Genetic Bone Diseases:

Cherubism:

It is a benign hereditary condition of the maxilla and/or mandible, in bilateral symmetrical manner. The condition’s name is derived from clinical appearance of young patients, it give chubby, or cherub cheeks especially if all quadrants are involved.

Clinical features: It usually found in children (2-5) years as painless slowly growing expansion of posterior region of the mandible or maxilla. The angles and ascending ramus of the mandible may be involved. Milder maxillary involvement occurs in the tuberosity areas, in severe cases, the entire maxilla is involved. The expansion of the jaw progress until puberty, then stabilize and slowly regress, with progressive reduction of facial deformity.

The characteristic facial deformity is a fullness of the cheek and jaw producing chubby face. In addition there is an" eye upturned to heaven" appearance that is due to a wide rim of exposed sclera noted below the iris. This feature is due to the involvement of the infraorbital rim and orbital floor that tilts the eye ball upward, as well as to stretching of the upper facial skin that pulls the lower lid downwards. On occasion, affected patients also reveal marked cervical lymphadenopathy.

Extensive bone involvement causes a marked widening and distortion of the alveolar ridges. In addition to the aesthetic and psychologic effect. It causes displacement of the teeth within the jaw leading to malocclusion or failure of eruption, impair mastication, create speech difficulties.
**Radiographic findings:**

It consists of large areas of multilocular expansile radiolucencies in the jaw bone. The appearance is diagnostic as a result of their bilateral location. Both erupted and unerupted teeth are randomly distributed within enlarged arches.

**Histopathology:** it is composed of vascular fibrous tissue, containing variable number of multinucleated giant cells. The giant cells tend to be small and aggregated focally. The stroma of cherubism often tends to be loosely arranged. A distinctive feature that is often present is eosinophilic perivascular cuffing of collagen surrounding small capillaries throughout the lesion.
**Treatment:** is directed toward maintaining speech and mastication, because the condition is self-limiting, with regression and remodeling take place after puberty, evaluation and cosmetic surgery are delayed until that time.

**Osteopetrosis (Marble Bone Disease):**

Is uncommon hereditary bone condition characterized by generalized symmetric increase in skeletal density and defective bone resorption. The characteristic feature is an absence of physiologic bone resorption caused by reduced osteoclastic activity. The lack of bone remodeling results in accumulation of bone mass and manifest itself in skeletal disturbances, including sclerosis of bone marrow, decrease hemopoietic activity and growth retardation.

It can be divided into:

- *Infentile-malignant:* it is inherited as autosomal recessive in nature and is fatal within 2-3 years of life if not treated.

- *Intermediate autosomal recessive type,* nonfatal but clinically aggressive with onset usually within the first decade.

- *Autosomal dominant form* is the least severe form, with full life expectancy but with considerable morbidity resulting from orthopedic alteration.
**Clinical features:** Bone pain is the most common symptom. Cranial nerve compression due to narrowing of cranial foramina may result in blindness, deafness and facial paralysis. The normal bone is replaced by dense poorly structured fragile bone and has propensity for pathologic fractures. Excessive endosteal bone formation result in anemia and pancytopenia. The patient may die as a result of anemia or secondary infection.

**Dental findings:** include, delayed eruption, congenitally missing teeth, unerupted and malformed teeth. Decreased alveolar bone production with thickened periodontal ligament and marked mandibular prognathism, elevated caries index due to enamel hypoplasia, increase development of osteomyelitis resulting from inadequate host response because of the diminished vascular supply of osteopetrotic bone.

**Radiographic findings:** an increase in bone density of the whole skeleton with no distinction between cortical and medullary bone. Jaw bone involvement is variable the bone appears so dense that dental root morphology in invisible on radiographs.

The laboratory values of blood indicates the type of anemia. Calcium, phosphorus and alkaline phosphatase are normal.
**Histopathology:** The involved bone showing thickened cortices and reduced marrow cavities.

**Treatment:** recent medical advances designed to increase osteoclastic activity. Dental extraction should be done in conjunction with antibiotic therapy to prevent osteomyelitis.

**Osteogenesis Imperfecta:**

It represents a genetically heterogenous group of heritable disorders characterized by impairment of collagen maturation. Except on rare occasions, the disorder arises from heterozygosity for mutations in one of two genes that guide the formation of type I collagen: the COL1A1 gene on chromosome 17 and COL1A2 on chromosome 7. Collagen forms a major portion of bone, dentine, sclera, ligaments and skin.; Osteogenesis imperfecta (OI) demonstrates a variety of changes that involve these sites. Several different forms of OI are seen, and they represent the most common type of inherited bone disease. Abnormal collagenous maturation results in bone with a thin cortex, fine trabiculation and diffuse osteoporosis. Upon fracture, healing will occur but may be associated with callus formation.

