Our Casebook

By Richard Braun, MD

Dr. Braun is Vice President & Chief Medical Officer for SCOR Global Life Americas. He received a Bachelor of Science degree from the Towson State University (1975) and earned his medical degree from the University of Maryland (1979). Dr. Braun is board certified in Internal Medicine and Insurance Medicine, and is a past President of the American Academy of Insurance Medicine.

Case #1
Renal Infarction

About a year before applying for life insurance, a 43-year-old male nonsmoker presented to his doctor with flank pain, nausea and vomiting for 10 days. At the time of the illness, an abdominal Computed Tomography (CT) scan revealed a renal infarct in the upper pole of the right kidney. The applicant had an insurance blood profile with total cholesterol of 180 mg/dl and an HDL cholesterol of 45 mg/dl. His serum creatinine was 1.1 mg/dl and the BUN was 25 mg/dl. The remainder of the insurance bloodwork and urinalysis was normal. At the time of application he was on a statin, Plavix & aspirin. He reportedly had a cardiac work-up at the time of the episode, but there were no details in the record.

Question
What causes a renal infarct and what are the implications for future mortality?

Answer
Renal infarction (RI) is caused by the obstruction of blood flow in the renal artery or one of its smaller branches, resulting in ischemia to a segment of kidney tissue. It is a rare disorder, with one autopsy study from the 1940s showing a prevalence of 1.4%. Another study looked at all emergency-room cases over a 4-year period and found an RI diagnosis in only .007% of these cases.

The clinical diagnosis of renal infarction is likely often missed due to the nonspecific nature of the symptoms. Flank pain, abdominal pain, nausea and vomiting are the most common presenting symptoms, and these can be mistaken easily for kidney stones or infections. One laboratory test that may aid in differentiating between RI and these other disorders is the serum lactate dehydrogenase. Serum levels routinely are reported as being two to

(Continued on Next Page)
four times the upper limit of normal in the setting of renal infarction and normal in the setting of stones or infection.

Trauma may result in renal infarction at any age, but the etiology of non-traumatic RI varies somewhat by age group. The elderly are more likely to have atherosclerosis of the aorta or renal arteries which may spawn emboli that occlude an arterial branch. Atrial fibrillation is often mentioned as a cause of renal infarction, and a study of almost 30,000 patients with atrial fibrillation noted an RI incidence of 2% over a 13-year follow-up period.

One more recent study of 94 RI cases (61 men and 33 women) was designed to place subjects into one of four categories based on underlying cause:

- Infarction in the youngest group (average age 44) was due to “renal injury.” This group was 86% male and comprised 31% of the total cases.
- The next youngest group (average age 46, 16% of total) presented RI due to an underlying hypercoagulable disorder. One-third of this group suffered from bilateral renal infarction.
- The third group (average age of 65, 24% of total) exhibited cardiac causes like atrial fibrillation, endocarditis, etc.
- The final group (average age 56, 29% of total) was the second largest group. This group was deemed idiopathic and had no discernable cause for renal infarction. A prior history of arrhythmic heart disease was reported in 11% of this idiopathic group and a history of previous embolic event in 7.4%.

In this study the overall frequency of hypertension...
at the time of RI diagnosis was 39%. Separately mentioned in medical literature are several case reports of individuals suffering a renal infarction soon after smoking or injecting cocaine.

**Diagnosis and Treatment**

When there is a suspicion of renal infarction, the most commonly used test for diagnosis is CT scan with contrast enhancement. Ultrasound of the kidney is not very sensitive and may appear normal in acute RI. Angiography is usually reserved for extensive infarction or in the setting of planned endovascular procedures.

There are no standardized treatment guidelines for renal infarction, likely due to the rarity and the varied underlying causes. Clinicians often initialize heparin followed by warfarin. If an embolus or clot is identified quickly, thrombolysis or endovascular intervention may be pursued. Anti-hypertensive treatment may be indicated, and dialysis may be needed if renal damage is severe. Anticoagulants are often continued indefinitely in the setting of atrial fibrillation.

The prognosis after renal infarction depends on the underlying cause/coexisting conditions, the extent of infarction and the resulting renal function. The extent of kidney damage and ultimate outcome may be related to the time it takes to make the diagnosis, as earlier treatment may save more renal tissue. Additional clots from an embolic source may also put other organs at risk. A study of 44 patients with atrial fibrillation and renal infarction (average age 69) found a mortality rate of 11.4% in the first month after diagnosis. At a follow-up of three years: 61% had normal renal function; 13% had mild impairment; 18% had more severe impairment (serum creatinine > 2 mg/dl), and 8% were on dialysis. Additional embolic events occurred in 13% of these patients.

