Diseases of Growth and Development (and a few other diseases)

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OPTH 727

Errors in facial development

- Numerous syndromes/diseases affect facial growth and development
  - Cleft Lip/Palate
    - Most important congenital abnormality for our profession
    - Will not be tested/discussed in this class (will get this material in ortho and peds classes..
- Many other syndromes produce facial anomalies

General consideration

- Up to 4% of live births (in USA) have some type of congenital or developmental abnormality
  - Most “defects” produce no significant symptoms.
    - Congenital heart malformations may be incidental findings on autopsy
  - Signs and symptoms may present congenitally (at birth/gestation); or during childhood (pediatric)

- Diseases of growth and development may be due to:
  - A known genetic cause -
    - A known defect/mutation in a particular single gene
    - A known defect in chromosome (deleted, translocated, duplicated, inverted) OR an extra or missing chromosome.
      - Trisomy 21 (Down Syndrome), etc
  - An known “environmental” cause - i.e. maternal disease/insult
    - Infections: rubella, syphilis, HIV, hepatitis
    - Medications/drugs
      - Fetal alcohol syndrome
    - Disruption of immune tolerance - Immune tolerance in pregnancy is the absence of a maternal immune response against the fetus
    - Other maternal conditions – i.e. hypertension, diabetes, obesity may produce pre-eclampsia which could then become eclampsia;
  - Idiopathic (i.e. we don’t know the cause for sure – probably a mix of factors)
    - These may be “presumed” to have a genetic origin, but we may not be able to determine for sure.
      - One example is Hirschsprung disease – some cases are familial; some are not; some are associated with other genetic diseases (i.e. Down Syndrome).

General considerations

- Often a spectrum of signs/symptoms in a particular disease
  - Prognosis may be variable.

- Disclaimer: The diseases discussed below are far more complex than what is written on the slides. My goal is to distill down to the basics.

- More “dentally” relevant diseases will be covered again in oral pathology as well as other courses, pediatric dentistry, ortho, etc…

Down Syndrome

- Trisomy 21
  - Most often cause
  - Third copy of chromosome due to nondisjunction during meiosis
- 1:1000 of overall population. Most common trisomy
- Symptoms-
  - Intellectual disability, stunted growth
  - Numerous abnormal facial features
    - Oral: narrow roof of mouth, proportionally large tongue
  - Increased propensity for blood cancers and congenital heart diseases
- Main risk factor is advanced maternal age
  - Genetic testing in utero often done

Edward Syndrome

- Trisomy 18
- Second most common trisomy (1:5000)
  - Advanced maternal age major risk factor
- Disease far more serious than Down Syndrome
  - Patients usually die in first year.
  - Congenital heart abnormalities are very common.

Turner Syndrome

- ~1:2000 – 5000
- Females missing an X chromosome
  - Only one X chromosome
  - 45 total chromosomes (45, X0)
- Highly variable signs and symptoms
  - Related to growth and development
    - Stunted growth, delayed puberty
  - Prognosis is often very good
    - Growth/sex hormones often needed to promote growth and puberty.