Classically this condition may include fragile bones, blue sclera (due to thin transparent sclera abnormally that pigmented choroids shining through giving the
blue color), hearing loss and dentinogenesis imperfecta. Some affected patients exhibit extreme bone fragility with numerous fractures and die during the perinatal period; others suffer only mild bone fragility and live normal life span. Four distinct types have been identified:

Osteogenesis Imperfecta Type I: characterized by osteoporosis, bone fragility, blue sclera and hearing loss in adolescents and adults, dentinogenesis imperfect.

OI Type II: lethal syndrome, half of all patients stillborn. It has autosomal recessive mode of transmission. It is characterized by low birth weight, short stature, short limbs, defects in skeletal ossification lead to extreme bone fragility and bone fractures even during delivery.

OI Type III: it is recessive inheritance, in neonates characterized by severe bone fragility, multiple fractures & progressive skeletal deformity. Blue sclera at birth but the color normalize with age adolescents and adults are with normal sclera. Dentinogenesis imperfect may be found in some patients.

OI Type IV: dominant inheritance, bone fragility without other classic features of OI, normal color sclera,
**Cleidocranial Dysplasia (Cleidocranial Dysostosis):**

It is aplasia or hypoplasia of the clavicles, it has autosomal-dominant mode of inheritance, characterized by craniofacial malformations, the presence of numerous supernumerary and unerupted teeth.

**Clinical features:**
1) Hypoplasia, Malformation, absence of clavicle
2) Short stature, Large head, Frontal bossing
3) Depressed Nasal bridge
4) Open skull suture and fontanels

**Oral findings of cleidocranial dysplasia**
1) cleft palate or narrow palate
2) Unerupted permanent and supernumery teeth
3) Narrow ascending mandibular ramus
4) Thin zygomatic arch
6) maxillary hypoplasia gives mandible a relatively prognathic appearance

**Metabolic Bone Diseases:**

**Paget’s Disease of Bone (Osteitis Deformans):**

It is a chronic slowly progressive bone condition. It is a disease characterized by uncoordinated resorption and deposition of bone, producing larger but weaker
bones. The cause of Paget’s disease is unknown, but inflammatory, genetic mutation, viral (as paramyxovirus), or endocrine factors may be contributing agents.

A relationship to altered osteoclast development and function has been suggested. Paget’s disease generally progresses through several stages including an initial resorptive phase, followed by a vascular phase, and by a sclerosing phase.

**Clinical features:**

- It occurs in patients over 40 years of age with slight predominance to males.
- Patients with Paget’s disease show varying degree of bone deformity and distortion of weight-bearing portions of the skeleton with curvature of the spine and bowing of the legs.
- Bones most affected are sacrum, spine, skull, femur and pelvis.
- It is widespread and symmetrical.
- It cause progressive enlargement of the skull and facial bones leading to marked deformity.
- Thickening of large bones.
- Bone pain which can be severe and almost intractable.
- Vault of the skull is more affected than facial bones.
- The most serious concern is the involvement of base of the skull, in this location lead to narrowing of various foramina and this can result in compression of the spinal cord and cranial nerves and lead to facial paralysis, blindness and deafness.
- **Serum alkaline phosphatase** is high, while serum calcium and phosphorus are normal.
Oral Manifestations: -

- Maxillary involvement is far more common than the mandible. results in enlargement of the middle third of the face In extreme cases, the alteration results in a lionlike facial deformity (leontiasis ossea)
- Progressive enlargement of the maxilla causing thickening and widening of the alveolar ridge. the palate is flattened.
- The bony enlargement leads to incompetent lips.
- In dentate patients there is spacing of teeth, enlargement in occlusion.
- Edentulous patients, complain that their dentures no longer fit because of increased alveolar size.
- Hypercementosis of teeth leads to ankylosis causing difficulty in extraction.

Radiographic Features:

The early stages of Paget's disease reveal a decreased radiodensity of the bone and alteration of trabecular pattern. Particularly the skull large circumscribed areas of radiolucency may be present. During the osteoblastic phase of the disease. Patchy areas of sclerotic bone are formed. The patchy sclerotic areas often are described as having a "cotton-wool" appearance. Teeth often demonstrate loss of lamina dura and extensive hypercementosis.
**Histopathology:**

Microscopic examination shows that in early osteolytic phase (resorptive stage) numerous osteoclasts surrounding bone trabeculae in deep indentations of resorption simultaneously, osteoblastic activity is seen with osteoblasts forming osteoid rims around bone trabeculae. A highly vascular fibrous connective tissue replaces the marrow. A characteristic feature is the presage of basophilic reversal lines in the bone, which indicate the junction between alternating bone resorption phase and bone formation phases and results in "jigsaw puzzle" or "mosaic" appearance of bone.

