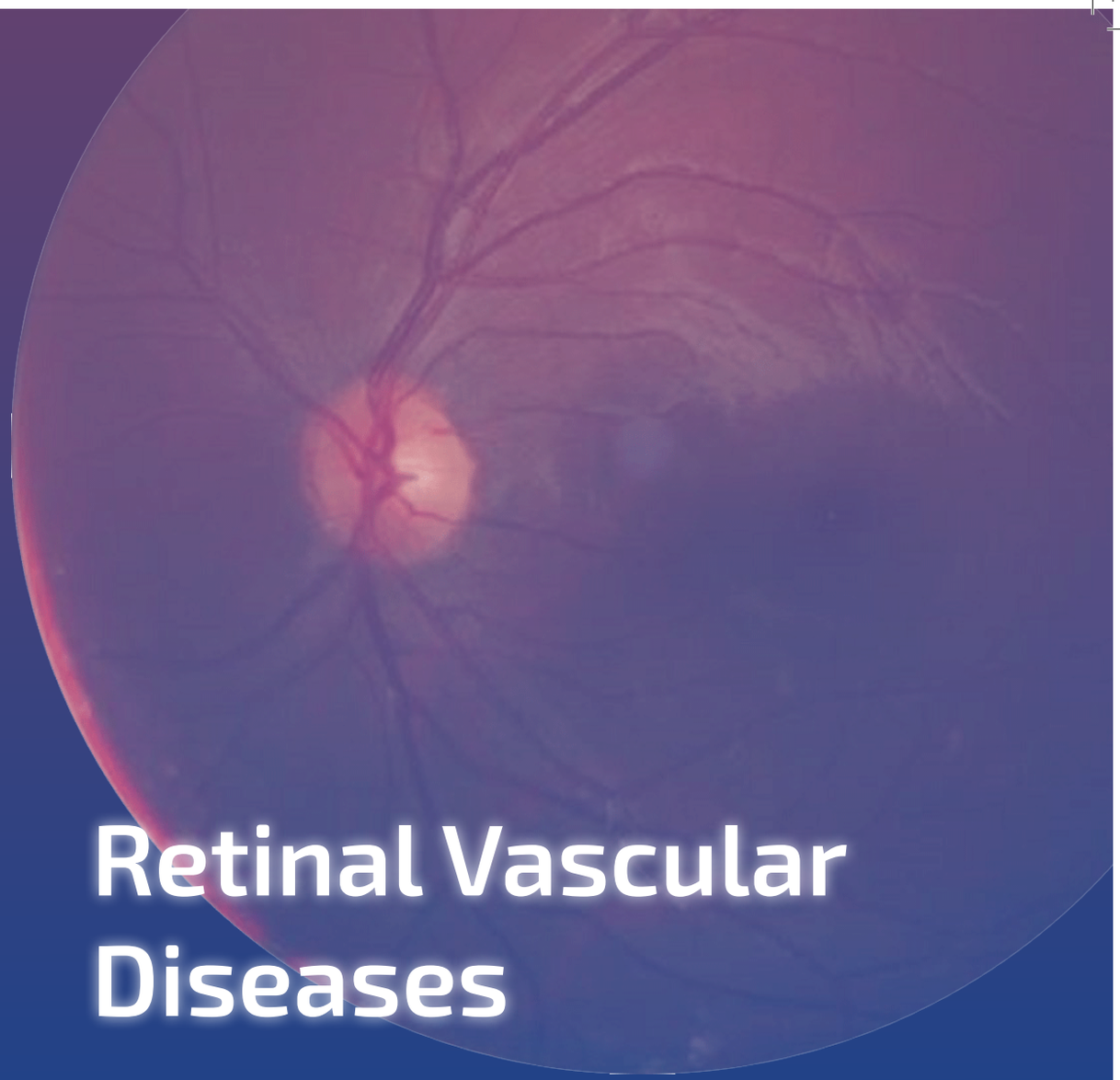

Retinal Vascular Diseases

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Editor

Dr. Cetin Akpolat

ISBN: 978-2-38236-174-0

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Health Sciences

LIVRE DE LYON
Lyon 2021

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LIVRE DE LYON
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Editor • Dr. Cetin Akpolat • Orcid: 0000-0002-7443-6902
Cover Design • Mirajul Kayal
Book Layout • Mirajul Kayal
First Published • August 2021, Lyon

ISBN: 978-2-38236-174-0

Publisher • Livre de Lyon
Address • 37 rue marietton, 69009, Lyon France
website • http://www.livredelyon.com
e-mail • livredelyon@gmail.com

PREFACE

Considerable developments have been recently provided in the therapy of retinal vascular diseases, which give hope to us for greater developments in next years. The introduce of anti-VEGF therapies, intravitreal steroid injection progressions, retinal laser interventions, and modern applications of pars plana vitrectomy are among treatment options for retinal vascular diseases and their complications. Despite these new or developed therapy modalities and knowledge explosion on the disease mechanisms, retinal vascular diseases remain important reasons for blindness in the world.

The topics included in this book range from basic clinical appearance and specific pathology to the treatment of retinal vascular diseases. The comprehensive emphasis of this book includes demographic features, clinical course supported with clinical images, and treatment options. Meanwhile, issues including inflammation and ischemia with their associated pathological mechanisms have been emphasized. Modern diagnostic procedures and therapy strategies have been discussed with respect to their relevance for clinical decision process. Experimental approaches have also been reviewed that may help in the investigation of the retinal vascular diseases.

Several experts in the field contributed to this state-of-the-art review of basic and clinical science aimed to enhance the understanding of retinal vascular diseases and to help the clinicians in the assessment of current and future diagnosis and therapy approaches. The authors are among internationally recognized ophthalmologists in clinical ophthalmology, including medical retina and vitreoretinal surgery areas.

The editor gratefully acknowledges the support of the contributing authors who, besides their large clinical work and scientific investigations, provide time to make such a large contribution to complete this project. Due to multi-authored text nature, many literary styles exist. The editor did not sacrifice the style and originality of the authors. Although some aspects could be discussed in several chapters, the unique interpretation of each author have justified some overlap, which may provide an attractive feature.

I hope that ‘Retinal Vascular Diseases’ will inspire clinicians in the future to have further efforts and provide developments in this field. I gratefully thank the authors who contributed to the creation of this book and helped in conveying up-to-date information, our colleagues who peer-reviewed the book, and the publishing house and its staff who contributed to the publication of the book.

Istanbul, Turkey
August 2021

Best Regards,
Dr. Cetin Akpolat
Editor

This book is dedicated to my parents, Bekir Akpolat (1957-2020) and Yeter Akpolat (1947-). Their values, instilled in me (honesty, morality, education, hard work combined with a dedication to family and friends, and spiritual soul), have become the cornerstone of a thoughtful and peaceful way of my life.

Dr. Çetin Akpolat
Editor

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CHAPTER 1

RETINAL ANATOMY AND BLOOD CIRCULATION

Elif AKSAKAL
Samsun Gazi Community Hospital, Department of Ophthalmology, Samsun
e-mail: etemiz51@hotmail.com
ORCID: 0000-0002-5530-6600

RETINAL ANATOMY

1. Introduction

The retina is a delicate membranous structure that lines the posterior aspect of the eye. The internal part of the retina is called the neurosensory retina and the external part of the retina is called the retina pigment epithelium (RPE). The retina is adhered firmly to the optic nerve head posteriorly and the ora serrata anteriorly. The primary purpose of the eye is to focus light on the retina (1).

2. Embryogenesis

The retina is derived embryologically from the optic vesicle of the embryonic forebrain. It develops from two neuroectodermal layers. The RPE is derived from the same neural tube tissue that forms the neural retina (2).

3. Neurosensory Retina

Except for the fovea, ora serrata, and the optic disc, the neural retina is organized in layers, dictated by the direction of the müllerian glia. The layers of the neurosensory retina can be seen easily in cross-sectional histologic preparations (3). The 10 layers listed progress from the inner(vitreous) to the outer retina (choroid) (Figure 1).

1) Internal limiting membrane (ILM)

2) Nerve fiber layer (NFL)
3) Ganglion cell layer (GCL)
4) Inner plexiform layer (IPL)
5) Inner nuclear layer (INL)
6) Outer plexiform layer (OPL)
7) Outer nuclear layer (ONL)
8) External limiting membrane (ELM)
9) Photoreceptor cell layer (rod and cone inner and outer segments)
10) Retinal pigment epithelium (RPE) and its basement membrane

Figure 1. Layers of the retina in histological sections

Internal Limiting Membrane (ILM)

The müllerian glia elaborates the internal limiting membrane.

Nerve Fıber Layer (NFL)

It consists of the ganglion cell axons (4), The branches of the central retinal artery and vein exist in this layer (5).

Ganglion Cell Layer (GCL)

There are neuroglial cells and ganglion cells in the ganglion cell layer. Ganglion cells are multipolar cells that are in the inner layer of the retina. Their dendrites synapse with the axons of bipolar cells and amacrine cells (5, 6). Optic nerve consists of the fusion of ganglion cell axons (7).

Internal Plexiform Layer (IPL)

The bipolar cells and amacrine cells of the inner nuclear layer synapse with the dendrites of the ganglion cells in the inner plexiform layer (4). The neuronal signal is transmitted to the ganglion cells due to this synapse.

Internal Nuclear Layer (INL)

The inner nuclear layer is home to the nuclei of the müllerian glia, bipolar cells, and horizontal and amacrine cells (5). The amacrine cells lie on the inside and the horizontal cells lie on the outside of the inner nuclear layer. The inner nuclear layer has plexiform layers on either side, which connect it to the outer photoreceptor layer and the inner ganglion cell layer (6).

Bipolar cells transmit signals from photoreceptors to ganglion cells. Horizontal cells are multipolar cells located near the terminal enlargements of rods and cones. They are antagonistic interneurons that inhibit photoreceptors (7). Amacrine cells are also mostly inhibitory interneurons. They are axonless cells with abundant cytoplasm, fragmented nuclei, and numerous dendrites

Müllerian cells are the most important cells that make up the glial cell structure of the retina. There are 2 types of non-neuronal cell groups in the retina, namely, microglia and macroglia (muller cells, astrocytes, oligodendrocytes, and Schwann cells). Microglial cells are auxiliary immune cells, and macroglial cells are cells that regulate the functions of retinal neurons (7). Müller cells, which form the support structure of the retina, extend from the outer limiting membrane to the inner limiting membrane. They contribute to proliferative vitreoretinopathy (PVR) (5).

External Plexiform Layer (EPL)

Rods and cones, which are located in the photoreceptor layer, synapse with bipolar and horizontal cells of the internal nuclear layer in the external plexiform layer (4,5). In the region of the macula, the fibers are elongated and spread outward from the fovea to form the fiber layer of Henle. The layer of Henle is probably the most favorable tissue for hemorrhage and exudate deposition due to its position at the edge of the central retinal circulation.

External Nuclear Layer (ENL)

It is a layer of nuclei of photoreceptors. Cone nuclei form the outer group, and rod nuclei form the inner group (5).

External Limiting Membrane (ELM)

It consists of junctional complexes of adjacent photoreceptors and Müller cells.

Photoreceptor Cell Layer

It is a layer of neuroepithelial cells called rods and cones. Photoreceptors convert light into neuronal signals (8,9). These stimuli are transmitted to the visual center in the brain by the optic nerve formed by the ganglion cell axons located in the innermost layer of the retina (10).

There are cones in the macula and rods in the periphery. Rods are responsible for twilight and night vision (scotopic vision), while cones are responsible for bright light vision (photopic vision), color vision, and sharp vision.

There are approximately 7 million cones and 130 million rods in the entire retina (11). The rods are not found in the 350-micron diameter center of the fovea, and their number increases towards the periphery and decreases slightly in the most periphery (6). Condensation of cones in the fovea is maximum (6).

Photoreceptor cells consist of 4 main parts: outer segment, inner segment, nucleus, and synaptic terminal (12). The outer segment is the center of photosensitivity and the inner segment is associated with metabolic activity.

Retinal Pigment Epithelium (RPE)

The RPE is a monolayer of hexagonal cells. This layer extends from the margin of the optic disc to the ora serrata and is continuous with the pigment epithelium of the ciliary body.

RPE has got pigmented cytoplasmic granules named melanosomes and lipofuscin (9). On the apical side, long microvilli of RPE contact with the outer segments of the photoreceptors. The basal portion is attached to Bruch's membrane. Cells of the RPE are tall and dense in the macular region than in the peripheral regions. RPE is a vital tissue for the maintenance of photoreceptor function (13,14). The density of photoreceptors varies across the retina, but the number of photoreceptors that overlie each RPE cell remains constant (45 photoreceptors per RPE cell).

RPE cells can repair local defects in the retina (unlike the neural retina). RPE cells have a critical role in the pathogenesis of PVR. When the blood-retina barrier is disrupted for various reasons, RPE cells that pass into the vitreous cavity proliferate pathologically and form contractile membrane structures. As a result, they cause the development of tractional (fibrotic) retinal detachment (5,15).

The function of RPE

1) Absorb stray light
2) Transportation of metabolites in retinal layers
3) Digestion of waste of retinal cells
4) Visual pigment metabolism
5) Vital in vitamin A metabolism
6) The outer segments of photoreceptors are renewed by the RPE. They protect the photoreceptors from the damage of free radicals by phagocytizing the outer segments of the rod and cone (4,16).
7) Retinal adhesion by the formation and maintenance of the interphotoreceptor matrix (6, 17).
8) Free radical stabilizer and engage actively in oxidative metabolism
9) Elaboration of growth factors that control vascular supply, permeability, growth, repair, and other processes vital for retinal function.
10) The lateral surfaces of adjacent RPE cells are closely apposed and joined by tight junctions (zonulae occludentes); which block the free passage of water and ions. Thus, they keep the subretinal space dry. This helps to protect the neural environment of the retina. They can form and maintain of the outer blood-retinal barrier between the choriocapillaris and the neurosensory retina (5).

The retina is topographically divided into:

1) Central retina (Macula)
   a. Fovea
   b. Foveola and umbo
   c. Parafovea
   d. Perifovea
2) Peripheral retina
   a. Equator
   b. Ora serrata
   c. Pars plana

Macula

The macula (Figure 2) is the portion of the posterior retina containing xanthophyll (yellow) pigment and two or more layers of ganglion cells. It is

5-6 mm in diameter and is centered vertically between the temporal vascular arcades. The center of the macula is the foveal avascular zone (FAZ), a small, slightly concave area devoid of retinal capillaries and occupied by cones. The umbo, foveola, fovea, parafovea, and perifovea constitute the macula. The central area can be differentiated from the extra-areal periphery by the ganglion cell layer. The ganglion cell layer is several cells thick in the macula, however, it is only one cell thick in the periphery. The macular border has an approximate diameter of 5.5mm, which comprises the diameter of the fovea (1.5mm), twice the width of the parafovea (1mm), and twice the width of the perifovea (3mm) (18). Topographically, the macula consists of 4 parts.

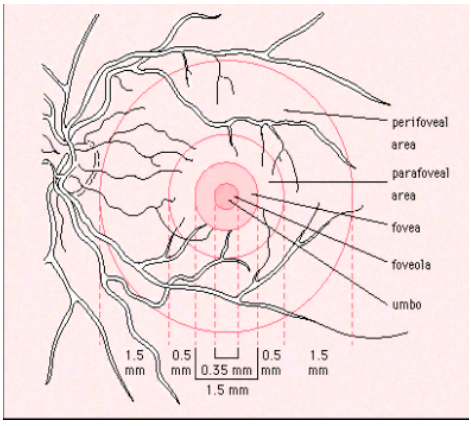

Figure 2. Macular Topography

1a) Fovea

The fovea (fovea centralis) is a depression in the inner retinal surface in the center of the macula. It is approximately 1.5 mm in diameter. The fovea consists of a thin bottom, an angle of 22, concavity named clivus, and a thick margin. The declivity of 22 angles denotes the lateral displacement of the second and third neurons in the inner nuclear layer, which includes most of the nuclei of müllerian glia. The margin of the fovea is often seen biomicroscopically as a ring-like reflection of the internal limiting membrane, which measures 1500 micrometer (disc size) in diameter and 0.55mm in thickness.

1b) Foveola

The central floor of the fovea is termed the foveola, and the depression in the center of the foveola is called the umbo. Both the umbo and foveola represent

the precise center of the macula, the area of the retina that results in the highest visual acuity.

The predominant photoreceptor of the foveola and umbo is the cone. An area of 150-200 micrometer diameter, referred to as the central bouquet of cones (19). During foveal maturation, the foveal cones result from the first, second, and third neurons, which occur 3 months before and 3 months after term (20). The inner cone segments are connected laterally by a junctional system, the external limiting membrane. The inner fibers (axons) travel radially and peripherally as fibers of Henle in the outer plexiform layer.

The bouquet of central cones is surrounded by the foveal bottom, or foveola, which measures 350 micrometers in diameter and 150 micrometers in thickness. This avascular area consists of cones that are elongated and connected by the external limiting membrane.

The avascular foveola is surrounded by vascular arcades, a circular system of capillaries. These vessels are located at the level of the internal nuclear layer and they form an avascular zone of 250-600 micrometers between them. Internal limiting membrane thickness and the strength of vitreal attachment are inversely proportional, so adhesions are strongest in the foveola (21).

1c) Parafovea

The parafoveal area is a 0.5mm wide zone where the ganglion cell layer, inner nuclear layer, and outer plexiform layer are thick and it surrounds the fovea. It includes 4-6 layers of ganglion cells and 7-11 layers of bipolar cells (22). In this region, the ratio of cones-rodes is 1:1.

1d) Perifovea

The perifovea surrounds the parafovea as a belt that measures 1.5 mm wide. The region is characterized by several layers of ganglion cells and six layers of bipolar cells (22). In this region, the ratio of cones-rodes is 1:2.

Peripheral Retina

The peripheral retina is divided into near, middle, far, and extreme peripheries (23).

2a) Equator

It lies between the perifovea and the ora serrata. It is a 3mm wide region. Vortex veins are located on the equator at 1,5,7, and 11 o'clock dials. The upper nasal

and temporal vortex veins are at a distance of 7-8 mm, and the lower vortex veins are at a distance of 5-6 mm. The circumference of the eye is 72 mm at the equator and 60 mm at the ora serrata.

2b) Ora Serrata

It is located between the equator and the pars plana. There are no photoreceptors in the ora serrata. The peripheral retina thins and ends as it approaches the ora serrata. The width of ora serrata is 2.1 mm temporally and 0.7 mm nasally. The name ora serrata is given because of the toothed appearance of this zone. This toothed appearance is greatest in the upper nasal. The ora serrata is 6 mm posterior to the nasal limbus and 7 mm posterior to the temporal limbus. In the ora serrata, the sensory retina is attached firmly to the pigment epithelium.

2c) Pars Plana

Pars plana is the most extreme peripheral region of the retina. Its width is 3mm nasally, 4mm temporally.

RETINAL BLOOD CIRCULATION

Retina receives its nutrition from the ophthalmic artery, which is the first branch of the internal carotid artery. The major branches of the ophthalmic artery are the central retinal artery, posterior ciliary arteries, lacrimal artery, supraorbital, and supratrochlear artery (24). There are two circulatory systems in the retina: retinal blood vessels and the uveal (choroidal) blood vessels.

Typically, two posterior ciliary arteries exist (medial and lateral) and they divide into two long posterior ciliary arteries and numerous short posterior ciliary arteries (6-8). The posterior choriocapillaris is supplied by these short posterior ciliary arteries, which enter the choroid in the peripapillary and submacular region. The anterior choriocapillaris is supplied by the long posterior ciliary arteries and the anterior ciliary arteries.

The choroid is drained through the vortex venous system, which has one or two major vessels in each quadrant, located in the equator. The vortex veins drain into the superior and inferior orbital veins, which drain into the cavernous sinus (25, 26). The central retinal vein drains the retina and the prelaminar aspect of the optic nerve into the cavernous sinus. Thus, both the retinal and choroidal circulatory systems are in communication with the cavernous sinus.

The retinal blood vessels (central retinal artery and posterior ciliary arteries) provide nourishment for the inner retinal layers (2/3 inner part) and carry waste products from them. The outer retina layers (RPE, Photoreceptor layer) are avascular and are supplied by diffusion from the choriocapillaris. The central retinal artery is an end artery that has no significant anastomoses.

The retinal arteries and arterioles remain in the inner retina and retinal veins are in the inner retina nearly to the arteries too. When a retinal artery and retinal vein cross, the artery lies anterior to the vein, and the two vessels share a common adventitial coat. The crossings are important in branch retinal vein obstructions.

1. Retinal Capillaries

Retinal capillaries are arranged in laminar meshworks (27). The thickness of the meshwork is more in the posterior than the periphery retina. The meshwork configuration is important to ensure adequate perfusion to all retinal cells. Retinal capillaries exist in the superficial (nerve fiber layer) and deeper retinal layers (internal nuclear and plexiform layers).

Capillary free zones are present in three areas of the retina. Retinal capillaries are absent in the 0.5 mm region in the fovea, around the larger retinal arteries and veins, and at the far retinal periphery, (6, 7).

2. Choroid

The choroid envelops the retina and RPE. It is a densely pigmented and richly vascularized layer that nourishes the outer retina and RPE (28). The high rate of blood flow in the choroid may facilitate its ability to dissipate heat and help regulate ıntraocular pressure (IOP). The basement membrane of the choroid's innermost layer; the choriocapillaris forms the outer layer of Bruch's membrane.

Choroidal circulation is entirely separate from the retinal circulation. It is supplied by the short and long posterior ciliary arteries and the anterior ciliary arteries. Choroidal arteries soon branch to form a monolayer capillary named the choriocapillaris. Unlike the retinal vasculature, the choroidal arteries and veins do not run parallel to each other; and the choriocapillaris has large fenestrations, which allows more rapid transport of molecules. The stroma of the choroid consists of collagenous and elastic tissue with melanocytes. The pigment in these melanocytes in choroid and RPE is melanin and it gives the color of the posterior segment.

Retinal blood flow represents %5 of total ocular blood flow (29). Blood flow to the temporal retina is three times larger than to the nasal retina due to large macular component. There is no difference between the superior and inferior retina.

3. Blood Retinal Barrier

The blood-retinal barrier is formed by both the retinal capillaries (related to the inner blood-retinal barrier) and RPE (related to the outer blood-retinal barrier) (30). The barrier function depends on tight junctions and glial cells around the retinal capillaries. It is interesting to note that no intraocular lymphatic channels exist. The retina is protected by blood-retinal barriers. The choriocapillaris, with its numerous fenestrations and lack of tight junctions, does not have much significance in the blood-retinal barrier.

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CHAPTER 2

DIABETIC RETINOPATHY

Muhammed Mustafa KURT
Samsun University, Faculty of Medicine,
Department of Ophthalmology, Samsun
e-mail: musti_art@hotmail.com
ORCID: 0000-0002-4667-3046

1. Introduction

Diabetes Mellitus (DM) is a systemic disease that occurs as a result of the absence, insufficiency, or inability of endogenous insulin to be used by the tissues. In addition to chronic hyperglycemia, impaired carbohydrate, protein, and fat metabolism, capillary membrane changes and accelerated atherosclerosis accompany the disease (1).

The effect of diabetes on the eye was first described by Jaeger in 1855. Subsequent studies have revealed many pathologies ranging from retinal capillary ischemic changes, macular edema (ME), ischemia, optic neuropathy, and vitreous hemorrhage to tractional retinal detachment (RD). (2)

Diabetic retinopathy (DR) findings are detected in approximately 25% of patients with diabetes (3). DM is the most important systemic disease-causing blindness and is one of the leading causes of loss of visual function in the 20-65 age group (4). Diabetic macular edema (DME) is the most common cause of visual acuity loss among diabetic maculopathies. This maculopathy can occur at any stage of DR, can be seen in two different ways as macular edema and macular ischemia. Macular edema is an indicator of fluid accumulation in the extracellular space within the retina in the macular region and threatens visual acuity if the retina in the macular center thickens (5).

Depending on the severity of the retinopathy, the frequency of macular edema increases. Macular edema has been reported in 3% of mild nonproliferative diabetic retinopathy (NPDR), 38% of moderate/severe NPDR, and 71% of PDR (6). The diagnosis of DME can be determined by fundus examination, however, methods such as optical coherence tomography (OCT), fundus fluorescein

angiography (FFA), and color fundus photo are used for diagnosis, treatment, and follow-up. The prevalence of DME increases as the duration of diabetes increases. The prevalence of DME is 5% in the first 5 years of diabetes diagnosis, and around 15% in the first 15 years (3). In 10-year incidence studies, DME was found in 29% of patients with type 1 diabetes and 14% of patients with type 2 diabetes (7,8).

Caused by hyperglycemia or insulin deficiency; It can be defined as a picture of microangiopathy and neuropathy in which capillaries, venules, and precapillary arterioles in the retina are involved (10). DR is the most common and treatable chronic complication of diabetes. In the advanced stages of DR, abnormal neovascularizations are observed in the retina secondary to ischemia (pathological angiogenesis). It is known that this new vessel formation is caused by growth factors released from hypoxic retinal tissue (11). DME, characterized by thickening of the macular region, has been detected in diabetic patients at any stage of the DR process. DME occurs as a result of leakage from dilated capillaries with increased permeability and microaneurysms and disruption of the blood-retina barrier. Early diagnosis and tight regulation of blood sugar levels are important to control DR and DME.

1. Epidemiology

In 1921, it was found that insulin is secreted from beta cells in the islets of Langerhans of the pancreas. Insulin was first used in 1925. With the use of insulin and other antidiabetic drugs in the treatment, the life expectancy of diabetic patients has increased. As a result, there was a significant increase in the incidence of DR, which is one of the major complications of diabetes along with other complications. Today, DR is the most common cause of blindness in the 40-65 age group in developed western countries (12,13).

2. Risk Factors

While the incidence of PDR is high in type 1 diabetes, the incidence of DME is high in type 2 diabetes. The duration of diabetes is the most important risk factor. While the incidence of DR development within 10 years is 50% in patients diagnosed with diabetes before the age of 30, this rate increases to 90% in patients diagnosed after the age of 30. The development of DR within 5 years of the onset of diabetes and before puberty is extremely rare. Approximately 5% of non-insulin-dependent diabetics will have DR at their first examination. As

the duration of the disease increases, the probability of detecting DR increases. 20 years after the diagnosis of DM, 90% of patients with type 1 diabetes and more than 60% of patients with type 2 diabetes have DR at any level (14).

Metabolic control of diabetes (15), pregnancy (16), hypertension (17), diabetic nephropathy, dyslipidemia (18,19), anemia, oral contraceptive drug use, menopause, puberty, smoking (20), alcohol (21), aspirin, genetic factors (8) and cataract surgery (22) can be counted among the systemic causes of DR. Factors such as high myopia, glaucoma, old chorioretinopathy, posterior vitreous detachment, central retinal artery occlusion, carotid artery stenosis, and optic atrophy are protective factors for DR (23).

3. Pathogenesis

DR is a microangiopathy that affects precapillary arterioles, capillaries, and venules in the retina. In retinopathy, there are findings due to both microvascular occlusion and leakage. The main pathological biochemical mechanisms that play a role in the emergence of pathological changes related to DR can be grouped under three headings; non-enzymatic glycosylation, oxidative stress, and sorbitol pathway (24,25).

4. Classification

The currently accepted classification for DR was made by the "Early Treatment Diabetic Retinopathy Study" group. It is based on the modified Airlie House classification and is performed by staging stereoscopic fundus photographs. According to ETDRS, DR is divided into two main groups as NPDR and PDR. NPDR is subdivided into very mild, mild, moderate, severe and very severe, while PDR is subdivided into early, high-risk, advanced, and involutional (26). This classification is accepted as the gold standard for clinical DR staging. Stage lesions are microaneurysm, intraretinal hemorrhage, venous calibration changes, intraretinal microvascular anomalies (IRMA), optic disc neovascularization (NVD), neovascularization in other areas of the retina (NVE), fibrous proliferation, pre-retinal hemorrhage, vitreous hemorrhage, and tractional retinal detachment (TRD).

Non-proliferative DR

Findings in NPDR are limited to the retina. Findings related to retinal vascular permeability changes and retinal vascular occlusions causing ischemia are

observed. Pericyte loss in the capillary wall and basement membrane thickening are seen in diabetic vasculopathy. The lack of perfusion that develops as a result of autoregulation of retinal vessels causes hypoxia and in response to this, retinal vessels expand and increase their flow. Microvascular enlargement follows hyperglycemia, followed by capillary occlusion and microaneurysm formation. In very mild NPDR, only microaneurysms are observed. In mild NPDR, there are superficial retinal hemorrhages, and hard exudates in addition to microaneurysms. In moderate NPDR, there are soft exudates and/or mild IRMA- venous pilling in addition to mild NPDR findings. Severe intraretinal bleeding in 4 quadrants, prominent venous pillin of at least 2 quadrants, and prominent IRMAs of at least 1 quadrant can be seen in severe NPDR.

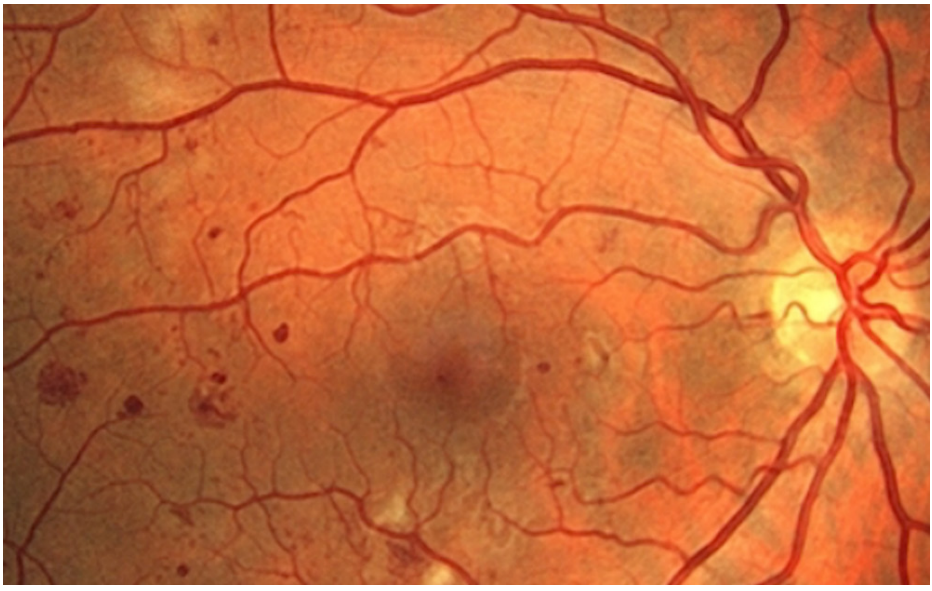

Figure 1. Moderate non-proliferative diabetic retinopathy with retinal hemorrhages and exudates

Proliferative DR

NVD or NVE, pre-retinal or intravitreal hemorrhage, fibrous tissue proliferation are components of PDR. More than a quarter of the retina must be out of perfusion for PDR to develop. Various angiogenic growth factors are released secondary to retinal hypoxia. The most important of these is VEGF, and the other is the placental growth factor. In pathological conditions, it is thought that the balance between VEGF and antiangiogenic factors is disrupted in favor

of VEGF (25). Neovascularization is present in early PDR. In high-risk PDR, any of the findings of NVD, vitreous or pre-retinal hemorrhage accompanying NVD, NVE ≥ ½ optic disc diameter, and accompanying vitreous or pre-retinal hemorrhage can be detected. Significant vitreous hemorrhage, tractional retinal detachment involving the macula, and phthisis may be present in advanced PDR. Involutional PDR shows regression in neovascularization, reduction in retinal vessel diameters, severe retinal ischemia, and low vision after total vitreous detachment. Neovascularization is the main marker of PDR. Hemorrhages may be in the vitreous gel but are often pre-retinal. TRDs occur as a result of progressive contraction of fibrovascular membranes over large areas of vitreoretinal adhesion.

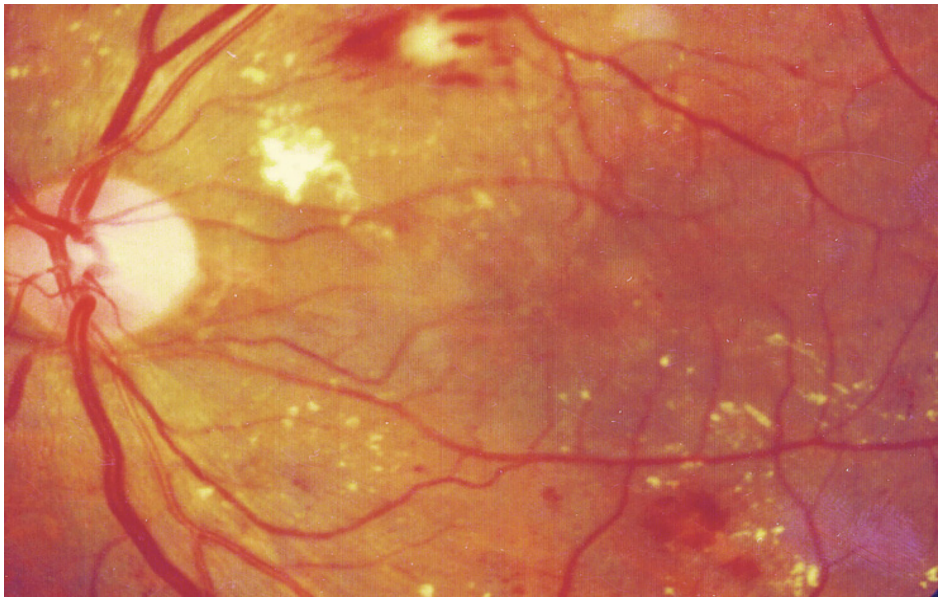

Figure 2. Proliferative diabetic retinopathy (PDR) with exteretinal hemorrhages, neovascularization and macular edema

5. Diabetic Macular Edema

Diabetic maculopathy is the most important cause of vision loss in NPDR, and DME is the most common cause of vision loss together with vitreous hemorrhage in all DR patients. Macular edema is detected in 10% of all diabetic patients and the central macula is involved in 40% of these cases. Macular edema has been reported in 3% in NPDR, 38% in pre-proliferative DR and early proliferative retinopathy stage, and 71% in PDR stage (27). DME is a microvascular

complication of diabetes and accounts for three-quarters of vision loss in diabetic eyes. In various epidemiological studies; It has been reported that the incidence and prevalence of DME show significant differences depending on the type of diabetes (Type 1 or Type 2), the type of treatment (insulin, oral hypoglycemic agent or diet), and the mean duration of the disease (26). Generally, the risk of developing retinal complications (macular edema or PDR) that threatens vision is 50% in Type 1 diabetes and 33% in Type 2 diabetes (28). While macular edema is less common in young-onset diabetes, it is more common in adult-onset diabetes. Adult-onset insulin-dependent diabetes has the highest incidence of maculopathy with 5% macular edema at diagnosis. The risk of macular edema is slightly lower in non-insulin-dependent diabetes. It is known that macular edema is strongly associated with the duration of diabetes. If diabetes is diagnosed before the age of 30, the incidence of macular edema is 0% at 5 years and 29% at 20 years or more. If the diagnosis of diabetes is made after the age of 30, these rates are 3% and 8%, respectively (4). DME tends to be a chronic disease. Spontaneous recovery is rare. DME has three clinical manifestations: retinal thickening, hard exudate deposits, and fluorescein leakages.

