Running head: Stroke work-up for CRAO

Title: Stroke risk and risk factors in patients with central retinal artery occlusion

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Abstract

Purpose: Central retinal artery occlusion (CRAO) is mechanistically similar to a stroke. Current guidelines recommend a standardized and systematic evaluation of risk factors for patients who have had a stroke. This study evaluates the yield of this evaluation in patients with CRAO and frequency of stroke in this population.

Design: We evaluated the diagnostic yield of an expedited inpatient evaluation of cerebrovascular risk factors in a cohort of patients presenting with an acute CRAO within the period from 2009-2017 at an academic hospital.

Methods: Vital signs, laboratory parameters including low-density lipoprotein level, hemoglobin A1c fraction, erythrocyte sedimentation rate, C-reactive protein level, platelet count and troponin level were collected. Echocardiography, cardiac telemetry, magnetic resonance imaging, and cerebrovascular imaging were obtained to screen for strokes and vascular risk factors. All new diagnoses and clinical treatments stemming from the inpatient evaluation were documented. Outcomes included the frequency of stroke on MRI, hypertensive emergency, critical carotid disease, or critical cardiac disease including high-grade valvular lesions, new myocardial infarction or arrhythmias. We documented the frequency of a change in medication, acute surgical intervention or new diagnosis of systemic disease as a result of the inpatient evaluation. Finally, we evaluated the rate of symptomatic stroke, myocardial infarct and death risk in the 24 months after CRAO.

Results: In this cohort of 103 patients with CRAO and systematic risk factor screening, 36.7% of patients had critical carotid disease, 37.3% had coincident acute stroke, 33.0% presented with hypertensive emergency, 20.0% had a myocardial infarction or critical structural cardiac disease, 25% underwent an urgent surgical intervention and 93% had a change in medication as a result of the inpatient evaluation. Patients with CRAO had similar risk of subsequent stroke, myocardial infarction and death as patients with high-risk transient ischemic attack.

Conclusions: Patients with CRAO are at significant risk of future cardiovascular and cerebrovascular events and often have undiagnosed risk factors that may be modifiable.

Introduction

Central retinal artery occlusion (CRAO) is an ischemic injury to the retina that frequently results in permanent blindness.[1] The central retinal artery has a lumen diameter of roughly 2mm and occlusion of this artery is usually the result of an embolus lodging either at the point where the vessel penetrates the optic nerve or just prior to the point where it enters the globe as it crosses the lamina cribrosa, both of these points being areas of slight narrowing in the diameter of the artery.[2-4] The emboli most frequently arise from a carotid or cardiac source, although occlusion of the vessel from a wide array of sources as been reported.[5] CRAO is analogous in many ways to an ischemic stroke, but whether it should be treated as a "stroke equivalent" in terms of risk factor screening and treatment has been a matter of some controversy.[6] We recently conducted a poll of neurologists and ophthalmologists who treat patients with acute CRAO and discovered significant variability in the approach to the treatment and screening of these patients.[7] For this reason, we undertook the current study to assess the diagnostic yield of the standardized "stroke work-up" in patients with acute CRAO and to evaluate the rate of stroke, myocardial infarction and death in this population.

