Skeletal Dysplasias

Listed here according to the anagram MACHO MEN OF GOD:

- Marfan’s Syndrome
- Achondroplasia
- Cleidocranial dysostosis
- Hypophosphatemic rickets
- Osteogenesis imperfecta

- Multiple hereditary exostoses
- Enchondromatosis (Ollier’s disease)
- Neurofibromatosis

- Osteopetrosis
  - (with osteopetrosis, you get pyknody sostosis for free)
- Fibrous dysplasia
  - usual form (Jaffe-Lichtenstein)
  - with skin pigmentation and precocious puberty (McCune-Albright)

- Gaucher’s Disease
- Osteopoikilosis
- Dactyly
  - Brachydactyly
  - Camptodactyly
  - Polydactyly
  - Sydactyly
Marfan's Syndrome

This is a familial disorder of connective tissue, primarily involving the eye, skeleton, and cardiovascular system. Although sporadic cases occur, most cases are due to autosomal dominant gene with a high degree of penetrance. Investigators are still uncertain of whether the primary defect lies in collagen, elastic fibers, or both. The skeletal overgrowth characteristic of this disorder is especially puzzling, and none of the current theories of defects in collagen synthesis do a very good job of explaining this overgrowth.

With this build-up, you would expect these patients to be characteristically tall and thin. The limbs are disproportionately long with respect to the trunk, especially in the hands and feet, giving the appearance of "arachnodactyly". These subjective impressions of the patient may be objectified somewhat by looking for the "thumb sign" (the thumb protrudes beyond a clenched fist), and measuring the segmental index (distance from pubic symphysis to floor / distance from top of head to floor) and the metacarpal index (length / width). Other common skeletal findings include scoliosis and hypermobile joints.

Common ocular abnormalities include bilateral ectopia lentis\(^1\), myopia, and retinal detachments. Associated cardiac abnormalities lead to a shortened life expectancy for these patients. These abnormalities include cystic medial necrosis of the aorta or pulmonary arteries (leading to dissection or rupture), aortic and mitral valve insufficiency ("floppy valve), and septal defects.

Achondroplasia

First, a few words on dwarfism. Most types are very rare and quite a few are lethal. Of the nonlethal types, the only really common type of short-limbed dwarfism is achondroplasia.

Classic achondroplasia is a common autosomal dominant disorder, and is compatible with a long life span. The homozygous form, born of two heterozygous parents, is quite rare and lethal. However, most cases of achondroplasia are due to new mutations, rather than inheritance from a parent.

The very name of this syndrome suggests that the primary problem here is a generalised defect in enchondral bone formation. Once you know this, you can predict a lot of the findings seen in these people. Most of the appendicular skeleton is formed by and grows in size by enchondral bone formation. Therefore, we can accurately predict that the long bones (and therefore the patient) will be short. The characteristic shape of the skull and face in achondroplasia are also a logical extension of these principles. The calvarium is modelled on membranous bone, and its eventual size is merely a reflection of brain size. These people have brains of normal size, so their calvaria are likewise of normal size. However, the face and skull base come from enchondral bone, and end up relatively small, in comparison to the skull. The foramina of the skull base and spine and the spinal canal are often small, which may lead to prominent neurological problems and spinal stenosis.

\(^1\) Ectopia lentis – dislocation or subluxation of the lens of the eye. Anterior malposition can predispose to uveitis and glaucoma
**Cleidocranial Dysostosis/Dysplasia**

This is an autosomal dominant disorder whose very name tells us a lot about it. Dysostosis indicates an abnormality in the development of bone, while “cleido” and cranial tell us the major abnormalities are in the clavicle and head. This disorder occurs in both membranous and enchondral bone, and has a striking propensity for affecting midline structures. If you painted a big, broad stripe down the midline with a paintbrush from skull to groin, you'd paint over a lot of structures involved with this syndrome.

