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SECTION I – SKELETAL FEATURES OF NEUROFIBROMATOSIS

General Information
Neurofibromatosis is the most frequent single-gene disorder affecting all of mankind. The transmission is on the long arm of chromosome 17. It is autosomal dominant and is a defect in neural crest cells that involve neuroectoderm, mesoderm and endoderm. Two main categories of neurofibromatosis (NF) exist known as type 1 and type 2 while some add two additional categories known as segmental and mixed. Type 2, known as central neurofibromatosis affects only 1:50,000 individuals, is characterized by bilateral acoustic neuromas, but has no skeletal manifestations and thus will not be addressed in this seminar. Neurofibromatosis type 1 (NF-1) is the most common and accounts for ninety percent of the cases. Type 1 is also known as von Recklinghausen disease or peripheral neurofibromatosis. While it is an inherited disorder, approximately half of the cases occur as a spontaneous mutation. There is no race or sex predilection and it occurs in approximately 1:2500 live births. The only known risk is having a dad of advanced age when conceived, so yes, old dads can cause chromosome abnormalities just like old moms. They just cause different defects. NF-1 is manifested as a combination of skin findings, neurofibromas and skeletal alterations. The official criteria for diagnosing NF-1 were developed in 1987 by the National Institutes of Health on Neurofibromatosis. Two of the seven criteria must be met to diagnose a patient with NF-1. The table below lists the criteria.
Table 1. Diagnostic criteria for NF-1

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<tr>
<th>Criteria</th>
<th>Description</th>
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<td>Six or more café-au-lait macules greater than 5mm in greatest diameter</td>
<td>in prepubertal individuals and greater than 15mm in greatest diameter in post-pubertal</td>
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<tr>
<td>Two or more neurofibromas of any type or more than one plexiform</td>
<td>neurofibroma</td>
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<td>Freckling in the axillary or inguinal regions</td>
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<td>Optic glioma</td>
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<td>Two or more Lisch nodules (iris hamartomas)</td>
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<td>A distinctive osseous lesion, such as sphenoid dysplasia or thinning of</td>
<td>the long bone cortex, with or without pseudoarthrosis</td>
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<td>A first degree relative (parent, sibling, or offspring) with NF-1 by the</td>
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Unfortunately, unlike many chromosome abnormalities, NF-1 cannot be diagnosed prenatal because the gene is large, has a high mutation rate, lacks locations where the mutation will arise, and has a variable expressivity.

Key points:
- Neurofibromatosis is classified as NF-1 peripheral neurofibromatosis or NF-2 central neurofibromatosis
  - NF-1 is known to have skeletal changes
- NF-1 is diagnosed based on at least two of seven criteria presented by the National Institutes of Health on Neurofibromatosis
- Neurofibromatosis is a single gene autosomal dominant disorder of neural crest cells

**NF-1 Atlantoaxial Dislocation**

For a chiropractor, probably, the most significant NF-1 finding would be atlantoaxial dislocation. Why NF patients are prone to atlantoaxial dislocation is not fully understood but the theory is that the mesodermal dysplasia is the cause or the presence of neurofibromatous tissue anterior to the odontoid process. No matter the cause, knowing the dimension of the atlanto-dental interspace (ADI) and the stability of this segment is essential for determining proper treatment. The easiest way to determine the ADI is to perform a lateral radiograph. The ADI is measured from the front of the dens to the posterior aspect of the C1 anterior arch. This measurement should be no more than 3mm in adults and 5mm in children. If the ADI is large on the lateral, take an extension radiograph. In an unstable segment, the ADI will diminish with extension. If instability is noted, DO NOT TAKE A FLEXION RADIOGRAPH. Yes, it will take more time in the x-ray suite to take and process the films individually, but you do not want to do a flexion radiograph on an unstable ADI. When an unstable ADI assumes the flexed position, the atlas and axis move away from one another and possibly impinge on the spinal canal. (Figure 1)
In one case report of NF-1 from the 2010 literature, a ten-year old boy presented with acute onset of flaccid quadriplegia from a minor fall due to his ADI instability. You definitely don’t want to be the cause of these symptoms with your high velocity low amplitude adjusting so take the time to process the films in sequence. Advanced imaging that can be used to confirm an enlarged ADI would be magnetic resonance imaging (MRI). MRI can adequately show the impact the ADI is having on the spinal cord and rule out any neurofibromas that may be the culprit. If MRI is unavailable, use an axial CT.