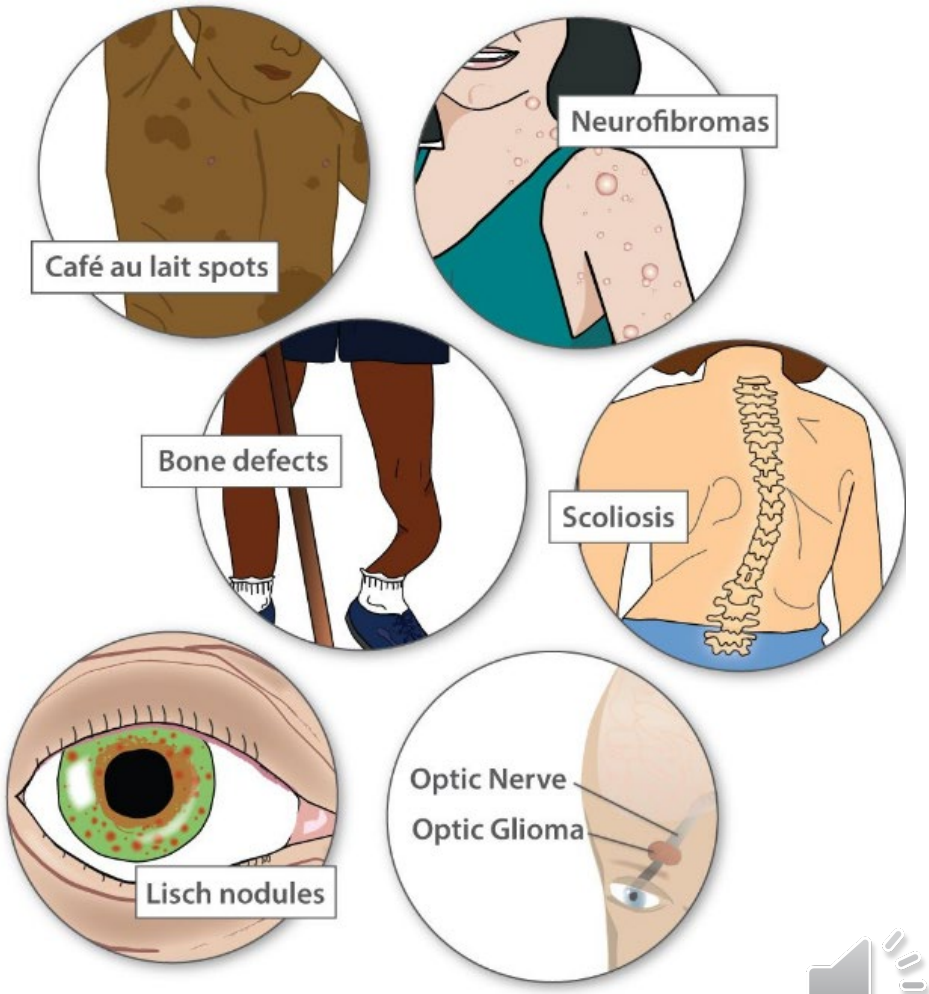
Klinefelter Syndrome

- Males with two or more X chromosomes
  - Karyotypes (47 XXY) usually; can be (48 XXXY), etc.
- Symptoms usually manifest during puberty
  - Hypogonadism, low testosterone, gynecomastia
    - Testosterone replacement therapy often indicated

Neurofibromatosis Type I

- Eight different types of neurofibromatosis: Type I is by far the most common.
- Genetic mutations of NF1 gene
- ~ 1:3000 incidence

- Signs of disease
  - Café au lait skin pigmentations
  - Multiple neurofibromas (benign proliferations)
    - Usually on skin, but can be anywhere including oral cavity
  - Optic glioma (benign tumor of optic nerve)
  - Axillary freckling
  - Lisch nodules (brown spots on iris)
  - Bone defects
- Usually patients live normal lives (esthetics aside)
  - Most dangerous complication is cancerous transformation of a neurofibroma



Neurofibromatosis

- Type I is most common (90%)

- Type II Neurofibromatosis is similar to type I (skin manifestations)
  - Type II has vestibular schwannomas (benign)
    - Tumors on auditory nerve
      - May lead to hearing deficits
    - Other brain tumors (benign) also more likely

Craniosynostosis

- What is craniosynostosis?
  - Premature closing of fibrous sutures in skull
    - One or more sutures may be affected
    - Prevents normal growth of head
    - Result
      - An abnormally shaped head – shape is dependent on which suture closes prematurely.
      - May produce mental disability (due to increased intracranial pressure during development)
      - Visual/auditory deficiency
    - With modern medicine, this can be corrected surgically and often prevent more severe sequelae.

- Incidence? 1:2500 live births
  - Most cases of craniosynostosis are not associated with syndromes (~10% syndromic)
  - Serious cases - more often associated with syndromes such as:
    - Crouzon Syndrome (1:65,000)
    - Apert Syndrome (1:65,000)

Crouzon Syndrome

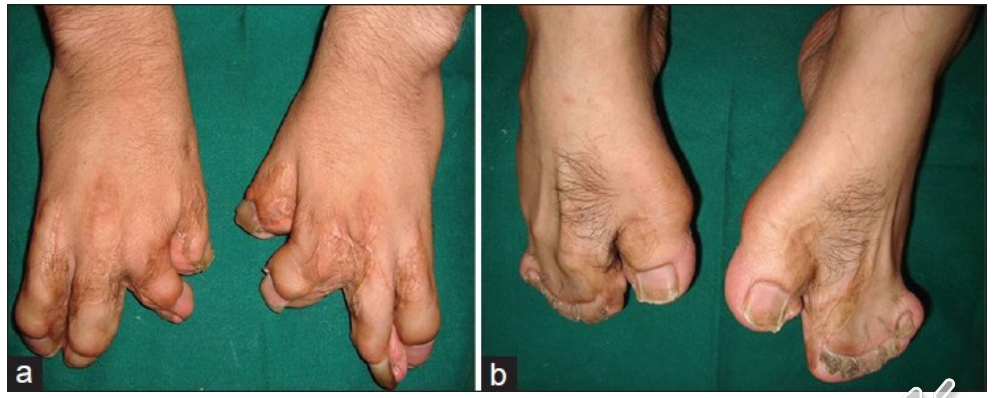
- A more severe type of craniosynostosis that is often genetic.

- A person with Crouzons syndrome has craniosynostosis (and all that potentially goes with it- see previous slide)
- Plus:
  - Bulging eyes (proptosis)
  - Midface hypoplasia
    - Underdeveloped maxilla

Apert Syndrome

- What is Apert Syndrome?
  - Apert Syndrome has all characteristics of Crouzon syndrome with one addition…
    - LIMB DEFECTS
    - No limb defects in Crouzon syndrome

- What are the limb defects in Apert Syndrome?
  - "Syndactyly" of hands and feet
    - Fusion of fingers and toes
      - Variable severity
        - Webbed hand vs. synonychia
        - One digit vs. multiple digits



Other terminologies related to craniosynostosis, Crouzon Syndrome and Apert Syndrome

- Brachycephaly (short head)
- Scaphocephaly (boat shaped head)
- Trigonocephaly (triangle shaped head)
- Acrobrachycephaly (tower skull)

<u>Do not need to know these</u>: just know the suffix "-cephaly" refers to abnormality of the head.

