# Rare Diseases: Why You Should Care

George Everett MD MS

# Rare Diseases

- Rare Diseases are often defined as present in less than 1/2000 people
- 7000 rare diseases are identified and more are found each year
- Most rare diseases are new mutations, not transmitted genetically
- Up to 10% of all **patients** may have a rare disease.

# Rare Diseases

- Keep your practice fun and interesting
- Knowing “stuff” is what IM is all about
- Generalist often knows as much or more about a rare disease as compared to a specialist/subspecialist
- Often don’t fall into a single traditional IM specialty domain
- Patients may need multispecialty support, especially Pediatrics

# Rare Diseases – Notes and Disclaimers

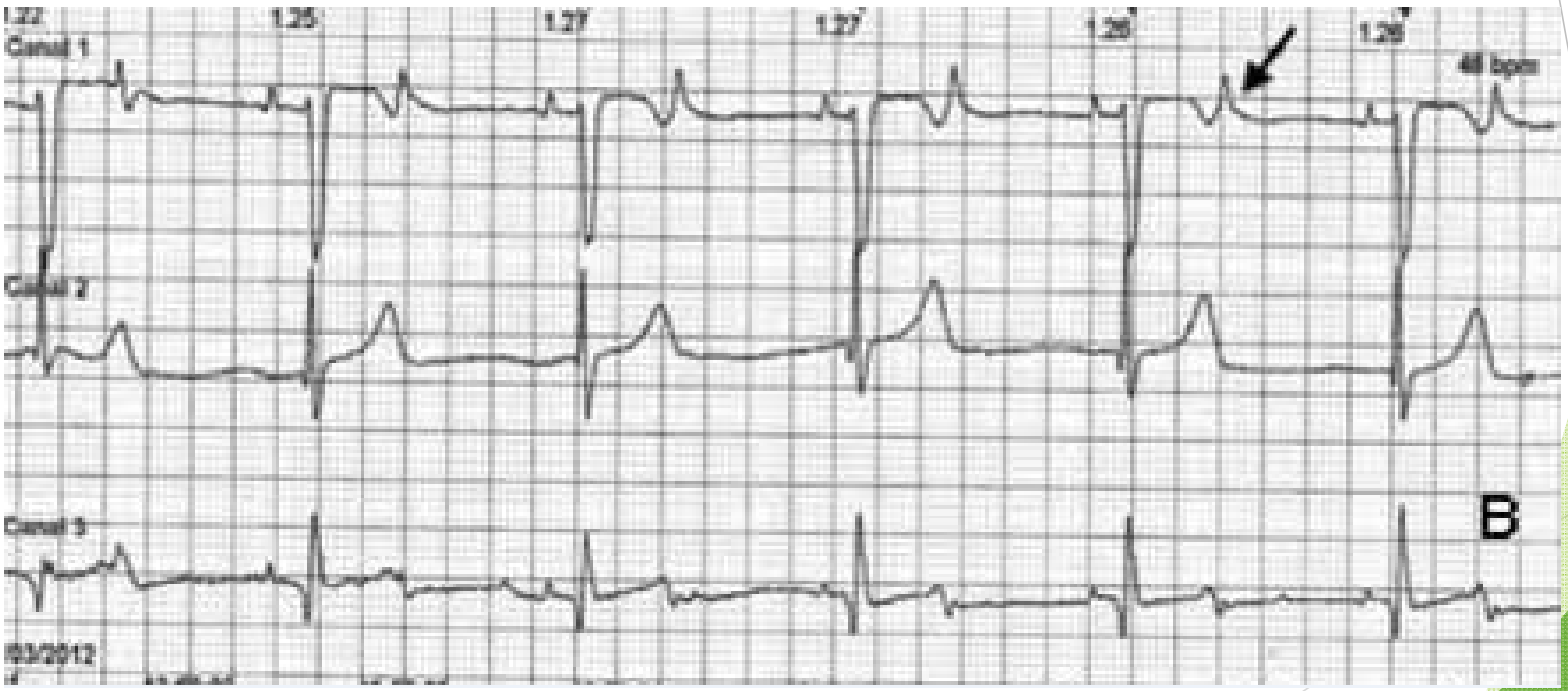
- All of these cases received direct care by me at some point.
- Some are from my own clinic and are still are under my care.
- Most pictures are not of the actual patients I am seeing/have seen due to confidentiality problems.

# Rare Diseases: Format

- Cases will be presented in summary form with pictures/images as appropriate.
- Feel free to call out a diagnosis if you know or suspect what the diagnosis is.
- After the diagnosis is established, I will give some relevant facts including diagnostic confirmation and treatment options.

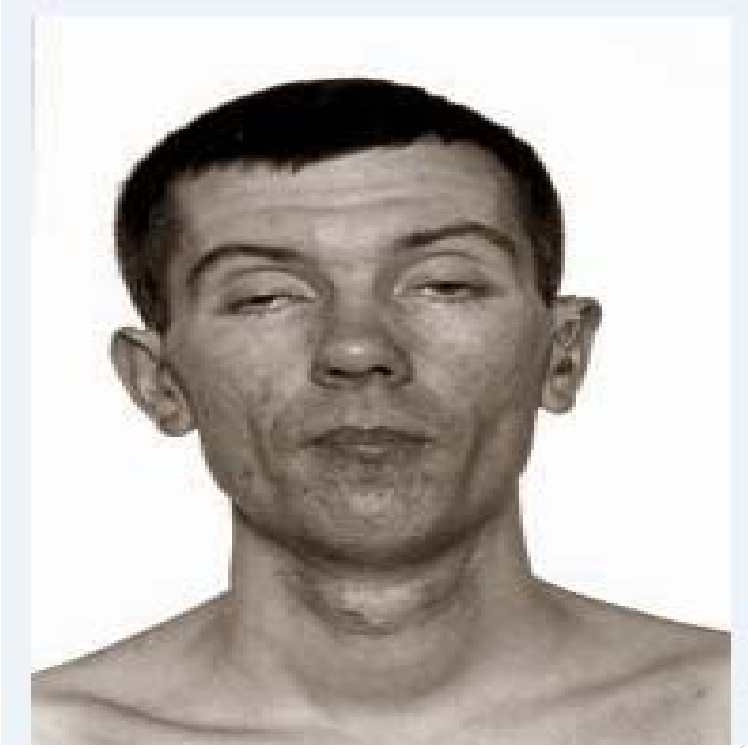
# Rare Disease number 1

- 22 year old man transferred to my hospital due to the following EKG



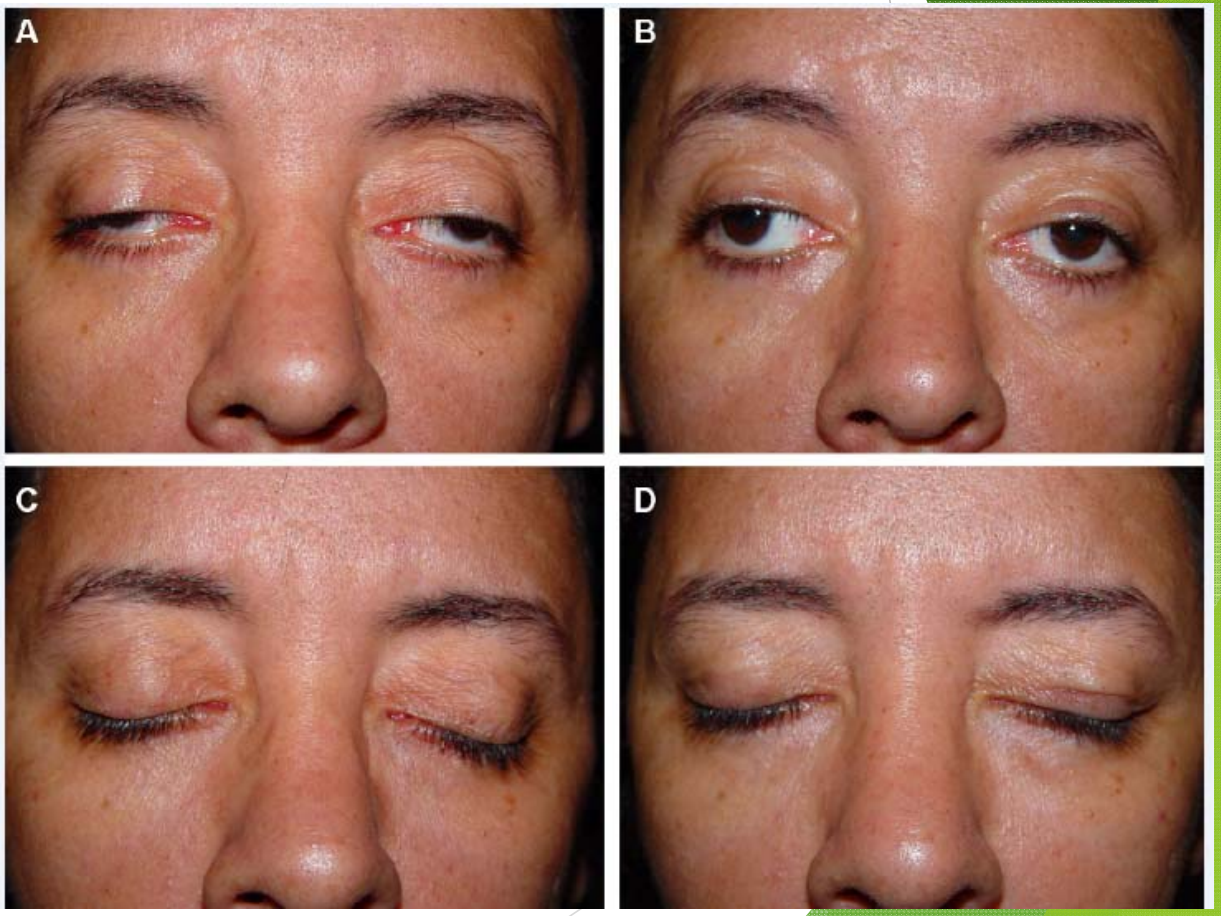
# Rare Disease #1

- Patient was characterized as mentally delayed due to appearance of face per his family members
- He was “cross eyed” and eyelids were droopy



# Rare Disease #1

There were no other family members who were similarly afflicted. The closeup eye exam is  like this.



# Rare Disease #1

- What is the likely diagnosis and what is the differential diagnosis?