Key points:
- Check for an ADI of greater than 3mm in adults and 5mm in kids
- ADI instability will be evident as an increase in ADI with flexion that decreases on extension radiographs

NF-1 Scoliosis
Scoliosis is the MOST COMMON skeletal manifestation of NF-1. It is believed that the story of the hunchback of Notre Dame was based on a NF-1 patient and although, there is debate, many people believe that “The Elephant Man” suffered from NF-1. From these two examples, the skeletal changes associated with NF-1 can be disfiguring with much
morbidity associated. One such morbidity concern is spinal cord impingement by a displaced rib in scoliosis. Most NF-1 scoliosis occurs in the thoracic spine. While we are often measuring the scoliosis with Cobb-Lippman method or Risser-Ferguson method, we may not think about the contortion of the ribs with this skeletal defect. The intervertebral foramina of NF-1 patients are often enlarged due to neurofibroma eroding the bone, dysplastic bone or meningoceles. (Figure 2a, b shows the enlarged intervertebral foramina in a patient with NF-1). Couple the enlarged neural foramina with a contorted rib and it becomes evident how the rib can impact the spinal cord. In all case reports of rib impingement, the rib entered the spinal canal on the convex side of the curve at the apex, where maximal rotation was evident. In one such case report, the patient felt a “shock” when he rolled on to his right side. Surgery was scheduled to remove the rib for fear of paraplegia development but the rib had adhered to the cord in this case. Much of the rib was removed and the patient suffered no complications. The authors suggested that CT and MRI of the curve apex should be done on severe scoliosis patients with clinical symptoms.

Key points:
- Severe scoliosis with enlarged intervertebral foramina can cause the rib to impinge the spinal cord.

Figure 2a,b. Oblique cervical radiographs of a patient with NF-1
References:

SECTION II – SKELETAL FEATURES OF NF CONTINUE

Assessing scoliosis
The Cobb-Lippman method for scoliosis assessment is probably the most familiar. In this method, a line is drawn along the superior endplate of the most tilted vertebra at the top of the scoliosis and a line is drawn along the inferior endplate of the most tilted vertebra at the bottom of the scoliosis. An angle is created by the perpendiculars drawn from the two endplate lines. (Figure 3)

According to Dr. Grayhack, curves less than twenty-five degrees should be followed until the child stops growing but no major intervention is needed. Bracing is suggested for children with curves twenty-five to fifty degrees. Bracing can have compliance issues because many patients with NF-1 have cognitive impairment, seizures or psychological problems. Dr. Grayhack states that NF-1 patients may suffer from any one of three types of scoliosis. They may have the typical idiopathic juvenile scoliosis seen in other children and is first identified between ages eight and twelve. There is no bone abnormality with this type of scoliosis. The second type of scoliosis is called dysplastic and shows bone abnormalities with sharply angled scoliosis. Non-dystrophic curves can become dystrophic as the child develops and neurofibromas form; therefore, even idiopathic scoliosis cases should be monitored regularly for potential transformation. The last type of scoliosis is the combined kyphosis with scoliosis. This same type of measurement can be used to assess a kyphosis but one would use the lateral radiograph rather than the AP radiograph used in Cobb-Lippman. According to Yochum and Rowe, the normal thoracic kyphosis in females aged ten to nineteen is forty degrees and thirty-nine degrees in males. A complete listing by age of normal thoracic kyphosis measurement is found in the measurements chapter of Yochum and Rowe.
Remember a scoliosis occurs in the coronal plane while a kyphosis occurs in the sagittal plane. (Figure 4a and b).

Bracing is typically not effective for the dysplastic scoliosis and usually an anterior and posterior fusion becomes necessary. Both anterior and posterior fusion is necessary because the unfused section will continue to grow significantly shortening the patient and creating a “crankshaft” deformity. “Crankshaft” is defined as increasing rotation of the spine in the presence of a posterior tether caused by the surgical fusion. While back pain can occur in any scoliosis patient, NF patients typically have more rapid progression, significant pain and abnormal neurologic signs. What bone changes are seen in dystrophic scoliosis? Vertebral scalloping is common and can occur posterior, lateral or anterior (Figure 5). Rib penciling or spindling of the transverse processes is common as well as wedging of the vertebral bodies, soft tissue masses at or within the spine, short curves with apical rotation, foraminal enlargement and defective pedicles (Figure 6). These bone features can be primary or secondary to intraspinal abnormalities. With three or more of these dysplastic features being present, the risk of curve progression increases.
to eighty-five percent. Rib penciling is the most likely dystrophic feature that predicts a progressing scoliosis (Figure 4a).

Figure 5. Posterior vertebral scalloping noted at multiple vertebral levels.

