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Branch Retinal Artery Occlusion Associated with Patent Foramen Ovale During Pregnancy

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ABSTRACT

Patent foramen ovale, an embryological defect presenting in approximately 25% of the adult population, has been associated with ischemic stroke and retinal artery occlusion, particularly in combination with other pro-embolic risk factors such as pregnancy. This report presents that case of a pregnant patient who presented with a branch retinal artery occlusion. Systemic work-up revealed a patent foramen ovale. Branch retinal artery occlusion, a form of acute, ischemic stroke, is a medical emergency, and patients presenting with such should be urgently referred to a emergency department or stroke center. Patent foramen ovale should be considered as a potential etiology of retinal artery occlusion, particularly in young patients lacking vasculopathic risk factors

INTRODUCTION

Branch retinal artery occlusions represent a form of acute, ischemic stroke. They are associated with increased risk of cerebral stroke and mortality, particularly when underlying systemic aetiologies are not treated.[1–4] As such, health care providers encountering acute, symptomatic branch retinal artery occlusions should immediately refer these patients to a dedicated stroke center or emergency department for thorough systemic evaluation.[1,2] Unfortunately, widespread adoption of this practice is lacking amongst eye care providers.[5,6] In young patients, particular attention should be made to vasculitis, cardiac pathology, and hypercoagulable states.[2]

This case report describes a branch retinal artery occlusion occurring in a young, pregnant female which was the presenting feature of patent foramen ovale. This report with review retinal artery occlusion, its presentation, natural history and will discuss the importance of a prompt systemic evaluation in the setting of retinal artery occlusion. The necessary acute investigations and etiological work-up will be outlined.

CASE REPORT

A 30 year-old female presented with complaint of a dark spot in her vision in the right eye for the past two days. She denied other changes to vision, and denied recent eye injuries or trauma. Ocular history was unremarkable. Medical history included hypothyroidism, and the patient was 9-weeks pregnant. She was a former smoker. She denied hypertension, diabetes, or previous stroke. Current medications included 100 mcg levothyroxine once per day and a pre-natal multivitamin.

Presenting unaided distance Snellen visual acuity was 20/20 in both the right and left eyes. Extraocular motilities were smooth, full and unrestricted. Confrontation visual fields were full to finger count in both eyes. Pupils were equal, round and reactive to light in both eyes without relative afferent pupillary defect. Right-arm, seated blood pressure was 111/75 mmHg.

Anterior segment examination was unremarkable. The conjunctiva was white and quiet, the cornea was clear, the anterior chamber was deep and quiet and both irides were flat and intact. The crystalline lens was clear in both eyes. Intraocular pressure was 12 mmHg and 15 mmHg in the right and left eyes respectively by Goldmann applanation tonometry.

Dilated fundus examination using 1 drop of 1.0% tropicamide with punctal occlusion was remarkable for localized pallid retinal swelling within the superior aspect of the right macula. There was no visible embolus. This area corresponded to hyperreflective inner retinal thickening with posterior shadowing on optical coherence tomography (OCT). Using OCT-Angiography there was partial superficial and deep capillary plexus non-perfusion in the corresponding area. The right optic nerve head was pink and distinct with 0.4 cup-to-disc ratio in both eyes. There was a normal course and caliber of blood vessels. Peripheral retinal examination was unremarkable. The left eye posterior segment was unremarkable.

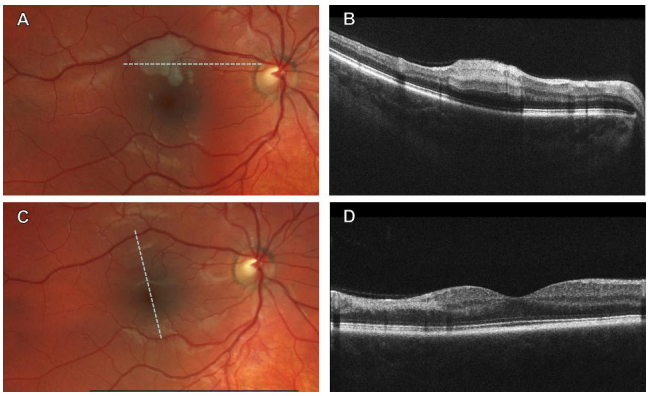

Figure 1: Serial colour fundus photography and optical coherence tomography imaging of the right eye. Baseline: A & B. 1-month follow-up: C & D. A) Pallid retinal edema is appreciated within the superior aspect of the macula. No embolus is visible. B) Corresponding hyperreflective, inner retinal thickening with posterior shadowing. C) Resolving, trace retinal edema. Reperfusion of the occluded retinal arteriole. D) Early, atrophic inner retinal thinning. Normal foveal architecture. Outer retinal layers are intact.