Any retinal thickening or hard exudate located in an area of one disc diameter from the center of the macula is considered a stand-alone sign of diabetic macular edema. However, every fluorescein leakage detected in angiography cannot be considered as a stand-alone finding of macular edema. Fluorescein leaks may be a clinical manifestation of macular edema if accompanied by retinal thickening or hard exudate formations. It develops histopathologically in 2 forms:

1. Fluid accumulation in the retinal folds as a result of the breakdown of the inner or outer blood-retina barrier.
2. As a result of diffuse ischemia:
   - Dilatation and permeability disorder of remaining capillaries
   - Retinal edema is caused by substances resulting from ischemia

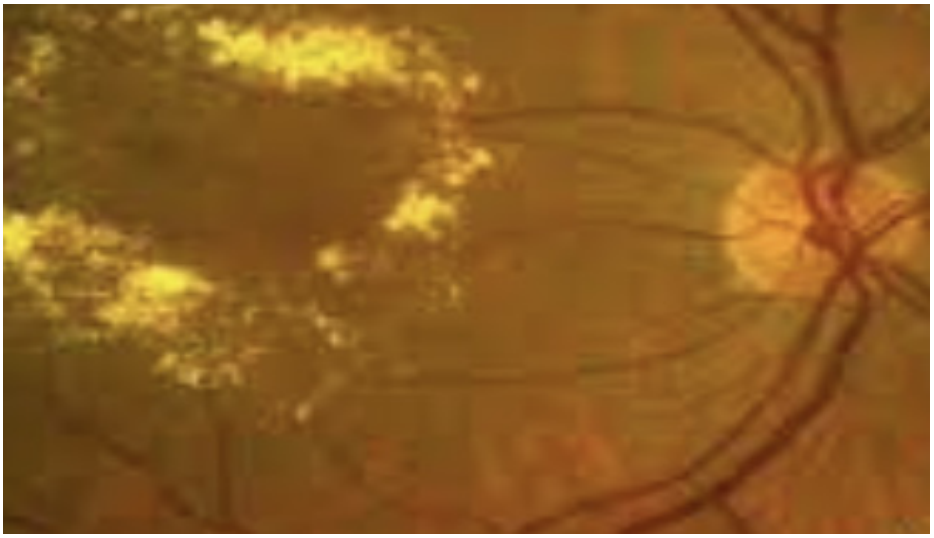

Figure 3. Fundus photo of a case with diabetic macular edema

Focal Macular Edema

Microaneurysms are areas of local retinal thickening caused by leakage from dilated retinal capillaries and rarely from intraretinal microvascular anomalies. Any retinal thickening or hard exudate within one disc diameter from the center of the macula is defined as focal macular edema. Clumps of hard exudate often surround the macular edema. The accumulation of hard exudates around the ring-shaped microaneurysms is called circular retinopathy. Clusters of microaneurysms are seen in the middle of hard exudates in the circus. Their abnormal vascular permeability is indicated by FFA. Rarely, fibrous plaque may develop due to fibrous metaplasia of the RPE stimulated by subretinal exudates under the macula. In these cases, permanent photoreceptor damage occurs and the prognosis is the worst. Hard exudate accumulation is closely associated with systemic disorders such as hyperlipidemia (29). In addition, thickened posterior hyaloid affects vascular permeability as a result of shrinkage in capillary structures and leads to an increase in focal edema. Focal macular edema is divided into clinically insignificant, that is, non-sight-threatening, and clinically significant macular edema (CSME), that is, vision-threatening macular edema. The diagnosis of CSME is made by ophthalmoscopic observation of hard exudate clumps and areas of retinal thickening. Considering the prevalence and location of these changes, CSME comes in three forms.

1. Retinal edema 500 microns from the center of the macula
2. Exudates within 500 μm of the center of the macula, if associated with retinal thickening (which may be outside the 500 μm)
3. Retinal thickening of 1 disc diameter or greater within 1 disc diameter from the center of the macula

CSME is a purely ophthalmoscopic diagnosis. FFA has no place in diagnosis. However, after the diagnosis of CSME is made, FFA is performed to rule out extensive central ischemia. There is a high probability of permanent visual acuity reduction following macular laser photocoagulation in the presence of significant perifoveal nonperfusion. Visual acuity is not considered as a criterion in the diagnosis of CSME. A diagnosis of CSME can be made even if the vision is complete. With FFA, the status of treatable lesions, foveal avascular zone, and macular perfusion can be determined. In FFA, focal hyperfluorescence due to leakage and hypofluorescence plaques due to lipid deposits are observed in the late period (30, 31).

Diffuse Macular Edema

Retinal thickenings of two or greater disc diameters involving the foveal avascular zone are defined as diffuse macular edema and are the result of severe micro-vasculopathy. In diffuse macular edema, there is a generalized leakage from the enlarged capillaries in the posterior pole (26). Diffuse macular edema is usually symmetrical in both eyes, very rarely the edema may resolve spontaneously. In FFA, there are obstructed capillaries as well as adjacent capillary dilatation areas and increased visibility of the retinal capillary bed. With diffuse capillary pilling and enlargement of capillaries, capillary bed filling increases in the early phase of FFA. Edema is accompanied by cystoid changes in the macula. The fluid collected in the Henle layer creates large extravascular potential spaces due to the oblique placement of the nerve fibers in this layer. This situation can be detected especially in the late stage of FFA.

Ischemic Macular Edema

Enlargements and irregularities in the diameter and configuration of the foveal avascular zone are called “Ischemic Maculopathy”. This is a perfusion anomaly that develops as a result of the occlusion of capillaries in the perifoveal area. If

leakages from the microaneurysm and dilated capillary segments adjacent to the ischemic area are added to this table, it is called "Ischemic Diabetic Macular Edema". Findings are variable and the macula may even appear relatively normal, accompanied by decreased visual acuity. Therefore, FFA is required. This reveals that macular microcirculation disorders directly affect the visual acuity of patients (31).

Patients with ischemic maculopathy have severe vision loss and the prognosis is very poor. On clinical examination, it is indistinguishable from edema due to leakage from the microaneurysm. Deep retinal hemorrhages and cotton-like exudates may be observed in the ischemic retina or the area adjacent to it. Ischemic areas tend to be enlarged in the macula or often on the temporal side. The presence of multiple ischemic areas is typical. However, these areas are not so prominent as to cause clinical symptoms. Macular nonperfusion areas can be demonstrated early in FFA (32,33).

Mixed macular edema

It is characterized by the coexistence of diffuse macular edema and ischemia.

Cystoid macular edema

It occurs with the progression of retinal edema. It is characterized by intraretinal edema containing honeycomb-like cystoid areas. As the retinal thickness increases, the cystoid spaces that first appear in the outer nuclear layer gradually increase in number and area and progress to the retinal inner nuclear layer surface. Despite good perifoveal perfusion in FFA, massive dilatation of the entire retinal capillary bed and pan-endothelial leakage is seen in the macula. In the late stages, fluorescein pooling is noticed in the cystoid spaces. The classical flower crown appearance is seen due to the Henle layer (34,35).

6. Diagnostic Methods in Diabetic Macular Edema

Early diagnosis and appropriate treatment of diabetic maculopathy are critical in preventing permanent vision loss (32).

Stereoscopic fundus examination

The first thing to do is a good fundus examination. Contact and non-contact lenses are used in indirect ophthalmoscopy and slit-lamp biomicroscopy. It is

helpful in evaluating retinal thickening, distinguishing exudative and edematous macula, determining the extent and localization of macular thickening, tracking hard exudates and finding ischemic areas, observing pale or faintness of the foveal light reflex, determining complications, and diagnosis of cystoid macular edema.

Fundus fluorescein angiography

FFA, which is the diagnostic method used in the diagnosis, treatment planning, and follow-up of macular edema, provides very useful information. Normal retinal vessels prevent the passage of fluorescein molecules into the extravascular space, while areas with fluorescein leakages indicate abnormal vascular permeability.

The first finding that can be seen in FFA in DME is microaneurysm diverticula developing around the veins. As the retinopathy continues, diverticula development around the arteries and dilatation of the capillary bed are observed (36). FFA is helpful in treatment planning and is useful in estimating retinal thickness, level, and localization of leakages with images taken in the late phases.

Optical Coherence Tomography (OCT)

OCT is a new high-resolution technique that shows cross-sections of tissues. The physical basis of imaging is based on optical reflection differences of the microstructures of the tissues (37). Since OCT is a digital technique, quantitative measurements can be easily obtained from tomographic scans. Thanks to the availability of quantitative information, it is very easy to follow the course of the disease with OCT. Axial distance measurement is essential in OCT and is similar to A-mode USG. The rays reflected from different structures of very small sizes in the eye give information about the different axial dimensions of these structures (38).

The fovea region is observed as retinal thinning on the tomogram, and the retinal folds between the photoreceptors are seen slide to the side. The highly reflective red layer shows the posterior border of the retina on the tomogram. This place corresponds to the RPE and the choriocapillaris. This back layer ends appropriately at the optic disc margin with the termination of circulation in the lamina cribrosa. A very weak scattering returns from the deep choroid and sclera as the signal weakens after passing through the RPE and choriocapillaris. The low reflectance black layer is located just in front of the choriocapillaris layer

and fits into the outer segment of retinal photoreceptors. The middle layers of the retina in front of these layers show moderate backscattering. The inner edge of the retina is another region with bright backscattering, and this red layered region fits into the retinal nerve fiber layer in terms of location and anatomical variation. As expected in normal anatomy, the nerve fiber layer thickness increases from the macula to the optic disc (39).

In the fovea, the anterior border of the retina is observed as a nerve fiber layer, and the posterior border is observed as highly reflective layers corresponding to the RPE and choriocapillaris. The RPE looks different from the choriocapillaris directly below the fovea, where pigmentation is greatest. Medium and low reflective layers on the minimally reflective photoreceptors reveal the multilayer structure of the retina. Moderate backscattering is observed from the inner and outer plexiform layers, which are composed of fibrous structures lying parallel to the predicted beam. Minimal backscatter was noted from nuclear layers with photoreceptors and cell bodies oriented parallel to the oppositely expected beam. Retinal blood vessels can be identified on the tomogram by shadowing reflections from the RPE and choriocapillaris, and increased backscattering of vessels. Larger choroidal vessels are also visible in the image. Analogous to computed tomography or magnetic resonance image, information on the three-dimensional structure can be obtained by using the optical shear feature of OCT to obtain successive thin sections of the retina. For this purpose, sagittal sections of the macula can be taken. The characteristic features of the retina are continuously monitored in serial sections. The anterior and posterior surfaces of the neural retina are separated by a layer of nerve fibers and a backscattering red layer at the vitreoretinal interface, which represents the RPE and the choriocapillaris. Tomogram series reveal the resolution and development of foveal depression reaching maximum depth in the fovea centralis. Retinal blood vessels arise from the lower and upper branches of the central retinal artery and are distinguished by partial shadowing of the deep retinal structures beneath the vessels on the tomogram (40).

Retinal thickness is important in determining macular edema. The high axial resolution of OCT, combined with the well-defined contrast in reflectivity at the anterior and posterior borders of the retina, makes OCT unique in measuring these parameters. Intraretinal fluid accumulation causes both an increase in retinal thickness and changes in the scattering properties of the tissue. Localization, which is important in measuring retinal thickening, is edema in

the fovea, which directly causes profound effects on visual acuity. This type of measurement is particularly useful in monitoring patients with DME. In macular edema, low reflective intraretinal fluid, non-reflective intraretinal cystoid spaces with dome-shaped elevation in the foveal region, and hard exudates with high reflectivity can be observed. Retinal edema can be differentiated from retinal traction by the identification of cystoid spaces within the retina, indicating cystic macular edema, or by the exposure of a posterior hyaloid or epiretinal membrane that may cause retinal traction. Decreased retinal thickness may be focal or diffuse, often with atrophy or scarring. Changes in retinal architecture or cell morphology cause changes in optical properties observed on OCT. The apparent reflectivity measured by OCT is the combination of the true reflectivity, scattering, and absorption characteristics of the overlying medium. Therefore, the reflectivity required for retinal imaging can be affected by abnormalities in the cornea, aqueous, lens, vitreous, and anterior retinal layers. Retinal thickness measured with OCT, unlike FFA, is compatible with the patient's vision (39).

Optical coherence tomography angiography (OCTA)

OCTA allows noninvasive and dye-free imaging of the retinal vasculature, providing high-resolution images of the different retinal vascular layers. At the same time, quantitative and automatic measurements of retinal vessels, such as density (VD) and fractal size (FD), can be obtained reliably and reproducibly. OCTA is currently taking its place with increasing applications in the diagnosis and treatment of diabetic retinopathy and DME (41).

Retinal Thickness Analyzer (RTA)

It has the advantage of being faster and producing fewer motion-related artifacts than OCT. A three-dimensional image is obtained. However, it is insufficient to show intraretinal pathologies. Its use is limited only to topographic changes in macular thickness (42).

Fundus Photography

It has a place in the diagnosis and more often in the follow-up of macular edema.

Scanning Laser Ophthalmoscopic (SLO) Microperimetry

The decrease in visual acuity due to macular edema is determined by the SLO as a decrease in retinal sensitivity. As a new noninvasive diagnostic tool,

SLO microperimetry provides functional information by imaging the macular area, allowing a point-to-point agreement between the fundus image and the perimetric results (43).

Electroretinography (ERG)

Clinical ERG is the recording of diffuse electrical responses obtained from stimulation of retinal cells by a short flash of light. It can be used to monitor the treatment of macular edema. Foveal ERG provides objective information about whether there is an organic pathology in the macula (44).

7. Treatment

Systemic therapy

Glycemic control (26), blood pressure control (17), dyslipidemic control (45), kidney dysfunction, and treatment of anemia (46) are important to slow or stop the progression of DME. Protein kinase c-β inhibitors (47), aldose reductase, and advanced glycosylation product inhibitors (48), which are used as systemic pharmacotherapy, and antioxidants are also included in the treatment of DME.

Local Treatment

VEGF was isolated by two groups independently, the first group was named as vascular permeability factor and the second group was named as endothelial cell mitogen (49). It is an important factor that triggers angiogenesis in vitro and is secreted by RPE cells, ganglion cells, retinal vascular endothelial cells, pericytes, and glial cells. It affects many steps of angiogenesis (endothelial proliferation, continuation, and migration) and vascular permeability. There are 5 subtypes known as A, B, C, D, E. The VEGF-A gene is located on chromosome 6p21.3, contains 8 exons and 7 introns. It is the most potent among these subtypes and is divided into 121, 145, 165, 183, 189, 206 subgroups (50).

(i) Pegaptanib sodium

It is a nuclease-resistant, 28-nucleotide RNA aptamer that binds to VEGF-165 with high affinity but has low affinity for VEGF-121. With the addition of 40 kDa polyethylene glycol, its clearance from the vitreous is reduced (51). Aptamers are chemically synthesized oligonucleotides that are specifically coiled and act as antibodies that bind to extracellular targets with a very high affinity.

(ii) Ranibizumab

It is a recombinant human anti-VEGF antibody and inactivates all VEGF isoforms. The vitreous half-life is 3.2 days, and due to its low molecular weight (48,000 D), it can pass into the retinal layers (52).

(iii) Bevacizumab

It is a human monoclonal antibody and inhibits all isoforms of VEGF-A. It has been approved by the FDA in the treatment of colorectal cancer, and its use for the eye is off-label. It can pass all layers of the retina, but there is a risk of thromboembolism at a rate of 1.9-4.4%. Indications for use in diabetic retinopathy; macular edema, iris neovascularization, retina and disc neovascularization, reproliferation after vitrectomy, and protection from rehemorrhage (53).

(iii) Aflibercept

Aflibercept is a 115 kD fully human, recombinant fusion protein; It consists of key VEGF binding domains of human VEGF receptors 1 and 2 fused to the constant Fc domain of human immunoglobulin G1,12 and binds VEGF-A with a high affinity. Unlike ranibizumab and bevacizumab, aflibercept also binds to placental growth. Intravitreal aflibercept injection (IAI), also known as "VEGF Trap-Eye" is approved by the FDA for DME and diabetic retinopathy (DR) in patients with co-existing DME (54).

Steroids

(i) Anecortave acetate

Anecortave acetate is a synthetic cortisone derivative with an angiostatic effect. The drug shows its effect by inhibiting the proteases necessary for vascular endothelial cell migration (55). The difference of Anecortave acetate from other VEGF inhibitors is that it inhibits angiogenesis that may occur after many ocular angiogenic stimuli. A single dose of posterior juxtascleral injection was found to provide therapeutic levels in the choroid and retina for 6 months.

(ii) Intravitreal implants

Currently, implants such as fluocinolone acetonide (Retisert -Bausch, and Lomb) and dexamethasone (Posurdex -Oculex DDS) are being studied to provide a longer duration of corticosteroid concentration in the vitreous. Its

advantages are that it is lipophilic, long-acting, easy to eliminate, has few side effects, and provides a stable drug level. The disadvantages are the development of complications such as material leakage, endophthalmitis, retinal detachment (56-59).

(iii) Triamcinolone Acetonide

In ophthalmology, corticosteroids (KS) have been used for years to prevent extravasation from leaky vascular structures and suppress inflammation. The antiproliferative, anti-edematous, anti-inflammatory, and angiostatic effects of KS have been proven in animal experiments, and then it has been used in ocular inflammation and NV (58,59). Effective results were first reported in 2001 by Jonas (60) in patients with DME who did not respond to lasers. Clinical studies are showing that it is effective in edematous and neovascular diseases (62-66).

Surgical treatment

There is controversy about the outcomes of vitrectomy surgery for DME. Many researchers have performed vitrectomy in the treatment of persistent macular edema and reported that macular edema resolved and visual acuity increased with the release of tractional forces on the vitreomacular surface. In addition, several groups of investigators have reported data to suggest vitrectomy reduces macular thickening but does not improve visual acuity 67-68).

Focal/grid laser photocoagulation

The exact mechanism of action of laser photocoagulation therapy in improving DME is not known. In summary, with laser-induced destruction of oxygen-consuming photoreceptors, the transient temperature rise in the tissue during laser causes cell death and cicatrization (gliosis and retinal pigment epithelial hyperplasia). Oxygen, which normally diffuses from the choriocapillaris to the outer retinal layers, diffuses into the inner retina due to laser scarring. Thus, hypoxia in the inner retinal layers is regressed (69). Isolated ischemic maculopathy cannot be treated with laser photocoagulation. However, laser therapy is indicated if ischemic maculopathy is accompanied by CSME (70).

Laser photocoagulation for proliferative retinopathy

The first photocoagulation study for ophthalmic diseases in humans was performed by L'Esperance in 1968 (71). Widespread use of thermal laser in

ophthalmology was published by the Diabetic Retinopathy Study Group. This article describes the effects of pan-retinal photocoagulation on vision in patients with PDR. It has been proven to reduce the risk of loss by 50% or more (72). Panretinal photocoagulation should be applied to eyes with PDR diagnosed with retinal and/or optic nerve head neovascularization and intense retinal ischemia. In photocoagulation treatment, an average of 1500-2000 shots should be taken. Spot diameter may be 500-1000 microns in the mid-periphery and periphery, but should be 50-100 microns in the paramacular area. Spots should be applied with a duration of 0.1-0.2 ms to obtain a slight whiteness, leaving a spot distance in between. According to the Diabetic Retinopathy Study group, to reduce laser side effects (such as choroidal detachment, CME, anterior chamber angle narrowing), treatment sessions should be 2 weeks apart and not more than 900 laser shots in each session should be done (73).

Under the guidance of FFA, it should be started from the ischemic areas, first the nasal and lower quadrants, then the upper quadrant, and finally the temporal quadrant. The area up to the equator is photocoagulated by avoiding major vessels, hemorrhagic and pigmented areas, by approaching the optic disc by one disc distance and the macula by at most one disc diameter. Lower power laser to the areas at 3 and 9 o'clock in front of the equator corresponding to the ciliary nerves will reduce the patient's pain and increase the comfort (72,74).

It is important to note that in clinical practice, panretinal photocoagulation is less expensive when compared to anti-VEGF therapy and can sometimes be performed in a single session, and does not carry the risk of endophthalmitis. However, when DME is present, anti-VEGF injections will treat both DME and PDR and may delay or reduce the need for panretinal photocoagulation. The exact mechanism by which laser therapy reduces DME and causes regression of neovascularization is not known. It is hypothesized that direct closure of leaking microaneurysms, decreased retinal blood flow, and increased oxygenation, as well as stimulation of the retinal pigment epithelium (RPE) may be responsible. Laser therapy can cause permanent damage to retinal cells, resulting in side effects such as mild loss of central vision and reduced night vision (75,76)

Surgical Treatment in Diabetic Retinopathy

The most effective way to prevent vision loss in Diabetic Retinopathy is regular blood sugar controls, early diagnosis of DR through community screenings, and

effective panretinal photocoagulation treatment at the right time. It is possible to get rid of surgery in Diabetic Retinopathy with the treatments done at the right time.

Currently, vitrectomy continues to play a critical role in the management of some complications in DR. These include unresolved vitreous hemorrhages, anterior macular hemorrhages, tractional retinal detachment in PDR, and vitreomacular traction syndromes. Numerous studies have demonstrated the beneficial effect of vitrectomy. Theoretically, removal of the majority of the vitreous body along with the hyaloid membrane during vitrectomy has been shown to improve retinal oxygenation. Controversy still exists regarding the necessity of removing the ILM during vitrectomy for DME (77-79).

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CHAPTER 3

RETINAL ARTERY OCCLUSION

Alper Halil BAYAT
Istanbul Medipol University, Department of Ophthalmology, Istanbul
e-mail: alperhalil76@hotmail.com
ORCID:0000-0003-1827-968X

1. Etiology

The inner retina is supplied by the central retinal artery (CRA), while the outer retina is supplied by ciliary arteries (choriocapillaris) (1). The CRA and ciliary arteries are both branches of the ophthalmic artery (2). Majority of the cases of retinal artery occlusion are secondary to atherosclerosis-related embolism and thrombosis. Systemic vasculitis such as giant cell arteritis, systemic lupus erythematosus, polyarteritis nodosa and migraine (vasospasm), systemic hypotension are the other causes of retinal artery occlusion (3). The emboli usually come from an atheromatous carotid plaque. The morphological appearance of emboli can aid in determining the cause of retinal artery occlusion. Hollenhorst plaques which can be seen as small, yellow, refractile plaques, and the presence of small, yellow and refractile plaques indicate cholesterol emboli, however, single, white, and non-scintillating plaques indicate calcific emboli and fibro-platelet emboli are seen as small pale bodies (4,5).

Systemic assessment of patients with retinal artery occlusion

- Symptoms of giant cell arteritis
- Smoking
- Pulse and blood pressure
- Cardiac consultation and electrocardiography (ECG)
- C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) tests for giant cell arteritis
- Echocardiography
- Lipid tests, hemogram, electrolytes

- Carotis ultrasonography must be assessed in all patients (6,7).

In younger patients with age under 50, proatherogenic states, such as hyper-homocysteinemia, factor V Leiden, protein C and S and anti-thrombin deficiencies, anti-phospholipid antibodies or prothrombin gene mutations, and sickle cell disease should be assessed (8).

2. Clinical types of retinal artery occlusion

Amaurosis fugax

Amaurosis fugax is characterized by transient painless monocular vision loss (9). The patient described as a "curtain coming down to my eye". The causes of amaurosis fugax were divided into five categories by the Amaurosis Fugax Study Group as embolic, ocular, hemodynamic, neurologic, and idiopathic reasons (10). Amaurosis fugax is used to refer to transient visual loss due to emboli in clinical practice. Embolic visual loss usually lasts a few minutes. The frequency of attacks can vary from several times a day to once a month. Investigation of amaurosis fugax should be undertaken urgently because of the high risk of stroke.

Branch retinal artery occlusion

Branch retinal artery occlusion (BRAO) comes with sudden and painless altitudinal or sectoral visual field loss. Visual acuity is variable. If central vision is spared, it may be asymptomatic. Relative afferent pupillary defect (RAPD) is often present.[11]

In fundus examination;

- Attenuation of the arteries and veins with the segmentation of the blood column and sludging
- The white edematous retina in the area of ischemia (Figure 1)
- Occluding emboli can be seen (11,12)

The defect can be confirmed using visual field tests. Fundus fluorescein angiography shows delay in arterial filling and hypo-fluorescence in the damaged retina (11,12).

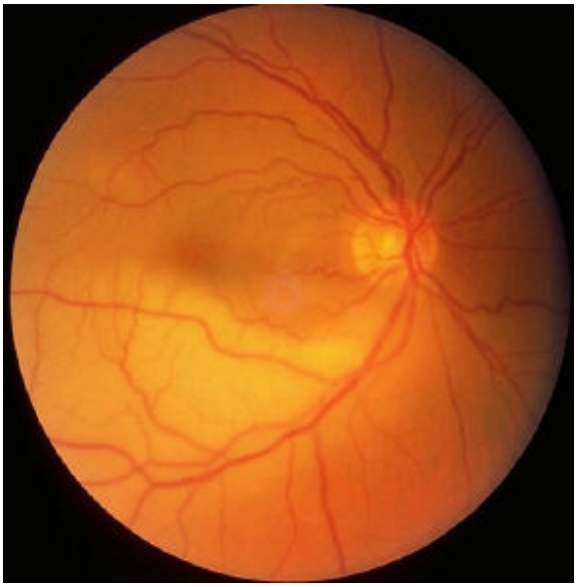

Figure 1. A fundus image of branch retinal artery occlusion

Central retinal artery occlusion

The central retinal artery occlusion (CRAO) comes with sudden painless monocular vision loss (except giant cell arteritis). The incidence is estimated to be 1 in 100 000 people. A prospective study with 260 eyes of CRAO patients has shown that with 80% of people suffer monocular visual loss had a visual acuity (VA) of 20/400 or worse (3). If the cilioretinal artery presents, the central vision may be preserved. If the absence of the light perception is present, this usually indicates the giant cell arteritis or ophthalmic artery occlusion. The prognosis is poor unless recovery occurs in the first few hours of the occlusion (13).RAPD is severe and profound. Some patients have total RAPD (amaurotic pupil).

In fundus examination;

- Cherry red spot appearance; the orange reflex from the intact choroid in the foveola and pale retina (Figure 2)
- Emboli are visible in 20% of the patients
- The peripapillary retina may appear swollen and opaque
- If cilioretinal artery presents, macula will remain normal
- In later stages optic atrophy, vessel sheathing and retinal pigment epithelium (RPE) changes can be seen

- 2% of CRAO patients develop neovascularization
- Rubeosis iridis may occur in some patients (13,14). Optical coherence tomography may show embolic plaque. Fundus fluorescein angiography shows a delay in the arterial filling (13).

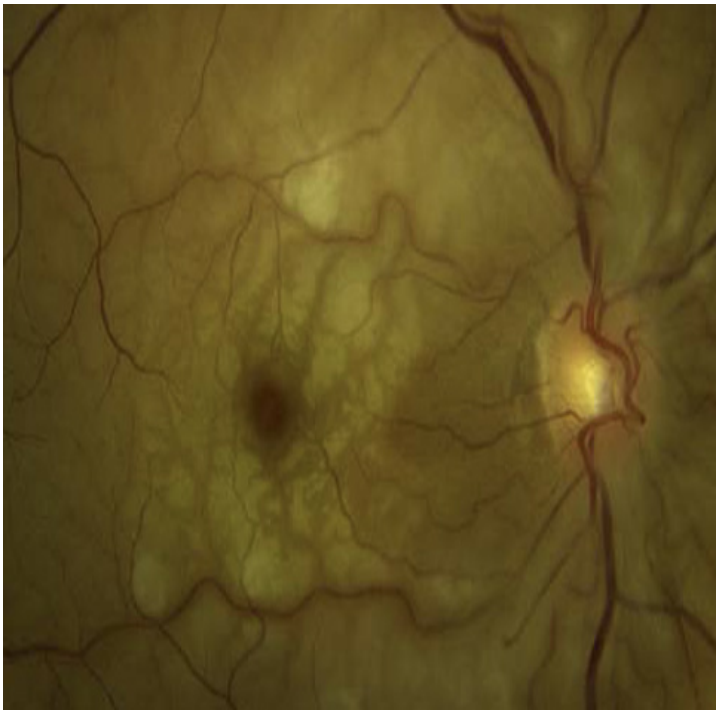

Figure 2. A fundus image of central retinal artery occlusion

Cilioretinal artery occlusion

The cilioretinal artery is derived from posterior ciliary circulation and provides the retina with a second arterial supply. It presents in 1/3 of the eyes. If it is presented, it may preserve the central vision loss in case of central retinal artery occlusion (15,16).

Cilioretinal artery occlusion may occur as isolated or combined with central retinal vein occlusion or anterior ischemic optic neuropathy. Isolated form is rare and may occur in young patients with systemic vasculitis. Combined form with central retinal vein occlusion has a better prognosis than the isolated form. Combined form with anterior ischemic optic neuropathy may affect patients with giant cell arteritis and has a poor prognosis (15,16). (Figure 3)

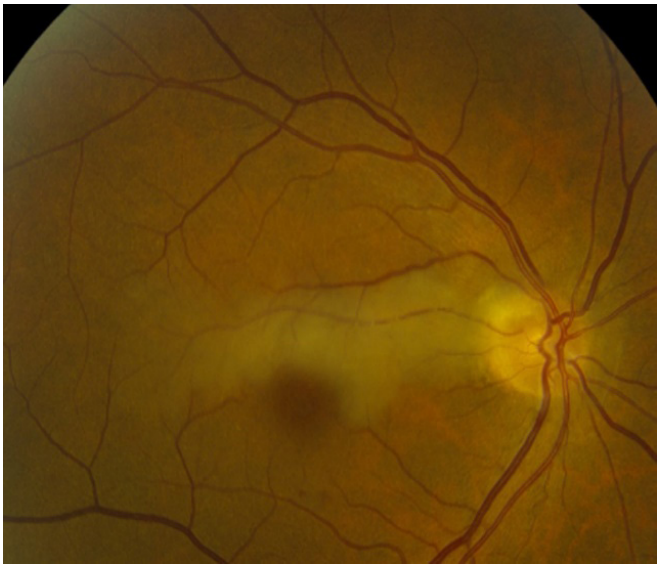

Figure 3. A fundus image of cilioretinal artery occlusion

3. Treatment of retinal artery occlusion

Retinal artery occlusion is an ophthalmic emergency. There are some treatment modalities in retinal artery occlusion:

Ocular massage: Ocular massage can be done using a three-mirror contact lens. The purpose of ocular massage is to mechanically compress the vessel lumen to provide flow in the vessel and to increase perfusion with the movement of the thrombus with the flow (17).

Anterior chamber paracentesis: anterior chamber paracentesis can be done using a 27-gauge needle to withdraw 0.1-0.2 ml of aqueous. Povidone-iodine and topical antibiotic drops must be instilled before the procedure (17).

Topical timolol, apraclonidine, and intravenous acetazolamide: The aim is to reduce intraocular pressure (17).

Sublingual isosorbide dinitrate: The aim is to induce vasodilatation (17).

Hyperosmotic agents: Mannitol and glycerol can be used to reduce intraocular pressure and increase intravascular volume (17).

Thrombolysis: Thrombolytic agents could be used as a treatment option. Intraarterial injections of tissue plasminogen activator, streptokinase, and

urokinase have been tried and successful results have been reported in some selected cases (17-22).

Transluminal Nd: YAG laser embolysis: If an occluding embolus is visible, transluminal Nd: YAG laser embolysis can be used. Although there are not many studies with this procedure, some studies have reported good results. Nd: YAG laser shots are applied directly to the embolus in this procedure. If the embolus is ejected into the vitreous, the procedure is successful. The main complication of this treatment is vitreous hemorrhage (23).

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CHAPTER 4

RETINAL VEIN OCCLUSION

Alper Halil BAYAT
Istanbul Medipol University, Department of Ophthalmology, Istanbul
e-mail: alperhalil76@hotmail.com
ORCID:0000-0003-1827-968X

1. Introduction

Retinal vascular diseases are among the most common causes of vision loss in developing countries. Among retinal vascular diseases, retinal vein occlusion (RVO) is the second most common vascular disease after diabetic retinopathy (1).

Rogers et al. collected and analyzed data from 15 population studies from 4 different continents and different age and ethnic groups. According to the data of this prevalence study, 4.42 out of every 1000 people had branch retinal vein occlusion (BRVO); 0.8 of them were found to have central retinal vein occlusion (CRVO) (2).

2. Retinal Vein Occlusion Classification

In the intrauterine period, the central retinal vein consists of two branches. Although one branch regresses spontaneously before birth, there is no regression in these branches at a rate of 20.5% in the population, and there are two central retinal veins in these cases (3). These two branches can be found in the upper-lower, nasal, temporal, or diagonal directions. Based on this information, RVO is analyzed in three anatomical groups according to the location of the obstruction:

1- Central retinal vein occlusion (CRVO) if thrombosis occurs during the passage of the central retinal vein through the lamina cribrosa
2- Branch retinal vein occlusion (BRVO) if thrombosis occurs at the crossing points of arteries and veins in the retina
3- If thrombosis occurs in one of these veins in cases with two central retinal veins, it is called hemi-retinal vein occlusion (HRVO).

These cases are also classified as ischemic and non-ischemic according to the location of the occlusion as well as capillary perfusion. The Central Retinal Vein Occlusion Study Group defined ischemia as capillary non-perfusion in an area larger than 10 optic disc diameter in fundus fluorescein angiography (4,5). Classification according to perfusion status changes the clinical evaluation of patients and the treatment algorithm. In the presence of ischemia, the release of VEGF and other cytokines increases. With the increase of these cytokines, neovascularization may develop in the iris, iridocorneal angle, and retina.

3. Etiology of Retinal Vein Occlusion

The main factor in the pathology of RVO is thrombus formation. The most common cause of RVO is the deterioration of hemodynamics in veins due to compression caused by atherosclerotic changes in the adjacent retinal artery. The central retinal vein is particularly sensitive to occlusion in the lamina cribrosa region, where the retinal vein and the central retinal artery pass close to each other. Atherosclerosis of the adjacent central retinal artery can cause compression of the central retinal vein, which impedes blood flow. Decreased blood flow results in increased pressure and may cause thrombosis, which causes vascular occlusion (6,7). Although thrombus formation is the main pathology, we should not forget that there are risk factors affecting thrombus formation.

4. Risk Factors in Retinal Vein Occlusion

Many risk factors can cause BRVO and CRVO. These can be roughly grouped under two headings: systemic causes and eye-related causes

Systemic causes

- Hypertension
- Diabetes Mellitus
- Hyperlipidemia
- Atherosclerosis
- Hematological causes
- Medications (Oral contraceptives, steroids, etc.)
- Pregnancy
- Inflammatory causes

Causes related to the eye

- Primary open-angle glaucoma (POAG)
- Hyperopia
- Short axial length
- Trauma
- Optic disc lesions (8-10)

It has been shown that RVOs are highly associated with glaucoma, arterial hypertension, and optic neuritis (11,12). Hayreh et al. compared 1090 RVO patients to the healthy group: The prevalence of arterial hypertension, peptic ulcer, diabetes mellitus (especially ischemic type), and thyroid diseases were higher in patients with CRVO and HRVO, and the prevalence of arterial hypertension, chronic obstructive pulmonary disease, cerebrovascular diseases, peptic ulcer, diabetes mellitus (especially in young patients) and thyroid diseases were higher in patients with BRVO (11). In the same study, the prevalence of arterial hypertension and diabetes mellitus was found to be higher in ischemic-type CRVO obstruction compared to non-ischemic CRVO.

The risk of developing CRVO and BRVO in glaucoma patients was found to be equal. Obstruction is thought to develop as a result of venous stasis due to increased IOP in glaucoma patients (13). It has been shown that optic nerve edema and optic disc drusen can cause CRVO by compressing the vein in the lamina cribrosa (14).

5. Clinical Findings in Retinal Vein Occlusions

In BRVO, the complaints of the patients vary according to the place of involvement of the occluded vessel and the severity of the occlusion. While there may be sudden onset vision loss, patients may also be asymptomatic. Defects in the visual field can also be seen (15).

In CRVO patients, the most common symptom is sudden painless vision loss. In rare cases, patients may experience a temporary vision loss that lasts for a few seconds and completely recovers. These symptoms may recur over days to months, and then vision may decrease or return to normal completely. Especially in ischemic type CRVO, although it is very rare, patients may present with pain and vision loss due to neovascular glaucoma. The initial visual acuity of patients is important in understanding the severity of CRVO. Initial visual

acuity may be affected by macular hemorrhage, macular edema, and ischemia. In the long term, impairments in vision may be observed due to conditions such as chronic cystoid macular edema, cystoid degeneration, or retinal pigment epithelial damage. In the chronic process, visual impairment may be detected in cases such as epiretinal membrane and macular ischemia, which develop secondary to the disease (16).

6. Diagnostic Methods in Retinal Vein Occlusions

The most important step in the diagnosis of the disease in RVO is a good anamnesis and clinical examination. The diagnosis of the disease can be made by ophthalmoscopic examination. In order to plan the treatment, the presence of ischemia and the presence of macular edema should be demonstrated by methods such as fundus fluorescein angiography (FFA) and optical coherence tomography (OCT).

Ophthalmoscopy

In patients with BRVO, ophthalmoscopy may show venous dilatation and increased curvature above the arteriovenous crossing region, limited flame-shaped and dot-speck hemorrhages in the retinal region where the vein is occluded, thrown out cotton exudates related to ischemia, retinal edema, and hard exudates (Figure 1a). Bleeding (Bonnet's sign) can be observed in the arterio-venous intersection area. Less hemorrhage is seen in incomplete partial vein occlusions. The closer the obstruction is to the optic disc, the more severe it tends to be clinical. Collateral vessel formation and sheathing in the vessels are the sign of chronic BRVO. Macular edema is observed with an ophthalmoscope as a thickening in the macular area or as cysts in cystoid macular edema (17).

In CRVO, venous dilatation is accompanied by superficial and deep bleeding areas in the four quadrants of the retina. Increased folds in the veins, optic disc edema (disc borders are blurred or fuzzy), discarded cotton exudates, and retinal edema might be observed (Figure 2a). Hemorrhages and macular edema may be seen in the macula. In the chronic phase of the disease, retinal hemorrhages may decrease in a few months and disappear completely, or peripheral hemorrhages may be observed for years. The increase in curvature and enlargement of the veins may decrease over time or sheathing may be

observed. Collaterals in the optic disc and pigment epithelial irregularity in the macula may be observed (18).