Figure 6. Note the defective pedicle and foraminal enlargement.
The list of dystrophic changes most associated with a rapidly progressing curve include the following: young age at presentation, severity of curve at presentation, kyphosis of greater than fifty degrees, apex of curve in the lower thoracic region, severe apical vertebral rotation of more than eleven degrees and severely notched anterior vertebral body.

Strangely, many of the severe angular deformities have no neurological deficit. The thecal sac expands as a result of dural ectasia at the expense of bone, often causing the scalloping of the vertebra. The widened canal relieves the pressure on the spinal canal. If cord compression is found, anterior decompression via vertebrectomy is suggested followed by fusion. Laminectomy is not effective.

Rarely, thoracic lordosis can occur which results in respiratory compromise and mitral valve prolapse. This is treated with anterior discectomy and posterior fusion. Surgery can be challenging in the NF-1 patient because neurofibromatous soft tissue increases the frequency of postoperative hemorrhage and hematoma. NF-1 patients suffer more from hypertension, renal artery stenosis and pheochromocytoma than the general population.

Whole spine magnetic resonance imaging (MRI) showed 36.3 percent more dysplastic vertebrae than plain film and thus because the dystrophic scoliosis has such an aggressive progression, patients with NF-1 and scoliosis should have a full spine MRI.

As seen in figure 4b, cervical deformities may also be present; therefore, AP and lateral radiographs are necessary. Oblique cervical radiographs can also be helpful to show dumbbell lesions, as shown in figure 6. Cervical kyphosis is the most common deformity in this location often requiring anterior fusion. Most of these kyphoses result from previous surgery that caused vertebral destabilization so be sure to monitor patients with prior cervical surgery.

Key points:
- Abnormal curves in the spine are common in NF-1
- Thoracic scoliosis can be one of three types
  - Idiopathic
  - Dysplastic
  - Scoliosis with kyphosis
- Cobb-Lippman measurements are appropriate to determine the degree of scoliosis
  - This measurement often determines management
- Dysplastic scoliosis is usually rapidly progressing
- Cervical kyphosis can also result usually after previous surgery

Other spinal changes in NF-1
Posterior vertebral scalloping has no defined measurement and is somewhat subjective since the posterior vertebral body is already slightly concave (Figure 5). Even kids without NF-1 who have scoliosis are known to have scalloping but not to the degree of NF-1 patients. Most NF-1 scalloping is evident by age ten. To assess scalloping, lateral radiographs are most appropriate although three-dimensional computed tomography is
the most accurate. Remember that computed tomography has higher radiation than plain film and that children are more susceptible to radiation compared to adults. One study suggested that to make scalloping an objective finding that 4 mm or more of concavity in the lumbar vertebrae should be considered scalloping.

Key point:
- Posterior lumbar vertebral scalloping can be an objective finding if you use a concavity of 4mm or more as the cut-off

Patients with NF-1 suffer from Vitamin D deficiency and low bone mineral density. The problem for NF-1 patients is that their bone has an unusually high turnover and an accumulation of osteoid. Their bone has reduced trabecular bone volume and low calcium content. One study showed that patients with NF-1 have high parathyroid hormone levels. Parathyroid hormone is used to raise blood calcium levels when they are low. Where does the calcium come from that is going to elevate the blood levels? It is coming from the bone. Excessive parathyroid hormone will increase the numbers and activation of osteoclasts that break the calcium out of the bone to put into the blood. The NF-1 chromosome defect is known to have osteoblast-specific inactivation. Osteoblasts are what combat osteoclasts and they deposit bone minerals. Because of this mismatch between osteoblasts and osteoclasts, the patients are prone to osteomalacia. The severity of NF-1 scoliosis and the lack of bone mineral density were directly related meaning that patients with the lowest bone mineral density were the most likely to develop severe scoliosis. Even female children with idiopathic scoliosis without NF-1 were shown to have higher rates of osteoporosis. Thus, assessment of bone mineral density in any child with scoliosis may warrant bone mineral density assessment.