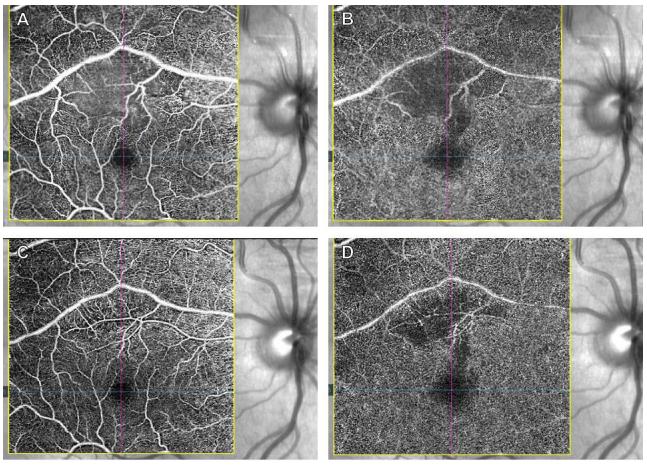

Figure 2: Serial optical coherence tomography angiography (OCT-A) imaging of the right eye. Baseline: A & B. 1-month follow-up: C & D. A) Superficial Vascular Plexus (internal limiting membrane to inner plexiform layer) showing a focal area of capillary non-perfusion. B) Deep vascular plexus (outer plexiform layer) showing a focal area of capillary non-perfusion with partial shadowing. C) Superficial Vascular Plexus showing reperfusion of the previously occluded arteriole. Minimal superficial capillary plexus non-perfusion. D) Deep vascular plexus showing residual capillary non-perfusion.

The patient was diagnosed with a right branch retinal artery occlusion and was subsequently seen in the hospital's emergency department for a comprehensive stroke evaluation that day. This included neuro-imaging with magnetic resonance imaging (MRI) and MRI-angiography of the head, carotid artery ultrasound, echocardiogram with bubble study, and a hypercoagulability panel. The latter included erythrocyte sedimentation rate, C-reactive protein, prothrombin time, International Normalized Ratio, fibrinogen, antithrombin III, Protein S, Protein C, beta-2 glycoprotein, lupus anticoagulant, prothrombin/Factor II G20210A variant, factor VIII, and cardiolipin antibodies. Remarkable findings included decreased protein C and protein S function, and increased pro-thrombin time and International Normalized Ratio. Echocardiogram revealed patent foramen ovale with right to left shunt. The emergency department physician prescribed clopidogrel 75mg once per day and aspirin 81mg once per day as secondary stroke presentation.

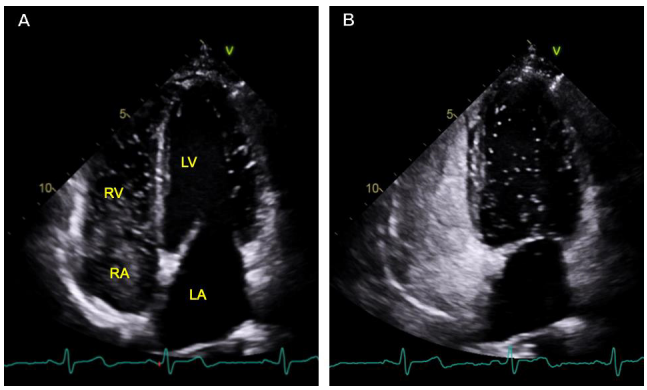

Figure 3: Trans-thoracic echocardiography bubble study revealing patent foramen ovale with right-to-left shunt. A) Apical 4-chamber view of heart immediately following intravenous injection of agitated saline. Microbubbles can be observed in the right atria and right ventricle. B) Apical 4-chamber view of heart several seconds after intravenous agitated saline injection. Microbubbles are visualised in left ventricle. Dense bubbles in right atria and ventricle cause opacification. RV: Right ventricle; RA: Right atrium; LV: Left ventricle; LA: Left atrium; V: Ventral.

The patient was evaluated by out-patient neurology, and assessment was unremarkable. The neurologist recommended consideration of post-partum surgical closure of the patent foramen ovale and referred her to a cardiologist for assessment. Assessment was also completed by a hematologist who attributed decreased protein C and protein S function to physiological changes during pregnancy and recommend observation.

The patient was seen in the optometry clinic for follow-up evaluation 1-month after initial presentation. At this time, unaided distance visual acuity was 20/20 in both eyes. Extraocular motilities, confrontation visual fields and pupil assessment was unchanged from previous assessment. Anterior segment examination was unremarkable, and there was no neovascularization of the iris. Intraocular

pressure was 14mmHg in the right and left eye by Goldmann applanation tonometry. A resolving branch retinal artery occlusion with trace retinal edema was noted with dilated fundus examination following 1 drop of 1.0% tropicamide with punctal occlusion. On OCT there was inner retinal disorganization and early atrophic thinning in the corresponding area. OCT-angiography revealed reperfusion of the previously occluded retinal arteriole, however there was persistent deep capillary plexus non-perfusion.