## Rare Disease #1

- Diagnosis: Kearns-Sayre syndrome

- Differential Diagnosis:
  - Myotonic Muscular Dystrophy
  - Oculopharyngeal Dystrophy
  - Facioscapulohumeral Dystrophy
  - Myasthenia Gravis
  - Other Mitochondrial diseases

# Rare Disease #1

- Many mitochondrial disorders have yet to be recognized or named.
- Some clinical features that might suggest a mitochondrial disorder include:
  - Ptosis, Ophthalmoplegia, Retinitis Pigmentosa
  - Muscle weakness
  - Unexplained lactic acidosis
  - “Ragged red” muscle fibers on muscle biopsy
  - Leukoencephalopathy on MRI of brain
  - Seizures or myoclonus or Stroke-like neurological findings
  - Maternal pattern of family history

# Rare Disease #1

- Some other recognized mitochondrial disorders:
  - PEO: Progressive External Ophthalmoplegia
  - Leigh syndrome
  - MERRF: Myoclonic Epilepsy and Ragged Red Fibers
  - MELAS: Mitochondrial Encephalopathy, Lactic Acidosis and Stroke-like episodes
  - NARP: Neurogenic weakness, Ataxia and Retinitis Pigmentosa

# Rare Disease #1

- Mitochondrial Diseases are highly variable is clinical expression.
- Mitochondrial Diseases can be caused by defects in either Nuclear DNA that codes for structure of mitochondria or the Mitochondrial DNA which codes for the respiratory chain components
- Nuclear DNA defects will be transmitted as Mendelian disorders, usually autosomal recessive
- Nuclear DNA disorders include: Leigh syndrome, several cardiomyopathies, encephalopathies and hepatopathies
- Mitochondrial DNA defects are transmitted maternally.
- Mitochondrial DNA defects include: Kearn-Sayre syndrome, Leber Optic neuropathy, MELAS, and MERRF

# Rare Disease #1

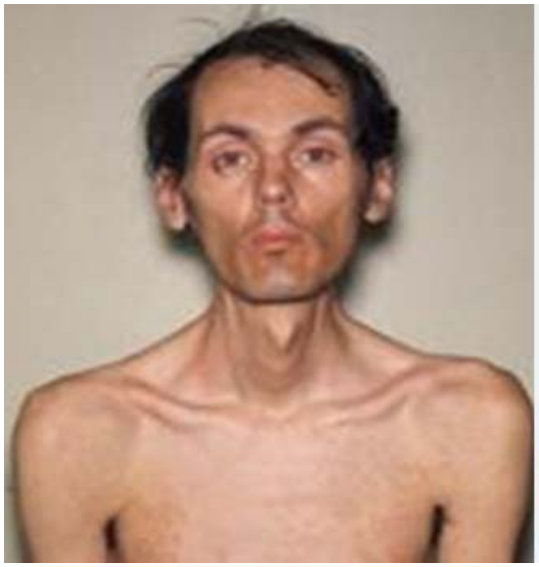
- Diagnosis of mitochondrial diseases:
  - Nuclear DNA mitochondrial disorders usually found with blood samples but Mitochondrial DNA disorders may require muscle tissue
  - Muscle biopsy showing “ragged red” fibers
  - Mitochondrial DNA analysis for specific point mutations
  - Classic clinical patterns of recognized disorders
  - MRI brain with leukoencephalopathy
  - Laboratories with expertise in Mitochondrial DNA analysis:
    - Mayo Clinic Laboratories:  fax: 507-284-0670
    - Arup Laboratories, Utah:  800-522-2787

# Rare Disease #1

- The patient had a pacemaker placed to regulate his cardiac rhythm
- He was found to have only slightly below average intelligence
- Family was educated on the patient's disorder
- Specific treatment is not available at this time

# Rare Disease #2

- 21 year old male who worked at Walt Disney World in Orlando as a dancer. He reported that he had developed a cough. A chest x-ray revealed a typical right lower lobe pneumonia. His physical appearance was lean and muscular. An immediate concern for HIV was raised but the test was negative. His facial appearance was similar to this:



## Rare Disease #2

While undergoing antibiotic therapy for pneumonia, the patient noted a chronic cough and some difficulty swallowing from time to time. Physical examination revealed a thin facial structure and early balding. Family history was completely unremarkable except that his father had cataracts removed at age 35.

What is the diagnosis?

What is the differential diagnosis?

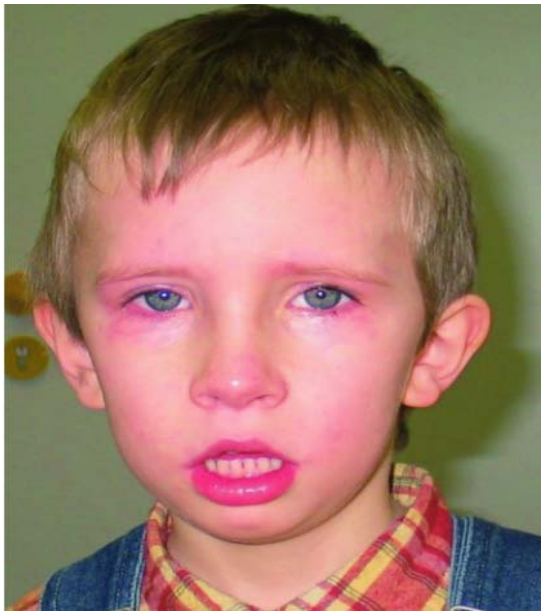
# Rare Disease #2

- Diagnosis: Myotonic Muscular Dystrophy type 2

- Differential Diagnosis: Facioscapulohumeral muscular dystrophy, MMD type 1, Kearns-Sayre syndrome, Oculopharyngeal Dystrophy, Myasthenia Gravis, Myotonia Congenita.

# Rare Disease #2

- Myotonic dystrophy type 1 is the most common adult muscular dystrophy and transmits as an autosomal dominant inheritance pattern. It is caused by CTG repeats on chromosome 19q. The more repeats, the worse the disease clinically. This explains why it tends to have generational worsening (genetic anticipation).



# Rare Disease #2

- Common findings in Myotonic muscular dystrophy =
  - “Hatchet” face = “hangdog” : ptosis (not ophthalmoplegia), sternomastoid and masseteric atrophy and wrinkled forehead
  - Nasal voice, pharyngeal weakness, prone to aspiration
  - Premature balding, teeth malpositioning
  - Cardiomyopathy: prolonged PR interval, AV block, Brady-tachy syndrome, Dilated cardiomyopathy
  - Variable degree of myotonia
  - Atypical cataracts with blue-green coloration in 90%
  - Variable cognitive deficit
  - Testicular atrophy and hypogonadism are common

# Rare Disease #2

- Myotonic Dystrophy type 2 is much less common
- CCTG repeat error rather than CTG
- The CCTG repeats are on Chromosome 3q
- Symptoms and signs are similar to MMD 1 except tend to be milder
- Cardiac involvement is uncommon
- Cataracts in 50%

## Rare Disease #2

- Diagnostic confirmation in suspected cases:
  - Classic appearance with appropriate family history may require no confirmation by testing
  - EMG may show myotonic features
  - Muscle biopsy shows central nucleation and fiber atrophy/necrosis
  - Nuclear DNA analysis provides confirmation of CTG or CCTG repeats exceeding the expected numbers
  - Up to 30 repeats may be normal but MMD may show thousands of repeats in severe cases
  - Use the same laboratories

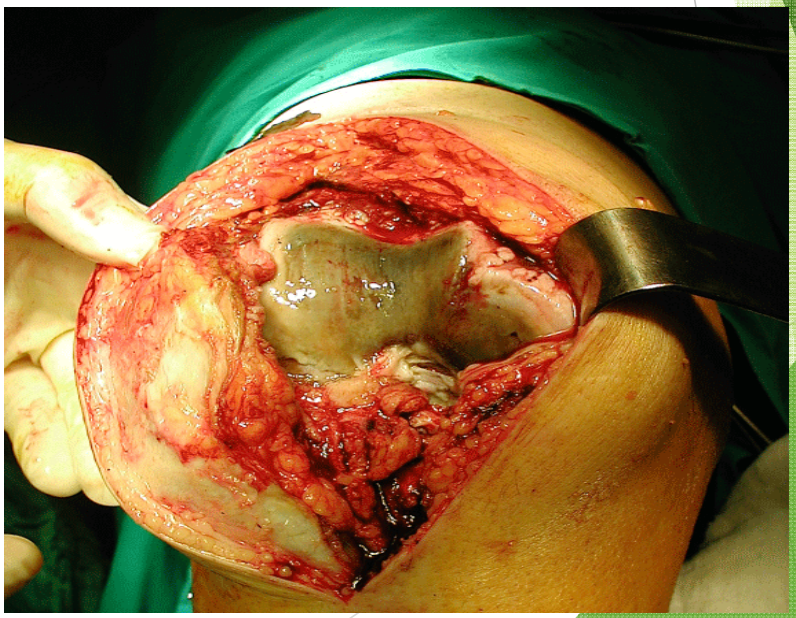
# Rare Disease #2

- The patient recovered from his presumed aspiration pneumonia.  He returned to work shortly thereafter. His diagnosis was confirmed by a combination of muscle biopsy showing typical findings and EMG showing myotonic features.
- The patient's father declined our offer to assess him for Myotonic Muscular Dystrophy which we suspected he had from the report of very early cataract removal.

# Rare Disease #3

- A 58 year old school teacher came to my office to establish medical care. She is morbidly obese with very severe arthritis of the knees, shoulders, hips and spine. She had an arthroscopy which revealed darkly pigmented cartilage. She wanted to know if I was aware of such a condition. She stated that she first became aware of her disease at the time of her arthroscopy.

- This is what the knee would look like.



# Rare Disease #3

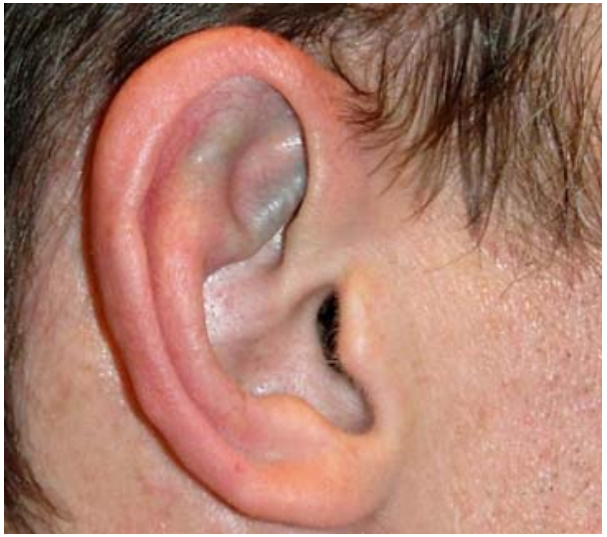
- What is the diagnosis?
- What is the differential diagnosis?