The gold standard for bone mineral density assessment is dual energy x-ray absorptometry (DXA). DXA uses x-ray beams of two different intensities to determine density. It works just like other x-ray equipment where x-ray photons travel through the patient. Dense body parts will not allow many photons to travel through which is called beam attenuation and shows up on film as white areas. Thin body parts do not attenuate the beam and that creates blackness. This works the same way but instead of film being placed behind the patient, sensors hooked to a computer assess the beam. Thus, the denser the bone, the more attenuated the beam and the more osteopenic the bone the less attenuated. The amount of beam received by the sensors can be analyzed against suspected bone density and the results are displayed as z-scores and T-scores. The z-score states how many standard deviations the patient’s bone density is compared to someone of their same demographics. The T-score states how many standard deviations the patient’s bone density is compared to peak bone density. The main concern here is that these scoliosis patients are children and this is a source of ionizing radiation. However, research has shown that giving the patients 1000 IU of cholecalciferol and 1000mg of calcium per day over a year improves bone mineral density so DXA can help to determine treatment. DXA can also detect patients at highest risk for progressive scoliosis and therefore, a cost/benefit analysis should be done before imaging the patient.
Key points:
- NF-1 patients commonly have low bone mineral density
- This low bone mineral density is a predictor of progressive scoliosis formation
- DXA can be used to determine bone mineral density
- Low bone mineral density can be treated with cholecalciferol and calcium

References:

SECTION III- NF-1 FINDINGS BEYOND THE SPINE

Malignant peripheral nerve sheath tumors
As the name implies, neurofibromas are a common feature of neurofibromatosis 1. The most dreaded finding for the NF-1 patient is the malignant peripheral nerve sheath tumor (MPNST). MPNST are found slightly more often in the extremities than in the trunk. Large and medium nerves are the most likely candidates for this malignancy. NF-1 patients have a five percent lifetime risk of developing this tumor. Seventy percent arise from plexiform neurofibromas, commonly seen in NF-1. The patient typically becomes aware of the malignant degeneration of plexiform neuofibromas when there is a new onset of pain, rapid growth or development of neurologic dysfunction. The typical neurofibroma is easily removed surgically but the MPNST is more vascular and invasive. Without complete resection, the prognosis is poor and most cannot be completely resected. In one case study, a thirteen-year-old girl was diagnosed with MPNST and she died only three months after diagnosis. Neurofibromas on T2-magnetic resonance imaging are easily recognized by the target sign. The target sign is a hyperintense rim around a central area of low signal due to the dense central area of collagenous stroma. Magnetic resonance imaging (MRI) cannot clearly distinguish benign from malignant tumors in this case so the best imaging modality is positron emission tomography (PET). Malignant soft tissue tumors have high glucose metabolic rates. This makes intuitive sense because if our own cells need glucose to grow how much more glucose must be needed for something that is growing at a faster rate than our normal cells. PET scans
can trace this glucose through the use of 18F fluorodeoxyglucose-PET (FDG-PET). For a complete understanding of PET, see my course on PET imaging on chirocredit.com. PET can be used to grade the tumor. Higher degrees of FDG uptake mean a worse histologic grade of the tumor because more glucose uptake means a faster growing mass. PET can also be used to pick appropriate biopsy sites if the mass is heterogenous. If the mass was completely benign and has gone through malignant degeneration, the doctor may accidentally biopsy a benign site when malignant areas were available. PET helps to prevent that.

Where PET is unavailable, MRI is the diagnostic imaging modality of choice for evaluating MPNST. MRI has the ability to show the planes of mass invasion, the tumor’s morphology, its margins and any surrounding edema. To look for distant metastasis, computed tomography is indicated and the chest is the main location of screening. Metastasis occurs in descending order in the lung, bone and pleura. Fifty percent will show local recurrence and fifty percent will show distant recurrence.

Beyond surgical resection, treatment can include radiation and chemotherapy but mortality is high for these tumors.

Key Points:
- Malignant peripheral nerve sheath tumors arise from plexiform neurofibromas which are commonly found in NF-1 patients
- Malignant peripheral nerve sheath tumors have a high mortality due to the difficulty in achieving a full resection and common recurrence or metastasis
  - Metastasis usually occurs in the lung, bone or pleura

While MPNST tumors are scary, most tumors on NF-1 patients are benign neurofibromas. Neurogenic tumors in NF-1 can involve the cerebrum, spine, cranial nerves or peripheral nerves. The neurofibroma is a peripheral nerve sheath tumor associated with Schwann cells, perineural cells and fibroblasts. These growths can occur as focal dermal, cutaneous or subcutaneous growths. They can occur in the spinal nerves located in the intervertebral foramen or be diffuse plexiform neurofibromas. Spinal neurofibromas are classified into two groups - (a) one or few spinal tumors and (b) multiple bilateral spinal tumors. From this list, it is obvious that there are lots of manifestations of neurofibromas. One case report diagnosed a patient with NF-1 based on the presentation of a spontaneous pneumothorax. The CT of the patient showed pleural based soft tissue masses arising from the neuroforamina. In this case, the neurofibroma caused the pneumothorax. Neurofibromas can also occur in the abdomen.

