Branch Retinal Vein Occlusions (BRVO)

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Course Description

- This course offers an overview on branch retinal vein occlusion (BRVO), focusing on the clinical features, diagnosis and management, and proposed mechanisms for vessel occlusion and retinal edema. Additionally, background and statistics on BRVO is also presented.
Course objectives

• Understand the general background and current statistics of BRVO
• Understand the classifications systems of BRVO and its implications
• Understand the etiology, risk factors and mechanistic causes
• Know the retinal signs and presenting symptoms of BRVO patients
• Know the potential retinal complications and how it is managed
• Know how to manage and co-manage these types of patients
BRVO: Introduction

• Definition:
  – An obstruction of a branch of the retinal venous system
    • Sup-temp: 66%
    • Inf-temp: 22-43%
    • Nasal: 0.5-2.6%
    • Macular: 24%
      – * Closer to optic nerve = greater area of retina involved and more serious the complications
Facts about BRVO

• Most common cause of **SUDDEN, PAINLESS, UNILATERAL** loss of vision
• Retinal vein occlusion is the **SECOND** most common vascular disease after diabetic retinopathy
• **Three** times more common than central retinal vein occlusion
• First case of BRVO reported by Leber in 1877

• Around 13.9 million adults are affected globally
• The 15 year incidence rate is estimated to be 1.8%
BRVO: Major vs Macular

• BRVO is divided into two entities:
  – 1. Major BRVO
    • Major branch retinal vein is occluded
      – Quarter or more of retina is affected
    • Usually asymptomatic
    • Involves section of visual field corresponding to area of BRVO
  – 2. Macular BRVO
    • Macular venule is occluded
      – Only part of macula affected
    • Always central VA loss
    • Normal peripheral visual field
BRVO: Ischemic vs Non-ischemic

- **Two types:**
  - **Non-ischemic** (64%): <5 disc areas of capillary non-perfusion on FA
  - **Ischemic**: ≥ to 5 disc areas of capillary non-perfusion on FA
Symptoms

• Asymptomatic
• Blurring of vision (if macula involved)
  – Normal vision (if macula not involved)
• Sudden
• Unilateral
• Painless
• Blind spot in VF or VF loss
• Might worsen over the first few days

*Probability of developing 2\textsuperscript{nd} episode of BRVO in other eye within 4 years is 7%
Signs: Acute

• Acute: first 3-6 months
• Unilateral
  – Bilateral (extremely rare) – may indicate systemic thrombophilia
• Acute signs
  – Dilated tortuous vein distal to occlusion
  – Intraretinal hemorrhages (respecting horizontal raphe)
  – Soft (CWS-ischemia) and hard exudates
  – Retinal/macular edema
  – Subhyaloid heme (occasionally)
  – Vitreous heme (rare)
Signs: Chronic

- Chronic BRVO: 9-12 months
  - Vessel abnormality
    - Collaterals around area of occlusion
    - Arteriolar narrowing & sclerosis
    - Vascular sheathing
    - Retinal capillary telangiectasia
    - NVD or NVE (36% with nonperfusion >5DD)
  - Macular abnormality
    - Macular edema (50%)
    - Pigment clumps at macula
    - Macular nonperfusion (assessed with FA)
  - Retinal abnormality
    - Loss of retinal transparency
    - Hard exudates
    - Epiretinal membrane (20%)
    - Retinal detachment (rare)
Epidemiology

• Usually occurs in elderly patients
  – 50-70yrs old

• No racial or gender predilection
  – Possibly slight male and hyperopic predilection
Etiology

- Arteriosclerosis
  - Atherosclerosis
- Inflammatory conditions that cause systemic vasculitis
  - Behcet’s disease
  - Polyarteritis nodosa
- Thrombophilic conditions

Hypertension: 50-70%
Hyperlipidemia
Coronary artery disease
Peripheral vascular diseases
DM (least likely)
Etiology (cont.)

