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Fibrous Dysplasia, Paget’s Disease and Uncommon Bone Lesions of the Craniofacial Bones.

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Abstract

Imaging studies of the brain, head and neck, sinuses and dental CT are among the most frequent performed procedures in radiological departments. Systematic evaluation in bone window may reveal common and uncommon sclerotic osseous abnormalities of the craniofacial skeleton.

Most of these findings are incidental and unrelated to the initial clinical indications. Sporadically symptoms may arise due to lesional mass effect with compression on adjacent structures and neuroforaminal encroachment, resulting in proptosis, vision or hearing loss. Other symptoms include craniofacial deformity, mandibular occlusion deformity and local pain.

This article reviews the most common disorders characterized by an increased bone density involving the craniofacial bones, including Fibrous Dysplasia, Paget's disease, meningioma with associated hyperostosis and osteoma. Finally, typical examples of more rare sclerosing bone dysplasias will be discussed as well.

Emphasis will be placed on imaging features and the differential diagnosis.

Keywords

Fibrous dysplasia; Paget's Disease; Sclerotic bone lesions; Craniofacial bones;
Meningioma with hyperostosis.
Fibrous dysplasia

Definition

Fibrous dysplasia (FD) is a benign, non-hereditary condition in which normal bone structure is replaced by expanding cystic and/or fibrous connective tissue. The entity was first described by Von Recklinghausen 1891 and later termed ‘Fibrous Dysplasia’ by Lichtenstein and Jaffe in 1938\(^1\). FD can be either monostotic (80%) or polyostotic (20%), with craniofacial bone involvement occurring in 25% of the monostotic form and up to 50% in the polyostotic subtype\(^3\). McCune-Albright syndrome consists of polyostotic FD with ‘café-au-lait’ skin spots and associated endocrinopathies, such as hyperparathyroidism, acromegaly or Cushing’s syndrome.

Histopathology

Three different histological subtypes can be distinguished. The first is called the ‘Chinese writing’ or ‘Alphabet soup’-pattern, referring to its typical thin and disconnected trabecular bone on a largely fibrous background. This subtype seems to correlate with the well-known ‘ground glass’ imaging appearance of FD\(^4\).

Secondly, the ‘Pagetoid’ subtype is characterized by a predominant dense sclerotic trabecular bone and a less prominent fibrous component. This subtype is mainly found in craniofacial FD. Thirdly, the ‘hypercellular’ form consists of large amounts of osteoid tissue ordered in a parallel fashion, often with discontinuous trabeculae\(^5\).

Prevalence & Etiopathogenesis

The pathologic bone metabolism of FD consists of an overstimulation of osteoblasts, resulting in formation of dysplastic bone\(^6\). 75% of patients are younger than 30 years
old and patients with the polyostotic form even present under the age of 10. FD is equally distributed amongst men and women. Overall FD accounts for 2% of all bone tumors and 5-7% of all benign bone tumors.

Clinical features

Involvement of the craniofacial bones often presents with painless enlargement of the affected bone and consequent facial asymmetry. The most commonly affected facial bone is the zygomatico-maxillary complex and the sphenoid bone. Mandibular involvement is rare (online supplementary Fig. 1). Mild hearing loss in temporal bone involvement is a less common complication. Vision loss due to orbital involvement is only reported in 5%. Development of aneurysmal bone cysts in FD foci is possible and may contribute to rapid progressive symptoms due to compression on adjacent structures. Malignant transformation to osteosarcoma, chondrosarcoma, fibrosarcoma or fibrohistocytic sarcoma (formerly known as malignant fibrous histiocytoma) is reported to occur in 2.5%. This degeneration is associated with radiation exposure or hormone therapy.

