Our Casebook

By Richard Braun, MD

Dr. Braun is Vice President & Chief Medical Officer for SCOR Global Life in the 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, Insurance Medicine and is a past President of the American Academy of Insurance Medicine.

In this issue we present two cases and a Puzzler. One case is Wilson (or Wilson’s) Disease. It is a metabolic disease that causes accumulation of copper in bodily tissues. We also have a case of Kawasaki Disease, the etiology of which is still uncertain. Both of these diseases were named for the physician who first described them in the medical literature.

At one time this sort of immortality (having your name forever associated with a disease) was felt to be an honor for the discoverer. But in 2015 the World Health Organization issued best practice guidelines for naming of new infectious diseases or diseases that have never been described in man and suggested that individuals’ names not be used. They also warned against using geographic locations (i.e., Spanish Flu or Lyme Disease), animals (Swine Flu or Bird Flu), cultural, industry or occupational references (Legionnaires’ Disease) and terms that incite fear (deadly or fatal).

They suggested using more descriptive names or clinical symptoms, physiologic or anatomic processes, systems affected, age group affected, time course, epidemiology, severity, seasonality, and if known, causative agent. We will have to see if these guidelines catch on moving forward.

Speaking of names, we have a new member of the Medical staff at SCOR Global Life Americas. Dr. Kadouch recently joined the Charlotte office as Vice President, Medical Director. He has served as an Associate Medical Director in our Paris office since 2009. In addition he has had a private Cardiology practice in Paris since 1990.

Dr. Kadouch received his medical diploma from Louis Pasteur University in Strasbourg and his specialty certificate in Cardiology and Vascular Diseases from the Pierre and Marie Curie University in Paris.

He is the author of today’s case review of Kawasaki Disease.

Inside this issue

Case #1 – Kawasaki Disease with Coronary Artery Aneurysms ................................................. 2
Case #2 – Wilson Disease................................................................. 5
Underwriting Puzzler ....................................................................... 8
A 35-year-old male applies for life insurance. He was diagnosed at age 3 with Kawasaki Disease and was later told that several coronary aneurysms had been detected by echocardiography.

Unfortunately, old records were not available, and he reported that no follow up was performed since childhood. He has remained completely asymptomatic for more than 30 years, but within the year prior to application he complained of chest pain. He underwent a treadmill exercise test, achieving 14 METS which was negative for chest pain, ST depression or arrhythmia.

**Question**
What is Kawasaki Disease (KD) and what are the prognostic implications of associated coronary aneurysms?

**Answer**
Kawasaki Disease, also known as muco-cutaneous lymph node syndrome, is an acute systemic vasculitis of small and medium-sized arteries that predominantly affects patients younger than five years.

It is usually a self-limited condition with fever and other acute inflammatory manifestations lasting for an average of 12 days if not treated. The vasculitis of KD can be complicated by cardiac disorders and especially coronary aneurysms which occur in 25 to 30% of cases if not treated.

KD represents the most prominent cause of acquired coronary artery disease in childhood in industrialized countries and can lead to a coronary artery disease at adult age.

The cause of Kawasaki Disease is unknown. Because the illness frequently occurs in outbreaks, an infectious disease such as a virus and/or the body's response to this infection combined with genetic factors may cause the disease.

Named after Dr. Tomisaku Kawasaki, a Japanese pediatrician, the disease has probably been in existence for a long time but was not recognized as a separate entity until 1967.
Children of all races and ethnic groups can develop KD, but its annual incidence is higher in Asian populations and in Japan in particular (112/100,000) compared to the United States (19/100,000) and the UK (8.1/100,000).

Approximately 75% to 80% of cases in the US occur in children younger than 5 five years of age; the median age is 1.5 years, and the male to female ratio is 1.5.

In 2004, the American Heart Association (AHA) published diagnostic criteria for classical (typical) and incomplete (atypical) KD.

KD is a clinical diagnosis (Table 1); there is no specific diagnostic test, although laboratory and echocardiographic findings may be helpful in evaluating and differentiating KD from other conditions. Coronary abnormalities such as aneurysms may develop within the first week to 10 days of disease onset, making early diagnosis and treatment essential.

The natural and typical course of KD is favorable most of the time in absence of coronary complications, and the symptoms usually resolve within 4 to 6 weeks.