Fundus Fluorescein Angiography

FFA is an imaging method used to determine the vascular structure and tissue perfusion of the retina and choroid with the help of a special camera following the intravenous administration of fluorescein. FFA is frequently used because it can show the presence of ischemia in RVO, which is important for the treatment protocol. Ischemia in CRVO was defined as a non-perfusion area >10 optic disc diameter in FFA (4). Optic disc edema is more common in ischemic CRVO than in the non-ischemic type and causes increased hyperfluorescence in FFA. In CRVO, hyperfluorescent areas are seen as a result of extravasation of the fluorescein substance due to the deterioration of the internal blood-retina barrier caused by the increase in pressure (Figure 2b). Diffuse and focal macular edema are also hyperfluorescent in FFA images. FFA can also differentiate shunt vessels developing between retina and choroid from neovascularization (NV), which occurs an alternative to impaired venous drainage due to RVO. While shunt vessels fill slowly in the venous phase and do not cause any leakage, NV foci fill early in the arterial phase and cause leakage in the venous phase. The distinction of these two structures is very important in terms of arranging the treatment protocol of the patients. Fluorescein substance extravasation occurs due to damage of the inner-blood-retinal barrier, which is also impaired in BRVO (Figure 1b). This extravasation is observed in the affected area, while capillary fluorescence loss is observed in the presence of non-perfused areas. NV develops in the optic disc or retina in only less than 25% of BRVO cases (19). FFA can also differentiate collateral vessels from NV in non-perfused BRVO cases. While there is no leakage in the collateral vessels, there is leakage in the venous phase in NV.

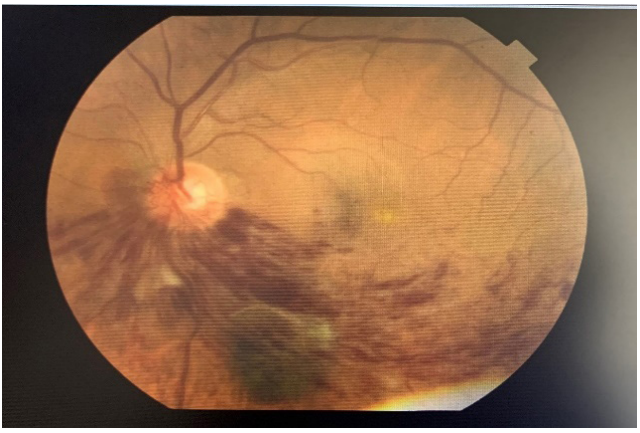

Figure 1a. Fundus photo of branch retinal vein occlusion

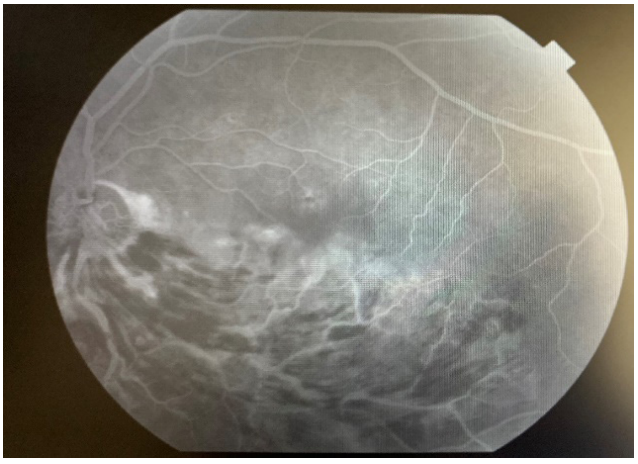

Figure 1b. Fundus fluoresceine angiography of branch retinal vein occlusion

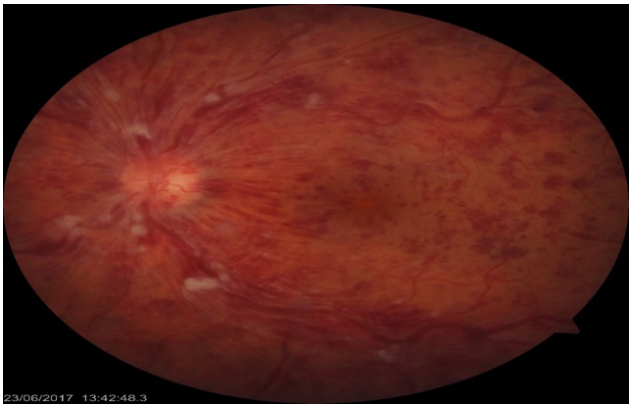

Figure 2a. Fundus photo of central retinal vein occlusion

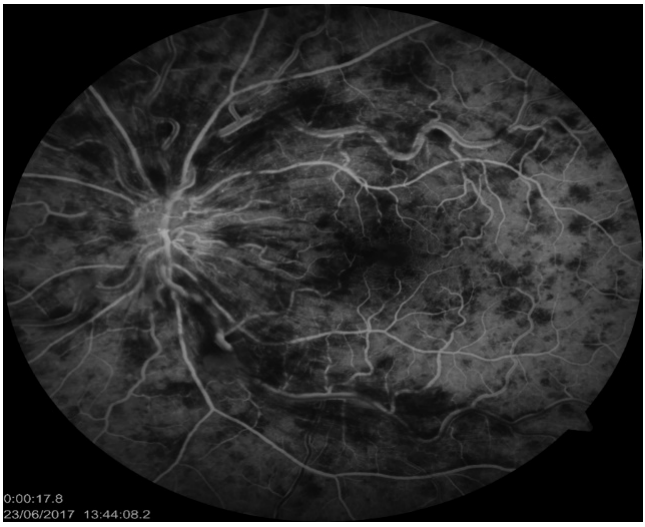

Figure 2b. Fundus fluoresceine angiography of central retinal vein occlusion

Optical Coherence Tomography

Optical coherence tomography (OCT) is a new method that provides high-resolution cross-sectional imaging in biological tissues. OCT is also used in ophthalmology to examine other tissues besides imaging the retina (20). Brezinski et al. obtained images with OCT in vascular pathologies (21). Since real-time, non-contact cross-sectional images of the retina and anterior segment are obtained with the OCT device, this technology is effectively used in ophthalmology. In addition to imaging anatomical sites such as optic disc and macula in the retina, OCT also can provide an examination of intraretinal structures such as retinal nerve fiber, photoreceptors, and retinal pigment epithelium. Since OCT provides morphometric or quantitative measurements of the retina, it is also an important diagnostic method in the diagnosis and follow-up of diseases. OCT is used in macular edema follow-up and treatment decisions of CRVO patients.

Retinal thickness analyzer

Retinal thickness analyzer (RTA) sends a laser slit at an oblique angle to the retinal surface and evaluates the reflections from the vitreoretinal and chorioretinal surface, giving information about retinal thickness. In a study conducted by Otani et al., it was shown that the sensitivity of RTA for diabetic macular edema is between 69-100% (22).

Fundus photography

It is used in the diagnosis and more often in the follow-up of macular edema and optic disc edema in CRVO.

Scanning laser ophthalmoscopic (SLO) microperimetry

The decrease in visual acuity due to macular edema is determined by the SLO as a decrease in retinal sensitivity. As a non-invasive diagnostic tool, SLO microperimetry provides functional information from the macular area, allowing a point-to-point agreement between the fundus image and the perimetric results (22).

Electroretinography

Clinical electroretinography (ERG) is the recording of diffuse electrical responses from stimulation of retinal cells with a short flash of light. It can be used in the follow-up of macular edema treatment. Decrease in b wave amplitude and b:a ratio, and prolongation in b wave latency can be seen in ERG of CRVO patients (23).

7. Treatment Options in Retinal Vein Occlusions

Treatment indications in RVO include macular edema, which causes vision loss, and ischemia or NV, which is treated with laser photocoagulation (24).

Observation

In the absence of ischemia or NV and in case of retinal edema sparing the fovea and stabile visual acuity, patients can be followed up without any treatment. Spontaneous regression is also higher in BRVO than in CRVO in cases where the macula is affected (2).

Laser Photocoagulation

In the study conducted by the BRVO study group, the visual gains of the patients were found to be 1.3 logMAR at a 3-year follow-up after laser photocoagulation treatment. In this study, it was found that 40% of the patients had a visual acuity lower than 1.00 logMAR. As a result of this study, laser photocoagulation was recommended only in a limited group of patients, and new treatment options were suggested to be explored (25).

CRVO study group found that anterior segment NV regressed 90% when pan-retinal laser photocoagulation was performed in ischemic type CRVO. In addition, it was determined that laser photocoagulation performed in the early period did not prevent anterior segment NV and it was reported that pan-retinal laser photocoagulation should be applied in eyes with NV in ischemic type CRVO. This study also recommended a careful examination including gonioscopy of the iris monthly, especially in the first 6-8 months, in patients at high risk for NV, and the application of pan-retinal laser photocoagulation when NV is observed in the anterior segment (26).

Intravitreal Corticosteroids Applications

Corticosteroids inhibit the formation of arachidonic acid from membrane phospholipids by inhibiting phospholipase A2. Thus, they create an anti-inflammatory effect by inhibiting both prostaglandin and leukotriene production. They reduce intercellular edema with their local vasoconstrictive effects (27). They also contribute to the resolution of edema by blocking the calcium channel (28).

a) Intravitreal Triamcinolone Acetonide

Apart from its anti-inflammatory effect, triamcinolone acetonide is a long-acting steroid that reduces endothelial cell permeability and stabilizes the blood-retinal barrier by modulating intercellular adhesion molecule-1 and regulates the pump function of the retinal pigment epithelium (27-29). It has also been shown that corticosteroids decrease VEGF levels (30). The use of intravitreal triamcinolone acetonide (IVTA) in CRVO is effective in the treatment of macular edema (31). It has been reported that RVO induced-macular edema was resolved and visual acuity improved 2-6 weeks after IVTA injection (32). In studies with multiple doses (4mg-25mg), it has been reported that the effect is short-term and repeated injections are required to prolong the effect. However, studies have shown that this decreasing effect with repeated injections has been attributed to tachyphylaxis (33). In the SCORE (Standard care vs. COrticosteroid for REtinal vein occlusion) study, 1mg, 4mg triamcinolone injection, and the control groups were compared in terms of macular edema secondary to CRVO and BRVO. IVTA (1mg and 4mg) was compared with the observation group in CRVO patients. In this comparison, it was determined that the visual gains of IVTA groups were better than the observation group. Despite the decrease of macular thickness in

all groups after 2-year follow-up period, the visual gain was achieved only in the IVTA groups. Considering the side effects such as glaucoma and cataract, a 1 mg dose of IVTA arm was found to be safer than 4 mg in this study. IVTA (two groups of 1mg and 4mg) and grid laser photocoagulation were compared in BRVO patients. After a 1-year follow-up, a decrease in macular thickness was observed in all three groups. There was no statistically significant difference between the three groups. When the 3rd year follow-up of the same patients was published, visual acuity was found to be better in the grid laser photocoagulation group. The grid laser photocoagulation group was found to be safer than the IVTA group in terms of glaucoma and cataract formation (33,34). Various complications such as acute and sterile endophthalmitis, increased intraocular pressure, cataract, retinal tear, and detachment, vitreous hemorrhage have been observed after IVTA injections (35).

b) Intravitreal Dexamethasone Implant

Although IVTA treatment was successful, it was observed that the effect was short-term. Therefore, more potent and longer-lasting steroids were warranted. A more potent steroid, the dexamethasone implant, was developed. Ozurdex (OZURDEX, Allergan, Inc., Irvine, Calif.) developed a biodegradable dexamethasone implant containing lactic acid and glycolic acid and injectable with a 22-gauge applicator. Over time, the implant undergoes hydrolysis and separates into carbon dioxide and water components. In the GENEVA study including 1267 patients on the use of Ozurdex for the treatment of macular edema secondary to RVO, the dexamethasone implant was compared with the sham administration. Of these patients, 35% had CRVO and 65% had BRVO. In the GENEVA study, it was observed that the Ozurdex implant provided better and faster visual acuity gain than the sham group. Ocular pain, increased IOP, and the presence of cells in the anterior chamber were more common in the Ozurdex implant group. No case of endophthalmitis was observed in this study. There was no difference between the groups in terms of cataract formation, which was thought to be due to the short follow-up period (36).

Li X. et al. compared the dexamethasone implant with the sham group. In this study, it was determined that the dexamethasone group was superior to the sham group in visual and anatomical success for 3-4 months with a single implant. It has been reported that the most important side effect was increased IOP (37).

c) Intravitreal Anti-vascular Endothelial Growth Factor (Anti-VEGF) Injection

VEGF is a member of the platelet-derived growth factor (PGF) family. The VEGF gene family consists of VEGF-A, VEGF-B, VEGF-C, VEGF-D, and placental growth factor (PGF) located on chromosome 6p12.3. VEGF has been identified as the most important central mediator of angiogenesis and plays a key role in angiogenesis. In this step, VEGF is a rate-limiting step that is critical in the initiation and continuation of physiological angiogenesis (38).

VEGF is a heparin-binding growth factor in homodimeric glycoprotein structure specific to vascular endothelial cells (39). VEGF expression is also accelerated secondary to inflammation. Especially, VEGF-A is the factor that has the strongest relationship with angiogenesis and is the most studied factor. Therefore, most of the anti-VEGF studies have focused on this factor (40).

i. Pegaptanib sodium

Its structure is an extracellular aptamer of 165 amino acids, consisting of 28-base ribonucleic acid bonded in two branches to 20kD polyethylene glycol moieties. Pegaptanib binds to VEGF165, preventing VEGF165 from binding to VEGFR2. Bennet reported that a decrease in macular edema, improvement in visual acuity, and retinal perfusion were observed in his study conducted in 7 patients with macular edema secondary to RVO with a 6-month follow-up (41). Wroblewski et al. administered pegaptanib with doses of 0.3 mg and 1 mg at 6-week intervals to BRVO patients, and they found improvement in visual acuity and a decrease in macular edema at the end of a 54-week follow-up (42).

ii. Bevacizumab

It is a monoclonal antibody produced by recombinant DNA technology against human VEGF-A. Its molecular weight is 149 kDa. It has the feature of inhibiting all VEGF-A isoforms and their active degradation products. It has been approved by the FDA for use in the treatment of metastatic colorectal cancers. In electrophysiological tests performed after intravitreal bevacizumab injection in 9 patients with age-related macular degeneration, improvement in macular function was observed (43). In a study, it was shown that 1.25 mg intravitreal bevacizumab administered for the treatment of RVO did not cause electroretinographic adverse changes in scotopic and photopic functions between 1 week to 2 months after the treatment (44). In a recent study, Ito Y. et al. reported

that the results of a single dose of bevacizumab and three consecutive doses of bevacizumab treatment in BRVO patients were effective and similar (45).

iii. Ranibizumab

Ranibizumab is a recombinantly produced humanized mouse monoclonal fragment. It blocks all isoforms and all degradation products of VEGF-A. It was approved for the treatment of macular edema secondary to RVO after the CRUISE study (Ranibizumab for the Treatment of Macular Edema after Central Retinal Vein Occlusion) and the BRAVO study (Ranibizumab for the Treatment of Macular Edema following Branch Retinal Vein Occlusion) (46,47). Both studies compared 0.3mg, 0.5mg, and sham injections after 6-month follow-up; A decrease in central macular thickness and improvement in best-corrected visual acuity were observed more in the ranibizumab group than in the sham group. In addition, in the BRAVO study, it was shown that there was less need for grid laser photocoagulation as rescue therapy in the ranibizumab group. In the HORIZON (Ranibizumab for Macular Edema Due to Retinal Vein Occlusions: Long-term Follow-up) study, long-term effect of ranibizumab was investigated in patients who completed the BRAVO and CRUISE studies. In this study, a relationship was found between decreased follow-up and ranibizumab use in patients with CRVO. Visual acuity was stable in patients with BRVO. Researchers stated that follow-up intervals should be less than 3 months in patients with CRVO after 2 years of follow-up (48).

iii. Aflibercept

Aflibercept is a 115 K Dalton recombinant fusion protein and consists of a combination of the Fc portion of human IgG with mimicry of VEGF receptors 1 and 2. It also shows a very high affinity for all VEGF-A isoforms. Thus, it inactivates VEGFs by allowing VEGFs to bind to itself before reaching the relevant receptors. Aflibercept has a long half-life and binds and inactivates the entire VEGF family, as well as placental growth factors 1 and 2, which play an important role in vascular permeability. The COPERNICUS (VEGF Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion) study compared 2 mg aflibercept and sham injection in 189 patients with CRVO. At the end of 24 weeks, regression in macular edema and an increase in visual acuity were detected. NV was not detected in the aflibercept group (49). Aflibercept

was approved for use in the treatment of macular edema secondary to BRVO with the VIBRANT study, which is a multi-center and randomized trial (50).

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CHAPTER 5

HYPERTENSIVE EYE DISEASE

Tuğba ÇETİNKAYA
Samsun Gazi Community Hospital, Department of Ophthalmology, Samsun
e-mail: mdtubacetinkaya@gmail.com
ORCID: 0000-0001-6085-8488

1. Introduction

The systemic arterial hypertension, described as the systemic blood pressure above 140 mm Hg and the diastolic blood pressure above 90 mm Hg by Liebreich in 1859, causes some target-organ damages including the systems of cardiovascular, cerebrovascular, renal, and retina (1). Hypertensive retinopathy behaves as a predictor of systemic morbidity and mortality due to target-organ damages. Previous studies showed a relationship between the incidence of retinopathy and the degree of severity and duration of hypertension (2).

Poorly controlled hypertension may cause some pathophysiologic changes in the retinal circulation resulting in some clinical signs known as hypertensive retinopathy, hypertensive optic neuropathy, and hypertensive choroidopathy (3).

2. Etiology

2.1. Race

The prevalence of hypertension and hypertensive retinopathy is more in Afro-Caribbeans than Europeans. However, there is a poor relationship between hypertension and the prevalence of retinopathy among Afro-Caribbeans as compared to Europeans (4).

2.2. Gender

The prevalence of hypertensive retinopathy is higher in women when compared to men (4).

2.3. Smoking

Previous studies showed a strong association between smoking and grade IV hypertensive retinopathy, especially in malignant hypertension. Besides, other lifestyle and socio-economic factors can be effective on this relationship (5).

2.4. Genetic Factors

Genetic factors can also play a role with certain genotypes associated with an increased risk of hypertensive retinopathy. It was shown that the deletion allele of the angiotensin-converting enzyme (ACE) gene has a higher risk for the development of target-organ damage in patients with systemic hypertension and causes 2-4 fold higher risk of retinopathy (6).

Previous studies demonstrated a significantly higher risk of retinopathy in patients who carry the apo epsilon 4 alleles of apolipoprotein E gene and who have the homozygous point mutation in the gene encoding 5,10-methylenetetrahydrofolate reductase (7).

2.5. Renal Status

Studies have demonstrated a positive correlation between renal dysfunction (persistent microalbuminuria and low creatinine clearance), as an indicator of early target-organ damage, and hypertensive retinopathy (8).

2.6. Cardiac Status

The left ventricular hypertrophy and retinal vascular disease show a positive correlation in patients with severe hypertension. The concentric left ventricular hypertrophy is more related to the severity of hypertensive retinopathy than eccentric left ventricular hypertrophy (9).

2.7. Serum Leptin Levels

Leptin is an angiogenesis factor and is related to the damage of the vascular endothelium. The critical plasma leptin levels were identified as 10.2ng/ml for the development of retinal vascular damage. Studies demonstrated an increase in plasma leptin levels in patients with hypertensive retinopathy (10).

2.8. Salt Sensitivity

Patients with salt-sensitive hypertension are more prone to hypertensive retinopathy than patients with salt-resistant hypertension (11).

2.9. Secondary Hypertension

The causes of secondary hypertension, including renal hypertension caused by focal segmental sclerosis or membranoproliferative glomerulonephritis, atherosclerotic renovascular disease, and pheochromocytoma, are associated with more severe retinopathy than essential hypertension (12). However, primary hyperaldosteronism does not relate to severe hypertensive retinopathy (13).

2.10. Refractory Hypertension

Patients with refractory hypertension cause an advanced retinal involvement as a target-organ damage.

3. Epidemiology

Studies demonstrated that the incidence of hypertensive retinopathy is correlated with the severity and the duration of systemic hypertension. Patients with the chronic renal disease show an increased risk for hypertensive retinopathy (1). Erden et al. detected the incidence of hypertensive retinopathy as 66.3%[3], however, Kabedi et al. noted that as 83.6% in their study (1). In another study, the incidence of grade 1 hypertensive retinopathy was noted as 37% and grade 2 hypertensive retinopathy was noted as 17% of hypertensive patients (14).

4. Pathophysiology

The retinal vascular structure has more different features than other blood vessels, such as blood-retinal barrier, blood flow autoregulation, and absence of sympathetic nerve supply (15). So, elevated blood pressure is initially compensated with the vessel constriction. However, steady increase in the blood pressure overcomes this compensation and causes endothelial and muscle layer damages.

The stages of vascular damage (3)

***Vasoconstrictive stage:** The vascular autoregulatory mechanisms play a role in this stage. As a result, vasospasm and retinal arteriolar narrowing occurs. Thus arteriole to venule ratio decreases (normal: 2/3) in fundus examination. Patients with arteriosclerosis show focal arteriolar narrowing, because sclerotic vascular segments are non-functional.

***Sclerotic stage:** Persistently elevated blood pressure causes definite changes in vascular structure, including thickening of the intimal layer, hyperplasia of the media layer, and hyaline degeneration of the arteriolar

wall. Consequently, more severe arteriolar narrowing, arteriovenous crossing abnormalities, and widening and accentuation of light reflex (silver and copper wiring) occur. When a thickened arteriole crosses over and compresses to a venule, the vessels share a common adventitial sheath and the distal part of the venule turns into a dilated and torturous form.

***Exudative stage:** This stage appears with severely increased blood pressure. Therefore, the blood-retinal barrier deteriorates and a leakage of blood and plasma occurs from the vessel wall. After all, retinal hemorrhage (flame-shaped and dot blot), hard exudate formation, necrosis of smooth muscle cells, and retinal ischemia (cotton-wool spots) occur.

Unlike the retinal and optic nerve vascular system, the choroidal vascular system has not autoregulation and a blood-ocular barrier, but has both sympathetic and parasympathetic nerves.

Poorly controlled hypertension results with common structural and functional microvasculature changes such as the reduction in the density of the microvasculature (rarefaction) in target organs including eyes and kidneys (16). The presence of microvascular rarefaction is thought to be an essential pathological change in hypertension (17).

Rarefaction in the retinal circulation has been demonstrated using computer algorithms (18). After the introduction of spectral-domain optical coherence tomography angiography (SD-OCTA), the rarefaction of retina capillaries has been documented and shown to be correlated with elevated blood pressure and poor renal function (19).

A previous study demonstrated a decrease in perifoveal arterioles and venules in patients with essential hypertension although adequate blood pressure control (20). And also it was shown that, there was an irregular vascular reactivity in response to acute hyperoxic and hypercapnic stres in patients with hypertension (21).

The optic nerve head and ocular blood flow are directly related to perfusion pressure and inversely related to the resistance to blood flow. The perfusion pressure is equal to mean arterial pressure minus intraocular pressure and the resistance to blood flow depends on the state and caliber of the ocular arteries that are influenced by hypertension and autoregulation (22). Endothelial-derived factors (endothelins, thromboxane A2, prostaglandins, nitric oxide) play a role in autoregulation (23). Disruption of the autoregulation causes an increase or decrease of the perfusion pressure.

Acute hypertension disrupts the blood-retinal barriers which are formed by the tight junctions of the retinal endothelium and the retinal pigment epithelium (22). All these differences in ocular tissues cause different clinical manifestations, such as retinopathy, optic neuropathy, and choroidopathy (22).

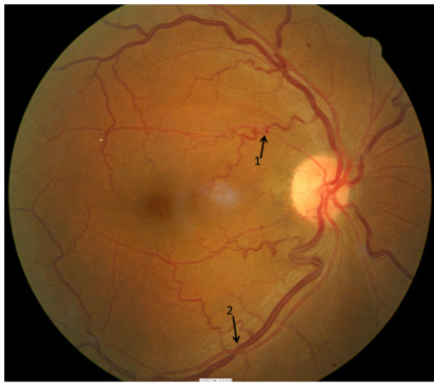
5. Clinical Features

5.1. Hypertensive Retinopathy

Hypertensive retinopathy has usually an asymptomatic clinic diagnosis by fundus examination. The fundoscopic signs of hypertensive retinopathy are shown in Table 1.

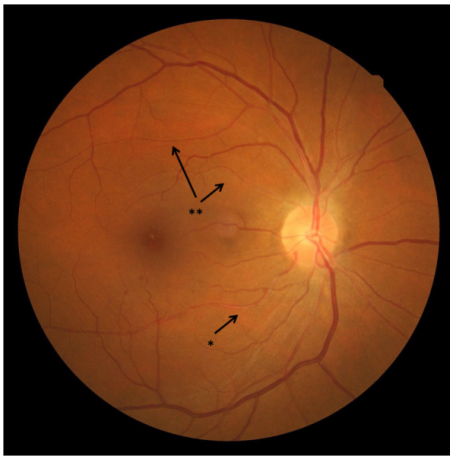
Table 1. The fundoscopic signs of hypertensive retinopathy

Changes in arteriovenous crossing (Figure 1)	
Salus's sign	The deflection of the retinal vein is due to crossing by the arteriole
Gunn's sign	The tapering of the retinal vein on both sides of the AV crossing
Bonnet's sign	The banking of the retinal vein distal to the AV crossing
Changes in the arterioles (Figure 2)	
Decrease of the arteriovenous ratio to 1/3 (normally 2/3)	
Change in the arteriolar light reflex (copper wiring and silver wiring-arteriolosclerosis)	
Changes in the retina	
Hemorrhages	
Dot-blot hemorrhages	The bleeding in the inner retinal layer
Flame-shaped hemorrhages	The bleeding in the superficial retinal layer
Exudates	
Hard exudates	The lipid deposits in the retina
Soft exudates / Cotton wool spots	Appear due to ischemia of the nerve fibers
Changes in the macula	
Circinate or macular star formation due to deposition of hard exudates around the macula	
Changes in the optic nerve	
Optic disc swelling / Hypertensive optic neuropathy	



[1]The Salus's sign, [2]The Gunn's sign

Figure 1. Changes in arteriovenous crossing in patients with hypertensive retinopathy



[*]Change in the arteriolar light reflex, [**]Generalised arteriolar narrowing.

Figure 2. Changes in arterioles in patients with hypertensive retinopathy

Wong et al. documented some retinal signs, including AV nicking, focal arteriolar narrowing, microaneurysms, cotton wool spots, retinal hemorrhages and decreased AV ratio, to be related to increased risk for stroke (15).

The primary response of the retinal circulatory system to systemic hypertension is vasoconstriction. Persistent hypertension causes the disruption of the blood-retinal barrier, increased vascular permeability, and secondary arteriolosclerosis (24). Though it's easier to diagnose the focal arteriolar narrowing than generalized narrowing in clinical practice, using new computer-assisted quantification has solved this differentiate (25).

Abnormal vascular permeability of retinal vessels causes flame-shaped hemorrhages, retinal edema, and lipid exudated. Progressive hypertension produces deeper blot hemorrhages indicated worsening ischaemia (26). The leakage of the lipid around the fovea occurs as macular star (27).

Acute hypertension causes an obstruction in the precapillary arterioles and nerve fiber layer infarcts (cotton-wool spots) or papilledema. Severe acute hypertension forms a macular star and papilledema with minimally change in vessels (27). The hyalinization of the arteriolar wall causes the arteriolar light reflex in grade II and III retinopathy.

In animal studies, focal intraretinal periarteriolar transudates, cotton-wool spots, retinal hemorrhages, and edema were described as the early signs of acute hypertensive retinopathy (22). At the same time, retinal arteriolar changes, cystoid macular changes, hard exudates, and nerve fiber loss were described as late manifestations (22).

5.2. Hypertensive Optic Neuropathy

Although papilloedema or bilateral optic disc swelling was considered as a criterion of malignant hypertension, current clinical and experimental studies showed that papilloedema was not a necessary feature for malignant hypertension (28).

The pathogenesis of papilloedema secondary to systemic hypertension include ischemia, raised intracranial pressure, and a part of hypertensive retinopathy/ encephalopathy. Clinical studies demonstrated the most essential etiological factor is ischemia in hypertensive optic neuropathy.

Papilloedema secondary to hypertension resolve with good control of the blood pressure despite some cases developed disc pallor (29). Persistent hypertension may cause to loss of the retinal nerve fibers.

As differential diagnosis, diabetic papillopathy, radiation retinopathy, central retinal vein obstruction, anterior ischemic optic neuropathy, and neuroretinitis should be considered.

5.3. Hypertensive Choroidopathy

The choroidal lesions secondary to elevated blood pressure are less documented than hypertensive retinopathy (30). The fibrinoid necrosis of choroidal arterioles causes focal infarction of the choriocapillaris. Elschnig spots form focal areas of degenerative retinal pigment epithelium and diffuse patchy atrophic retinal

pigment epithelial degeneration in patients with chronic hypertension (31). Siegrist's streak is linear retinal pigment epithelial hyperplasia over choroidal infarcts and indicates acute hypertensive choroidopathy with a poor prognosis (32). As a less common clinical feature, the neurosensorial retinal pigment epithelium detachments may occur (33).

Macular edema, serous retinal detachment, and optic nerve necrosis are the most important pathologies that cause less visual acuity. The most clinical conditions associated with hypertensive choroidopathy are preeclampsia, eclampsia, pheochromocytoma, and renal hypertension.

6. Classification

Many classifications, such as a two-grade classification included non-malignant (non-accelerated) retinopathy and malignant (accelerated) retinopathy (34), three grade classification included mild (generalized arteriolar straightening, arteriovenous nicking, and arteriolar wall opacification), moderate (mild retinopathy plus microaneurysms, hemorrhages, cotton-wool spots and hard exudates) and malignant (moderate retinopathy plus optic disc swelling) or mild and severe form according to the density of the perifoveal capillaries and capillary blood vessel in angiographic results (35), suggested for understanding the association between clinical features and prognosis. A similar classification has been formed according to the risk stratification and therapeutic decision of the hypertensive target-organ damage (36). The main classification systems of hypertensive retinopathy have been proposed by Keith-Wagner-Barker and Scheie.

6.1. Keith-Wagner-Barker Classification (24)

Group 1: Mild generalized retinal arteriolar narrowing
Group 2: Definite focal narrowing and arteriovenous nicking additional to group 1
Group 3: Flame-shaped retinal hemorrhages, soft (cotton wool spots), and hard exudates additional to the second group.
Group 4: The above and optic disc swelling (papilloedema)

6.2. Scheie Classification

Stage 0: With no definite retinal vascular changes

Stage 1: Diffuse arteriolar constriction
Stage 2: The above and focal arteriolar narrowing with light reflex changes
Stage 3: Copper wiring and retinal exudates and hemorrhages additional to the second stage.
Stage 4: Grade 3 plus silver wiring, hard exudates, and retinal and optic disc edema.

7. Ocular Complications Secondary to Systemic Hypertension

Systemic hypertension has been associated with some ocular diseases including retinal vein and artery occlusion, retinal arteriole macroaneurysm, anterior ischemic optic neuropathy, cranial nerve palsies, diabetic retinopathy, age-related macular degeneration (37), glaucoma (38), retinal arteriolar emboli, epiretinal membrane formation, and cystoid macular edema.

Several studies showed an association between systemic hypertension and increased risk of developing central, hemi-central, and branch retinal vein occlusions (39). The central or hemi-central retinal vein occlusions occur at the level of the lamina cribrosa and branch retinal vein occlusions occur at an arteriovenous crossing (40). These patients complain of sudden painless visual loss or a field defect.

Retinal arterial macroaneurysms, described as focal aneurysmal dilations of the retinal arterioles have been seen as star-shaped exudation and complicated with pre-retinal and intravitreal hemorrhage in systemic hypertension (41). Retinal arterial macroaneurysms may resolve spontaneously or may be treated with laser photocoagulation.

Recent studies documented a relationship between systemic hypertension and optic nerve head ischaemic disorders. Patients complain about unilateral painless visual loss, altitudinal field defects, or central scotoma. The underlying mechanism may be chronic hypoperfusion of the small end-arterial optic nerve head vessels (42).

The cranial nerve palsies, such as the third, fourth, sixth, and seventh cranial nerve, are related to systemic hypertension. Patients complain about acute symptomatic diplopia and usually resolve spontaneously (43).

Systemic hypertension is known as a major risk factor for the progression of diabetic retinopathy by impaired retinal perfusion and microvasculature.

Most studies, including UKPDS 50, EUCLID, and HOPE, demonstrated the relationship between elevated blood pressure and progressive diabetic retinopathy (44).

8. Diagnosis

Hypertensive retinopathy is diagnosed with clinical examination. The retinal vascular changes in fundus examination facilitate understanding of hypertensive retinopathy. Fluorescein angiography is a useful tool for identifying microvascular abnormalities (45). The cotton wool spots and flame-shaped retinal hemorrhages are demonstrated as hypo-fluorescent areas and the macular edema, retinal edema, and leakage of retinal capillaries are demonstrated as hyperfluorescent areas by using fluorescein angiography in patients with hypertensive retinopathy. The optic nerve leakage has been shown as a hyperfluorescent area in patients with hypertensive optic neuropathy. The Elschnig spots have been seen as focal hyperfluorescent areas in patients with hypertensive choroidopathy. Disseminate hyperfluorescent areas may point out the serous detachment in the late phasis of angiography (46).

9. Differential Diagnosis

Other clinical conditions, such as central retinal vein thrombosis, diabetic retinopathy, papilledema, ischemic optic neuropathy, vasculitis, radiation retinopathy, can mimic the grade III or grade IV hypertensive retinopathy with common symptoms. (Table 2).

Table 2. Other clinical conditions that can mimic grade III or grade IV hypertensive retinopathy

Presents with optic disc swelling	**Mimics chronic hypertensive retinopathy**
Diabetic papillopathy	Diabetic retinopathy
Central retinal vein occlusion	Retinal venous obstruction
Anterior ischemic optic neuropathy	Hyperviscosity Syndrome
Neuroretinitis	Ocular ischemic Syndrome
	Radiation retinopathy

Central retinal vein thrombosis has usually been seen unilaterally and the decreasing of the visual acuity is more evident than hypertensive retinopathy.

The fundus examination demonstrates venous tortuosity, distinct macular edema, intensive hemorrhage on the papilla, circle-shaped hemorrhages besides flame-shaped hemorrhages, pre-retinal hemorrhages, and intravitreal hemorrhages. The fluorescein angiography indicates ischemia and macular edema (47). In patients with ischemic optic neuropathy, the visual acuity decreases prominently and unilaterally. Ischemic optic neuropathy does not show any retinal vascular changes (48).

Diabetic retinopathy is characterized by microaneurysms, hard exudates, and evident macular changes. In the progressive non-proliferative stage, diabetic retinopathy mimics hypertensive retinopathy with retinal changes including cotton-wool spots, flame-shaped hemorrhages, and papilledema. Fluorescein angiography is essential in these stages to differentiate these clinical conditions. Diabetic retinopathy causes poor visual acuity, intraretinal microaneurysms, and extensive retinal ischemia in fluorescein angiography (49).

Papilloedema mimics hypertensive retinopathy with being bilaterally and constant visual acuity, however hypertensive retinopathy demonstrates additional retinal vascular changes, such as flame-shaped hemorrhages and cotton wool spots (50).

Rheumatological diseases, such as systemic lupus erythematosus, Behcet's disease, etc. may cause vasculitis. Systemic lupus erythematosus shows bilaterally retinopathy with more cotton wool spots and fewer hemorrhages. In fluorescein angiography, the ischemia may be detected (51). Behcet's disease shows retinitis focuses with hemorrhage which mimics cotton wool spots. The optic nerve involvement may mimic hypertensive retinopathy. In differential diagnosis, the vitreous reaction, generalized involvement in the fundus, and distinct macular edema are essential (52).

10. Treatment

The retinal vessels, a kind of unique visible blood vessels, that give important information about the effects of chronically elevated blood pressure on routine fundus examination.

Hypertensive eye disease may resolve in a few months with regular controlled blood pressure. However acute hypertensive attack has severe ocular and systemic morbidity and mortality (53).

The management of hypertensive retinopathy depends on the severity of the disease. While patients with mild hypertensive retinopathy only need a

regular controlling of the blood pressure, moderate hypertensive retinopathy needs investigation about other associated factors like diabetes mellitus and any cardiovascular abnormalities. The controlling and monitoring of blood pressure is a necessity. Severe hypertensive retinopathy requires urgent treatment due to a strong association with mortality.

11. Prognosis

Acute clinical findings in the retina, such as papilloedema, macular edema, and neurosensorial detachment, resolve in a few weeks after the regulation of blood pressure. However, chronic clinical findings, including arteriolar narrowing and arteriovenous nicking persist. Even so, persistent hypertensive retinopathy rarely causes significant visual loss except for secondary optic atrophy and prolonged exudative retinal detachment. Previous studies documented the incidence of mortality for untreated malignant hypertension as 50% within 2 months of diagnosis and 90% by the end of one year (54).

