



HOUSECALLS.



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THIS ISSUE

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HOUSECALLS WINTER 2011 EDITION

Welcome to the fourth case study edition of the 2011 Housecalls series. As you will see from the table of contents, we have outlined several case studies from our recent submissions. We appreciate receiving the many compliments on our prior editions. Please feel free to let me know if you have any particular topics or questions for future issues or our webinars. You can email me directly: rbraun@generaliusa.com

Generali USA is proud to be the host for the Midwest Medical Directors' Association annual meeting. It is scheduled for May 10-11, 2012 at our headquarters in

Leawood, Kansas. We are working closely with MMDA and will be sending more specific information soon.

Again, thanks to the hundreds of you who logged into our October Housecalls webinar on Alcohol Abuse. If you are interested in receiving a copy of the presentation, please email Chris Duffy: cduffy@generaliusa.com

Additionally, the entire presentation is available for replay or download. Just click on the link below:

<https://generaliusa-events.webex.com/generaliusa-events/lsr.php?AT=pb&SP=EC&rID=4391272&rKey=25d2f84d2c6a847d>

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OUR CASEBOOK

By Richard Braun, M.D., VP & Chief Medical Officer



KOUNIS SYNDROME

- ⇒ **Concurrence of acute coronary events with allergic or hypersensitivity reactions**
- ⇒ **Two variants have been described**
- ⇒ **Causes include reactions to drugs...contrast media, intravenous anesthetics,...environmental allergens etc.**

Case 1: Kounis Syndrome

A 43 year-old applied for life insurance. He had a history of hyperlipidemia and treatment with statins. His family history was remarkable for a father with a Myocardial Infarction (MI) at age 55, and a grandfather with CAD in his 50's. Three years prior to application, he was hospitalized with chest pain that radiated to his left arm. There was ST elevation on his ECG and both CPK-MB (nl 0-5 ng/ml) and Troponin I (nl .01-.5 ng/ml) were elevated at 51 ng/ml and 9.05 ng/ml respectively. An urgent cardiac catheterization was performed which showed "clean" coronaries, mild inferior hypokinesia, and an Ejection Fraction of 50%. The CPK-MB peaked at 80 ng/ml and the Troponin I at 9.96 ng/ml on the day after admission. On the evening before the admission for chest pain, the applicant had been stung on the left arm by a wasp. He reported swelling, pain and redness in the area. His discharge diagnoses from the hospital were Kounis Syndrome and Myocardial Infarction. Current labs showed a Total Cholesterol of 120 and HDL cholesterol of 30 mg/dl. A stress test, done 3 months after his release from the hospital was negative for ST changes or arrhythmias at duration of 14 minutes and maximum heart rate of 165 BPM. He has been stable and asymptomatic since the hospitalization. He continues to take a Statin, a Beta-Blocker, and daily Aspirin.

Q: What are the mortality implications of Kounis Syndrome?

A: The Kounis syndrome, also called hypersensitivity myocarditis, was described over 20 years ago as the concurrence of acute coronary events with allergic or hypersensitivity reactions as well as anaphylactic or anaphylactoid insults. A variety of metabolites, enzymes, cytokines and chemokines are

released during an allergic response, including histamine which is known to cause coronary spasm. During an allergic attack various cells such as macrophages, T-lymphocytes, and Mast cells become activated, and have been implicated in the inflammatory response within the myocardium. Two variants of Kounis syndrome have been described. The type I variant, includes patients with normal coronary arteries and represents a manifestation of endothelial dysfunction or coronary spasm; the type II variant, includes patients with preexisting atherosclerotic disease that becomes active with the allergic insult. Causes of Kounis syndrome include reactions to drugs such as antibiotics, contrast media, intravenous anesthetics, analgesics, skin disinfectants, corticosteroids, thrombolytics, anti-inflammatories, and antineoplastics. Of course, environmental allergens like insect venom, plant toxins, shellfish, etc. can trigger events in those allergic to them.