Methods

Patient cohort

The institutional review board of Vanderbilt University Medical Center approved this study prior to its initiation, IRB#160767. We conducted an analysis of the yield of an acute "stroke work-up" using the recommended risk modification evaluation for stroke/TIA patients with the addition of a detailed ophthalmologic exam and screening for arteritis.[8] A protocol was implemented at Vanderbilt University Medical Center in 2009 to refer patients with acute CRAO to the general emergency department with co-management by the vascular neurology and ophthalmology services. Patients were admitted to the vascular neurology service for a "stroke work-up" consisting of angiography of the head and neck by CT or MR angiography, MRI of the brain, echocardiography, cardiac telemetry and basic labs, including low-density lipoprotein, hemoglobin A1c fraction, erythrocyte sedimentation rate, C-reactive protein level and complete blood count. When no explanation for the CRAO was discovered, patients were asked to undergo long-term cardiac telemetry, usually for 30 days to evaluate for atrial fibrillation. Patients presenting between Jan 2009 and Dec 2017 were included. The Vanderbilt University medical record system (StarPanel) was systemically queried to identify records of patients presenting with CRAO within 7 days of symptom onset. The primary inclusion criteria was a diagnosis of CRAO made in the setting of acute painless vision loss with a visual acuity in the affected eye worse than 20/200 with confirmation by funduscopic examination and ancillary testing when necessary. Patients who met these criteria were considered for inclusion when the clinical diagnosis by an experienced ophthalmologist was deemed most consistent with CRAO. Clinical variables for these patients were abstracted from their charts by two authors (MS and MH) and included LDL, HgbA1c, ESR, CRP and platelet counts, MRI brain, MR/CT angiography of the head and neck, echocardiography and telemetry (both in hospital and extended ambulatory monitoring) results. Any diagnosis, acute procedure or change in medications made on the basis of the inpatient admission was recorded. Clinical events in the following two years were recorded for those patients who obtained their long-term medical care at VUMC or an affiliated institution. Patients with less than 90 days of clinical follow-up were considered lost to follow-up and not recorded in this data; for patients with between 90 and 730 days of clinical follow-up, their last-known clinical status was carried forward. When evaluating the rate of strokes on MRI immediately after acute CRAO, a radiological definition of a stroke was used (diffusion-restricting lesion on imaging most consistent with a stroke, regardless of clinical symptoms); when evaluating stroke-risk after CRAO, only clinically symptomatic strokes were counted (new focal neurological deficit lasting >30 minutes) and neuroimaging confirmation of a new stroke was required. MI was counted when a clinical diagnosis of MI was applied by a treating physician with at least one of the following: abnormal troponin level, acute EKG changes suggestive of ischemia or cardiac catheterization study with coronary artery narrowing felt to be clinical significant. Data were presented as mean and standard deviation if normally distributed, median and interquartile range if skewed. Comparison of event rates in our cohort to historical controls was evaluated with the 'N-1' Chi square test.[9]

Table 1: Clinical characteristics of patients with acute CRAO

Clinical features (n=103)	**Data (SD unless indicated)**
Age (mean, SD)	65.1 +/- 12.8
% female	45.6%
% right sided	53.4%
Time to presentation in ER (median, IQR)	8.0 hrs (5.5-23)
Time to first contact with any provider (median, IQR)	3.9 hrs (2.0-12)
Presenting visual acuity (logMAR)*	Between CF and HM (1.5 +/-0.2)
Final visual acuity (logMAR)*	20/400 (1.3 +/- 0.5)
% with clinical recovery**	13.7%
Presenting intra-ocular pressure	15.2 mmHg +/-3.8
Erythrocyte sedimentation rate	28.5 +/-26.0
C-reactive protein	19.8 +/-52.6
Percent with either ESR or CRP >50	22.5%
Platelet count	228 +/- 71
Hemoglobin A1c fraction	5.9 +/- 0.9
Low-density lipoprotein level	105 +/- 44
Presenting blood pressure (systolic)	156.0 mmHg +/- 27.1
Presenting blood pressure (diastolic)	86.3 mmHg +/- 19.4
Hypertensive crisis (SBP >180 or DBP >100)	33%
Funduscopic examination findings	
Emboli	8.4%
Retinal whitening	72.2%
Optic nerve head pallor or edema	30.9%
Arterial narrowing or “boxcar-ing”	70.0%
“Cherry red” macula	77.6%
Relative afferent papillary defect	87.0%

*logMAR >1.3 up to counting fingers (CF) recorded as 1.4, hand movement (HM) as 1.5, light perception as 1.6 and no light perception as 1.7. ** clinical recovery defined as final logMAR </= 0.7 (20/200).
Abbreviations: SD – standard deviation, ER – emergency department, IQR – interquartile range, ESR – erythrocyte sedimentation rate, SBP – systolic blood pressure, DBP – diastolic blood pressure