Imaging findings

Although ground glass opacity is typically seen in FD (Fig. 1), the radiographic appearance of FD may show cystic to sclerotic and mixed patterns (Fig. 2A & online supplementary Fig. 2), therefore imaging findings are not always pathognomonic. The ground glass appearance histologically originates from small, thin, calcified, woven trabeculae in fibrous stroma. Change of imaging appearance throughout follow-up has been documented, but spontaneous resolution has not. The involved craniofacial bone usually shows expansion. The mixed pattern of FD
can exhibit similar findings to Paget's Disease, hence also termed the ‘Pagetoid’ subtype, which may cause a diagnostic dilemma. In Table 1 we summarize diagnostic clues, which may aid the differentiation between FD and PD.

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Interpretation of MRI may be more confusing than CT because of the wide range of signal intensities, enhancement patterns and the inability to evaluate the bone matrix. The cystic subtype is of intermediate to low signal intensity on T1-Weighted Imaging (WI) and high on T2-WI ( Fig. 2B-C). In case of the sclerotic or Pagetoid subtype, the signal intensities are low on T2-WI. The degree of enhancement is variable, ranging from subtle to vivid. Enhancement pattern may also vary from central patchy, peripheral rim, heterogeneous ( Fig. 2D) or homogeneous.

**Paget disease of bone**

**Definition**

Paget disease (PD) consists of a multi-phasic, abnormal and excessive bone turnover, resulting in a distorted architectural appearance of bone. It was first described as ‘osteitis deformans’ by the English surgeon and pathologist Sir James Paget in 1877. PD can be mono-ostotic (50%) or polyostotic. Virtually any bone of
the human body can be affected with the pelvis (73%), spine (53%), skull (25-65%) and femur (25-35%) being the most frequent sites\textsuperscript{13}. Mono-ostotic craniofacial bone involvement is rare. There are some sporadic reports of isolated mandibular involvement\textsuperscript{14–16}.

Histopathology

Histologically, three consecutive phases are seen. The first \textit{active} or \textit{lytic} phase exhibits bone resorption, followed by a mixed phase of bone resorption and deposition and ultimately a sclerotic phase\textsuperscript{17}. On a microscopic level, osteoblastic activity predominates. Fibrovascular tissue replaces normal fatty marrow\textsuperscript{18}. The number of osteoclasts in PD foci are increased in numbers and exhibit a significantly higher amount of nuclei compared to normal osteoclasts, up to more than 100 per cell. The second phase is characterized by increased osteoblastic activity. New disorganized woven bone is produced in a typical ‘mosaic’ pattern, which is mechanically weak. The disappearance of the physiological border between cortex and medulla can be observed. Although the fibrovascular component persists, it is less prominent. In the third phase \textit{mineral deposition} by osteoblasts results in a significant ossification\textsuperscript{17}.

Prevalence & Etiopathogenesis

According to Poör et al., the prevalence of PD is generally declining, but increases with age, affecting 2% of the Anglo-American population above the age of 55\textsuperscript{19–20}. There is a slight male predilection with a 1,6:1 male-female ratio\textsuperscript{21}. Currently it is believed that the etiology is complex and several genes have been postulated as causative factors\textsuperscript{22}. 
Clinical features
PD remains mostly asymptomatic. Complaints arise in 15% of affected individuals with bone pain being most common. Craniofacial involvement causes increased head size and possible cranial nerve compression\textsuperscript{23}. Deafness is reported in up to 85% of cases with temporal bone involvement\textsuperscript{24}. Transformation to osteosarcoma (1%), chondrosarcoma or giant cell tumor is a well-known albeit rare complication\textsuperscript{25}.

Imaging findings
‘Osteoporosis circumscripta’ represents the characteristic radiographic and CT-appearance of the first, lytic phase (\textbullet{} Fig. 3A), consisting of a focal radiolucent area with sharply demarcated borders. The T1-signal will be lower than normal bone marrow and isointense to muscle, with interspersed areas of normal fatty bone marrow. The presence of remnants of normal bone fatty marrow is an important discriminator with a malignant osseous process, that will not exhibit normal yellow marrow\textsuperscript{23}. T2-signal is high in this phase and enhancement is present, owing to its hypervascularity\textsuperscript{26}. Due to the hypervascular nature of PD, scintigraphy will show increased uptake even before lytic area’s develop on CT\textsuperscript{18}.