Other NF-1 tumors
There are five types of tumors that occur in the abdomen in NF-1 patients and they include: neurogenic tumors (neurofibromas, malignant peripheral nerve sheath tumors and ganglioneuromas), neuroendocrine tumors (pheohromocytomas and carcinoids), nonneurogenic gastrointestinal stromal tumors (GIST), embryonal tumors, and miscellaneous. You always need the undefined category for patients who don’t read the textbook before they decide to get a disease. The reason for so many tumors in NF-1 is
because the gene mutation affects a tumor suppressor gene. Beyond the abdomen, patients are prone to gliomas, ependymomas, lymphomas, myeloid leukemia, Wilms tumor, and breast cancer.

While neurofibromas and MPNST have been discussed, let’s look at a few of the other tumors found in NF-1. Ganglioneuromas are benign and arise from the sympathetic ganglia and so are located paravertebral. GISTs are mesenchymal neoplasms and usually originate in the bowel and are rarely solitary. GIST tumors often present with abdominal distension, palpable mass and pain. Adrenal pheochromocytomas have a clinical presentation consisting of hypertension, palpitations, flushing and headache. Patients with NF-1 need an annual clinical evaluation because these various tumors can cause complications such as hemorrhagic obstruction of the bowel, organic complications, or malignant transformation.

Meningioma is not technically a neoplastic tumor but it is a mass and therefore is most appropriately discussed in this section. NF-1 patients are prone to development of meningiomas that are hamartomas arising from dural fibroblasts. One case reported a nine-year girl with a history of headache and vertex mass. A meningioma had invaded her dural and sagittal sinus. The mass was resected and the area was irradiated.

NF-1 patients have a 84% cumulative risk for developing breast cancer under the age of fifty. The connection between NF-1 and breast cancer is the Breast Cancer 1 (BRCA-1) and the NF-1 genes are found in close proximity on chromosome 17. Because of their skin masses, most breast cancers are missed by NF-1 patients on self-breast exams until the cancer is quite advanced. Therefore, the prognosis is dismal. As a result, NF-1 patients should begin mammograms at age 40.

Key points:
- The five abdominal tumors found in NF-1 include the following: neurogenic tumors, neuroendocrine tumors, nonneurogenic gastrointestinal stromal tumors, embryonal tumors, and miscellaneous
- These tumors can cause complications such as bowel, organic complications, or malignant transformation therefore annual clinical evaluation of NF-1 patients is suggested.
- Meningiomas are not neoplastic tumors but they are masses that occur in NF-1 patients.
- Annual mammograms should begin at age 40 for NF-1 patients due to their increased risk of breast cancer.

Vascular complications
While only five percent of NF-1 patients suffer from vascular abnormalities, the finding can be significant. The most common sites of arterial lesions are in descending order of occurrence and include: aorta, renal, cerebral, subclavian. The reason for the vascular compromise is because of the alteration of the normal process of vessel repair and maintenance regulated by neurofibromin. Many of these lesions are asymptomatic and usually involve multiple vessels. The result can be either stenosis or aneurismal. The
features of rupture include the following: pain, hemothorax, expanding mass, dypnea, and dysphagia. In one case report, the thrombosed fusiform aneurysm compressed the cervical nerves and the presentation was progressive radiculopathy.

Key points:
- NF-1 patients are prone to stenosis or aneurysm as a result of vasculopathy.

Strange case
I would like to close this talk on NF-1 with a patient who met the criteria for NF-1 and NF-II. The patient had two of the seven criteria required for NF-1 and presented with imbalance, tinnitus and hearing loss due to vestibular schwannomas. There have only been two reported cases of a patient qualifying for both NF-1 and NF-II at the same time. This shows that there is great diversity in NF patients and that the presentation for NF-1 and NF-II can have overlapping features.

Key points:
- While extremely unusual, it is possible to have NF-1 and NF-II in the same patient.

References:

SECTION IV – PAGET’S DISEASE

Figure 7a and b. Osteosarcoma secondary to Paget’s disease
Osteosarcoma (Figure 7)
I will start the discussion of Paget’s disease with the one thing that you MUST not miss when using plain film to assess Paget’s disease patients. The biggest fear for Paget’s patients is the development of osteosarcoma because the tumor is usually rapidly fatal.