The underlying process whereby Kounis syndrome causes myocardial damage in those without atheroma is thought to be an inflammatory reaction involving the release of histamine, leading to coronary spasm. The condition is rare enough, that most of the medical literature on Kounis Syndrome consists of case reports. There are however, studies on the outcome of coronary spasm. A series of 76 patients without underlying athero-

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sclerosis, who had spasm with acetylcholine provocation, were followed for 3 years. There was one non-cardiac death in the group, but no cardiac deaths or myocardial infarctions were observed. At least one prior study documented dangerous arrhythmias (complete atrioventricular block, ventricular fibrillation, and severe sinus arrest) in the setting of coronary spasm without atheromatous lesion. Over a median follow-up of 26 months, however, there were no deaths in that group either. In this case there is the additional risk of the presumed underlying allergic causation of the spasm, which could recur with another wasp sting. Immunomodulation (allergy shots) can be effective in reducing the likelihood of anaphylactic reactions in hymenoptera allergy cases, but were not mentioned in the records. This applicant also has a low HDL cholesterol and a family history of early CAD, increasing the overall risk for coronary events. A rating consistent with coronary spasm appears most appropriate.

Kounis syndrome: myocardial infarction secondary to an allergic insult--a rare clinical entity. Caglar FN, et al, Acta Cardiol 2011 Aug;66(4):559-62.

Hymenoptera sting-induced Kounis syndrome: effects of aspirin and beta-blocker administration. Ioannidis TI, Int J Cardiol 2007 Sep 14;121(1):105-8.

Kounis syndrome (allergic angina and allergic myocardial infarction) a natural paradigm? Kounis NG- Int J Cardiol 2006;110:7-14.

Histamine-induced coronary artery spasm the concept of allergic angina. Kounis NG, Zavras GM, Br J Clin Pract 1991;45:121-128.

Kounis syndrome secondary to ibuprofen use. Kumar A, Int J Cardiol 2009;137(3):e79-80.

3-year follow-up of patients with coronary artery spasm as cause of acute coronary syndrome: the CASPAR (coronary artery spasm in patients with acute coronary syndrome) study follow-up. Ong P, J Am Coll Cardiol 2011;57(2):147-52.

Coronary vasospasm-induced acute coronary syndrome complicated by life-threatening cardiac arrhythmias in patients without hemodynamically significant coronary artery disease. Hung MJ, Int J Cardiol 2007;117(1): 37-44.

Case 2: Osteogenesis Imperfecta

A 32 year-old man applied for life insurance. In his medical history on the paramedical exam, he mentioned that he was diagnosed with "Brittle bone disease". His APS was from a mental health professional and dealt entirely with his history of depression and suicidal ideation with no attempts about 8 years prior to the application. He was reported to be stable on 2 anti-depressants on his last visit. The medical history in the APS mentioned a history of Osteogenesis Imperfecta diagnosed as a child, which the applicant remembered as Type III. There was no mention of fractures or difficulty with ambulation in the APS, but it was focused on counseling with no physical exam.



Q: What is Osteogenesis Imperfecta, and what are the mortality implications?

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A: Osteogenesis Imperfecta (OI) is a disorder due to quantitative defects

in Type I collagen. Other names for the disease are brittle-bone disease, blue-sclera syndrome, and fragile-bone disease. The disease adversely affects the ossification of bone in addition to being a generalized disease of connective tissue. It manifests with one or more of the following: blue sclera, triangular facies, macrocephaly, hearing loss, defective teeth, joint laxity, barrel chest, scoliosis and kyphosis, bowed limbs, fractures, and/or growth retardation. The spectrum of disease ranges from severe forms causing stillbirths or fractures of most every bone in the body to the mildest form manifest by going into adulthood never having had a fracture (only discovered due to family members being affected). It affects approximately 1 in 20,000 births. The disorder can present at any age, with the more severe forms tending to be manifest at birth or in childhood. There have been 8 "Types" of OI described, although the well-known Sillence Classification only has 4 types.

