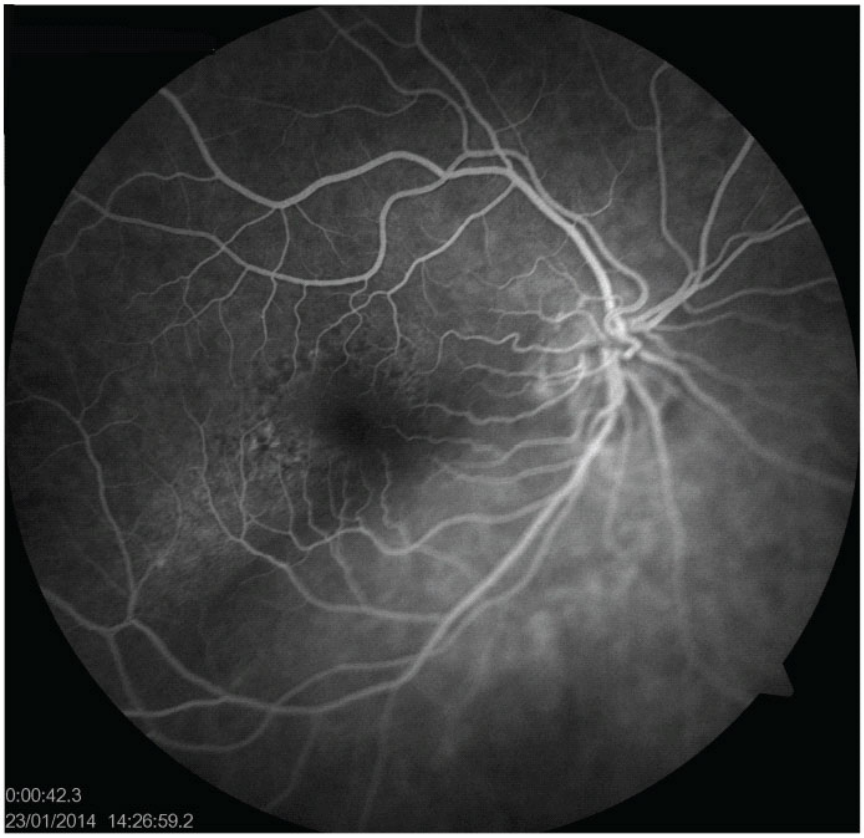

Fig. (4). Late frame of the fluorescein angiography showing pigmentary changes in the macular area.

When present, PCV always occurs at the border of the staphyloma. The choriocapillaris in this location is not well developed and may result in hypoxia which in turn stimulates the formation of CNV or PCV. PCV eyes were treated with photodynamic therapy with relatively good results in the short term [6]. Anti-VEGF agents may be beneficial in eyes complicated by CNV [7].

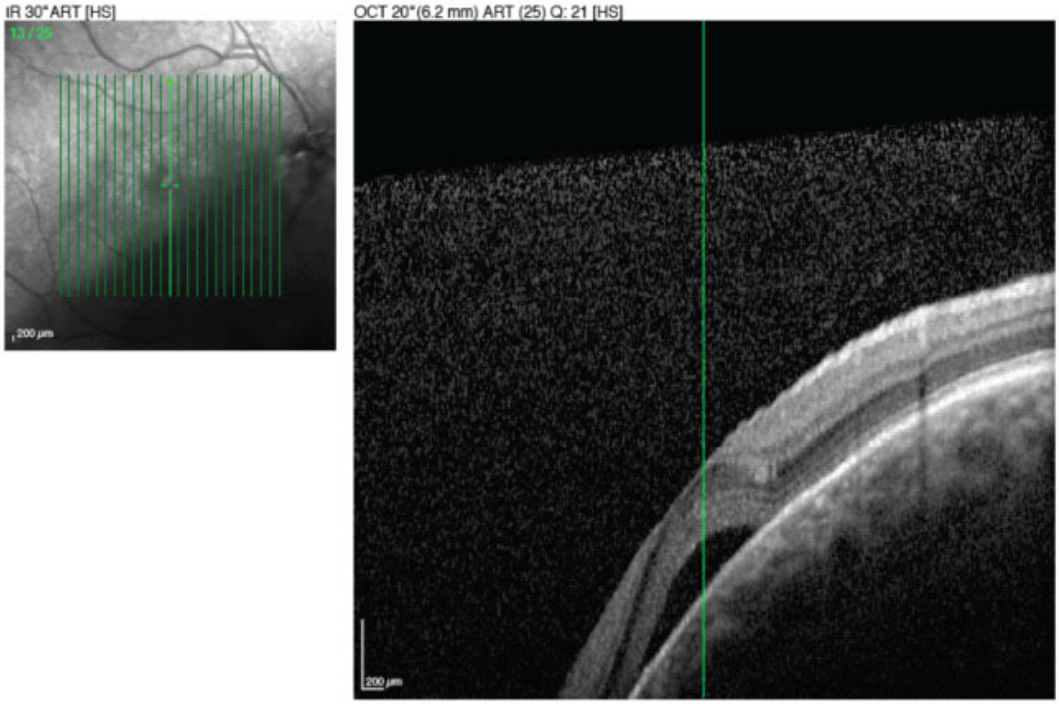

Fig. (5). Vertically oriented SD-OCT demonstrating a serous macular detachment.

CONFLICT OF INTEREST

The authors confirm that they have no conflict of interest to declare for this publication.

ACKNOWLEDGEMENTS

Declared none.

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CHAPTER 26

Retinitis Pigmentosa

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Retinitis pigmentosa (RP) is the most common retinal dystrophy worldwide, with a prevalence of 1 in 4000 individuals [1]. It comprises a heterogeneous group of inherited retinal disorders with degeneration of the photoreceptors and the retinal pigment epithelium (RPE), characterized by nyctalopia and visual field constriction, leading to progressive visual loss [1, 2]. RP can be inherited as an autosomal dominant, autosomal recessive or X-linked trait [1 - 3].

The word "retinitis" is controversial because it indicates inflammation, which is not observed in the course of the disease [4]. In some countries, the term "retinosis" has also been adopted [3].

ESSENTIALS OF DIAGNOSIS

The age of onset of RP ranges from infancy to adulthood [1]. Difficulties with dark adaptation are the initial symptom, and as the disease progresses, peripheral vision loss occurs causing tunnel vision, progressing to central vision loss [1, 3].

At early stages, mild RPE changes suggesting atrophy are observed. Vitreous cells are always seen from the beginning of the disease. Pigmentary changes (which usually are distributed in a pattern that resembles bone spicules) start at the equator and slowly progress to the posterior pole and the periphery (Figs. **1**-**7**).

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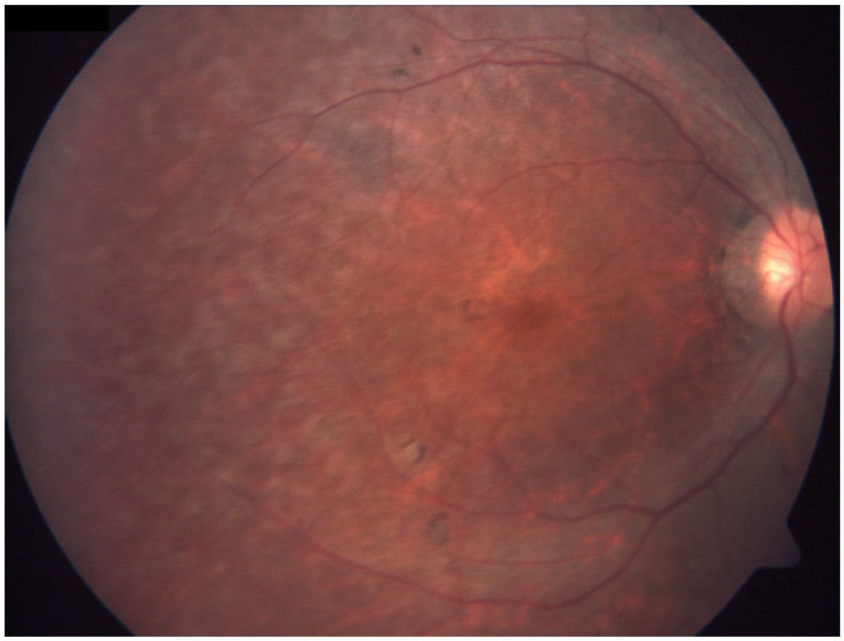

Fig. (1). Colour fundus photograph of a right eye showing diffuse RPE changes in the posterior pole.

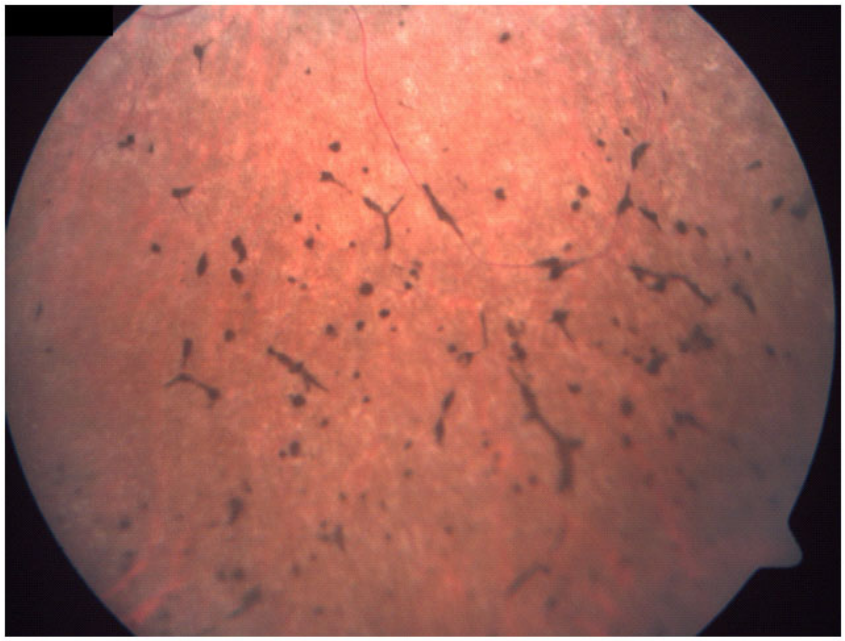

Fig. (2). Colour fundus photograph of the same eye as Fig. (**1**), showing hyperpigmented changes with a shape that resembles bone spicules.

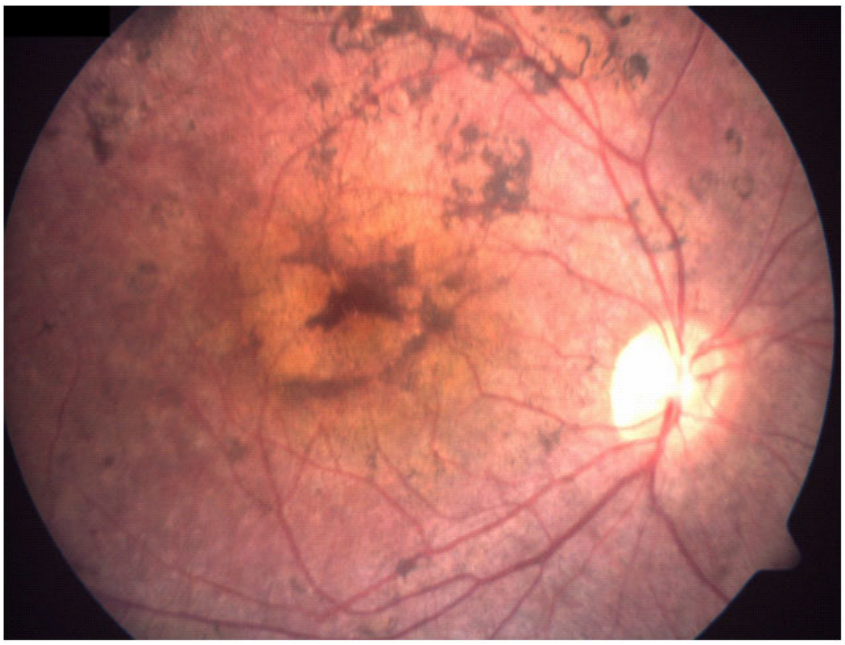

Fig. (3). Colour fundus photograph of a right eye showing diffuse RPE changes in the posterior pole.

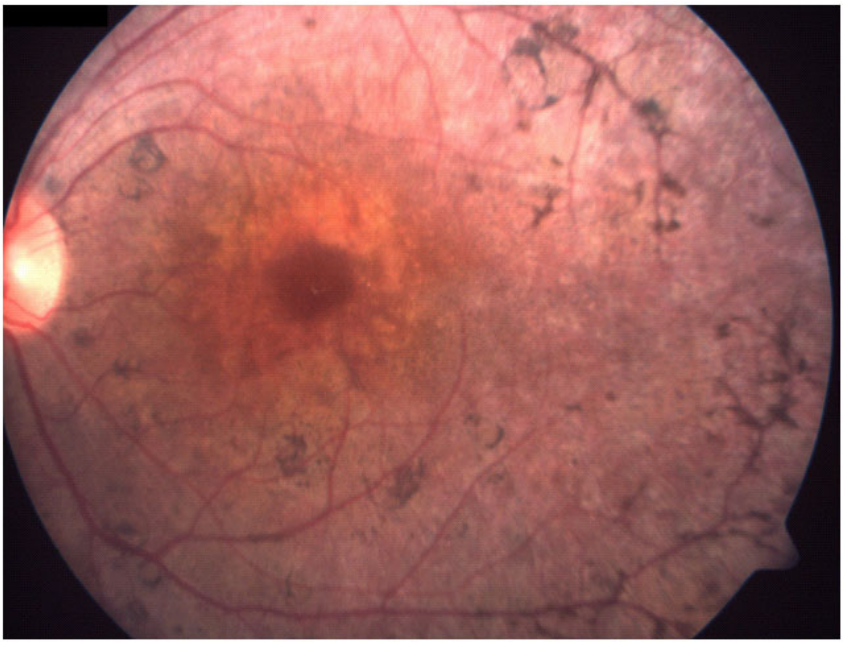

Fig. (4). Colour fundus photograph of the left eye of the same patient as Fig. (**3**), showing RPE changes in the posterior pole.