In the second mixed phase, skull radiography may exhibit the characteristic ‘cotton wool’ appearance. This imaging feature corresponds to lytic foci, interspersed with nodular areas of thickened trabeculae (\textbullet{} Fig. 3B-C), which may mimic osteoblastic metastases\textsuperscript{26}. On panoramic radiography, mandibular or maxillary involvement shows root resorption of teeth during the lytic phase and gradual hypercementosis in the mixed phase. Bone expansion will result in increased spacing between teeth\textsuperscript{27}. CT will show a disorganized, coarse trabecular pattern, with cortical thickening and
bone deformity. In the early mixed phase MRI will demonstrate an overlap in the first phase, with a heterogenous ‘speckled appearance’ due to enlarging fibrovascular components and abnormal, disorganized bone mineralization. The most common encountered MR-imaging pattern – however -, occurs in the relative longstanding, late mixed phase, showing preservation of areas of normal fatty marrow signal on all MR-pulse sequences.

The last sclerotic phase is characterized by bone thickening and sclerosis on radiography and CT. The affected areas will appear hypointense on all pulse sequences. There will be no abnormal radionucleide uptake in this late phase and thus bone scintigraphy will appear false negative. Potential neuroforaminal narrowing must always be reported. MRI is particularly suitable for evaluation whenever sarcomatous degeneration is suspected.

**Meningioma and hyperostosis**

**Definition**

A meningioma-en-plaque (MEP) describes a lesion composed of proliferating meningeal cells with a broad and flat dural base and associated (diffuse) hyperostosis of the overlying bone. Intra-osseous meningioma (IOM) is similar to MEP but the term IOM is restricted to lesions with bone involvement, without any intracranial extension or dural invasion.

**Histopathology**

Bone marrow is replaced by fibrosis, fat and tumor cells from meningotheelial origin. Prominent eosinophilic tumor cells with nuclear pseudoinclusions and psammoma
bodies, concentric dystrophic calcifications, can be seen as well\textsuperscript{32}. The overlying hyperostosis may be of reactive nature and does not necessarily imply bone infiltration of tumor cells at a MEP\textsuperscript{33}.

Prevalence & Etiopathogenesis

Although a certain degree of reactive hyperostosis is a common finding in a meningioma, MEP and IOM are regarded as separate entities, representing less than 2\% of all meningiomas\textsuperscript{23}. Men and women are equally affected, unlike the common type of meningiomas which occurs twice as often in women\textsuperscript{34}. The peak incidence is around the second decade in contrary to common intradural meningiomas\textsuperscript{34}. IOM are usually located in the frontoparietal and periorbital region, often in close proximity to a suture. This supports the hypothesis that during closure of the craniofacial sutures, meningeal cells can become entrapped inside bone\textsuperscript{32}.

Clinical features

MEP and IOM often remain asymptomatic and are usually discovered incidentally as sclerotic foci in the skull. Local mass effect may cause ophthalmoplegia, proptosis, visual defects, headache, tinnitus and hearing loss.

Imaging findings

Differentiation between meningioma with reactive hyperostosis, MEP and IOM solely on imaging is challenging as a similar presentation may be seen. On radiography and CT the hyperostotic component is readily evaluated as a sclerotic lesion with irregular and spiculated borders (\textsuperscript{Fig. 4A}), which may simulate a malignant primary bone tumor. Another possible differential diagnosis is an osteoblastic metastasis. These
are – however - often multiple and knowledge of a primary tumor, such as prostate carcinoma, is often the clue to the correct diagnosis. In these cases reactive thickening of the overlying dura might be mistaken for plaque-like tumor component, which enhances similar as MEP. Rarely IOM present as osteolytic lesions. The T1-signal of affected bone is hypointense (Fig. 4B). Signal intensity on T2-weighted images can be variable (Fig. 4C & supplementary Fig. 3C). MEP is characterized by a plaque-like dural tumor component which enhances (Fig. 4D & supplementary Fig. 3E). Enhancement is absent in the intra-osseous component.