Complications in KD primarily result from cardiovascular involvement and include coronary artery (CA) aneurysms (Figure 1), depressed myocardial contractility and heart failure, myocardial infarction, arrhythmias and peripheral arterial occlusion. Non-cardiac complications are generally uncommon, but may include shock and multiple organ dysfunction syndrome, macrophage activation syndrome, altered renal function, acute abdominal catastrophes, and sensorineural hearing loss.

The risk of developing coronary aneurysms is greater for children who are younger than age six months and when fever lasts more than two weeks. These aneurysms regress within two years in 60% of the cases. However, aneurysm dimensions greater than 4 mm are predictive of a high likelihood of intimal and medial thickening in the future, which can lead to CAD.

The recommended initial therapy includes intravenous immune globulin (IVIG) and aspirin. The effectiveness of IVIG therapy is best established for patients treated within the first 7 to 10 days of illness. There are few data on the efficacy of IVIG therapy administered more than 10 days after the onset of KD in preventing CA aneurysms.

Long-term morbidity of KD is primarily related to the degree of CA involvement. Recurrence of KD is uncommon.

The reported mortality rate of all cases of KD is low (0.1% to 0.3%). The rare fatal outcomes from severe cardiac involvement in KD are generally the result of either myocardial infarction or arrhythmias, although aneurysm rupture can also occur.

Long-term morbidity for patients following KD depends upon the severity of CA involvement (Table 2).

- Children without cardiovascular abnormalities detected in the acute and subacute phase (up to eight weeks after onset of disease) appear to be clinically asymptomatic 10 to 21 years later.

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>Description</th>
<th>Suggested Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>No CA changes at any time</td>
<td>CV assessments every 5 years</td>
</tr>
<tr>
<td>II</td>
<td>Transient ectasia of CA, resolves within 8 weeks</td>
<td>CV assessments every 3-5 years</td>
</tr>
<tr>
<td>III</td>
<td>One small to medium CA aneurysm</td>
<td>Annual Cardiology follow up with periodic imaging and ECG</td>
</tr>
<tr>
<td>IV</td>
<td>&gt;1 aneurysm 8+ mm or multiple or complex aneurysms without obstruction</td>
<td>Cardiology follow up twice per year with imaging or angiography as needed</td>
</tr>
<tr>
<td>V</td>
<td>CA obstruction</td>
<td>Cardiology follow up twice per year with imaging or angiography as needed</td>
</tr>
</tbody>
</table>

Adapted from Newburger et al.
Kawasaki Disease (cont.)

• CA dilatation <8 mm generally regresses over time, and most aneurysms <6 mm in diameter fully resolve by echocardiogram.
• Patients with giant aneurysms (GA) (maximum diameter ≥8 mm) are at the greatest risk for myocardial infarction resulting from CA occlusion.

In the world’s largest cohort of patients with KD complicated by GA who have been followed up for the longest time, Suda et. al. have shown a survival rate of 88% up to 30 years (Figure 2), with a 59% cumulative intervention rate at 25 years after the onset of KD.

Returning to the Case
From the history, the proposed insured fits in Risk Category IV or V. Several studies indicate that ongoing remodeling of coronary arteries affected by KD might continue long after the initial infection, leading to the development of coronary stenosis years after the onset of the disease.

The proposed insured has not done the recommended follow up until he developed chest pain. Furthermore, the treadmill exercise test is the least sensitive method to detect myocardial ischemia in these patients. In our case, it appears prudent to postpone and offer to reconsider after a more sensitive and specific CAD test and CA imaging, such as Magnetic Resonance Angiography, Computed Tomographic Angiography or stress echocardiography with attention to the coronary arteries.

References
UpToDate – Kawasaki Disease, last accessed 08/08/2016
A 26 year-old man applies for life insurance. He was diagnosed with Wilson Disease at age 7. Currently he takes Cuprimine 750 mg daily and is without symptoms. Labs done two months prior to application showed a normal CBC, normal lipids and liver function tests. Serum Copper was 38 mcg/dl (72-166) and Alpha-fetoprotein was 3.3 ng/ml (<6.1). Ceruloplasmin was 4.6 mg/dl (16-31). The remainder of the laboratory tests were within normal ranges. His physical examination was reported as normal. A recent ultrasound of the abdomen showed normal liver size with some increased echogenicity of the liver noted.