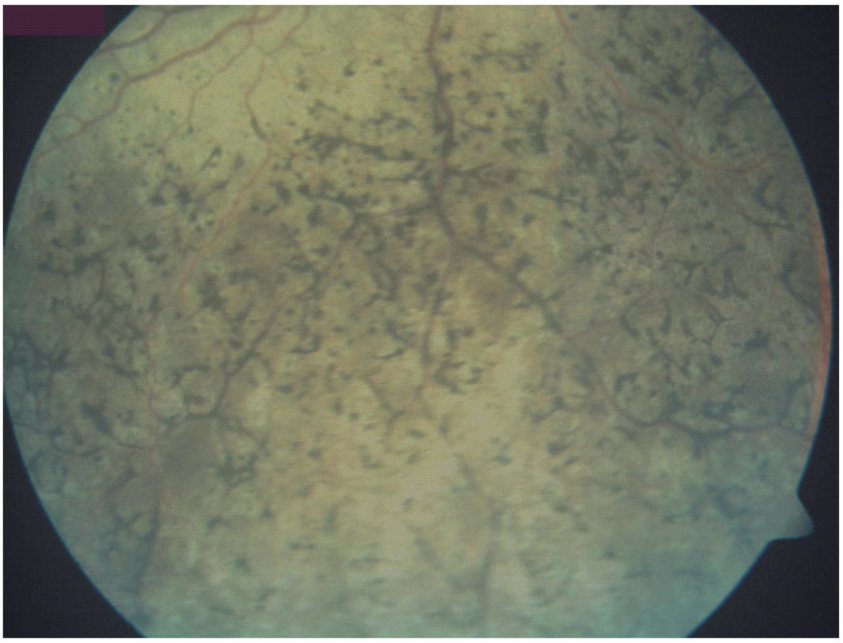

Fig. (5). Colour fundus photograph of a right eye showing hyperpigmented changes with a shape resembling bone spicules.

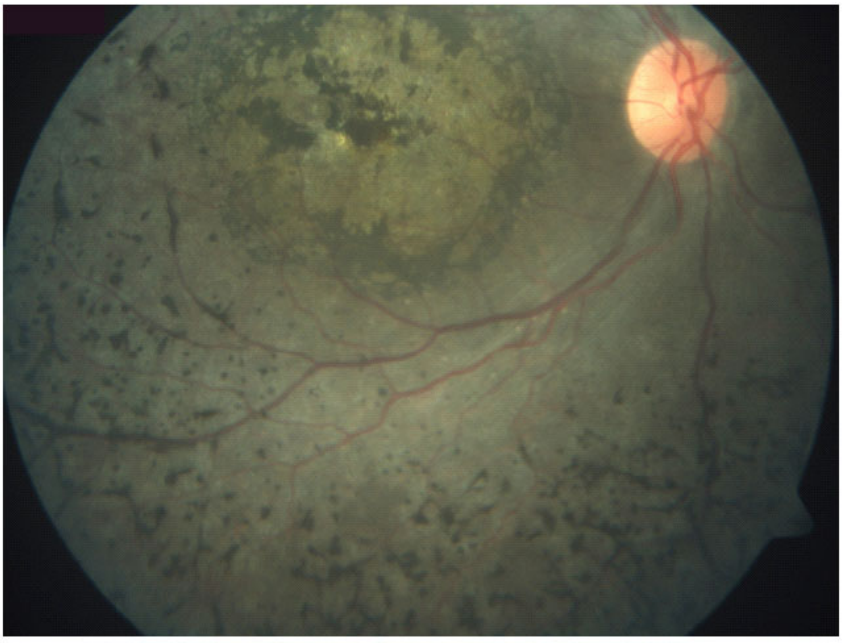

Fig. (6). Colour fundus photograph of the same eye as Fig. (**5**), showing hypo and hyperpigmented changes.

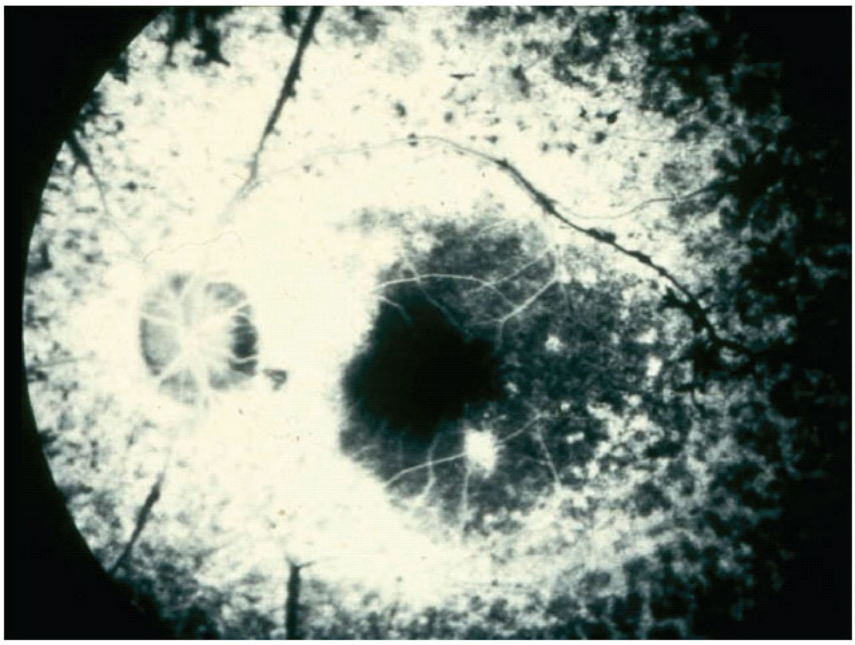

Fig. (7). Fluorescein angiogram of an eye with retinitis pigmentosa, showing diffuse RPE changes with multiple window defect and blockage effects, and vessel attenuation (Image courtesy of Juan Manuel Jiménez-Sierra, MD).

Other findings that cause loss of visual acuity are posterior subcapsular cataracts, present in 50% of patients, and cystoid macular edema (CME). Attenuation of retinal vessels and pallor of the optic nerve head can also be observed in advanced stages of the disease [1 - 4]. The prevalence of primary open angle glaucoma in patients with retinitis pigmentosa ranges from 2-12%, therefore these patients should be closely followed up for glaucoma [5].

Perimetry shows scotomas in the mid-periphery and evaluates residual peripheral and central vision [1], being useful in the follow-up of the disease [3]. Color vision tests might be normal at the beginning of the disease, and then become abnormal as it progresses [3]. Electroretinogram shows reduced rod and cone response amplitude [1]. Electrooculogram is abnormal [3]. Fluorescein angiography is useful to delimitate the RPE atrophic areas and to CME. Optical coherence tomography of the macula confirms the presence of CME and assesses the status of the photoreceptor layer. Autofluorescence shows higher concentration of lipofuscin in the RPE of some patients [6].

Other clinical presentations of the disease are: RP *sine pigmento* (without pigment), unilateral, sectorial (well-defined areas of RPE atrophy with hyperpigmentation, more frequent in inferior quadrants) (Figs. **8** and **9**), pericentral (hyperpigmentation surrounding the optic nerve and the temporal vascular arcades) [3], preserved para-arteriole RPE distribution [7] and punctata albescens (multiple white dot-like deposits distributed over the posterior pole and midperiphery, sparing the fovea) [8].

RP is also a feature of several genetic syndromes, 20-30% of patients with RP have associated non-ocular disease [1]. The most frequent related syndromes are Usher syndrome, Bardet-Biedl syndrome and Kearns-Sayre syndrome [1 - 3].

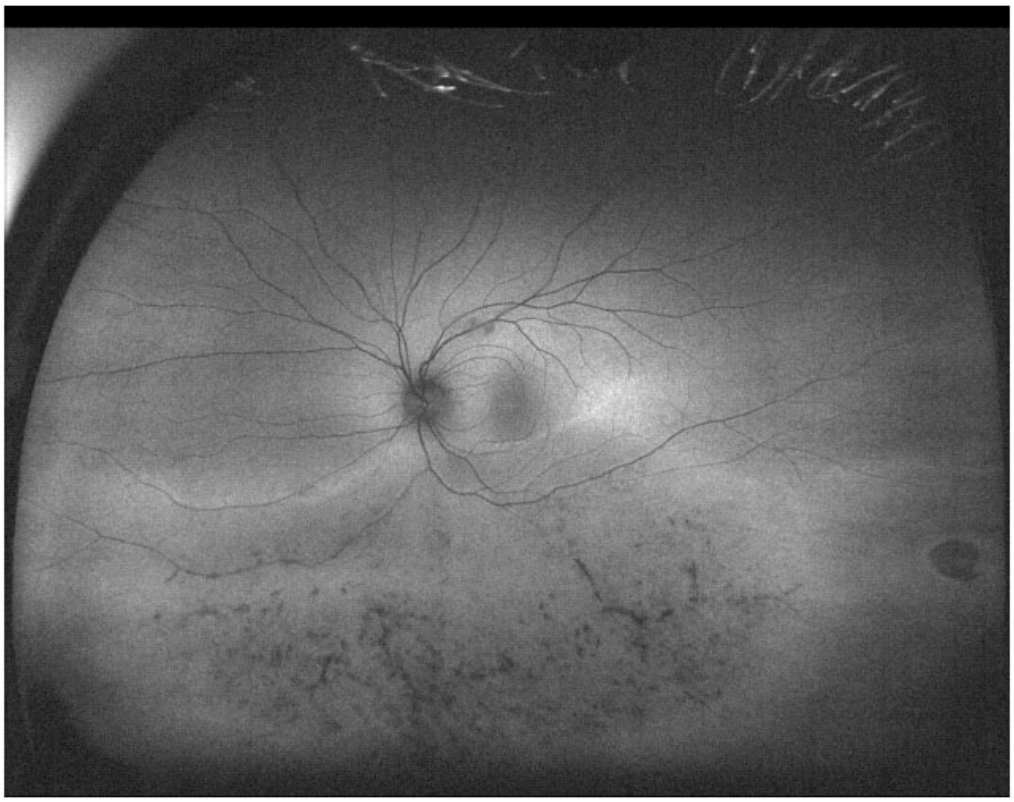

Fig. (8). Autofluorescence wide field image of an eye with sectorial retinitis pigmentosa, showing hyper and hypoautofluorescent changes in the inferior retina.

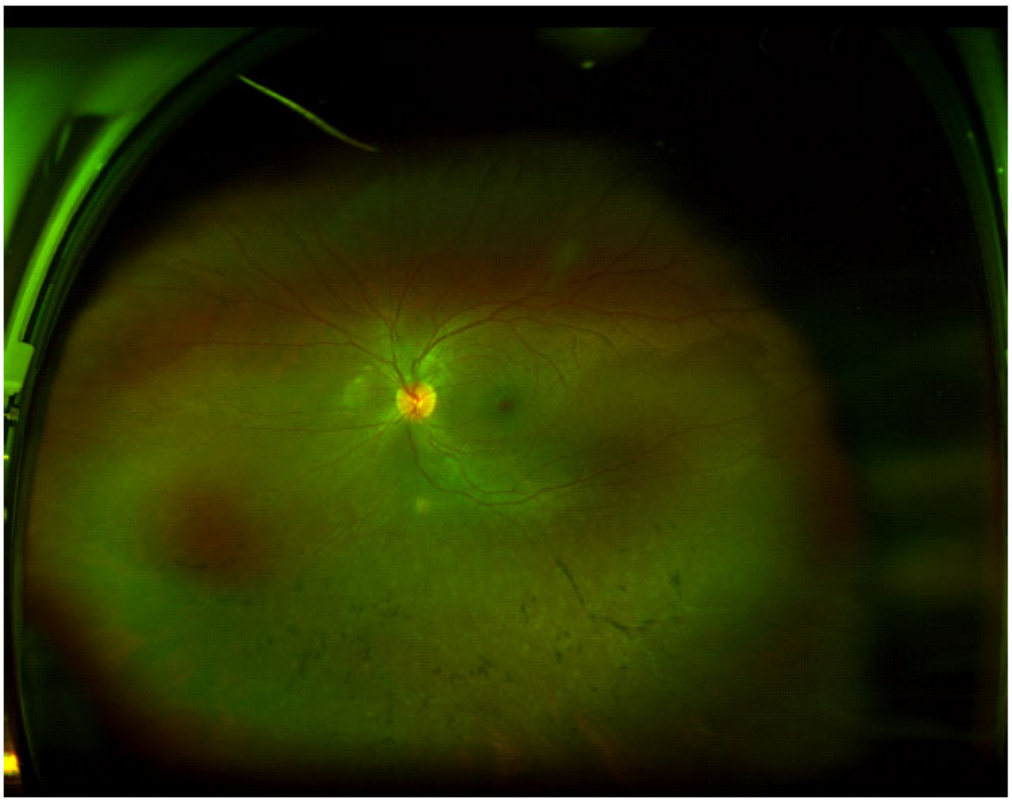

Fig. (9). Wide field image of the same eye as Fig. (**8**), showing a sectorial retinitis pigmentosa. Hyperpigmented changes with a shape that resembles bone spicules limited to the inferior retina can be observed.

DIFFERENTIAL DIAGNOSIS

Other conditions can cause chorioretinal atrophy and pigmentary changes and should be ruled out: Retinal dystrophies such as choroideremia and gyrate atrophy in advanced stages, cone and cone-rod dystrophy. Inherited retinal disorders like congenital stationary night blindness and fundus albipunctatus. Infectious diseases such as syphilis, toxoplasmosis, herpes and rubella. Drug toxicity by thioridazine, chlorpromazine, chloroquine, hydroxychloroquine and quinine. Chorioretinal changes due to preeclampsia and eclampsia, vitamin A deficiency retinopathy, cancer-associated retinopathy, melanoma-associated retinopathy, diffuse unilateral subacute neuroretinitis, traumatic retinopathy [8], pigmented paravenous chorioretinal atrophy [9] and retinal detachment sequels.

