Paget's disease of bone

Synonym: osteitis deformans

What is Paget's disease?

Sir James Paget described Paget's disease of bone in 1877. There is increased bone turnover in focal areas of the skeleton and one or many bones can be affected:[1]

- There is a lytic phase to the disease process with an increase in bone resorption and abnormal osteoclast activity. This leads to a rapid increase in bone formation by osteoblasts. In the sclerotic phase, the focus is on bone formation.
- The structure of this new bone is disorganised and it is mechanically weaker, more bulky, less compact, more vascular, and liable to pathological fracture and deformity.
- Burnt-out Paget's disease is the term for when the abnormal activity and hypercellularity die down.
- Paget's disease of bone has a predilection for the axial skeleton, particularly the lumbosacral spine and pelvis, as well as the skull, femur and tibia.[2]
- The thoracic spine, sacrum and humerus may also be affected. The hands and feet are rarely affected.

Juvenile Paget's disease is a separate disease[3] - see the separate Juvenile Paget's Disease article. See also the separate Paget's Disease of Breast article.

For the rest of this article 'Paget's disease' means 'Paget's disease of bone'.

How common is Paget's disease? (Epidemiology)[4]

- Paget's disease of bone (PDB) is the second most common metabolic bone condition after osteoporosis.[5]
- The diagnosis of Paget's disease is rare before age 50. The disease affects men and women, but in most series males predominate.
- One series found a prevalence of 3% in over 4,600 autopsies of individuals above 40 years of age.
- Paget's disease occurs most commonly in people of British descent. The disease is also common in British migrants to countries like Australia, New Zealand and North America, as well as in other countries in Europe, such as in France, Germany, Spain, or Italy.
- There is evidence that Paget's disease has become less common and less severe over the past quarter of a century in the UK and many other countries
- One study evaluated the age- and gender-specific incidence of Paget's disease in England and Wales in the adult population, and concluded that the disorder was more frequent among men of all ages over 55 years:
    - The incidence increased steeply with age among men and women, and was estimated at 0.3 cases per 10,000 person-years among women aged 55-59 years and 0.5 cases per 10,000 person-years among men of similar age.
    - At the age of ≥85 years, this rate rose to 5.4 among women and 7.6 among men.
    - Based on these assumptions, the prevalence of clinically diagnosed Paget's disease is 0.3 % among men and women ≥55 years old.

What causes Paget's disease? (Aetiology)

- Both genetic and environmental factors are thought to play a role.
- Autosomal dominant inheritance has also been described in some families.[6]

- Mutations have been identified in four genes that cause Paget's disease, of which sequestosome 1 (SQSTM1) mutation is the most important.[1] Patients carrying this mutation seem to be severely affected by Paget's disease and there is a high degree of penetrance.
- The mechanisms underlying the focal nature of the disease are unclear. Mechanical stress may play a role.
- Paramyxovirus infection (including measles and respiratory syncytial virus) has been suggested as a possible trigger but this has been disputed.[1]

Paget's disease symptoms (presentation)[7]

Most cases of PDB are diagnosed incidentally on X-rays or as an isolated elevation of serum alkaline phosphatase. Symptomatic patients present with bone pain, deformity, fractures, arthritis and features of compression neuropathy.

- Pain may be present at rest, at night and on movement but does not tend to be focused around a joint.[1]
- Other presentations include pathological fractures or one of the other complications listed below.
- Skin temperature may be increased over areas of active disease.[1]
- It is monostotic (affecting one bone) in a third of cases and polyostotic (affecting two or more bones) in the remaining two thirds.

Complications[1]

Complications from Paget's disease depend on the site affected and the activity of the disease.

Common

- Bone pain.
- Bone deformity (including sabre tibia (bowing of the tibia), kyphosis, frontal bossing of the skull, an enlarged maxilla, an increase in head size).

- Pathological fractures (may produce heavy bleeding from the very vascular bone).
- Osteoarthritis (due to Paget's disease around a joint).
- Deafness and tinnitus may be due to compression of cranial nerve VIII, effects on ear ossicles (eg, stapes fixation) and cochlear dysfunction.

Less common

- Spinal stenosis.
- Nerve compression syndromes and cauda equina syndrome.

