



HOLY C.O.W.!

IT'S...

**Clinical Question of the Week #4
July 21st, 2008 through July 28th, 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, July 28th, 2008. The resident or intern with the most correct answers at the end of each month will receive a prize!

Case: A 17-year-old woman presents to your clinic with headaches, palpitations, and irregular menses. Over the past few months, she noticed a small lump in her throat which has gradually increased in size. Her childhood history was relatively unremarkable, with her height falling in the 95% percentile. When she was younger, she did have some intermittent pain in her legs, which her pediatrician attributed to "growth pains." She also has some chronic lumps on her leg bones, which have been attributed to the effects of playing years of soccer on a traveling team. She achieved menarche at the age of 10. Inspection of the skin reveals the finding below, which the patient dismisses as a birthmark she has had since birth.



Questions:

1. What is the diagnosis? What are the grounds for this diagnosis?

McCune-Albright syndrome or familial gonadotropin-independent precocity with polyostotic fibrous dysplasia (try saying that three times fast) is a genetic syndrome which was initially described by Donovan James McCune and Fuller Albright in 1937. The incidence is estimated around 1:1,000,000. It is characterized by premature puberty, endocrinopathies, abnormal skin pigmentation in the form of café-au-lait spots, and fibrous dysplasia.

Approximately 20-30% of individuals with McCune-Albright syndrome will develop fibrous dysplasia, with 2/3 of these presenting prior to the age of ten. Pathologically, normal bone is replaced with overgrowth of fibrous soft tissue, which may cause substantial deformity. Symptoms include pain, impaired mobility, and occasional hearing/visual loss. Characteristic locations include the tibia, femur, pelvis, skull, jaw, ribs, spine and clavicle. Surgery may be required to correct the deformity, though this does not alter the process and there is no cure. (1)

2. Name three metabolic abnormalities that are associated with this condition.

Precocious puberty is one of the hallmark metabolic abnormalities seen in MAS, with cases of menarche in girls before the age of two years as the presenting symptom. This is felt to be related to hyperestrogen state due to ovarian cysts, and testolactone (which inhibits aromatization of androgen to estrogen) has been used to slow progression of puberty. Tamoxifen has also been used in girls. Testolactone, spironolactone, and ketoconazole have been used in boys for their anti-androgen and anti-estrogen properties.

One half of individuals with MAS will have abnormal thyroid function, usually hyperthyroidism, which may be associated with goiter or thyroid cysts, and can be treated with conventional thyroid suppressive medication.

Occasionally, hypersecretion of growth hormone from the pituitary will result in acromegaly, which is treated with somatostatin analogs or surgery.

Hypophosphatemia and hypovitaminosis D resulting in rickets is seen due to excessive urinary phosphorus loss, and is treated with phosphorus and vitamin D replacement.

Finally, in rare instances, Cushing's syndrome due to functional adrenal enlargement may be seen, and is treated with surgery and/or adrenal suppressive medication. (0.5)

3. What is the genetic abnormality in this condition, and what is unique about this abnormality?

The genetic abnormality is a post-zygotic (sporadic) mutation of the gene GNAS1 (Guanine Nucleotide binding protein, Alpha Stimulating activity polypeptide 1). This gene is involved in G-protein signaling, and prevents downregulation of c-AMP signal, resulting in increased cell cycling and function. As it is a post-zygotic somatic mutation which occurs after fertilization, it is not an inherited disease. However, not all somatic cells of the body are affected, which results in mosaicism, which results in the café-au-lait spots. These are present at birth and do not change over time, and typically are easier seen in lighter-skinned individuals. The thing is, the severity of the disease depends on when the mutation occurs – the earlier the mutation, more cells arise from the mutated cell, and thus the disease is more severe and widespread. (1)

4. Name the motion picture and release year in which the title character may have suffered from this condition.

The Elephant Man (1980). Saravia (2008) also accepted, which is a documentary on the life of artist Mauricio Saravia, who suffers from MAS (www.saraviafilm.com). (0.5)



A



B

Joseph Carey Merrick (A), in 1889, on whom the film *The Elephant Man* was based, and artist Mauricio Saravia (B).