MANAGEMENT

In order to help patients to maximize their vision, specular correction and low-vision evaluation should be done. Regarding the effectiveness and safety of vitamin A and fish oils (docosahexaenoic acid) in preventing the progression of the disease, there is no statistically significant benefit on the progression of visual field or visual acuity loss [10]. Topical dorzolamide and oral acetazolamide have shown improvement of CME in some eyes [11]. Cataract surgery may improve visual acuity in the majority of the eyes in patients with RP, however, its impact will depend on factors such as the presence of CME and the integrity of the outer retinal layers [12, 13].

Other different approaches to restoring sight in patients with an advanced stage of the disease include stem cell therapy and gene therapy, which are still experimental [1, 9]. To this date, retinal prostheses are the most promising treatment for patients with extremely low vision [14].

CONFLICT OF INTEREST

The authors confirm that they have no conflict of interest to declare for this publication.

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Declared none.

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[http://dx.doi.org/10.1016/j.ophtha.2015.04.032] [PMID: 26162233]

CHAPTER 27

Best's Disease

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Best disease is an autosomal dominant maculopathy associated with a mutation in the Bestrophin (BEST1) gene.

ESSENTIALS OF DIAGNOSIS

Although its clinical appearance may vary, it classically is known for a vitelliform or "egg-yolk" lesion centered in the macula of each eye. At this stage, the lesions are typically round, solitary, yellow, slightly raised, and often asymmetric [1] (Figs. **1** and **2**). The mutations in the BEST1 gene show variable penetrance and expressivity with carriers developing a range of findings from no clinical signs to manifestations such as multi-focal Best disease [1]. It is therefore important when making a definitive diagnosis to employ other diagnostic methods such as electrooculogram (EOG), optical coherence tomography (OCT), or genetic testing.

Lesions tend to go through a characteristic progression of the disease beginning with a normal appearing fundus at birth. Sharply demarcated yellow macular lesions develop in early childhood (vitelliform stage). Lesions may become large, but surprisingly, despite dramatic anatomic changes, the vision is usually very good. Breakdown of the vitelliform deposit leads to separation of the photoreceptors from the RPE (Fig. **3**). Vision loss may occur at this point, but often develops later with absorption of vitelliform material leading to RPE and/or

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photoreceptor degeneration. Patients in the atrophic stage are susceptible to choroidal neovascularization (CNV) and/or fibrotic scarring. Vision is usually fairly well preserved into adulthood, at least in one eye. However, slowly progressive central visual impairment is not uncommon after the age of 60 [2].

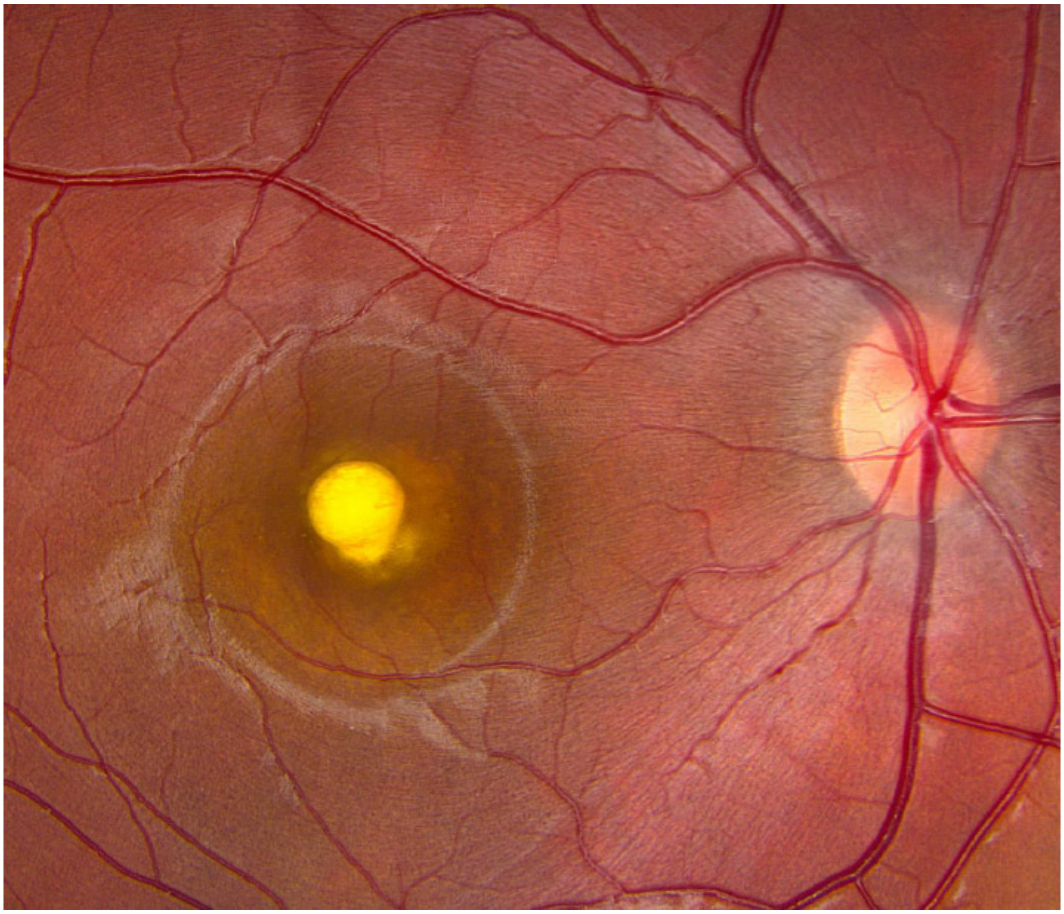

Fig. (1). Colour fundus photograph of the right eye demonstrating the classic "egg-yolk" appearance of the macula.

The mutation responsible for Best's Disease was first cloned by Petrukhin *et al.* in 1998 [3]. It is expressed primarily on the basolateral plasma membrane of the RPE and functions as a calcium-dependent chloride channel, which is believed to regulate the flow of chloride, bicarbonate, and calcium ions across the RPE membrane [4, 5]. Calcium aids in regulation of RPE functions including

epithelium adhesion to the photoreceptors and phagocytosis of photoreceptor outer segments. Although the underlying mechanism is controversial, some authors believe that mutations in BEST1 lead to separation of RPE from the retina with poorly phagocytized outer segments accumulating in the potential space and forming lipofuscin. Eventually this leads to the formation of the characteristic vitelliform lesion seen on examination [6].

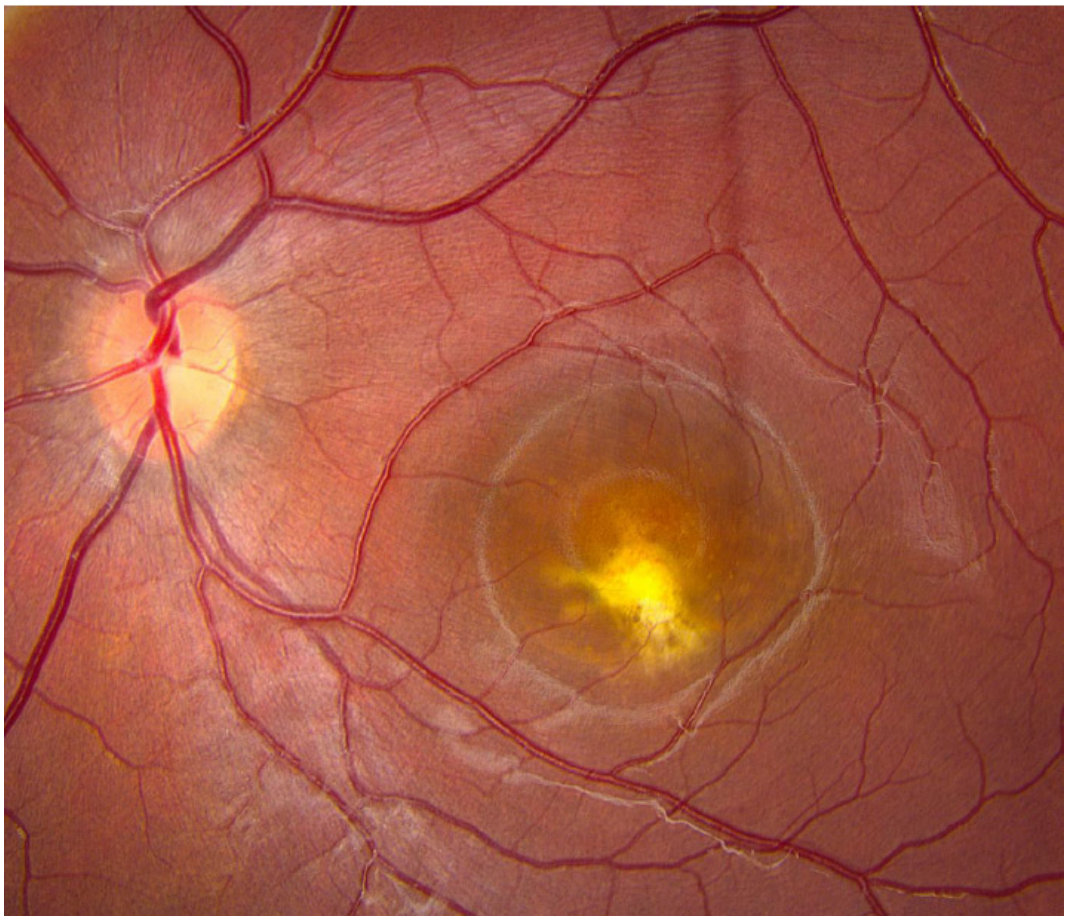

Fig. (2). Colour fundus photograph. The left eye of the same patient demonstrates a "scrambled-egg" appearance.

The molecular basis of Best disease directly affects the electrical potentials measured across Bruch's membrane. Changes in the chloride ion channel lead to an abnormal EOG, typically recorded as a diminished Arden ratio (AR). The AR

is the maximum electrophysiologic potential measured in light conditions divided by the minimum potential measured in dark conditions. A normal AR is 1.85 or above while in Best disease, it is usually less than 1.5 (Fig. **4**) [7 - 9].

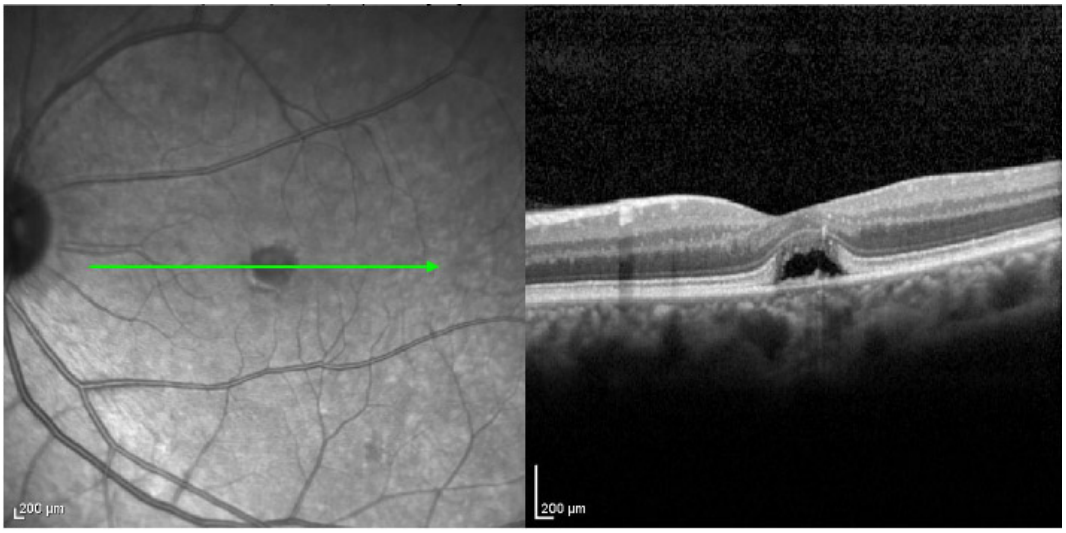

Fig. (3). Ocular coherence tomography shows a homogenous collection of sub-retinal material corresponding to the egg-yolk lesion on exam.

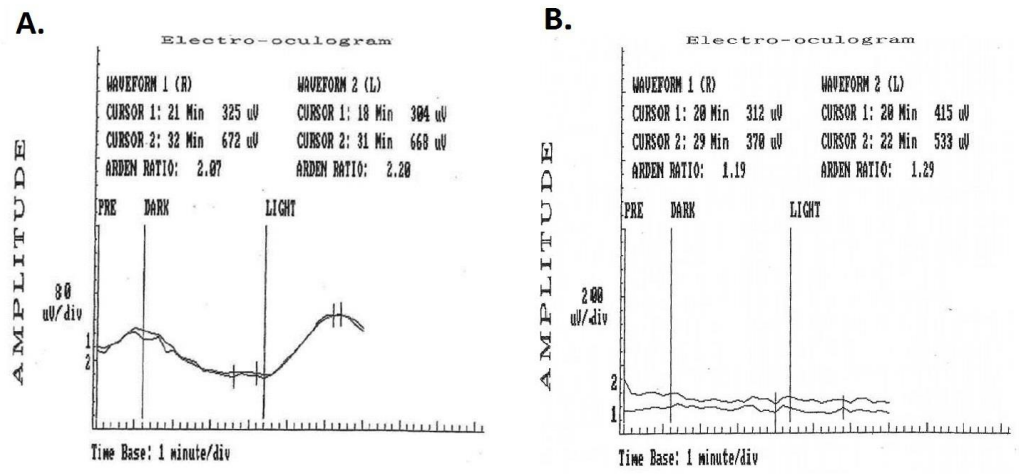

Fig. (4). Electro-oculogram of a normal patient (**A**) and a patient with Best disease (**B**). In the normal patient, the amplitude increases considerably when going from dark to light conditions, leading to a large Arden ratio. In Best disease, the amplitude does not change based on light conditions, leading to an Arden ratio less than 1.5.