Paget may have been the sixth person to describe Paget’s disease, also known as osteitis deformans, but he was the first to associate the disease with malignancy. Bone sarcomas are the most serious complication of Paget’s disease while none of the malignancies are a common finding in these patients. Osteosarcoma is seen in about one percent of Paget’s patients but when found, the prognosis is poor. Most osteosarcoma victims will succumb to the disease with the most common site of metastasis being the lung. Fifty-three percent of patients with sarcoma are alive after one year, twenty-five percent after two years and none survive beyond five years. Metastasis is quick due to the increased vascularity seen in Paget’s disease. Most patients are elderly and too frail to undergo chemotherapy.

Patients at highest risk of developing osteosarcoma are those with multifocal Paget’s disease, patients in the sixth and seventh decades of life and males are more likely to develop the malignancy. Osteosarcoma development has been linked with the distal portion of chromosome 18q. Osteosarcoma commonly occurs at the site of fracture but whether the fracture incited the tumor or the tumor resulted in fracture is undetermined. What is known is that one third of osteosarcoma Paget’s patients have a pathologic fracture in the area of the sarcoma. Locations for sarcoma occur in the following bones in descending order: femur, pelvis and humerus. Beyond osteosarcoma, patients are at higher risk for developing fibrosarcoma and possibly chondrosarcoma.

On plain film, the tumor will usually show lytic predominance. It will look aggressive meaning that the pattern is ill-defined and permeative within an already Paget diseased bone. Most will show cortical destruction and soft tissue mass. Bone scan using technecium-99m will show a photopenic area among the increased activity normally seen in Paget’s bone. Paget’s bone will show increased activity on bone scan due to the hypervascular nature of the disease. Magnetic resonance imaging and computed tomography are typically not indicated. Sarcoma will show as absent normal marrow fat on magnetic resonance imaging and computed tomography. The absent fat will show as low on T1-weighted and high on T2-weighted magnetic resonance images.

Key points:
- Paget’s disease patients have a small increased risk of developing osteosarcoma and perhaps fibrosarcoma or chondrosarcoma
- Osteosarcoma is aggressive and has a poor prognosis
- Osteosarcoma is easily identified as a lytic, ill-defined permeative lesion in a Paget’s disease bone
General information
Now that I’ve gotten the scariest part of Paget’s disease out of the way, let us now look at what Paget’s disease is all about. This is the second most common metabolic bone disease after osteoporosis. It has a prevalence of approximately five percent. There is a slight male predominance. It can present in one bone or many but it is not progressive meaning that whatever bone or bones it starts in will likely be the only bones ever affected by the disease. One interesting feature is that if Pagetic bone is used in bone grafting, the disease can transfer to the grafted bone. While most cases are asymptomatic and become an incidental finding on plain film, some patients suffer from bone pain, skeletal deformities, increasing hat sizes or deafness and pathologic fractures. The bone pain is typically described as being worse at rest and relieved by movement, which may help to differentiate Paget’s disease from the common osteoarthritis. Osteoarthritis typically has pain in the evening after overuse all day. Pain in Paget’s disease is typically found in the skull and left lower extremity.

The cause of Paget’s disease is unknown but several predisposing features are seen. For one, patients typically have Anglo-Saxon ancestry, especially those from England. The prevalence of Paget’s disease in an area directly correlates with population migrations from England. For example, Australia and New Zealand also have higher incidences of Paget’s disease than other areas because they were settled by the English. The indigenous people of these countries do not get Paget’s disease and the almost zero incidence of Paget’s disease in Africa suggests that Paget’s disease has a genetic predisposition. Only recently have several cases been reported in South India. Some studies have shown mutations in the gene SQSTM1 that encodes for p62. While half of patients with Paget’s disease do not have this mutation, those with the affected gene tend to show a greater severity to the disease.

There must be more than genetics involved however, because family members carrying the same gene often do not show the same severity in the disease state. The other issue is that the disease is showing up later and in few people. In those with the SQSTM1 mutation, the disease is showing up about a decade later than in previous generations. The disease is of less severity than their parents and although people are living longer, the incidence of Paget’s disease is on the decline.

As with most disease, a genetic factor only predisposes a person to contracting a disease but an environmental trigger must initiate its start. Paget’s patients have abnormal osteoclasts, the cells responsible for breaking up bone during the normal bone turn-over process. Observations of the osteoclasts have detected paramyxoviral-like nuclear inclusions suggesting that a virus may be the inciting event to the development of Paget’s disease. The nuclear inclusions cross-reacted with antibodies against respiratory syncytial virus and measles virus. Another linkage is with canine distemper virus and most Paget’s patients were seen to be in possession of dogs. Thus, there appears to be a linkage between Paget’s disease and paramyxoviruses although other studies have not shown this correlation. It is speculated that the decreasing incidence of Paget’s disease may be the widespread vaccination for measles in humans and distemper in dogs. On the other hand, the ubiquitous nature of measles prior to immunization and yet the disease
being restricted to Western Europeans supports the genetic theory. Plus, measles is usually an infection of children so why doesn’t Paget’s disease occur before the age of fifty. While this debate could go on without ceasing, the answer is probably a mixture of viral and genetic.