12. Conclusion

Hypertensive retinopathy, hypertensive neuropathy, and hypertensive choroidopathy have been reported as target-organ damages in patients with systemic arterial hypertension. To realize and manage elevated blood pressure is essential for avoiding ocular and systemic morbidity and mortality.

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CHAPTER 6

RETINOPATHY OF PREMATURITY

Ferhat EVLIYAOGLU
Emory University, Department of Pediatric Ophthalmology, Atlanta, USA
e-mail: ferhatevliyaoglu@yahoo.com
ORCID: 0000-0003-3260-686X

1. Background

Retinopathy of prematurity (ROP) is a vascular developmental disease of the retina which is one of the important causes of vision impairment worldwide and is incrementing in incidence in developing and developed countries and occurring mainly in preterm babies. Even though neonatal care and management guidelines have been improved tremendously during the last century, ROP stays a considerable reason for childhood visual impairment around the world.

2. Epidemiology

The incidence of ROP changes with weight at the delivery but is estimated to be around 50-70% in infants whose weight is less than 1250 g at birth based on recent studies. One of these studies which were conducted in the United States showed the incidence of ROP was 68% among babies weighing <1,251 (1). Another study from Korea showed a 20.7% incidence (88 of 425 premature babies) and showed that a GA of 28 weeks or less and a birth weight of 1000 g or less were the most important risk factors (2). Regarding developed countries, a study conducted in 2010 reported that 6,300 of 32,700 babies with any type of ROP progressed to therapy-requiring retinopathy, and 1,700 babies lost their vision or were severely visually impaired from ROP (3).

3. Screening Guidelines

All infants with a delivery weight of ≤1500 g or a gestational age of 30 weeks or less (as determined by the attending physician in charge) and selected babies

with a delivery weight between 1500 and 2000 g or a gestational age of >30 weeks who are classified by their pediatrician or neonatologist to be at risk for ROP (such as babies with hypotension requiring inotropic support, babies who received supplemental oxygen for a period longer than average, or babies who supported with oxygen without monitorization should undergo ROP screening (4). The ROP screening should be started based on the baby's postmenstrual age because severe ROP has a correlation with postmenstrual age (gestational age at birth plus chronologic age) than with postnatal age (5) A table has been developed based on Multicenter Trial of Cryotherapy for Retinopathy of Prematurity natural history data which shows recommended time table for ROP follow up exams. (Table 1). It represents a recommended schedule for the timing of the first eye examinations based on postmenstrual age and chronologic (postnatal) age to diagnose ROP before it becomes severe enough to result in retinal detachment while minimizing the number of potentially disturbing examinations. (6).

Table 1. Timing of Initial Eye Exam According to Gestational Age at Birth

Gestational Age at Birth, weeks	Initial Examination Age, weeks	
	Post-menstrual	Chronologic
22[a]	31	9
23	31	8
24	31	7
25	31	6
26	31	5
27	31	4
28	32	4
29	33	4
30	34	4
Older gestational age, high-risk factors	-	4

[a]This guideline should be considered tentative rather than evidence-based for infants with a gestational age of 22 to 23 weeks because of the small number of survivors in these postmenstrual age categories.

4. Pathogenesis

ROP disease developed in premature babies who are born before the vessels in the retina complete their regular development. In the ROP disease, preterm birth ceases the development and other factors play a role in the initial halt in regular vascular growth and possible oxygen-related vascular anomaly. The effect of oxygen on the retina during the development of retinal vascular structure was

described in two different stages: (1) Vasoconstrictive Stage: This happens during exposure to hyperoxia and due to suppression of the normal anterior segment vascularisation of the retina. This mechanism of the vasoconstrictive and obliterative effect of oxygen is seen predominantly in the developing retinal vessels. This in turn leads to suppression of vascular endothelial growth factor; and (2) Vasoproliferative stage: This occurs during the transition from oxygen to room air and causes dilatation and tortuosity of the existing anomaly developed vessels with neovascularization and proliferation of new vessels into the vitreous. This occurs mainly due to the sudden surge in vascular endothelial growth factor levels (7)

5. Classification

The ICROP (International Classification of Retinopathy of Prematurity) has been the primary tool used around the world to describe retinopathy of prematurity (ROP) in clinical practice and research. Nevertheless, with the development in retinal imaging technology, a revised version of ICROP classification has been published which was described the zones better (8).

Zones

Three concentric zones, centered on the retina define the anteroposterior location of retinopathy (Figure 1).

Zone I: The area defined by a circle centered on the optic nerve, the radius extending from the central optic disc to twice the width from the central optic disc to the central macula.

Zone II: The area extending centrifugally from the edge of zone I to a circle with a radius equal to the distance from the center of the optic disc to the nasal ora serrata.

Zone III: The residual crescent in the temporal area of the retina located anteriorly to zone II. By convention, zones II and III are considered to be mutually exclusive.

The zone is based on the most posterior zone (as the retina may be vascularized to different extents in different regions of the retina, i.e. nasal vs temporal vs superior vs inferior)

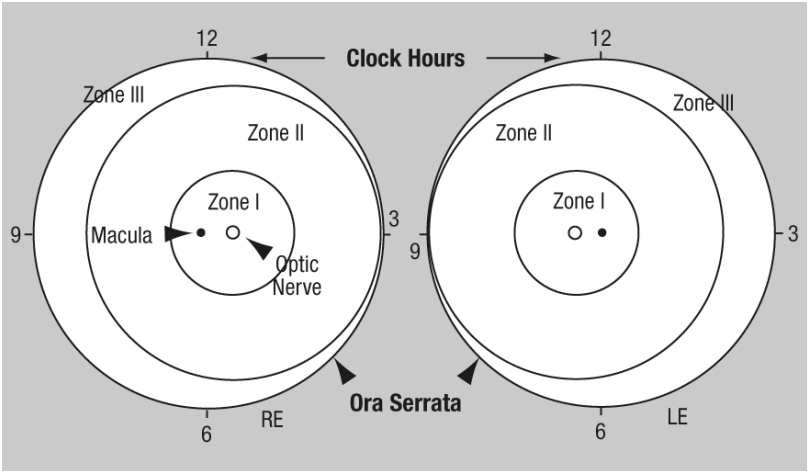

Figure 1. RE: Right eye, LE: Left eye

Stages

It denotes the degree of vascular changes. Prior to the development of ROP in the premature infant, vascularization of the retina is incomplete or "immature" (Stage 0) (Figure 2). Five stages of ROP has been described;

Stage 1- demarcation line: A demarcation line is seen between the vascular and avascular retina. It is a thin structure that lies in the plane of the retina (Figure 3).

Stage 2- ridge: The demarcation line grows to occupy a volume and has a height and width to form a ridge above the plane of the retina (Figure 4). Small tufts of new vessels also called "popcorn" vessels may be seen posterior to the ridge.

Stage 3- ridge with extraretinal fibrovascular proliferation: In this stage extraretinal fibrovascular tissue is seen arising from the ridge into the vitreous (Figure 5). It may be continuous or non-continuous and is posterior to the ridge.

Stage 4- subtotal retinal detachment: Here a partial detachment of the retina is seen which may be exudative or tractional. It is subdivided into the following: (1) Partial retinal detachment not involving the fovea (stage 4A) (Figure 6); and (2) Partial retinal detachment involving the fovea (stage 4B)

Stage 5- total retinal detachment: Here a total retinal detachment is seen in a child who usually presents with leukocoria (white pupillary reflex) (Figure 7).

Plus disease: It indicates the disease severity and is described as tortuosity of arteries and venule enlargement in the posterior pole (Figure 8).

Pre-plus disease: It is described as vessel enlargement and tortuosity in the posterior pole, that is with less involvement than plus disease, but prominent than normal.

Extent: The extent of disease is recorded as hours of the clock or as 30° sectors. As the examiner looks at each eye, the 3-o'clock position is to the right and nasal in the right eye and temporal in the left eye, and the 9-o'clock position is to the left and temporal in the right eye and nasal in the left eye. Extent is beneficial in Stages 4 and 5 ROP but, in general, is no longer necessary in the diagnosis treatment-required ROP.

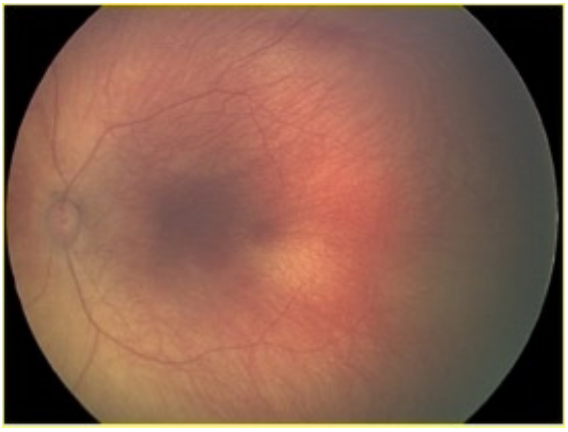

Figure 2. Stage 0 or Immature retina

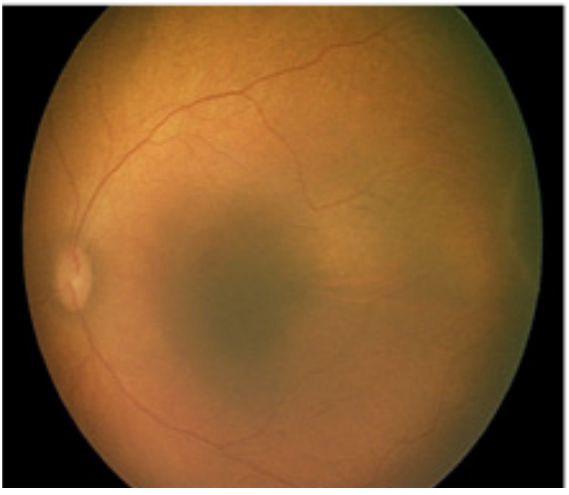

Figure 3. Stage 1 ROP

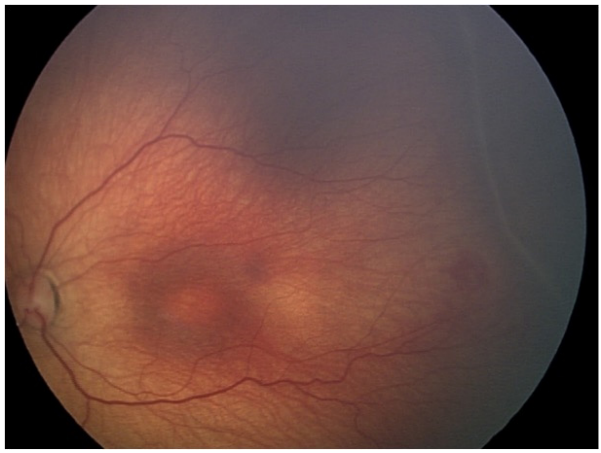

Figure 4. Stage 2 ROP

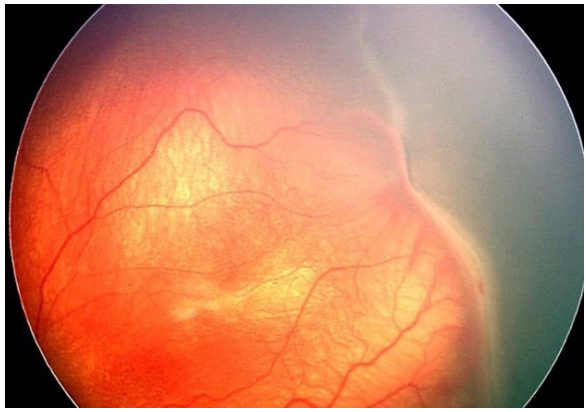

Figure 5. Stage 3 ROP

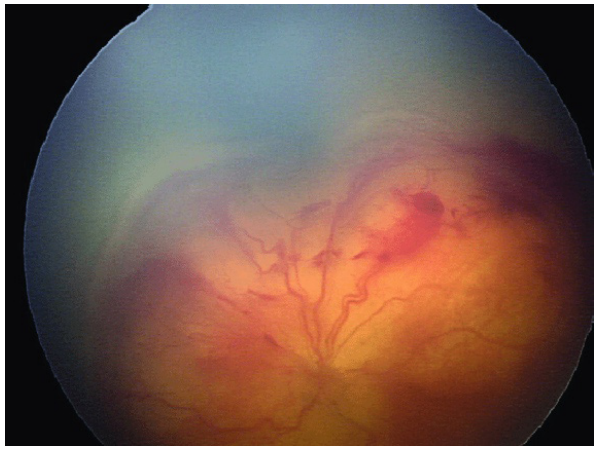

Figure 6. Stage 4A ROP

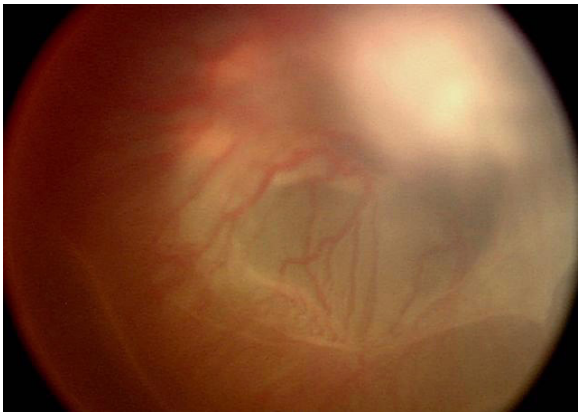

Figure 7. Stage 5 ROP

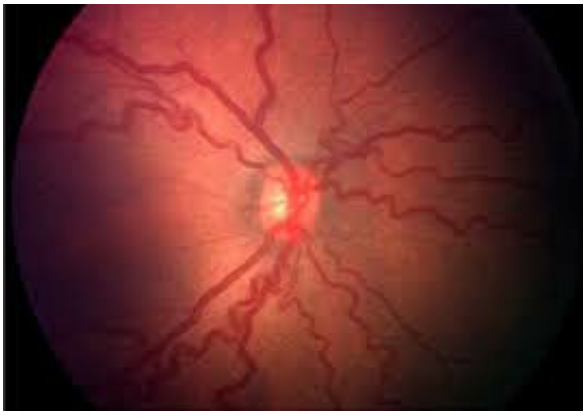

Figure 8. Plus disease

6. Types and Treatment:

Retinopathy of prematurity (ROP) treatment decisions are based on clinician practice and guidelines derived from outcomes from the Early Treatment for Retinopathy of Prematurity (ETROP) randomized clinical trial. Based on treatment decisions, ROP may be divided into five different types.

No ROP: The retina is not completely vascularized until 40 weeks' gestation. Premature infants may have immature retinal vessels without having ROP. In that stage, no treatment is needed but observation is required.

Mild ROP: Mild ROP indicates the presence of ROP that is at a low risk of requiring treatment. Mild ROP is described as low stage disease and ROP is located in a peripheral location where it is unlikely to affect the visual axis.

Type 1 (requires treatment)

- zone I, any ROP stage accompanied by plus disease
- zone I, ROP in stage 3 ± plus disease
- zone II, stage 2 or 3 with plus disease

Type 2 (can be observed)

- zone I, stage 1 and 2 ROP without plus disease
- zone II, ROP in stage 3 but no plus disease

Aggressive posterior ROP: This uncommon type has a rapid progression, and was an ROP form referring to "rush disease" in the past. It specifically involves posterior pole, severe-plus disease, and smooth intra-retinal neovascularization (Figure 9). It can progress very fast to stage 5 ROP and blindness, if not intervened early. The flat neovascularization can be quite subtle and can easily confuse less experienced examiners.

Figure 9. Aggressive ROP

7. Follow-up Assessment

Follow-up assessment should be conducted on the basis of retinal signs based on the International Classification. The recommended schedule is below:

- 1 week in case of Stage 1 or 2 retinopathy within zone I (the lack of Plus Disease) or Stage 3 retinopathy within zone II (the lack of Plus Disease).

- 1 to 2 weeks if there is immature vascularization within zone I without ROP, Stage 2 retinopathy within zone II, or recovery of retinopathy within zone I.
- 2 weeks if Stage I retinopathy within zone II or recovery of retinopathy within zone II.
- 2 to 3 weeks if immature vascularization within zone II without retinopathy, Stage 1 or 2 retinopathy within zone III, or recovery of retinopathy within zone III.

Signs recommending that follow-up assessment could be decreased 3 weeks are as follows:

- Vascularization in Zone III retinal, but no history of zone I or II retinopathy (In case of any doubt regarding the zone involvement or in case of the postmenstrual age 35 weeks, confirmatory examinations may be warranted).
- Postmenstrual age of 45 weeks and no pre-threshold disorder (described as stage 3 retinopathy within zone II, any retinopathy within zone I) or the existence of worse retinopathy.
- Regression of ROP (5) (attention should be considered whether there are abnormal vessels that may cause reactivation of the ROP and retinopathy progression).
- If Plus Disease (defined as dilation and tortuosity of the posterior retinal blood vessels) is present within zone I or II, peripheral ablation might be preferred to observation (9).

8. ROP Treatment

Timely management for ROP is critically important to prevent vision loss or severe visual impairment. So far it is known that the most effective treatments for ROP are laser therapy or cryotherapy. Both treatments are performed only on infants with severe ROP, particularly stage III with “plus disease. Retinal findings requiring treatment should be determined based on the early treatment for retinopathy of prematurity trial study (10). Cryotherapy is a treatment modality that uses a cryoprobe to reduce unwanted outcomes of ROP like retinal folds and retinal detachment nevertheless it is disturbing for the infants, requires general anesthesia, and causes a variable amount of periocular inflammation. Because of these drawbacks, it’s not a preferred treatment modality anymore. On the other hand, laser photocoagulation of the peripheral retina has been reported as the gold standard (11).

Anti-vascular endothelial growth factors treatment has been using widely in the management of the ROP nowadays. Anti-vascular endothelial growth factor (VEGF) medications directly stop the effects of VEGF. The BEAT-ROP (Bevacizumab Eliminates the Angiogenic Threat of ROP) study (12) is the only randomized clinical trial that is conducted comparing anti-VEGF vs laser photocoagulation. It has been shown a better outcome with anti-VEGF treatment than laser therapy for stage 3+ ROP in zone I. On the other hand, it could not be determined in severe ROP in zone II since the sample size was inadequate. One of the major concerns in the use of anti-VEGF medication is safety and recent studies also reported that systemic VEGF levels remain suppressed at least for 8 weeks following intravitreal bevacizumab injection (13). The surgery is usually reserved to reattach the retina in stage 4 to prevent progression to stage 5 ROP and to save the visual axis. The vitrectomy which is sparing the lens is a treatment modality that is preferred in severe cases. Regarding the best techniques, laser photocoagulation is still the gold standard in the treatment of ROP and anti-VEGF therapy should be reserved only in selected cases.

Treatment should be initiated for the Type 1 ROP, plus diseases which were described above, and the clinician should be alert for the Type 2 ROP and pre-plus diseases. Treatment should be done, when possible, within the first 72 h of diagnosing of treatable ROP to decrease as much as a possible risk of retinal detachment and visual impairment in Type 1 ROP. On the other hand, infants presenting aggressive involvement of posterior retinopathy should undergo therapy preferably within less than 48 h. ROP requiring intervention without the involvement of posterior retinopathy should undergo therapy within 48–72 h.

The treatment with anti-VEGF should only be applied under research protocols. Anti-VEGF treatment is a recent treatment modality in ROP. In a randomized clinical trial, intravitreal injection of bevacizumab an anti-VEGF agent was reported to be more effective than laser photocoagulation in preventing the recurrence in zone I, but without the involvement of posterior retinopathy within zone II (14).

9. Prognosis

If ROP progresses causes to retinal detachment, the outcome is visually disappointing. The CRYO-ROP study reported that with the 15-year follow-up treatment, the risk of unfavorable outcomes decreases from 52% to 30% (15).

The same study reported better outcomes in the group who underwent treatment, who has a better visual acuity at the 3-year, 10-year, and 15-year follow-ups. Anti-VEGF treatment is also reassuring, and better outcomes are being reported in recent studies and additional studies are awaited.

Screening for ROP should be started timely after birth to prevent visual impairment. It is the responsibility of the caring primary care pediatrician or neonatologist to start screening by informing the attending ophthalmologist and it is the responsibility of the ophthalmologist to conduct screening and start treatment whenever required.

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CHAPTER 7

OCULAR ISCHEMIC SYNDROME

Ali Cihat ASLAN

Malatya Trainig Research Hospital, Department of Ophthalmology, Malatya

e-mail: alicihataslan@gmail.com

ORCID: 0000-0001-5889-0462

1. Introduction

Ocular ischemic syndrome (OIS) is ocular hypoperfusion that consists of hypoxic changes of the anterior segment, posterior segment, and finally the orbit. It is a vision-threatening condition related to the severe common carotid artery (CCA) and/or internal carotid artery (ICA) occlusive disease.

In 1963, Hedges described a case of a 48-year-old patient with total obstruction of the left ICA on whose fundus, observed peripheral blot hemorrhages and dilated retinal veins. He related these signs with retinal hypoxia due to carotid artery stenosis (1). In the same year, Kearnst and Hollenhorst reported the same ocular symptoms and signs in association with advanced carotid artery stenosis. They called the condition venous stasis retinopathy and found it in 5% of their patients with unilateral stenosis or occlusion of the internal carotid artery (2).

In the following years, many other terms were introduced to describe ocular changes secondary to carotid artery stenosis, such as ischemic ocular inflammation, ischemic coagulopathy, and ischemic ophthalmopathy. It was observed that the signs of ischemia were present in both the anterior and the posterior segments of the eye, and eventually, the term ocular ischemic syndrome has been coined for the sum of ocular symptoms and signs that may accompany carotid artery occlusive disease (3).

Main symptoms include transient or permanent visual loss, changes of the visual field, and ischemic ocular pain. OIS has a significant systemic association with the CCA or ICA causing ocular symptoms after a while and that could turn into cerebrovascular disease (4).

2. Epidemiology

The ocular ischemic syndrome appears at an average age of 65 years, and is rare before 50 with no racial choice (5). OIS commonly occurs in men that are affected twice as often as women, because of the higher prevalence of atherosclerosis and cardiovascular disease in men. In 20% of cases, the involvement is bilateral (6). The certain incidence of OIS is not known but it is estimated about 8 cases per million every year (7). Since OIS is probably misdiagnosed as diabetic retinopathy or retinal vein occlusions in many cases, this figure may be miscalculated (8). About 30% of patients with symptomatic carotid occlusion have obvious retinal vascular changes that are usually asymptomatic, however, 2% of them progress to symptomatic OIS per year (9). 18% of the patients with ICA occlusion undergoing surgical anastomosis between the superficial temporal artery and the middle cerebral artery presented with OIS (6).

3. Pathogenesis

OIS occurs particularly in patients with weak collateral circulation between the ICA and external carotid artery (ECA) systems or between the two ICAs. Patients with a healthy collateral circulation may not develop OIS even with total occlusion of the ICA, however, in those with weak collaterals, stenosis of ICA by even 50% may be adequate to develop OIS. Types of occlusion variable from less than 50% stenosis to total occlusion of at least one CCA or one ICA, frequently accompanied by occlusion or stenosis of the opposite carotid arterial system (9). The rate of stenosis, the presence of collateral vessels, chronicity of carotid artery disease, its bilaterality, and associated systemic vascular diseases determine the severity of OIS (8).

Patients who develop OIS show decreased blood flow in the retrobulbar vessels and reversal of blood flow in the ophthalmic artery (OA) (10). The OA may behave as a steal artery shunting blood flow away. In these cases, blood flow is shunted away from the eye to the low-resistance intracranial circuit, with a further decrease of retrobulbar blood flow (11).

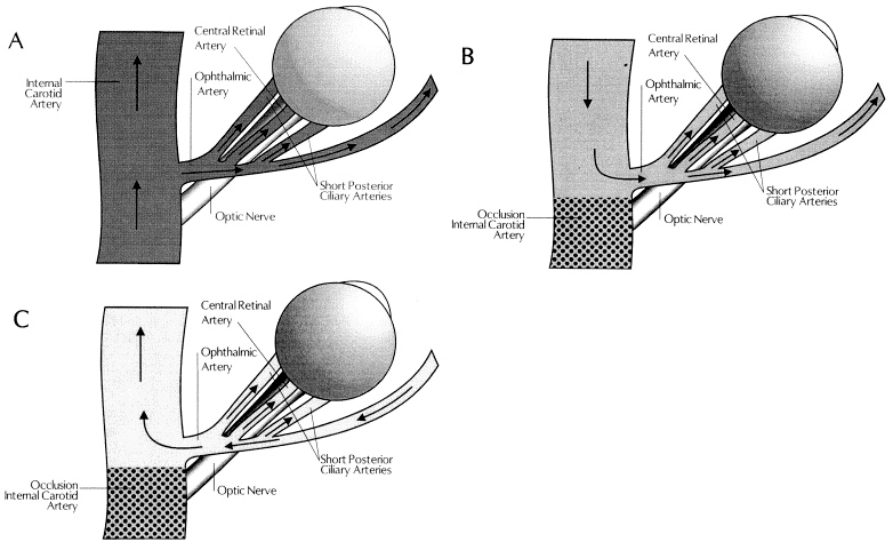

Figure 1. Blood flow in the ophthalmic artery (OA) and its branches. (A) in a normal individual; (B) compensation in a patient with internal carotid artery occlusion and collateral circulation via the circle of Willis (forward ophthalmic artery flow) and (C) decompensation in a patient with internal carotid artery occlusion and collateral circulation via the ophthalmic artery (reversed flow)

Atherosclerosis is the principal reason for OIS. On the other hand dissecting aneurysm of the carotid artery, fibrovascular dysplasia, Takayasu arteritis, aortic arch syndrome, Behçet's disease, giant cell arteritis, trauma or inflammation causing stenosis of the carotid arteries and complications after intravitreal anti-VEGF injections and after radiotherapy for nasopharyngeal carcinoma are also another reasons for OIS (7). Patients mostly have other related co-morbidities since OIS is associated with atherosclerosis. Hypertension is found in 73% of the patients and diabetes mellitus in 56%. Myocardial infarction occurs in approximately 4% of patients with OIS. The mortality rate is as high as 40% within 5 years of onset. Cardiovascular disease is the major cause of death (almost 66%), followed by cerebrovascular disease as the second leading cause of death (7), therefore patients with OIS should be consulted to the cardiologist, radiologist, and vascular surgeon for imaging studies of the carotid arteries and its treatment.

4. Symptoms

A decrease in visual acuity (VA) is present in over 90% of patients with OIS. It is generally related to chronic or acute retinal and choroidal hypoperfusion and

also damages to the optic nerve because of secondary glaucoma. In a series of 43 patients' first symptoms, 35% of eyes had a VA of 20/20 to 20/40 and in 35% of eyes had a vision of counting fingers or worse (5). Similarly, in 52 patients studied by Sivalingam et al, 43% of the affected eyes had an initial VA of 20/20 to 20/50, and 37% had a vision of counting fingers or worse (7). Mizener et al. reported an initial VA of 20/40 or better in 15% of their cases, however, 65% had a VA of 20/400 or less (8). Visual fields in patients with OIS can vary from normality to the presence only of a temporal or central island, centrocecal defects, nasal defects, and central scotoma (8).

Transient visual loss (amaurosis fugax) is present in about 10–15% of patients with OIS and lasts from a few seconds to a few minutes. It is frequently caused by transient embolization of the central retinal artery (CRA) or its branches, while in some patients vasospasm may be the causative factor. It must be kept in mind that most patients with transient visual loss do not have OIS. Less commonly, severe carotid artery disease causes transient visual loss as a result of choroidal hypoperfusion. Recovery of visual function after exposure to bright light is usually delayed in patients with severe carotid artery stenosis. Bright light amaurosis fugax, with slow adaptation, the phenomenon may be accounted for macular ischemia. This has been reported after postural change or after eating a meal.

Pain may be present in up to 40% of the eyes with OIS (6, 8). Pain may be the result of increased intraocular pressure (IOP) and/or may be ischemic in origin. Ischemic pain begins gradually over hours to days and is described as a dull, continuous ache in the affected eye, over the orbit, upper face, temple, and may worsen when the patient is upright. Lying down relieve and decrease the pain. The definition "ocular angina" may be used to explain this disturbance. Ischemic pain may be confused with that from secondary glaucoma, but the pain in the eyes with OIS would not be explained by a mild IOP elevation. Also in some patients with normal IOP, it may be caused by hypoxia of the eyeball and/or dura mater. In older patients, giant cell arteritis should be excluded.

5. Signs

Anterior segment signs may be the only presentation of OIS but usually, posterior segment signs are more than anterior segment signs (7). In about 66% of patients, rubeosis iridis and fibrovascular tissue at the iridocorneal

angle are diagnosed, which may cause an impaired outflow of aqueous humor. However, increased IOP and neovascular glaucoma are observed in only 50% of patients, while in some patients ocular hypotony may be observed due to ischemia of the ciliary body, and production of aqueous humor is decreased. In most patients opalescence of the aqueous humor is noted and in 20% of patients, inflammatory cells are seen in the anterior chamber (5). They are not countless, are uncommonly over grade 2, and are mostly related to iritis. Even more, unusual precipitates are on the corneal endothelium, which occur in cases of clinically silent iridocyclitis. Inflammatory conditions in the anterior segment may result in posterior synechiae. As a result of ischemia and atrophy of the sphincter muscle of the pupil, the pupil is fixed and semi-dilated. There is a weak reaction to light, which also may be due to retinal ischemia (4). The other signs of OIS may include dilatation of conjunctival and episcleral vessels and corneal edema, which may lead to bullous keratopathy. In very rare cases, liquefactive necrosis of the cornea may develop (3).

Regarding posterior segment signs on fundus examination, the retinal arteries are narrowed and the retinal veins are dilated. In some cases, both arteries and veins may be narrowed. Sometimes, spontaneous retinal arterial pulsations are examined. Retinal hemorrhages are very characteristic and are seen in about 80%-85% of affected eyes. Hemorrhages are mostly located in the external retinal layers at the mid-periphery (Figure 2). Hemorrhage points are not many in numbers and are rarely confluent. They are most presumably due to leakage of blood from the small retinal vessels or ruptured capillary microaneurysms (3,4). Microaneurysms are very frequent in OIS and may be located both in the macula and at the mid-periphery (Figure 3). Furthermore, diffuse macular capillary telangiectasias are observed in fundus examination, which together with microaneurysms, and may cause macular edema (3). Small branches of the central retinal artery may be occluded spontaneously, or the occlusion may be caused by cholesterol emboli with the result of hypoperfused retinal areas. Sometimes, retinal arterio-venous communications proximal to areas of the avascular retina may be present. A cherry-red spot, which is a characteristic of retinal ischemia mostly in the macula is observed in 12% of eyes, predominantly when IOP is over the perfusion pressure within the central retinal artery in the eyes with neovascular glaucoma or in some cases as a result of embolic occlusion of the central retinal artery (5). Neovascular glaucoma usually damages the optic disk quickly. In some patients, reduction of the retrobulbar blood flow and

ischemia of the optic disk may lead to nerve atrophy in the course of normal-tension glaucoma. In OIS, retinal neovascularization may also ocur as a result of increased production of the vascular endothelial growth factor (VEGF). New vessels are formed more often at the optic disk than in the retina. New vessels can bleed, with resulting hemorrhages into the vitreous body and, rarely, fibrovascular proliferation (3). Further signs of OIS include anterior and posterior ischemic optic neuropathy, choroidal neovascular membrane, cotton-wool spots in the retina (consider local ischemia), edema of optic axons in the optic nerve layer of the retina, and areas of chorioretinal atrophy resulting from choroidal ischemia.

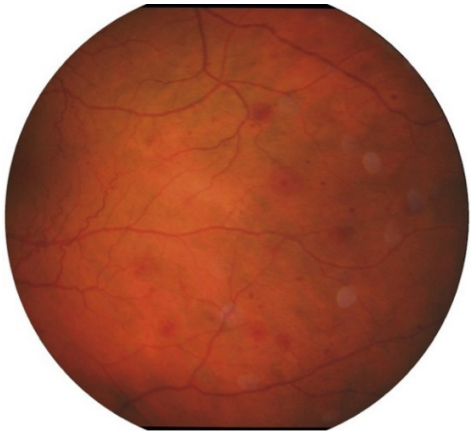

Figure 2. Fundus photograph of the left eye: retinal hemorrhages at the mid-periphery from the patient with the left internal carotid artery stenosis

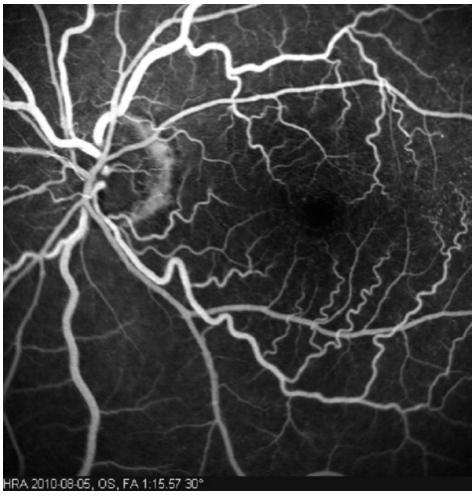

Figure 3. Fluorescein angiography of the left fundus: macular capillary telangiectasias with microaneurysms from the patient the left internal carotid artery stenosis

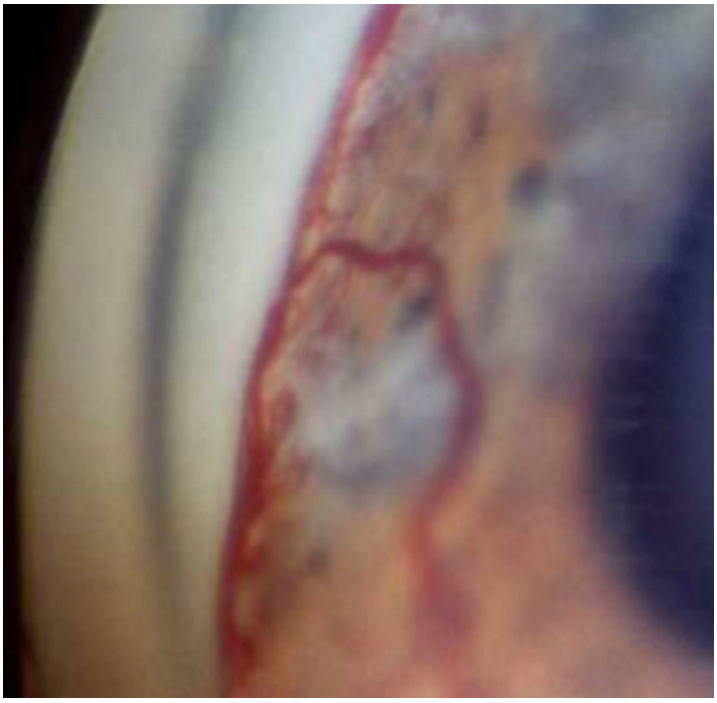

Figure 4. Gonioscopic image showing neovascularization of the iris at the iridocorneal angle

Table 1. Clinical manifestations of the ocular ischemic syndrome

Anterior Segment	Posterior Segment	Orbital
Conjunctival and Episcleral Injection	Retinal hemorrhages (mid-peripheral)	Orbital pain
Corneal edema and Descemet's folds (sometimes with bullous keratopathy)	Microaneusyms (mid-peripheral)	Anterior and posterior segment ischemia with intraocular inflammation and hypotony
Corneo-scleral melting	Dilated retinal veins	Ophthalmoplegia
Corneal hypoesthesia	Narrowed retinal arteries	Ptosis
Spontaneous hyphema	Retinal arteriovenous communications	
Iris atrophy	Macular capillary telangiectasia	

Anterior Segment	Posterior Segment	Orbital
Fixed semi-dilated pupil or sluggish reaction to light with relative afferent pupil defect	Cholesterol Emboli, Spontaneous retinal arterial pulsations, anterior ischemic optic retinopathy, wedge-shaped areas of chorioretinal atrophy	
Anterior and posterior synechiae	Cherry-red spot	
Uveal ectropion	Neovascularization of disc	
Rubeosis iridis	Neovascularization elsewhere	
Neovascular glaucoma	Choroidal neovascular membrane	
Iridocyclitis (cell, flare, keratit precipitates)	Vitreous hemorrhage	
Asymmetric Cataract	Cotton-wool spots	
	Asymmetric diabetic retinopathy	
	Hard exudates are usually not seen in OIS alone	

6. Diagnosis

The main diagnostic test in OIS is imaging studies of the carotid arteries. The most commonly used methods include non-invasive tests such as doppler ultrasound and invasive techniques such as carotid arteriography. Non-invasive tests determine carotid artery stenosis in at least 75% of cases. If the doppler ultrasound scan of the carotid arteries is within normal limits, doppler imaging of retrobulbar vessels, particularly of the ophthalmic artery should be done. New minimally invasive methods like computed tomographic angiography and magnetic resonance angiography can be also used as the second-line test in carotid artery stenosis (3).