Type I is the most common and the mildest form. Patients present with blue sclerae and may have a fracture or two at birth. Fractures tend to decrease after puberty, but may increase again at older ages as age and sex-related osteoporosis occurs. Kyphosis and/or scoliosis occur in about 20% of cases.

Type II is a severe form of the disorder, and those affected usually die at birth or shortly thereafter.

Type III patients often suffer multiple fractures at birth. Deformity of the teeth and blue sclerae are common. Fractures continue and may be seen throughout life, although the chest and ribs are often

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spared. They frequently have a barrel chest and a pectus carinatum deformity. When affected in childhood, they often become confined to a wheelchair.

Type IV is most similar to Type I, but the sclerae are white instead of blue. Again there is a variable course with frequent involvement of the spine.

The other 4 types are clinically similar, but have different x-ray or microscopic pathology.

A recent study out of Norway investigated the anecdotal observation that patients with OI had a higher incidence of cardiac abnormalities. They compared 99 patients with OI to age and gender matched controls. Blood pressures (both systolic and diastolic) were significantly higher and body-surface area was significantly smaller among OI patients vs controls. Left Ventricular mass was significantly higher in the OI group as were aortic diameters. 10.1% mild aortic regurgitation (AR), 10.1% moderate AR, and 7.1% moderate mitral regurgitation were found in the OI group vs no moderate or worse valve lesions found in the controls. Type III OI patients were found to have significantly larger left ventricular internal diameter during diastole and aortic diameters than controls and patients with Types I & IV.

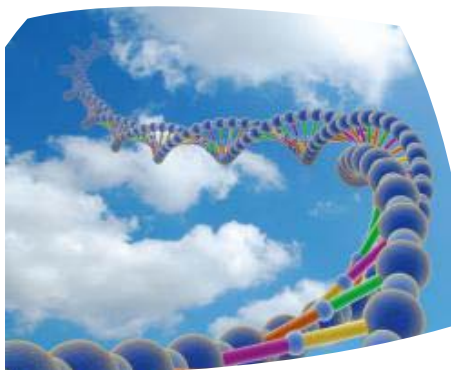
Mortality risk is related to the underlying fragility of the bones, as manifest by the number of fractures, underlying cardiac abnormalities, and any disabling deformities. Fractures are painful, and chronic pain can become an issue that affects the long-term mental health of the affected patient. Individuals confined to wheelchairs or beds run risks of skin infections, hypoventilation of the lungs, and/or adverse effects on the kidneys.

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Osteogenesis Imperfecta (OI)

OI is a disorder due to quantitative defects in Type 1 collagen. Other names for the disease are brittle-bone disease, blue-sclera syndrome and fragile-bone disease.

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In this particular case there are no details about past fractures, spinal deformities, cardiac abnormalities or mobility. Either an APS concerning general health or an MD exam with attention to fracture history and heart sounds would be necessary to evaluate the risk. If the face amount is large enough, echocardiography might be cost-effective. If the fracture history is minimal and there are no cardiac abnormalities, he may not experience any adverse effect on life span from OI.

Kliegman: **Nelson Textbook of Pediatrics**, Chapter 692, 19th Ed., Copyright 2011 Saunders, An Imprint of Elsevier.

Cardiovascular abnormalities in adults with osteogenesis imperfect. Radunovic Z, et al. *Am Heart J* 2011;161(3):523-529.

A population-based study of demographic variables and ability to perform activities of daily living in adults with osteogenesis imperfecta. Wekre LL, et al. *Disabil Rehabil* 2010;32(7):579-87.

Case 3: Hereditary Angioedema

A 43 year-old female with Hereditary Angioedema (HAE) applied for life insurance. The disorder was diagnosed at age 16. Up until a few years ago she was treated with Stanazolol, but that was changed to infusions of Complement (C1) inhibitor (Cinryze) 3 times per week in 2009. No episodes of angioedema are reported since the infusion therapy began. She is being monitored for liver complications of Stanazolol with echo showing 3 stable, moderately-sized hemangiomas of the liver.