The patient was advised to continue care with neurology, cardiology, and primary care. Follow-up in 3-months was arranged.

DISCUSSION

Branch retinal artery occlusions are a form of acute, ischemic stroke which presents with retinal whitening and opacification in the distribution of the occluded retinal arteriole due to acute ischemic retinal edema.[7] Ancillary imaging using OCT will typically demonstrate increased inner retinal thickness and disorganization.[7,8] Acute edema typically resolves spontaneously over several months after which retinal appearance is typically normal on funduscopy.[7] However, due to permanent inner retinal damage, OCT imaging will show atrophy, thinning and disorganization of inner retinal layers.[7,9] Additional retinal sequelae of branch retinal artery occlusion include sectoral optic nerve head pallor, and retinal arteriolar attenuation and sheathing.[7] Ocular neovascularization following branch retinal artery occlusion is an exceedingly rare complication,[10] and did not occur during the course of follow-up for this patient.

Epidemiological studies estimate that the annual incidence of branch retinal artery occlusions is 5.12 per 100 000 person-years.[11] The incidence of branch retinal artery occlusion increases with age, with the greatest incidence in the 80 to 84 years age group for males, and 75 to 79 years age group for females.[11] Several systemic health conditions have been associated with increased risk of retinal artery occlusions. Most commonly, these include diabetes mellitus, hypertension, ischemic heart disease, transient ischemic attack, cerebral vascular accident, carotid artery disease, and current smoking.[12,13] Other risk factors for retinal arterial occlusion include atrial fibrillation, renal disease, sleep apnea, systemic inflammatory disease, hypercoagulable states, and glaucoma.[13,14] Additionally, both patent foramen ovale and pregnancy have been associated with increased risk of retinal artery occlusions.[15,16]

Branch retinal artery occlusion is associated with an increased risk of ischemic cerebral stroke, especially within the initial weeks following acute presentation.[3,4] Fallico et al. estimate that approximately 25% of acute, branch retinal artery occlusions have concurrent acute cerebral ischemia on MRI.[3] In this patient's case, no evidence of cerebral stroke or ischemia was noted during neuro-imaging and neurological assessment was unremarkable. Retinal artery occlusion is also associated with an increased risk of myocardial infarction and mortalities, particularly due to cardiovascular and cerebrovascular disease.[11,17,18] Increased mortality rate is more significant for females, particularly in individuals younger than 50 years.[11] As such, acute, retinal artery occlusions are medical emergencies and eye care providers should promptly refer individuals presenting with acute branch retinal artery occlusion to an emergency department or dedicated stroke centre for evaluation.[1,2] Initial evaluation in the emergency department should typically include neuro-imaging of the brain with non-contrast computed tomography or diffusion-weighted magnetic resonance imaging, vascular imaging of the head and neck with computed tomography angiography, magnetic resonance angiography or cervical artery ultrasound, and point-of-care laboratory investigations (Fig. 4).[19–21] Investigations to rule-out giant cell arteritis, including erythrocyte sedimentation rate, C-reactive protein and platelet count, should be concurrently performed, especially in older patients (>50 years) with central retinal artery occlusion.[1,22] In patients without a clear cause of retinal artery occlusion, additional investigations should be pursued.[1,23] These may include ambulatory cardiac rhythm monitoring to detect atrial fibrillation, transesophageal or transthoracic echocardiography to examine for a cardioembolic source, and additional laboratory investigations to assess for hypercoagulable states or septic emboli.[1,19,21,23] Echocardiography with bubble study should be obtained for young patients (<60 years) with presumed cryptogenic stroke.[21]

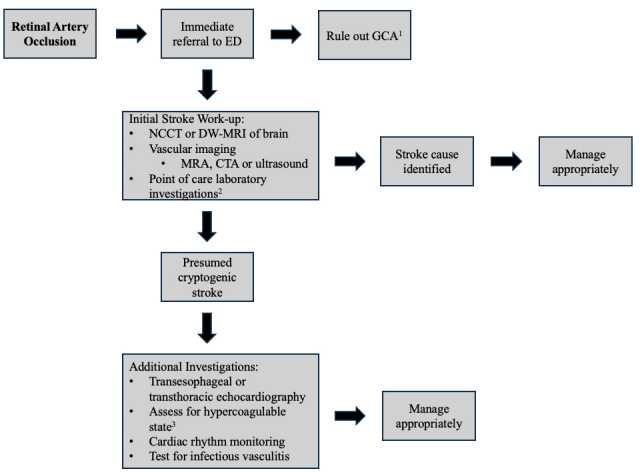

Figure 4: Proposed systemic evaluation and etiological work-up for patients with retinal artery occlusions.