Fluorescein angiography of the fundus is commonly used in the diagnosis of OIS. The prolonged arm-to-choroid and arm-to-retina circulation time is a

frequent sign. Irregular and/or prolonged retinal filling time is present in almost 60% of patients with OIS. The normal retinal filling time is roundly 5 seconds, but in the affected eyes it may be 1 minute or longer. This is the most specific (but not the most sensitive) fluorescein angiography sign of OIS (12). The most sensitive angiographic sign of OIS is prolonged retinal arteriovenous time, which is present in up to 95% of cases, but it is not OIS-specific. In 85% of affected eyes, staining of the major retinal vessels (mostly arteries) and their branches may be observed at the late phase of the test and is attributed to the increased permeability of the vessels (3). It may be accounted for endothelial cell damage due to chronic ischemia. Macular edema is seen in 17% of eyes with OIS (4).

Leakage from microaneurysms or telangiectasia may result in increased retinal thickness. Intraretinal fluid accumulation is usually mild to moderate, does not have a cystoid pattern, and is often associated with hyperfluorescence of the optic disk attributed to leakage from blood vessels. Non-perfusion in retinal capillary can also be seen, mostly located at the mid-periphery. It is related to the loss of endothelial cells and pericytes in these vessels and obliteration of their lumen in some eyes. The staining of arteries is more prominent with OIS. Besides, optic disc hyperfluorescence, peripheral microaneurysms, peripheral perivascular staining are other angiographic features (6).

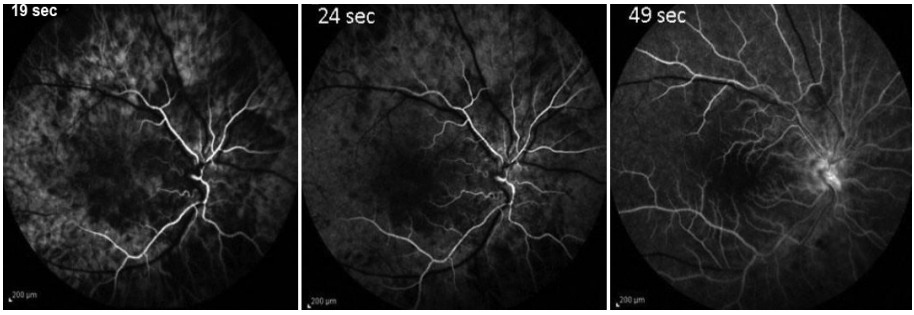

Figure 5. Fluorescein angiography in ocular ischemic syndrome (OIS). Prolonged retinal and choroidal circulation in OIS in internal carotid artery (ICA) occlusion at 19, 24, and 49 seconds

Indocyanine green angiography can also help to determine the diagnosis of OIS. The test shows abnormalities of the choroidal circulation. As in fluorescein angiography, arm-to-choroid circulation time and intra-choroidal circulation time are prolonged. Choroidal hypoperfusion is mainly seen as areas of vascular filling defects in the posterior pole of the eye (13). Another characteristic

angiographic finding is a slow filling of the watershed zones (areas between zones supplied by two different vessels). This may be observed between the macula and the optic disc (14).

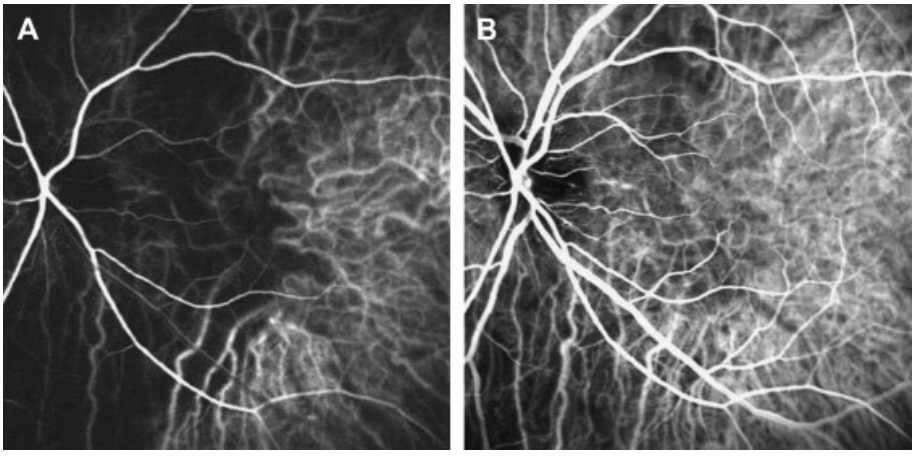

Figure 6. Indocyanine green angiography in ocular ischemic syndrome. (A) Choroidal hypofluorescence corresponding to the main posterior watershed zone between the medial and lateral posterior ciliary arteries. (B) Filling of the choroidal watershed zone is delayed, with some part of it remaining hyperfluorescent 10 seconds later Other ophthalmologic studies such as visual-evoked potentials (VEP) and electroretinography (ERG) are rarely used to establish the diagnosis of OIS.

7. Differential Diagnosis

The differential diagnosis of OIS should certainly include diabetic retinopathy, moderately advanced central retinal vein occlusion (CRVO) hyperviscosity syndromes, and autoimmune uveitis (especially when the presentation of anterior choroiditis predominate).

The main sign that helps to differentiate OIS from CRVO is the lack of tortuous retinal veins in OIS. Furthermore, retinal arterial pulsations are difficult to be shown in CRVO. In OIS, intraretinal hemorrhages are less numerous than in diabetic retinopathy. While cotton-wool spots, a typical finding in diabetic retinopathy, may be also present in OIS, the presence of hard exudates suggests changes in the fundus due to diabetes. Diabetic retinopathy may coexist with OIS; patients with marked asymmetry of retinopathy should be examined for possible carotid artery stenosis because approximately 20% of such patients have hemodynamically significant carotid artery stenosis (14).

Lack of retinal arterial stasis and choroidal filling defects detected by fluorescein angiography in diabetic retinopathy and CRVO is an important feature distinguishing these two conditions from OIS.

In hyperviscosity syndrome, fundus signs caused by serum or blood hyperviscosity include optic disk swelling, retinal capillary microaneurysms, cotton-wool spots, retinal hemorrhages, dilated retinal veins, and retinal venous occlusion. A basic workup should therefore include a complete blood cell count with differential, serum protein electrophoresis, and immunoelectrophoresis.

Table 2. Differential diagnosis of the ocular ischemic syndrome, diabetic retinopathy, and central retinal vein occlusion

Clinical Sing	**Ocular Ischemic Syndrome**	**Central Retinal Vein Occlusion**	**Diabetic Retinopaty**
Laterality	%80 unilateral	Usually unilateral	Bilateral
Age	50's to 80's	Variable	50's to 80's
Retinal Veins	Dilated but not tortuous	Dilated and tortuous	Dilated and beaded
Hemorrhages (location)	Dot and blot (mid-periphery) and in deeper retinal layers	Flame shaped (all quadrants) in the nerve fiber layer	Dot and blot (Posterior pole and mid-periphery)
Microaneurysms (Location)	Common (Mid-periphery)	Uncommon	Common (Posterior pole)
Other Microvascular abnormalities	Macular telangiectasias, retina AV communications, capillary dropout	Opto-ciliary shunts, capillary dropouts	Intraretinal microvascular abnormalities, capillary dropout
Hard exudates	Absent	Rare	Common
Optic Disc	Normal	Edema (common)	Diabetic papillopathy(rare)
Central retinal artery perfusion pressure	Decreased	Normal	Normal
Fluorescein Angiography			
A-V transit time	Prolonged	Prolonged	Usually normal
Retinal Vessel Staining	Arteries>Veins	Veins>Arteries	Usually absent
Macular edema	Rare	Common	Common
Choroidal filling	Delayed, patchy	Normal	Usually normal
Microaneurysm	Mid-peripheral	Usually at the posterior pole	Usually at the posterior pole

Clinical Sing	Ocular Ischemic Syndrome	Central Retinal Vein Occlusion	Diabetic Retinopaty
Optic disc hyperfluorescence	May be present	Usually present	Absent except papillopathy or new vessels at the disc or optic neuropathy

8. Treatment

OIS should not be treated only by an ophthalmologist, but also (and, in some cases above all) by a multidisciplinary team of other specialists, including vascular surgeons, cardiologists, neurologists, and primary care physicians. The treatment can be ocular (conservative, laser, and surgical) and systemic (conservative and surgical).

8.1. Ocular Treatment

The ocular treatment is directed toward control of anterior segment inflammation, retinal ischemia, increased IOP, and neovascular glaucoma. Topical therapy includes steroids to prevent anterior segment inflammation and cycloplegics to stabilize the blood-aqueous barrier and restrict iris movement in order to decrease the possibility of a spontaneous hyphema. Medical treatment of increased IOP consists of ocular antiglaucoma agents that reduce aqueous outflow (topical β-adrenergic blockers, or α-agonists that also increase uvea-scleral flow), along with topical and/or oral carbonic anhydrase inhibitors. Prostaglandins, pilocarpine, and other anticholinergic agents should be avoided because they may increase ocular inflammation.

When neovascular glaucoma develops, IOP control is usually refractory to medical therapy and surgery (trabeculectomy with antimetabolites or aqueous shunt implants), or diode laser cyclo-photocoagulation is often required. In patients with poor vision and ocular pain who are thought to have limited potential for visual recovery, cyclo-ablation is a suitable option. If the eye remains painful, retrobulbar injection of alcohol or chlorpromazine may provide relief. If these fail to ease pain in a blind eye, enucleation or evisceration should be considered. Panretinal photocoagulation may be effective in the same patients may prevent the development of neovascular glaucoma. In eyes with poor fundus visualization, 360° transconjunctival cryotherapy or transscleral diode laser retinopexy should be considered (15, 16).

Intravitreal anti-vascular endothelial growth factor (bevacizumab, ranibizumab, aflibercept) and triamcinolone have been used in the treatment of iris neovascularization and cystoid macular edema complicating OIS.

8.2. Systemic Medical treatment

OIS patients should be referred to a primary care physician as well as a neurologist for full medical and neurological assessment. It is necessary to treat related systemic diseases. In addition, lifestyle modifications such as cessation of smoking and weight reduction need to be recommended.

9. Surgical Treatment

9.1. Carotid Artery Endarterectomy

The North American Symptomatic Carotid Endarterectomy (NASCET) trial demonstrated the superiority of carotid endarterectomy (CEA) and acetylsalicylic acid therapy in preventing cerebrovascular disease compared with acetylsalicylic acid therapy alone for both symptomatic and asymptomatic carotid artery stenosis (17, 18). Based on these clinical trials, the American Academy of Neurology and the American Heart Association/American Stroke Association recommend CEA for symptomatic stenosis of 50–99% if the perioperative risk of stroke or death is <6%. In asymptomatic patients, CEA is recommended for stenosis of 60–99% if the perioperative risk of stroke or death is <3% (19).

CEA has been shown to be effective in reversing or preventing the progression of chronic ocular ischemia or in increasing ocular blood flow (20). Peak systolic velocity of flow in the ophthalmic artery rises after surgery (21) and ophthalmic artery flow is improved (22).

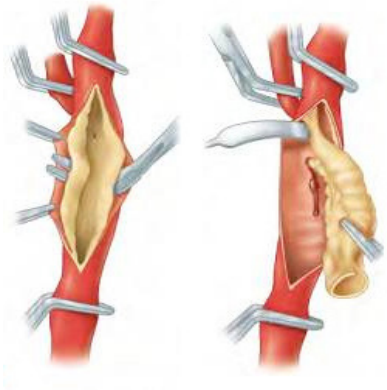

Figure 7. Removal of carotid plaque during endarterectomy

Therefore, carotid artery surgery can reduce ocular ischemia and improve retinopathy as well as reducing the risk of cerebrovascular disease. However, it is important to note that the presence of iris neovascularization shows a greater degree of ocular ischemia and damage, which results in limited visual recovery after CEA.

9.2.Carotid Artery Stenting

Endovascular carotid artery stenting (CAS) is an alternative treatment in patients who need CEA. CAS has been used for patients who are considered to be at high risk for complications after CEA including those with anatomic conditions rendering surgery technically difficult, such as previous neck radiation therapy or radical neck surgery, recurrent stenosis after CEA, contralateral recurrent laryngeal-nerve palsy, tracheostomy, and carotid stenosis above the C2 vertebral body (23). Medical conditions that increase the risk of surgery, such as unstable angina, recent myocardial infarction, multivessel coronary disease, congestive heart failure, are also indications for CAS. Carotid artery stenting has been shown to improve the ocular blood flow in patients with acute and chronic forms of OIS (24).

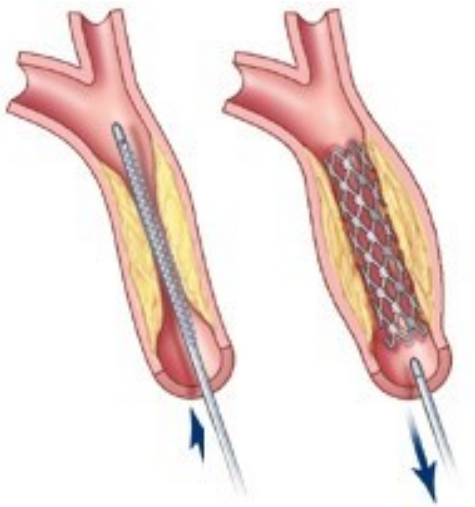

Figure 8. Carotid artery stenting

9.3.Extracranial–Intracranial (EC-IC) Arterial Bypass Surgery

EC-IC bypass surgery involves the surgical anastomosis of the superficial temporal artery (STA) with a branch of the middle cerebral artery (MCA). It is indicated when there is total occlusion of the ICA or the CCA or when

ICA stenosis is inaccessible (at or above the C2 vertebral body) to CEA (25). The aim is to increase cerebral blood flow and prevent the development of cerebral ischemia. CEA usually improves ocular hemodynamic parameters, but stabilization or improvement in vision seems to occur only when performed early before the development of neovascular glaucoma. Carotid endarterectomy is also beneficial in preventing cerebral infarctions.

10. Prognosis

Although many patients present with relatively good vision, it has been shown that up to 50% of patients who present with OIS will have a vision at count fingers (CF) or less within one year. Neovascularization of the iris (NVI) has been shown to be a bad prognostic indicator, with progression to CF or worse in 80% of those who presented with NVI or had NVI within three months of presentation. Treatment with panretinal photocoagulation (PRP) may have a positive effect with regards to the reduction of neovascularization in glaucoma (7).

In a review of 25 patients with OIS, 17 patients (68%) subsequently developed neovascular glaucoma (NVG). In this study, the development of NVG was significantly associated with IOP at the time of diagnosis, length of time between symptom onset and diagnosis, and extent of ipsilateral carotid artery stenosis. The development of NVG was also shown to be associated with multiple pre-existing conditions, including hypertension, diabetes, and dyslipidemia. However, there was no significant difference in follow-up best-corrected visual acuity (BCVA) between NVG and non-NVG groups, since both groups had a poor prognosis (26).

Ultimately, the overall mortality rate for patients with OIS is 40% at 5 years. The leading cause of death is cardiovascular disease, usually myocardial infarction (67%), followed by cerebral infarction (19%) (7). Physicians must adopt appropriate therapeutic options aiming at primary prevention of myocardial and cerebral infarction.

11. Conclusions

Although the ocular ischemic syndrome is a rare condition, its complications may cause irreversible vision loss. Considering that, signs of severe carotid artery stenosis may be first observed in the eye before they are manifested in the

cerebrovascular system. So, the ophthalmologist has a very important role in the proper diagnosis and referral for further investigations. Collaboration between the ophthalmologist, vascular surgeon, cardiologist, neurologist, and primary care physician is essential for the appropriate management of the OIS patient.

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CHAPTER 8

SICKLE CELL RETINOPATHY AND THALASSEMIA RETINOPATHY

Tuğba ÇETİNKAYA
Samsun Gazi Community Hospital, Department of Ophthalmology, Samsun
e-mail: mdtubacetinkaya@gmail.com
ORCID: 0000-0001-6085-8488

SICKLE CELL RETINOPATHY

1. Introduction

Sickle cell disease (SCD) was first named 'Herrick's Syndrome' in a case of severe anemia with peculiar elongated and sickle-shaped red blood corpuscules by James B Herrick, an American physician (1). Then in 1922, the term 'sickle cell anemia (SCA)' was first used by Verne R. Mason (2).

SCA is characterized by the production of abnormal hemoglobins that distort the red blood cells at low oxygen concentrations and cause microvascular occlusion results in retinal hypoxia, ischemia, infarction, detachment, and neovascularization (3).

2. Etiology

A population-based study demonstrated the risk of SCA is much higher in HbSC (45%) disease than in HbSS (14%) disease (4). In both genotypes, including HbSC and HbSS, the prevalence of SCA increase with age (5, 6). The risk factors for SCA are summarized in table 1 (6).

Table 1. The clinical and hematological risk factors for proliferative sickle retinopathy

In HbSS individuals	**In HbSC individuals**
Older age	Older age
Longer disease duration	Pulmonary involvement
Splenectomy	Deafness or tinnitus
Splenic sequestration	Splenic sequestration
Pain crisis	Pain crisis
Male sex	Male sex
Acute pyelonephritis	High mean cell volume in males
Lower fetal hemoglobin	Lower fetal hemoglobin
Lower weight	Lower platelet count
	Higher reticulocyte count
	No history of osteomyelitis

3. Epidemiology

Although SCD was mainly seen in tropical and subtropical regions caused by malaria, it has occurred all over the world with forced migration (7). It has been reported as 1-38% in some parts of Africa, 0-29% in Eastern Mediterranean, 7-30% in India, and globally 7% of the world population (8).

Sickle cell retinopathy (SCR) appears in 42% of sickle cell patients mainly in the second decade of life (9). The incidence of proliferative sickle retinopathy (PSR) has been found in about 10-20% in the fourth and fifth decades of life (10).

4. Pathophysiology

Sickle hemoglobin is characterized by a mutation on chromosome 11 that involves an amino acid shift valine for glutamate in the sixth position of the b-globin chain (11). The types of SCD are homozygous (HbSS), heterozygous or sickle cell trait (HbSA), hemoglobin C trait (HbSC), hemoglobin D trait (HbSD), and thalassemia genotype (HbS-thal). The most common type is HbSS. While the patients with HbSS are related with more severe and mortal clinical manifestations, HbSC disease is related with more severe retinal findings, including hemorrhages, exudates, angioid streaks, acute chorioretinal infarction, chorioretinitis, vitreous hemorrhage, and retinal vascular abnormalities (such as tortuous retinal veins, microaneurysms, central retinal artery occlusion, and retinal proliferation) (5, 6).

During the hypoxia, acidosis, oxidative stress, and infection, erythrocytes containing abnormal hemoglobin deform and change from the normal round disc shape to a sickle shape. These newly shaped erythrocytes are less flexible and more prone to be removed from the circulation (12). Consequently, anemia and vaso-occlusive events occur. The vaso-occlusion leads to retinal hypoxia, tissue ischemia, endothelial activation, inflammation, oxidative stress, and production of pro-angiogenic factors, such as vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF), which cause pathological blood vessel proliferation named as 'sea fans' in PSR (13). Secondary to the angiogenesis formation, the pigment epithelium-derived factor (PEDF) increases in viable vessels of sea fans (14).

In patients with SCD, plasma angiopoietins (Ang-1 and Ang-2), von Willebrand factor, intercellular adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM 1), and p-selectin molecules increase (15). Generally, endothelial cell adhesion molecules, inflammatory cytokines, and leukocytes have been shown to play a role in the pathogenesis of retinopathy (15).

5. Clinical Features

SCD causes many disorders, including neurological, ophthalmologic, cardiac, pulmonary, gastrointestinal, renal, splenic, and muscular abnormalities (16). Ophthalmologic disorders include orbital, conjunctival, uveal, papillary, and retinal changes (17). Retinal changes are characterized by non-proliferative and proliferative stages (9).

5.1. Non-Proliferative Sickle Retinopathy (nPSR)

5.1.1. Venous tortuosity

Vascular tortuosity is a nonspecific sign caused by blood hyperviscosity in several diseases (18). The prevalence has been shown as 50% in patients with HbSS disease (19).

5.1.2. Hemorrhage, iridescent bodies, black sunburst

The vaso-occlusion caused by sickled cells leads to ischemic necrosis of the vessel wall, which results in hemorrhage. The hemorrhage is round or oval-shaped, bright red, and one-quarter to one disc diameter. In days or weeks, the color of the hemorrhage turns orange-red and then salmon color on the

retinal pigment epithelium (RPE) and this lesion is named as salmon patch (4). Subsequently, the sickled hemoglobin degrades and the color of hemorrhage turns into bright yellow dots at the several levels of the sensory retina, called iridescent bodies (4). If the hemorrhage occurs in the outer retinal layers, the proliferation of RPE is stimulated, then dark, oval, or round, one-quarter to two-disc diameter shaped chorioretinal lesions occur. These lesions are known as black sunbursts (4). Due to the hemorrhages are temporary, observing them is difficult and the rate of their late signs, including iridescent bodies and black sunbursts is approximately 25-40% in HbSC individuals (18).

5.1.3. Macular Changes

The ischemic macular changes due to the occlusion of arteriolar circulation around the foveal avascular zone and branches are the reason for sickle-cell maculopathy. The incidence of this is approximately 10-40% of patients with SCD, mostly in HbSS genotype (20). The extensive foveal avascular zone means the perifoveal capillary loss and the nerve fiber layer infarcts. The angiographic findings and the visual symptoms usually show a mismatch. For example, some individuals demonstrate low visual acuity with a well-perfused macular capillary network and others show normal visual acuity with a very enlarged foveal avascular zone (21). In addition, microaneurysm-like dots and vascular loops, which occur mainly in the non-perfused areas and do not cause leaking of fluorescein can be seen in sickle-cell maculopathy (22).

5.1.4. Angioid streaks

The incidence of angioid streaks has been documented as 1-2% in the general population (10).

5.1.5. Other vascular changes

Central retinal artery occlusion may infrequently occur in patients with SCD (10).

5.1.6. Optic nerve sign

The vascular changes of the optic nerve, such as dark, small, and red dilated capillaries with an occlusion in fluorescein angiography are temporary and with normal visual acuity (23).

5.2. Proliferative Sickle Retinopathy (PSR)

PSR is a rare, but vision-threatening complication of SCD. The PSR is much more seen in HbSC genotype than the HbSS genotype with an incidence of approximately 10-20% of the cases (24). PSR generally begins asymptomatically in the first decade of life and can be symptomatic with ocular complications including vitreous hemorrhage, and retinal detachment in the second and third decades of life (25). 20-60% of the cases showed spontaneous regression of the neovascular complexes approximately two years after the development of proliferative lesions. The vaso-occlusive events usually occur permanently in the temporal peripheric retina because of the thin vascular diameter and the insufficient number of capillaries for collateral circulation in this region (26). If the remodeling process is efficient, the new vascular structures resemble normal vessels. If the remodeling process is insufficient, an irregular vascular pattern develops. PSR has been defined in five stages by Goldberg et al (26).

Stage I: Peripheral arteriolar occlusion that looks like a ‘silver wire’.

Stage II: Tortuous elongation and dilation in the arteriovenous communications in the boundary between the vascular and ischemic retinas

Stage III: Neovascularization that originates from the venous side of the circulation (Proliferative sickle cell retinopathy). Sea fan formation (Figure 1)

Stage IV: Vitreous hemorrhage

Stage V: Tractional retinoschisis or retinal detachment

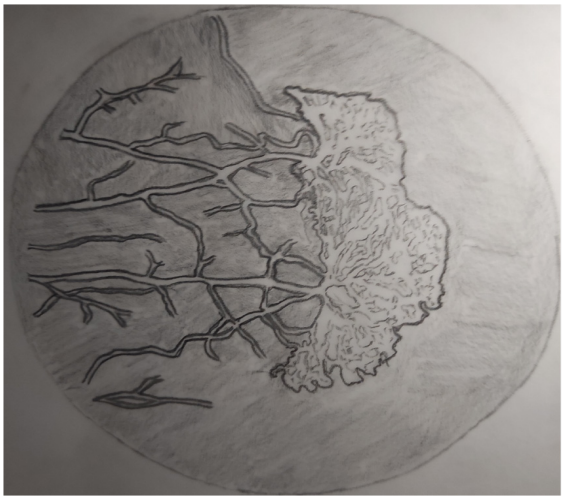

Figure 1. Sea fan formation originated from neovessels

The neovascular tuft is flat with thin walls and placed at the boundary between the non-vascularized and vascularized zones of the peripheral retina (Figure 2). This morphology is named 'Sea fan'. The sea fans are prone to form anastomoses into the vitreous and to develop a fibro-glial tissue membrane. The amount of perfusion of these lesions can be demonstrated by fluorescein angiography. The prevalence of stage III retinopathy is more common and more severe in the HbSC genotype (27).

Figure 2. Neovascularization that placed at the boundary between the non-vascularized and vascularized zones of the peripheral retina

Mostly, the sea fans are small and involve less than one clock hour of the peripheral retina (24). However, the involvement may sometimes be more common. The degree of spreading of sea fans defines the amount of vitreous hemorrhage.

The sea fans and fibrous bands may create abnormal retinal traction resulted in tractional retinoschisis and retinal detachment. The main causes of visual loss are vitreous hemorrhage and tractional retinal detachment. Besides, epiretinal membranes can cause significant visual morbidity (28).

The observational studies documented that HbSC genotype was associated with a greater degree of PSR than HbSS genotype (6) and progress with age (29). In SCD, the optic disc neovascularization is rare (19).

5.3. Other Ocular Abnormalities

The anterior segment manifestations in patients with SCD are conjunctival comma vessels, hyphema, cataracts, and iris atrophy (23). At the same time, glaucoma secondary to hyphema or occlusion of the trabecular meshwork by sickled cells was reported by Ballas et al (16, 17).

6. Diagnose

SCD can be diagnosed easily with advanced retinal imaging tools, including ultra-widefield fluorescein angiography (UWFA), spectral-domain optical coherence tomography (SD-OCT), and optical coherence tomography angiography (OCT-A) (30).

6.1. Ultra-widefield fluorescein angiography (UWFA)

UWFA demonstrates up to 200^0 of the retina in a single image different from conventional fluorescein angiography (FA) (31). FA imaging system allows to show the dynamic visualization of blood flow, the areas of dye leakage, pooling, and staining, and has been essential for detecting PSR for over 40 years (26). Although the data are limited in comparisons of UWFA and standard FA, UWFA is likely more sensitive in the detection of peripheral PSR.

6.2. Spectral domain optical coherence tomography and Optical coherence tomography angiography (SD-OCT and OCT-A)

SD-OCT and OCT-A are both non-invasive imaging techniques that use reflected light to produce detailed cross-sectional retinal images and to visualize the blood flow in retinal layers. SD-OCT can document the atrophy of ganglion cells, inner nuclear layer, and muller cells, retinal nerve fiber layer changes, and thinning or thickening of the retina due to ischemia and neovascularization (30) and OCT-A can show loss of macular vessel density (32).

OCT-A is probably more sensitive to identify the early stages of ischemia in the macula against traditional FA (33). However, FA remains the primary imaging tool for evaluating retinal perfusion in SCD. As a result, stage I and II retinopathy may be identified on UWFA, temporal macular thinning may be screened by SD-OCT, and vessel structure may be demonstrated by OCT-A.

7. Screening

Screening for SCR aims to detect patients who have a risk from lesions and if necessary aims to refer to an ophthalmologist. In the early stages, SCD is asymptomatic, so careful ophthalmologic monitoring should be performed. Although an ideal screening method has not been identified for detecting SCR yet, the measurement of visual acuity, intraocular pressure, dilated fundus examination, and evaluation of the anterior and posterior segment structures by using FA may have been done. Digital photography may be useful for saving information from early-stage to late stages.

8. Differential Diagnosis

Retinal diseases that cause macular ischemia or neovascularization, should be considered in the differential diagnosis of SCR. In SCR, the neovessels are placed at the boundary between the vascularized and non-vascularized retina, and there is no leakage from the perfused retina in FA as there is no inflammation. The diseases that should be considered in the differential diagnosis of SCR are summarized in Table 2 (34).

Table 2. The diseases that should be considered in the differential diagnosis of SCR

Causes of macular ischemia	**Causes of peripheral retinal neovascularization, vitreous hemorrhage, and retinal detachment**	**Inflammatory disease with possible ischemia**	**Other**
Diabetic retinopathy	Ischemic vascular disease	Sarcoidosis	Incontinentia pigmenti
Retinal vascular occlusion	Proliferative diabetic retinopathy	Retinal vasculitis	Autosomal dominant vitreoretinochoroidopathy
Embolic phenomena	Branch retinal vein occlusion	Intermediate uveitis	Old retinal detachment
Infectious diseases	Ocular ischemic Syndrome	Acute retinal necrosis	
	Retinopathy of prematurity		

	Eales' disease		
	Familial exudative vitreoretinopathy		
	Chronic myelogenous leukemia		
	Scleral buckle		
	Hyperviscosity syndrome		

9. Treatment

Treatment of SCD consists of diathermy, cryotherapy, argon or xenon photocoagulation, intravitreal anti-VEGF agents, surgical treatment, and disease-modifying drugs.

Patients in stages I and II do not need to be treated, due to spontaneous involution and neovascular tissue infarction in SCD. An observational study reported a 32% rate of spontaneous regression of PSR (5). The treatment is usually used to treat patients in stage III (sea fans) of PCR.

In 1956, Hannon experimented with the scleral surface diathermy of sea fans in PSR (35). Cryotherapy has been shown to be effective for sea fans, but some complications such as retinal tears and tractional retinal detachment have occurred (36). Goldberg et al. documented the efficiency of argon and xenon photocoagulation in stage III of PSR (37). Laser treatment aims to reduce the release of VEGF that causes neovessels.

The studies noted that the feeder vessel photocoagulation with scatter laser was thought to be safer and effective in reducing rates of visual loss and decreasing the incidence of vitreous haemorrhage (37), despite the complications of choroidal hemorrhage and ischemia, rupture of Bruch's membrane, retinal tears, and choroidal neovascularisation (38) Even so, it has been shown that new sea fans can develop in up to 34% of eyes (39).

Although there is no consensus, laser photocoagulation has been preferred in patients with bilateral PSR, large elevated sea fans, the rapid growth of neovascular tissue, accompanied by vitreous hemorrhage, or vision loss in the fellow eye because of PSR (40). While VEGF is associated with sea fan formation, intravitreal anti-VEGF treatment may be applied to manage the neovascular conditions, such as choroidal neovascular membranes (41).

Patients in stage IV and V, with vitreous hemorrhages, tractional or rhegmatogenous detachment, epiretinal membranes, and macular holes require surgical management, such as conventional cryo-buckle surgery and vitrectomy (42). Because of the ocular morbidity of surgical treatment, these individuals are followed for at least six months to allow spontaneous improvement. The most destructive complication of cryo-buckle surgery is anterior segment ischaemia (43), and cataract formation, iatrogenic retinal breaks, anterior segment ischemia, recurrent vitreous hemorrhage, and secondary glaucoma related to vitrectomy (23).

Studies have shown that disease-modifying drugs provide preventing the inflammation and vaso-occlusive complications through increasing fetal hemoglobin (Hydroxyurea, omega-3, erythropoietin, 2-deoxy-5-azacytidine), decreasing of HbS (transfusion and apheresis), erythrocyte hydration (clotrimazole, magnesium pidolate), anti-adhesive and anti-inflammatory effect (anti-adhesion antibodies, anti-integrin antibodies, anti-Willebrand factor, sulfasalazine, statins), antioxidant therapy (glutamine, deferiprone), antithrombotic effect (heparin, ticlopidine, warfarin), vasodilation (nitric oxide, arginine, flocor), and hematopoietic stem cell transplantation and gene therapy (44).

10. Prognosis

Despite SCD relates to significant morbidity, in developed countries more than 90% of children survive until adulthood (45). In contrast, the mortality of SCD before the age of 5 years has been reported as more than 50% in sub-Saharan Africa (46). In studies, the mean life expectancy has been documented as 42 years for men and 48 years for women (47).

11. Conclusion

The periodically ophthalmologic follow-up is essential for early treatment and preventing of SCR which causes severe morbidity in patients with anemia since childhood.

THALASSEMIA RETINOPATHY

1. Introduction

Thalassemia is one of the most common hereditary blood disorder characterized by various abnormalities in the globin genes, including alpha, beta, gamma, and delta (48). The most common type of thalassemia is beta-thalassemia.

2. Epidemiology

The thalassemias, autosomal recessive hemoglobinopathy, are the most common single-gene disorders in the world. Even though the developing countries have a high prevalence (49), population migration has lead to spreading it all over the world (50). In b-thalassemic individuals, the prevalence of ocular abnormalities has been reported as between 10.5 and 74% (51).

3. Pathophysiology

The classification of beta-thalassemia according to the severity of the disease is shown below (50):

1- Beta-thalassemia minor: The hemoglobin chain deficiency is not severe enough to cause malfunction.
2- Beta-thalassemia intermedia: The hemoglobin chain deficiency is severe enough to cause severe anemia, skeletal deformities, and spleen enlargement.
3- Beta-thalassemia major: The hemoglobin chain deficiency is significantly severe to cause life-threatening anemia and the patients need regular blood transfusions.

The abnormal globin chains cause ineffective erythropoiesis and reduced red blood cell survival lead to persistent anemia (50). Individuals with thalassemia major require a regular transfusion regimen to survive (50). On the other hand, patients with thalassemia intermedia have milder symptoms and do not need regular transfusions (52).

Iron is a vital element for cytochrome protein and metabolic processes in the body. Even though many enzymes require iron and it is essential for ATP production, excessive iron levels cause oxidative stress in many organs, including the heart, liver, spleen, glands, and eyes especially retinal pigment epithelium (RPE), and lead to death (53). Therefore, patients with thalassemia are required iron chelators, such as deferoxamine, deferasirox, and deferiprone, for removing excessive iron (53).

4. Clinical Features

Retinal disorders, such as RPE degeneration, RPE mottling, peripheral and central retinal thinning, venous tortuosity and engorgement, retinal hemorrhage,

retinal edema, cup to disc ratio enlargement, and macular scar, may be associated with the disease itself, iron accumulation or iron-chelating Therapy (48, 53). Older age and splenectomy have been documented as predisposing factors for retinal pathologies (54).

4.1. Thalassemia-associated retinal disorders (55)

4.1.1. Pseudoxanthoma (PXE) -like retinal abnormalities

Pseudoxanthoma is characterized by calcium mineralization of elastic fibers in blood vessels, skin, and Bruch's membrane under the retinal pigment epithelial cells (56).

4.1.1.1. Peau d'orange

Calcification of the Bruch's membrane occurs at the posterior pole of the retina, then spreads centrifugally, and is visualized like small confluent dark yellowish lesions at the level of RPE. This lesion was reported as the most frequent and initial finding in patients with thalassemia major (57).

4.1.1.2. Angioid Streaks

The structural changes such as irregular crack-like dehiscences in the Bruch's membrane associate with atrophic degeneration of the overlying RPE (58). These changes can occur in pseudoxanthoma elasticum, Paget's disease, Acromegaly, Ehler-Danlos Syndrome, diabetes mellitus, sickle cell anemia, and beta thalassemia (59).

Angioid streaks remain asymptomatic until expanding to the foveola or develop complications such as macular choroidal neovascularization (CNV) and traumatic Bruch's membrane rupture (54, 55, 59).

4.1.1.3. Optic nerve head drusen

The prevalence of drusen deposition in the optic nerve head increases in patients with PXE. Studies showed that patients with thalassemia intermedia have a higher risk of developing PXE-like retinal abnormalities than thalassemia major (54).

4.1.2. Non-PXE-like retinal abnormalities

4.1.2.1. Retinal venous tortuosity

Retinal venous tortuosity occurs as a result of tissue hypoxia due to mild or chronic anemia in patients with thalassemia major (60). Some studies have

demonstrated that the levels of lower hematocrit and hemoglobin, increased ferritin and Aspartate Aminotransferase (AST) are related to vascular tortuosity (61). Additionally, splenectomized individuals are prone to thrombotic events resulted from retinal vascular tortuosity (54, 58).

4.2. Iron-associated retinopathy

Despite multiple transfusions can decrease mortality, the accumulation of iron leads to multiple organ failure (62). Iron is an important element for many metabolic processes, however, systemic iron overload causes oxidative damage to the retina through the ferrous iron (Fe^{++}) increase (63). The regulatory mechanisms control the import and export of iron from entering the retina through the intercellular tight junctions of the neuroretinal vasculature and RPE (63).

Some researchers have claimed that iron-associated oxidative stress causes elastic fiber damage in thalassemic individuals (54). A postmortem study has demonstrated the accumulation of iron in the non-pigmented ciliary epithelium, ciliary muscle, choroidal stromal cells, sclera, peripheral retina, photoreceptor layer, and RPE (64).