• **Younger patients:**
  - Oral contraceptive pills
  - Collagen vascular disease
  - Acquired immunodeficiency syndrome (AIDS)
  - Protein S/protein C/antithrombin III deficiency
  - Factor XII deficiency
  - Antiphospholipid antibody syndrome
  - Activated protein C resistance

• **Rare:**
  - Hypercoagulable states
    - clot
  - Hyperviscosity states
    - thick
  - Systemic lupus erythematosus
  - Syphilis
  - Sarcoid
  - Homocystinuria
  - Malignancies
  - Optic nerve drusen
  - External compression
Risk Factors

• Systemic hypertension
  – STRONGEST independent risk factor (>50 age group)
• Hyperlipidemia
  – Twice as common in BRVO
  – Hypertension + hyperlipidemia = independent risk factor
• Cardiovascular disease
• Increased body mass index (BMI) at 20 yrs of age
• Smoking
• High intraocular pressure
  – Primary Open Angle Glaucoma
    • CRVO: deformation of lamina cribrosa in glaucoma
Risk Factors (cont.)

• High serum levels of $\alpha_2$ globulin
• Hyperhomocysteinaemia
• Deficiency in the protein C pathway
• Higher activated factor VII concentrations
• High blood viscosity
• Hyperopia: shorter axial length eyes
Not a risk factor

• DM is lacking evidence to be an independent risk factor
• Higher serum levels of high-density lipoprotein
• Greater alcohol consumption
BRVO

what's the Problem?
Let’s Review Blood Vessels

**Tunica externa (Adventititia):**
- Connective tissue

**Tunica media**
- Elastic fiber, connective tissue, polysaccharide substances
- Smooth muscle, controls caliber of vessels

**Tunica intima**
- Single layer of simple squamous endothelial cells

*Small veins and arteries SHARE the tunica externa (adventitia)*
At the site of the problem

• Three mechanisms:
  – Compression of vein at arteriovenous (A/V) crossing
  – Degenerative changes of vessel wall
  – Abnormal hematological factors causing stagnation of venous circulation forming a thrombus

**Can be due to combination of these mechanisms!!**

At the site of the problem

- Three mechanisms:
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At the site of the problem

Compression of vein at arteriovenous (A/V) crossing

- First reported 1928 by Koyanagi
- Venous lumen narrowing at AV crossings
- Sharing common adventitial sheath
- Site: AV crossings
- Where a retinal artery crosses over (anterior) the vein
  - Duker and Brown: 26 eyes with BRVO, 100% artery over vein
  - Zhao et al.: 106 eyes with BRVO, 99% artery over vein
  - Normal eyes without BRVO: 60% artery over vein
- Risk increases with arteriolar sclerosis
At the site of the problem

• Three mechanisms:
  – Compression of vein at arteriovenous (A/V) crossing
  – Degenerative changes of vessel wall
  – Abnormal hematological factors causing stagnation of venous circulation forming a thrombus
Degenerative changes of vessel wall

- Jefferies et al.
  - No expected venous compression in histological view, vein bends into nerve fiber layer
  - Yes thrombus (months to several years) with varied extent of recanalization

- Seitz
  - BRVO caused by changes in venous endothelium and intima media via compression from overlaying artery
  - Thrombus formation is a secondary process
  - Supported by Frangieh et al. : 90% of the patients had evidence of intima layer hypertrophy and intravenous thrombosis
At the site of the problem

- Occlusion of vein
- Damage to venous endothelium and intima media
- Turbulent blood flow
- Mechanical obstruction of vein
- Contraction of adventitial sheath shared by artery and vein
- Sclerosis of retinal artery

**Confirmed by Christoffersen and Larsen: used FA in 250 patients with BRVO**
At the site of the problem

• Three mechanisms:
  – Compression of vein at arteriovenous (A/V) crossing
  – Degenerative changes of vessel wall
  – Abnormal hematological factors causing stagnation of venous circulation forming a thrombus
At the site of the problem

Abnormal hematological factors causing stagnation of venous circulation forming a thrombus

1. BRVO linked to hyperviscosity
   - Viscosity depends on:
     * Hematocrit: greater erythrocytes = larger aggregation
     * Plasma fibrinogen (required for aggregation)
   - Low blood flow + erythrocyte aggregation = higher blood viscosity

2. Dysregulation of thrombosis-fibrinolysis balance
   - Coagulation cascade
   - Sequence of coagulation is checked and inhibited by anticoagulants: protein C, protein S and antithrombin

*Inconsistent findings – unsure role of coagulation factors
SO THE VEIN IS BLOCKED, NOW WHAT?
Pathogenesis: mechanism

Compromised or obstructed venous flow → Retinal ischemia downstream from occlusion site → Ischemia up-regulates vascular endothelial growth factor (VEGF)

VEGF
- Increases proinflammatory cytokines
- Increases proangiogenic cytokines
- Breaks down blood-retinal barrier → macular edema
Mechanism for Macular Edema