Q: What is the anticipated prognosis in this case?

A: Hereditary Angioedema is an autosomal dominant, inherited disorder with variable penetrance that is estimated to affect 1 in 50,000 to 150,000 people. The clinical course appears to be slightly worse in women. It is estimated that HAE accounts for 15,000-30,000 Emergency Room visits per year in the US. The characteristic presentation of HAE involves a prodrome of sensory changes, mood changes, anxiety, etc. followed 1-2 hours later by swelling. The swelling can affect any part of the body and can be fatal if it involves the airway or the larynx. About a third of attacks are precipitated by trauma, even minor trauma like prolonged standing or pressure from pushing a vacuum cleaner may cause swelling of the feet or hands. Swelling most often affects the extremities, the genitalia, or the face, although it may affect internal organs causing abdominal pain, vomiting or diarrhea. Attacks may also be precipitated by infections or emotional stress. The swelling typically worsens over 12-24 hours and usually resolves within 72 hours. Attacks usually start in childhood and worsen in adolescence. The course is highly variable with some experiencing weekly attacks while others might go for a year or more without attacks.

There are three types of HAE described. Type I (~85% of cases) is characterized by a deficiency of C1 complement inhibitor (C1-INH). Type II (15%) has normal or elevated levels of C1-INH, but it is dysfunctional. And Type III (also called Familial) has normal levels of functional C1-INH, and appears to be sensitive to estrogens and much more common in women. Some Type III patients may have a defect in factor XII allowing the inappropriate activation of the kinin cascade, but others do not and

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Hereditary Angioedema (HAE)

HAE is an autosomal dominant, inherited disorder...the clinical course appears to be slightly worse in women.

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remain to be fully elucidated. It has been noted that treatment of Type III HAE with C1-INH does not affect the attack. What links the types of HAE are the dysregulation of the Complement, Coagulation, and Contact Cascades resulting in vascular endothelial leaks, pain, tissue edema, and inflammation. The release of bradykinin causing leakage of fluid into extravascular spaces appears to be a common final pathway.

Mortality risk in HAE is related to angioedema of the airway or larynx, chronic pain syndromes, surgeries due to the abdominal pain, and there may be a slight increased risk of autoimmune disorders. Older studies have shown 20-30% mortality rates with HAE. The good news is that advances in treatment have alleviated much of the risk of HAE. 17 α -Alkylated androgens have been used prophylactically to effectively reduce the number and severity of attacks. In 2008, purified C1-INH was approved by the FDA for prophylactic use in HAE. Intravenous C1-INH is expensive to purchase and administer, but there appear to be few side effects. For acute attacks ecallantide, a kallikrein inhibitor, and icatibant, a selective bradykinin B2 receptor antagonist, have been approved within the past 2 years. Both drugs have shown the ability to reduce swelling and symptoms during attacks of HAE. Fresh Frozen Plasma has also been used prophylactically before surgical or dental procedures. There have been reports of association of HAE with other immune

disorders such as inflammatory bowel disease, Systemic Lupus, and rheumatoid disease, although the small numbers do not appear to achieve statistical significance. There have also been anaphylactic reactions to some of the IV medications mentioned above, prompting the suggestion that the administration be performed under the supervision of someone who can perform a resuscitation. Ratings should be based on prior swelling of the airway and the number of recent attacks. Someone not having attacks, or controlled on medication should have minimal risk, up to a moderate risk in those with recent or frequent ER visits and/or attacks threatening the airway.

Hereditary Angioedema: New Findings Concerning Symptoms, Affected Organs, and Course. Bork K, Am J Med 2006;119:267-274.

Hereditary Angioedema. Zuraw B, N Engl J Med 2008;359:1027-36.

Hereditary Angioedema — Therapies Old and New. Morgan P, N Engl J Med 2010;363(6):581-3.

Complement disorders and hereditary angioedema. Frank M, J Allergy Clin Immunol 2010;125:S262-71.

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