In the literature, iron-associated retinal pathologies documented as RPE degeneration, RPE mottling, angioid streaks, retinal vessel tortuosity, retinal hemorrhages, retinal edema, pseudo-papillitis, and macular scarring (53, 63). Patients may present with night-blindness, blurred vision, decreased visual acuity, color vision impairment, photopsia, and metamorphopsias.

4.3. Iron chelation-associated retinopathy

Iron chelation therapy (ICT) has been required for preventing iron toxicity in patients treated with regular blood transfusions for hematologic conditions such as thalassemia (65). Studies demonstrated that intravenous DFO-related retinopathy depends on the dosage of the drug (65), improves after discontinuing the drug (65, 66), and has a greater risk of retinal toxicity compared to oral chelators (66). RPE opacification, foveo-macular, macular, paramacular, papillary or peripapillary and peripheral degeneration, RPE pigment changes, optic disc edema, and optic atrophy may be seen in patients treated with DFO (67).

The chelation-induced retinopathy presents with night-blindness, blurred vision, decreased visual acuity, color vision impairment, or cataract (51, 55).

Oral iron chelators, including Deferiprone and Deferasirox, are effective systemic iron chelators, too (68). Additionally, Deferiprone (DFP) can cross the blood-retinal-barrier and chelate intracellular iron without retinal toxicity (69), however, there is no evidence about retinal penetration of Deferasirox (65).

4.5. Other Ocular Disorders

4.5.1. Refractive error and ocular biometric components

Skeletal abnormalities, including craniofacial anomalies and long bone deformities can be observed in thalassemic individuals due to the expansion of bone marrow for preventing anemia. The craniofacial changes may cause abnormal orbital growth and result in a shorter axial length and higher prevalence of hyperopia (70).

4.5.2. Dry eye

Increased iron levels in glands and decreased vitamin E levels in thalassemic patients cause cytotoxic effects, and endocrine and exocrine dysfunction which affects the tear film production (71).

4.5.3. Cataract

The free radical damage due to iron overload has been considered as a cause of cataract formation in b-thalassemic patients (72). Besides that, some studies demonstrated cataract formation in patients treated with iron-chelators, too. The reported subtypes of crystalline lens opacities are posterior subcapsular haze, posterior cortical haze, streaks in the posterior capsule, and peripheral punctate lens opacity at the cortex (51).

5. Diagnosis

Dilated fundus examination, fluorescein angiography (FA), indocyanine green angiography (IGA), optical coherence tomography (OCT), fundus autofluorescence (FAF), and electroretinogram (ERG) are used to evaluate thalassemic patients (73).

Dilated fundus examination and FA is useful to diagnose patients with angioid streaks and to treat when choroidal neovascularization develops. In the earliest stages of FA, a patchy pattern due to blocked fluorescence is seen, then late staining because of loss of outer retinal atrophy and RPE transparency

occurs. Besides that, mottled fluorescence in the early phase, mottled macular hyperfluorescence, or optic disc hyperfluorescence may be demonstrated by angiography. The late hyperfluorescence indicates active retinopathy.

Studies have documented that contrast sensitivity may reduce in patients with b-thalassemia (74). Electrophysiologic tests, including ERG and EOG can show more widespread retinal dysfunction than funduscopy alone. Prolonged rod and cone implicit times or reduced scotopic and photopic a and b wave amplitudes may be observed in ERG. In thalassemic patients, visual evoked potential (VEP) responses are influenced by chronic hypoxia, intraocular iron overload, bone marrow expansion, and DFO toxicity (75).

OCT can show an accumulation of multiple hyperreflective deposits primarily in the choroid, RPE, and inner segment and outer segment junction, a significant decrease in foveal thickness, and a thinner RNFL in all quadrants of b-thalassemic patients (76). FAF is a helpful, fast, and non-invasive tool for detecting early changes of retinal toxicity (77) and monitoring the progressive RPE damage. RPE mottling can be identified as hyper-and hypo-autofluorescence on FAF imaging.

Microperimetry is an advanced visual field technology that shows decreased macular sensitivity and attenuation in the inferotemporal macula in patients with iron-chelator-induced retinopathy (78). The most common visual field defect is general depression because of the toxic effects of chelating agents in these patients (79). The contrast sensitivity tests, electrodiagnostic tests, such as ERG and electrooculography (EOG), and FAF may be used for early diagnosis in b-thalassemic patients.

6. Treatment

The basic treatment of b-thalassemia is regular blood transfusion and iron chelation therapy for preventing iron toxicity. Ophthalmic abnormalities in b-thalassemic patients might be originated from the disease itself, iron accumulation, and toxicity of chelating agents (80). Regular ophthalmic evaluations should be performed in the second decade of life, and if choroidal neovascularisation occurs, the treatment should be started for preventing retinal hemorrhages and vision loss.

7. Prognosis

The prognosis of thalassemia depends on adequate blood transfusion and other therapeutic management. Destroying the blood-retinal barrier facilitates the

development of retinopathy. Despite RPE mottling does not improve with drug discontinuation, iron-chelators should be discontinued in symptomatic patients without life-threatening iron overload. Early diagnosis and long-term follow-up of retinal findings, including PXE-like and related to chelator drugs are essential in the decision to stop or switch the therapy to prevent ocular complications.

8. Conclusion

b-thalassemia may cause various ocular abnormalities due to anemia, regular blood transfusion, iron overload, and chelation therapy. Yearly follow-up ocular examinations are suggested in patients on iron chelators. However, more frequent examinations may be required in patients on high-dose intravenous DFO treatment.

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CHAPTER 9

RETINAL VASCULITIS

Ibrahim Cagri Turker
University of Health Sciences, Sisli Hamidiye Etfal Training and Research Hospital, Department of Ophthalmology, Istanbul
e-mail: drcagriturker@hotmail.com
ORCID: 0000-0002-1625-3382

1. Introduction

Retinal vasculitis is a pathology characterized by inflammation of the retinal vessels, secondary to local or systemic inflammatory changes. They can often occur together with systemic inflammatory diseases, infections, autoimmune diseases, or malignancies. The underlying etiologic factor should be investigated and evaluated using a multidisciplinary approach to make the right diagnosis and provide treatment.

Rheumatologists and ophthalmologists may use different terms for vasculitis. Rheumatologists often detect vasculitis histologically, but ophthalmologists may make the diagnosis by combining multimodality ocular imaging with systemic studies. Retinal vasculitis is a broad term that encompasses perivascular sheathing, vascular leakage or occlusion, cotton wool spots, retinal hemorrhages, and retinal ischemic alterations. Arteritis/arteriolitis in arteries refers to artery involvement, whereas phlebitis refers to venous involvement.

Retinal vasculitis can be symptomatic or asymptomatic. When vascular changes are localized in the peripheral retina without vitreous involvement, the patient may be asymptomatic. In contrast, patients with severe vasculitis, intense vitreous inflammation, or macular involvement may present with visual loss (1).

Retinal vasculitis can be considered primary or secondary in two groups. In the primary form, the target of the inflammatory process is directly the retinal vessels, whereas, in the secondary form, retinal vascular involvement may be seen secondary to localized or systemic inflammation of the eye.

Retinal vasculitis can be divided into three main groups: arteriole-predominant, venule- predominant, or combined involvement of both arteries and veins (2,3). While diseases such as systemic lupus erythematosus, syphilis, idiopathic retinal vasculitis, aneurysm and neuro-retinitis (IRVAN), polyarteritis nodosa, acute retinal necrosis, Churg Strauss Syndrome more often involve the arteries, intermediate uveitis, sarcoidosis, multiple sclerosis, Eales', HIV are presented mostly with venous involvement. Toxoplasma, Wegener's, Chron's, Frosted Branch Angiitis are diseases that can affect combined arteries and veins (Table 1). There are two types of retinal vasculitis: occlusive and non-occlusive. Neovascularization can be seen in the occlusive form, causing retinal ischemia and intraocular hemorrhage.

Primary Retinal Arteritis	**Primary Retinal Phlebitis**	**Arteritis And Phlebitis**
Systemic lupus eritematosous	Multple sclerosis	Frosted branch angiitis
IRVAN	Behçet's disease	Tuberculosis
Viral Retinitis(HSV/VZV)	HİV associated vasculitis	Crohn's disease
Churg-Strauss syndome	Sarcoidosis	Relapsing polichondiritis
Syphilisis	Eales disease	
Poliarteritis nodosa		
Toxoplasmosis		
Susac syndrome		

Table 1. Systemic and local diseases associated with retinal vasculitis

1.1. Pathophysiology

Although the pathophysiologic mechanism in retinal vasculitis is not clearly understood, destruction of the blood-retinal barrier resulting from intense vascular inflammation is the most valid theory. Retinal vasculitis is often the local form of underlying systemic pathology. Therefore, an increase in local epithelioid cells may be observed in granulomatous diseases such as sarcoidosis, and an increase in CD4+ T cells may be observed in eyes with intermediate uveitis and retinal vasculitis secondary to lymphoma. Increased expression of cell adhesion molecules like serum interferon-β, E-selectin, and s-intracellular adhesion molecules was noted (4). Toxins or heat shock proteins (HSP) are

known to cause vascular damage in infectious retinal vasculitis rather than endothelial damage (5). Vascular damage, which occurs at the end of all these inflammatory processes forms the basis for pathologies secondary to vascular occlusion.

1.2. Findings

Perivascular sheathing: The presence of yellow-white exudates around the affected vessel is referred to as perivascular sheathing. The form occurring in sarcoidosis is called 'candle wax drippings.

Cotton wool spots: These are lesions secondary to ischemic infarcts in the retinal nerve fiber layer. They are commonly seen in Churg-Strauss, polyarteritis nodosa, and systemic lupus erythematosus. The dense cotton wool spot may indicate increased uveitic inflammation and severe ischemia.

Intraretinal infiltrates: They may be seen in Behçet's disease and infectious uveitis. Retinal atrophy and retinal tears may develop in these areas.

Retinal Necrosis: It is often seen secondary to infections. Although it is seen in viruses such as herpes, cytomegalovirus, varicella, it is also common in toxoplasma retinitis. Segmental retinal periarteritis secondary to retinal necrosis occurring in toxoplasma is termed 'Kyrieleis arteriolitis.'

Frosted Branch Angiitis: A descriptive term for retinal vasculitis secondary to lymphocytic infiltration in the perivascular space.

1.3. Diagnosis

Multimodal imaging is crucial for diagnosis. Fundus fluorescein angiography (FFA) is an important imaging technique in diagnosing and following retinal vasculitis. It can be used to visualize the leakage in inflamed vessels, in the follow-up of ischemic areas, the diagnosis and follow-up of macular edema. Diffuse, segmental, or focal areas of leakage may also be seen in FFA secondary to inflammation in the retinal vasculature due to the destruction of the retinal artery. While arteriolar leakage is more common in systemic vasculitis and infections, venous involvement is more common in retinal vasculitis. Although optic disc neovascularization secondary to retinal ischemia and optic disc involvement secondary to retinal vasculitis may also show hyperfluorescence in the optic disc, differentiation between inflammation and neovascularization can be made with FFA. Choroidal flow patterns, choroidal neovascularization, and retino-choroidal anastomoses can be assessed with indocyanine green angiography (ICG). Optical

coherence tomography (OCT) can be used to diagnose and follow-up macular edema, epiretinal membranes, and choroidal neovascular membranes. The use of optical coherence tomography angiography (OCT-A) in the diagnosis and monitoring of silent choroidal membranes is beneficial.

1.4. Laboratory Tests

It is critical to request accurate and supportive testing for the preliminary diagnosis in the differential diagnosis of infectious, non-infectious, and inflammatory retinitis. Systemic inflammatory markers, including erythrocyte sedimentation rate and C-reactive protein, are the most frequently used laboratory tests.

Laboratory tests to support the preliminary clinical diagnosis are essential. Anti-neutrophil cytoplasmic antibodies, anti-DNA antibodies, anti-nuclear antibodies, and rheumatoid factors should be checked in autoimmune retinitis. HLA-A29 can be helpful in the diagnosis of disorders such as birdshot chorioretinitis and systemic lupus erythematosus. The tuberculin skin test may investigate tuberculosis in retinitis secondary to granulomatous infections. A chest x-ray, computed tomography, and whole-body ultrasound are required to support the diagnosis. When the viral or parasitic disease is considered, specific antigen-antibody tests are useful.

1.5. Treatment

In non-infectious retinal vasculitis, systemic or local corticosteroids, as well as immunomodulatory therapies may be performed. Local treatment may be by intravitreal or periocular injections. The ocular manifestations, etiology, and systemic comorbidities should all be considered when selecting immunosuppressive agents. Long-term immunosuppression can be achieved with cyclosporine, azathioprine, cyclophosphamide, mycophenolate mofetil, and biologic agents (infliximab, adalimumab).

Infectious retinal vasculitis should be treated with antimicrobials that are appropriate for etiology. Treatment can be chosen between local, systemic, or combined methods of treatment.

2. Diseases Causing Primary Retinal Arteritis

2.1. Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is a systemic, autoimmune disease and is seen nine times more frequently in women than in men, with a prevalence

of 20-150/100,000 (6). Immune complexes are occurring in SLE cause microangiopathy and micro embolism. SLE can affect the orbit, adnexes, and optic nerve. The most common pathology is keratoconjunctivitis sicca, and the most vision-threatening sequelae occurs secondary to retinal vascular occlusion.

The earliest findings are intraretinal hemorrhages, hard exudates, microaneurysms, and cotton wool spots due to the microvascular damage. The histopathologic examination may reveal perivascular monocellular infiltrates, fibrinoid necrosis, immunoglobulin, and complement deposition. Rarely, the disease may have a worse prognosis due to the involvement of the veins and arterioles (7). Purtscher-like retinopathy due to severe vascular occlusion may also occur.

Specifically, ICG is valuable for evaluating choroidal vascular inflammation, while FFA is helpful in identifying optic nerve inflammation, retinal ischemia, and macular edema. FFA is very helpful in imaging areas of vascular leakage, retinal capillary dilatations, microaneurysms, optic disc edema, and choroidal nonperfusion. In ICG, focal hypofluorescence may occur in the early phase due to perfusion delay and diffuse hyperfluorescence in the late phase. In the middle phase of angiography, punctate staining may be seen in the choroidal stroma due to the involvement of large choroidal vessels. Due to choroidal vascular involvement, OCT may show a decrease in choroidal thickness and subretinal fluid.

Controlling systemic inflammation and reducing ocular complications should be the goals of ocular involvement in SLE. When systemic immunosuppressants are used for systemic diseases, laser photocoagulation is performed on ocular major capillary nonperfusion areas.

1.2. *Syphilis*

Syphilis is an infectious disease caused by the spirochete Treponema pallidum. Ocular manifestations may occur at any stage of the disease with a variety of clinical presentations. Syphilis may affect almost all ocular structures, but posterior uveitis and panuveitis are the most common presentations.

While ocular involvement is not usually seen in the primary form, conjunctivitis, episcleritis, scleritis, keratitis, and anterior uveitis may occur in secondary syphilis (8). Involvement of the posterior segment is seen in secondary syphilis and vitritis, necrotizing retinitis, chorioretinitis, retinal vasculitis, and optic neuritis may be commonly seen in this form. Chorioretinitis is the

most common manifestation of syphilis and is typically multifocal, often with superficial serous retinal detachment and prominent vitritis. Acute syphilitic posterior placoid chorioretinitis is a rare presentation of ocular syphilis which has been described in patients with secondary syphilis.

Typically, in retinal vasculitis, the arteries are more involved. FFA exhibits early hypofluorescence followed by late hyperfluorescence (Figure 1). OCT findings include disruption of the border between the inner and outer segments, nodular thickening of the RPE, subretinal fluid, and punctate hyperreflectivity of the choroid.

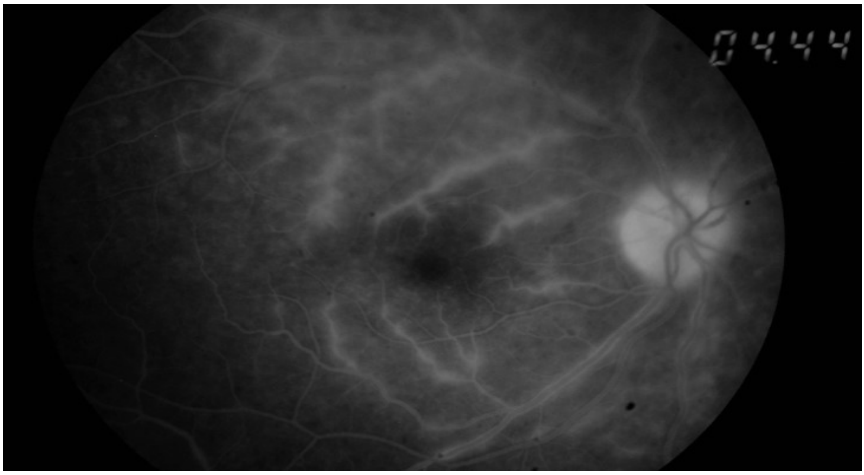

Figure 1. FFA of the right eye showing a hot disc with perivascular leakage suggestive of active vasculitis in syphilitic vasculitis

Antibiotics of the penicillin group are used in the treatment of syphilis. Primary syphilis is treated with a single intramuscular dose of 2.4 MU benzathine penicillin, secondary and tertiary syphilis with a single dose of 2.4 MU benzathine penicillin per week for three weeks. In neurosyphilis, treatment is given for 10-14 days, 12-24 MU per day (9).

1.3. *Toxoplasmosis*

Ocular toxoplasmosis is a disease that causes focal necrotizing retinitis with recurrences. It accounts for about 60% of posterior uveitis and is often bilateral. It can be seen in congenital or acquired form. Toxoplasma infection is asymptomatic in immunocompetent patients and it is usually self-limited. The most common symptoms are floaters and reduced vision. Visual impairment may

be secondary to a macular lesion or optic nerve involvement. A hypersensitive reaction in the vascular structure, vitreous, and choroid develops when the parasite infiltrates the ocular tissues. The diagnosis is made clinically with the appearance of the characteristic lesions on examination.

Ocular toxoplasmosis usually presents with focal necrotizing retinitis and is frequently associated with vitritis and granulomatous or non-granulomatous anterior uveitis. Due to intense vitritis, active foci typically look like headlights in a fog. Lesions may also be seen as active retinitis next to an inactive scar. In active retinochoroiditis, vitritis, retinal vasculitis (periphlebitis, periarteritis), macular edema, papilla edema can be seen. Ocular toxoplasmosis may also present with retrobulbar neuritis, pars planitis, retinal arterial or venous occlusion.

Although venules are commonly involved in ocular toxoplasmosis, nodular arteritis may occur in addition to the active lesion, which is called kyrieleis arteriolitis in the form of diffuse or segmental vasculitis. Clinical findings are commonly used to make the diagnosis. Since Toxoplasma antibody positivity is common in the population, serologic tests are supportive for diagnosis.

Complications such as choroidal neovascularization, cystoid macular edema, and vasculitis are diagnosed using FFA and ICG. Cystoid macular edema, macular hole, epiretinal membrane, and optic disc involvement can be evaluated with OCT. In the treatment of ocular toxoplasmosis, systemic antibiotics are used. The most commonly used agents are pyrimethamine, sulfadiazine, clindamycin, and trimethoprim-sulfamethoxazole (10).

1.4. Viral Retinitis

Viruses such as herpes simplex type 1/2, varicella-zoster, cytomegalovirus (CMV), Epstein-Barr virus (EBV) may play a role in the etiology of retinitis.

2.4.1. Acute Retinal Necrosis

Acute Retinal Necrosis (ARN) is a viral retinitis that can occur in immunosuppressed individuals as well as in individuals with normal immune systems. While granulomatous or non-granulomatous keratic precipitates are seen in the anterior segment involvement, findings of vitreous inflammation, necrotic foci in the retina, vascular sheathing, retinal hemorrhages along with the vessels, optic neuropathy may be seen in the posterior segment. Most cases

are unilateral at the time of presentation. Foci of necrotizing full-thickness retinitis start from the periphery and progress toward the posterior pole.

Complications such as optic disc leakage and occlusive vasculitis, cystoid macular edema, and neovascularization may also be seen in FFA. In areas of retinitis, ICG may show choroidal hypoperfusion, subclinical vasculitis, and segmental vascular ischemia. Fundus autofluorescence (FAF) can be helpful in monitoring and detecting early reactivation. Hyperreflective inner retinal layers in areas corresponding to yellow-white lesions, diffuse areas of full-thickness hyperreflective retinal necrosis, choroidal thickening, and disorganized retinal structure are all possible OCT findings in acute lesions (11).

The use of systemic or intravitreal antiviral agents reduces the duration of the active phase of ARN and may reduce areas of retinal necrosis. Intravenous acyclovir minimizes the involvement of other eyes. Treatment of ARN involves intravenous (IV) acyclovir induction followed by 6- to 12-week oral aciclovir therapy. Intravitreal antiviral injections support systemic treatment. For vision-threatening lesions, severe disease, and disease that does not respond to or cannot be treated with systemic treatment, intravitreal ganciclovir or foscarnet may be added. Corticosteroids are commonly used in the treatment of ocular inflammation under antiviral treatment.

Prophylactic laser photocoagulation of areas surrounding the atrophic retina may be required to prevent retinal detachment at ARN. However, even after laser treatment, retinal detachment might develop. Iatrogenic tears may occur if laser applications are performed during the acute period.

2.4.2. Cytomegalovirus Retinitis

Cytomegalovirus (CMV) is the pathogen that commonly causes infections in people with organ transplants, leukemia, lymphoma, intensive immunosuppressive therapy, or immunocompromised individuals. CMV retinitis has become more common in recent years as a result of intravitreal steroid injections. CMV infection spreads hematogenous to the eye. Retinitis develops in the retina's periphery and spreads to the posterior pole centrifugally. Patients may be asymptomatic in the early phase because involvement begins in the retinal periphery.

CMV causes necrosis in the retina, which affects all layers. There are three different clinical manifestations of CMV retinitis: The classic/fulminant form of

hemorrhagic necrotizing retinitis is localized along the major vascular arcs in the posterior retina. In the granular form, inactive granular, slowly progressive retinitis with minimal retinal edema and vascular sheathing in the peripheral retina is often seen (Figure 2). There is a clinical picture resembling Frosted Branch Angiitis in the perivascular form (12).

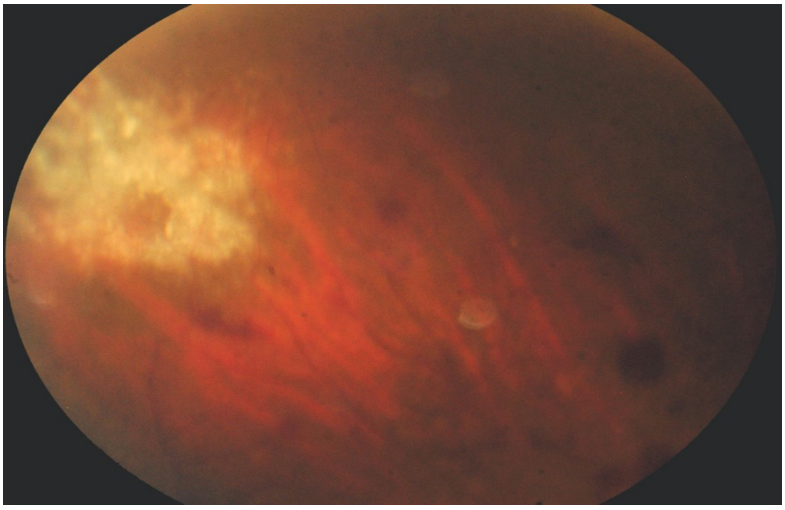

Figure 2. CMV retinitis lesion with retinal granular necrotic appearance

Blockage in hemorrhage areas and vascular leakage in active areas can be observed in FFA. Deterioration of the inner retinal layers, destruction of the outer limiting membrane, and abnormalities of the ellipsoid zone may be observed in active retinitis lesions represented with OCT. In CMV retinitis, medications including ganciclovir, valganciclovir, cidofovir, and foscarnet are used. However, long-term treatment with these drugs may cause high toxicity, so their duration of use should be limited.

1.5. Idiopathic Retinitis, Vasculitis, Aneurysms, and Neuro-retinitis (IRVAN)

Idiopathic retinitis, vasculitis, aneurysms, and neuro-retinitis (IRVAN) are rare pathologies with unknown etiology. IRVAN syndrome is a retinal vasculitic disease characterized by idiopathic retinal vasculitis, aneurysms, and neuro-retinitis. Young women are most affected, and most cases are not related to a systemic disorder.

Prominent multiple aneurysms are typical located in the branch points of the arteries and may be fusiform or Y-shaped. Arterial aneurysms are clinically

multiple and sequentially localized. The vasodilatation may be a consequence of the inflammatory process in the walls of the retinal arteries. In addition to aneurysmal dilatations, exudative retinopathy, optic disc involvement, and areas of peripheral capillary nonperfusion are seen. With peripheral capillary drop out and ischemia, disc neovascularization can be observed. Since arterial involvement may be associated with multiple aneurysmal dilatations of the retinal and optic nerve head arterioles, pathologies such as Behçet's disease, sarcoidosis, multiple sclerosis, polyarteritis nodosa, and systemic lupus erythematosus should be considered in the differential diagnosis (13).

The clinical characteristics of IRVAN are divided into two categories: major and minor criteria. The three major criteria are retinal vasculitis, aneurysmal enlargement of arterial bifurcations, and neuroretinitis, while the minor criteria are peripheral capillary non-perfusion, retinal neovascularization, and macular exudation (14).

Exudative retinopathy and diffuse peripheral retinal nonperfusion areas leading to neovascularization are the main pathologies affecting vision. Hyperfluorescence secondary to aneurysmal dilatations in the vessel walls, optic disc leakage, and capillary non-perfusion areas are seen in the late phases of FFA. Dilated and leaking large choroidal vessels are seen in the early-mid phase of ICG due to damaged vascular structures. In the mid to late phase of the ICG, areas of hyperfluorescent are seen. OCT is important to detect findings such as macular edema, vitreomacular traction, and epiretinal membrane causing visual impairment and to assess treatment response. Treatment options include retinal laser photocoagulation, intravitreal anti-VEGFs, intravitreal or periocular steroids, cryotherapy, and vitrectomy for ischemic areas.

1.6. Churg-Strauss Syndrome

The Churg-Strauss syndrome is a systemic pathology characterized by asthma, hypereosinophilia, and necrotizing vasculitis affecting small and medium-sized vessels with granulomatous inflammation.

The Churg-Strauss syndrome is a giant cell necrotizing vasculitis affecting mainly small arteries and veins and progresses with extravascular and interstitial granulomas, eosinophilic infiltrates in the interstitium, alveoli, and vascular structures. The most common organs involved are the lungs, heart, peripheral nervous system, gastrointestinal tract, and skin. As a result of lung involvement, the disease frequently manifests with asthma-like symptoms.

Ocular involvement may occur as idiopathic orbital inflammation and with complications secondary to ischemic vasculitis. In the anterior segment, peripheral ulcerative keratitis, corneal ulceration due to corneal involvement, and corneal melting might be observed. In the retina, retinal hemorrhages, cotton wool spots secondary to ischemia, macular edema, papilledema, and ischemic optic neuropathy can be seen. Ischemia in the choroidal vessels causes Elschnig spots in the posterior pole.

Large areas of macular nonperfusion, obstruction in areas of retinal hemorrhage, leakage in arteries and veins, and staining of the optic disc can all be detected in FFA. Treatment options include systemic corticosteroids and immunomodulatory agents. Photocoagulation therapy can be applied to ischemic areas in the retina.

1.7. Susac Syndrome

Susac syndrome is an occlusive arteriolar microangiopathy that causes ischemia in the retina, cochlea, and brain and commonly occurs in young women. Encephalopathy due to the involvement of the precapillary arterioles is often the initial finding.

Retinal vasculitis, occlusion of retinal arterial branches, and optic atrophy may be observed with ocular involvement. Refractile or non-refractile glass plaques in retinal arterioles are an important finding in the diagnosis. These plaques may be confused with emboli. Retinal arterial branch occlusions are usually found bilaterally in several areas (15).

While retinal artery branch occlusions are detected in the active period of FFA, sequelae can be detected in the retina in the chronic period. In the early period, OCT examination shows thickening and increased reflectivity in the inner retinal layers, while in the late period, atrophy is seen in the retinal layers. Although immunosuppressive and immunomodulatory agents are used in the active period of treatment, sequelae in the retina are treated in the chronic period.

3. Diseases Causing Primary Retinal Phlebitis

1.1. Ocular Sarcoidosis

Sarcoidosis is a granulomatous multisystem disease that presents with hilar lymphadenomegaly, lung parenchymal involvement, ocular and cutaneous involvement and is more common in young adults. Ocular sarcoidosis can

involve any part of ocular tissues, adnexa, and orbit. Granulomatous uveitis is the most common involvement.

Keratic precipitates in the corneal endothelium, intense anterior chamber reactions, iris nodules, posterior synechiae, cataract, and band keratopathy are seen with anterior segment involvement, while vitritis and periphlebitis are the most common findings with posterior segment involvement. Intermediate uveitis is also a common presentation of ocular sarcoidosis. Patients may complain of floaters and blurred vision. Vitreous opacities and cystoid macular edema (CME) are the main causes of impaired vision.

In sarcoidosis, vitreous inflammation is frequently characterized by inferiorly located white round snowball opacities. Perivenous and rarely periarterial sheathing is frequently seen in vascular involvement, while venous occlusion is one of the most important complications. Choroidal granulomas similar to Dalen-Fuchs nodules with serous retinal detachments are seen in choroidal involvement. Perivascular exudates have been described as "candle-wax dripping" in severe forms with diffuse whitish-yellow perivascular retinal exudates along the retinal vessels.

FFA may show blockage in sarcoidosis due to granulomas in the early phase and leakage in the late phase. In patients with chorioretinal lesions, FAF can be used to detect inflammatory changes and monitor treatment response. OCT can be used to assess and monitor macular edema. The transition between the inner and outer photoreceptor segments, the integrity of the outer limiting membrane, and anatomic changes after treatment of macular edema can be detected in OCT.

Treatment indications are pulmonary involvement and uveitis. The use of topical, periocular, intravitreal, or systemic steroids depend on the severity of the ocular involvement. Pulse steroid therapy may be used for severe involvement. Cyclosporine A, chlorambucil, or methotrexate can be used to reduce the side effects of corticosteroids in patients who require long-term treatment. Cyclosporine and tacrolimus (T cell inhibitors) have been shown to be effective in controlling uveitis-induced inflammation. Steroid-resistant patients often benefit from biological agents. Interferons are used to treat macular edema associated with uveitis. The treatment aims to control inflammation and prevent complications and photoreceptor damage in cystoid macular edema. Laser photocoagulation is required when peripheral ischemia or neovascularization is present despite systemic immunosuppressive therapy (16).

1.2. Multiple Sclerosis

Multiple sclerosis (MS) is a chronic inflammatory and demyelinating central nervous system illness. MS can cause ocular pathologies including optic disc involvement or uveal inflammation. While intermediate and posterior uveitides are commonly seen, anterior uveitis and panuveitis are less common. Intermediate uveitis is the most prevalent form of uveitis in MS patients, characterized by vitreous condensation, inflammation, and snowball appearance in the pars plana.

Inflammatory cells are mostly found in the vitreous in this type of uveitis. Retinal venules are the source of these inflammatory cells. Therefore, intermediate uveitis often presents with retinal periphlebitis, which is seen clinically as a retinal vascular sheathing or vascular leakage in FFA. In the active phase of MS, periphlebitis is more prevalent, and leakage due to perivenous inflammation can be observed in FFA. The ganglion cell layer, retinal nerve fiber thickness, photoreceptor layer, and outer nuclear layer can be assessed with OCT. During the acute attack of MS optic neuritis, an increase in RNFL thickness and subretinal hyporeflective areas are seen in OCT scans. Optic nerve flow index can be assessed with OCT-A in MS (17).

Patients may also apply to the hospital with granulomatous changes in the anterior segment. In these patients, the presence of a vasoproliferative tumor associated with cystoid macular edema or occlusive vasculitis usually makes management of the disease difficult; high-dose corticosteroids or laser therapy are required. While pulse methylprednisolone treatment is used for optic neuritis secondary to MS, laser photocoagulation treatment with high-dose steroids can be used for occlusive vasculitis associated with vasoproliferative tumors. In MS patients with uveitis, it has been reported that IFNβ 1a effectively suppresses intraocular activity and positively enhances visual acuity.

3.3. Pars Planitis

Pars planitis is a form of idiopathic chronic uveitis that mostly affects children and adolescents. Its etiology is still unknown. The most common symptoms on hospital admission are floaters and blurred vision. Pars planitis is characterized by diffuse vitreous cells, haze, snowballs, and snowbanks. Peripheral retinal vasculitis, optic nerve edema, and anterior uveitis frequently accompany this clinical picture. Although pars planitis is not an aggressive form of uveitis, secondary complications such as cataracts, cystoid macular edema, vitreous opacities, and optic disc edema can lead to severe visual loss.

Increased tortuosity in retinal arteries and veins, sheathing in veins, and neovascularization can be observed in pars planitis. Vascular sheathing, mainly behind the iris and ciliary body junction, exhibits a cellular infiltration dominated by T cells in histopathological studies (18).

Band keratopathy, epiretinal membrane formation, neovascularizations, vitreous hemorrhages, retinal detachments, cyclic membranes are serious complications that follow the chronic course of the disease.

FFA is frequently used in the diagnosis and is very helpful in diagnosing cystoid macular edema, perivasculitis, and retinal neovascularization. OCT is used to diagnose and follow-up macular edema, epiretinal membranes, macular holes, and atrophies. Pars planitis can cause severe inflammation and require aggressive treatment. While drug treatment involves corticosteroids, immunosuppressants, and anti-TNF agents, pars plana vitrectomy may be required for severe complications.

3.4. Behcet's Disease

Bechet's disease (BD) is an idiopathic, chronic systemic vasculitis. Although ocular involvement is often asymmetrically bilateral, it can rarely be observed in unilateral involvement. BD may involve anterior segment in the form of non-granulomatous anterior uveitis, conjunctival ulcer, episcleritis, and scleritis. Non-granulomatous anterior uveitis is the most common type of involvement. In contrast to HLA B27 uveitis, a mobile hypopyon is seen due to the low fibrin content.

Perivascular soft exudates and hemorrhage are seen when the vessel walls are sheathed by perivascular cell infiltration in the posterior segment and when the vessel is occluded. Telangiectasias and microaneurysms may develop secondary to ischemic retinal vasculitis in the long term. Diffuse leaky periphlebitis is prominent in BD. Occlusive veins may be involved in the main veins as well as in small venules. While disc neovascularisations in Behçet's disease are secondary to uncontrolled inflammation, peripherally located neovascularizations are secondary to ischemia.

FFA is important in diagnosing and following retinal vasculitis and may show more extensive involvement than vasculitis detected on fundus examination. Neovascularization can be identified with FFA, which can detect vessel wall staining, capillary involvement, macular edema, and the presence and extent of ischemia (Figure 3). OCT is used to diagnose and monitor macular edema, while ICG can indicate leakage and irregular filling in choroidal vessels.

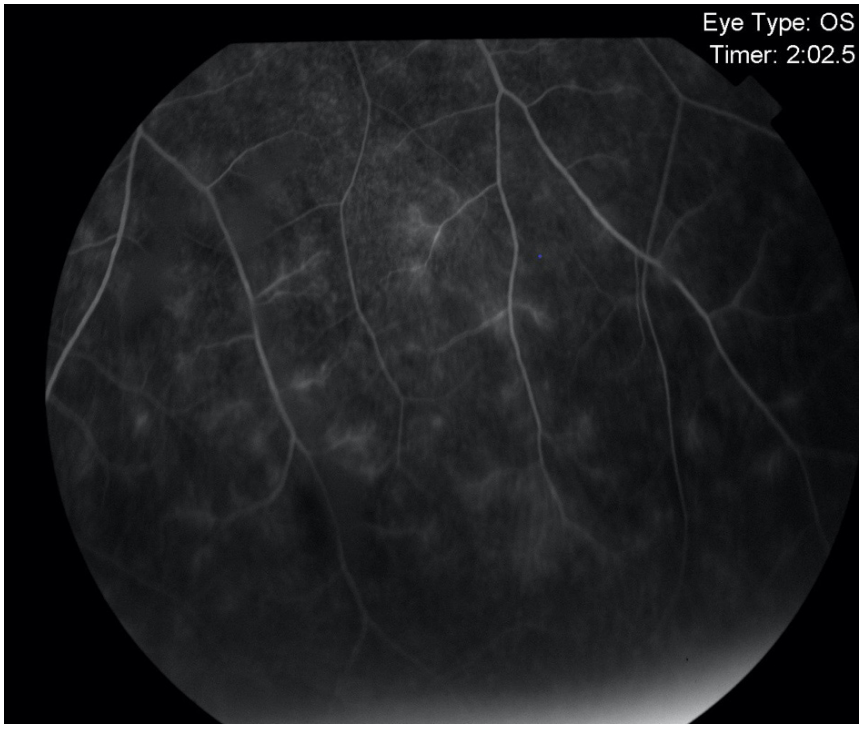

Figure 3. Fluorescein angiogram showing focal venous leakage in Bechet's uveitis

Corticosteroids, cytotoxic agents, antimetabolites (Methotrexate, mycophenolate mofetil, Azothiopurine), T-cell inhibitors (CyclosporinA, Tacrolimus), alkylating agents (chlorambucil, cyclophosphamide), TNF-α inhibitors (Infliximab, Adalimumab), and interferon-α can be used for the treatment.

