A 34-Year-Old-Male with Progressive Neurologic Decline

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Case Studies

Patient
34-year-old white male.

Chief Complaints
Change in speech pattern; difficulty walking; inability to ambulate.

History of Present Illness
The patient presented to the emergency room with change in speech pattern and difficulty walking that progressed during 3 days to inability to ambulate. In the emergency room, he experienced respiratory arrest and was admitted to the neurology service for a presumed cerebral infarct.

Past Medical History
Marfan syndrome.

Past Surgical History
Repair of thoracic aorta, abdominal aortic and left popliteal aneurysms; aortic valve replacement; and clipping of an intracerebral artery aneurysm.

Family History
Father with Marfan syndrome and thoracic aneurysm.

Medications
Toprol XL and Coumadin.

Chief Complaints
Change in speech pattern; difficulty walking; inability to ambulate.

Questions:
1. What are the most common causes of aneurysms?
2. What is the most likely cause of this patient’s aneurysm?
3. Name and describe the most likely underlying histologic diagnosis.
4. What are the clinical features of this patient’s disease?
5. Are there any laboratory tests to help in the diagnosis of this patient’s disease?
6. How is this patient’s disease managed, and what is the expected clinical outcome?

Possible Answers:
1. Common causes of aneurysms include atherosclerosis, Marfan syndrome, Ehlers-Danlos syndrome, bacterial and fungal infections, syphilis, arteritis, and trauma. A rare cause is copper deficiency, which inhibits lysyl oxidase leading to non-crosslinked elastic muscle fibers. Atherosclerosis destroys the elastic fibers and muscle cells in the medial layer of the artery thus weakening the vessel leading to dilatation. In the ascending aorta, aneurysms are most likely caused by degenerative changes in the elastic media while in the descending aorta, the majority of aneurysms are caused by atherosclerosis.

2. Because this patient had aneurysms in multiple sites (intracerebral, ascending and descending aortic, popliteal, subclavian, and splenic) the most likely cause is a diffuse elastic medial degeneration. In the ascending aorta, aneurysms are most likely caused by degenerative changes in the elastic media while in the descending aorta, the majority of aneurysms are caused by atherosclerosis.

3. Cystic medial degeneration (necrosis) is a non-inflammatory, age-related intrinsic defect of the arterial wall that is often associated with Marfan syndrome or can occur as a separate entity. No true cysts are present. Histologically, there is disruption and fragmentation of the elastic fibers in the arterial media with an increase in the amount of basophilic ground substance including collagen and mucopolysaccharides. These changes can be seen most easily with special stains for elastin.

4. Marfan syndrome is an autosomal dominant heritable disorder of connective tissue. It affects approximately 2 to 3 per 100,000 people.
10,000 population; however, 25% of patients have no family history.4,5 There is variable expression of symptoms affecting multiple organs of the skeletal, ocular, cardiovascular, pulmonary, and integumentary systems. The diagnostic criteria for Marfan syndrome were defined in 1996 and are known as the Ghent nosology. It includes major and minor criteria for each of the above mentioned organ systems as well as family history. To make a diagnosis of Marfan syndrome, major criteria in at least 2 different organ systems and involvement of a third organ system are required.6 However, in a patient with a positive family history and in the presence of a mutation known to cause Marfan syndrome, the diagnosis requires 1 major criterion from only 1 organ system plus involvement of a second organ system.6 Skeletal manifestations of Marfan syndrome include reduced upper to lower segment ratio or arm span to height ratio >1.05, scoliosis, and arachnodactyly (spider-like fingers) as evidenced by positive wrist and thumb signs. A positive wrist sign occurs when there is considerable overlap between the thumb and the little finger when clasped around the opposite wrist. A positive thumb sign occurs when the entire thumbnail extends beyond the ulnar margin of the hand when the fingers are closed over the thumb. The most common ocular symptom of Marfan syndrome is displacement of the lens of the eye (ectopia lentis). Cardiac complications include dilatation and dissection of the ascending aorta, calcification of the mitral valve annulus under the age of 40, mitral valve prolapse with or without regurgitation, and dilatation or dissection of the descending thoracic or abdominal aorta before the age of 50 years. Other signs of Marfan syndrome include spontaneous pneumothorax, apical blebs on chest radiograph, and lumbosacral dural ectasia by CT or MRI.