Most cases of craniosynostosis are not this severe

Treacher Collins Syndrome (Mandibulofacial Dysostosis)

- Genetic disease
- Defects of structures derived from 1st and 2nd branchial arches
- Characteristics
  - Hypoplastic zygomatic arches
  - Coloboma (notch on outer eyelid)
  - Downward slanting palpebral fissures
  - Underdeveloped mandible
  - Ear defects/ hearing loss

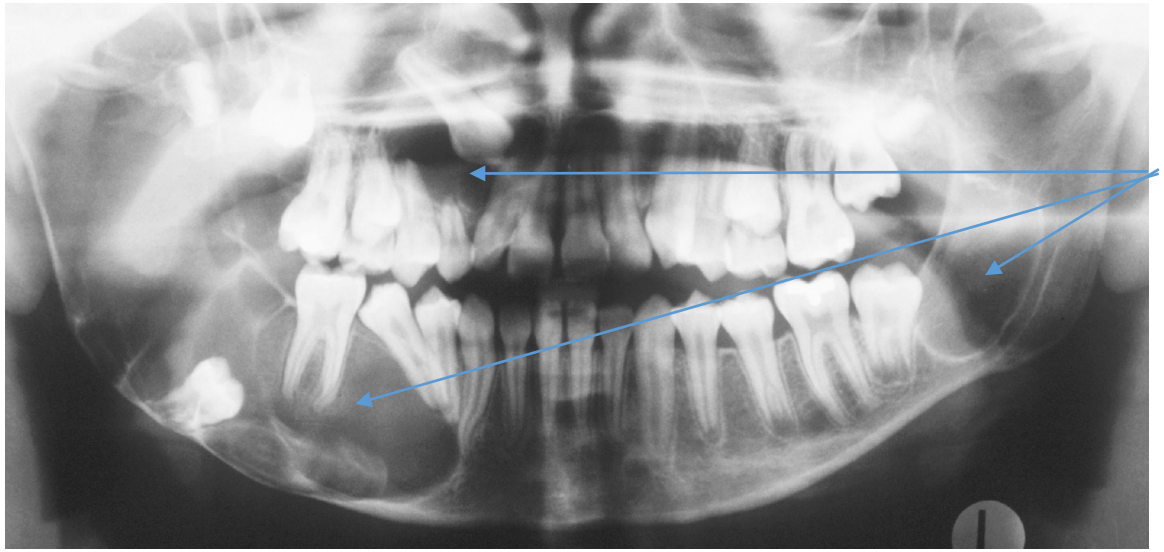
Nevoid Basal Cell Carcinoma Syndrome (Gorlin Syndrome)

- This is a very important syndrome related to dentistry? Why?
  - Presence of multiple jaw cysts (odontogenic keratocysts)… therefore, you may be involved in diagnosing the disease.
- Numerous clinical features: more in oral pathology courses

- Major clinical criteria- often times, these present in kids:
  - Multiple basal cell carcinomas
  - Multiple odontogenic keratocysts
  - Pitting of palms and soles of feet
  - Calcified falx cerebri
  - Greater propensity for medulloblastoma (1%)

- Minor criteria: skeletal abnormalities (particularly facial skeleton and ribs) and ocular abnormalities,