![Histopathology Image](image)

**Figure 14-16: Paget's disease.** Prominent osteoblastic and osteoclastic activity surround the bone trabeculae. Note the resting and reversal lines.

Development of malignant bone tumor osteosarcoma, may be recognized as a complication of Paget's disease, but the skull and jaws are very rare sites for sarcomas associated with this disease.
Giant Cell Lesions

Giant cell lesions include a group of lesions of markedly identical histopathological features, although they vary in their clinical behavior.

These are:

- Central Giant cell granuloma
- Peripheral Giant cell granuloma
- Brown tumor of hyperparathyroidism
- Aneurysmal bone cyst,
- Cherubism.

Hyperparathyroidism:

Excess production of parathyroid hormone (PTH) results in the condition known as Hyperparathyroidism. PTH normally is produced by the parathyroid gland in response to decrease in serum calcium levels.

Hyperparathyroidism may be one of three types: primary, secondary or hereditary.

**Primary hyperparathyroidism:** is characterized by uncontrolled hyper-secretion of parathyroid hormone from hyperplastic parathyroid gland, parathyroid adenoma or an adenocarcinoma. Characteristically, abnormal elevation of parath hormone, calcium and alkalin phosphatase levels resulting from parathormone stimulation of osteoclast-mediated bone resorption, from decreasing calcium excretion in the kidneys and from increased intestinal resorption.

**Secondary hyperparathyroidism:** Develops when PTH is continuously produced in response to chronic low levels of serum calcium, a situation usually associated with chronic renal disease, in patients undergoing renal dialysis, and in those with intestinal malabsorption syndrome. In these patients there is reduction in vitamin D3 which is required in for calcium absorption and metabolism.
Hereditary hyperparathyroidism has been shown to be an autosomal dominant condition. Multiple endocrine neoplasia type 1 or type 2a or Hyperthyroidism-jaw tumor syndrome (in this condition the patients develop multiple jaw lesions and there is increased risk for parathyroid carcinoma).

Clinical and radiographic features:

- The incidence increases with age, and is greater in menopausal women.
- Early symptoms include fatigue, weakness, arrhythmias, polyuria, bone pain and headache.
- Lesions of the kidneys, gastrointestinal tract and nervous system.
- Sever osseous changes are the result from significant bone demineralization with fibrous replacement producing radiographic changes that appear cystic like.

Patient with the classic triad of signs and symptoms of hyperparathyroidism are described as having "stones, bones and abdominal groans".

Stones: in Primary hyperparathyroidism have kidney stones nephrolithiasis) because of elevated serum calcium levels.

Bones: Variety of osseous changes. Generalized loss of lamina dura is seen as early manifestation. Alteration of the trabecular pattern, the decrease of trabecular density and blurring of the normal trabecular pattern occurs resulting in "ground glass" appearance. With persistent disease, Brown tumor of hyperparathyroidism develops. In patients with secondary hyperparathyroidism caused by end stage renal disease (renal osteodystrophy), striking enlargement of the jaws has been known to occur.

In the jaw bones, radiographically, osteoporotic appearance of the mandible and maxilla showing multiple radiolucencies, reflecting a more generalized resorption, overall cortical thinning, partial loss of lamina dura.
Abdominal groans: tendency to development of duodenal ulcers

**Histopathology:** bone lesions of hyperparathyroidism although non specific, are important in establishing diagnosis. Bone trabiculae show osteoclastic resorption. Delicate fibrocellular stroma contains numerous multinucleated giant cells. Accumulation of hemosidirin and extravasated RBCs. As a result the tissue may appear reddish brown accounting for the term (*Brown tumor*). The lesion is microscopically identical to central giant cell granuloma.

**Diagnosis:**

Brown tumor of hyperparathyroidism is clinically, radiographically and histopathologically similar to central giant cells granuloma therefore, a bone
chemistry profile should reveal elevation of serum parath hormone (PTH), and alkaline phosphatase with decrease of phosphorus.

**Treatment:**

After diagnosis of hyperparathyroidism the patient should be referred to a surgeon for excision of the parathyroid gland or for renal function evaluation. The jaw lesion should resolve after treatment.

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**Central Giant Cell Granuloma (CGCG):**

The giant cell granuloma is considered widely to be a non-neoplastic. Some lesions demonstrate aggressive behavior similar to that of a neoplasm.

- Central giant cell granuloma of bone (CGCG) affect a wide age range, although 60% of cases occur before the age 30. It is more common in females.