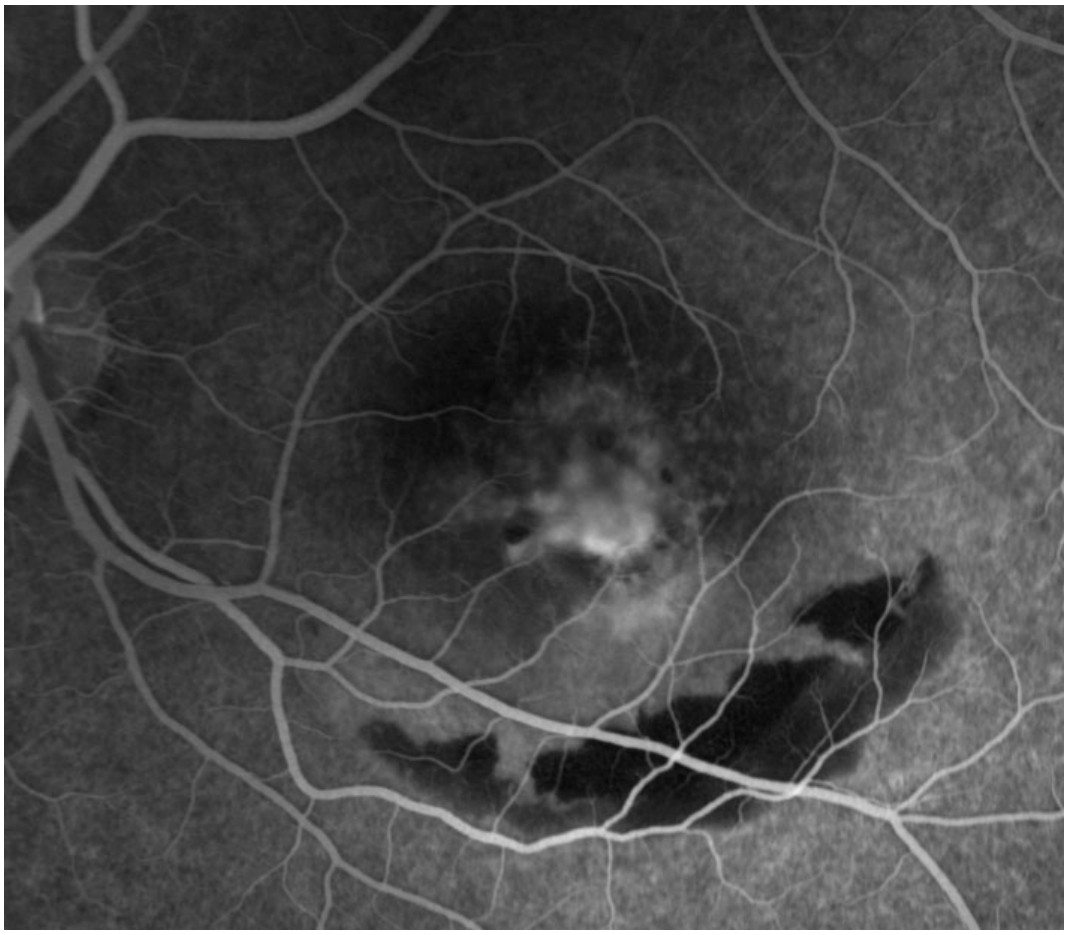

Fig. (5). Fluorescein angiography demonstrates a "pseudohypopyon configuration". The superior half is hyper-fluorescent and fills with dye while the lower half blocks the underlying choroidal circulation.

During the vitelliform or egg-yolk stage, OCT shows a homogenous collection of subretinal material corresponding to the lesion seen on exam (Fig. **3**). Over time, the deposits coalesce and become associated with a variable amount of subretinal fluid-like lucency interspersed with dense deposits. This transformation may predate or correspond to break down of the egg-yolk deposit leading to the serous detachment or "scrambled egg" phases. Ultimately, the subretinal deposits are absorbed leading to atrophy with or without fibrotic scarring. FA findings vary depending on stage and lesion age. Early lesions are typically hydrophobic and therefore do not uptake fluorescein or stain leading to an area that blocks the

underlying choroidal circulation. In time, the lesion will stain on late FA. In the pseudohypopyon stage, the superior half of the lesion slowly stains with dye while the inferior portion does not (Fig. **5**). Vitelliform lesions may show marked variation with fundus autofluorescence (FAF), ranging from silent to hypoautofluorescent (blocking of background autofluorescence) to uniformly hyper autofluorescent. Lesions that are hypoautofluorescent are thought to be associated RPE atrophy or fibrosis [2]. FAF patterns may reveal information about retinal function and progression of the disease (Fig. **6**) [10].

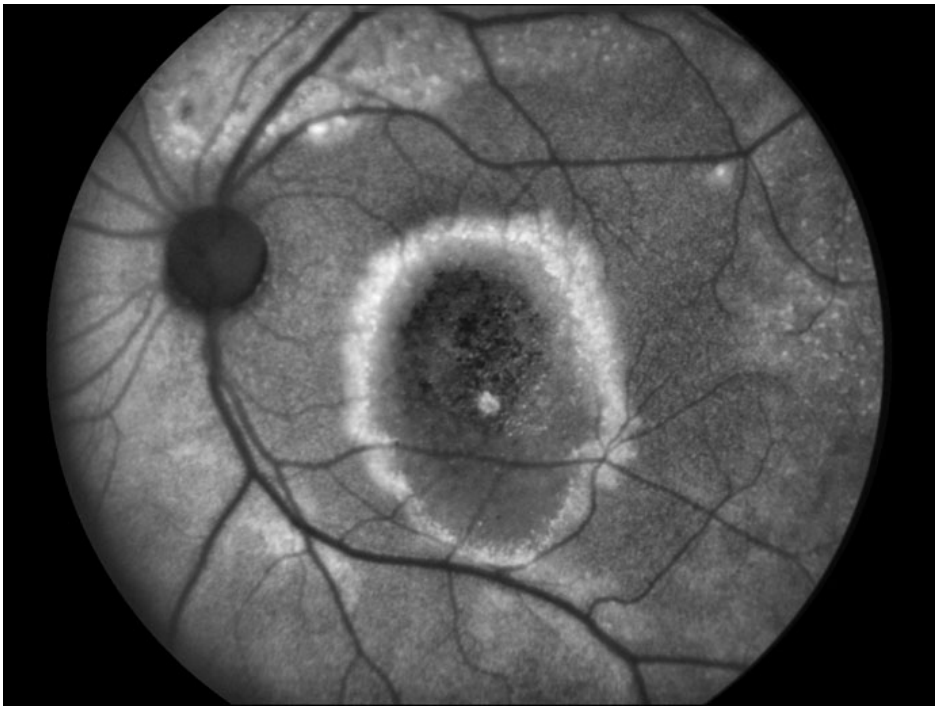

Fig. (6). Fundus auto-fluorescence in Best disease typically shows an area of hyperautofluorescence in the central fovea. The picture above shows disease progression in later stages where the central fovea shows hypoautofluorescence with a surrounding ring of hyperautofluorescence. The evolution is representative of centrifugal spreading of retinal dysfunction from the center toward the periphery.

DIFFERENTIAL DIAGNOSIS

The primary differential diagnosis is adult-onset vitelliform dystrophy (AOVD), which falls into the spectrum of pattern dystrophies. AOVD is differentiated from Best disease based on later age of onset (most commonly at 40-70 years of age),

normal EOG, and lack of BEST1 mutation [11]. Yellow subretinal deposits can present in various macular pathologies including basal laminar or cuticular drusen, pattern dystrophy, chronic central serous chorioretinopathy, macular vitreous traction, pseudoxanthoma elasticum, angioid streaks, and age-related macular degeneration [12, 13]. Other inherited pediatric macular disorders such as Stargardt disease and North Carolina macular dystrophy can present with macular atrophy that may mimic the appearance of Best disease [14].

MANAGEMENT

Genetic counseling is generally advised for new diagnosis. Given generally preserved visual function in Best disease, the principal management is observation for secondary processes that may lead to worsening of vision such as CNV [15]. Subretinal hemorrhages may occur without CNV (especially after even minor trauma) and can resolve spontaneously with good prognosis [2]. However, anti-VEGF therapy has been shown to improve vision when CNV develops [16 - 19]. Some authors suggest using visual acuity to guide anti-VEGF therapy rather than OCT features, which may not respond to prolonged treatment [2]. The reason may be that vitelliform material itself can mimic subretinal fluid on OCT in the absence of CNV, possibly due to its homogeneous consistency.

CONFLICT OF INTEREST

The authors confirm that they have no conflict of interest to declare for this publication.

ACKNOWLEDGEMENTS

Declared none.

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CHAPTER 28

Stargardt's Disease

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Originally described by Stargardt in 1909 [1], Stargardt's macular dystrophy (SMD) is a chronic and progressive disease that affects the macula in young patients. Its mode of inheritance is autosomal recessive, and is caused by a mutation in the ABCA4 gene [2 - 4]. Mutations in this gene may cause classic SMD, fundus flavimaculatus (which is a variant of SMD) and are associated to several other disorders, such as cone-rod dystrophy and retinitis pigmentosa [3, 5, 6]. Individuals heterozygous for ABCA4 mutations may also be in greater risk of having age-related macular degeneration [7].

Stargardt's disease (including fundus flavimaculatus) is one of the most common causes of macular disease in childhood and accounts for 7% of all retinal dystrophies [8]. Disease prevalence is around 1 in 10, 000 [9]. First symptoms appear early in childhood or adolescence. The disease affects males and females alike, without predilection for race.

ESSENTIALS OF DIAGNOSIS

Similar to other dystrophies, patients with SMD are asymptomatic when the disease is in its early stages. Eventually, patients complain of decreased central vision, photophobia, abnormal color vision and slow dark adaptation. Slit lamp examination shows a typical clinical picture, where pigment changes with a

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greenish discoloration are observed in the central macula [1 - 4]. Flecks, which are the yellow-white lesions characteristic of fundus flavimaculatus, may or may not be present (Figs. **1** and **2**). In later stages, the macula is often described as having a "beaten bronze" appearance. However, disease phenotype may be highly variable [2].

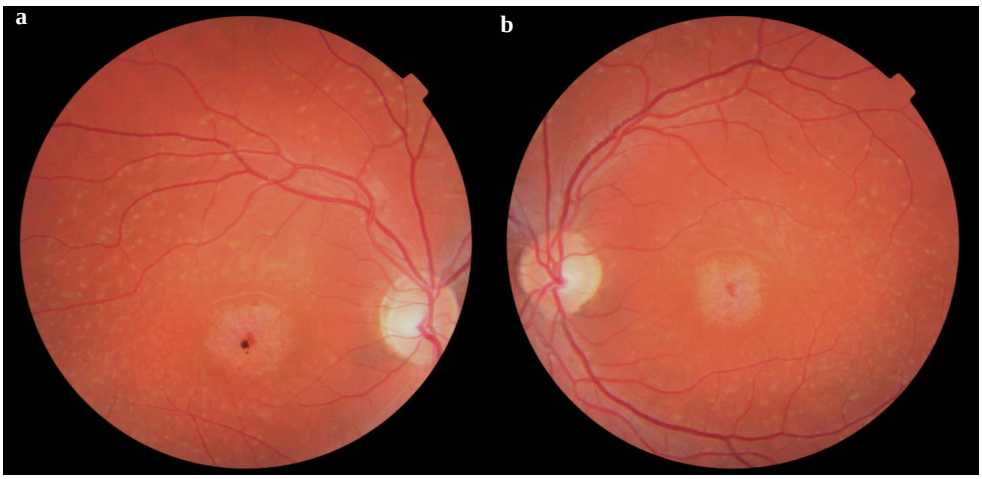

Fig. (1). Colour fundus photographs. (**A**) and (**B**) 25-year-old female with Stargardt disease. Note the diffuse yellow pisciform flecks in posterior pole and central macular atrophy in both eyes.

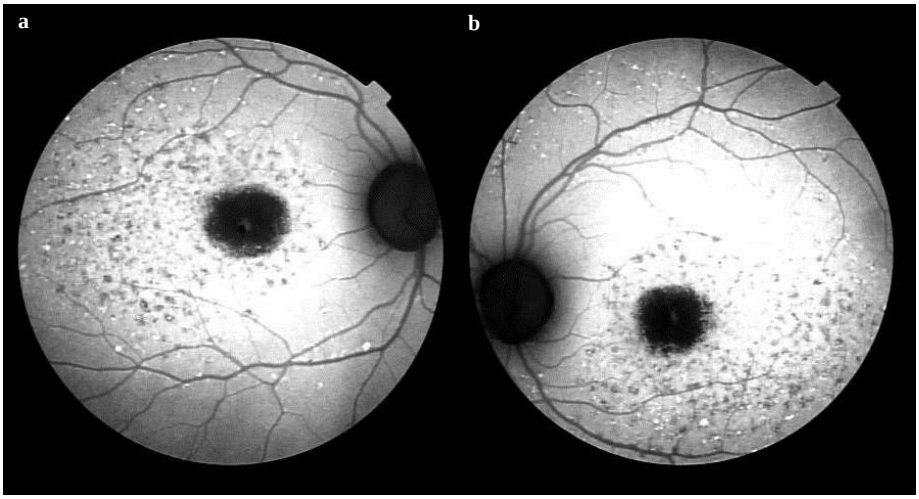

Fig. (2). (**A**) and (**B**) Autofluorescensce of the same patient of Fig. (**1**). Pisciform lesions and macular atrophy.

Patients with fundus flavimaculatus (retinal flecks without macular atrophy) often have a later disease onset and slower visual deterioration [4].

Visual field testing is often normal early in the disease. Eventually, central scotomas are observed, which progress to absolute scotomas over time.

