The Global Nature of Medicine

In our jobs we usually must focus on mortality and morbidity risk, underwriting standards, products, governmental rules and regulations for our own regions. We assess risk based on our regional population rates for standard and excess risks, even though we know that pathogens can affect other regions of the world significantly differently than at home.

Consider the Epstein-Barr virus (EBV). Worldwide, 90%-95% of adults are seropositive for EBV. In the US it is primarily known as the causative agent for Infectious Mononucleosis, a self-limited disease manifest primarily by sore throat and fatigue. EBV is rarely associated with malignancy in the West, outside of immunosuppressed individuals. In contrast, 95% of children in equatorial Africa are infected with EBV. There the virus is associated with Burkitt’s lymphoma, the area’s most common childhood cancer. It is likely that Malaria/EBV co-infection plays a key role in this cancer’s development. Meanwhile, in southern China, where rates of nasopharyngeal carcinoma can reach 55 per 100,000, EBV is found in nearly all anaplastic nasopharyngeal carcinoma cells. This is likely due to a dietary/exposure trigger in this area. Most EBV-infected individuals fortunately do not develop malignancies, but hopefully an effective vaccine might reduce prevalence even further.

We see differences also in allocation of research monies around the world. North America, and the US especially, spent about $117 billion, or 44% of all medical research spending globally, in 2012. However, figures for 2009 show that the US published 122,659 medical research articles, while the EU published 120,421 and Asia contributed another 60,666 studies. The annual growth rate in medical publications from China is 18.7%, versus 0.6% in the US. A lot of medical research is going on half a world away.

In line with our global theme, we are pleased to have Dr. John Evans, Associate Medical Director for SCOR Global Life Paris, examine a case in this issue of Housecalls involving patent foramen ovale (PFO). Many of our readers may know Dr. Evans from his attendance at North American and international insurance medical meetings. I write about an interesting case involving spinal syrinx and present this issue’s Underwriting Puzzler. Rest assured that Dr. Rooney will return to this newsletter very soon. And remember to look up from your work occasionally to absorb some knowledge from other parts of the world.

References

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Our Casebook

Case #1
Patent Foramen Ovale

By John Evans, MB, BCh
Associate Medical Director, SCOR Global Life Paris

Dr. Evans has had an atypical medical career. After qualifying in Cardiff and occupying junior hospital posts at the University Hospital of Wales, he was accepted as Interne Resident Etranger in the Cardiology Department at the Pitié-Salpêtrière Hospital in Paris where he worked in the Catheter and Echocardiography laboratories. He continued his hospital appointments in the Institute of Cardiology and established his own cardiology practice in Paris.

Dr. Evans has been actively involved in representing SCOR Global Life on the international scene. He is a member of the International Committee for Insurance Medicine (ICLAM) for France and was a moderator at one of the scientific sessions at its 2013 conference in Madrid. He was one of the speakers at the ELHUA Brussels meeting and also participated in a breakout session in Vienna. He is an Associate Member of the American Academy of Insurance Medicine and l’Association des Médecins Conseils en Assurance des Personnes.

A 36-year-old female non-smoker applied for $250,000 of life insurance two years after an isolated, 18-hour episode of dysarthria (slurred speech). She had been admitted to the hospital at that time for investigation. There was no previous medical history and, by the time she was seen in the emergency department, there were no abnormal physical signs. Cardiac rhythm was normal and blood pressure registered 126/84 mmHg. Her resting ECG was within normal limits.

She had a normal Computed Tomography (CT) brain scan, normal hematology and blood biochemistry. She was seen by a cardiologist who ordered a 24-hour Holter ECG, which showed normal sinus rhythm with rare, isolated supraventricular extrasystoles. She also underwent transesophageal echocardiography with intravenous contrast injection which demonstrated a patent foramen ovale (PFO).

Since her discharge from the hospital on anticoagulant treatment with apixaban, there has been no recurrence and she has a normal clinical examination.

Question
What is PFO, and what are the mortality implications of transient ischemic attack (TIA) and PFO?

Answer
PFO is an atrial malformation that traces its beginnings to embryonic gestation. At around four weeks of pregnancy, the embryonic single atrium divides into right and left sides by the formation and fusion of two septa: the septum primum and septum secundum.