Results

One-hundred and three patients presented between January 2009 and December 2017 with a confirmed CRAO diagnosis. The clinical characteristics and funduscopic findings of the patients are shown in table 1. Twenty-three percent of patients had evidence of a serious systemic inflammatory reaction (indicated by ESR >50mm/hour or CRP >50mg/liter), and 33% had a hypertensive crisis (SBP >180 or DBP >100 mmHg). MRI of the brain was obtained in 66% of patients and revealed a stroke in 37.3%; in many of those cases the area of ischemia was small and without an obvious clinical correlate (Figure 1). In most cases, the stroke was ipsilateral to the CRAO and associated with carotid disease. In six subjects, one or more cerebral infarcts were outside the vascular territory supplied by the internal carotid artery ipsilateral to the CRAO; two were related to aortic valve disease, one patient had an acute MI with atrial fibrillation, one was arteritic in etiology, one was provoked as a complication of conventional angiography and one occurred as a complication of Rocky Mountain Spotted Fever.

Critical carotid artery disease ipsilateral to the CRAO was discovered in 36.7% of patients (see Table 2). Twenty percent had a critical finding on echocardiography, including severe valvular disease, severely depressed ejection fraction, acute MI or infective endocarditis. Atrial fibrillation was present in 10.6% of

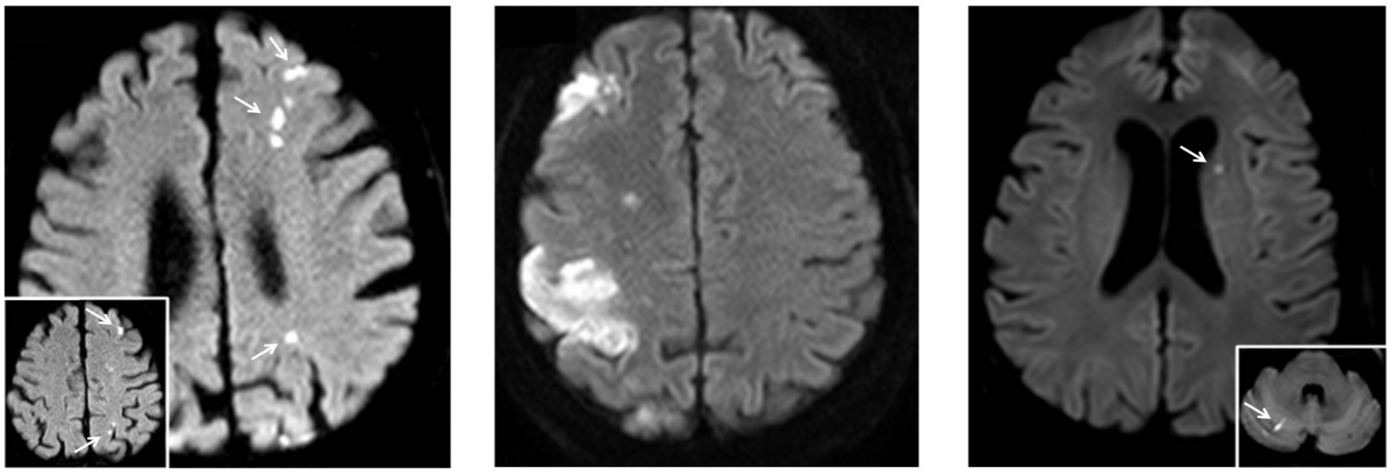

Figure 1: Brain MRI patterns in patients with acute CRAO can help identify source of emboli
Left: diffusion-weighted image from a patient with a left-sided CRAO and severe stenosis of the left internal carotid artery. Numerous small strokes were present in the watershed zone. Middle: a number of embolic-appearing strokes in the right MCA territory are ipsilateral to this patient's CRAO and distal to a thrombosed aneurysm in the carotid artery. Right: small strokes in multiple vascular territories with a left CRAO in a patient with atrial fibrillation. The pattern of findings on diffusion-weighted imaging can help to clarify the source of emboli in CRAO.