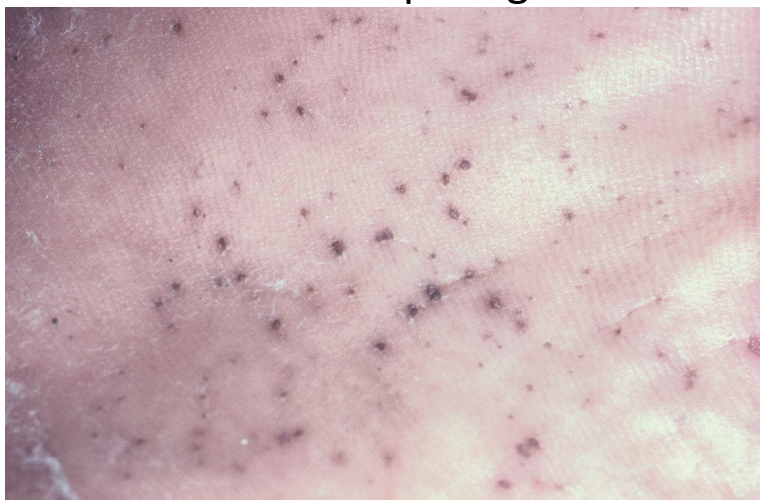
Nevoid Basal Cell Carcinoma Syndrome



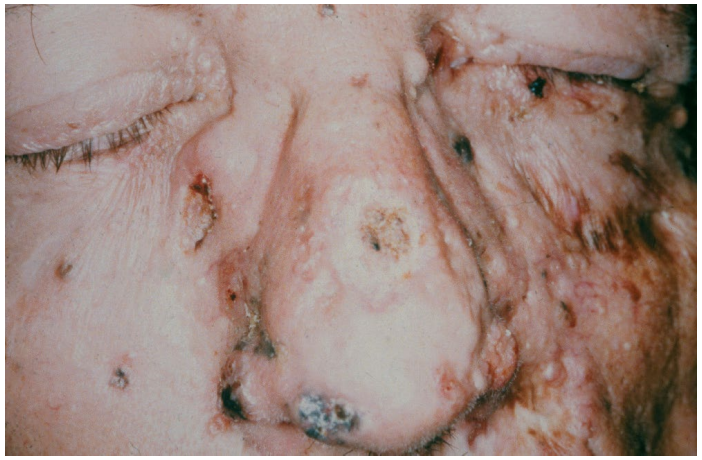
Several odontogenic keratocysts

Calcified falx cerebri

Plantar pitting



Numerous BCC



Sturge Weber Angiomatosis

- Vascular proliferations involving the brain and face
  - Found along branches of trigeminal nerve (V1, V2 and/or V3 involvement)
- Usually unilateral
- Clinical presentation
  - Skin:
    - "Port wine" stain aka nevus flammeus
  - Oral cavity
    - Hypervascular changes to mucosa
  - Neural:
    - Angiomas in the meninges and cerebral cortex
    - Neural symptoms may be present shortly after birth or develop later in life
    - Symptoms: headaches, convulsions, ocular disturbances
      - Serious cases: contralateral hemiplegia (paralysis occurs on other side of body where visible lesions are)

As you would imagine this is the serious stuff

Sturge Weber Angiomatosis

Sturge Weber???

Ectodermal dysplasia

- An inherited diseases in which several ectodermally derived structures fail to develop.
  - Many different diseases exist affecting various genes with different types of inheritance patterns.
  - Many types are X-linked recessive – males more frequently affected
- Which structures often affected? Skin, teeth, hair, sweat glands, salivary glands, nails
  - Skin
    - Decreased number of sweat glands – if serious, may lead to inability to regulate body temperature
  - Teeth
    - Anodontia – partial or complete
    - Tooth malformations
  - Hair
    - Very fine, sparse hair
    - Sparse eyebrows, eyelashes

Ectodermal dysplasia

Peutz-Jegher Syndrome

- Rare, well recognized, genetic disease.

- Main clinical characteristics
  - Freckle-like lesions of hands, peri-oral skin and oral mucosa
    - Mucocutaneous lesions often first to appear and recognition plays a large role in diagnosis of disease.
  - Gastrointestinal polyposis and predisposition to develop GI (and other)cancers
    - What other diseases produce GI polyposis??
    - For PJS, the small intestine more commonly affected
      - Gardner Syndrome, large intestine is far more common
    - Polyps may develop into cancer
    - Polyps may obstruct bowels

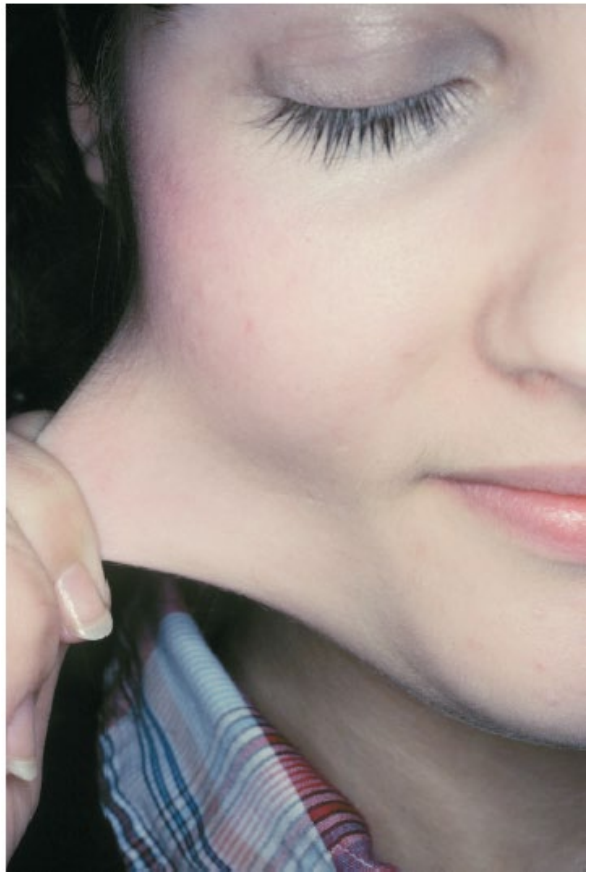
Peutz-Jegher Syndrome

Ehlers-Danlos Syndrome

- Genetic connective tissue disorder resulting in impaired collagen synthesis
  - Many types- many clinical presentations
    - Many types of collagen I, II, III, V, etc.
- Most cases are “classical type”
  - May have mild or severe symptoms
- Clinical presentation:
  - Hypermobility of joints
    - Constant hip dislocations
  - Hyperelasticity of skin
    - Easy bruising,
    - Abnormal scarring after stretching
  - Oral
    - Ability to touch tongue to nose
    - Some types produce severe periodontal disease