**Question**
What is Wilson Disease (WD) and what are the prognostic implications of this chronic condition?

**Answer**
In London in 1912 Samuel Alexander Kinnier Wilson described four patients with lenticular degeneration and hepatic cirrhosis. He also found eight additional cases in the medical literature. The condition has since been known as Wilson Disease (WD). WD is also known as hepatolenticular degeneration due to the accumulation of copper in the liver, the cornea (Kayser-Fleischer rings) and the lens of the eye.

WD is an autosomal recessive disorder, and estimates are that about 1 in 90 carry a defective copy of the ATP7B gene. It is estimated WD occurs in one person in 10,000 to 30,000 persons worldwide, although there are some isolated regions (e.g., mountainous Crete) where prevalence is much higher.

Adults take in about 1.5 mg of dietary copper a day, while our daily requirement is .75 mg. The majority of excess copper is excreted in the bile and feces, and a lesser amount is excreted in the urine.

The ATP7B gene (on chromosome 13) encodes for the ATP7B protein. This protein is responsible for transporting copper within hepatocytes. Normal hepatocytes incorporate copper to form ceruloplasmin. Ceruloplasmin in the blood stream functions as a ferroxidase vital for iron metabolism. When ATP7B malfunctions, copper is not efficiently formed into ceruloplasmin nor is it efficiently excreted in the bile, causing copper to accumulate in bodily tissues.

More than 300 genetic mutations have been described in the ATP7B gene. Most of those affected have different mutations on each copy of chromosome 13, a condition known as compound heterozygotes.

In WD copper accumulates in hepatocytes causing cell damage and is released into the blood stream as free serum copper. While ceruloplasmin levels may be normal or low due to decreased production, free serum copper is elevated. This leads to gradual accumulation of copper and damage to other organ systems (eye, central nervous system, etc.)

Patients with WD most commonly present with liver disease, neurologic disease or psychiatric symptoms.

**Table 1 – Clinical manifestations of liver disease in WD**

<table>
<thead>
<tr>
<th>Sign or Symptom</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kayser-Fleischer Rings (Figure 1)</td>
<td>50%</td>
</tr>
<tr>
<td>Hepatomegaly and/or splenomegaly</td>
<td>15-49%</td>
</tr>
<tr>
<td>Jaundice, anorexia, vomiting</td>
<td>14-44%</td>
</tr>
<tr>
<td>Ascites and/or edema</td>
<td>5-50%</td>
</tr>
<tr>
<td>Upper GI bleeding (Variceal bleeding)</td>
<td>3-10%</td>
</tr>
<tr>
<td>Clotting problems</td>
<td>3-8%</td>
</tr>
<tr>
<td>Hemolysis</td>
<td>1-20%</td>
</tr>
<tr>
<td>Fatty liver</td>
<td>13%</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>5-23%</td>
</tr>
</tbody>
</table>

**Table 2 – Clinical manifestations of neurologic disease in WD**

<table>
<thead>
<tr>
<th>Sign or Symptom</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysarthria</td>
<td>85-97%</td>
</tr>
<tr>
<td>Ataxia or gait abnormalities</td>
<td>30-75%</td>
</tr>
<tr>
<td>Muscle spasm or rigidity</td>
<td>11-69%</td>
</tr>
<tr>
<td>Tremor</td>
<td>22-55%</td>
</tr>
<tr>
<td>Parkinson-like symptoms</td>
<td>19-62%</td>
</tr>
<tr>
<td>Drooling</td>
<td>48-86%</td>
</tr>
</tbody>
</table>
The age of onset ranges from 5 to 35 years of age. Patients may present with liver disease (steatosis, hepatitis or cirrhosis), which is seen more commonly in children. Those manifesting neurologic disease as a first symptom have mean age of onset between 15 and 21 years. But even these patients will have some amount of liver damage.

Diagnosis of Wilson Disease can be made through screening of relatives of known patients. Common findings are low ceruloplasmin levels, elevated aminotransferases, low platelets and specific genetic mutations if the index mutation is known.

If family history is not contributory, WD can be a very challenging diagnosis due to the wide variety of clinical presentations, which generally fall into three categories: hepatic, neurologic and psychiatric. See Tables 1 and 2 for manifestations and approximate frequencies in hepatic and neurologic disease.

Other less common neurologic findings include: seizures, cognitive impairment/dementia, autonomic dysfunction.