patients, either by history or diagnosed on admission; three additional cases of 34 screened were found to have occult atrial fibrillation on long-term monitoring. Overall, 79% of the patients with CRAO in our study were found to have some other significant acute problem that would have required hospitalization in the absence of the CRAO; 25.2% underwent an acute surgical procedure, and 93% had a change in medication on the basis of the inpatient evaluation. Patients were followed after CRAO to evaluate the risk of stroke, MI and death; 28 were lost to follow-up within 90 days of the CRAO. Of the 75 remaining, 8% died, 11% had incident stroke, 17% a MI (combined stroke, MI or death occurred in 32%) within two-years after the CRAO (Figure 2). The stroke and MI rates after CRAO are higher than reported rates after TIA.[10] A recent report by Amarenco et al[11] evaluated the stroke, MI and death risk associated with TIA or minor stroke with aggressive risk factor modification, comparable to the approach we took with our cohort with acute CRAO.[11] They reported a 1 year combined stroke/MI/death rate of 6.2% after TIA or minor stroke compared to a 25.3% risk in our cohort after acute CRAO ($p<0.0001$). In patients with high-risk TIA (measured by ABCD2 score of 6-7), they reported a stroke rate at 12 months of 7.8% which is not different statistically from the 9.3% stroke rate at 1 year after acute CRAO observed in our cohort ($p=0.64$), suggesting that CRAO confers at least equivalent risk as a high-risk TIA.[11,12]

Table 2: Yield of diagnostic studies and outcomes in patients with acute CRAO

Diagnostic study or outcome	**Frequency of positive result**
Stroke on magnetic resonance imaging of the brain	25/67 (37.3%)
Critical carotid disease (>70% stenosis, dissection or intra-arterial thrombus)	36/98 (36.7%)
Critical finding on echocardiography	17/86 (20.0%)
Patent foramen ovale	7/86 (8.1%)
Atrial fibrillation by history or diagnosed on presentation	11/103 (10.6%)
Atrial fibrillation discovered on subsequent 30 day cardiac event monitor	3/34 (8.8%)
Any new significant diagnosis from inpatient work-up	81/103 (78.6%)
Any change in medication from inpatient work-up	95/103 (92.2%)
Required an acute surgical procedure as a result of inpatient work-up	26/103 (25.2%)
Death prior to two year follow-up	6/75 (8.0%)
Incident symptomatic stroke, myocardial infarction or death at 2 year follow-up	24/75 (32.0%)