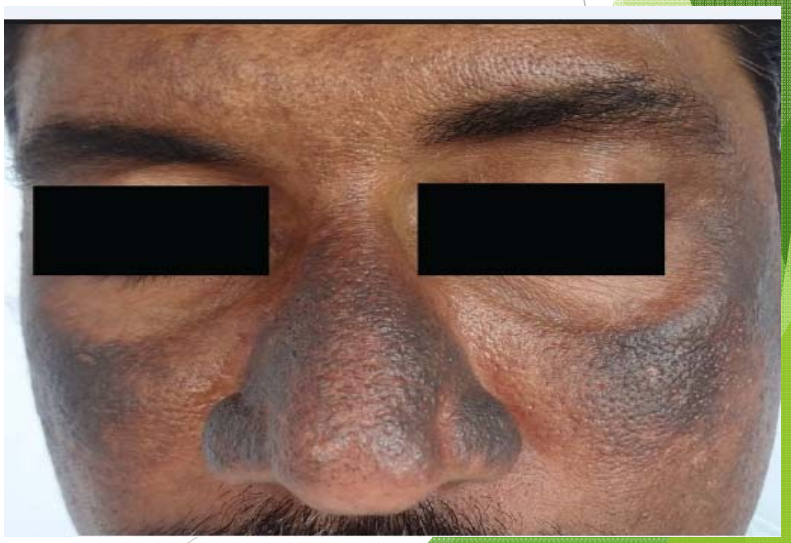
# Rare Disease #3

- Diagnosis: Alkaptonuria or ochronosis
- Differential Diagnosis:  hemophilia, hemochromatosis, pigmented villonodular synovitis, and metastatic melanoma
- Joint fluid will darken by sitting or by adding alkali

# Rare Disease #3

- Alkaptonuria is an autosomal recessive metabolic defect in homogentisic acid oxidase which allows the homogentisic acid and it's metabolites to deposit in tissues as a metabolic polymer which is pigmented. There is a gradual accumulation of dark pigmentation in skin, sclera, and cartilage. Children have no symptoms although diapers may show darkened urine. Eventually, cartilage is damaged by the oxidation products of





# Rare Disease #2

- Alkaptonuria was one of the first inborn errors of metabolism proven to be of autosomal recessive inheritance. The condition was first described by Virchow in 1866 and later expanded upon by Garrod in 1908. The earliest case was documented in an Egyptian mummy from 1500BC.
- The disease is very rare and only about 1000 cases are known worldwide with prevalence estimates of 1/1,000,000
- The highest prevalence is in Slovakia (1/19000)
- Prevalence in Europe and India is much higher than in the Americas

# Rare Disease #3

- The diagnosis of the condition is very straight forward. Urine for homogentisic acid is used for confirmation.
- Treatment is developing
  - Ascorbic acid, especially if started in childhood may help reduce the damage to cartilage. The dose is 1 gram per day. Larger doses not helpful. It is thought to work by decreasing homogentisic conversion or deposition.
  - Dietary restriction of phenylalanine and tyrosine will reduce production of homogentisic acid but is difficult to comply with
  - Taking nitisinone, a herbicide, markedly decreases homogentisic acid production by 95%. It is currently used for hepatorenal tyrosinemia, a very rare metabolic disease.
  - Joint replacement is the mainstay of late disease
  - Aortic and mitral valve calcification is a later life complication that may require valve surgery

# Rare Disease #3

- The patient continues to follow with me in my office practice.  She has now had replacements of both knees, hips and shoulders. She has been seen at the NIH where she has entered a registry for her condition and provided multiple samples of blood and tissue to enable research.  She continues to work as a teacher but finds it very hard to remain mobile.

# Rare Disease #4

- A 36 year old male came to the hospital due to jaundice. He resides in the central Florida area. He works as a construction worker. He consumes several beers on weekends and his hobby is wild hog hunting which he does frequently. He has 2 children and a wife who have been well.
- Physical examination is normal except for obvious jaundice and several ecchymoses. The patient was encephalopathic with an agitated delirium. Vital signs were normal and fever was absent.
- Laboratory examination reveals Hgb 7, WBC 13, Plts 100, AST 350, ALT 150, Alk Phos 48, Bili 14, INR 3, ammonia 93. Abdominal ultrasound shows enlarged liver, splenomegaly, ascites, and no dilation of gallbladder or bile ducts. Liver masses were not present.

# Rare Disease #4

- What is the diagnosis?
- What is the differential diagnosis?

# Rare Disease #4

- Diagnosis: Wilson's disease with fulminant hepatic failure

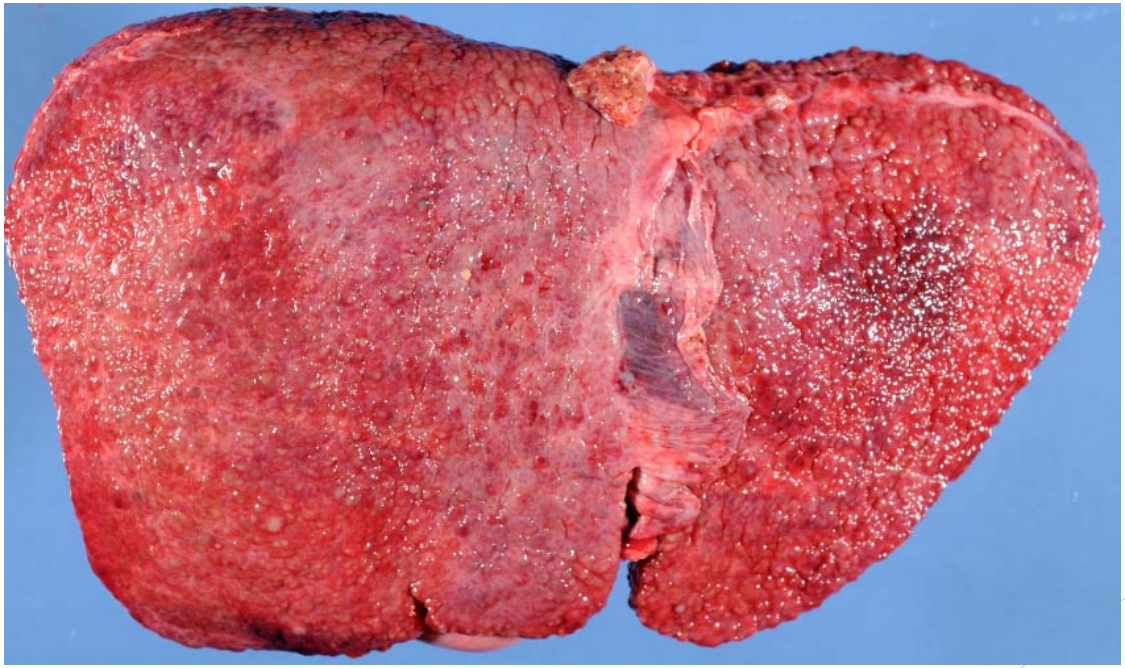
- Differential diagnosis: viral hepatitis, alcoholic hepatitis, autoimmune hepatitis, leptospirosis, toxin hepatitis (mushroom, Tylenol, etc.)

# Rare Disease #4

- Evaluation was urgently completed due to the appearance of fulminant hepatic failure.
- Liver transplant team was consulted to seek available emergent transplantation.
- Laboratory results revealed ceruloplasmin 50 (200-350), 24 hr urinary copper 700 (<50), leptospirosis titer negative, anti-smooth antibody positive, Tylenol level undetectable, hepatitis A,B,C delta and HIV negative. Kayser-Fleischer rings were not seen by ophthalmology.
- CT scan of head negative for subdural or other significant abnormality.
- The patient received lactulose, and rifaximin but he remained agitated and combative. His wife was unable to control his behavior so he required restraints in the ICU to avoid self injury.

# Rare Disease #4

- Due to high MELD score of 33 and lack of improvement clinically, the patient underwent emergent liver transplant.
- His liver appeared similar to this picture

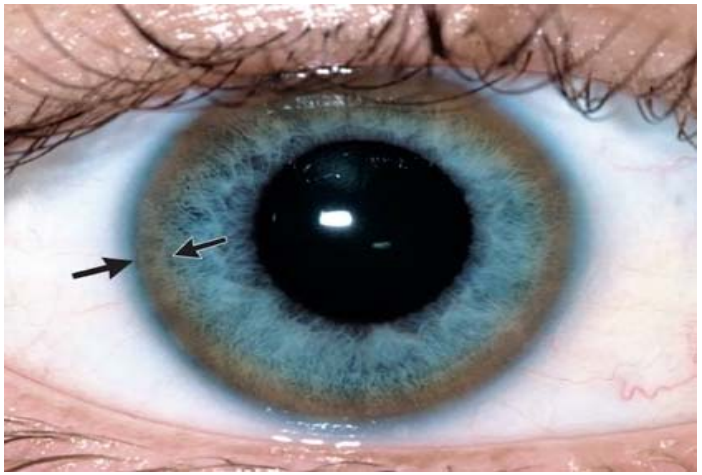


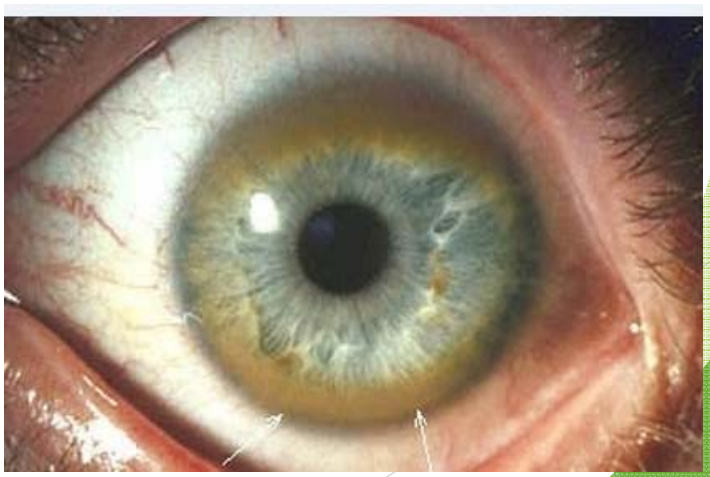
# Rare Disease #4

- The patient encountered severe bleeding post transplantation requiring multiple units of red blood cells and plasma.  He eventually recovered and left the ICU 2 weeks after his transplant had been done and he returned home 4 days later.
- The resected liver revealed very high levels of copper.
- The patient was advised to refrain at least temporarily from wild hog hunting due to infection risk.
- The patient continues to follow up at the hepatology clinic and has been compliant with the anti-rejection program.
- His children were screened for the disorder and none were found to have abnormal ceruloplasmin or excess urinary copper.