**Osteoma**

**Definition**

Osteomas are benign, nodular, pedunculated or sessile tumors most commonly arising from the extern table and rarely from the inner table of the calvaria. The lesions are mostly located in the head and neck region, often found in the paranasal sinuses, the temporal bone or less frequently in the jaw. Involvement of the craniofacial bones is rare. Of the paranasal sinuses, the frontal sinus is most frequently involved (online supplementary Fig. 4A-B) followed by the ethmoid sinus, the maxillary antrum and the sphenoid sinus. They can be either solitary or multiple, as found in the Gardner Syndrome (online supplementary Fig. 5A-B), where they are associated with soft tissue tumors, gastro-intestinal polyps and multiple supernumerary impacted teeth.

**Histopathology**
Osteomas are composed of dense, compact or cancellous bone with broad trabeculae and a paucicellular fibrous stroma. They are covered with a thin, layered periosteum lined with osteoblasts and osteoclasts. They blend in seamlessly with the underlying normal cortex\textsuperscript{36}.

Prevalence & Etiopathogenesis
Men are affected more than women and the lesions are commonly diagnosed incidentally in the fourth or fifth decade\textsuperscript{36}. The origin of the lesion may be either congenital, inflammatory or reactive to osteogenic stress such as trauma or muscle activity.

Clinical features
Osteomas are often asymptomatic until a certain size. Symptoms may arise due to local mass effect and may include headache, trismus, sinusitis due to obstruction and occlusion disturbances in case of mandibular involvement. Large lesions can cause facial asymmetry or even erode into the dura mater\textsuperscript{37}.

Imaging findings
Plain film and CT findings include a well-defined, homogenously dense nodular bone lesion located adjacent to the cortex (\textsuperscript{5A-B}). MRI reveals a low T1 signal and a variable T2 intensity, dependent to the amount of fibrous components (online \textsuperscript{supplementary Fig. 6A-B}). Osteomas may be misdiagnosed as ossified meningiomas, although osteomas do not entail an enhancing dural component (online \textsuperscript{supplementary Fig. 7})\textsuperscript{38}. 
Hyperostosis frontalis interna

Definition
Hyperostosis frontalis interna (HFI) consists of new bone formation at the intern table of the frontal bone, often with a multinodular appearance. There is typical sparing of the external table of the frontal bone and the midline is almost always unaffected\textsuperscript{39}.

Histopathology
Microscopic evaluation of HFI specimens exhibits normal external table morphology, but prominent remodeling of medullary cavities with irregular shape and size and increased cancellous bone in the diploe\textsuperscript{39}.

Prevalence & Etiopathogenesis
HFI occurs in 12\% of the general population, with relative frequencies of 25\% in women and 5\% in men. The incidence increases with age and HFI is more prevalent in post-menopausal women, obese patients and in males with severe hypogonadism, testicular atrophy or castration\textsuperscript{40}. HFI may be associated with several syndromes but is generally considered to be an isolated condition\textsuperscript{41}.

Clinical features
There are hardly any symptoms. Local mass effect and compression on brain tissue are a very rare occurance. Neuropsychiatric disorders and links between HFI have been investigated, but failed to deliver any significant proof\textsuperscript{39}.

Imaging findings
HFI is often incidentally discovered on CT imaging as irregular, nodular thickening of the internal table of the frontal bone (online supplementary Fig. 8). HFI can be differentiated with hyperostosis cranii ex vacuo, a condition often associated with intracranial hypotension.

**Intra-osseous Hemangioma (Venous Malformation)**

**Definition**

The term intra-osseous hemangioma (IH) is currently considered as a misnomer and the term venous malformation (VM) is preferred\(^43\). The lesion consists of a benign, slowly growing, highly vascular lesion within the diploe of the skull.