The septum primum grows from the top of the atrium down towards the endocardial cushion. The area between the leading edge of the septum primum and the endocardial cushion is known as the ostium primum, which closes when the septum primum fuses with the endocardial cushion.

A second orifice, the ostium secundum, develops at the top of the septum primum following the coalescence of multiple small perforations. The septum secundum then develops on the right atrial side of the septum primum. The septum secundum covers the ostium secundum but does not completely divide the atria. This persisting orifice within the septum secundum is the foramen ovale.

Fetal circulation of blood through the foramen ovale allows oxygenated blood from the umbilical cord to pass from the right atrium into the left atrium and, thereafter, into systemic circulation. Following birth, the changes in pressure within the atria lead to closure of the foramen ovale in most individuals. A PFO results from a failure to close, allowing a right atrial-to-left-atrial shunt because of the flap covering the foramen from the left side. There are no risk factors for the development of PFO, but familial cases have shown an autosomal dominant mode of transmission.
Clinical Implications

A functional opening of the foramen ovale is likely only in a situation in which resistance to flow in the right side of the heart is higher than in the systemic circuit, causing right atrial pressure to be higher than on the left.

Clinically, this pressure could occur in the cases of obstruction at the right ventricular level, pulmonary valvular or vascular level, which are usually associated with right ventricular and right atrial hypertension. A PFO with a large right-to-left shunt could cause cyanosis on crying, breath-holding, or any activity which raises right atrial pressure. PFO can worsen hypoxemia in conditions such as valvular pulmonary stenosis, Ebstein’s anomaly, right ventricular myocardial infarction, chronic obstructive pulmonary diseases, or pulmonary hypertension (primary or secondary). Severity depends on the size of the PFO, the pressure gradient between the right and left atria, and the direction of inferior vena caval blood flow.

A potential hazard is an increased risk of nitrogen gas embolism across PFO in deep-sea divers. As only a small percentage of divers with PFO develop decompression sickness (“the bends”), the feasibility of screening them all is a controversial issue. However, PFO can worsen hypoxemia at great depths and may even lead to death in untrained divers.

Some causes of increased left atrial pressure (for example, mitral stenosis) can dilate the foramen ovale causing it to become patent and result in a left-to-right inter-atrial shunt, which is generally silent clinically.

The main clinical concerns of PFO are its association with neurological conditions. PFO is thought to predispose to hemostasis and clot formation, with reports of increased incidences of PFO in patients with thrombophilia.

Patients with headache (migraine with aura) were also found to have a high incidence of PFO, and migraine symptoms improved on medical treatment in the form of antplatelet and anticoagulant drugs, or disappeared on the closure of PFO.

More importantly, PFO is associated with neurological signs and symptoms such as hemiplegia, visual disturbances, and slurred speech due to paradoxical embolism causing cryptogenic (i.e., in absence of any obvious cause) brain infarction. These emboli may originate from any thrombosis of systemic veins or from a clot within the right atrium.

High-risk PFOS are those associated with atrial septal aneurysm and spontaneous right-atrial-to-left-atrial passage of bubble on contrast echocardiogram in the absence of any provocative measures.
Diagnosis
Echocardiography is the diagnostic investigation of choice, while Transesophageal Echo (TEE) is more sensitive than transthoracic echo in diagnosing PFO. Sometimes it is possible to visualize the gap in the atrial septum or demonstrate a septal aneurysm with septal perforation on the echocardiogram. Intravenous injection of contrast/micro bubbles (agitated saline) is extremely helpful in the diagnosis, which manifests via the appearance of the contrast medium in the left atrium within 3 cardiac cycles of its appearance in the right atrium (Figure 2, previous page). The sensitivity of the TEE can be improved further by asking the patient to perform a Valsalva maneuver during the injection, thereby increasing the right atrial pressure and exposing the right-to-left shunt.

Treatment
Discovering an asymptomatic PFO during echocardiography performed for another indication is relatively common as studies show it to be present in approximately 25% of adults. In these cases, no treatment is usually prescribed. However, there is a case for treating patients with “high risk” PFO with antiplatelet drugs, but there are no formal recommendations.