Patients presenting with primarily psychiatric manifestations can face a long delay in diagnosis due to the common symptoms being depression, personality change, irritability, and unusual behavior. These manifestations can go unrecognized as Wilson Disease in children, adolescents, and young adults.

Other than identifying a specific mutation that matches with an affected relative, there is no pathognomonic lab test for WD. Laboratory tests often performed for diagnosing WD include:

**Serum Ceruloplasmin**
The typical value in WD is low (<20 mg/dl); however, this is not specific for WD as any liver disease, malabsorption syndromes and heterozygous carriers often have low levels. Those with WD may also have normal levels as ceruloplasmin rises with estrogens, pregnancy and inflammation.

**Serum Copper**
The portion that is not bound to ceruloplasmin is called nonceruloplasmin-bound or free serum copper. Typically this will be elevated >20 to 25 mcg/dl in cases of WD. It also may be elevated in any cause of acute liver failure, chronic cholestasis or copper intoxication. In treated WD patients levels <5 mcg/dl may indicate copper depletion.

**Urinary Copper Excretion**
Typically 24-hour urinary copper excretion is >100 mcg (>1.6 micromol) in most patients with WD. However, elevated values can be seen with other active liver disease and in heterozygotes. Up to 25% of WD patients will have lower excretion levels >40-100 mcg/24 hours (.64 – 1.6 micromol).

**Penicillamine Challenge or Liver Biopsy**
These tests are usually reserved for borderline cases where the diagnosis is equivocal. Penicillamine is thought to increase urinary copper excretion proportionally more in WD than in other forms of liver disease. However, lack of standardization impairs its use in adults. Liver biopsy with staining for copper and quantitation of copper can also aid in the diagnosis. Using a cutoff of 250 mg copper per gm of liver, the sensitivity was 83% and specificity 99% for WD in one study.

The Leipzig Scoring System for Wilson Disease was developed and distributed through a European Association for the Study of the Liver Practice Guideline in 2012. It uses point totals from a combination of clinical findings and test results to establish the diagnosis of WD.

The treatment of Wilson Disease is lifetime therapy with medications. Typically chelators D-penicillamine or Trientine have been used as initial therapy to remove copper from the tissues. Later, chelators can be continued at a reduced dosage, or zinc salts can be used to reduce the absorption of copper. Diet is also altered to avoid foods with high copper content such as:

- **Figure 1 – Copper deposits in Descemet's membrane in the cornea causes visible golden to reddish rings (see arrow)**
as mushrooms, cocoa, chocolate, peas, beans, nuts, shellfish, kidney or liver.

Prognosis of Wilson Disease is related to the amount of damage that was present when it was discovered and treatment was started. Acute liver failure and cirrhosis have the prognosis of those conditions. In one series of patients undergoing liver biopsy, 54% had cirrhosis at the time of diagnosis of WD. The neurologic, hepatic and psychiatric manifestations generally start to improve with treatment.

Long-term survival of WD has been reported from a study of 229 patients in Austria. At 20 years the survival rate of those with WD was 0.92 compared to age and sex matched Austrian population survival of 0.97. However, those WD patients with cirrhosis were almost seven times more likely to die than those without cirrhosis (Figure 2).

It is not clear if there is an excess risk of developing cancer due to WD in the absence of cirrhosis. There is a known increased risk of hepatocellular carcinoma (HCC) in patients with cirrhosis of any cause. Currently, screening for HCC is recommended only in those patients with WD and cirrhosis.

When decompensated liver disease is present, liver transplant may be required. The transplant cures WD, and long-term survival has been reported as good (Figure 3). Characteristics associated with a poorer survival were male gender, pre-transplant renal insufficiency, emergent transplant procedure and a neurological indication for transplant.

Returning to the Case

While we do not have the details of how Wilson Disease was discovered in this applicant, the recent examination shows no evidence of neurologic or hepatic disease. Therefore, excess mortality risk would be minimally to slightly increased.

**References**


Up To Date last accessed 9/1/16

Underwriting Puzzler...

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Vice President, Medical Director

Dr. William (Bill) Rooney is Vice President, Medical Director at SCOR Global Life in the 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.

In this issue of the Puzzler Dr. Rooney presents another EKG. What is the major abnormality presented in this EKG? To find the answer, be sure to visit the Housecalls page on www.scorgloballifeamericas.com. Click on the "September 2016 Puzzler" Powerpoint presentation to confirm your findings. ∞