Guidelines for diagnosis and management of Paget’s disease of bone in Japan

Received: September 5, 2005 / Accepted: February 28, 2006

Abstract We here propose guidelines for the diagnosis and management of Paget’s disease of bone (PDB) in Japan. These guidelines provide basic information on the epidemiology, pathophysiology, clinical signs and symptoms, diagnosis, indications for treatment, and available therapy, including orthopedic surgery. PDB is a chronic disorder characterized by focal abnormalities of bone turnover. The characteristic feature of PDB is excessive osteoclastic bone resorption coupled to increased and disorganized bone formation. The most common symptom of PDB is pain in involved bones. The most serious complication of PDB is malignant bone or soft-tissue tumor. PDB is uncommon in Japan; our survey in 2003 found 169 patients with PDB. The prevalence of PDB in Japan is 0.15/100 000; in patients aged 55 years or more, the proportion reaches 0.41/100 000. A careful medical history and physical examination are essential for the diagnosis. The diagnosis of PDB is based on finding the typical features on radiographs. Bone scintigraphy and measurement of serum alkaline phosphatase are sensitive means of screening for PDB. Since PDB is a rare disease in Japan, bone biopsy is quite often used to exclude bone metastases. The only evidence-based indication for treatment of PDB is pain in involved bones. In Japan, etidronate and calcitonin are approved by the Ministry of Health, Labour and Welfare for treating PDB, but currently risedronate is also under development for treating PDB in Japan. Indications for surgical intervention in PDB include unstable fractures, osteoarthritis, malignant soft-tissue tumor, osteosarcoma, and bone deformity.

Key words Paget’s disease of bone · guideline · diagnosis · treatment

Introduction

In 1877, Paget’s disease of bone (PDB) was first described by Sir James Paget, an English surgeon, who named this skeletal disorder osteitis deformans [1]. Although PDB is uncommon in Japan, it is the second most common metabolic bone disease in European countries [2–5].
The characteristic feature of PDB is excessive osteoclastic bone resorption coupled with increased and disorganized bone formation. Clinical signs and symptoms depend on the location and number of involved bones and on the rapidity of abnormal bone turnover. The most serious complication of PDB is osteosarcoma, although this complication is rare. While special attention should be paid to the complications of PDB, it is important to remember that most patients with PDB are asymptomatic [4].

We here propose guidelines for diagnosis and management of PDB in Japan to provide basic information on the epidemiology, pathophysiology, clinical signs and symptoms, diagnosis, indications for treatment, and available therapy, including orthopedic surgery. These guidelines stress the importance of bone biopsy to differentiate PDB from secondary tumors such as metastases from prostate cancer or breast cancer, and other sclerosing bone dysplasias.

Epidemiology

In Japan, 169 patients with PDB were found in our survey in 2003 [6]. The prevalence of PDB in Japan is 0.15/100000; in patients aged 55 years or more, the proportion reaches 0.41/100000. Although PDB is rare in Japan, it is quite common in most European countries, except for Scandinavia. Paget’s disease is also common in Australia, New Zealand, and North America [2]. Radiographic studies performed in the 1980s showed that the prevalence of PDB in hospitalized patients aged more than 55 years in the UK was 4.6%, in France 2.4%, in Ireland 0.7%–1.7%, in Spain and West Germany 1.3%, and in Italy and Greece 0.5% [3]. Although the UK still has the highest prevalence of PDB in the world, a recent survey suggests that the disease has become less common over recent years, and the radiological prevalence in those aged over 55 years is now estimated as about 2% [7]. The ethnic differences in the prevalence of PDB, coupled with the change in prevalence over recent years, indicate that both environmental and genetic factors most likely contribute to the pathogenesis of PDB.

In Japan, as in other countries, PDB is rarely diagnosed in patients under the age of 40 years. Our previous survey revealed that the mean age of Japanese patients with PDB was 68 years (ranging from 25 to 98 years), with an increase in prevalence with increasing age [6].

The male/female ratio of PDB patients in Japan is 0.86 [6], indicating a slight female predominance. According to a recent study [7], in a radiographical survey of PDB in 10 British centers, the overall age/gender standardized prevalence rate was 2% with a male/female ratio of 1.6.

PDB often shows familial clustering [8–11]. We have not examined the frequency of a positive family history in Japan, but studies in Europe and the US have indicated that approximately 15%–30% of patients with PDB have a positive family history of the condition [8–11].

Pathophysiology

Since PDB shows geographical and ethnic clustering, two hypotheses of the etiology of PDB have been proposed. One hypothesis is that PDB results from a slow virus infection of osteoclasts with paramyxovirus [12,13]. The other is that PDB is a genetic disease [14,15].

Paramyxovirus infection

Immunohistochemical study has revealed that staining for measles virus antibodies is positive in cultured pagetic cells and pagetic bone samples [16]. Osteoclasts from patients with PDB have been found to exhibit characteristic nuclear inclusions consisting of paracrystalline arrays that resemble nucleocapsids of paramyxoviruses [17–19]. This led to the suggestion that PDB is caused by a chronic paramyxovirus infection. However, these nuclear inclusions are not specific for PDB and the role of paramyxovirus infection in the pathogenesis of PDB is still controversial [20].

Genetics

Family studies in the US have shown that 12.3% of patients had at least one affected relative, compared with only 2.1% of controls [8]. Similar findings have been reported in the UK [11]. Severely affected patients with PDB frequently have a positive family history of PDB [21], and patients who have a positive family history have an earlier onset of the disease than patients who do not [8].

Genome-wide scans have identified susceptibility loci of PDB and related conditions on chromosomes 18q21 [22], chromosome 5q35 [23], chromosome 5q31 [23], chromosome 2q36, and chromosome 10p13 [24]. Mutations in four genes have been discovered as a cause of PDB or related syndromes. These are receptor activator of nuclear factor kappa B (RANK) [9], osteoprotegerin (OPG) [25], sequestosome (SQSTM1) [23], and valosin-containing protein (VCP) [26]. Mutations affecting RANK, OPG, and VCP have been excluded as a cause of classical PDB [27–29]. However, mutations of SQSTM1 are a common cause of PDB and occur in between 40%–50% of Caucasian patients with familial PDB and in 8%–20% of patients who do not have a family history of PDB [30].

Signs and symptoms

Clinical signs and symptoms depend on the location and number of affected bones and on the rapidity of the abnormal turnover of bone. The clinical manifestations of PDB are shown in Table 1 and include bone pain, local warmth, and bone deformity [31]. Pain in the involved bones is the most common symptom of PDB and may be most severe at night. Bone pain can also result from pathological fracture and osteoarthritis.