5. There is no specific diagnostic laboratory test to make the diagnosis of Marfan syndrome. The diagnosis is based largely on clinical findings but does take into account the family history of relatives who have a mutation in the gene encoding the protein, fibrillin-1 (FBN1), a gene known to be associated with Marfan syndrome.6 The gene for FBN1 is found on the long arm of chromosome 15 at 15q21. Fibrillin-1 was discovered in 1986 by Sakai and colleagues. FBN1 is a glycoprotein with wide distribution in both elastic and non-elastic tissues and is the major component of extracellular matrix microfibrils.7 Microfibrils may act as a scaffold for elastogenesis and help determine the orientation and deposition of elastic fibers.3 More than 500 mutations have been identified in the FBN1 gene in patients with Marfan syndrome and related diseases including familial aortic aneurysm/dissection and Shprintzen-Goldberg syndrome. This group of disorders is known as type 1 fibrillinopathies.
Molecular DNA analysis for evaluation of Marfan syndrome is useful and practical in two situations. When the specific FBN1 mutation is known in a person with Marfan syndrome and the information can be used to help diagnose family members and when linkage analysis is performed in families with several persons affected with Marfan syndrome to assess involvement in remaining undiagnosed relatives. Molecular diagnosis of Marfan syndrome plays a minor role in sporadic cases with no family history because mutation identification is very costly, time consuming, and not 100% reliable. Tissue immunofluorescence studies with monoclonal antibodies against fibrillin show decreased staining intensity in patients with Marfan syndrome. However, this test is neither specific nor sensitive because of the genetic heterogeneity of Marfan syndrome and because other diseases may also be caused by mutations in the FBN1 gene. Therefore, diagnosis of Marfan syndrome remains mostly a clinical one.

6. The management of Marfan syndrome is different during each stage of life. Infants with Marfan syndrome often have many disease manifestations, and parents must adapt to caring for a child with a serious health problem. The parents must become educated about the disease, the expectations, and the genetics of Marfan syndrome. A comprehensive genetic evaluation of other family members is required to answer questions about the risk of passing on the disorder to future children. Prompt cardiac evaluation from someone familiar with the disorder is necessary to establish baseline values of mitral valve competency and regurgitation. Parents can expect normal language and cognitive development. However, joint laxity may delay motor milestones, but normal function can be expected. Management during childhood is similar to infancy. Yearly cardiac evaluation is necessary to evaluate the condition of the aorta as the child grows. Aortic root enlargement leading to aortic insufficiency, aortic dissections, and aortic aneurysms are major risk factors for children with Marfan syndrome. Physical activity that suddenly increases cardiac output is potentially dangerous. Sports that require sudden bursts of activity, such as soccer, football, basketball, and weightlifting, should be avoided. Ophthalmologic evaluation is needed to evaluate retinal detachments and cataracts. Yearly orthopedic monitoring is necessary to ensure linear growth, to evaluate spinal conditions such as scoliosis, and to evaluate joints. Adolescents should be counseled on the reproductive issues associated with Marfan syndrome. Patients with Marfan syndrome carry a 50% chance of passing the condition to an offspring. Pregnancy poses a serious physical risk, especially to the cardiovascular system for female patients with Marfan syndrome. These patients should be followed both by a cardiologist and an obstetrician specialized in high risk pregnancies. The treatment for Marfan syndrome of the child and adult has evolved into the prevention of catastrophic cardiovascular events by beta-adrenergic receptor antagonist and pre-emptive surgical intervention for aortic and valvular disease. Based on these 2 approaches, the life expectancy of patients with Marfan syndrome has improved dramatically. Surgical intervention is recommended in patients with an aortic root diameter greater than 5.0 to 5.5 cm. Aortic aneurysms are generally repaired if they are greater than 5 cm, or the rate of growth is greater than 1 cm per year. The long-term management of patients with Marfan syndrome is complex and requires a multidisciplinary approach. With the advent of improved early detection methods, improved surgical technique, and beta-adrenergic receptor antagonist use, the prognosis for patients with Marfan syndrome has improved dramatically.

Keywords: Marfan syndrome, connective tissue, Ehlers-Danlos syndrome, aneurysm, fibrillin-1

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