3.5. HIV Retinopathy

HIV is a retrovirus that replicates in CD4 T lymphocytes and is transmitted by blood and body fluids. AIDS occurs when the CD4 T cell count is less than 200/ microliter. Micro-vasculopathy, opportunistic infections, and malignancies can cause retinal involvement in HIV/AIDS. Most of the patients are asymptomatic in HIV retinopathy, and routine fundus examination may reveal cotton wool spots, intraretinal hemorrhages, microaneurysms, and telangiectasias. Although large arterial or venous occlusions are rarely seen, viral retinitis should be considered when they are present. HIV micro-vasculopathy is often asymptomatic and does not require treatment.

Although CMV retinitis has recently decreased with HAART treatment, it can occur in patients with AIDS. It has been reported that the risk of developing CMV retinitis is higher in individuals with a CD4+ cell count of fewer than 50 cells/mm3. There are three forms of CMV retinitis. Retinal necrosis and hemorrhages are seen along the vascular arches at the posterior pole in the classic form. In the peripheral form, granular lesions are found in the retina's periphery, and no hemorrhages are observed. On the other hand, Frosted Branch Angiitis is characterized by vascular swelling. Vision loss in CMV retinitis is often secondary to macular and optic disc involvement. CMV retinitis is treated with drugs such as valganciclovir, oral or intravenous ganciclovir, ganciclovir implant, fomivirsen, foscarnet, and cidofovir (20).

3.6. Eales Disease

Eales disease is an idiopathic occlusive vasculitis involving the mid-peripheral retina characterized by periphlebitis, vascular occlusion, and retinal neovascularization. It often affects young men in their second decade. Although it is usually observed bilaterally, it can also be seen as unilateral.

Recurrent vitreous hemorrhage may occur secondary to periphlebitis as a result of retinal ischemia and neovascularization. Although there is no precise clinical classification in Eales, the disease can be divided into three stages (21).

a) Early Stage (Inflammatory): Peripheral and mid-peripheral periphlebitis, venous dilatation, and perivascular exudates are seen in several areas.
b) Intermediate Stage (Ischemic): Diffuse retinal ischemia is seen. Between perfused and non-perfused areas, arteriovenous shunts, venous beadings, and micro-aneurysms exist.
c) Late Stage (Proliferative): There is neovascularization between perfused and non-perfused retinal areas. Vitreous hemorrhages and tractional retinal detachments may occur.

It is necessary to use multimodal imaging in diagnosis. In FFA, active vessels show leakage, while inactive vessels stains without leakage (Figure 4). Peripheral ischemia can be seen in wide-field FFA. While macular edema and epiretinal membranes can be followed with OCT, choroidal neovascular membranes can be detected with OCT-A.

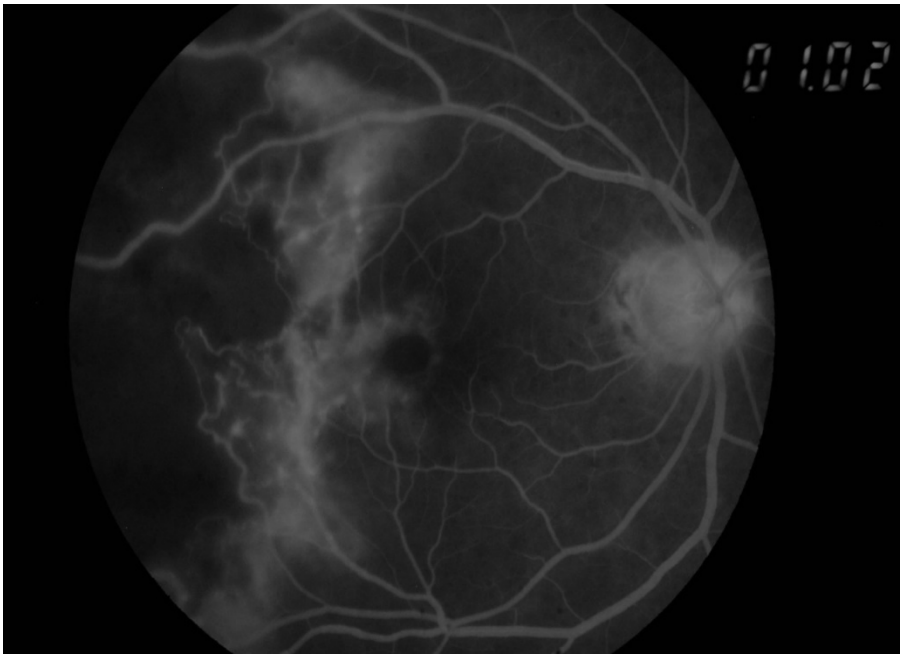

Figure 4. FFA shows the neovascularization and an extensive area of capillary non-perfusion in Eales' disease

Treatment may include systemic corticosteroids and laser photocoagulation to ischemic areas of the retina in the active inflammatory stage. While laser photocoagulation is not used in early-stage disease, laser treatment can be used in moderately advanced retinal neovascularization and ischemic areas. Anti-Vascular Endothelial Growth Factor (anti-VEGF) may be used to treat retinal neovascularization and macular edema. Anti-VEGFs also reduce the need for surgery for recurrent vitreous hemorrhage. Systemic corticosteroid therapy may be administered in conjunction with antituberculous treatment in the case of retinal periphlebitis associated with a positive tuberculin skin test/QuantiFERON Gold test. Surgical treatment is required for vitreous hemorrhages and retinal detachments that do not resolve spontaneously (22).

4. Diseases Causing Retinal Arteritis and Phlebitis

4.1. Crohn's Disease

Although Crohn's disease often affects the terminal ileum, it is a disease that can involve the entire gastrointestinal tract. In the pathogenesis of the disease,

inflammation that damages the mucosa of the intestinal epithelium is thought to lead to the production of antibodies or antigen-antibody complexes that cause systemic inflammation.

Local involvement is seen secondary to illness exacerbation in primary involvement and regresses with systemic treatment. Keratitis, episcleritis, and scleritis can be observed in this form. There are two possible theories to explain the association between Crohn's disease and retinal vasculitis. The first links vasculitis to thromboembolic events in the involved vessels. This theory is attributed to the occurrence of both coagulation disorders and thromboembolic events in Crohn's disease. A second possible explanation is that vasculitis caused by inflammatory cell infiltration of the vessel walls secondary to inflammatory bowel disease may also affect blood flow to the retina. In this form, posterior uveitis may be seen secondary to retino-choroidal vascular involvement, multifocal or diffuse choroiditis, chorioretinitis, retino-choroiditis, retinitis, neuro-retinitis.

Control of systemic inflammation is essential in the treatment. Corticosteroids, cytotoxic agents, antimetabolites (Methotrexate, mycophenolate mofetil, Azothiopurine), T-cell inhibitors (CyclosporinA), sulfasalazine (5- ASA derivative), and TNF-α inhibitors (Infliximab, Adalimumab), Interferon-α can be used.

4.2. Frosted Branch Angiitis

Frosted branch angiitis (FBA) is a rare retinal vasculitis and was given this name because it resembles frozen tree branches due to the sheathing of the retinal vessels (Figure 5). In pathogenesis, viral antigens are thought to be responsible for direct viral invasion or form immune complexes by accumulation in retinal vessels causing vasculitis. While primary idiopathic FBA affects young and healthy people, it can occur in secondary form due to infections such as cytomegalovirus, herpes simplex virus, toxoplasmosis, HIV, or autoimmune diseases such as systemic lupus erythematosus, Crohn's disease, Bechet's disease. Vitritis, retinal edema, hemorrhages, submacular serous detachment, optic disc edema, and iritis are commonly seen (23).

Delayed filling of the arteries in the early phase, more extensive leakage in the veins in the late stage, capillary non-perfusion areas, artery-venous anastomoses, and hyperfluorescence of the optic disc can be seen in FFA.

Leakage from the choroidal vessels can be seen in ICG. High reflectivity, intraretinal edema, and neurosensory detachments in the inner retinal layers secondary to intracellular edema are seen in OCT.

When it comes to treatment, it's critical to distinguish between infectious and non-infectious conditions. While the non-infectious form responds well to systemic corticosteroid treatment, systemic steroids combined with systemic therapy of the specific agent can be used in infectious form.

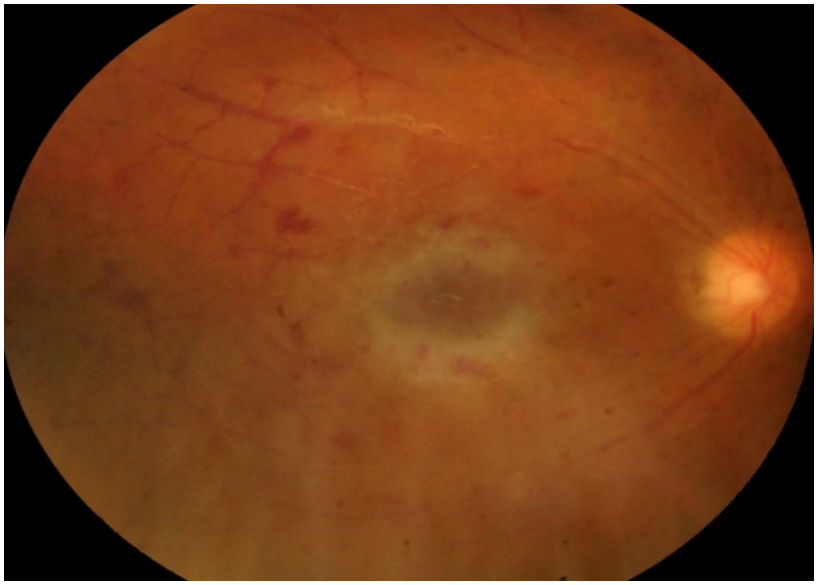

Figure 5. Frosted branch angiitis with retinal haemorrhages

4.3. Relapsing Polychondritis

Recurrent polychondritis is a rare systemic autoimmune disease. Auricular, nasal, and tracheal cartilage chondritis, audiovestibular dysfunction, ocular inflammation, vasculitis, myocarditis, and non-erosive arthritis are clinical features of the disease.

Male predominance is seen in eye involvement of recurrent polychondritis. The most common findings are scleritis, episcleritis, and conjunctivitis. Corneal melting, pannus formation, necrotizing scleritis, anterior uveitis may be seen with involvement of the anterior segment. Chemosis and proptosis may be seen secondary to inflammation in the retrobulbar area. Intraretinal hemorrhage, retinal vein occlusion, exudative retinal detachment, chorioretinitis, ischemic optic neuropathy, cystoid macular edema, and retinal infiltrates have also been

reported. In retinal vascular involvement, diffuse leakage is seen in arteries and veins with FFA (24,25).

There are medical treatment options. Immunosuppressive medications such as systemic steroids, methotrexate, cyclophosphamide, and azathioprine are useful in the treatment of severe polychondritis, ocular involvement, laryngotracheal involvement, and systemic vasculitis.

4.4. Tuberculosis

Ocular tuberculosis (TBC) may be associated with both an active pulmonary form and reactivation of a latent pathogen in ocular tissue. Ocular TB usually tends to be unilateral and asymmetrical. It can occur in a variety of uveitis presentations. Although it occurs most commonly as posterior uveitis, it may affect the entire choroidal tissue. Although choroid and retina are commonly involved in TB, isolated retinal involvement is rarely seen. The various clinical manifestations seen include vitritis, retinitis and/or choroiditis, retinal vasculitis, choroidal tuberculoma, choroidal tubercles, multifocal choroiditis, and serpiginous-like choroiditis (Figure 6). Choroidal granulomas are the most common findings. TBC may also present as optic neuritis or papillitis involving the optic nerve (26).

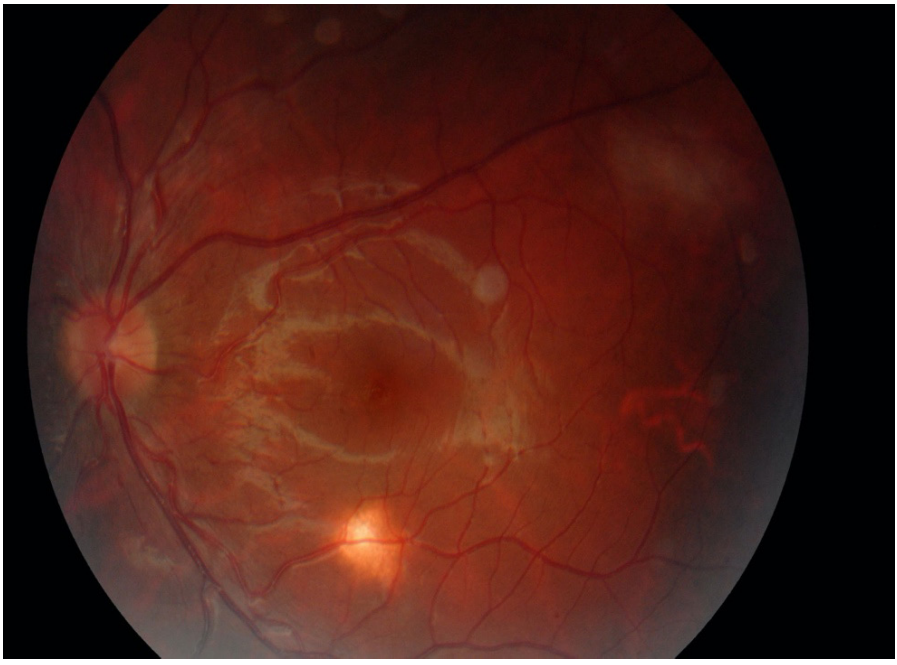

Figure 6. Choroidal tubercle near the inferotemporal arcade of the left eye

Multimodal imaging is crucial for diagnosis. Choroidal tuberculomas show early hypofluorescence and late hyperfluorescence in the late phase of FFA (Figure 7). On the other hand, large choroidal tuberculomas may show early hyperfluorescence because of the dilated vessels. FFA is very valuable in diagnosing choroidal neovascular membranes of retinal angiomatous proliferation secondary to the lesion. Staining of the vessel walls and vascular leakage can be observed in retinal vasculitis. FFA can be used to assess capillary nonperfusion and neovascularizations in the peripheral retina. On ICG, subclinical lesions can be detected. In the early and mid-phase, these lesions appear hypo-, iso-, or hyperfluorescent. OCT is used in the diagnosis and follow-up of macular pathologies and neovascular membranes. In the differential diagnosis of non-TBC melanomas and metastatic masses, orbital ultrasound is essential. On A-scan, tuberculomas have a moderate or low reflectivity and appear as a solitary raised mass on B-scan (27).

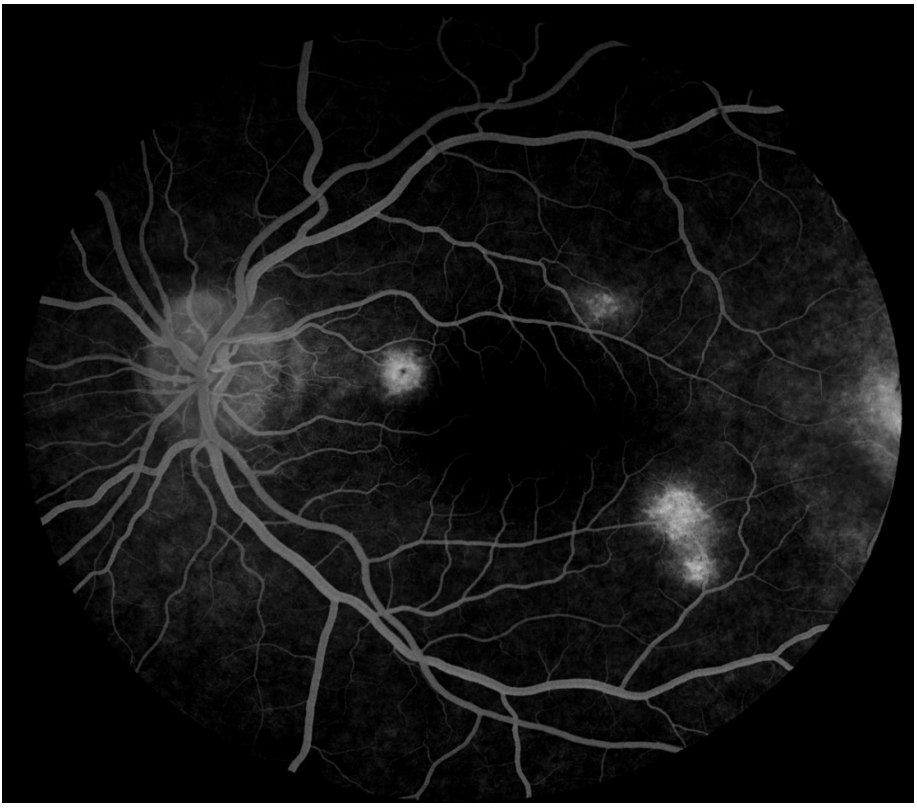

Figure 7. FFA shows increasing hyper-fluorescence and intense leakage in the area of choroidal tubercle

After the diagnosis of ocular tuberculosis, systemic antituberculosis treatment should be started. Isoniazid, rifampicin, ethambutol, pyrazinamide, or streptomycin drugs are used for ocular treatment of TB, which is similar to the recommended treatment protocol for pulmonary involvement.

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CHAPTER 10

RETINOPATHY OF BLOOD DISORDERS

Muhammed Mustafa KURT
Samsun University, Faculty of Medicine,
Department of Ophthalmology, Samsun
e-mail: musti_art@hotmail.com
ORCID: 0000-0002-4667-3046

1. Leukemia

Leukemias are a group of hematological malignancies originating from white blood cells (WBCs). It results from acquired clonal abnormalities of hematopoietic stem cells replacing normal bone marrow cells. Although patients classically present with fatigue, fever, and bleeding, ocular findings are seen in up to 90% of patients (1).

Classification

The most widely used clinical classification of leukemia is acute and chronic form. Acute leukemias can be defined as the presence of immature cells called blasts in the bone marrow. Chronic leukemias are associated with well-differentiated (mature) leukocytes. Two main variants have been identified in acute and chronic forms of leukemia: lymphocytic and myelocytic. There are four leukemia patterns in this simple classification:

1. ***Acute lymphocytic (lymphoblastic)***, which usually affects children; overall, about 70% are cured.
2. ***Acute myelocytic (myeloblastic)*** is most common in adults and can be cured in 30% of cases.
3. ***Chronic lymphocytic***: it has a chronic course and the mortality rate is low.
4. ***Chronic myelocytic*** has a progressive course and a worse prognosis. (2-3)

Leukemia causes ocular changes in several ways. The retina can be infiltrated not only by the neoplastic cells, but also can be affected by secondary causes such as hemorrhage and ischemia that may occur as a result of occlusion of capillaries by clustered leukocytes (3-5). The most common retinal manifestations are venous dilatation and tortuosity. Retinal hemorrhages can occur at any level, usually at the posterior pole (6) (Figure 1). A cotton wool spot is often seen as a sign of retinal ischemia (7). Excessive leukocytosis, especially in patients with chronic lymphocytic leukemia, can lead to peripheral nonperfusion and neovascularization (8–10).

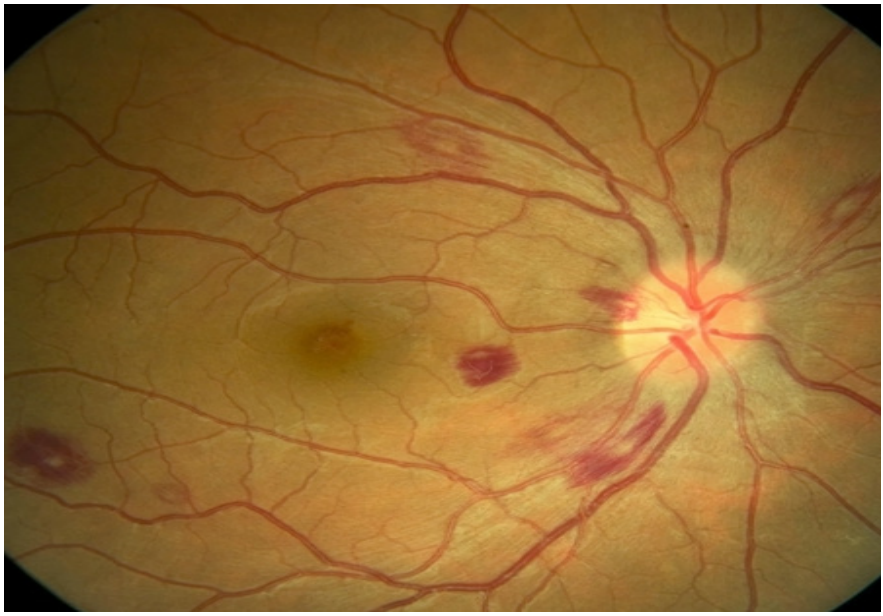

Figure 1. Acute myeloid leukemia showing retinal hemorrhages

Choroidal infiltration may result in serous fluid accumulation. Serous detachment of the retina may occur in all types of leukemia and after chemotherapy (3). Rarely, it can occur in the form of secondary RPE changes called leopard spot retina. Vitreous infiltration is also possible. Tumor cells can be detected from the vitreous sample obtained in vitrectomy (11-12).

The frequency of fundus findings differs between acute and chronic forms of leukemia. Although anemia and thrombocytopenia are more closely associated with acute leukemia, hyperviscosity is more common in chronic leukemia. This may present as bilateral central retinal vein occlusion (13). (Figure 2)

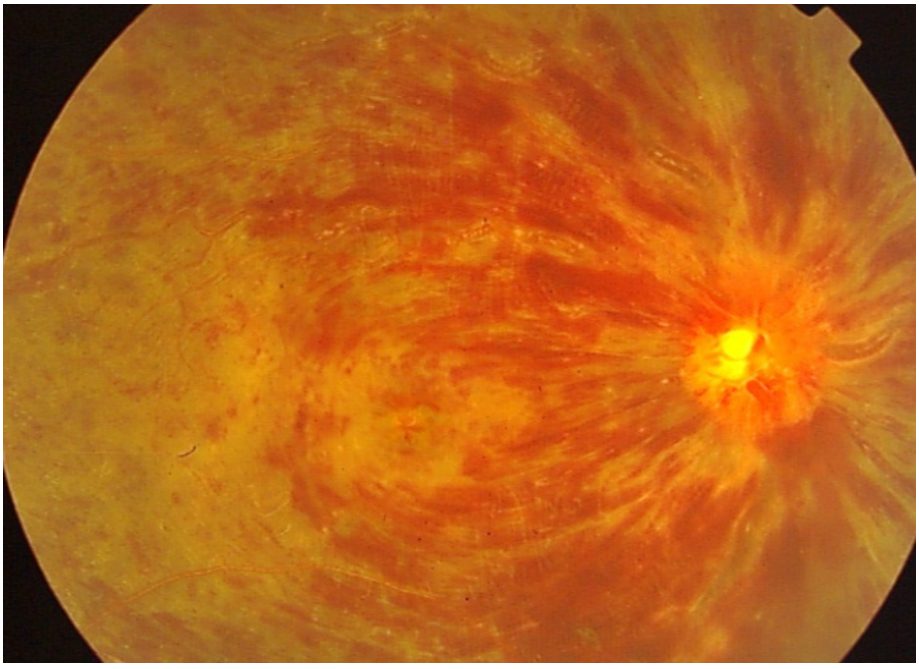

Figure 2. Central retinal vein occlusion in a case of chronic leukemia

There is evidence that optic nerve infiltration involves central nervous system involvement and has a lower survival rate. It is more common in acute leukemia than in chronic forms. In a study conducted in children with leukemia, it was reported that the survival rate was significantly reduced in children with leukemic retinopathy (14).

2. Anemia

Anemias are a group of disorders that manifest as a decrease in the number of circulating red blood cells and/or a decrease in the amount of hemoglobin in the cell. Retinal changes in anemia are rarely of clinical importance.

Aplastic Anemia

A decrease in all blood cells (anemia, leukopenia, and thrombocytopenia) is called pancytopenia (aplastic anemia). In most cases, the cause of aplastic anemia is idiopathic. In about 20% of patients, the disease is caused by an inherited disease such as Fanconi Anemia. Aplastic anemia can also be caused by exposure to high doses of radiation or certain chemicals or viruses (15). Retinal

hemorrhages, Cottonwool spots, vitreous hemorrhage in 13%, and papillary edema have been reported in aplastic anemia (16). (Figure 3)

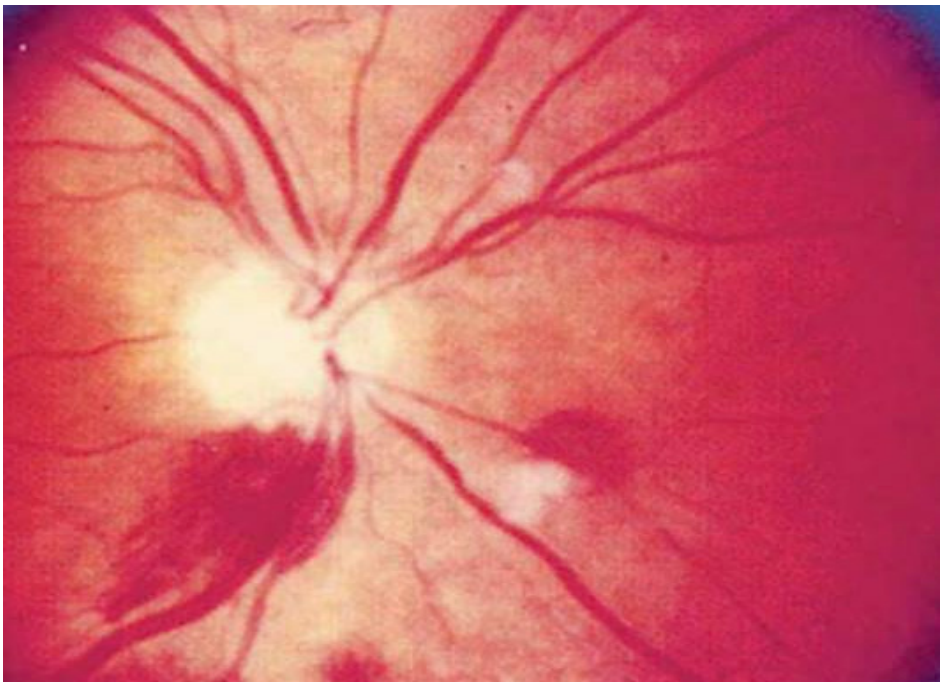

Figure 3. Retinal hemorrhages in a case of aplastic anemia

Megaloblastic Anemia

Megaloblastic anemia is characterized by anemia with macrocytosis due to the deficiency of vitamins (such as Vit B12 and folic acid) necessary for pyrimidine metabolism. Rarely, they can be seen due to some metabolic defects. The most important pathological finding is ineffective erythropoiesis.

Retinopathy due to megaloblastic anemia has been reported rarely in the literature (17-19). The mechanism of retinopathy in this disease may be due to hypoxic damage. It causes increased permeability in vessels, endothelial leakage, and intraretinal hemorrhage.

In severe anemia, flaming hemorrhages can be seen within the nerve fiber (Figure 4 to 6). Retinal hemorrhages in patients with leukemia and bacterial endocarditis are frequently seen in the form of Roth spots, which are rarely seen in megaloblastic anemias (18-20).

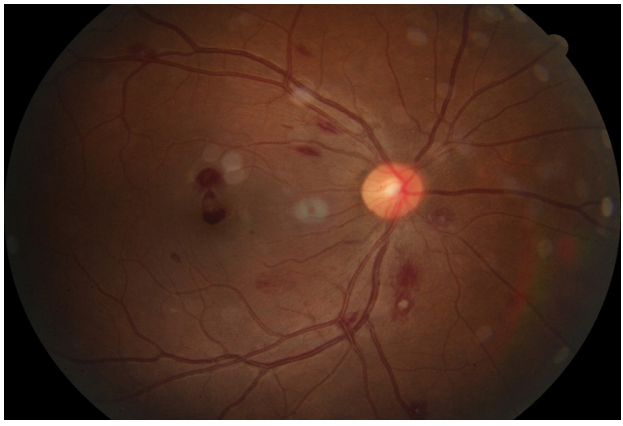

Figure 4. Retinal hemorrhages in a case of megaloblastic anemia

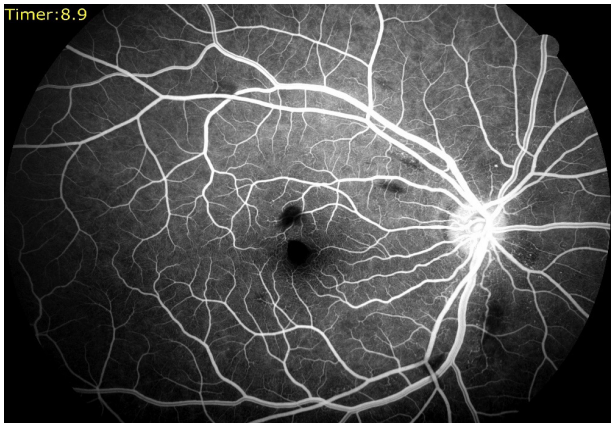

Figure 5. Fundus fleurescein angiography image in the same megaloblastic anemia case

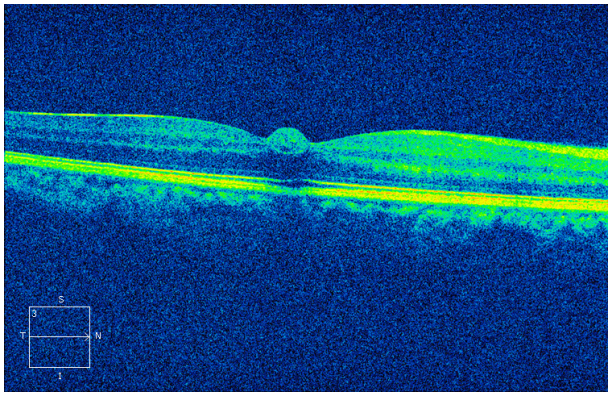

Figure 6. Optical coherence tomography image in the same megaloblastic anemia case

Thrombocytopenia

Idiopathic thrombocytopenic purpura (ITP) is a rare disease characterized by a low platelet count in the blood. ITP occurs when the human body defense system creates autoantibodies against platelets. These autoantibodies mark and destroy platelets. Even if severe, thrombocytopenia alone is not sufficient to cause retinal hemorrhage. Retinal hemorrhages have often been reported in association with severe anemia concurrent with ITP.

Hemorrhagic ophthalmic manifestations in ITP include vitreous hemorrhage associated with intracranial bleeding in a Terson type phenomenon (21), hemorrhage within the optic tract (,22) nonarteritic anterior ischemic optic neuropathy (23), and subconjunctival hemorrhage (24). (Figure 7)

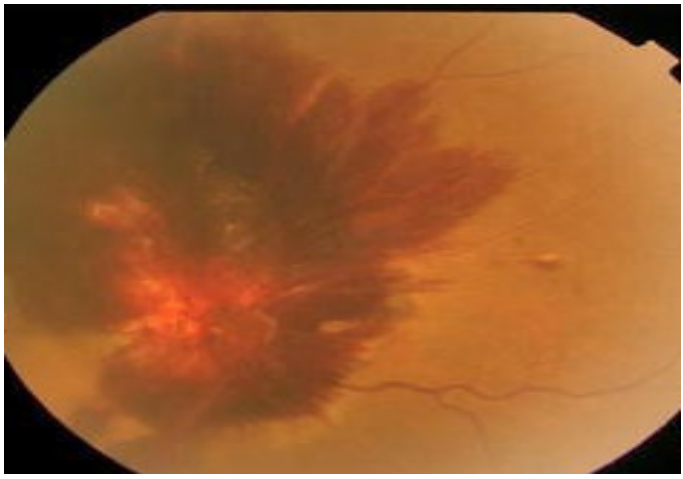

Figure 7. Retinal hemorrhages in a case of idiopathic thrombocytopenic purpura

Hyperviscosity

Hyperviscosity syndrome is a collection of symptoms and clinical manifestations reflecting an increased serum concentration of a monoclonal protein. Hyperviscosity syndrome is most commonly associated with Waldenström's disease, but has been reported in other pathologies such as multiple myeloma, light chain gammopathies, cryoglobulinemia, and more rarely rheumatoid arthritis (25).

Hyperviscosity syndrome leads to retinopathies with the mechanism of retinal venous stasis, which can lead to venous occlusion with disruption of both

central and peripheral retinal microcirculation. Classically, retinal hemorrhages appear in the fundus with dilated vessels, as well as spots or flares (Figure 8). This retinal stasis may mimic central retinal vein occlusion in the most severe cases. Treatment includes rehydration, phlebotomy, and plasmapheresis (26-28).

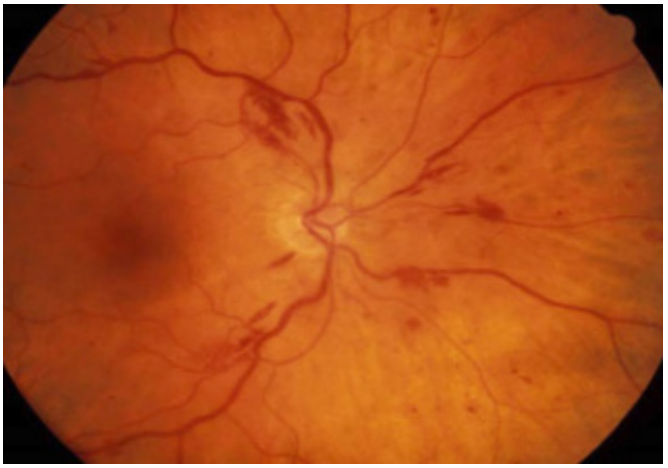

Figure 8. Hyperviscosity demonstrating retinal hemorrhages and venous tortuosity.

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CHAPTER 11

OTHER RETINAL VASCULAR DISEASES

Çetin AKPOLAT

University of Health Sciences, Şişli Hamidiye Etfal Training and Research Hospital, Department of Ophthalmology, Istanbul

e-mail: akpolatcetin@yahoo.com

ORCID: 0000-0002-7443-6902

1. Macular Telangiectasia

Macular telangiectasia has 3 subdivisions (1). Macular telangiectasia type 1(MacTel 1) is a congenital or acquired unilateral parafoveal telangiectasia, macular telangiectasia type 2 (MacTel 2) is a bilateral parafoveal telangiectasia, and macular telangiectasia type 3 (MacTel 3) is a bilateral parafoveal telangiectasia with retinal capillary obliteration.

Macular Telangiectasia Type 1

MacTel 1 (or aneurysmal telangiectasia) has a unilateral tendency and young male predominancy with typical aneurysmal enlargements in the temporal macular vessels with surrounding exudates and cystic macular edema. MacTel 1 is also assumed as a variant of Coats disease in the macula. Peripheral vascular alterations might also be examined (Figure 1.1). Although anti-vascular endothelial growth factor (VEGF) treatment has no successful results, aflibercept may induce a treatment response via blocking placental growth factor (PDGF) besides the VEGF. This outcome allows us to hypothesize the role of PDGF in the pathophysiology of the MacTel 1 (2).

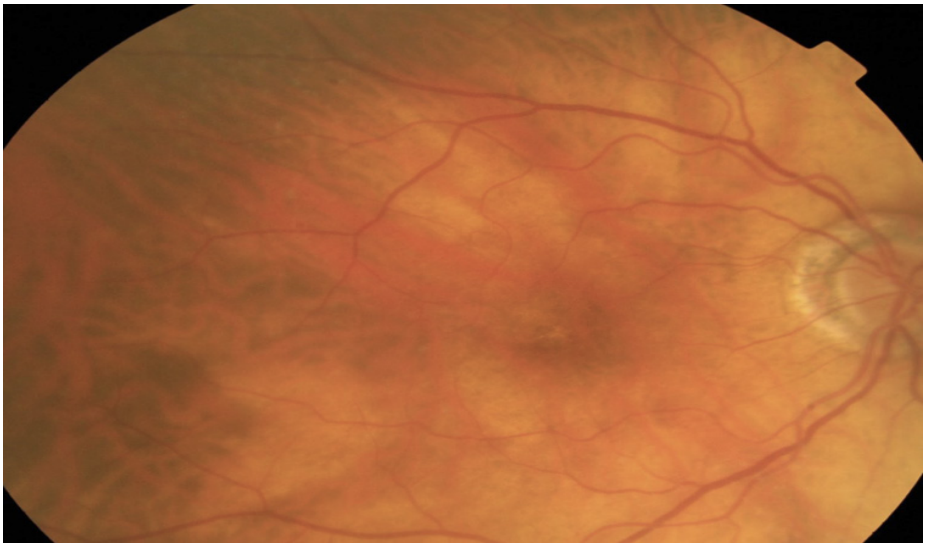

Figure 1.1. Fundus photo of type 1 macular telangiectasia

Macular Telangiectasia Type 2

MacTel 2 (or juxtafoveal telangiectasia) is a rare progressive bilateral idiopathic neurodegenerative disease of the macula between the fifth and seventh decades. MacTel 2 is characterized by vascular and neural dysfunction in the macula, which means the essential role of Müller cells in the pathophysiology of the disease (3). It is the most common type of macular telangiectasia with specific features including superficial retinal crystalline deposits, loss of retinal transparency, greying macular appearance, macular pigment hyperplasia, decreased foveolar reflex, foveal atrophy, ectatic retinal capillaries, dilated blunted retinal venules, and subretinal neovascularization (3). (Figure 1.2).