Ehlers-Danlos Syndrome

Hyperelasticity of skin



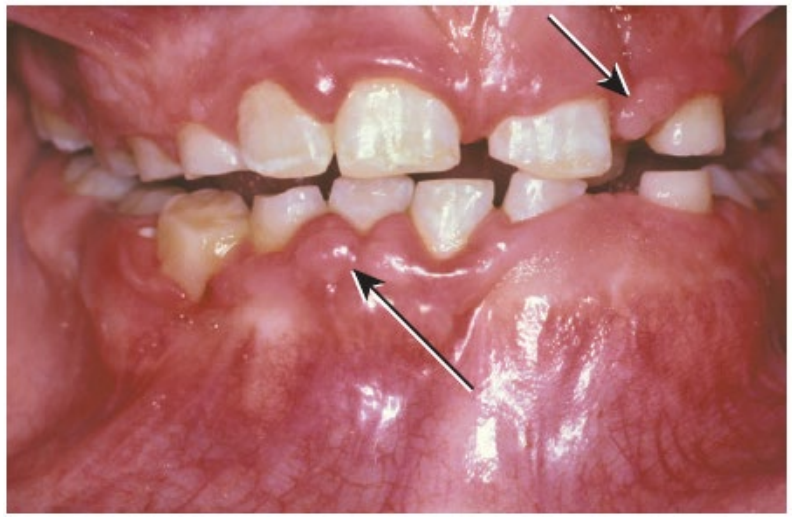
Abnormal scarring after stretching

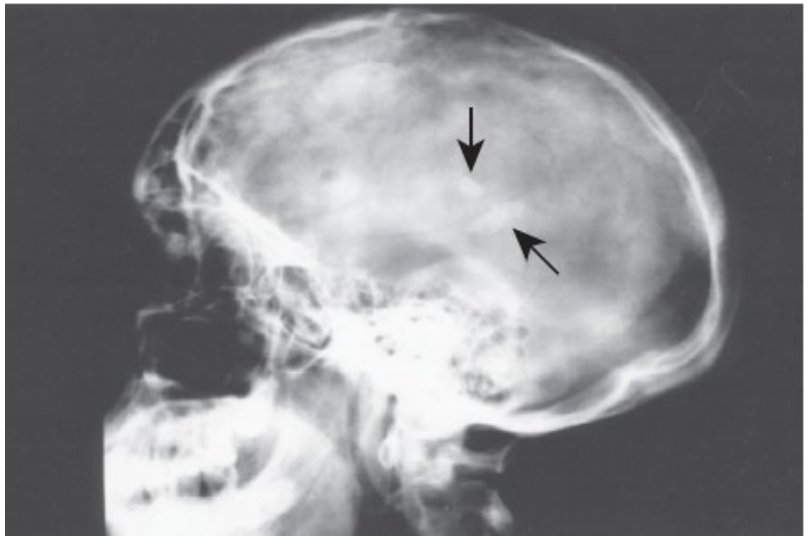
Tuberous Sclerosis

- Genetic disease
- Main clinical characteristics:
  - Intellectual/behavioral abnormalities
  - Seizure disorders
  - Angiofibromas of the skin
    - Face and nails
  - Oral cavity: Benign soft tissue tumors in oral cavity may be present. Enamel pitting.
- Disease is characterized by benign growths that may present in numerous tissues
  - Growths in brain cause CNS symptoms
  - Other benign tumors or other growths include cardiac rhabdomyomas, renal angiomyolipomas, retinal hamartomas