Prominent features include a large head with delayed suture closure, Wormian bone\(^2\), hypertelorism\(^3\), a small face, dental dysplasia, hypoplasia or aplasia of the clavicles, a narrow pelvis, and several varieties of spinal abnormalities. Just about every other bone in the body may be involved as well, including the ossicles of the ear. Despite the midline tendency, the appendicular skeleton is also frequently involved.

These patients have a normal life expectancy. Prominent complications of this syndrome include dental anomalies, hearing loss, scoliosis, and dislocations of the shoulder, radial head or hip.

**Hypophosphatemic Rickets**

This has also been called X-linked hypophosphatemia, primary renal hypophosphatemic rickets or familial vitamin D-resistant rickets. As one of these names implies, it is due to a hereditary defect of the renal tubules, leading to decreased reabsorption of phosphate and therefore reduced serum phosphate levels. As the name also implies, this decreased reabsorption does not respond to usual amounts of vitamin D. This defect is passed on with an X-linked dominant mode of inheritance.

In general, this disorder exhibits rachitic (rickety) epiphyseal and metaphyseal abnormalities predominantly in the lower limbs. This is best seen when comparing knee and wrist radiographs in the same patient. These patients also may demonstrate a generalised bone modelling error resulting in short, squat bones.

**Osteogenesis Imperfecta**

This inherited, generalised disorder of connective tissue is characterised by abnormal maturation of collagen. It affects the skeleton, ligaments, skin, sclera, and teeth. The major clinical diagnostic triad is generalised osteoporosis with skeletal fragility, blue sclera, and odontogenesis imperfecta\(^4\). Any two of these features suffice for the diagnosis.

Growth retardation occurs in most cases, and may be marked to the point of dwarfism in several cases. This short stature is due to not only defects in collagen synthesis but also the cumulative fracture deformities secondary to the fragile bones.

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\(^2\) Wormian bone – extra pieces of bone within the sutures of the cranium

\(^3\) Hypertelorism – widening of distance between left and right side structures such as the eyes

\(^4\) Odontogenesis imperfect – deficient formation of enamel and dentin causing the affected teeth to exhibit a marked reduction in radiopacity. Unusually large pulp chambers with thin enamel, that can fracture easily.
The most common radiographic finding is that of generalized osteopenia. Multiple fractures resulting from insignificant trauma or normal muscle pull are also seen commonly, and may result in considerable deformity. Exuberant callus formation and pseudarthroses may also be seen. Persistent Wormian bones may be seen in the skull.

This entity should be considered when one is entertaining the diagnosis of the battered child syndrome, as another cause of multiple fractures in multiple stages of healing. The workup of a potentially battered child is extremely serious, and involves significant legal and social investigations of the parents. It would be tragic to mistakenly invoke this massively invasive process on a family by missing the findings of osteogenesis imperfecta. The take-home message: always look carefully for other classic signs of osteogenesis imperfecta, such as generalised osteoporosis, Wormian bones, blue sclera and odontogenesis imperfecta.

**Multiple Hereditary Exostoses**

Osteochondromas usually have an absolutely pathognomonic appearance. The key word here is continuity. The cortex and medullary space of normal bone flows continuously into that of the osteochondroma (see figure below).

![Figure 1 - Exostosis](image)

Multiple hereditary exostosis (MHE) is characterised by multiple osteochondromas throughout the skeleton, and this disorder seems to be hereditary. Unfortunately, this syndrome is associated with an increased likelihood (up to 10 %) that one or more of these osteochondromas will undergo transformation to a chondrosarcoma. Some patients without this syndrome will occasionally develop one or more osteochondromas. The likelihood of malignant degeneration is much lower (< 1 %) with sporadic osteochondromas such as this.
As it turns out, this fascinating syndrome has many points of similarity with some of the colonic polyposis syndromes. For example, the lesions may be pedunculated or sessile, they may be single or too numerous to count, and they may undergo malignant change. The trick, is determining which folks have the syndrome and which ones don't. The answer in both cases is that one looks for evidence that the process is a systemic disorder and not just a focal, sporadic lesion. In the polyposis syndromes, one may look for other manifestations, such as associated buccal pigmentation (Peutz-Jegher syndrome). With MHE syndrome, one looks for other dysplastic bones. A very common place to find this is in the femoral and humeral necks. Patients with MHE generally have short, thick necks in both anatomic sites. For this reason, after finding the first osteochondroma, one should request a radiograph of the patient's hips.