# Rare Disease #4

- Wilson's disease can have many types of presentations. The most common one in childhood is acute hepatitis, often similar to autoimmune hepatitis.
- Neuro-psychiatric symptoms increase with age. Teenage onset of psychiatric symptoms is relatively common and Parkinson like neurological findings tend to appear in the adult age ranges.
- Kayser-Fleischer rings are nearly always present when neurological symptoms occur.

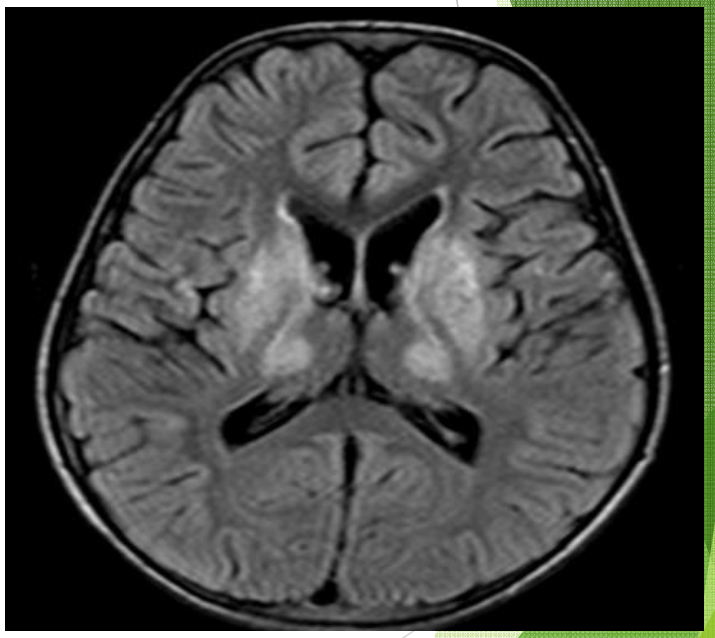




# Rare Disease #4

- Wilson's disease is an autosomal recessive condition although hemizygotes may accumulate excess copper if intake is excessive.
- The defective gene is ATP7B on chromosome 13. The gene is relatively prevalent at 1:90 in the population but the disease is found in 1:30,000. The gene defect results in reduced excretion of oral copper from the bile, leading to liver accumulation.
- Neurological symptoms reflect deposition

  in caudate and putamen

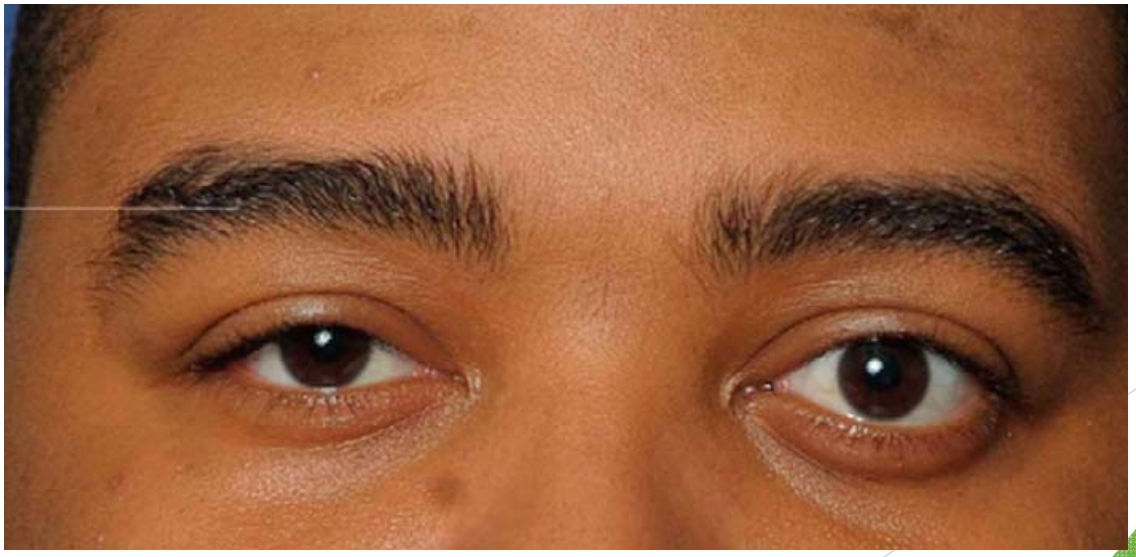


# Rare Disease #4

- Diagnosis or screening may include serum ceruloplasmin, urinary and serum copper, liver biopsy, slit lamp examination of eyes or genetic testing. Only genetic testing is reliable in children under age 10.
- Treatment of established cases can be with D-penicillamine, trientine or zinc. Target is less than 100ug of copper per 24 hrs after initially depleting excess copper. D-penicillamine and trientine are chelators but zinc causes reduced copper absorption from the gut. Chelators are used initially when extensive copper stores are present.
- Liver transplant is curative and requires no subsequent chelation.
- Mouse studies of a viral vector to replace the defective gene segment have shown initial success.

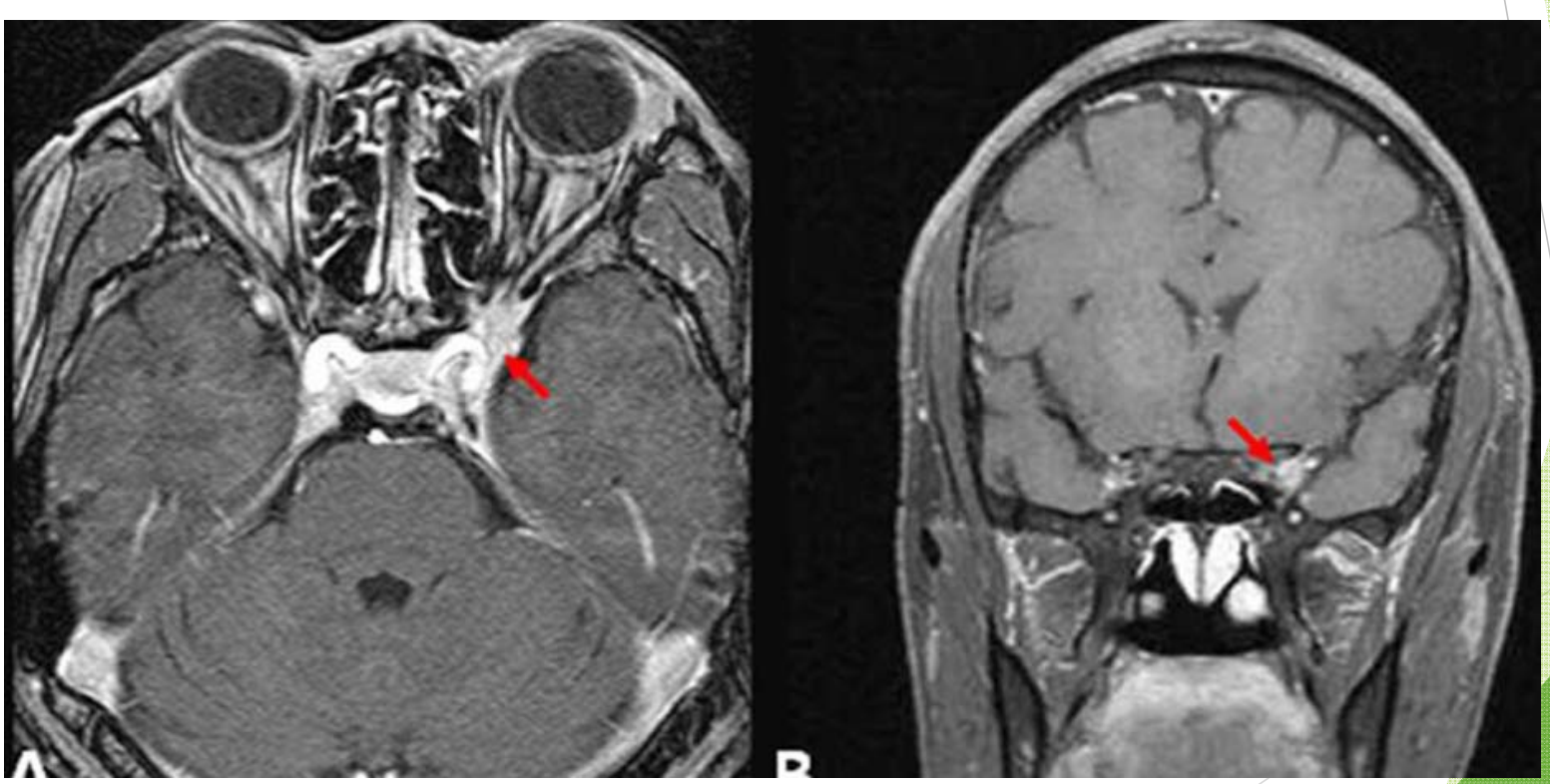
# Rare Disease #5

- A 27 year old female came to the emergency department with a painful, red, edematous right eye that had developed over 3 days. Vision was blurry but still able to recognize letters on a 20/40 visual acuity card. The patient had a history of a previous attack 4 years previously that resolved with the use of "steroids".



# Rare Disease #5

- An MRI was urgently performed.



# Rare Disease #5

- What is the diagnosis?
- What is the differential diagnosis?

# Rare Disease #5

- Diagnosis: Tolosa Hunt syndrome or orbital pseudotumor or superior orbital fissure syndrome
- Differential diagnosis:
  - Cavernous sinus thrombosis or infection
  - Ramsey Hunt syndrome
  - Sarcoidosis
  - Carotid artery aneurysm or carotid-cavernous fistula
  - Orbital tumor or infection
  - Trigeminal area cephalgia (TAC) or migraine
  - Optic neuritis
  - Thyroid ophthalmopathy

# Rare Disease #5

- Tolosa Hunt and Orbital pseudotumor are overlapping or potentially the same disease process. There is inflammation in the superior orbital fissure as seen on the MRI. Findings may be limited to inflammation of a single orbital muscle.
- Corticosteroids at 1mg/kg of prednisone result in rapid improvement and are essentially diagnostic.
- Because the differential diagnosis includes several conditions that also respond to corticosteroids, the diagnosis must be made cautiously.
- Vision is usually not significantly affected unless treatment is markedly delayed.

