Paget's disease of bone

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Abstract

Paget's disease of bone is a bone modelling disorder, characterized by skeletal deformity. Although the aetiology is largely unknown, environmental and genetic theories have been proposed. Serum alkaline phosphatase and plain radiographs remain the most commonly utilised investigations for diagnosis, and allow monitoring of the disease process. Second-generation bisphosphonates continue to be the mainstay of treatment, but surgical intervention may be required to treat complications including fracture, deformity and arthritis. This article reviews the epidemiology, aetiology, clinical features, investigations and treatment, including both medical and novel surgical options.

Keywords arthroplasty; bisphosphonates; metabolic bone disorder; Paget's disease

Introduction

Paget's disease of bone (PDB), initially termed osteitis deformans, was first described by Sir James Paget, an English surgeon and pathologist. He noticed several cases of abnormal bone growth and deformities, including curvature of the long bones and enlargement of the skull. Paget initially believed these signs to be a result of a chronic inflammatory process of the bone.[1]

Epidemiology

PDB is the second most common bone modelling disorder after osteoporosis. PDB is more prevalent in males than females, at a ratio of 3:2, and in the later years of life. PDB is extremely rare in patients under the age of 25, unusual before the age of 40 and presents five times more commonly in those over the age of 85 than those under 60 years.

There appears to be an ethnic/geographical link in PDB, with the disease being prevalent in those of British descent, most commonly found in the UK, Australia, New Zealand and North America. Conversely, it is rare in Scandinavia, Asia, the Middle East and Africa. The overall prevalence worldwide is believed to be approximately 0.3%, which has gradually been reducing over recent years.[2,3]

The disease shows increased incidence in men between ages 55–59, 0.5 cases per 10,000 person-years, compared with women, 0.3 cases per 10,000 person-years. After the age of 85, the incidence increases to 5.4 and 7.6 in men and women respectively.[4]

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Aetiology

Evidence has suggested PDB to be a complex multifactorial disease with a likely genetic predisposition as well as links with environmental factors. Other factors implicated include vascular, immune and metabolic causes.

Genetic causes

PDB is evidenced to have a strong genetic component, seemingly inherited in an autosomal dominant manner. Studies have shown up to 40% of individuals affected with the disease also have an affected relative.[5]

Multiple loci have been implicated as causative factors in PDB including: 6p21.3 (PDB1 locus), 18q21-22 (PDB2), 5q35 (PDB3), 5q31 (PDB4), 2q36 (PDB5), 10p13 (PDB6) and 18q23 (PDB7). However, some of these identified may be false-positives.[6]

Further studies of patients with the PDB3 (chromosome 5q35) were found to have a significant mutation, the sequestosome 1 (SQSTM1). There have been 28 forms of the SQSTM1 mutation identified to date, with the first mutation identified, the P392L form, being the most commonly found mutation in PDB. This was first identified in two French-Canadian families in Quebec,[7] but studies have shown this mutation to be a factor in other populations including British, Belgian, Italian, American and Chinese populations.[6] The SQSTM1 mutation has been shown to alter bone metabolism by affecting osteoclast differentiation and function. Studies have shown the SQSTM1 mutation to be implicated in approximately 40% of familial cases and around 10% of sporadic cases.[7] The SQSTM1 mutation may predispose to the disease but is not necessarily a causative factor, implying the multifactorial aspect and hinting that environmental factors may play a role in the pathogenesis of PDB.[8]

In addition, another key genetic component of PDB is RANK, a receptor protein for RANKL, which activates NF-κB signalling. This is an important protein in osteoclastic differentiation and function and patients with both mutations in gene coding for RANK and SQSTM1 can increase the severity of PDB and other similar syndromes.[6]

Environmental causes

Environmental effects have also been identified as possible contributors to PDB; the variable penetrance of genetically predisposed individuals supports this theory. It was believed viral infections were a trigger, such as measles virus (MV), respiratory syncytial virus (RSV) and canine distemper virus (CDV). However, studies suggesting these slow paramyxovirus infections as possible causes of PDB have so far been inconclusive.[9]

The viral theory was hypothesized after identifying paramyxoviral-like nucleocapsid inclusion bodies in the nucleus and cytoplasm of osteoclasts in PDB individuals. However, multiple studies investigating this finding further *in vivo* could not show any significant difference between affected and control groups, failing to definitively prove the hypothesis of a persistent viral infection being a causative factor.[2,10–12]

Other possible environmental factors include contact with dogs during childhood, poor childhood dietary intake, consumption of non-purified water, excessive mechanical loading and exposure to environmental toxins.[2,6]

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Pathophysiology

Histological evidence has suggested that the pathophysiology of PDB is excessive osteoclastic bone resorption seen in the initial osteolytic phase, the first of three phases. Histology also shows the presence of osteoclasts in Howship's lacunae in cortical and trabecular bone which are much larger than normal, containing up to 100 nuclei compared with the 3–10 found in normal osteoclasts. As a result of excessive osteoclastic function in this first phase, there is a reduced bone volume, with highly vascular fibrocellular stroma in place of the normal fatty or haematopoietic marrow.