- Vein occlusion
- Expression of VEGF and Interleukin-6 (IL-6)
- Breakdown blood-retinal barrier by damaging tight junctions of capillary endothelial cells, vitreoretinal adhesion, and secretion of VEGF and IL-6 into vitreous
- Fluid flux from vessels to tissues (macula)
- Ischemia
- Hinder capillary perfusion
Macular Edema

• Macular edema is closely correlated with retinal hypoxia
• Central macular hypoxia is linked to decrease VA
• Persistent hypoxia causes structural changes and permanent VA damage

• Campochiaro et al. : ischemia is not all or none, non-ischemic types can still have varying degrees of retinal ischemia
Complications

• Macular
  – Chronic macular edema
  – Macular nonperfusion
  – Epiretinal membranes
  – Small foveal hemes
  – Hard exudates

• Neovascularization
  – NVD & NVE
  – Vit heme
  – NVI & NVA

• Retinal detachments
  – Rhegmatogenous
  – Tractional
  – Exudative
Differential Diagnosis

• Diabetic Retinopathy
• Hypertensive retinopathy
• Central retinal vein occlusion
• Venous stasis retinopathy
• Ocular ischemic syndrome
• Leukemic retinopathy
• Retinopathy of anemia
• Papilledema
• Papillophlebitis (younger patients)
Evaluation

• **Medical History**
  – Systemic disease:
    • HTN, HLD, DM, h/o stroke, MI, TIA, hypercoagulable states
  – Smoking
• **BCVA, pupils, VFs**
• **Gonio – neovascularization** (rare)
• **IOP**
• **Check BP!!**
Evaluation

• **OCT**
  – Measure retinal thickness quantitatively
  – Useful in f/u of patients with macular edema secondary to BRVO

• **Fluorescein angiography**
  – Indication: ~ 3 months later if vision is still decreased despite hemes cleared
    • Determine reason for vision loss: macular edema vs macular ischemia
      – Treatment available for macular edema
      – Capillary non-perfusion: hypofluorescence
        • Ischemic: ≥5DD of capillary nonperfusion
      – Collaterals & new vessels can be differentiated
Systemic Work up

• According to **Branch Vein Occlusion Study:**
  – Recommend **AGAINST** extensive testing in patients with **TYPICAL** BRVO
  – Lab studies for **ATYPICAL** cases
    • Bilateral cases
    • Young patients
    • Patients with personal or family history of blood dyscrasias
      – Thromboembolism, prothrombin time & activated partial thromboplastin time, Protein C, protein S, factor V Leiden and antithrombin III, homocystine, antinuclear antibody, lupus anticoagulant and anticardiolipin, serum protein electrophoresis
  – Lab tests: Fasting blood glucose, CBC with differential and platelets, PT/PTT, ESR, etc
  – Medical consultation for complete cardiovascular eval
What are the treatments?

TREATMENT FOR THESE PATIENTS??
Treatment: What are we treating?

• Potential complications:
  – Macular edema $\rightarrow$ Vision loss
  – Retinal neovascularization $\rightarrow$ Retinal damage/detachment
  – Iris/angle neovascularization $\rightarrow$ Neovascular glaucoma

• Goal:
  – Eliminate macular edema
  – Eliminate retinal/iris/angle neovascularization
Ocular Treatments

• **Surgical care**
  – Macular grid laser photocoagulation
  – Scatter photocoagulation
  – Laser-induced chorioretinal anastomosis
  – Vitrectomy and arteriovenous decompression

• **Pharmacotherapy**
  – Intravitreal corticosteroid therapy
    • Triamcinolone (Kenalog-40)
    • Dexamethasone intravitreal implant (Ozurdex)
  – Intravitreal anti-VEGF
    • Bevacizumab (Avastin)
    • Ranibizumab (Lucentis)
    • Afibbercept (Eylea)
Management: Follow Up

• Initially, every 1-2 months for the first 4 months and then every 3-12 months, check for neo and macular edema

Just what the Doctor ordered!
Prognosis

• One important prognostic factor for final VA is the initial VA!
• ME and intraretinal hemorrhage usually resolve within 6-12 months
  – Collateral systems often develop
• ME resolves: 41% of cases by 7.5 months
• VA generally improves with time
  – 50-60% improve to 20/40 or better without treatment
  – 25% remain 20/200 or worse
• Retinal neovascularization: 36% eyes with nonperfusion > 5DD
• Vit heme: 41% eyes
• Bilateral BRVO: 4.5-6.5% at presentation
Comorbidities