1: Testing to rule-out giant cell arteritis to consider includes erythrocyte sedimentation rate, C-reactive protein, platelet count, with or without temporal artery biopsy.[22]

2: Point of care laboratory investigations to consider include complete blood count, electrolytes, coagulation (International normalized ratio, prothrombin time, partial thromboplastin time), random blood glucose, renal function (creatinine, estimated glomerular filtration rate), and ALT (alanine aminotransferase). Additional testing to be completed following acute work-up may include lipid profile, glycated hemoglobin (HbA1c), and fasting glucose or glucose tolerance test.[21]

3: Hypercoagulable tests to consider include the following: anti-cardiolipin antibodies, antiphospholipid antibodies (anti-beta-2-glycoprotein), factor V Leiden mutation, prothombin gene mutation, factor VIII, protein S, protein C, homocysteine, and vitamin B12.[21]

ED: Emergency department.
GCA: Giant cell arteritis.
NCCT: Non-contrast computed tomography.
DW-MRI: Diffusion-weighted magnetic resonance imaging.
MRA: magnetic resonance angiography.
CTA: Computed tomography angiography.

In collaboration with a multidisciplinary healthcare team and considering the underlying etiology and comorbid diseases, secondary stroke prevention with anti-platelet therapies should be considered.[1,2] In the acute setting, this generally includes dual-antiplatelet therapy. Single agent anti-platelet therapy with aspirin 81 mg daily and clopidogrel 75 mg daily is typically used for maintenance therapy.[1,24] In the setting of patent foramen ovale, such as in this case, anti-platelet therapies as above are typically recommended.[24] Additionally, surgical closure may be considered, particularly in cases of high-risk features such as young age, high Risk of Paradoxical Embolism (ROPE) score, history of deep vein thrombosis, prior non-lacunar stroke or transient ischemic event, larger shunt size, or atrial septal aneurysm.[24,25]

Patent foramen ovale is an embryogenic defect present in approximately 25% of the adult population.[26,27] During embryological development, oxygenated blood derived from maternal circulation enters the heart through the inferior vena cava and passes from the right to left atrium through the foramen ovale to enter systemic fetal circulation.[28] The foramen ovale is covered by a flap-like valve, the septum primum.[28] Following birth, increased left atrial pressure due to pulmonary circulation causes apposition of the septum primum, and fusional closure of the foramen ovale is typically complete by 2 years.[28] Transthoracic echocardiography with bubble study, which was used in this case, is a common imaging technique used to detect patent foramen ovale; however, transesophageal echocardiography and transcranial Doppler may also be used.[25,29] In the presence of a patent foramen ovale, passage of microbubbles from the right to left atrium can be observed on transthoracic echocardiogram following intravenous injection of agitated saline.[29] A patent foramen ovale acts as a conduit for venous emboli to bypass filtration through pulmonary vasculature and cross as paradoxical emboli into arterial circulation where they can cause occlusion of cerebral or retinal arterioles.[30] Additionally, the presence of a patent foramen ovale may disturb blood flow within the heart and promotes in-site thrombus formation.[31] As such, patent foramen ovale has been associated with increased risk of ischemic stroke.[32] Despite this, patent foramen ovale typically remains asymptomatic and does not require treatment in most cases. Antithrombotic treatment or surgical closure may be recommended following ischemic events to reduce risk of recurrent ischemic stroke, as was done for this patient.[24,30,33]

Numerous physiological changes occur during pregnancy which induce a relative state of thrombophilia.[34] Early hemodynamic changes in pregnancy include increased plasma volume and decreased peripheral vascular resistance, together which increase venous stasis.[34] Additionally, physiological anticoagulation is reduced due to decreased protein S and C function, as was seen in this case, and decreased anti-thrombin III levels.[34] Activity of several pro-coagulant factors, including factors VII, IX, X, XII, and XIII, fibrinogen, and von Willebrand factor increases during pregnancy.[34] Together, these physiological changes increase risk of thrombus formation and ischemic stroke.[34,35] The risk of stroke during pregnancy increases additionally with the presence of a patent foramen ovale.[36] Chen et al. reported that the risk of stroke in these cases was greatest during the first and second trimester.[36]

CONCLUSION:

Urgent evaluation in an emergency department or dedicated stroke centre is necessary for acute, symptomatic retinal artery occlusions. In young patients, especially those who lack vasculopathic risk factors, cardiac pathology, thrombophilia, and vasculitis should be considered. These include patent foramen ovale and pregnancy, both of which may increase risk of thrombus formation and have been associated with increased risk of retinal artery occlusion. Retinal artery occlusions are associated with increased risk of cerebral stroke and mortality, and secondary stroke prevention should be tailored to the patient by a multidisciplinary care team following retinal artery occlusion.

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