Tuberous Sclerosis

Intraosseous fibrous proliferation

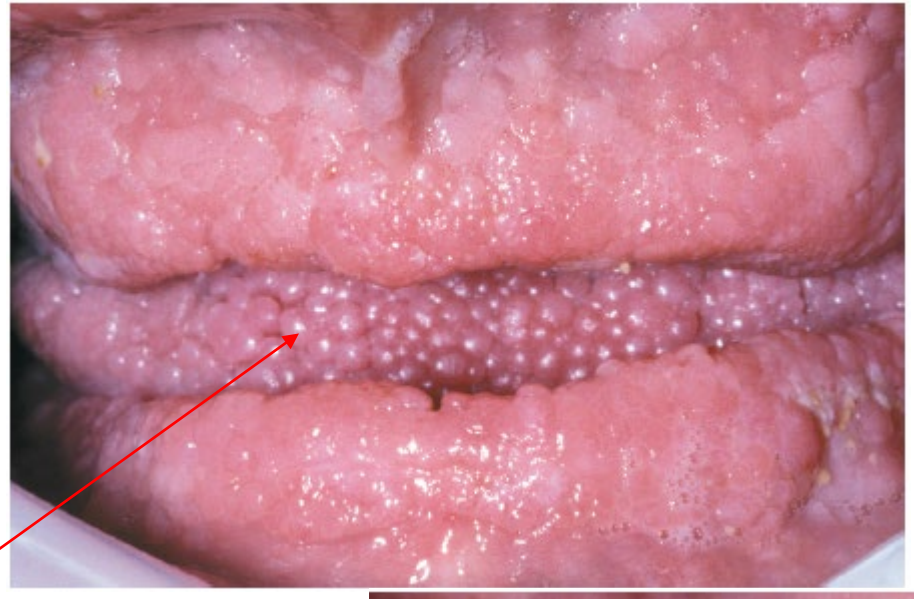


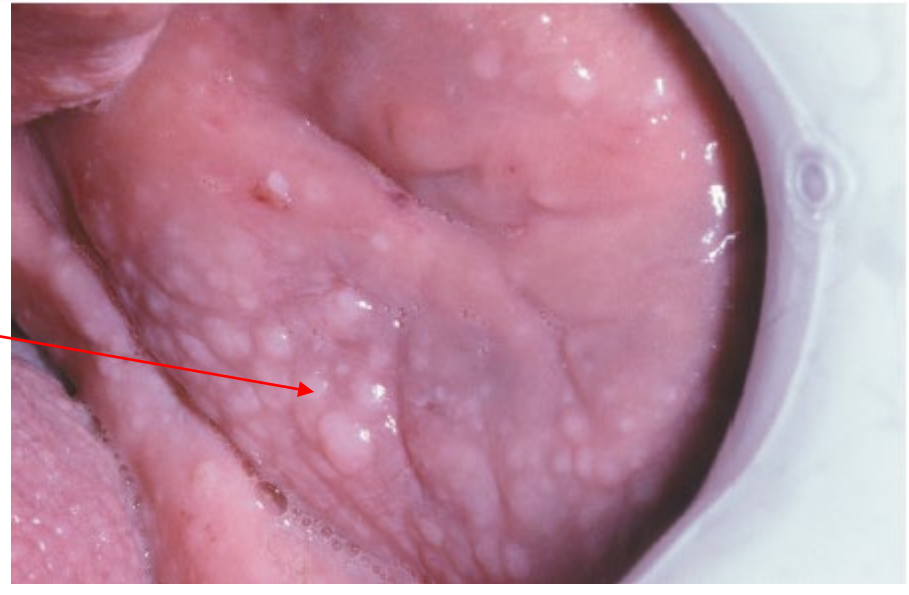


Cowden Syndrome (aka Multiple hamartoma syndrome)

- Genetic disease producing multiple benign growths in body.
  - Patients have higher risk of developing breast, thyroid, skin, uterine cancers
- Clinical presentation:
  - Multiple facial skin growths (trichilemmomas)
  - Multiple oral papules
  - Acral keratosis
    - Wart-like papules on skin of the hands and feet.

Cowden Syndrome (aka Multiple hamartoma syndrome)



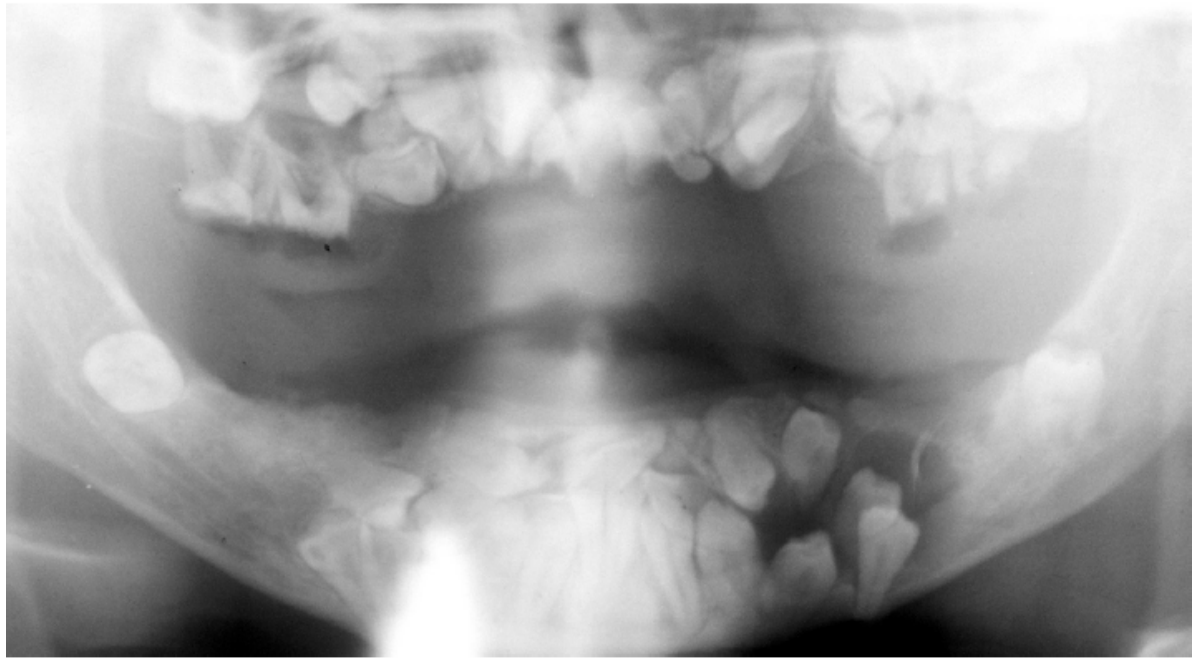


Multiple small, benign growths

Cleidocranial dysplasia

- A generalized bone disorder- many bones may be affected
  - Genetic disease
  - Very rare (1:million incidence)
  - Important for us because of significant dental manifestations
- Of bone defects: the most significant involve the skull and clavicles
  - Clavicles- hypoplastic or missing
    - May be unilateral or bilateral
    - Narrow shoulders
    - Ribs often affected
  - Skull
    - Misshapen. Many possibilities or clinical presentations possible.
- Dental manifestations
  - Numerous unerupted permanent and supernumerary teeth
  - Many patients have cleft palate also
- Prognosis: very good. No systemic diseases result cleidocranial dysplasia.