• Branch retinal vein occlusion was associated with:
  – Increase in vascular causes of death (both cerebral and cardiac)
  – Increased risk of subsequently developing hypertension, diabetes, congestive heart failure, and cerebrovascular disease
    • Therefore, emphasizing the importance of preventive initiatives
Summary of BRVO

• BRVO is the most common cause of sudden, painless, unilateral loss of vision
• Hypertension is the STRONGEST independent risk factor
• Complications can involve the macula, neovascularization and retinal detachment
• Systemic work up is recommended for ATYPICAL cases:
  – Bilateral, young, personal or family history of blood dyscrasias
• FA recommended if:
  – VA < 20/40 after 3 months: edema vs ischemia
  – >5DD retina involved: ischemic vs non-ischemic
• Treatments target macular edema and neovascularization
  – Anti-VEGF therapy
Thank you

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Question 1

Which of the following statements is TRUE?

a) The inf-temporal quadrant is the most common site for BRVO

b) Nasal BRVOs tend to be the most symptomatic

c) Central retinal vein occlusions are THREE times more common than BRVOs

d) BRVO is the most common cause of sudden, painless, unilateral loss of vision

e) None of the above are TRUE
Question 2

Which of the follow statements concerning BRVO classification is TRUE?

a) A major BRVO is defined as having less than a quarter of the retina affected
b) A macular BRVO is very likely to be asymptomatic
c) A non-ischemic BRVO will have less than 5 disc diameters of capillary non-perfusion on FA
d) An ischemic BRVO will have less than 5 disc diameters of capillary non-perfusion on FA
e) None of the above are TRUE
Question 3

Which of the following is an ACUTE sign of BRVO?

a) Soft and hard exudates
b) Collateral vessels
c) Neovascularization
d) Macular non-perfusion
e) None of the above are ACUTE signs of BRVO
Question 4

Which of the following is a risk factor for BRVO?

a) Hypertension
b) Increased body mass index (BMI)
c) Smoking
d) Hyperopia
e) All of the above
Question 5

Which of the following statements concerning blood vessels is TRUE?

a) The tunica media consists of a single layer of simple squamous endothelial cells
b) Small veins and arteries share the tunica externa (adventitial sheath)
c) The tunica externa consists of connective tissue and smooth muscles
d) The tunica intima helps control the caliber of the vessel
e) None of the above is TRUE
Question 6

Which of the following is NOT a proposed mechanism for the formation of a vein occlusion?

a) Compression of vein at arteriovenous crossing
b) Degenerative changes of vessel wall
c) Abnormal hematological factors causing stagnation of venous circulation forming a thrombus
d) Retinal ischemia upregulating VEGF which breaks down blood-retinal barrier
e) All of the above are correct
Question 7

Which of the following statements is TRUE?

a) Retinal ischemia increases production of proinflammatory cytokines and proangiogenic cytokines

b) Non-ischemic types of BRVO do not have any degree of retinal ischemia

c) Persistent hypoxia causes structural changes to the retina and nonpermanent VA damage

d) VEGF is mainly produced by the choroid and vitreous
Question 8

Which of the following statements is TRUE?

a) The OCT is helpful in measuring the retinal thickness quantitatively

b) Fluorescein angiography is indicated at 3 months if vision is still decreased despite hemorrhages being cleared

c) Fluorescein angiography can help differentiate between collaterals and new vessels (neovascularization)

d) The OCT is useful to follow patients with macular edema

e) All of the above are TRUE
Question 9

Which of the following statements is TRUE?

a) A young patient that presents with bilateral BRVO is a typical case

b) A patient with a personal or family history of a blood dyscrasia presenting with a BRVO is a typical case

c) Extensive testing is not recommended for typical BRVO cases

d) Extensive testing is not recommended for atypical BRVO cases

e) None of the above are TRUE
Question 10

Which of the following statements is TRUE?

a) One important prognostic factor for final VA is the extent of hemorrhages present during the initial exam

b) A goal for treating BRVO is to eliminate macular edema

c) Intravitreal corticosteroid therapy is the first line of treatment for macular edema secondary to BRVO

d) Recommended follow up is every 12 months to check for neovascularization and macular edema

e) None of the above are TRUE