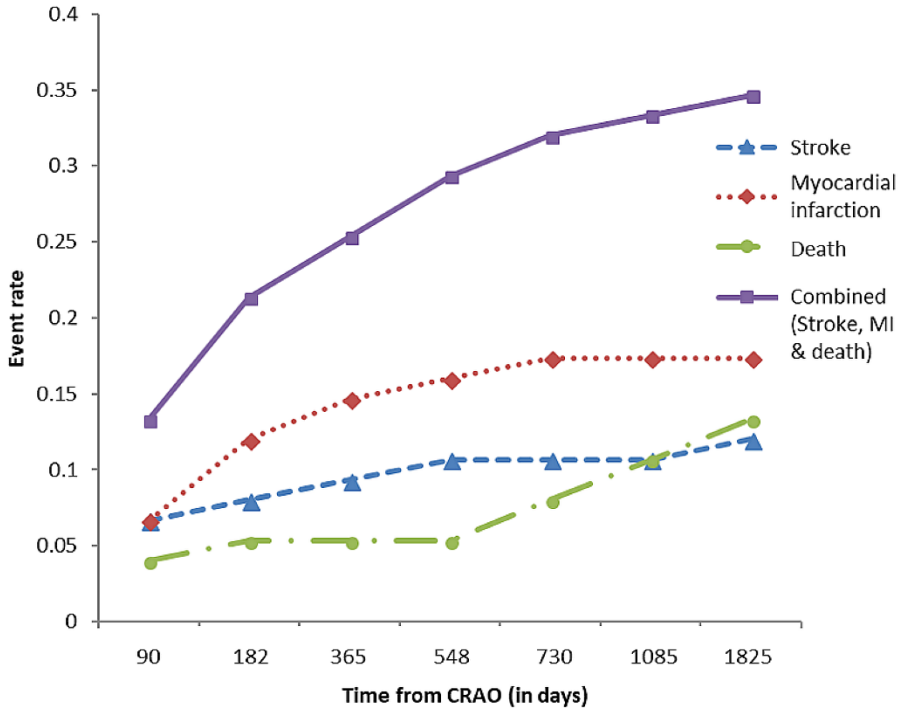

Figure 2: Stroke, myocardial infarction and death rate after CRAO
Acute CRAO is associated with significant risk of subsequent stroke, myocardial infarction and death. The individual event rates are shown above. Combined stroke, myocardial infarction and death rate at 24 months was 32%.

Discussion

We found in our cohort that evaluating patients with acute CRAO in an inpatient setting with a thorough standardized evaluation uncovered a high percentage with contributing systemic disease; 36.7 had critical carotid artery disease (mostly atherosclerotic disease or dissection) and 20.0% had a major abnormality on echocardiography (i.e. critical valvular disease, heart failure or myocardial infarction). Ninety two percent of the CRAO cohort had some medication change prompted by their inpatient evaluation, and more than 25% underwent an acute surgical procedure, mostly carotid revascularization, valve replacement or coronary artery interventions. Brain MRI of patients with CRAO demonstrated an ischemic stroke 37.3% of the time; often the pattern of strokes on MRI clarified the etiology of the CRAO. Cumulatively, our retrospective analysis demonstrated that patients with CRAO have significant modifiable cerebrovascular and cardiovascular risk factors which require thorough evaluation and expedited intervention. The current status quo for evaluating patients with acute CRAO may fail in many cases to identify these risk factors.[6,7]

Recent publications have shown that the highest stroke and myocardial infarction risk period after a TIA or CRAO is in the first week or two; these emphasize the urgency of rapidly instituting secondary prevention measures.[12-14] Studies evaluating stroke risk after CRAO which enroll patients sub-acutely, after this peak stroke-risk period, may underestimate the risk of stroke.[6,15] Also it is critical that the mechanism of CRAO is quickly and accurately identified as a modern approach to secondary stroke prevention is tailored to the mechanism of vascular occlusion.[16] Patients with severe carotid stenosis and watershed injury may require careful blood pressure management and urgent revascularization, while patients with carotid atherosclerosis and sub-critical stenosis may require antiplatelet therapies, and patients with atrial fibrillation may require anticoagulation -- our cohort study indicates all of these mechanisms are relevant to CRAO.

The retrospective cohort analysis was successful in identifying significant modifiable risk factors in patients with CRAO that may be missed by incomplete screening strategies, but our analysis was limited to a single academic medical center in the upper southeast portion of the United States. This region is known as the “stroke belt” of the United States due to higher than average rates of strokes and stroke-risk factors. This study provides key data to direct CRAO treatment in this region. A larger, nationwide study would provide valuable information for expanding the generalizability of CRAO treatment strategies. Never-the-less, the high rate of serious comorbid disease in our study and the high rate of subsequent stroke, MI and death suggests that CRAO

confers a similar risk of subsequent stroke and myocardial infarction as a TIA or stroke. Our study clearly shows that CRAO is a "stroke equivalent" and from a risk modification standpoint it is appropriate that patients undergo risk factor evaluation in an expedited fashion.

Author contributions: MH, PL, and HK were involved in the conception and design of the cohort, data collection and analysis and editing the manuscript for intellectual content. MP and KE were involved in data collection and analysis and edited the manuscript. MS was involved in all aspects of the study, supervised the study and drafted the manuscript.

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