Cleidocranial dysplasia



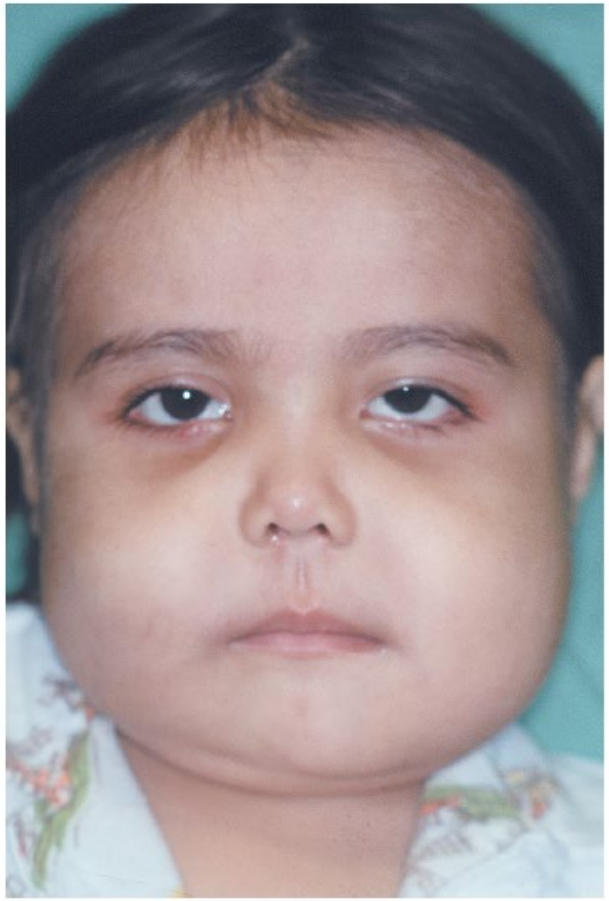
Cherubism

- Genetic disease leading to enhanced osteoclastogenesis
  - But not necessarily inherited
- Painless, bilaterally symmetric, lytic lesions of mandible – produces expansion
  - Age of onset- early childhood (age 2-5)
    - Lesions may get bigger through puberty and then often regress
  - Similar lesions in maxilla are also sometimes seen
    - Maxillary lesions may produce “eyes upturned to heaven”.
      - Expose sclera below the iris

- Histopathology of lytic lesions
  - Central giant cell granulomas
    - Fibrous connective tissue with multinucleated giant cells

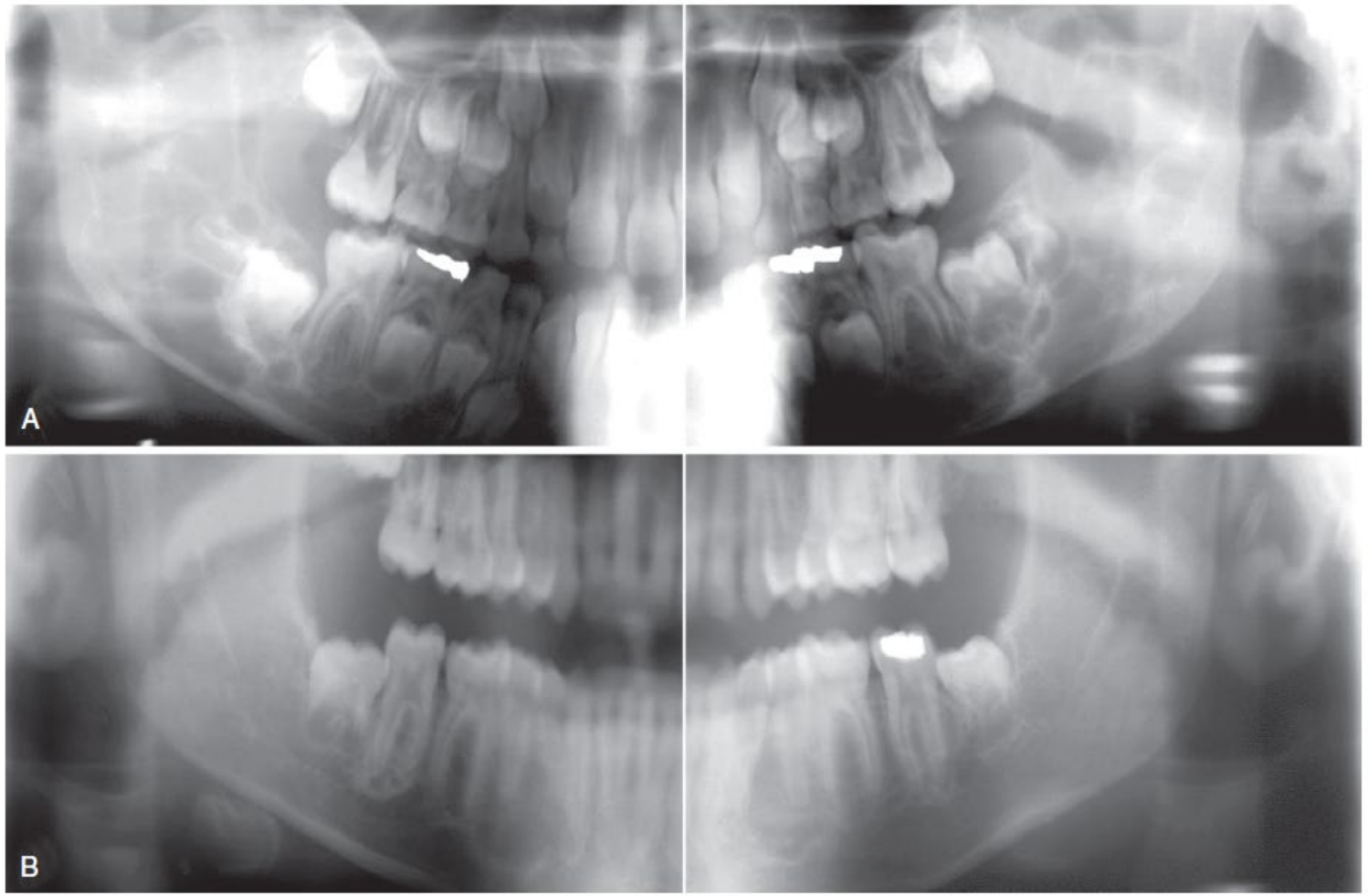
Cherubism

(cherubs – plump cheeked angels)