**Returning to the Case**

The etiology of the renal infarct is not apparent from the information provided. It would be important to obtain the cardiac work-up in hopes that an echocardiogram, an electrocardiogram and ambulatory, 24-hour heart monitoring were done. One would also like to see a work-up to exclude a hypercoagulable disorder. The rating for any of the underlying conditions that might have been discovered (atrial fibrillation, other arrhythmias, hypercoagulable state, etc.) would be a good starting point with additional moderate rating for the infarction. If no underlying etiology was discovered, it would be prudent in this age group to start with a rating for paroxysmal atrial fibrillation as a likely occult etiology.

**References**


UpToDate online, last accessed 2/10/15.
A 57-year-old man applied for life insurance. He had seen his Veterans Administration (VA) generalist about four months prior to application and complained of “cold feet for a couple of years.” He also complained of numbness and tingling in his right arm and his feet that he related to sleeping in the wrong position. He admitted to currently smoking cigarettes. The physical examination found bilateral femoral and dorsalis pedis pulses of 1+. He was tested in the clinic and his ABI was .8 on the right and .72 on the left. He returned to clinic two weeks later and the ABI was .82 on the right and .73 on the left. He was referred to the vascular clinic at the VA and there were no subsequent records.

**Question**
What is the ABI, and are these findings of any concern to mortality?

**Answer**
Ankle Brachial Index (ABI), also known as Ankle Brachial Pressure Index (ABPI), is the ratio of the systolic blood pressure in the lower legs to the systolic blood pressure in the arms. Blood pressure in the ankle significantly lower than in the arm is an indication of arterial blockage (peripheral arterial disease) of blood flow to the legs.

Doppler ultrasound provides the pressure reading, and the equipment is now simple, accurate and readily available. The measurement is performed with the patient lying flat, as having the legs dependent (sitting) would increase the pressure in the ankles and overestimate the ABI.

ABI is considered normal in the range of .91-1.3. In a patient with symptoms of claudication, an ABI below .9 is considered diagnostic for peripheral arterial disease (PAD). Only about one-third of patients with PAD will have classic claudication symptoms (pain in the legs with exercise that resolves within 10 minutes of rest). Studies have shown a sensitivity of 79%-95% and a specificity > 95% for detecting a > 50% obstruction by angiography when the ABI is below the .91 cutoff. There is less certainty about this cutoff in the asymptomatic population. But one study in patients age 65 and older showed a dramatic increase in major events (death, myocardial infarction, coronary artery bypass graft) as the ABI fell under .7 and again at under .5. An ABI below .4 reportedly represents multi-vessel PAD and may coexist with non-healing ulcers, pedal gangrene or claudication pain at rest.

We should also note that ABI has a “U” shaped association with mortality. Having an ABI > 1.3 is considered abnormal. Calcification of the vessels supplying the lower extremities may lead to higher systolic pressures when compared to the arms. It is estimated that individuals with high ABI account for ~20% of those with PAD.

Occasionally a patient will present symptoms of claudication but with an ABI in the normal range. In this setting, exercise ABI should be considered. Moderate arterial stenosis (50-70%) might be unmasked as the systolic pressure falls in the lower extremity with exercise. A fall in ankle systolic pressure of > 20% from baseline or an absolute pressure < 60 mmHg that persists for more than three minutes in recovery is considered abnormal and suggestive of PAD. When we bring together the symptoms and the ABI findings, it is highly likely that the applicant has PAD. Additional testing such as computed tomographic angiography (CTA), magnetic resonance angiography (MRA) or classic catheter-based angiography may be undertaken to better define the location or the extent of the disease in this relatively young individual. PAD is considered a coronary heart disease equivalent, so efforts to control risk factors for atherosclerosis should be implemented, including medications as needed.

**Returning to the Case**
This applicant is a smoker, and stopping smoking would top the list of treatments. One study comparing those with PAD who stopped smoking to those who
did not show a 10-year survival of 82% versus 46%, respectively. Exercise therapy is also a routine treatment and has been shown to improve maximum walking time and, based on some small observational studies, may improve survival. For this case it would be prudent to postpone coverage until the extent of disease is determined, and to see if the individual will be able to quit smoking. An ECG would also be of benefit in considering the mortality risk.