Rare

- Hypercalcaemia (with immobilisation, usually due to dehydration).
- Hydrocephalus.
- High-output cardiac failure (due to increased blood flow through affected bone).
- Paraplegia (can occur in disease affecting the spine).
- Osteosarcoma.

Differential diagnosis

- Osteoarthritis.
- Osteoporosis.
- Osteomalacia.
- Malignant skeletal metastases.

Investigations[8]

- Serum total alkaline phosphatase is recommended as a first-line biochemical screening test in combination with liver function tests in screening for the presence of metabolically active Paget's disease of bone.

- Serum calcium, phosphorus, and parathyroid hormone levels are usually normal but immobilisation may lead to hypercalcaemia.
- X-rays may show a number of signs:
    - Both osteolysis (seen as radiolucency) and excessive bone formation occur.
    - There are specific X-ray features of Paget's disease that include:
        - A classical V-shaped pattern between healthy and diseased long bones, known as 'the blade of grass' lesion.
        - The 'cotton wool' pattern in the skull that is also characteristic (multifocal sclerotic patches).
    - Osteosarcomas also have a distinct radiological appearance.
- Radionuclide bone scans, in addition to targeted X-rays, are recommended as a means of fully and accurately defining the extent of metabolically active disease.
- Bone biopsy may be needed if malignant change is suspected.

Paget's disease treatment and management[8]

- The objectives of treatment are control of pain and to reduce or prevent disease progression and complications.
- Treatment aimed at improving symptoms is recommended over a treat-to-target strategy aimed at normalising total alkaline phosphatase.
- Specific treatment is required for complications.
- Because of the risk of osteosarcoma, patients should be monitored indefinitely. Presentation of osteosarcoma is classically with increased bone pain that is poorly responsive to medical treatment, local swelling, and possibly a pathological fracture.[1] X-ray and bone biopsy can help to confirm the diagnosis (see 'Investigations', above).

Referral to secondary care is advisable in a patient thought to have pain or deformity so that further assessment can be performed and treatment offered if appropriate. Referral may not be required in older patients who are asymptomatic where Paget's disease is picked up as an incidental finding because there is currently no evidence that anti-Pagetic treatment is of clinical benefit in these circumstances.[9]

Non-drug treatment

- Orthotic devices, sticks and walkers may be useful for disease of the legs if it causes problems with walking.
- Patients taking bisphosphonates should maintain an adequate intake of calcium and vitamin D.

Drug treatment

- Non-steroidal anti-inflammatory drugs (NSAIDs) and paracetamol may be effective for pain.
- Anti-resorptive therapy is usually with bisphosphonates. For those intolerant of bisphosphonates, subcutaneous calcitonin can be used for a limited period due to its associated risk of malignancy with long-term use.[10]

- Bisphosphonates:
    - Bisphosphonates are recommended for the treatment of bone pain associated with Paget's disease. Zoledronic acid is recommended as the bisphosphonate most likely to give a favorable pain response.
    - A Cochrane review found moderate-quality evidence that bisphosphonates improved pain in people with Paget's disease of bone when compared with placebo.[11]
    - Any calcium and vitamin D deficiency needs to be corrected before starting a bisphosphonate to avoid hypocalcaemia.[1]
    - Bisphosphonate may cause osteonecrosis of the jaw. The risk of osteonecrosis of the jaw is substantially greater for patients receiving intravenous bisphosphonates in the treatment of cancer than for patients receiving oral bisphosphonates for osteoporosis or Paget's disease.[12]
- Serial monitoring of alkaline phosphatase is used to monitor the effects of treatment and disease activity.[13]

Surgery

- Bone deformity, osteoarthritis, pathological fractures and nerve compression may necessitate surgery.
- Bisphosphonates should be used pre-operatively to try to reduce disease activity in order to prevent severe bleeding during surgery.
- After surgery, bone healing may be prolonged, and lengthy rehabilitation may be necessary.
- Amputation may be necessary for osteosarcoma of long bones.
- Decompressive laminectomies may be necessary if medical therapy fails to help those with neurological problems from spinal cord compression.[14]
- Total hip or knee replacements are recommended for patients with Paget's disease who develop osteoarthritis in whom medical treatment is inadequate.

Prognosis

- This depends on the extent and degree of disease activity.
- Remission may be possible with successful treatment.
- Those who develop osteosarcoma have a very poor prognosis.

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