While the cause is unknown, the pathology is understood quite well. The disease is characterized by a localized excessive out of control osteoclastic bone resorption. This creates a lytic look to the bone. This process is compensated for by an increased osteoblastic activity. With this transition, the bone will look mixed lytic and blastic. With the predominance of the osteoblastic phase, the bone will increase in density. The fast osteoblastic bone deposition results in an unstable, unorganized bone pattern with unstructured fibroblasts. This makes the bone less stable in general. These bone changes will result in elevated levels of alkaline phosphate which are found in the blood and thus this blood test can help with diagnosis of Paget’s disease.

Key points:
- Paget’s disease is the second most common metabolic disease after osteoporosis
  - The age of onset is increasing and the incidence of disease is decreasing
    - This change may be a result of vaccination for distemper and measles
- Paget’s disease is found in Western Europeans and in areas where they have migrated
- Paget’s disease is characterized by an increased and rapid osteoclastic response with rapid osteoblastic compensation, lacking the organization of normal bone
- The worst complication is osteosarcoma but luckily only about one percent of Paget’s patients will develop this malignancy.

References:
SECTION V –

Plain film appearance of Paget’s bone

The first stage, the osteolytic phase, is characterized by a metaphyseal lytic lesion. The area involved is geographic with a clear delineation between Paget’s bone and normal bone. The lesion is expanded in the epiphysis and diaphysis and has been called the blade of grass or candle flame appearance. This phase is typically not detected in bones with high trabecular:cortex ratios. These bones consist of the vertebrae, sacrum and pelvis and they are typically first identified once the bone has begun the sclerotic phase (Figure 8). If by rare chance, a vertebra is seen in the lytic phase, it will present with osteopenia and has been called the “ghost vertebra”.

![Figure 8](image)

Figure 8. Both images show Paget’s disease in the pelvis. The right image also shows sclerosis in the left femur.

The mixed phase is next where sclerotic areas are evident presenting as a coarsening of the trabecular markings. The bone will be expanded and vertebrae are often called “picture frame” due to the thick cortical regions that trim the bone on film (Figure 9). The most common mechanism of bone expansion is due to periosteal apposition and endosteal absorption. The osteoblasts predominate in the periosteum and the osteoclasts predominate in the endosteum causing the vertebra to enlarge and the marrow space to expand. Sixty-three percent of Paget’s patients will show an enlarged vertebra on x-ray. The enlarged vertebra is circumferential and thus one complication can be the narrowing of the spinal canal causing spinal stenosis. While the girth of the vertebra has enlarged the vertical height of the vertebra remains unchanged. Sometimes the coarse trabeculae of the spine have been called “Rugger-Jersey spine” and must be differentiated from renal osteopathy or hyperparathyroidism. Spine involvement is most common at the L4 or L5 vertebral levels with thoracic being of intermediate incidence and cervical being the most rare. Both the body and neural arch are typically involved. These latter two locations do not show bone enlargement however. The neural arch is best assessed with CT. If the neural arch is involved, the facets are likely to be involved too. They present
with enlargement and sclerosis as well. Deformities in the pelvis may begin with protrusio acetabulae or hip osteoarthritis occurring. Protrusio acetabulae is exactly what it sounds like with the hip migrating into the pelvic bowl and protrusion of the acetabulum into the pelvis.

Figure 9. Note the vertebra is expanded circumferentially but not vertically. The lateral shows the “picture frame” vertebra.

Figure 10. Paget’s disease in the lower extremity long bones of two different patients. The next stage is the sclerotic phase where the remodeled bone is greater in volume and density (Figure 10). The expanding bone may cause nerve impingement or worse yet,
deafness. In the spine, the sclerosis may create the “ivory vertebra” where the entire vertebra is whiter than those surrounding it. The concern with the “ivory vertebra” is that it must be differentiated from more serious conditions such as metastasis, osteosarcoma, carcinoid and Hodgkin’s lymphoma, all of which are known to present with an “ivory vertebra”. The key is that these other diagnoses will not have expanded bone. On MRI, the whole vertebra will be low on T1- and T2 weighted images. The vertebral body affected by Paget’s disease will often interfere with intervertebral disc nutrition and thus incite degenerative disc disease. The sclerotic endplates do not allow for nutrient diffusion into the disc. Occasionally, radiographs will detect ossification in the anterior longitudinal ligament, posterior longitudinal ligament or ligamenta flava in Paget’s disease of the vertebra. Paravertebral swelling may also be seen on radiographs due to extra-medullary hematopoiesis.