References

O’Hare AM, et al. “Mortality and Cardiovascular Risk Across the Ankle-Arm Index Spectrum Results From the Cardiovascular Health Study.” Circulation 2006;113:388-393.


www.uptodate.com (last accessed 8/15/14). ∞

Hazard Ratios for Total Mortality Based on ABI

<table>
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<tr>
<th>ABI</th>
<th>Unadjusted</th>
<th>Adjusted*</th>
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<tbody>
<tr>
<td>&lt; .61</td>
<td>3.97</td>
<td>1.82</td>
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<tr>
<td>.61-.7</td>
<td>3.7</td>
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</tr>
<tr>
<td>.71-.8</td>
<td>3.73</td>
<td>1.8</td>
</tr>
<tr>
<td>.81-.9</td>
<td>2.98</td>
<td>1.73</td>
</tr>
<tr>
<td>.91-1.0</td>
<td>1.81</td>
<td>1.4</td>
</tr>
<tr>
<td>1.01-1.1</td>
<td>1.29</td>
<td>1.12</td>
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<tr>
<td>1.11-1.2</td>
<td>1.0 (Referent)</td>
<td>1.0 (Referent)</td>
</tr>
<tr>
<td>1.21-1.3</td>
<td>1.02</td>
<td>.92</td>
</tr>
<tr>
<td>1.31-1.4</td>
<td>1.22</td>
<td>1.13</td>
</tr>
<tr>
<td>&gt;1.4</td>
<td>1.88</td>
<td>1.57</td>
</tr>
</tbody>
</table>

*Adjusted for age, gender, race, diabetes, serum creatinine, body mass index, LDL cholesterol, HDL cholesterol, smoking, C-reactive protein, systolic blood pressure, diastolic blood pressure, antihypertensive medications, triglycerides, prevalent coronary heart disease, stroke and congestive heart failure. (Circulation. 2006;113:388-393.)

Case #3
Moyamoya Disease

By William Rooney, MD, FAAFP, EMBA
Vice President, Medical Director

Dr. William (Bill) Rooney is Vice President, Medical Director at SCOR Global Life Americas. Dr. Rooney’s responsibilities include facultative case review work, researching and updating SOLEM®, researching and writing articles for a variety of SCOR publications and more. He earned a medical degree from the University of Missouri – KC (1981) & an Executive Master’s in Business Administration from Benedictine College in Atchison, Kansas (2009). He is board certified in Family Medicine with the American Board of Family Medicine.

A 37-year-old female is applying for $1 million of life insurance. Very few medical records are provided; however, there is mention of a hospitalization six months previously for evaluation of the sudden onset of weakness in her left arm and associated clumsiness in her left hand. This event lasted for 15 minutes with complete resolution of the symptoms, but it prompted an emergency room visit and subsequent hospitalization. Her primary care physician’s notes after she was released mention an abnormal MRI of the brain, finding a few small white-matter lesions, possibly vascular infarcts. In addition, a cerebral angiogram report describes some early occlusive lesions in the distal carotid arteries and around the
Moyamoya Disease (cont.)

MMD is associated with two major anatomic findings. The first is the occlusion of multiple vessels around the circle of Willis. The second is the presence of very prominent collateral arterial circulation. This collateral circulation frequently creates a characteristic appearance on an angiogram, often referred to as a “puff of smoke” (moyamoya in Japanese).

MMD was first described by Japanese physicians in 1957. Since then, cases have been discovered throughout the world, but the incidence of the disease is highest in Asian populations. While the etiology of MMD is unknown, there is suggestive evidence that a genetic etiology might be involved. Ten to 15% of patients with MMD report a relative with the disease. Specifically, the RNF213 gene on the 17q25.3 chromosome may be involved, but associations with chromosomes 3, 6, and 8 are possible.

Moyamoya syndrome is different from moyamoya disease. Moyamoya syndrome describes typical moyamoya-type angiographic findings in the setting of an associated condition. These associated conditions include Down syndrome, sickle cell disease, neurofibromatosis type I and previous exposure to radiation treatment, among others. MMD is diagnosed when none of these associated conditions is present.

Moyamoya disease can occur in children or manifest itself in adulthood. In fact, the incidence appears bimodal with peaks in two age groups: in children approximately 5 years old and in adults in their mid-40s. The initial clinical findings of MMD are variable, most often presenting with ischemic events ranging from TIs to severe ischemic or hemorrhagic strokes.

**Question**

What are the mortality implications of moyamoya disease if the diagnosis is confirmed?