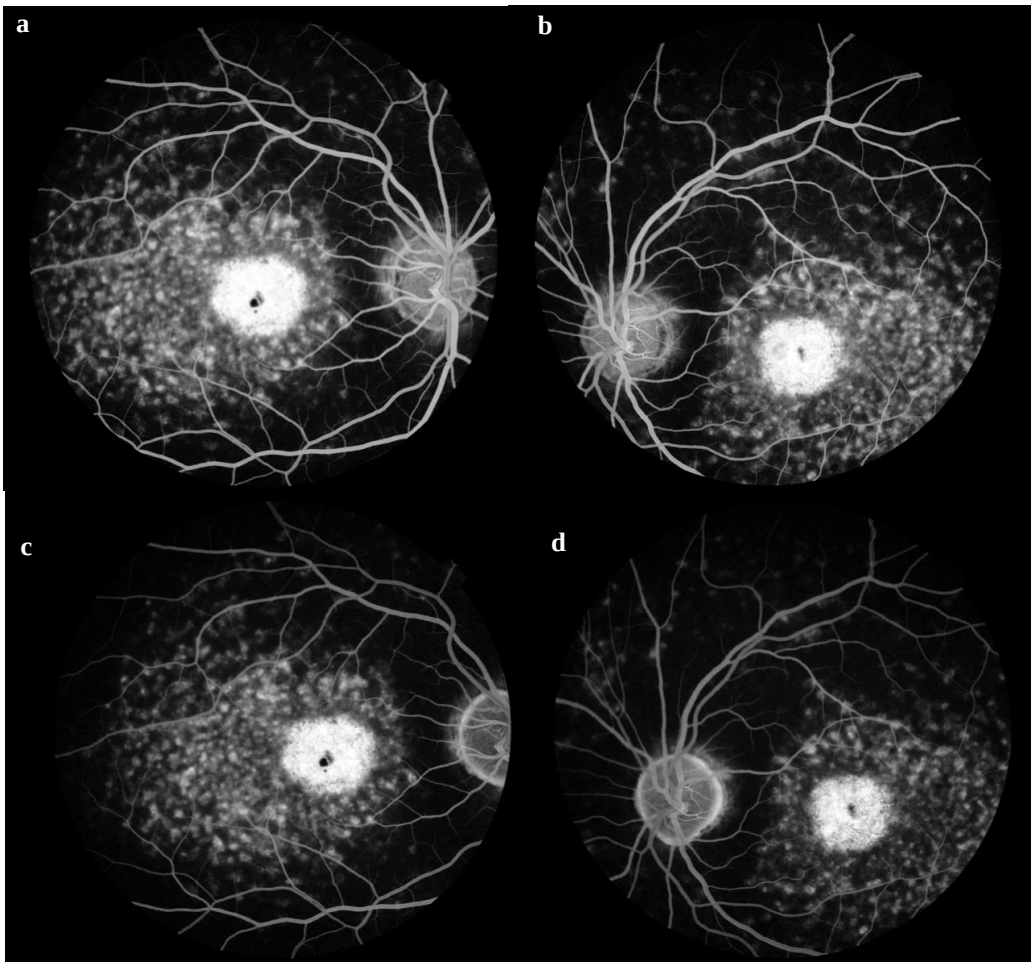

Fig. (3). Fluorescein angiography showing silent choroid Stargardt's disease (**A-D**) and central ovoid zone of hyperfluorescence, surrounded even in the early stages (**A** and **B**) by some hyperfluorescent flecks.

An acquired red-green dyschromatopsia may be characteristic in these patients with color testing. Fluorescein angiography in early cases shows a central ovoid zone of hyperfluorescence, mostly surrounded even in the early stages by some

hyperfluorescent flecks. At least 80% of SMD patients have a "silent choroid" when a fluorescein angiogram is performed (Fig. **3**). A2E accumulation in the RPE causes this phenomenon [10].

Generally, the implicit time and amplitudes of the photopic and scotopic ERG are normal. However, a slight delay in attaining the otherwise normal maximum b-wave is not infrequently seen. In cases of longer standing, however, in which pigmentations are often seen in the midperiphery, the ERG amplitudes may decrease. The EOG tends to be subnormal in most patients [11].

DIFFERENTIAL DIAGNOSIS

Differential diagnosis includes multifocal pattern dystrophy simulating SMD and retinal and/or macular dystrophies such as central areolar choroidal dystrophy (CACD), achromatopsia, cone dystrophy (CD), cone rod dystrophy (CRD) and dry age macular degeneration (AMD) of the late adult onset Stargardt's disease [12]. In addition, two autosomal dominant types of macular dystrophy exist that resemble SMD: STGD3 is caused by mutations in the ELOVL4 gene, and STGD4, associated with mutations in PROM1 [2].

MANAGEMENT

Currently, there is no treatment for Stargardt's disease. Avoidance of a diet rich in vitamin A is recommended because the ABCA4 gene encodes for a trans-membrane transporter of A2E intermediates, which are toxic byproducts of vitamin A [13].

Several therapies have been attempted, such as drug therapies that inhibit vitamin-A dimerization [14] or subretinal embryonic stem cell implantation [15]. Gene therapy may offer an attractive treatment alternative for this disease, in an attempt to induce the expression of a non-mutated ABCA4 [16].

Prognosis: Due to the high clinical variability, prognosis depends on certain parameters (notably age of onset and electroretinographic findings) that may help the clinician provide the patient with an indication of the course of the disease. It is important to subtype Stargardt patients for more adequate counselling regarding prognosis.

CONFLICT OF INTEREST

The authors confirm that they have no conflict of interest to declare for this publication.

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Declared none.

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CHAPTER 29

Choroideremia

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Choroideremia (CHM) is an X-linked degeneration of the choroid, retinal pigment epithelium (RPE), and retina caused by deletion or mutation of the CHM gene, encoding Rab escort protein-1 (REP1) [1, 2]. The estimated prevalence is 1 in 50,000 in the general population [3].

For many years it was assumed that the basic abnormality in choroideremia was a vasculopathy causing primary choriocapillaris atrophy. However, histo-pathological studies of choroideremia and studies of the localization of the CHM protein place the basic defect in the RPE [4, 5].

ESSENTIALS OF DIAGNOSIS

Since it is a X-linked recessive disease, only males are affected, and females are carriers. The first symptom is nyctalopia, which ensues in the first decade of life, followed by progressive visual field loss [3]. As the disease progresses, pigment changes and areas of choroidal atrophy begin to appear in the equator. At the end stages of the disease, there is generalized chorioretinal atrophy, with some degree of preservation of the choroidal vasculature in the macula and the far periphery. (Figs. **1, 2** and **3a**). In advanced stages, the retina and choroid are so atrophic that the sclera becomes visible.

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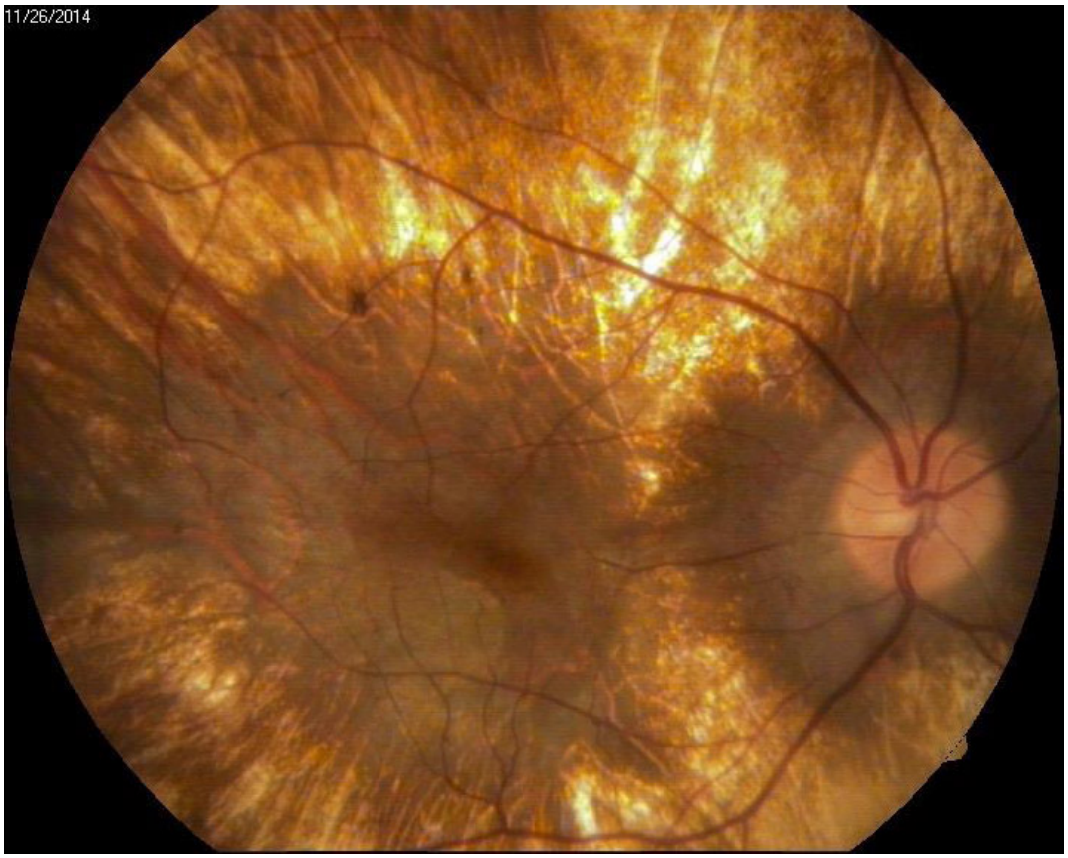

Fig. (1). Right eye fundus photography of male patient with diagnosis of Choroideremia. There is atrophy of the retinal pigment epithelium and choroid with exposure of the sclera and large choroidal blood vessels. Preservation of the central macula and near the optic disc are shown (Courtesy of Andrée Henaine Berra MD, Mexico).

Autofluorescence is decreased in the areas of chorioretinal atrophy with some relative hyperautofluorescence in the preserved retinal tissue. Fluorescein angiography (FA) shows atrophy of the retinal pigment epithelium with the scalloped areas of missing choriocapillaris appearing hypofluorescent next to brightly hyperfluorescent areas of patent choriocapillaris (Fig. **3b**). OCT reveals absence of the outer nuclear layer, ellipsoid layer, RPE and choroid [6, 7]. The ERG and EOG are abnormal early in the course of the disease and ERG is generally extinguished by midlife. However, there can be intrafamilial and interfamilial variabilities of ERG responses [6 - 10].

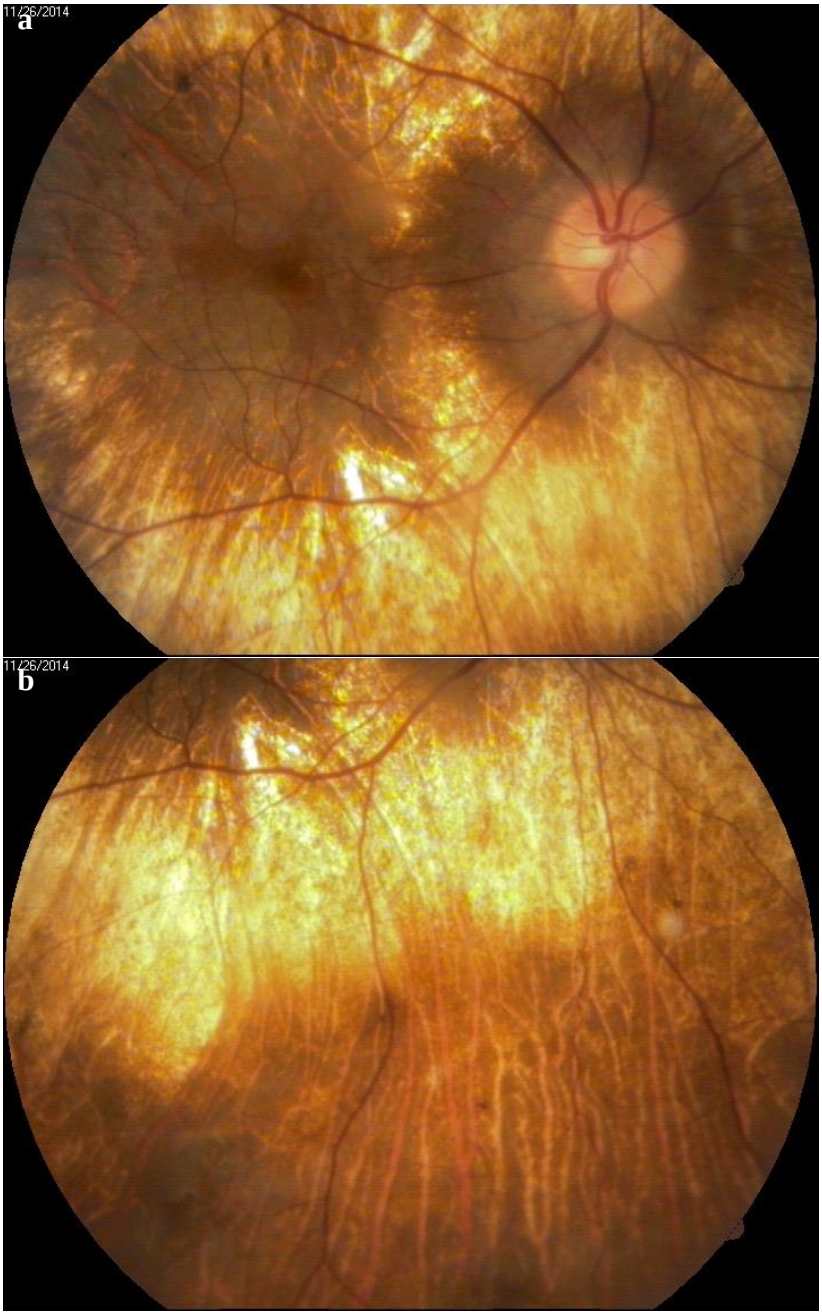

Fig. (2). Colour fundus photographs. The same patient as shown as Fig. (**1**). (**a** and **b**) There are RPE and choroidal atrophy in the equatorial and peripheral fundus, loss of choriocapillaris, and bare sclera (Courtesy of Andrée Henaine Berra MD, Mexico).