Fluorescein angiography demonstrates the leakage of the telangiectatic vessels of MacTel 2. Optical coherence tomography (OCT) visualizes a thinned central macular retina, including the fovea, with inner lamellar oblong foveal cavitation where the long axis is parallel to the retinal surface. OCT angiography demonstrates alterations in the deep capillary plexus. Although intravitreal anti-vascular endothelial growth factor (VEGF) treatment is used for the management of subretinal neovascularization, no effective therapy has been introduced in the literature for the MacTel 2 therapy.

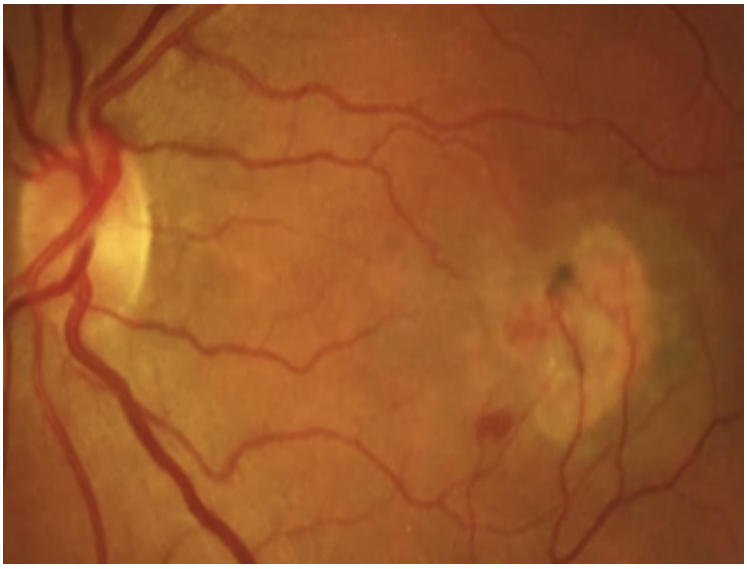

Figure 1.2. Fundus photo of type 2 macular telangiectasia

Macular Telangiectasia Type 3

Type 3 macular telangiectasia is also named occlusive idiopathic juxtafoveolar retinal telangiectasis. It is associated with the systemic or cerebral vascular occlusive disease. Type 3 macular telangiectasia is an extremely rare, acquired, and vaso-occlusive process that affects the parafoveal area and is different from type 1 and 2 macular telangiectasias (4). It is characterized by progressive visual impairment, caused by bilateral capillary telangiectasia, juxtafoveolar capillary occlusions, and minimal exudation.

2. Coats Disease

Coats disease is usually unilateral and predominant in males with high disease severity and rapid progression in the pediatric population under 4 years old. It has specific features of retinal telangiectasia, microaneurysms, ectatic arterioles, phlebectasias, and fusiform capillary dilatations, that are mostly related to serous retinal detachment (Figure 2) (5). No reports have been issued in the literature regarding any hereditary, genetic pattern, or any relation with systemic disorders.

Peripheral vascular leakages in children usually coexist with lipid deposition, but normal macular angiography is due to the tendency of hard exudate

accumulation in the macula. Similar results in adult patients may be due to late decompensation of previous anomalies in the retinal vasculature. However, the initial sign is frequently subretinal fibrosis or sub-macular lipogranuloma. Coats disease may lead to compromised peripheral and macular capillary vasculature, causing vascular leakage and thus result in the accumulation of subretinal fluid (6). Despite the angiographic vascular nonperfusion, the presence of neovascularization is rare. The clinical characteristics demonstrate a spectrum from minimal exudation and mild capillary abnormalities to massive fluid leakage associated with serous retinal detachment and large retinal telangiectatic areas. Massive serous retinal detachment might induce retinoblastoma or other reasons for leukocoria. Coats disease should be differentiated from several pathologies including, retinopathy of prematurity (ROP), diabetic retinopathy (DR), von Hippel–Lindau syndrome (VHL), branched retinal vein occlusion (BRVO), radiation retinopathy, dominant exudative vitreoretinopathy, juxtafoveal retinal telangiectasia, and facioscapulohumeral muscular dystrophy.

Although there is no effective therapy for Coats disease, intravitreal anti-VEGF, cryotherapy, photocoagulation and vitreoretinal surgery (in severe cases) are the treatment options (7). Cryotherapy and photocoagulation are effective options in obliterating the abnormalities of vascular structures and in ceasing disease progression. Anti–VEGF therapy might be used as adjunctive therapy in case of resistance to ablative treatment alone. Several therapy sessions might be required, and long-term follow-up is essential to identify and manage recurrences or progression of the disease.

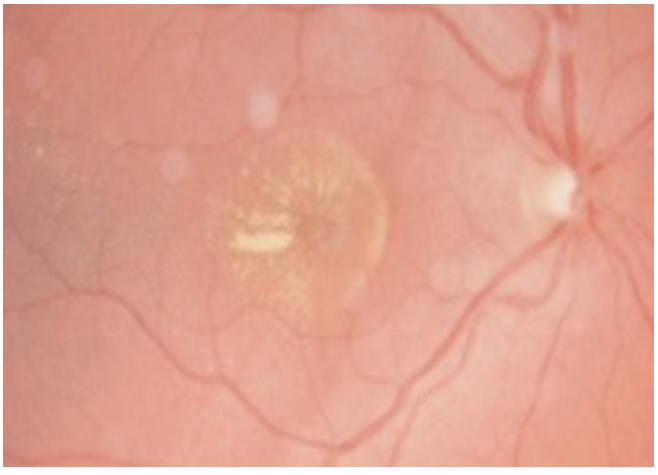

Figure 2. Fundus photo of the right eye with Coats disease

3. Phakomatoses

Most of the phakomatoses have a hereditary nature and involve the retina and its circulation (Except for Sturge-Weber syndrome). Many syndromes are referred to as phakomatoses and are grouped according to the common congenital ocular and/or systemic findings.

Von Hippel–Lindau Syndrome

The von Hippel–Lindau (VHL) syndrome (familial cerebello retinal angiomatosis) is an autosomal dominant disease with incomplete penetrance and variable expression. There is a tumor suppressor gene mutation on the short arm of chromosome 3 (3p26–p25). So, the confirmation of the disease diagnosis should be performed with genetic analysis. The disease may present with the central nervous system and retinal hemangioblastomas and systemic findings, including pheochromocytomas, renal cell carcinoma, cysts of the kidney, liver, and pancreas, endolymphatic sac tumors, and bilateral papillary cystadenomas of the broad ligament in the uterus (women) or the epididymis (men) (8). Presence of a retinal hemangioblastoma requires for systemic workup and genetic analysis. Cerebellar hemangioblastoma and renal cell carcinoma are the main reasons for the mortality in VHL syndrome. Central nervous system involvement and their therapy may cause severe disability in patients with VHL syndrome.

Unilateral or bilateral multiple hemangioblastomas might be examined. Hemangioblastomas located in the peripapillary area and optic nerve head are usually flat and so it is difficult to recognize them. Leakage from a hemangioblastoma might lead to visual impairment due to macular exudation with or without serous retinal detachment. Subsequently, vitreous hemorrhage or tractional detachment might also develop. Retinal hemangioblastomas may also develop sporadically without systemic involvement; these are called von Hippel lesions. Acquired vaso-proliferative lesions are another form of retinal angiomas (Figure 3.1). They might be rarely examined in the late stage of retinitis pigmentosa, ROP, or other diseases. These lesions differ from hemangioblastomas with the absence of the dilated feeder and draining vasculature.

Treatment of retinal hemangioblastomas in VHL includes photocoagulation, cryotherapy, and photodynamic therapy (PDT) (9). The aim is to shrink the hemangioblastoma, destroy the detected angiomatous lesions, attenuate the afferent vasculature and resolve the subretinal fluid. It is important to identify

recurrence or the development of new lesions with careful follow-up, especially using wide-angle fluorescein angiography (Figure), which allows the detection of early and small lesions. Photocoagulation and cryotherapy are successful to treat and destroy angiomatous lesions directly. However, PDT with verteporfin has a limited effect because this therapy does not destroy the lesions. Although cryotherapy can be used for larger lesions, it may lead to a temporary and marked increase in the amount of exudation and sometimes serous retinal detachment. Moreover, no studies have been reported regarding the meaningful and long-term effect of anti-VEGF usage in the treatment of retinal hemangioblastomas in VHL.

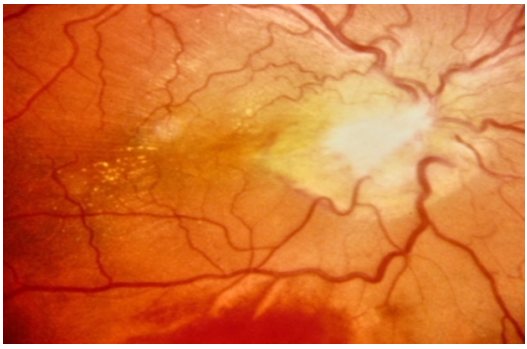

Figure 3.1. Fundus photo of von Hippel–Lindau

Wyburn-Mason Syndrome

Wyburn-Mason syndrome is characterized by the development of congenital retinal arteriovenous malformations (range from a single arteriovenous communication to a complex anastomotic system) with similar coexisting ipsilateral vascular malformations in the face, mandible, brain, and orbit (10). The lesions have abnormal blood vessels without an intervening capillary bed (racemose hemangioma) (Figure 3.2). Ocular lesions are mostly unilateral, asymptomatic, and located in the retina and optic nerve without angiographic leakage (10).

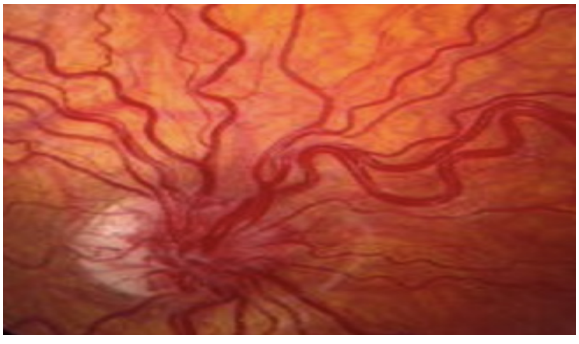

Figure 3.2. Fundus photo Wyburn-Mason Syndrome

Retinal Cavernous Hemangioma

Retinal cavernous hemangiomas are usually sporadic but sometimes with an autosomal dominant nature. These benign, vascular hamartomatous and "cluster of grapes" like pattern lesions are predominant in females, mostly unilateral and asymptomatic, and usually diagnosed incidentally (11). However, visual impairment occurs if the lesions are located within the macula or in the case of the development of macular fibrosis or epiretinal membrane. This 'clusters of grapes' like appearance is observed because of enlarged vascular sacs in the inner retinal layers without alterations in the adjacent arterioles (11). In FA, these lesions appear as slow filling sac-like regions with late staining, but with no leakage (Figure 3.3). Histopathologic investigations have shown sessile tumors with thin-walled channels including non-fenestrated endothelium and surface gliosis.

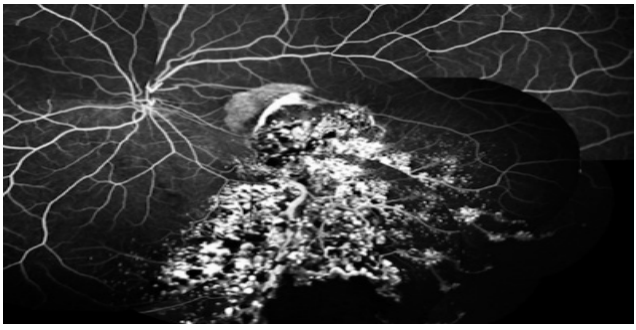

Figure 3.3. Fluorescein angiography of retinal cavernous hemangioma

Retinal cavernous hemangiomas are usually followed with serial exams and without any requirement of therapy. However, it is essential to keep in mind that despite its benign nature, the co-existence with systemic conditions such as skin and central nervous system involvement should be investigated.

4. Congenital Vascular Malformations (Figure 4)

Vascular tumors (e.g., retinal hemangioblastomas or capillary angiomas in VHL) and malformations of the retina are various and uncommon (12). However, most of them are related to life-threatening systemic disorders. The management of patients with these lesions is in an advancing process with the developments in ocular imaging, genetic testing, and therapy options. Patients with vascular

malformations should be referred to a medical center with an experienced multidisciplinary team and relevant expertise in treatment modalities including anti-angiogenic therapy and PDT (12). The management of these patients in specialized centers also provides research opportunities, to improve our understanding of the pathophysiology of the malformations and facilitating the assessment of novel treatment modalities. Nonetheless, ophthalmologists have an important role in identifying these lesions and in contributing to long-term care working together with a specialist in the field.

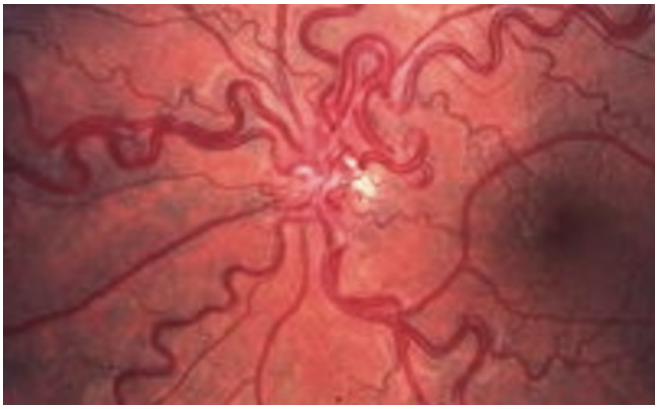

Figure 4. Vascular malformations of the retina

5. Retinal Artery Macroaneurysm

Retinal arterial macroaneurysms define the acquired ectasias of the first 3 orders of retinal arterioles with multiple and mostly unilateral involvements (13). Approximately 2/3 of the cases with retinal arterial macroaneurysms have systemic arterial hypertension. Large macroaneurysms can involve retinal full thickness. Visual impairment might result from hemorrhages/re hemorrhages in the intraretinal, subretinal, or sub–internal limiting membrane (frequently in combination) or from thrombotic or embolic occlusion of the end arteriole (white infarct) (13). Retinal arterial macroaneurysms may also cause exudation in the macula, retinal edema, capillary telangiectasia, and remodeling. (Figure 5)

Intravitreal Anti-VEGF injection and laser photocoagulation are the treatment options for the retinal arterial macroaneurysms. Anti-VEGF therapy can facilitate the resolution of macroaneurysms-induced macular edema, but the

final visual acuity usually without does not improve (14). Laser photocoagulation can be applied in case of macular edema threatening the central visual acuity. Some specialists prefer laser treatment adjacent to the macroaneurysm using 2–3 rows of large spot sizes (200–500 μm), whereas some specialists offer direct applications (15). Macroaneurysms in the macular arterioles should be treated with caution due to possible disease complications resulting in thrombotic occlusion of the retinal artery distal to the aneurysm.

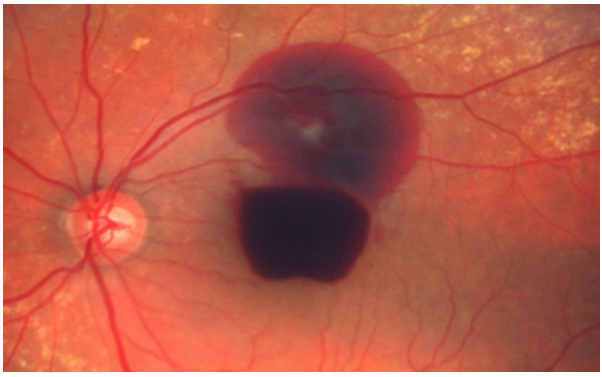

Figure 5. Fundus photo of retinal artery microaneurysm

6. Terson Syndrome

Terson syndrome is described as the presence of unilateral or bilateral intraocular hemorrhage in the subretinal space, beneath the internal limiting membrane, in the sub-hyaloid area or vitreous (Figure 6), which is related to traumatic brain injury, intracerebral hemorrhage, or subarachnoid hemorrhage (SAH) (16). However, there is no clear data regarding the location of the aneurysm. The hemorrhage mostly occurs in the first hour of SAH, but a delayed onset up to 47 days may also be observed. Terson syndrome develops in 8-19.3% of these conditions (17). Terson syndrome rarely develops in the pediatric population, most cases have been reported in adults.

Direct transmission of subarachnoid blood through the optic nerve sheath and a sudden rise in intracranial pressure causing rapid effusion of CSF into the optic nerve sheath may explain pathophysiologic mechanisms of Terson syndrome (18). FA may show a leakage site at the disc margin in vitreous hemorrhage of Terson syndrome. This appearance may explain the damage of the peripapillary retina. Funduscopic evaluation is the gold standard for the

diagnosis of Terson syndrome. Red reflex loss is observed in 20% of cases with Terson syndrome. In case of the invisible fundus, B-scan can be used to confirm vitreous hemorrhage. Orbital computer tomography also might be used as an axillary technique to detect intraocular vitreous hemorrhage Terson syndrome. Multiple ocular complications including epiretinal membrane (the most common), retinal folds/perimacular folds, proliferative vitreoretinopathy, preretinal fibrosis, retinal detachment, and ghost cell glaucoma have been reported in Terson syndrome (19). Low Glasgow coma scale is related to a higher incidence of Terson syndrome (17). Higher mortality rates and poorer neurological outcomes are observed in patients with SAH and Terson syndrome than patients with SAH alone (19).

Intraocular hemorrhage in Terson syndrome frequently resolves spontaneously with reversible visual impairment, but in some cases, permanent vision loss may develop (17). Although there is not an optimal timing for v pars plana vitrectomy (PPV) in Terson syndrome, vitreous hemorrhage can be followed-up for up to 3 months before the decision for PPV (19). If the hemorrhage is bilateral or develops at a young child with a high risk for the development of amblyopia, the surgical procedure should be considered sooner within 4-8 weeks. Although multiple studies have concluded good results following PPV, studies have demonstrated no significant difference in final visual acuity between conservative management and PPV (17, 19). However, visual recovery seemed to be earlier in PPV even denser vitreous hemorrhage. Regarding PPV outcomes, patients <45 years old presented with better final visual acuity than older patients. Surgical ILM peeling has been reported in the treatment of Terson syndrome (17). Intravitreal TPA and gas for persistent conditions and Nd-YAG for premacular subhyaloid hemorrhage have been also described in Terson syndrome (17).

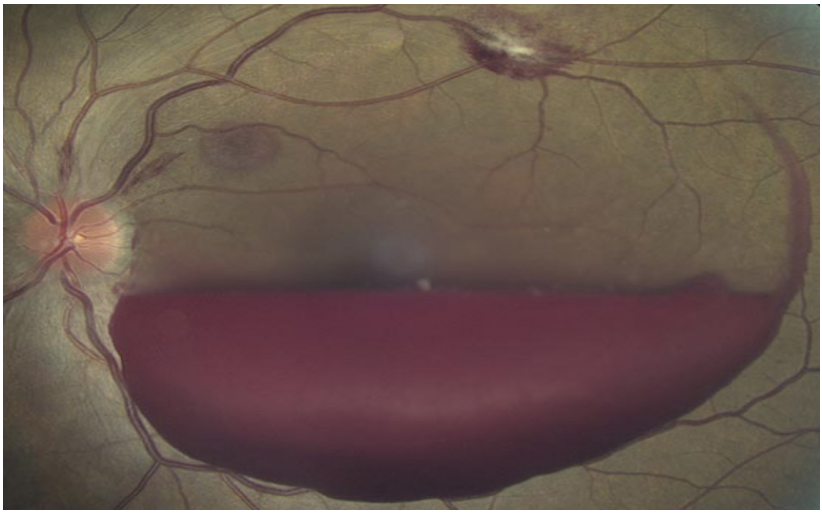

Figure 6. Fundus photo of Terson syndrome

7. Radiation Retinopathy

Ionizing radiation following external beam or local plaque therapy has the potential risk of damaging the retinal vessels (20). Exposure to doses of 30–35 grays (Gy) or more can cause clinical symptoms, but retinopathy might occur even at levels of 15 Gy in case of external-beam radiation (21). The volume of retina affected, total dose exposure and fractionation scheme play important roles in identifying the threshold dose for the development of radiation retinopathy (20, 21).

Slow progression and delayed onset (months to years), and ocular findings including microangiopathic alterations, microaneurysms, retinal hemorrhages, cotton-wool spots, capillary telangiectasis, perivascular sheathing, macular edema, and optic nerve head edema are among the features of radiation retinopathy (Figure 7). Retinal ischemia and subsequent neovascularization may be detected in FA images. These similar features are also observed in other vascular diseases, especially diabetic retinopathy. So, the history of radiation therapy should be asked in the diagnosis. Radiation retinopathy is usually examined earlier after brachytherapy when compared to external-beam radiation. Clinical signs may range from asymptomatic impact to visual impairing effect. The degree of visual impairment is associated with the involvement of the central macula.

Anti-VEGF may have an effective therapeutic impact on radiation retinopathy (22). Since laser photocoagulation causes retinal atrophy and scars,

it has less effective treatment outcomes (22). Radiation retinopathy may lead to complications including CRVO, central retinal artery occlusion, choroidal neovascularization, vitreous hemorrhage, tractional retinal detachment, optic atrophy, and neovascular glaucoma.

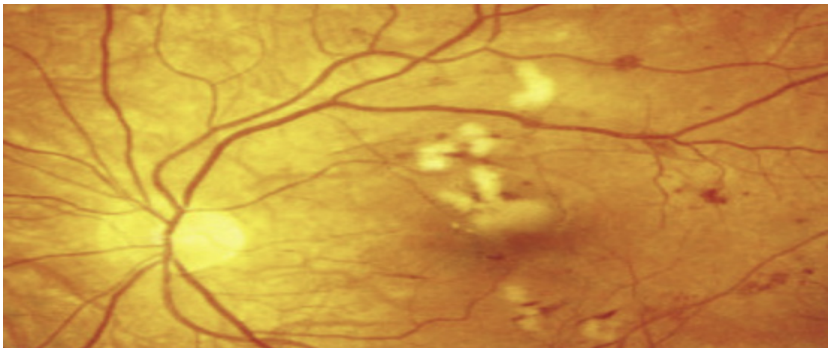

Figure 7. Fundus photo of radiation retinopathy

8. Purtscher Retinopathy and Purtscherlike Retinopathy

Purtscher retinopathy has been described following acute compression injuries to the head or thorax with the result of unilateral or bilateral vision loss. The pathophysiology of Purtscher retinopathy is explained as an outcome of injury-induced complement activation, leading to granulocyte aggregation and leukoembolization and subsequently occlusion of small arterioles. Hemorrhages, polygonal-shaped areas of retinal whitening (Purtscher flecken), Cotton-wool spots, and retinal edema are common findings examined around the optic nerve head (Figure 8), and FA imaging demonstrates vascular leakage and arteriolar obstruction (23). Additionally, afferent pupillary defect and optic nerve head edema may be examined. Optic atrophy development and infarction may cause permanent visual impairment (24).

Purtscher's original description is involved trauma-associated complement activation. So, various conditions other than trauma with activation of complement and having similar ophthalmic findings are defined as Purtscherlike retinopathy (23). These conditions include retinopathy related to pancreatitis, systemic lupus erythematosus, fat embolism, and amniotic fluid embolism.

No effective therapy option exists for Purtscher retinopathy related to traumatic injury. In patients with retinopathy associated with systemic vasculitis, steroid treatment may be theoretically effective (24). It is important to control

the underlying disease with other medications. Surgical management may be required for traumatic chest and head injuries that are related to Purtscher retinopathy.

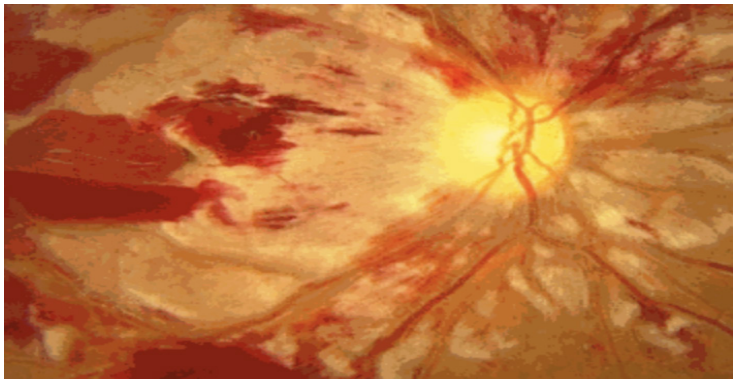

Figure 8. Fundus photo of Purtscher retinopathy

9. Valsalva retinopathy

Valsalva retinopathy is a specific form of retinopathy with pre-retinal and hemorrhage, secondary to a sudden increase in intrathoracic pressure (Figure 9.1) (25). Retinal hemorrhages are related to heavy lifting, coughing, vomiting, straining at the toilet, heavy physical exertion, sneezing, vigorous sexual activity, and compressive trauma. Preretinal hemorrhage in Valsalva retinopathy occurs secondary to rupturing of superficial retinal vasculature caused by any of these conditions. The mechanism of a Valsalva maneuver is described by a sudden increase in intrathoracic or intraabdominal pressure against a closed glottis, which causes a rapid increase of intravenous pressure within the eye, leading to spontaneous rupture of retinal capillaries (26). Prognosis is mostly good, with spontaneous resolution of the hemorrhage within months after onset. Patients with Valsalva retinopathy present with unilateral or bilateral vision loss. Visual impairment level depends on the location of the hemorrhage and the layer of retina involved. In case of Valsalva retinopathy-induced vision loss without a history of Valsalva maneuver and physical exertion, retinal vascular disease, other systemic conditions, and anticoagulants use should be investigated.

Patients with Valsalva retinopathy usually have the following symptoms: floaters, cloudy or hazy vision, red-tinged hue to the vision, sudden painless partial or total vision loss. Visual symptoms and ocular findings are associated

with the severity of the Valsalva force and the underlying status of the retinal vessels. The size of hemorrhages may vary including, a large pre-retinal hemorrhage as much as several disc diameters. Subconjunctival hemorrhage and skin petechia of the hand and neck may be observed. A well-circumscribed pre-retinal hemorrhage in either the sub-hyaloid or sub–internal limiting membrane (ILM) space and rarely in the subretinal area can be examined in fundus evaluation. Valsalva retinopathy tends to involve the macular area (both premacular and paramacular). Macular edema accompanied by edematous transudates and superficial intraretinal hemorrhages has also been defined.

Valsalva retinopathy might be complicated with the following results: Permanent vision loss, toxic damage of hemoglobin and iron to the retina, choroidal detachment, destruction of the retinal cellular structure, and postoperative epiretinal membrane formation following Nd: YAG laser membranotomy. Valsalva retinopathy should be differentiated from the following diseases including, retinal vein occlusion (RVO), diabetic retinopathy, hypertensive retinopathy, Purtscher retinopathy, and Purtscher-like retinopathy, Terson syndrome, anemic retinopathy, sickle cell retinopathy, retinal macroaneurysm, hemorrhagic posterior vitreous detachment, colonic polyps, and ocular parasitic Infection.

Serial color retinal photography may be performed to assess the progression and the resolution of retinal hemorrhages over time. FA should be used to localize the hemorrhage and to rule out ischemia, retinal or choroidal neovascularization, or other vascular pathologies not related to Valsalva retinopathy. In case of media opacity caused by blood, B-scan ultrasonography can be used to visualize the retina and to rule out a retinal break, retinal detachment, or tumor as the reason for the vitreous hemorrhage. Moreover, optical coherence tomography (OCT) can be used to preciously define the localization of the hemorrhage whether premacular hemorrhage (eg, subhyaloid, sub–internal) or perimacular (Figure 9.2) (27).

Conservative medical therapy is observation. Preretinal hemorrhage (sub–internal limiting membrane and sub-hyaloid) in Valsalva retinopathy mostly resolves within a few weeks or months. However, vitreous hemorrhage might resolve lately up to 6 months, depending on the location, layer of the retina, density, and size of the hemorrhage. Anticoagulant medication use and heavy physical activity should be avoided to prevent re-hemorrhage and sleeping in a sitting position should be instructed to facilitate the resolution

of the hemorrhage. Meanwhile, a fiber-rich diet and stool softeners should be suggested for patients with constipation. Although there is no certain method to prevent the occurrence of Valsalva retinopathy, patients should be instructed to refrain from holding breath during lifting, straining during bowel movements, sneezing, and coughing to decrease the risk. should also be avoided. In addition to observation, membranotomy with Krypton lasers, Q-switched Nd: YAG lasers, pulsed Nd: YAG lasers, and frequency-doubled Nd: YAG lasers have been recently described for the surgical treatment of large (>3-disc diameters in size) macular sub-hyaloid hemorrhages with less than the duration of 3 weeks (28). The membranotomy leads to prompt drainage of the hemorrhage into the inferior vitreous cavity, which provides rapid recovery of central visual acuity.

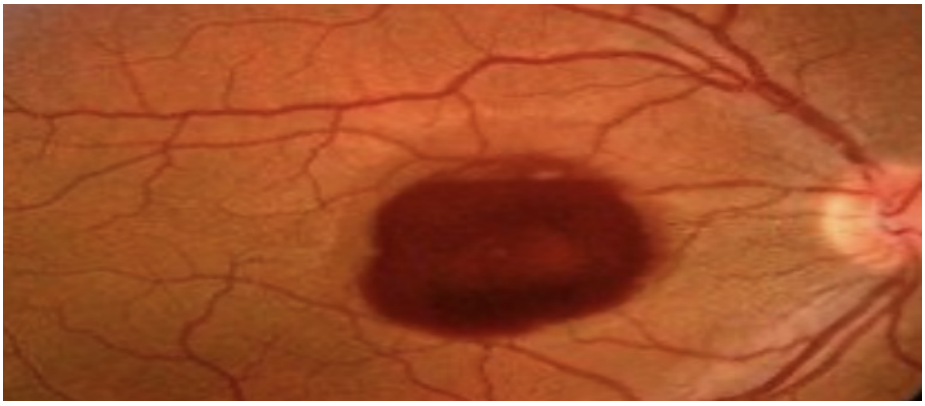

Figure 9.1. Fundus photo of Valsalva retinopathy

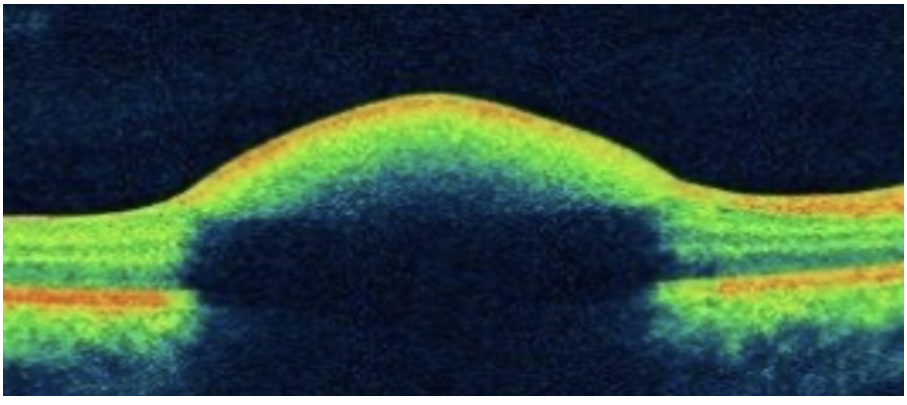

Figure 9.2. Optical coherence tomography of Valsalva retinopathy

10. Lipaemia Retinalis

Lipemia retinalis is a rare finding of hypertriglyceridemia representing the abnormal appearance of the retinal vasculature. Family history of lipid abnormalities should be investigated. Hypertriglyceridemia may develop as a primary familial disease or secondary to other disorders. These familial diseases include LPL deficiency, endogenous circulating LPL inhibitor, and ApoC-II deficiency (29). Lipemia retinalis usually develops when the serum triglyceride concentrations are higher than 1000 mg/dl in especially type 1-5 hyperlipoproteinemia with different underlying reasons including chromosome microarray and lipid gene sequencing error of homozygous lipoprotein lipase gene coding mutation (30).

Lipemia retinalis can be diagnosed with clinical assessment of dilated fundoscopic examination and coexistent hypertriglyceridemia. Ocular exam findings include fundoscopic changes and corneal arcus in patients with lipemia retinalis. In addition to the ocular examination, patients should also have cardiovascular exams including the evaluation of atherosclerotic alterations, the check of vital signs, and skin assessment for eruptive xanthomas. The early ocular manifestations of lipemia retinalis begin to appear in the peripheral retina, and while triglyceride concentrations rise, these signs spread to the posterior pole (Figure 10). At triglyceride concentrations of 2500–3499 mg/dL, a creamy and thin peripheral vasculature is observed, at levels of 3500–5000 mg/dL, posterior pole vasculature is affected and becomes creamy color, and at levels over 5000 mg/dL, the whole fundus appears in salmon-colored, with creamy vessels that might be differentiated by size only. The clinical appearance is classified as early, moderate, or marked (Stages I-III, respectively).

Other than fundus examination, there are some techniques to assess ocular findings in lipemia retinalis. Fluorescein and indocyanine angiography imaging modalities are usually unremarkable. Spectral-domain optical coherence tomography can show inner retinal alterations related to lipemia retinalis. OCT may represent white lesions, hyperreflective dots, and engorged retinal vasculature in the inner nuclear and ganglion cell layer that might gradually disappear within several months than gross following the normalization of lipid concentrations (31). This improvement in OCT is slower than the gross improvement, which usually occurs within 5 days following the normalization of serum triglyceride lipid levels (31).

Lipemia retinalis should be differentiated from hypertensive retinopathy, retinal artery or vein occlusion, and diffuse choroidal hemangioma. Lipemia retinalis is mostly asymptomatic and usually does not impair visual acuity unless retinal ischemia or retinal vascular occlusion develops. No treatment of lipemia retinalis itself is needed, but hypertriglyceridemia should be treated via controlling the lipid levels due to systemic complications including stroke, acute myocardial infarction, and cardiovascular accidents as well as the ocular effects such as retinal ischemia or retinal vascular occlusion. Decreasing and control of serum triglyceride concentrations can prevent the development of lipemia retinalis. Correction of the lipid concentrations can reverse the abnormal signs within 1 week (32). Low-fat diet without breast milk supplementation might be effective in the treatment of infants diagnosed with severe lipemia retinalis related to extensively high serum triglyceride concentrations (32).

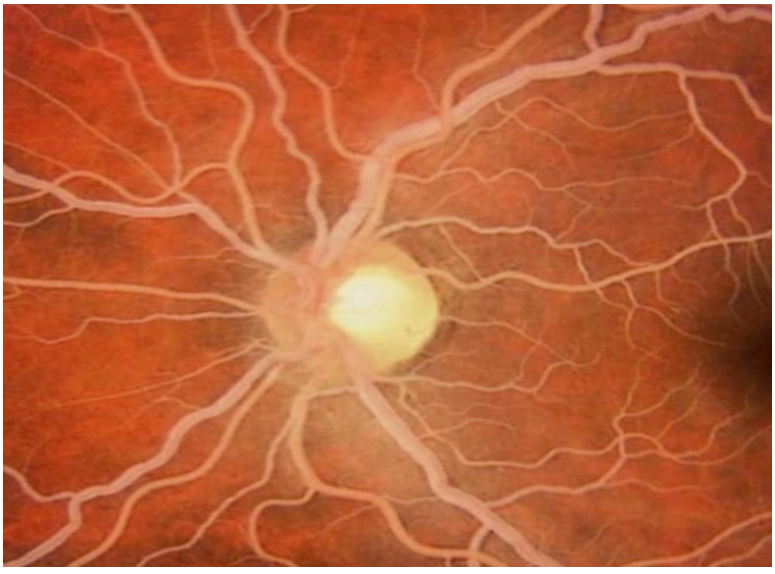

Figure 10. Fundus photo of Lipaemia Retinalis

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