# Rare Disease #5

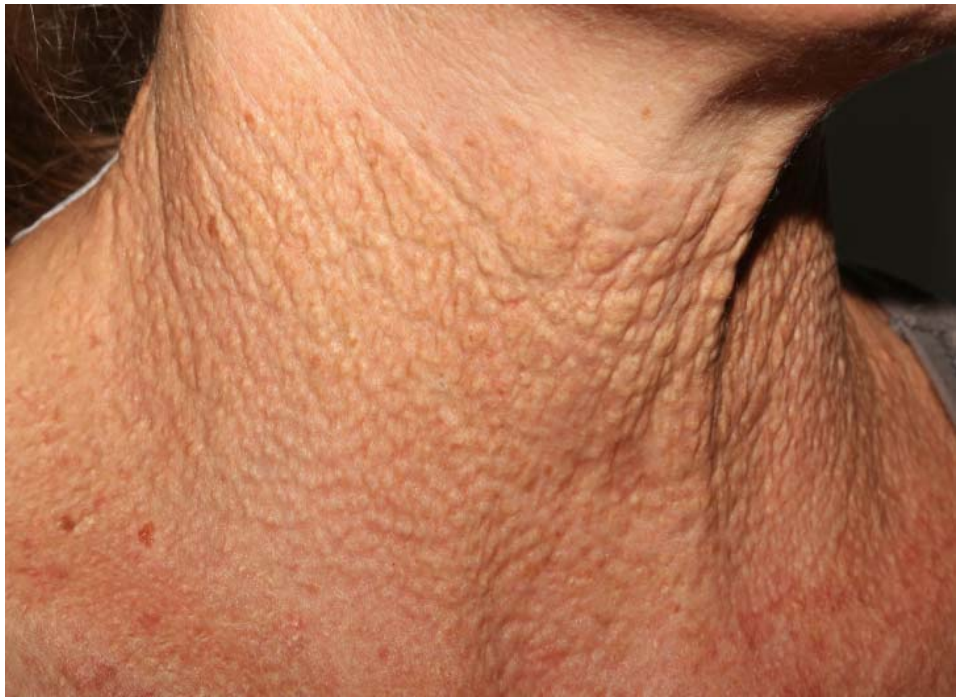
- The cause of Tolosa Hunt is unknown and does not have a hereditary element. The condition is recurrent and subsequent attacks may not require extensive repeated investigation.
- The case we encountered responded within 24 hours to treatment with 60mg of prednisone. She had previously been to an ophthalmologist who had affirmed the diagnosis.
- She followed up once in our clinic with complete resolution of her symptoms. Prednisone was stopped after 2 weeks of treatment.

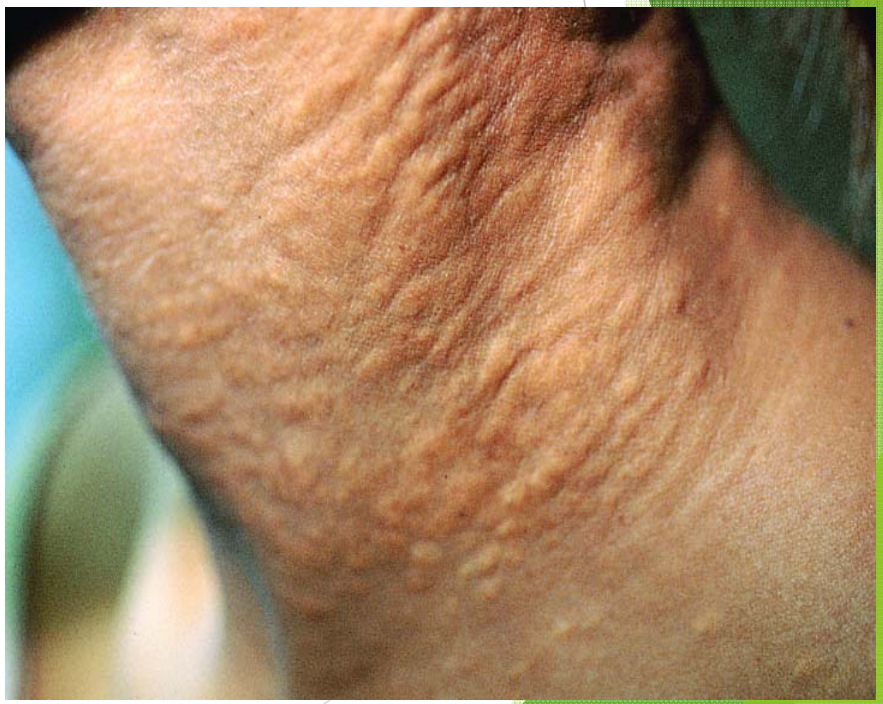
# Rare Disease #6

- A 40 year old lady came to the emergency department due to severe claudication of both lower extremities.  The symptoms had been progressive for several months.
- She was a never smoker and did not have a family history of vascular disease nor did she have diabetes.
- Examination revealed faint pulses in both femoral arteries and minimal to trace pulses at knees and below.
- In general she looked much older than her stated age.

# Rare Disease #6

- The patient's skin appeared like this:





# Rare Disease #6

- What is the diagnosis?
- What is the differential diagnosis?

# Rare Disease #6

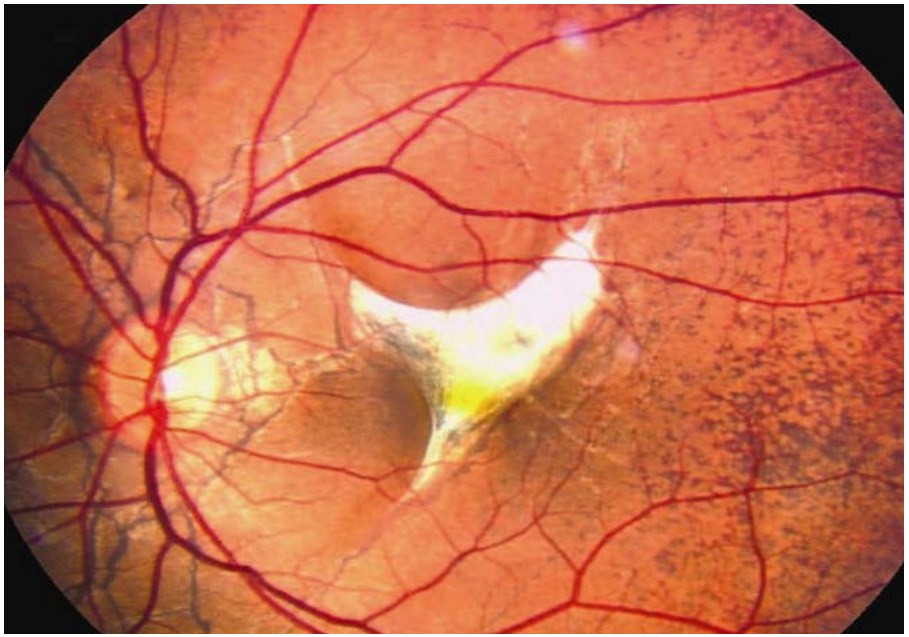
- Diagnosis: Pseudoxanthoma Elasticum
- Differential diagnosis:
  - Actinic sun damage, especially smokers with sun exposure
  - Cutis Laxa
  - Ehlers Danlos variants
  - D-penicillamine long term use

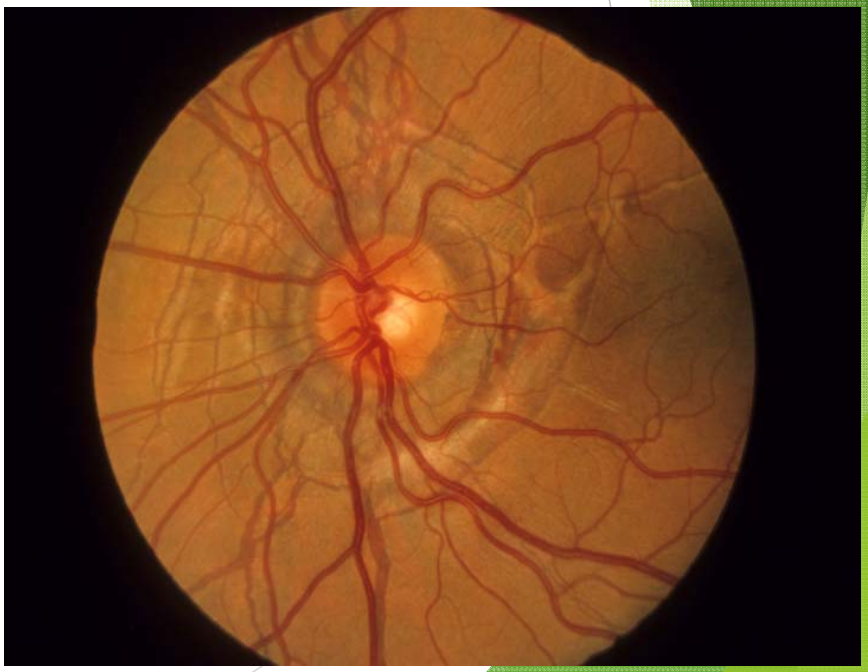
# Rare Disease #6

- Genetics: usually autosomal recessive with loss of function of ABCC6 gene on chromosome 16.
  - This gene somehow regulates the deposition of calcium into specific tissues and produces the MRP6 protein.
  - Pathophysiology is still not completely known
  - There are rare cases where autosomal dominant pattern appears
  - Women express the disorder twice as frequently as men

# Rare Disease #6

- Retinoscopy my reveal the following: Angioid streaks which are breaks in Bruch's membrane and can lead to hemorrhage into the foveal area.  This is treated and prevented with antiangiogenesis drugs such as Avastin

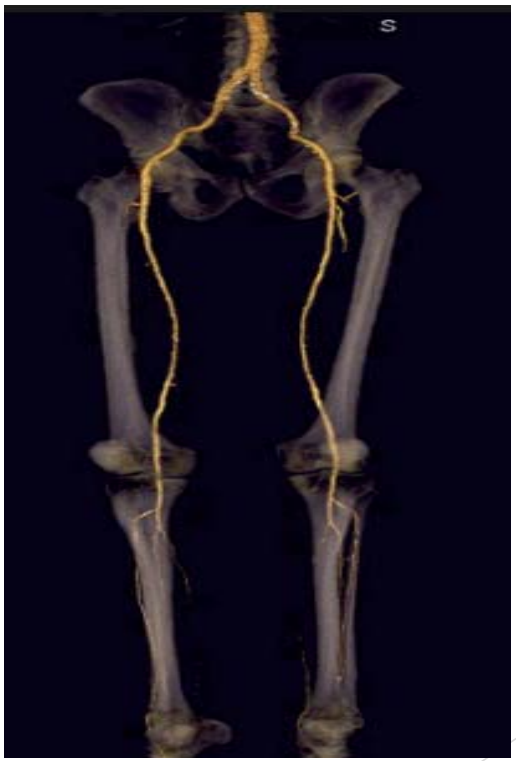




# Rare Disease #6

- Vascular disease is the most serious issue threatening the lives of patients with pseudoxanthoma elasticum.