- About 70% of lesions arise in the mandible, most commonly in the anterior portion of the jaws, mandibular lesions frequently cross the midline.

**Clinically:** most CGCG of the jaws are asymptomatic discovered either during routine radiographic examination or as a result of painless expansion of the affected bone. A minority of cases however, may be associated with pain, paresthesia, or perforation of the cortical bone plate, occasionally resulting in ulceration of the mucosal surface by the underlying lesion

Based on the clinical and radiographic features CGCG may be divided into two categories:

1. **Nonaggressive lesions:** which form most of the cases. they exhibit few or no symptoms, demonstrate slow growth. and do not show cortical perforation or root resorption of teeth involved in the lesion.

2. **Aggressive lesions:** are characterized by pain, rapid growth, cortical perforation, and root resorption. They show marked tendency to recur after treatment, compared with nonaggressive types.
Radiographically:

It is not specifically diagnostic. CGCG appear as radiolucent lesion, which may be unilocular or multilocular. The defect is usually well delineated. Buccal and lingual bone expansion is usually observed on occlusal radiograph.

Histopathology: Giant cell lesions of the jaw show a variety of features. The most common is the presence of few to many multinucleated giant cell in a background of ovoid to spindle- shaped connective tissue cells. The giant cells represents osteoclasts, although some suggests the cell may be aligned with macrophages. The giant cell may be aggregated focally in the lesion or diffusely throughout the lesion. They vary considerably in size & shape. Some are small irregular in shape & only contain a few nuclei. Others are large & round containing 20 or more nuclei. Area of erythrocyte extravasation & hemosiderin deposition often are prominent. Foci of osteoid & newly formed bone are occasionally present within the lesion.
**Treatment:** It is usually treated by curettage.

**Giant Cell Tumor:**
A true neoplasm that arise most commonly in the long bone. These tumors exhibit a wide spectrum of biologic behavior from benign to malignant. The relationship between this lesion and CGCG is controversial. Mostly it is regarded as giant cell tumor as distinct from CGCG, acknowledging the very rare occurrence of this tumor within the jaw. Although it is rare, this tumor affect jaw bones and other sites of head and neck including sphenoid, ethmoid and temporal bone. Giant cell tumors are most often seen in 3rd and 4th decades of life. Lesions exhibit slow growth and boney expansion, or they produce rapid growth, pain or paresthesia. Radiographically, the giant cell tumor produces a radiolucent image. Histopathologically, characterized by presence of numerous multinucleated giant cells dispersed evenly among mononuclear fibroblasts. Stromal cellularity is usually prominent with minimal collagen production. Giant cells are usually larger and contain more nuclei than corresponding cells in CGCG. Giant cell tumors may contain inflammatory cells and areas of necrosis. Osteoid formation is noted less than CGCG. Surgical excision is the treatment of choice with great tendency to recur after treatment than CGCG.

**Peripheral giant cell granuloma:**
Is a relatively common tumor-like growth of the oral cavity. PGCG is a reactive lesion occurring on the gingiva and alveolar ridge usually as a result of local irritating factors such as tooth extraction, poor dental restorations, food impaction, ill fitting dentures, plaque, and calculus. It seems to be influenced by hormonal stimulus, especially estrogen or increased circulating parathormon, i.e. primary and
secondary hyperparathyroidism. Clinically it can present as polyploidy or nodular lesion. It is most common than central giant cell granuloma. Radiographic examination generally have no findings, because the lesion is a soft tissue mass. Histological features of PGCG reveal a non capsulated mass of tissue containing a large number of young connective tissue cells and multinucleated giant cells. Hemorrhage, hemosiderine, inflammatory cells, and newly formed bone or calcified material may also be seen throughout the cellular connective tissue.

**Aneurysmal Bone cyst (ABC):**

**Etiology:** unknown, may be related to altered hemodynamics or abnormal healing of bone hemorrhage. It is through that primary bone lesion like fibrous dysplasia or central giant cell granuloma initiates a vascular malformation leading to this hemodynamic disturbance and cystic development.

**Clinical futures:** -
- Teenagers and young adults affected
- Arise in posterior part of the body & angle of the mandible.
- Presented as firm, painless swelling.

**Radiographically:**

Multilocular radiolucency with a characteristic ballooned-out appearance due to gross cortical expansion.
Histopathology:

- numerous, non-endothelial, blood-filled spaces lined by connective tissue and multinucleated giant cell.
- Differential diagnosis: central giant cell granuloma, Hyperparathyroidism, Cherubism.

**treatment:** Excision or curettage with supplemental cryotherapy is the treatment of choice.