The risk of neurologic insult is different after a stroke or transient ischemic attack with no other obvious cause. In this situation the prescription of antiplatelet drugs, traditional oral Vitamin K antagonists or one of the novel oral anticoagulants (anti-thrombin or anti-Xa) is justified. Recurrent cerebrovascular attacks despite optimal anticoagulation may require closure of the PFO which is usually performed by an endovascular approach with a Cardioseal umbrella or Amplatzer device (Figure 3). Surgical direct suture or patch closure is rarely performed.

Returning to the Case
When there are no heart defects resulting in abnormal pressures, the PFO is usually asymptomatic and is associated with normal health and life expectancy. The chance finding of an asymptomatic PFO would therefore qualify as a standard risk.

When found in association with other congenital heart malformations, the rating of the latter would cover the risk associated with the PFO. Even when detected “incidentally” during echocardiography to investigate a cryptogenic ischemic cerebrovascular accident, there is no additional risk beyond that for the TIA or CVA.

This applicant would be insurable with a moderate substandard loading to cover the possible risk of recurrent cerebral ischemia and of bleeding due to the oral anticoagulant drug. A major medical issue here would be the duration of her anticoagulant therapy, which normally would be life-long.

References


A 37-year-old female applied for life insurance. About three years prior to the application she presented with loss of sensation in her hands and back and some weakness in “the arms and legs.” Magnetic Resonance Imaging (MRI) of the brain was reported as normal. An MRI of the spine reported a syrinx in the central canal between the level of the 4th cervical (C4) and 12th thoracic (T12) vertebrae, with the maximal dimension of 1.6 mm. “Patchy narrowing” was described at the cervico-thoracic junction. Annual MRIs since that time have remained unchanged. Neurological examination six months prior to application was reported as “normal.”

**Question**
What is a spinal syrinx and what are the mortality implications?

**Answer**
Syrinx is from the Greek word for “tube,” and in medicine it describes a glial-lined cavity within the spinal cord. It may extend into or wholly exist in the brainstem, in which case it is syringobulbia. Syringomyelia is the process of the syrinx expanding over time. Most lesions occur between C2 and T9. Most often syringomyelia affects the central canal of the spinal cord, but rarely a syrinx can form in the parenchyma of the cord.

The central canal of the spinal cord derives from the neural groove at the 7th day of embryonic development. It closes into a neural tube on the 14th day and progressively forms a canal. At birth the central canal communicates with the 4th ventricle of the brain and usually measures .05 mm-.1 mm in diameter. It is usually visible only in newborns as it undergoes stenosis with age, until the central canal is obliterated in the majority of adults (Figure 1).

In some studies 50% or more of cases of syringomyelia occur in association with Chiari malformation (CM), a condition where the basal portion of the brainstem or cerebellum is displaced through the opening in the skull (foramen magnum). A survey of neuro-imaging centers in Japan suggested an estimated prevalence of ambulatory syringomyelia of 1.94 per 100,000. The asymptomatic proportion was 22.7%. A study in New Zealand found that the prevalence of symptomatic syringomyelia was 5.4 per 100,000 in Caucasian/East Asian people. In New Zealand the mean age of symptom onset was 27.5 years and the mean age of diagnosis was 33 years. The underlying cause of syringomyelia in the New Zealand study is illustrated in Figure 2 on the next page.

Syringomyelia most commonly affects the central spinal canal which results in central cord syndrome. This syndrome consists of loss of pain and temperature sensation in dermatomes that are adjacent to the lesion. Areas above and below the lesion are usually unaffected. As the syrinx expands muscle weakness can develop in the area of anesthesia with eventual loss of deep tendon reflexes in the affected area (Figure 3, next page).
Spinal Syrinx (cont.)

On a basic level, the etiology of most cases of syringomyelia is an interruption or imbalance in the flow of cerebrospinal fluid (CSF). Conditions that cause this interruption include CM, curvatures of the spine, spinal cord tumor, trauma and posttraumatic scarring, post-infectious arachnoiditis, and post-inflammatory arachnoiditis. When an underlying cause cannot be identified, the term idiopathic syringomyelia (IS) is generally used. However, as imaging techniques improve, it is more common for blockage or narrowing of the subarachnoid space to be detected. Reports of using cardiac-gated phase-contrast cine-mode MRI in multiple axial planes to precisely locate obstructions to CSF flow are appearing in medical literature.