![Radiograph](image)

**Figure 2 - The radiograph demonstrates short, widened femoral necks; also seen are several large osteochondromas (arrows)**

You can explain a lot of things about osteochondromas if you consider them to be an ectopic epiphysis. This means that they grow right along with the normal epiphyses, and stop growing when the plates close. They look just like physes on radionuclide images in children – hot until the plates close. These ectopic growth plates also sometimes will cause the bone to grow into strange shapes: too short, too long, or curved.

Once you have diagnosed this disorder, you must make sure that the patient knows the significance of their disorder and that they are now on a lifelong surveillance program. Any development of pain or growth after the plates have closed in an osteochondroma should be looked upon with suspicion for malignant degeneration. Follow-up imaging studies may include both radiographs and radionuclide images.
Enchondromatosis (Ollier’s Disease)

Most enchondromas are solitary. However, some unfortunate patients may have a syndrome of multiple enchondromas (Ollier’s disease). This syndrome, unlike multiple hereditary exostoses is not hereditary. Although any bone may be involved, the smart money is usually on the tubular bones of the arm and leg. Along with the classic central expansile pattern seen with classic solitary enchondromas, one may also see linear or columnar lucencies in the metaphyses, representing columns of growing cartilage. The main significance of this disorder is that some lesions will undergo malignant change to chondrosarcoma in 5-30 %, rising close to 100% in Mafucci’s syndrome.

Neurofibromatosis (von Recklinhausen’s Disease, 1882)

This disorder is seen in approximately 1 in 3000 births. It is usually inherited as an autosomal dominant disorder, but there is a high rate of new mutations. There are several reported manifestations, and virtually every part of the body is affected.

Type 1 is from a defect in chromosome 17 and manifestations are principally peripheral: Café-au-lait spots, 2+ cutaneous neurofibromas, or a single plexiform neurofibroma (large cluster), freckling in the groin or arm-pit, lisch nodules, optic gliomas, and skeletal anomalies.

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5 Mafucci’s Syndrome – multiple enchondromas associated with soft tissue hemangioma. These hemangiomas may contain phleboliths, making the diagnosis possible on plain radiographs.

6 Lisch nodule – harmartoma in the iris
Type 2 is caused by a mutation in chromosome 22 with more central pathology: bilateral acoustic neuromas (age 20) with hearing loss, headache, vertigo, deafness and tinnitus. They may develop spinal and brain tumours, as well as spinal deformity.

The skeleton will be affected in about 80% of patients. 50% of patients with this disorder may develop kyphoscoliosis, usually in the high thoracic spine. This deformity may progress quite rapidly, and may lead to paraplegia. Other skeletal manifestations include posterior scalloping of vertebral bodies, hemihypertrophy, pseudarthrosis of the tibia, and enlargement of the spinal neural foramina. There is an association with phaeochromocytoma as part of the Multiple Endocrine Neoplasias (MEN IIb)

**Osteopetrosis**

This is another very logical disorder. The prime defect may be a failure of osteoclasts. Without properly working osteoclasts, the whole bone remodelling process will fare badly, leaving one with short, weak, and oddly shaped bones. With abnormal osteoclasts, one might predict the following abnormalities:

- The bones are very dense. In fact, they are so dense that nothing else really looks like this (except for pyknodysostosis).
- The bones fracture easily, often with a linear fracture plane.
- A proper medullary space is not created as the bones grow. Without a proper medullary space for the marrow, the patient will develop pancytopenia, leading to anaemia, increased problems with infections, and bleeding problems. Because of these complications, few patients with this disorder survive childhood and adolescence, unless they have the "tarda" form of the disease.
- The neural foramina may not grow as the patient and their nerves grow, leading to spinal or foraminal stenosis, especially at the skull base.