In the intermediate phase of PDB, there is a predominance of osteoblastic activity causing the rapid chaotic deposition of lamellar interspersed in woven bone, giving the classic 'mosaic pattern' appearance, which replaces the parallel Haversian systems. This bone is structurally weak and prone to deformity and fractures. In the late osteosclerotic 'burnt-out' phase, the abnormal matrix may persist but osteoclastic activity is greatly reduced and bone turnover returns to normal.[13,14]

Clinical features

PDB is asymptomatic in most cases and tends to be incidentally diagnosed from a raised serum alkaline phosphatase (ALP) or an incidental radiographic finding. There are many complications and manifestations of PDB which have been outlined.[15]

Skeletal involvement

PDB frequently affects the pelvis (21–75%), femur (25–46%), spine (29–57%), skull (28–40%), tibia (35%), humerus (31%), scapula (24%), clavicle (11%), facial bones (11%), calcaneum (10%), patella (7%), and occasionally the small bones of the hands (6%) or feet (5%). Common presenting features include enlargement of the skull, frontal bossing and bowing of long bones.[14,16] PDB has a tendency to affect the axial skeleton, with the condition commonly having an asymmetrical polyostotic (involving more than one bone) involvement in 65–90% of cases and less frequently monostotic disease in around 10–35%. PDB tends to affect one locus within the bone, progressing to affect the entire bone. It does not progress to across joints to affect adjacent bones.[17,18]

Bone pain

Bone pain is a common feature of PDB, often experienced at night and dull in nature. Pain can also present on weight-bearing if an osteolytic lesion is present.[15] Severe pain can arise due to degenerative joint disease, commonly affecting the hip joint. The progression of bone deformity can affect biomechanics, which can accelerate the degenerative process. Other presenting complaints include: knee pain, joint effusion, bowing of the tibia, back pain and shoulder pain.[13]

PDB can present as a pathological fracture and should be suspected in any patient complaining of dramatically increasing bone pain, which may be due to insufficiency fractures. These are termed 'fissure fractures', 'banana fractures' and 'pseudofractures'. Fissure fractures are diagnosed by the presence of linear transverse radiolucencies on the cortex of the convex aspect of the bowed bone. Commonly affecting the femur, fissure fractures are usually found laterally, differing from the Looser zones of osteomalacia that are seen medially. As a result of their location, fissure fractures can progress to a complete transverse fracture with minimal or no trauma. These fractures typically show poor healing with high rates of non-union.[2,13,19]

Neurological

Neurological complications of PDB are commonly a consequence of skull involvement. PDB causes thickening of the skull, which traditionally presented with the individual constantly having to change the size of their hat. Hearing loss may ensue due to reduced bone density in the cochlear capsule and entrapment of cranial nerves. Involvement of the skull base can lead to platybasia and basilar invagination, which can in turn lead to hydrocephalus, headache, dizziness, syringomyelia and compression of the brainstem. Other intracranial clinical features described include anosmia, trigeminal neuralgia, facial and bulbar palsy.[20,21]

Spinal involvement can lead to further neurological complications due to impingement on the spinal cord or an affect on blood flow, causing quadriparesis or paraparesis depending on level involvement. Also, blood flow is increased to the affected bone and a phenomenon known as 'vascular steal' may develop. This occurs when blood is redirected to the wide channels of the abnormal bone in preference to its normal flow pattern, causing reversible spinal cord ischaemia. This can be treated medically, unless the structural integrity is compromised in which case surgery is indicated to prevent spinal cord collapse.[21] Other vertebral pathologies resulting from PDB include compression fractures, nerve root compression, muscle weakness, spinal stenosis, kyphosis and cauda equine syndrome.[20]

Cardiovascular

Cardiovascular complications have been described as a consequence of PDB, with high rates of cardiac failure due to the high cardiac output engendered by increased vascularity of PDB-affected bone.[21] Decreased peripheral vascular resistance in the early phases may lead to increased cardiac output, as found in a study assessing cardiac function by echocardiography.[22]

Other cardiovascular complications described include aortic stenosis, conduction abnormalities and increased vascular calcification.[2]

Malignant transformation

Sarcomas are the most common malignant transformations seen in PDB, with an approximately 1% incidence. Sarcomas present with worsening pain, lytic lesions on X-ray, fracture, palpable mass or a rise in serum ALP.[23] The variable histological forms of sarcoma include osteosarcoma, fibrosarcoma, chondrosarcoma and anaplastic sarcoma. Early stages of sarcoma in an affected bone may present with a symptomatic radiolucent focus with speckled regions of calcification, disrupting the cortex of the bone.[13] Patients diagnosed with PDB-associated sarcoma generally have a poor prognosis and mortality most commonly ensues due to local advancement of disease or pulmonary metastases.

PDB can also cause giant cell tumours, lymphoma, multiple myelomas, carcinomas and parathyroid tumours as well as metastatic spread to the more vascular areas of Paget's bone.[23]

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