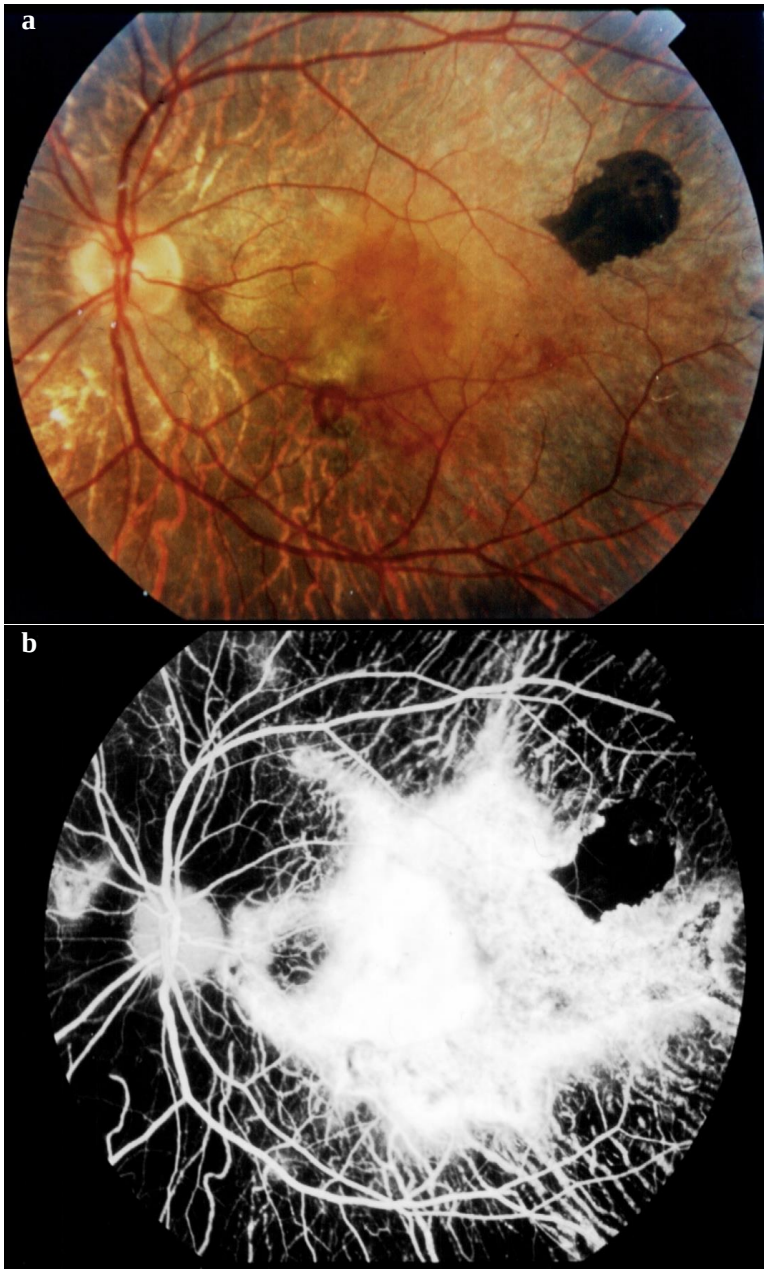

Fig. (3). (**a**) Fundus photography of the left eye of male patient with choroideremia. (**b**) The angiogram shows diffuse atrophy of the choriocapillaris with persistent visualization of the larger choroidal vessels and central hyperfluorescence due preservation of an island of choriocapillaris at the macular area (Courtesy of Juan Manuel Jiménez-Sierra MD, Mexico).

Carriers of X-linked choroideremia often show patches of subretinal black mottled pigment, that may progress to lobular patches of choriocapillaris and RPE loss in older females. Carriers of choroideremia are usually asymptomatic and electrophysiologically normal [4, 5].

Choroideremia is in most cases nonsyndromic, but has been reported in association with mental retardation and deafness as a contiguous gene syndrome [11 - 13].

Diagnosis is made based on the typical fundus appearance, on the results of visual field and electrophysiologic testing, and a family history showing an X-linked recessive pattern. Choroideremia genetic diagnosis includes mRNA and DNA CHM gene analysis to detect the mutations associated with the disease [2, 5, 6, 14].

DIFFERENTIAL DIAGNOSIS

X-Linked Retintis Pigmentosa: Although both share the mode of inheritance, pigment deposition is different between the two, and only CHM presents with atrophy of both the retina and the choroid, leaving areas where the sclera is bare.

Usher syndrome type 1 may also look similar, but again, the atrophy of both the retina and choroid are characteristic of CHM. The presence of deafness and vestibular disturbance in Usher syndrome also helps differentiate between the two.

Diffuse choriocapillaris atrophy and gyrate atrophy of the choroid and retina: Both diseases may resemble CHM, especially in the late stages. Fluorescein angiogram findings, serum ornithine levels, and family history are useful to differentiate between these entities [14].

MANAGEMENT

Management includes yearly ophthalmologic evaluation, the use of sunglasses that block UV light and low visual aids. Treatment is not currently available,

although gene therapy may prove useful in the future. Genetic counselling should be offered to the family [7].

CONFLICT OF INTEREST

The author confirms that author has no conflict of interest to declare for this publication.

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Declared none.

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[http://dx.doi.org/10.1016/j.ophtha.2006.05.045] [PMID: 16935340]

CHAPTER 30

Gyrate Atrophy

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Gyrate atrophy (GA) of the choroid and retina is a rare, autosomal recessive, chorioretinal dystrophy [1] that causes progressive chorioretinal atrophy due to hyperornithinemia resulting from ornithine d-aminotransferase (OAT) deficiency [2]. Many different OAT gene mutations have been described [3 - 5]. The actual cause of chorioretinal atrophy remains unknown [6].

ESSENTIALS OF DIAGNOSIS

The initial symptoms are reduction of peripheral vision and, in some patients, reduction of night vision (nyctalopia) in the first decade of life [7].

Loss of central vision occurs in patients over 40-50 years old [8], and their fundus reveals very well demarcated circular or ovoid areas of chorioretinal atrophy in the mid-periphery. These lesions have a hyperpigmented margin (Figs. **1** and **2**) [2]. With increasing age, these lesions grow in size and number, eventually coalescing (Fig. **2**) and involving the entire posterior pole.

Myopia, posterior subcapsular cataracts and cystoid macular edema may also occur [2, 9].

There is no autofluorescence in the atrophic areas. Fluorescein angiography (FA) demonstrates the sharp demarcation between normal and abnormal tissue, the

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former showing normal background fluorescence; the latter, atrophy of the choriocapillaris (Fig. **2**). Full-field electroretinogram shows severely reduced or undetectable amplitudes even at an early stage. OCT can be useful for detecting cystoid macular edema.

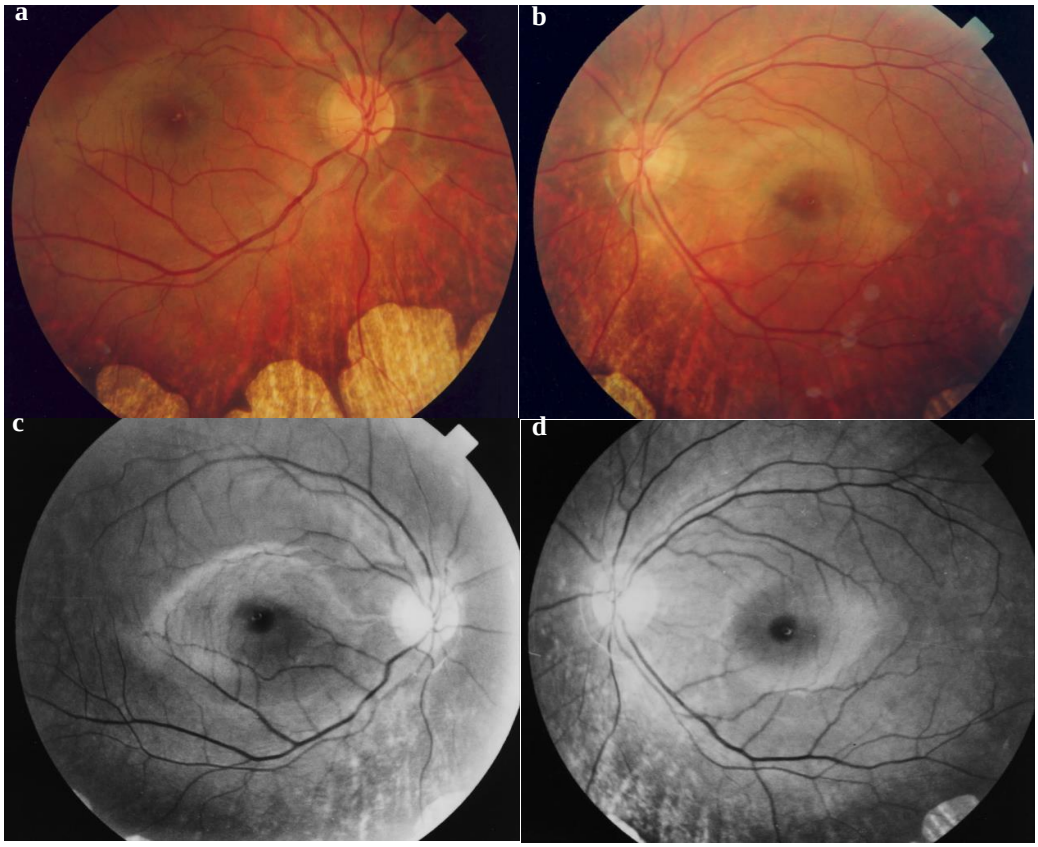

Fig. (1). Fundus photographs: Gyrate atrophy. (**a**) and (**b**) There are sharply defined areas of chorioretinal atrophy separated from each other by thin margin of pigment. (**c**) and (**d**) Red free images of the same patient (Courtesy of Juan Manuel Jiménez-Sierra, MD).

Patients present very high levels of serum, urine, and spinal fluid ornithine (10 to 20 times normal). Usually the typical fundus findings are sufficiently characteristic to make the diagnosis of GA.

In patients with suspected GA, serum ornithine concentration should be measured to confirm hyperornithinemia. Molecular genetic testing of the OAT gene can be

useful for confirming the diagnosis.

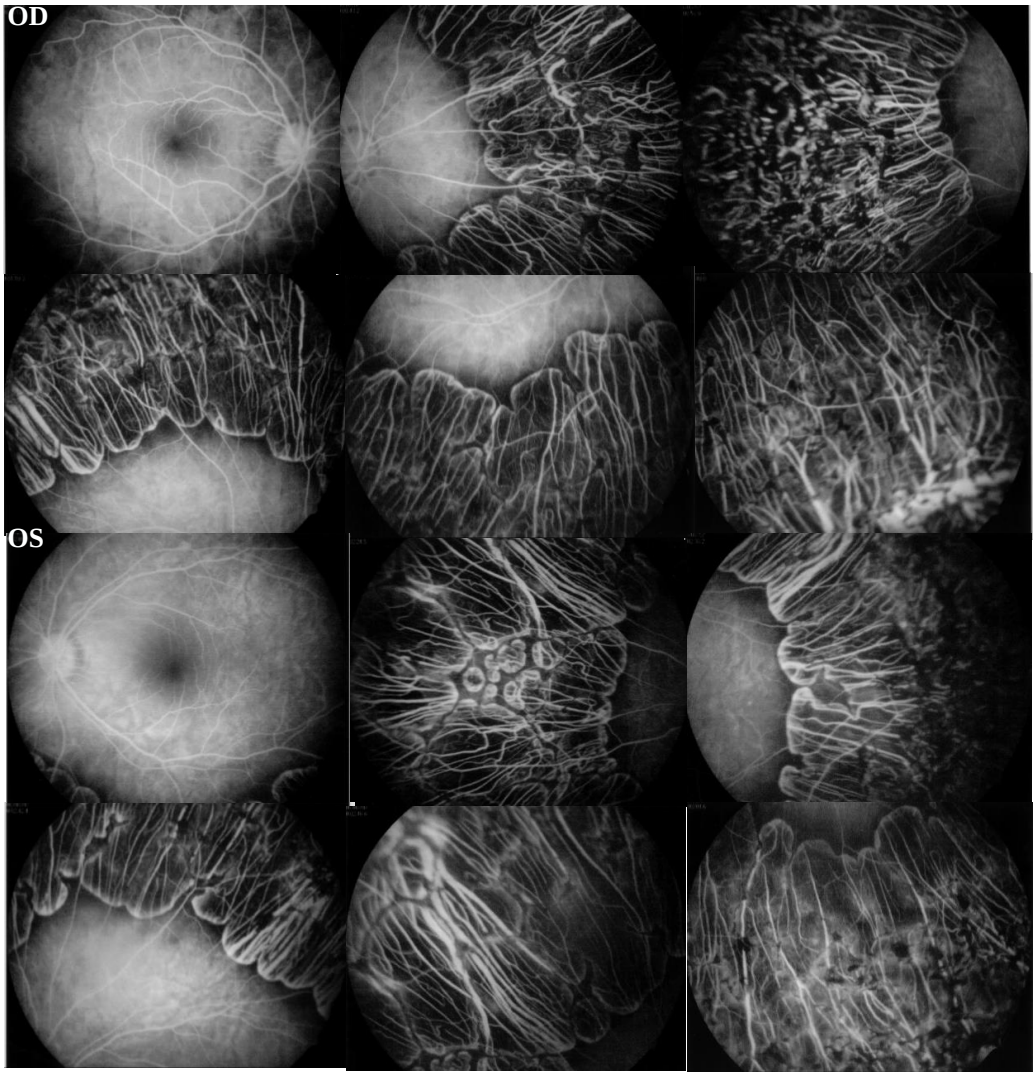

Fig. (2). Fluorescein angiography of the same patient of Fig. (**1**), after 5 years of follow up. The areas of choroidal atrophy show choriocapillaris atrophy on the angiogram and slight leakage at the margin of chorioretinal atrophy. Adjacent areas of normal-appearing retina have a normal background choroidal flush (Courtesy of Juan Manuel Jiménez-Sierra, MD).