- A representative CTA of lower extremities would often look like this.



# Rare Disease #6

- Diagnosis can be confirmed by a combination of clinical findings and then by genetic testing from one of the laboratories previously mentioned
- Treatment is mostly preventative at this time and not specific.
- Avoid NSAIDS due to increased risk of GI bleeding which is a common problem in PXE.
- Reduce intake of calcium to lower implantation of calcium in tissues
- See ophthalmologist regularly to treat neovascularization
- Reduce sunlight exposure
- Avoid smoking and other risk factors for early vascular disease.

# Rare Disease #6

- The patient eventually had aorto-bifemoral bypass grafting and did well post operatively.
- She had confirmed angioid streaks on ophthalmological examination but did not have loss of vision.
- She later reported that one of her 2 brothers had died of sudden death in his 30s.
- Follow-up was lost 6 months after her surgery
- Early coronary disease is not as prevalent as would be expected from the high propensity of PAD

# Rare Disease #7

- A 59 year old woman came to my office with the request for me to refer her to the best aortic surgeon in town because she thought she would eventually need such care again. She had had 2 previous aortic operations due to her condition, which she knew all about.
- What is your diagnosis?
- What is your differential diagnosis?

# Rare Disease #7

- Diagnosis: Marfan's syndrome
- Differential diagnosis:
  - Loeys Dietz Aneurysm syndrome
  - Ehlers Danlos syndrome, especially EDS 1,2,3,4,6
  - Homocystinuria
  - Familial Thoracic Aortic Aneurysm and Dissection Syndrome
  - Syphilis
  - Cystic Medial Necrosis

# Rare Disease #7

- Modern diagnostic criteria

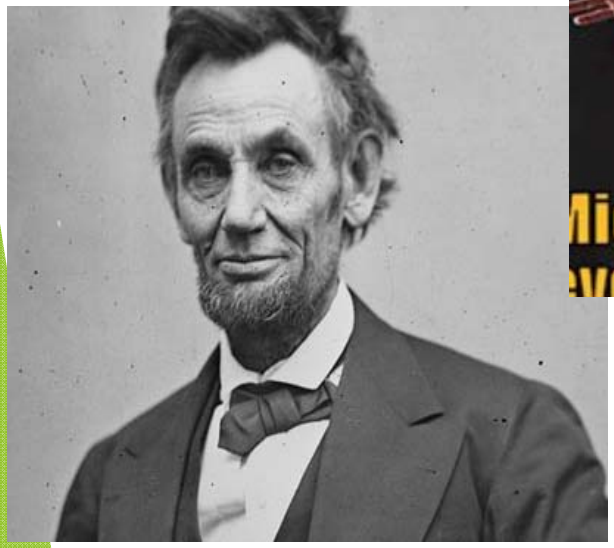
## Marfan syndrome

(Diagnostic Criteria: In the Absence of Family History)

- Aortic Root Dilatation Z score ≥ 2 AND Ectopia Lentis = Marfan syndrome
- Aortic Root Dilatation Z score ≥ 2 AND FBN1 = Marfan syndrome
- Aortic Root Dilatation Z score ≥ 2 AND Systemic Score ≥ 7pts = Marfan
- Ectopia lentis AND FBN1 with known Aortic Root Dilatation = Marfan syndrome

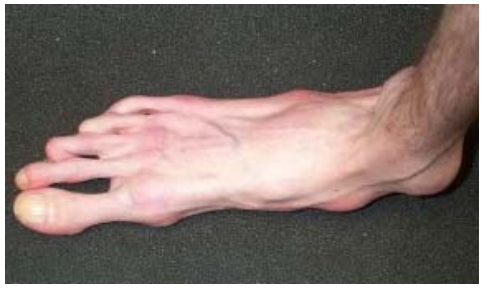
# Rare Disease #7

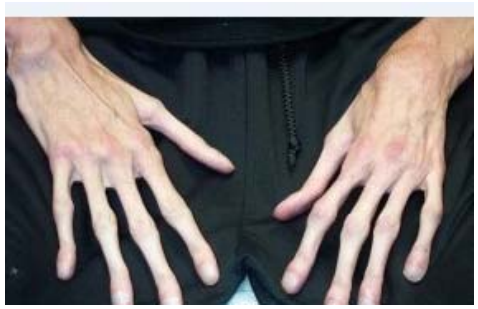
- Here are some famous people who have been proposed as having Marfan's syndrome

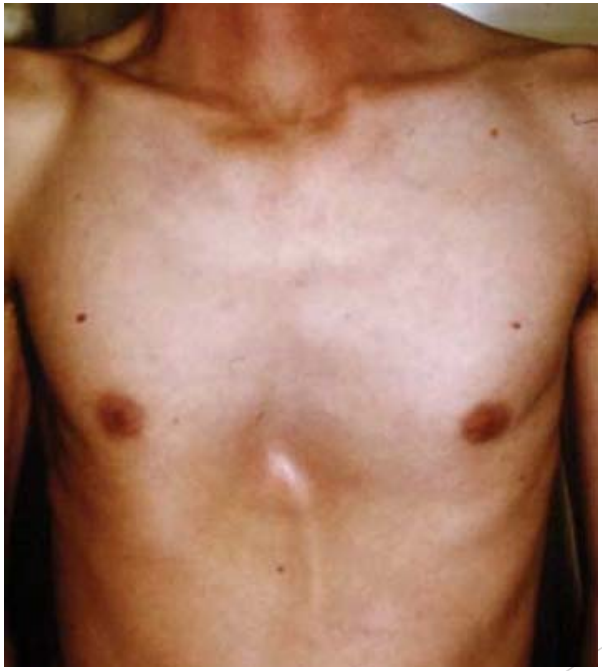


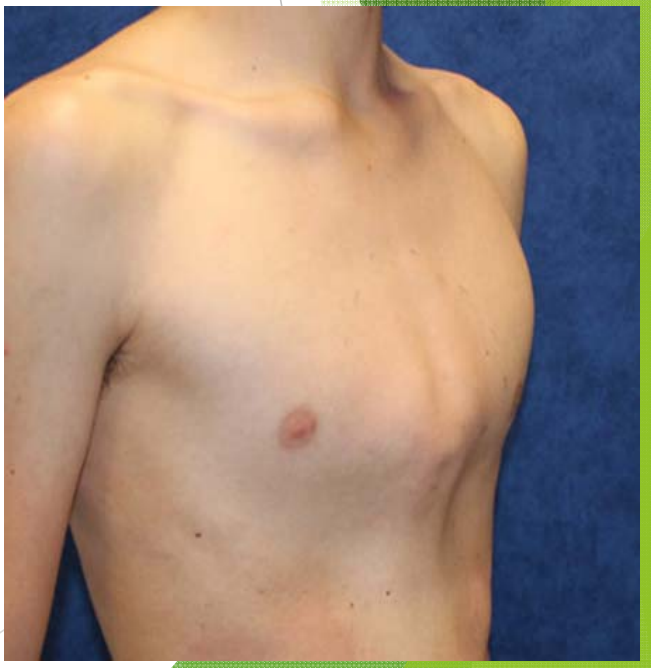

# Rare Disease #7

- Nearly every organ system is affected by MFS
- Skeletal system is often the most apparent:

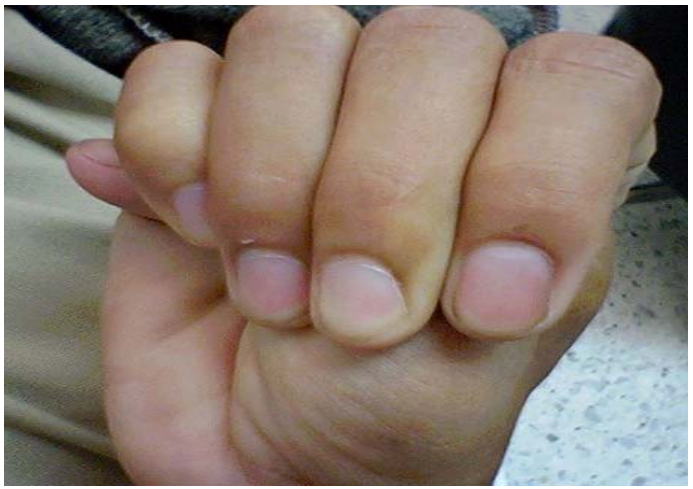


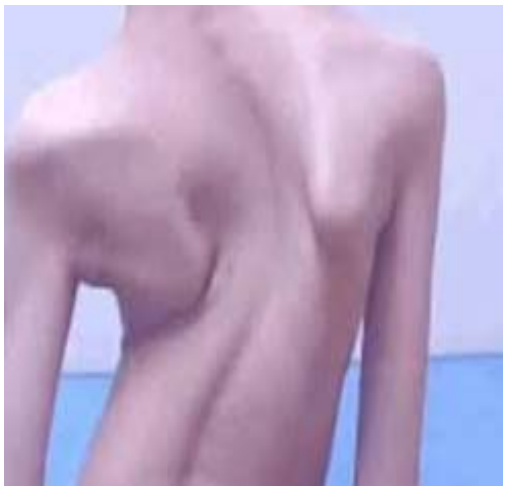


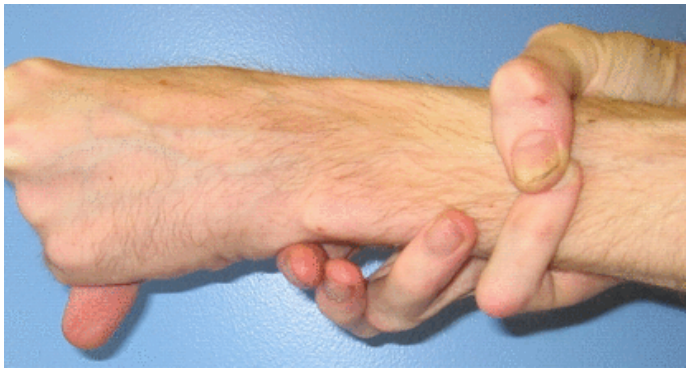


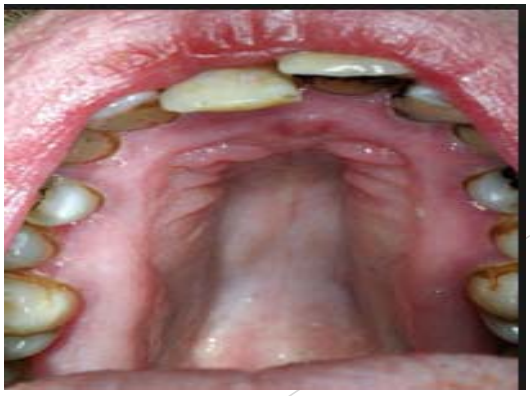


# Rare Disease #7



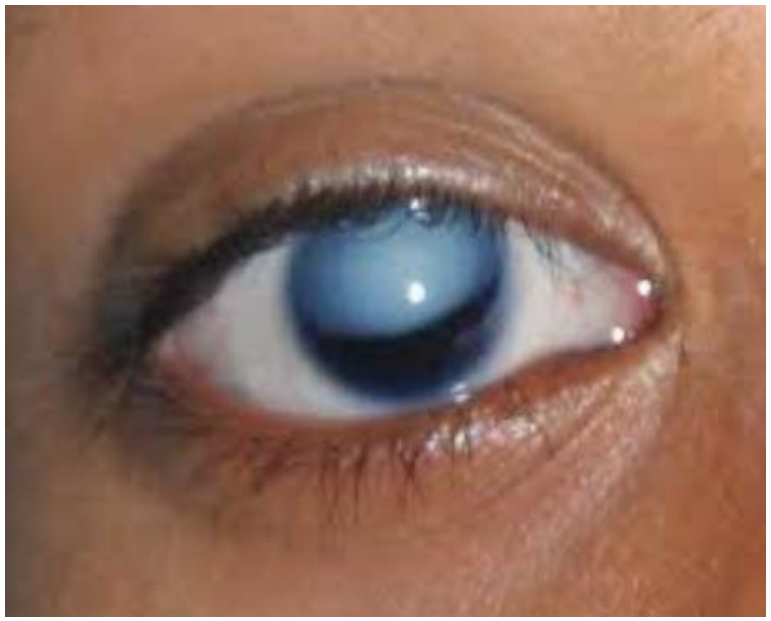


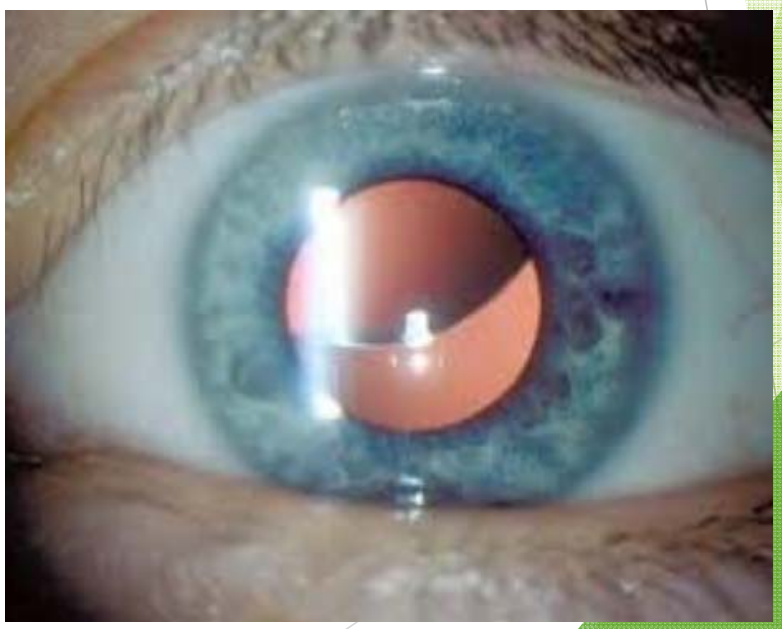




# Rare Disease #7

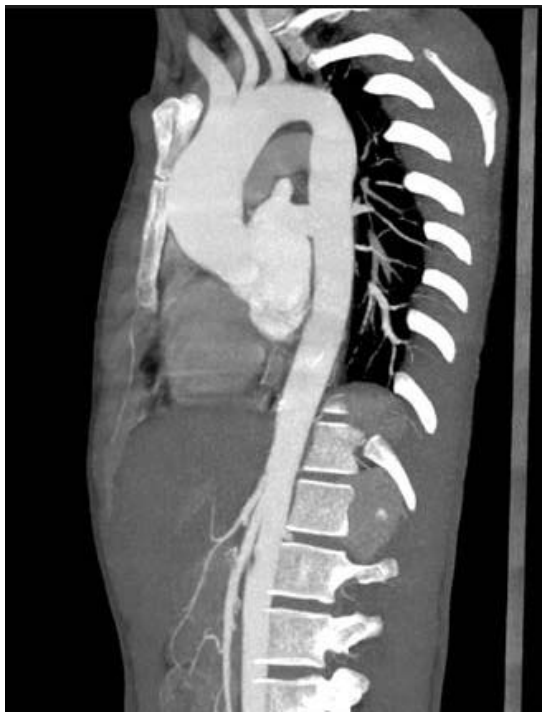
- Ocular disease: ectopia lentis (usually upward)

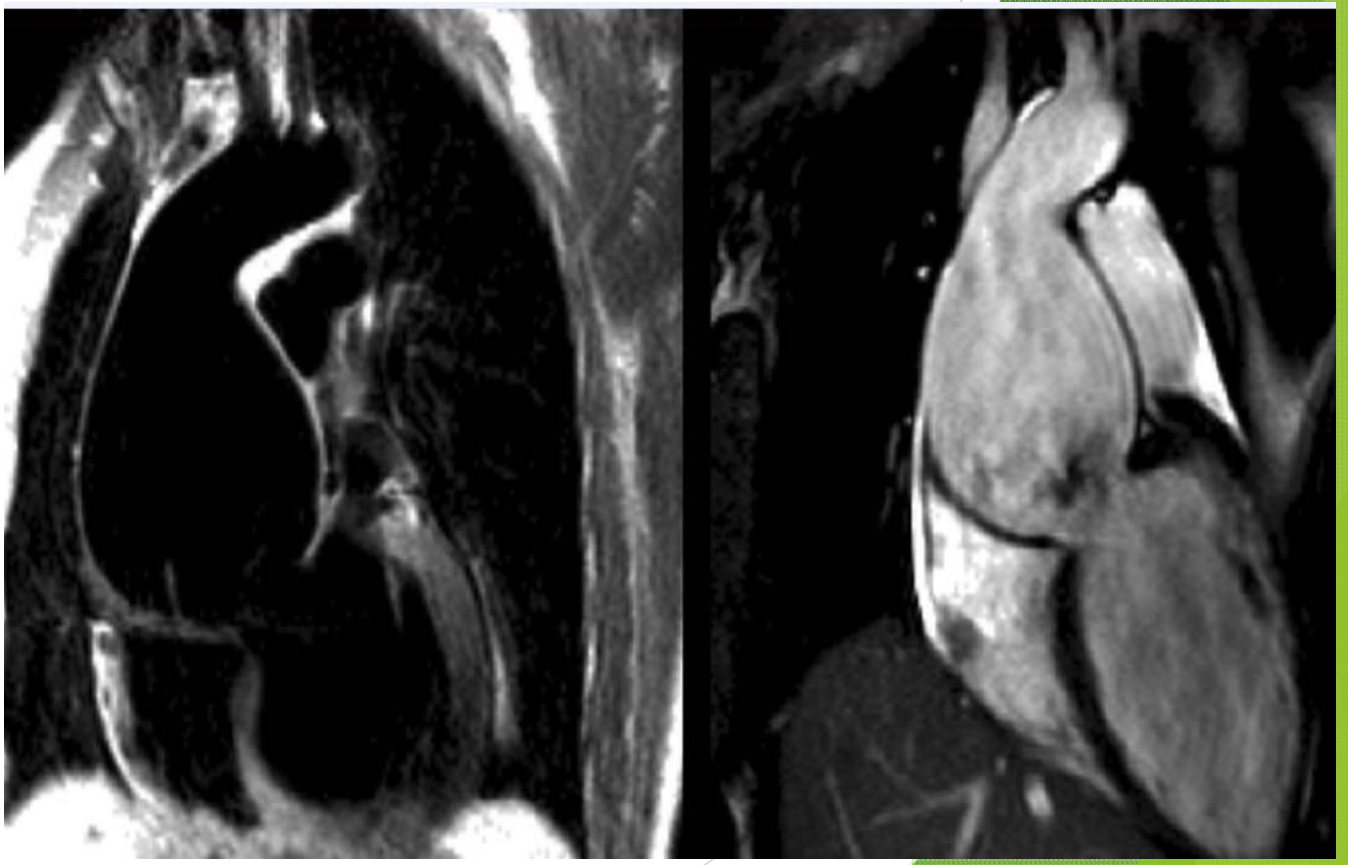




# Rare Disease #7

- Aortic aneurysms





# Rare Disease #7

- Genetics and pathophysiology
  - Defective Fibrillin-1 with mutation of FBN1 gene.  Over 800 mutations already described.
  - Acts as autosomal dominant transmission with highly variable manifestations due to multiple mutations.
  - Loeys-Dietz Aneurysm Syndrome (LDAS) has defective Fibrillin-2.
  - LDAS has defect in TGFB1 or 2 gene and does not have ocular disease like Marfan's.
  - LDAS is generally worse from the cardiovascular standpoint compared to Marfan's.
  - LDAS has characteristic facial dysmorphias and is less common than Marfan's.