**Histopathology**

Often VM are not entirely composed of venous tissue but contain a considerable lymphatic component. Microscopically a VM demonstrates thin walled, dilated veins and lymphatic tissue filled with serous fluid\(^43\). Fat content is variable and it appears that less fat content and more vascular components correlate with more aggressive growth\(^23\).

**Prevalence & Etiopathogenesis**

Slow flow VM are generally found in up to 1% of the general population and represent 2-10% of benign skull lesions\(^23,43\). VM often present in the 4\(^{th}\) – 5\(^{th}\) decade and women are more often affected than men. The frontal bone and the parietal bone are most commonly involved at the calvarium. The clivus might be involved as well\(^44\).
Clinical features

Most lesions are incidental imaging findings. Symptoms may arise due to local mass effect such as proptosis at orbital involvement. VM predominantly affect the outer table and thus the main presenting symptom is a palpable scalp lesion. There are some sporadic reports of intracranial expansion and even dural tail enhancement\(^{45}\).

Imaging findings

On radiography and CT, VM may exhibit aggressive growth patterns such as the sclerotic ‘sun burst sign’ and mimic malignancy (\(\text{Fig. 6A}\)). This appearance is the result of trabecular thickening accompanying an osteolytic component representing the angiomatous channels\(^{23}\). The inner table is often spared. The uptake on bone scintigraphy is variable and may be decreased, increased (\(\text{Fig. 6B}\)) or normal uptake \(^{46}\). FDG-PET CT is reported to exhibit increased uptake in (vertebral) VM\(^{47,48}\). On MRI these lesions are typically hyperintense on T2-WI (\(\text{Fig. 7C}\)), often exhibiting the characteristic ‘bunch of grapes’ sign or ‘spoke wheel’ sign. VM enhance vividly after injection of gadolinium contrast (\(\text{Fig. 7A-B}\)). Treatment of these slow flow lesions are dependent of symptoms, extensiveness and location and consists of analgesia, endovascular treatment (\(\text{Fig. 7D}\)), or surgery\(^{43}\).

**Sclerosing Bone Dysplasias**

There is a variety of rare genetic bone diseases that may cause craniofacial hyperostosis. Detailed discussion is beyond the scope of this review article and only characteristic prototypes are discussed here. For more details about the genetic causes we refer to De Ridder et al. (PMID:29656376)
Osteopetrosis

Definition

Osteopetrosis ("marble bone disease") is a genetic, heterogeneous group of bone disorders affecting the medullary cavity resulting in increased bone density.

Prevalence & Etiopathogenesis

Osteopetrosis is subdivided in autosomal dominant and autosomal recessive osteopetrosis, which differ in clinical presentation and prognosis\(^49\). The dominant form is far more prevalent than the recessive form. Both forms are linked to mutation in the CLCN-7 gene impairing optimal function of osteoclast cells, ultimately disturbing bone remodeling.

Clinical features

The recessive form is also termed the malignant form because it presents early in childhood and often results in early death due to severe anemia and infections. Deafness and blindness due to impairment of cranial nerves are often present. The dominant form presents later in adulthood. Symptoms are milder or even absent\(^50\).

Imaging findings

The most common adult form of osteopetrosis has 2 distinct phenotypic presentations. Type 1 presents as a uniform sclerosis of long bones, vertebrae and skull. Skull base sclerosis is the most common craniofacial manifestation on plain film and CT. Osteopetrosis type 2 may also show the characteristic ‘bone-within-bone’ sign (online \(\triangleright\) supplementary Fig. 9B) or the ‘Rugger Jersey’ spine (online...
supplementary Fig. 9C-D). The affected marrow spaces are typically of low signal on all MRI sequences. MRI may be valuable to detect osteomyelitis, a potential complication of the disease.

Van Buchem Disease and Sclerosteosis

Definition
Van Buchem disease (VBD) and sclerosteosis are craniotubular hyperostoses, initially described as ‘hyperostosis corticalis generalisata familiaris’, causing thickening the craniofacial and long tubular bones.