DIFFERENTIAL DIAGNOSIS

When GA reaches its final stages, it may not be differentiable from advanced

retinitis pigmentosa or choroideremia. Other differential diagnoses include choroidal dystrophies such as diffuse choriocapillaris atrophy, generalized choroidal dystrophy and central areolar choroidal dystrophy.

MANAGEMENT

According to many studies, an arginine-restricted diet (precursor of ornithine) or a low-protein diet can help reduce ornithine serum concentration and progression of chorioretinal atrophy and visual loss. Therefore, it is recommended that patients with GA follow up with a dietitian. Pyridoxine (vitamin B6) supplementation is another option, although most patients don't seem to respond to this therapy. There is no information available regarding the assessment of long-term effects of this treatment approach [6].

Following a diet low in arginine to reduce plasma ornithine levels at an early age before any chorioretinal changes have occurred would seem to slow the development of retinal lesions and to result in a different phenotype similar to early retinitis pigmentosa [7].

Some cases may require cataract surgery. Patients with visual loss at late stages should be provided with magnifying visual devices [10 - 13].

An early diagnosis and the success of the diet treatment are key determinants of the outcome of gyrate atrophy.

Genetic counselling should be provided to affected families.

CONFLICT OF INTEREST

The author confirms that author has no conflict of interest to declare for this publication.

ACKNOWLEDGEMENTS

Declared none.

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CHAPTER 31

Cone-Rod Dystrophy

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Dystrophies are inherited conditions, not congenital, usually bilateral, often symmetric and progressive, which develop on a retina with characteristic normal birth [1]. Prevalence of cone-rod dystrophy (CRD) is estimated at 1:40.000 [2]. All modes of Mendelian inheritance have been reported, and currently 17 genes and some additional loci have been reported. ABCA4 seems to be the most prominent causal gene; however, the etiologic fraction for this gene varies widely between studies (24%-65%) [3 - 9].

ESSENTIALS OF DIAGNOSIS

In this group of dysthrophies, the photoreceptors most affected are the cones and rods, which can commit secondarily. The most common initial symptomatology is photophobia, low vision and dyschromatopsia, and in some cases, nyctalopia, when the rod cells are affected [10]. The age of onset is variable; most patients present during the first two decades of life. Visual prognosis depends on age of onset, being worse if the disease is diagnosed earlier in life [11]. The fundus may be normal or progress to atrophic changes above all in the macula, resembling Bull's eye maculopathy, with areas of retinal pigment epithelium (RPE) atrophy that may extend beyond the temporal arcades, and develop areas of retinal atrophy

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similar to pigmentary retinitis (Fig. **1**) [10 - 12]. The optic disc may show a variable degree of pallor. It may also develop retinal vascular attenuation and peripheral pigmentary deposits resembling bone spicules [10 - 12].

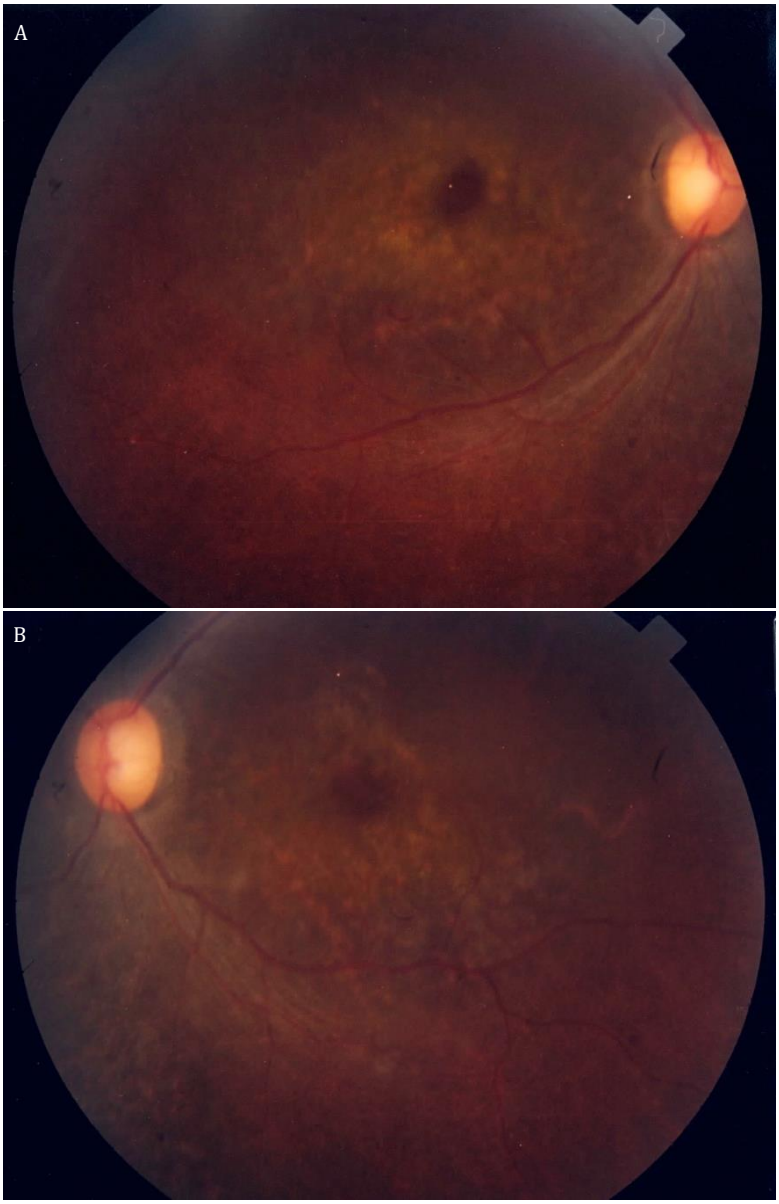

Fig. (1). (A). and **(B).** Fundus photographs of 39-year-old female show bilateral symmetrical peripapillary atrophy, bull's eye maculopathy, and attenuated retinal vessels.

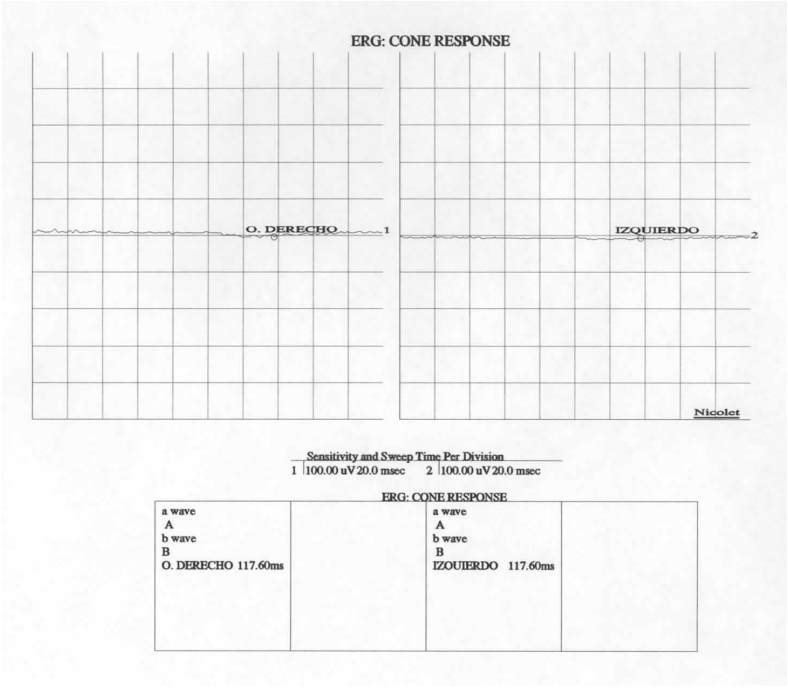

Fig. (2). Photopic ERG test reflects cone response is undetectable.

Full field electroretinogram (ERG) is the gold standard for diagnosis. Electroretinogram shows reduced cone and rod responses, the former being more severely affected (Figs. **2 - 4**). Electrooculogram (EOG) is usually abnormal (Fig. **5**) [1, 2, 11, 12]. Fluorescein angiography can detect an area of macular atrophy with hyperfluorescence due to a window defect, with or without the characteristic pattern of Bull's eye maculopathy (Fig. **6**) [12]. Autofluorescence imaging allows the visualization of an area of absence of RPE (that looks hypoautofluorescent) or RPE that is in distress (that looks hyper autofluorescent) which may enhance the visualization of RPE defects in these diseases. Visual fields reveal a concentric decrease of sensitivity with a central scotoma (Figs. **7** and **8**). Color vision tests show acquired intense dyschromatopsia [2, 10 - 12]. OCT demonstrates significant reduction in the thickness and structural changes in the outer layers of the retina in the central macula. Atrophy is evident, especially in the outer nuclear layer, the ellipsoid layer, and in the RPE (Fig. **9**). Visual acuity varies according to the degree to which the continuity of the ellipsoid layer is maintained. Eyes with a

better preserved neuroretinal structure in the fovea centralis have generally less reduced thickness of the retina and a better visual acuity [13].

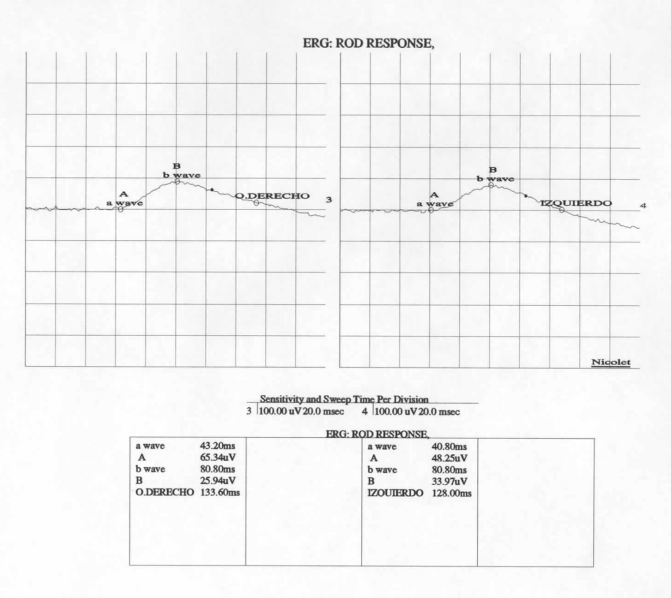

Fig. (3). Scotopic ERG test reflects rod response: the amplitude of b wave is markedly decreased.

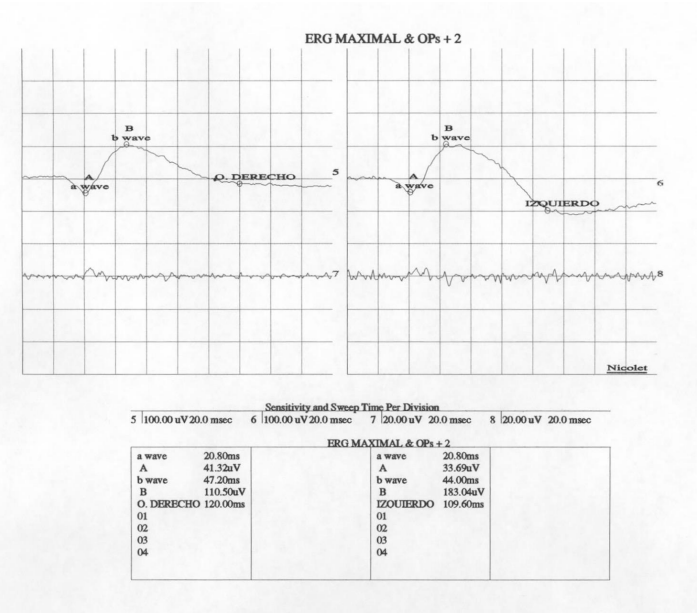

Fig. (4). The maximal scotopic ERG test reflects abnormal cone and rod response.

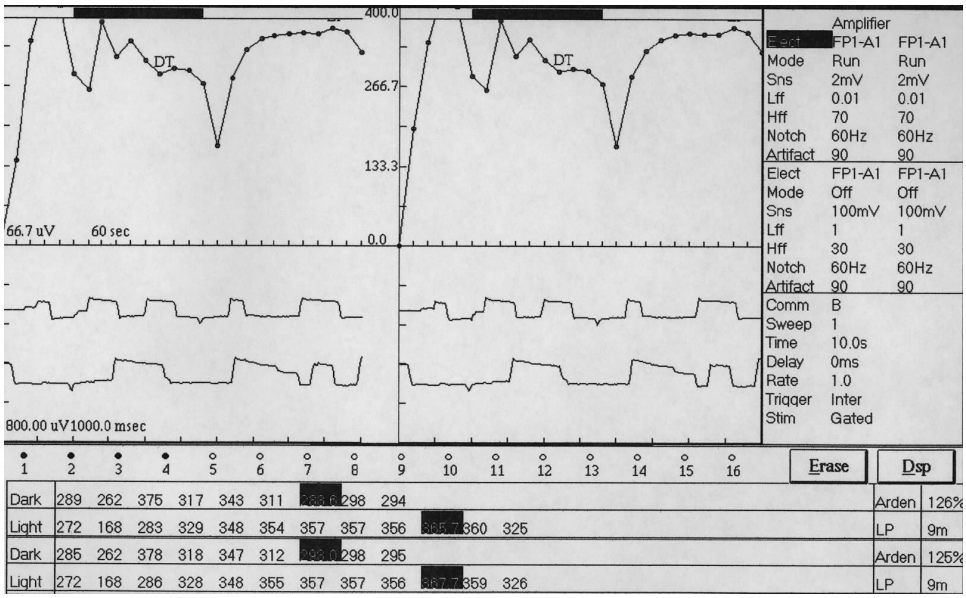

Fig. (5). EOG test is abnormal.