Arachnoid webs or adhesions that are not visible on MRI or CT can often be identified at surgery, and removed with favorable outcome in stopping the progression of the syrinx. Decompression of obstruction of CSF flow via crano-caudal decompression or laminectomy is successful in some cases. Shunts have been tried between the syrinx and various other spaces including the peritoneal space, the subarachnoid space, and the third ventricle. Shunts frequently become blocked and some medical professionals would consider them only as a last resort. An etiology-driven approach to treatment is essential, with conservative management often being successful.

As MRI and CT scanners have become more prevalent, there have been efforts to define an entity that consists of a widened central spinal canal in an adult that does not progress, and does not appear to be pathologic. Some authors would refer to this entity as hydromyelia, while others use the terms syringomyelia and hydromyelia interchangeably. Common features for the diagnosis of the non-progressive widening of the central canal are: relatively smaller diameter (mean transverse diameter in one study was 2.7 mm, range 1.5-5.8); relatively short vertical extension (mean of 3.5 vertebrae in one study); location in the thoracic, cervical or cervico-thoracic spine; presentation with diffuse pain as the primary symptom; and lack of abnormal neurological findings. When patients with these characteristics were followed over three years, there was no evidence of neurologic or radiologic progression.

The prognosis of syringomyelia is related to the underlying cause and the neurologic deficit. Spinal tumors or cysts requiring removal have the attendant

<table>
<thead>
<tr>
<th>Associated Condition*</th>
<th>Percent of total affected (%)</th>
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<tr>
<td>Chiari I malformation alone</td>
<td>38.2</td>
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<tr>
<td>Chiari malformation and spinal cord abnormality</td>
<td>20.6</td>
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<tr>
<td>Other Posterior fossa abnormality</td>
<td>2.9</td>
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<tr>
<td>Isolated spinal cord abnormality</td>
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<tr>
<td>Post-traumatic arachnoiditis</td>
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<td>Non-traumatic arachnoiditis</td>
<td>5.9</td>
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<tr>
<td>Idiopathic</td>
<td>17.6</td>
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</table>

*Patients with spinal cord tumors were excluded from this study

Chiari malformation – on its own or in concert with other complications – accounts for more than half of all cases of syringomyelia observed in a New Zealand study.

The white areas are spinal fluid surrounded by dark spinal cord.
mortality of the neoplasm. In the case of mechanical obstruction to CSF flow that has been relieved (CM, spinal deformities, arachnoid membranes or adhesions) the mortality will correspond to that of the residual neurological deficit after relief of the obstruction. Early in the course of idiopathic syringomyelia it is difficult to determine the longer-term prognosis. I outlined the characteristics associated with non-progression (at least for three years) in the paragraph above. However, it may also be that a patent, dilated central canal is a precursor to the development of a syrinx in response to future insult. The finding of a widened central canal has socio-economic and psycho-social implications for the individual, and further research is ongoing to better define outcomes.

**Returning to the Case**

This appears to be an idiopathic widening of the central canal with a relatively small diameter. There is no neurologic deficit reported, and annual MRIs indicate it has been stable. There would appear to be minimal, if any, excess short-term mortality attributable to the incidental finding of widened central spinal canal.

**References**


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**Underwriting Puzzler…**

By Richard Braun, MD

In this issue of the Puzzler Dr. Braun presents an EKG. How would you interpret this EKG?

To find the answer, be sure to visit the Housecalls page on www.scorgloballifeamericas.com. Click on the “June Puzzler” Powerpoint presentation to confirm your findings. ∞
Over the past 50 years, the insurance and reinsurance industry has seen tremendous changes. From products, services and distribution networks to risk management, capital management and regulation, nothing is how it used to be. Far from slowing down, the pace of this change is accelerating. New technology is having a profound impact on the way in which we assess, model, price and reserve risks. At SCOR, we have the experience and expertise to stay at the cutting edge of these developments.

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