

HOLY C.O.W.!

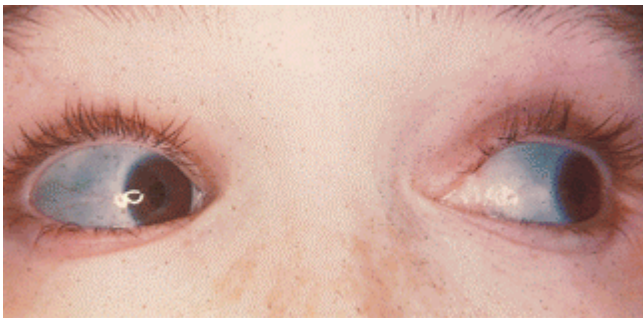
IT'S...

**Clinical Question of the Week #21
November 17th, 2008 through November
24th, 2008**

Please e-mail your answers to Kuo, Tim, Wendy, and Kevin (klian@mednet.ucla.edu; tprovias@mednet.ucla.edu; wsimon@mednet.ucla.edu; kbreger@mednet.ucla.edu) by 0800 on Monday, November 24th, 2008. The resident or intern with the most correct answers at the end of each month will receive a prize!

Case: A 28-year-old man presents for follow up evaluation at Simms-Mann Clinic for chronic intermittent aches and pains. He is employed on the cleaning staff at RR UCLA Medical Center, and describes being in good recent health. He attributes his chronic intermittent low back and bony/joint aches and pains to his occupation, and feels better after resting at home. His workplace is noisy and he is also concerned of some mild hearing loss bilaterally. His past medical history is notable for right arm and left ankle fractures in childhood, as well as mild scoliosis with no corrective intervention required. He does not smoke or drink. Examination reveals a well-developed male of 5' height and 165lb weight; other examination is unremarkable. He states that he has a brother of similar height who is healthy. Recent dual-energy x-ray absorptiometry scanning reveals L-spine and hip BMD T-scores of -0.8 and -0.6, respectively. A photo of the patient is shown.

**This case taken from a real patient seen at Simms-Mann.



The patient on lateral eye gaze.

Questions:

1. What is the diagnosis?

Osteogenesis imperfecta (OI), also known as "brittle bone disease," is a collection of inherited connective tissue disorders with phenotypic presentations ranging from premature osteoporosis to recurrent multiple fractures to fatal perinatal disease. The incidence is estimated at 1:20,000 live births, and over 200 genes have been associated with the condition.

Clinical variations vary widely, even amongst members of the same family, indicating a possible incomplete penetrance or other factors contributing to the development of poor collagen quality. Depending on the clinical type of OI, features may include short stature,

excess or atypical fractures, scoliosis, basilar skull deformities, blue sclerae (shown above), hearing loss, opalescent teeth with rapid decay (dentinogenesis imperfecta), increased ligamentous and skin laxity, and easy bruisability.

Diagnosis is clinical, however laboratory abnormalities may include elevated alkaline phosphatase, hypercalcemia, and hypercalcuria are observed. Bone formation markers may be decreased while bone turnover markers may be elevated. DNA testing is the diagnostic modality of choice. (0.5)

2. Describe the pathophysiology of the condition.

Most frequently, mutations occur in the *COL1A1* and *COL1A2* genes, which encode for collagen 1 – an integral component of bone, tendon, ligament, skin, and sclerae. In approximately 10% of cases, no mutation is found in either the *COL1* genes, and other genes have been attributed to the disease phenotype.

These genes encode for tropocollagen molecules, which under normal circumstances polymerize and form a triple helix with two alpha 1 chains and one alpha 2 chain. Mutation in the gene encodes for poorer quality collagen with resultant poor bone quality. (0.5)

3. Name the three clinical categories of the condition. Which does this patient fall into?

More than eight types of OI have been identified, based primarily on genetic mutations.

Generally speaking, these are grouped into three clinical categories:

- Mild (type I) – the least bone fragility with few fractures (predominantly before puberty) over a lifetime, normal stature without deformity, and progress to have accelerated osteoporosis and premature hearing impairment (usually 2-4th decade of life). Our patient falls into this category.
- Moderate to Severe (types III-VIII) – bone fragility is more severe in these types, with mild to moderate bone deformity, kyphoscoliosis, multiple fractures, short stature, joint laxity, early hearing loss and accelerated osteoporosis. Clinical manifestation may range from similar to Mild category to immobility with wheelchair requirement in childhood.
- Lethal Perinatal Form (type II) – individuals with type II OI usually die in utero or early infancy, primarily as complications of pulmonary failure and multiple severe fractures. In this scenario, supportive care and genetic counseling for affected families are provided. (1)

4. What surveillance is needed over time? What medical therapy is indicated, if any?

Surveillance usually includes regular hearing testing, dual-energy absorptiometry (DEXA) evaluation of bone mineral density, and spirometry on an intermittent basis for patients with moderate to severe disease. Specific types may also indicate the need for EKG and echo screening for valvular and aortic root problems. X-ray surveillance, including evaluation of the basilar skull, is undertaken on a case-by-case basis. Other considerations include vision and dental screening and care. Physical and occupational therapy is part of the multidisciplinary care of the patient, as is psychosocial and developmental/educational support as needed.

Bisphosphonate medical therapy for OI is currently evolving, however both IV pamidronate and oral alendronate have been used with some frequency in moderate to severe OI. In postmenopausal osteoporosis, consideration may also be given to therapy with SERMs. Both of these therapeutic options remain off-label use. Other experimental therapies include growth hormone, cell replacement therapy (BMT with transplant of bone marrow stromal cells), and gene therapy. (1)

**In the 2000 film *Unbreakable*, the character named Elijah Price (Samuel Jackson) suffers from OI and is nicknamed “Mr. Glass.”