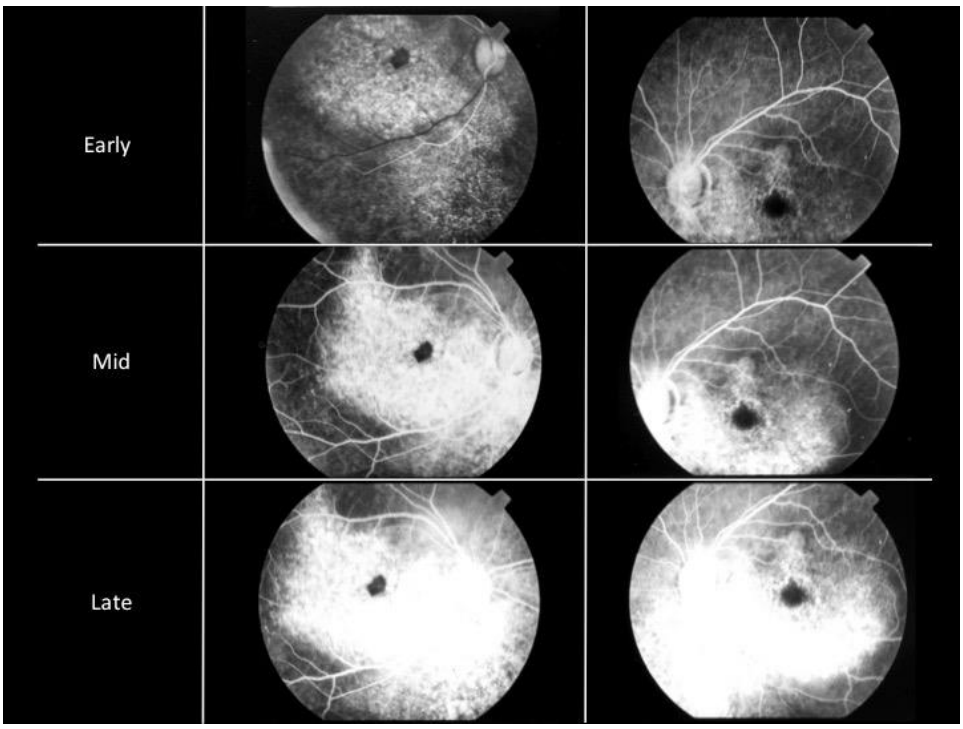

Fig. (6). Fluorescein angiography shows hyperfluorescent macular lesions (bull's eye).

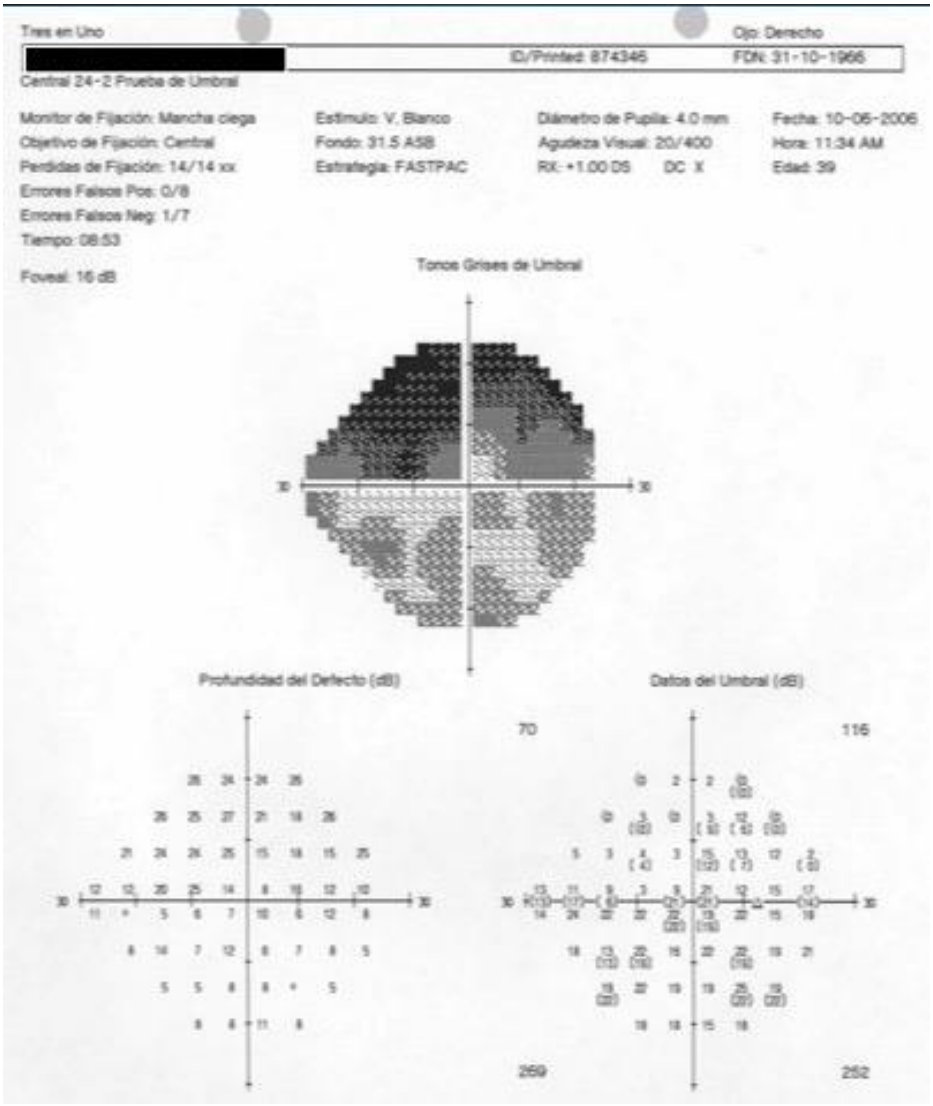

Fig. (7). The visual fields show a superior scotoma with peripheral loss in the right eye.

Syndromic cone-rod dystrophies: There are few syndromes in which retinal degeneration characteristically features CRDs rather than typical retinitis pigmentosa (RP):

Bardet Biedl syndrome: (BBS) is an autosomal recessive disease with a prevalence ranging from 1/13500 to 1/60000. It is characterized by a retinal

dystrophy (that most of the times is a RCD), postaxial polydactyly, obesity, hypogenitalism, mental retardation, and renal abnormalities.

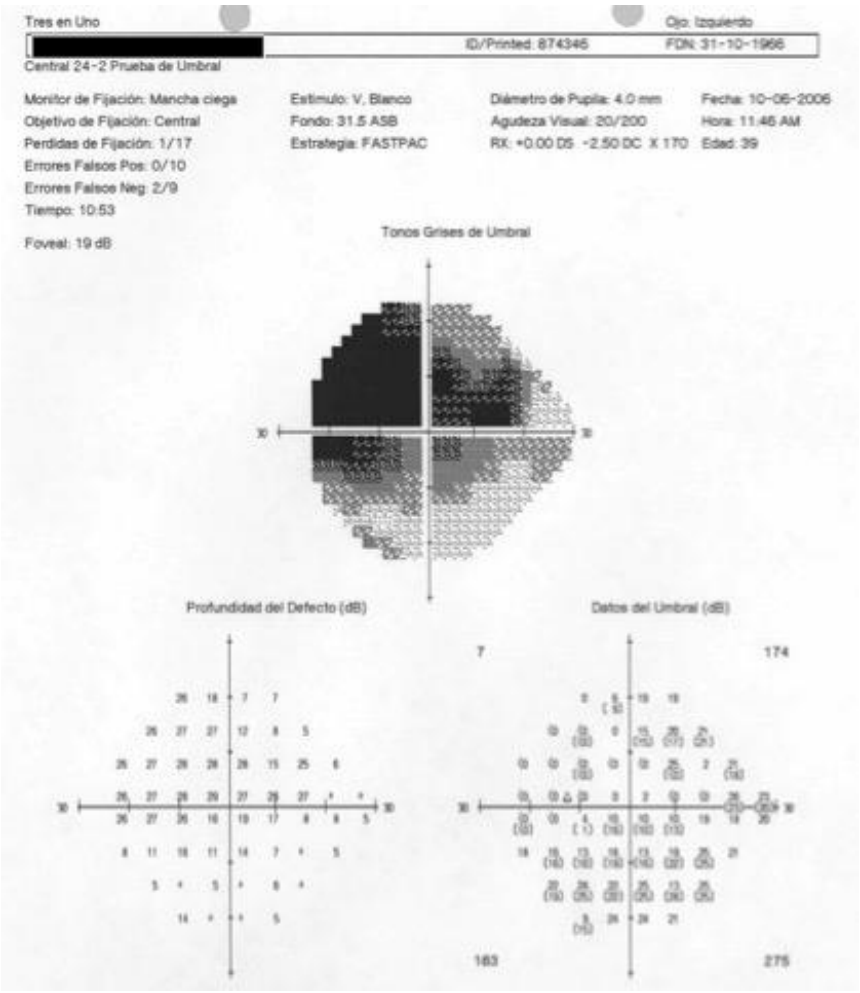

Fig. (8). The visual fields show a central scotoma with peripheral loss being more marked in the superior retina in the left eye.

Spinocerebellar Ataxia type 7: This is an autosomal dominant mutation of the ataxin gene, that leads to spinocerebellar degeneration. Retinal disease begins with a granular appearance of the macula that slowly progresses and affects the entire retina.

Ectodermal diseases: CRD is sometimes encountered in other rare diseases such as amelogenesis imperfecta, hypotrichosis with macular juvenile macular dystrophy, dysmorphic syndromes, and metabolic dysfunctions [10].

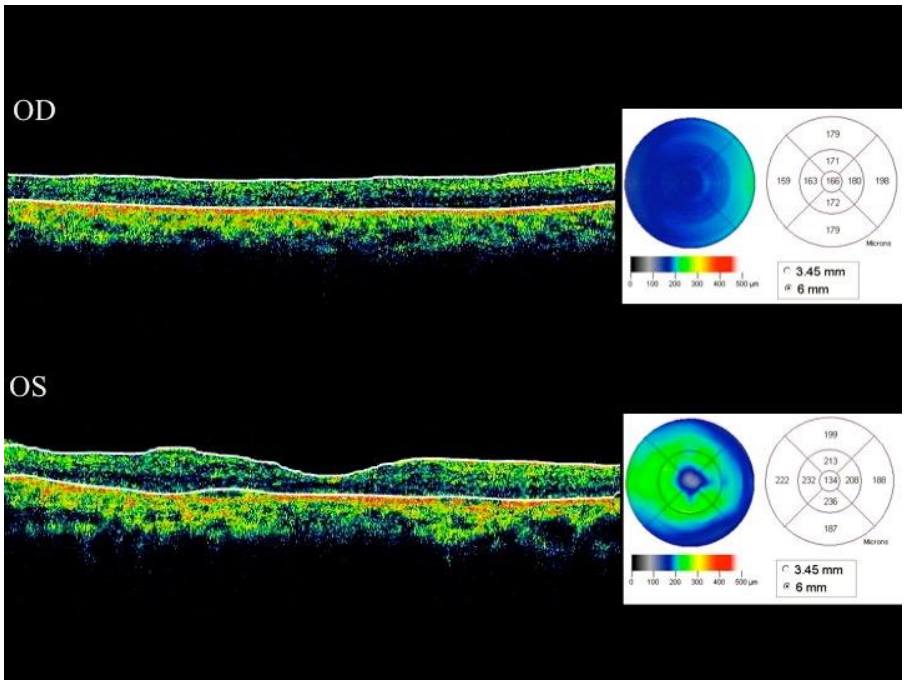

Fig. (9). OCT shows atrophy of the retina, more evident in right eye.

DIFFERENTIAL DIAGNOSIS

Cone dystrophies (CD): The main difference is that rods are unaffected in these diseases. Since cones are affected, there is visual acuity loss, dyschromatopsia and photophobia. Rod function is preserved in the ERG [1, 2].

Retinitis pigmentosa: In typical RCD, the first symptom is night blindness. Pigment changes in the fundus are very similar between both diseases, but tend to be more peripheral in RCD. On ERG, rod involvement with relative sparing of cone function may suggest RCD. When a patient is evaluated late in the course of any disease, ERG changes may be undistinguishable [1, 2].

Stargardt disease: This disease has several hallmark characteristics. There is a very typical discoloration in the central macula, that may be accompanied by

flecks (fundus flavimaculatus) and on fluorescein angiography there is a characteristic choroidal silence (very hypofluorescent choroid) [1, 2, 10, 12].

Leber congenital amaurosis (LCA): This disease may present with a normal fundus, buy may also display a clinical picture similar to RCD and retinitis pigmentosa. However, this disease is present at birth, has associated nystagmus, very low visual acuity and a flat ERG [1, 2, 10, 12].

Chloroquine maculopathy: This may be easily ruled out if the patient has no history of chloroquine use. Differential diagnosis may be challenging with an advanced chloroquine maculopathy [1, 2, 10, 12].

Achromatopsia: In this disease, patients have low vision since birth, that is stationary, with a normal-appearing fundus. ERG shows no cone response, with full function of the rods [10].

MANAGEMENT

Currently there is no treatment for these conditions. One may only prescribe visual rehabilitation with the best correction and lens wear, and red mica to decrease photophobia. With patients at a productive age, it is important to counsel them in professional activities that they can execute, as they are of working age [1, 2, 10 - 12].

CONFLICT OF INTEREST

The author confirms that author has no conflict of interest to declare for this publication.

ACKNOWLEDGEMENTS

Declared none.

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Dr. Mitzy E. Torres Soriano graduated with honors in medicine at the University of Carabobo, Maracay, Venezuela in 2001. Then in 2003 she began her postgraduate studies in Ophthalmology in Hospital Miguel Pérez Carreño (Caracas, Venezuela) where she also served as Chief Resident, and completed them in 2005. From 2006 to 2008, she did a fellowship in Retina and Vitreous in Asociación para evitar la Ceguera. Hospital Dr. Luis Sánchez Bulnes, in Mexico. She dedicates her clinical practice to the medical and surgical treatment of retinal and vitreous diseases.

She has taken many courses and attended numerous congresses on ophthalmology, and has also written various articles and book chapters. She provides review services to several science international journals about ophthalmology and contributes in retinal clinical research.

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