# Rare Disease #7

- Marfans type 2 is no longer applicable because nearly all are actually LDAS or variants when studied genetically.
- Some LDAS spectrum can show isolated aortic disease or isolated craniofacial findings
- Homocystinuria is very rare and shows many of the features of MFS: arachnodactyly, ectopia lentis (downward), aortic dilation, but differs by propensity to have seizures and low cognitive function. Diagnosis is relatively easy using homocysteine in urine and serum.
- Diagnosis in MFS and LDAS should be confirmed by genetic testing now for FBN-1/2 and TGFB-1/2. Because of the clinical implications, family members at risk should be studied clinically and potentially genetically.

# Rare Disease #7

- Treatment
  - Beta blockers reduce the rate of expansion of aorta in multiple randomized trials.  Propranolol was the drug initially used in the trials.
  - Losartan used alone or added to BB also reduces expansion of aorta especially if started in childhood.
  - MFS patients may need surgery when root diameter exceeds 5cm or if rapid expansion taking place
  - LDAS patients need surgery at 4.2cm due to greater risk of rupture/dissection
  - Calcium entry blockers are contraindicated due to evidence of increased risk of expansion and rupture.

# Rare Disease #7

- Case follow-up
  - Patient followed with me and with cardiovascular surgeon for several years. She did not require further surgery because of a stable aortic diameter
  - Patient later left the state and was lost to follow-up

# Rare Disease #8

- A 35 year old obese, African-American male came to the hospital in septic shock. He had a long history of recurrent infections since childhood. He had been admitted to hospital at least 10 times a year since birth, mostly from infections. At age 23 he developed diffuse, large cell lymphoma and received CHOP. He had experienced annoying rashes on his skin over the years. He had developed hepatitis C, possibly from a transfusion in childhood. His mother reported that he had a brother who had died as a child from a similar condition. There were no other siblings.

# Rare Disease #8

- Physical examination revealed a morbidly obese, nearly unarousable, chronically ill appearing male. He had diffuse rhonchi in his lungs, a peritoneal dialysis catheter without purulent drainage, a splenectomy scar, and a widespread scaly rash on most skin surfaces.
- BP 88/40, HR120, temp 102.8
- WBC 20K, Hbg 8.8, Plts 48
- Sodium 137, K 4.5, CO2 27, Cl 101, BUN 35, Creat 6.2

# Rare Disease #8

- What is the diagnosis?
- What is the differential diagnosis?

# Rare Disease #8

- Diagnosis: Wiskott-Aldrich syndrome (WASP absent)

- Differential diagnosis:
  - X-linked thrombocytopenia (WASP mutated)
  - SCID (severe combined immunodeficiency)
  - Ectodermal dysplasia with immunodeficiency
  - Chronic granulomatous disease
  - Ataxia Telangiectasia
  - Job syndrome
  - Childhood onset SLE

# Rare Disease #8

- Additional data on patient:
  - IgG level 822 (700-1500)
  - IgA level 121 (70-400)
  - IgM level 7  (40-230)
  - Normal SPEP and UPEP

  Additional history on patient:

  Chronic hepatitis C leading to liver cirrhosis and hepatic encephalopathy

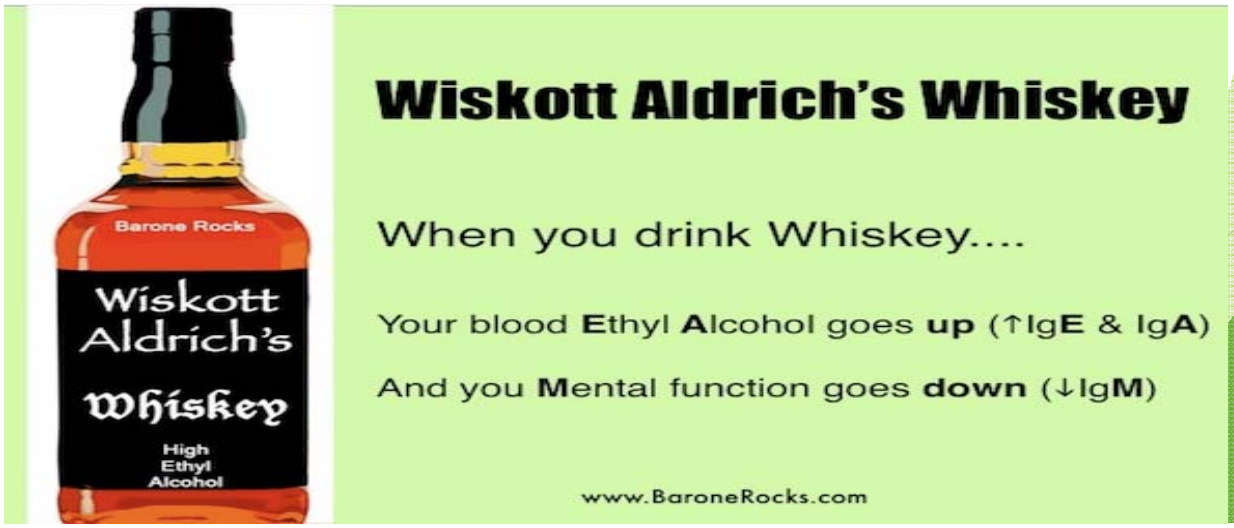
  Renal failure due to membrano-proliferative glomerulopathy

  Brother died in childhood from WAS,  there were no other children.

  Patient had multiple septic events from a variety of organisms over the years and died at age 35

# Rare Disease #8

- WAS is an X-linked disorder due to deficiency of WASP gene which codes for the WAS protein, which is essential for T and B lymphocyte activation and migration. Thus both humoral and cellular immunity are impaired. As expected, encapsulated organism sepsis is predominant, especially in childhood.
- Viral infections and Pneumocystis infections also occur frequently.
- Other classic features include thrombocytopenia with very small platelets, low levels of IgM with preserved or elevated IgA and IgE and variable IgG.

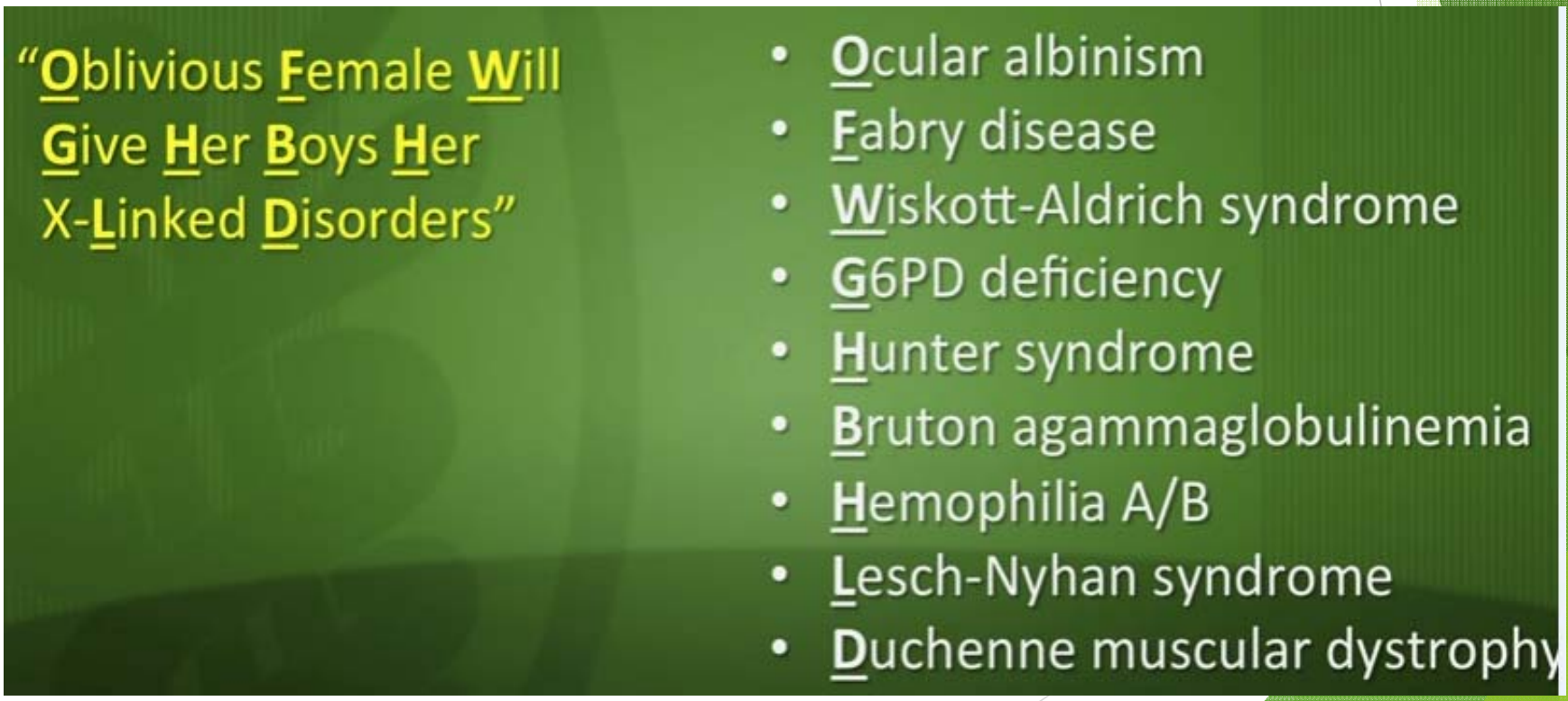


# Rare Disease #8

- WAS facts
  - Frequency is 1/100,000 male births
  - Survival is 15 years average
  - Females get WAS only if remaining X chromosome loses function
  - X-linked Thrombocytopenia is due to WAS Protein defect rather than deficiency
  - The only “curative” therapy is stem cell transplant which is successful in more than 80% of cases for unrelated donor and more than 90 % for matched related donor

# Rare Disease #8

- Here are some other classic X-linked diseases and a Mnemonic to remember them.



# Rare Diseases: Final Thoughts

- While individual rare diseases are rare of course, the collective of all rare diseases is more common
- Both generalists and subspecialists have an important role in the care of patients with rare diseases
- Enthusiasm for learning new things is the key to a challenging and enjoyable practice and taking on the responsibility for patients with rare diseases will stimulate new learning opportunities

# Rare Diseases: Resources

- Atlas of Inherited Metabolic Diseases by William Nyhan, Bruce Barshop, and Aida I Al-Aqeel, 3rd edition, CRC press, 2012
- Recognizable Patterns of Human Malformation by Kenneth Jones, Marilyn Jones, Miguel del Campo, 7th edition, Elsevier, 2013
- The Journal of Rare Disorders, SCG publications
- Orphanet Journal of Rare Diseases
- NCBI Bookshelf: National Institute of Health