The last stage, if it occurs at all, is the malignant degeneration. In the previous section, we discussed the bone malignancies of highest concern but remember that Paget’s disease is considered a tumor-like process. The lytic foci of Paget’s bone can appear to be a malignancy. This pseudotumor can easily be mistaken as a neoplasm and can occur with a single lesion or in multiple foci. The proliferation of periosteum can be mistaken as tumor and has been termed pseudosarcoma. MRI may be helpful because Paget’s bone will not have a true soft tissue mass unlike the sarcoma counterparts. Fat inside the mass is suggestive of pseudosarcoma and not osteosarcoma.

A fifth stage is sometimes suggested and is referred to as the “inactive sclerotic phase”. This stage is characterized by normal bone activity, meaning that the stimulation of new osteoblasts and osteoclasts is finally over. This is a physiological stage because from a radiological standpoint nothing has changed. The bone will continue to be sclerotic in appearance.

Some benign tumors occur with higher frequency in Paget’s bone with giant cell tumors being the most documented. Giant cell tumor is most frequent in polyostotic Paget’s disease and unlike naturally occurring giant cell tumors, Paget’s patients develop giant cell tumors at a more advanced age and in the skull or facial bones.

Some other secondary consequences of Paget’s disease can be post-immobilization lysis. After immobilization or fracture, Paget’s bone can go through an accelerated disuse osteoporosis that can look like malignancy. MRI can help differentiate osteoporosis from malignancy because there will be no soft tissue mass and there will be fat in the affected Paget’s bone. Lastly, a tumor-like appearance can occur with bisphosphonate use. The bone develops osteomalacia and thus looks to have malignant marrow infiltration. In general, remember that secondary malignancies are rare in Paget’s disease and thus a doctor should not be overzealous to call suspicious lesions malignant.
Key points:
- Plain film will show lytic lesions in stage 1, mixed sclerotic and lytic in stage 2, sclerotic enlarged bone in stage 3, and perhaps stage 4 which is malignancy or stage 5 inactive sclerotic phase
  - Most perceived malignancies in Paget’s bone are due to the lytic lesions, the periosteal bone formation, post-immobilization osteoporosis, or bisphosphonate induced osteomalacia
    - To differentiate malignancy from typical Paget’s disease, order MRI
      - Paget’s will show fat in the marrow and will not have a soft tissue mass
- Benign tumors like giant cell tumor occur with higher frequency in Paget’s patients than in the general population

**Treatment for Paget’s disease**
The goal for Paget’s disease treatment is to reduce bone pain and slow the bone resorption. Bisphosphonates and calcitonin are the drugs of choice. The issue with calcitonin is that after long-term use, calcitonin ceases to work with the same dosage. It’s kind of like drug addicts; in order to get the same “high” over time, higher and higher doses of the narcotic are needed. Eventually, in order to get that same “high”, overdose levels are needed. The same thing occurs with calcitonin. Over time, the body builds a resistance to the medicine. Thus, bisphosphonates have largely replaced calcitonin as the most common medicine prescribed. Intravenous Zoledronate is the most potent bisphosphonate used and produces biochemical remission of Paget's disease in 89% of patients.

Surgery is a common occurrence due to Paget’s bone complications. Secondary osteoarthritis occurs and thus knee and hip replacements are likely. The fragile bone commonly fractures and thus orthopedic surgical pinning occurs. The deformities like femoral bowing and protrusio acetabulae may result in surgery. The enlarging bone can cause spinal stenosis and thus spinal decompression may be warranted. Of course, there is the small percentage of patients who will need tumor resection.

While surgical management can greatly improve quality of life, Paget’s disease does complicate surgical procedures. The hypervascular nature of the disease can cause excessive surgical bleeding. Paget’s patients are prone to delayed union, compartment syndrome and heterotopic bone formation. Thus, conservative treatments should be exhausted before surgery is considered.

Key points:
- Bisphosphonates and calcitonin are medications commonly given to reduce bone pain and slow the disease progression
- Orthopedic surgery commonly improves quality of life
  - The biggest concerns with surgery are the increased risk of excessive bleeding, delayed union, compartment syndrome and heterotopic bone formation.
References