Prevalence & Etiopathogenesis
VDB and sclerosteosis are autosomal recessive disorders and are the result of deficiency of sclerostin which is encoded by the SOST gene. Van Buchem disease is caused by a 52-kb deletion, 35-kb downstream of SOST, which contains an enhancer region that is important for the expression of sclerostin in bone. As a result of the deletion, the expression of sclerostin is severely reduced. Sclerosteosis on the other hand is caused by loss-of-function mutations in the SOST gene itself.

Clinical features
Prominent enlarging of the craniofacial bones leads to morphologic changes such as macrocephaly, frontal bossing and a broadly enlarged, prognatic jawbone. Narrowing of the cranial base neuroforamina often leads to cranial nerve impairment.
The facial nerve is most often affected and sensorineural hearing loss is less common. Raised intracranial pressure is a rare complication.

Imaging findings
Radiographic and CT findings include a generalized hyperostosis of the calvarium and mandible, with nearly obliterated diploe. Neuroforaminal narrowing is best appreciated on CT. MRI will exhibit low signal intensities on all pulse sequences due to thick sclerotic bone. Based on imaging of the craniofacial bones alone differentiation between VBD and sclerosteosis is impossible. Sclerosteosis resembles VBD but is clinically associated with syndactyly.

**Camurati-Engelmann disease**

Definition
Camurati-Engelmann Disease (CED) or progressive diaphyseal dysplasia is another rare craniotubular hyperostosis, causing cortical thickening of the diaphysis of the long tubular bones.

Prevalence & Etiopathogenesis
CED is an autosomal dominant diaphyseal dysplasia with approximately 300 cases reported in the literature. In the majority of the cases, the disorder is caused by mutations in the latency-associated protein (LAP) domain of the transforming growth factor beta 1 (TGFβ1) gene. TGFβ1 is a ligand of the TGFβ signaling pathway which plays a role in the regulation of bone homeostasis. The LAP domain is important to keep TGFβ1 inactive in the bone matrix. As a result of the mutations, the release of
active TGFβ1 from the bone during bone resorption is increased which results in higher bone turnover.

Clinical features
Most complaints are related to the involvement of the appendicular musculoskeletal system and include a waddling gait and muscle weakness. Cranial involvement is only present in 54% of patients and causes sensorineural hearing loss in 15% of patients.

Imaging findings
Craniofacial involvement of CED is characterized by generalized sclerosis on radiography and CT of the skull often with obliteration of the paranasal sinuses. Scintigraphy shows increased uptake even before sclerosis is visible.

Article summary
- Craniofacial bones are affected in 25% of mono-ostotic and 50% of polyostotic FD.
- Craniofacial FD and PD may show similar imaging appearances. Features in favor of FD are: young age; ground glass matrix on CT; asymmetric craniofacial involvement; sphenoid bone and paranasal sinus involvement; thin cortex and associated soft tissue swelling or cyst-like components.
- PD disease is a triphasic sclerosing bone disease affecting the craniofacial bones as part of poly-ostotic involvement and most commonly encountered in the longstanding late mixed phase, exhibiting the 'cotton wool' sign or cortical
thickening and coarse trabecular bone on CT and normal fatty marrow signal on MR.

- A meningioma with associated reactive hyperostosis, meningioma-en-plaque and intra-osseous meningioma are difficult to distinguish on imaging. The parietal and frontal sutures are most often affected.
- Osteomas typically involve the external table of the calvarium. In case of multiple osteomas, Gardner syndrome should be excluded.
- HFI is frequently found in post-menopausal women and consists of nodular thickening of the internal table of the frontal bone.
- A venous malformation may mimic an aggressive lesion with rapid growth, spiculated borders and vivid enhancement. The characteristic ‘spoke-wheel’ sign and ‘bunch of grapes’ sign may aid in the diagnosis.
- Sclerosing bone dysplasias are a heterogeneous group of genetic bone disorders characterized by increased bone density either caused by impaired bone resorption or increased bone formation. They may affect both the axial and appendicular skeleton.
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