• **Fig. 14-22 Cherubism.** This young girl shows the typical cherubic facies resulting from bilateral expansile mandibular and maxillary lesions. (Courtesy of Dr. Román Carlos.)

Cherubism



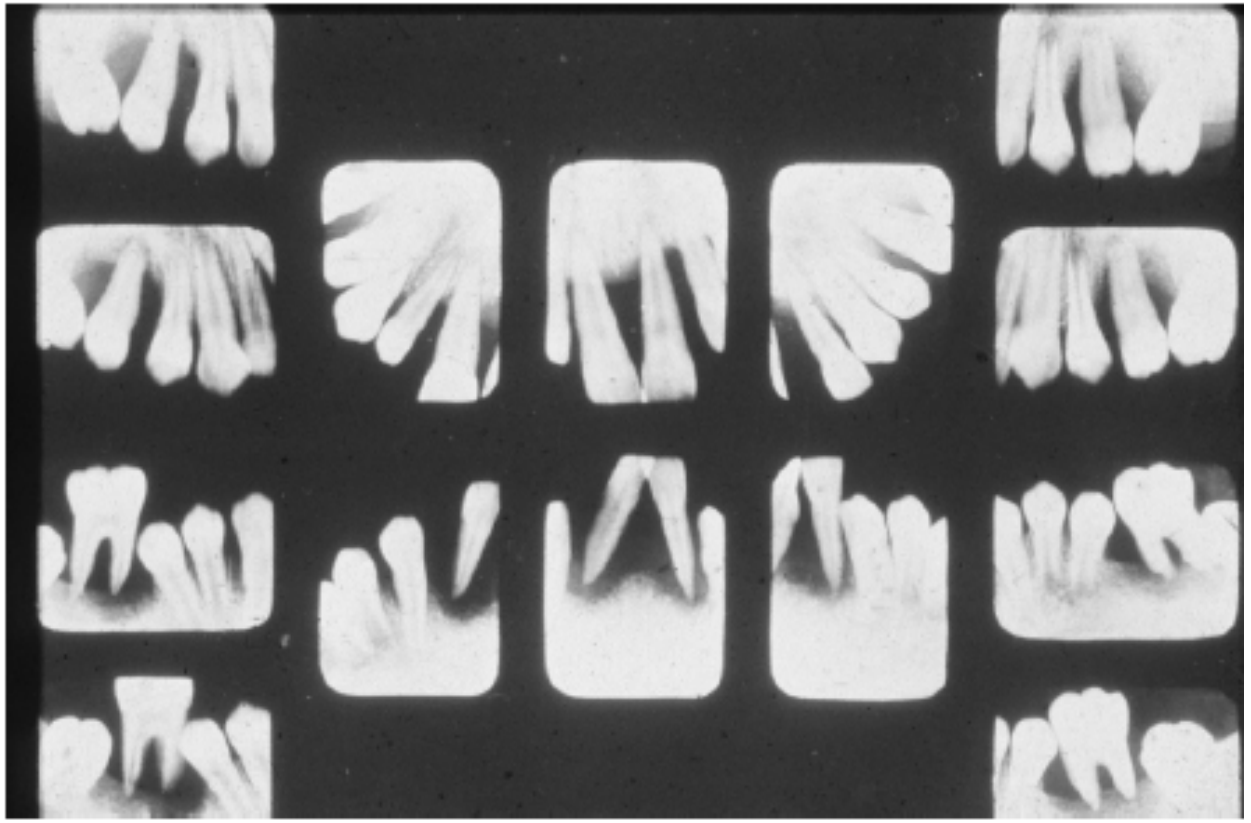
• **Fig. 14-23 Cherubism. A,** Panoramic radiograph of a 7-year-old white boy. Bilateral multilocular radiolucencies can be seen in the posterior mandible. **B,** Same patient 6 years later. The lesions in the mandibular rami demonstrate significant resolution, but areas of involvement are still present in the body of the mandible. (Courtesy of Dr. John R. Cramer.)

Papillon-Lefevre Syndrome

- A rare genetic disease
  - Caused by mutation of the Cathepsin C gene
    - Cathepsin C important for structural growth and development of skin and for immune response.
- Clinical features
  - Palmar or plantar keratosis
  - Dramatically advanced periodontitis
    - Marked alveolar bone loss in multiple quadrants
    - Periodontitis seen in primary and permanent dentition
    - Usually completely edentulous by age 15

Papillon-Lefevre Syndrome

• **Fig. 4-37 Papillon-Lefèvre Syndrome.** Plantar keratosis of the foot.



Severe bone loss in all four quadrants