**Answer**

Moyamoya disease (MMD) is a rare disease of the cerebrovascular circulation occurring at an annual incidence of .35 to .94 per 100,000 in Japan and .086 per 100,000 based on hospital records from California and the state of Washington. There is approximately a 2:1 female:male predominance.
Epilepsy and/or headaches may also be presenting symptoms. A small 2014 study evaluating MMD in the US found that problems in 19 of the 31 adults involved ischemic symptoms.

Suspicion for MMD is elevated when there are clinical findings of recurrent ischemic attacks in the same arterial region or intracerebral hemorrhage in the caudate region. Intraventricular hemorrhage within the lateral ventricles is also a red flag. Also, MMD is strongly considered in the differential diagnosis when stroke occurs in children or young adults.

**Diagnosis and Treatment**

Diagnosing MMD frequently involves brain imaging with transcranial Doppler ultrasonography, CT, MRI, MRA, CTA and/or conventional angiography. MMD is diagnosed when angiographic imagery indicates significant bilateral occlusive disease of the intracranial internal carotid and circle of Willis arteries, along with the presence of prominent basal collateral vessels.

The significance of MMD versus some other types of transient ischemic attacks or cerebrovascular attacks is that MMD tends to be a progressive cerebrovascular disease and a more diffuse vascular disease. The onset of symptoms occurs at a younger age than the more common atherosclerotic disease. All of these characteristics have relative mortality implications. The small observational studies that have been done indicate that the risk of stroke after an initial ischemic event may be up to 10% per year and 3.2% after diagnosis in an asymptomatic person.

**Treatment of MMD** is challenging. No curative treatment currently is available for the disorder. Medical treatment has unproven benefit. Antiplatelet therapy is occasionally used. Surgical procedures may be performed to try to improve blood flow, with some success. The surgical procedures range from evacuation of a brain hematoma to direct and indirect bypass procedures involving the arterial circulation. Unfortunately, the progressive nature of this disorder does impact mortality and morbidity despite treatment in most individuals. Factors that have been described as affecting prognosis include the speed and degree of arterial narrowing, extent of the infarct (including evidence of bilateral involvement), age at diagnosis and the neurological status at the time of diagnosis.

Screening family members of an individual diagnosed with MMD is not currently advocated by most clinicians. The familial incidence of first-degree relatives is felt to be about 7%-12% in Japan and approximately 6% in the US. Therefore, individual consideration for screening is recommended.

**Returning to the Case**

In this case the proposed insured’s abnormal imaging results are very worrisome. The mention of a moyamoya-like angiographic appearance with stenosis accompanied by bilateral prominent collateral vessels is not common with a TIA. Despite the quick resolution of the symptoms, the current symptom-free state and the normal neurological exam, there is a high index of suspicion for MMD. The MRI report should be reviewed for details of the possible vascular infarcts. The family history of a relative with early onset cerebrovascular disease raises the question of whether there might be a hereditary component. This case would be handled differently than one with normal imaging after a TIA-like event. Given the typically poor long term prognosis of MMD, postponement and reevaluation appear to be a prudent course.

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**Figure 3 - Major Features of Moyamoya Disease**

<table>
<thead>
<tr>
<th>Its rarity</th>
<th>Annual incidence reported to be approximately:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.086/100,000 in US</td>
</tr>
<tr>
<td></td>
<td>0.35 to 0.94/100,000 in Japan</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Its occurrence</th>
<th>Biomedical age distribution with peak in:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Childhood from 5-14</td>
</tr>
<tr>
<td></td>
<td>Adulthood from 35-49 years of age</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Its clinical expression</th>
<th>Variable and include hemorrhagic strokes or ischemic strokes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Epilepsy, headaches and TIAs are not uncommon</td>
</tr>
</tbody>
</table>

| Its diagnosis           | Neurovascular imaging with characteristic findings of stenosis in the distal carotid arteries and arteries close to the circle of Willis often with prominent collateral vessels in the basal region |

| Its course              | Progressive typically |

| Its prognosis           | No cure. Medical treatment has had poor results. Surgical treatments offer some success. Prognosis is variable and is impacted, it seems, by speed and severity of the arterial narrowing, as well as the age, extent of infarct and neurological condition at the time of diagnosis. |
Moyamoya Disease (cont.)

References


Zafar, SF, et al. “Adult moyamoya disease in an urban center in the United States is associated with a high burden of watershed ischemia.” J AM Heart Assoc. 2014;3(4)


Underwriting Puzzler...

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