Answer to Quiz: Images

The first image shows widening & coarsening of facial features without any enlargement of soft tissues like nose, lips etc. Chest X-ray reveals markedly increased bone density. Skull x-rays show thickening of the bones of skull vault & base of the mandible, maxilla & other visible bones. Sella turcica is normal. Para-nasal sinuses appear less aerated. No Fracture is seen. Enlargement of miniature long bones with widening of medullary cavities, thickening of cortices and coarse trabecular pattern are noted in the x-rays of hand & foot. CT scan of brain suggests normal brain with calvarial bone thickening.

Diagnosis: Osteopetrosis.

Review - Osteopetrosis

It is also known as Albers-Schonberg or marble bone disease. It’s an extremely rare inherited disorder whereby the bones harden, becoming denser.

Variants: Three types

1. Autosomal recessive (malignant type):
   - It is a severe bone disease that is usually fatal within the first decade of life.
   - It has been assumed that the defect is in genes responsible for osteoclast function. Osteoclasts may be increased in number but do not function normally due to the acidification defect that results from the mutated vacuolar proton pump.
   - Manifests in utero and progresses after birth with anemia (75%), thrombocytopenia, hepatosplenomegaly, hydrocephalus, cranial nerve involvement, and death, often due to infections.
   - In the severe infantile form, there is persistence of the primary spongiosa with central calcified cartilage cores surrounded by woven bone.

2. Autosomal dominant (benign type):
   - Less fulminant form of osteopetrosis.
   - Occurs in older children and adults and progresses with age.

   - Recurrent pathologic fractures are the main feature; anemia is not as severe, neurologic abnormalities are not as frequent.

3. Carbonic anhydrase II deficiency (Type 3 Renal tubular acidosis):
   - One of the isoenzymes of carbonic anhydrase (carbonic anhydrase II), is a major component of the system that generates the acid environment adjacent to the ruffled border of the osteoclast. Deficiency of this enzyme impairs bone resorption. The defect in remodeling results in disorganization of bone structure, with thickened cortices and lack of funnelization of metaphyses. Despite increased density, the bone may be abnormal mechanically and can fracture readily. Apart from the bones, the kidney and brain are also affected.
   - This disorder usually appears in the first few years of life in children of Mediterranean and Arab descent. Affected children develop calcium deposits in the brain and mental retardation, and about 3 out of 5 affected children develop blindness and/or hearing loss due to bone pressure on the nerves in the skull. Skeletal abnormality is associated with renal tubular acidosis and cerebral calcification.

Investigations:

- Blood tests: anemia, elevated acid phosphatase level in some cases. Hypophosphatemia and moderate hypocalcemia may occur in children.
- Imaging studies: markedly increased density of skeleton. Typical dense deformed sclerotic bones.

Complications:

Multiple fractures may occur. Anemia results from encroachment of bone on the marrow cavity. Extramedullary hematopoiesis leads to hepatosplenomegaly & hypersplenism. Encroachment on cranial nerves causes optic atrophy, nystagmus,
papilledema, exophthalmos, and impairment of extraocular muscles. Facial paralysis and deafness are frequent; trigeminal lesions and anosmia are less common. In infants, macrocephaly, hydrocephalus, and convulsions may occur, and infections such as osteomyelitis are frequent.

**Treatment:**
In children with severe osteopetrosis, bone marrow transplantation from allogeneic donors or HLA-identical siblings has resulted in histologic and radiologic increases in bone resorption and variable improvement in anemia, vision, hearing, and growth and development. Unfortunately, it is not always possible to find appropriate donors, or patients may not be good candidates for bone marrow transplantation.

Supportive therapy includes –

- **1,25-dihydroxy Vitamin-D₃ (calcitriol):** In some patients with the lethal forms of the disorder, calcitriol therapy is associated with the appearance of osteoclasts with normal ruffled borders and other evidence of increased bone resorption.
- **Interferon gamma-1b:** Interferon gamma-1b delays the progression of malignant infantile osteopetrosis because it causes an increase in bone resorption and in red blood cell production.
- **Prednisolone:** Helps to improve blood cell count and slows blood cell destruction. Large doses of glucocorticoid may be given for short periods of time to patients with impaired red blood cell or platelet production.
- **Nutritional support:** is important to ensure normal growth and development of children with osteopetrosis.
- **Physical and occupational therapy:** are also extremely useful in helping children to reach their full developmental potential.

**Prognosis:**
Untreated children with malignant infantile osteopetrosis have difficulty surviving beyond the age of 10 years. The variant resulting from carbonic anhydrase II deficiency is compatible with long survival.

*Courtesy: Department of Endocrinology, BIRDEM General Hospital*