**Fibrous Dysplasia**

This idiopathic disorder is due to excessive proliferation of the spindle cell fibrous tissues in bones. Although 2 cases of a congenital autosomal recessive form of fibrous dysplasia have been reported, every other case has been sporadic, without any known hereditary component. Although this process may occur rarely in the cortical bone, the vast majority of cases originate in the medullary space. Therefore, most cases present as bony enlargement with the process seeming to arise from an expanded medullary space.

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7 Pyknodysostosis – rare autosomal recessive lysosomal storage disease with mutation of cathepsin-K found in osteoclasts. Manifestations of dwarfism, osteopetrosis, partial agenesis of terminal digits of hands and feet (5th), cranial anomalies, frontal and occipital bossing, and hypoplasia of the angle of the mandible.
The main clinical significance of this entity depends upon exactly which bones are affected. These bones will exhibit deformity, enlargement, and pain. Occasionally, pathological fractures will develop, and malignant transformation to osteosarcoma is seen rarely (<0.5%).

Two forms of fibrous dysplasia are seen in general radiologic practice: the conventional form (Jaffe-Lichtenstein syndrome) which may be mono-ostotic or poly-ostotic. A poly-ostotic form associated with is McCune-Albright syndrome.

**Gaucher’s Disease**

This familial disorder has no gender predilection, and often occurs in Ashkenazi Jews. The usual form of the disorder is associated with a normal life span, although infantile and juvenile forms may result in mental retardation and an early demise. Gaucher’s is also called sphingolipidosis, oddly enough, because sphingolipids tend to accumulate in the reticuloendothelial cells. If you then consider where the reticuloendothelial cells hang out, you know where to look for abnormalities in the patient with Gaucher’s disease: the liver, the spleen, and the bone marrow. The liver and spleen are usually quite enlarged, as are the reticuloendothelial cells in the bone marrow (sometimes called Gaucher cells). The next concept to consider is that the marrow space in the bone is a closed space. As these Gaucher cells enlarge, the intramedullary pressure begins to rise, which eventually may lead to occlusion of the intramedullary veins and hence bone infarction. As these bone infarcts evolve, one will be able to see the typical findings on MRI and then other imaging methods. The osteonecrosis may also develop in a subchondral location such as the femoral head in about half of patients, leading to subchondral collapse and early arthrosis. These patients may also exhibit other osseous findings, including the so-called "Erlenmeyer flask" deformities of the femoral metaphyses. These widened metaphyses may be seen in 40-50% of patients, and may be due to the marrow packing of the Gaucher’s cells. These patients may also be at increased risk for osteomyelitis.

![Image of knee MRI](image)

**Figure 4 - Sagittal T1-weighted image of the knee demonstrates multiple segmental areas of osteonecrosis in the distal femur in this patient with Gaucher’s syndrome.**

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8 McCune-Albright Syndrome - precocious puberty, endocrine hyperfunction (hyperthyroid, acromegaly, ACTH independent Cushing’s Disease) and café-au-lait spots. Caused by a mutation in the stimulatory G-protein α-subunit. The poly-ostotic fibrous dysplasia is often unilateral
Osteopoikilosis

This disorder is considered to be very common. It is characterised by small round or oval foci of bone sclerosis located in the trabecular bone – particularly in the pelvis, metaphyses and epiphyses of long bones, tarsals, and carpals. The shoulders, hips and sacrum are especially good places to look for these findings. These little deposits of bone are essentially multifocal bone islands. Although some disagreeable things have been associated with osteopoikilosis (subcutaneous nodules, osteosarcoma, spinal stenosis, osteosclerosis, etc...) these associated findings are probably pretty rare. The main clinical significance is that these may be mistaken for sclerotic metastases. Most of the time, their classic distribution and appearance will distinguish them readily from evil entities like metastases.

![Figure 5 - osteopoikilosis of the pelvis and proximal femurs](image)

Dactyly

Various abnormalities of the fingers may be seen, either alone or in association with other findings in a variety of syndromes.

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