

Paget's disease of bone

Torrijos Eslava A

Responsable de la Unidad Metabólica Ósea - Servicio de Reumatología - Hospital Universitario La Paz - Madrid

e-mail: atenino13@gmail.com

On 14th November 1877, the British doctor James Paget presented to the Medical and Surgical Society of London five cases of a condition which was called "Osteitis Deformans", a slowly developing bone disease characterised by the lengthening, softening and deformation of the bones, above all affecting the cranial bones and the long bones of the lower limbs. He published the first report in *Medical-Surgical Transactions* in 1877, in which he described in detail a man he had treated over a period of 20 years¹. He subsequently published, more cases in 1882 as well as saying that he had not known that Czerney had used the term "Osteitis Deformans" in 1873.

Since this date many cases have been published and a large amount of information has been gathered relating to its etiology, prevalence, epidemiology, diagnosis and treatment, and "Osteitis Deformans" is now known as Paget's disease.

Today, Paget's disease of bone (PDB) is defined as a non-diffuse bone disease characterised by an increase in bone remodelling whose principle agent is the osteoclast. It is an entity of unknown etiology, sited segmentally in different areas of the skeleton. PDB may affect any bone and may be monostotic or polyostotic. The bones most affected are the pelvis (up to 70%), femur (30-55%), lumbar spine (25-50%) cranium (20-40%) and tibia (15-30%). The disease progresses along the affected bone and the appearance of a new location some years after the first diagnosis is very rare. This affection leads to deformation of the bone with an increase in its size and deformity which may produce bone pain, arthralgia and nerve compression syndromes in the cranial nerve pairs, spinal stenosis or compression of the spinal cord. It also results in a greater risk of fracture in the affected long bones. It should also not be forgotten that pagetic tissue may suffer a neoplastic transformation with a higher incidence of sarcomas, especially in the polyostotic type which develop in 0.3-1% of cases^{2,3}.

PDB is asymptomatic in 50-75% of cases, and the doctor is alerted when the typical deformities appear (increased growth in the skull or bowing

of the tibia), or when an increased level of alkaline phosphatase is detected in a routine analysis, or findings in an X-ray examination for another reason. In many cases the diagnosis of PDB is made after the complications have occurred, and if the Paget's is active, the markers for bone turnover are elevated. Among the markers for bone turnover the most useful appear to be amino-terminal telopeptide of collagen type 1, bone-specific alkaline phosphatase and amino-terminal propeptide of procollagen 1. However, taking into account its ease of use and low cost, the determination of concentrations of alkaline phosphatase is still a valid alternative.

The diagnosis of PDB is carried out primarily using X-rays with its characteristic images. Bone gammagraphy is not a specific method, but for us is useful to see the locations and spread of the disease. CAT and MRI scans are useful in evaluating neurological symptoms in the context of PDB and may also be of use to determine the extent and nature of neoplastic degeneration of the Pagetic tissue.

PDB has an interesting geographic distribution. The highest incidence is found in the United Kingdom (4.5% in those over 55 years of age) and within this country the highest incidence is in the northeast, with the best known concentration being Lancashire in which 7% of the population over 55 years of age is affected. It is quite common in the northeast of France, Spain and Italy. In Spain the prevalence of PPDB is at least 1% in people over 55 years of age, with notable variations according to geography and age. The best known predominant concentrations of PDB in our country are those of the province of Salamanca and the Sierra Norte de Madrid (Northern Sierra of Madrid) among others. It also occurs in the majority of other European countries, with the exception of the Scandinavian countries. In the rest of the world it is also common in countries which have seen high levels of immigration from Britain and other European countries during the 19th and 20th centuries such as: Australia, New Zealand, the United States and some regions of Canada. PDB is rare in the Indian sub-continent, Malaysia,

Indonesia, China and Japan. The disease affects both sexes, with a slight predominance in men in most series (the male/female ratio is approximately 1.4:1 in the United Kingdom), is rare before the age of 50, and its prevalence increases with age and affects up to 5-8% in the eighth decade of life in some countries^{4,7}. Although there is no doubt that PDB has a genetic basis, the incidence and seriousness of this disease has diminished over recent decades⁸⁻¹⁰.

Those patients with PDB often have a family history of the disease and it is estimated that the risk of PDB affectation in a first degree relative is increased seven-fold. In many families the disease is inherited in an autosomal dominant fashion with high incomplete penetrance, increasing with age. Great advances have been made in the last 15 years in the understanding of the genetics of PDB. Linkage analysis has identified some loci which are potential candidates in the chromosomes 2p36, 5q31, 5q35, 10p13 y 18q21¹¹.

The genes and loci which predispose for PDB have been identified through a correlation analysis of families. Among those genes and loci which have been associated with PDB or related syndromes are: CSF1 (located in 1p13), SQSTM1 (located in 5q35), in the 7q33 chromosome (the genes NUP205, SLC13A4, and CNOT4), TM7SF4 (also known as DCSTAMP, located in 8q22) TNFRSF11B (located in 8q24), VCP (located in 9p13), OPTN (located in 10p13), TNFRSF11A (located in 18q21) and RIN3 (located in 14q33) and in the chromosome 15q24 (genes GOLGA6 and PML). In some of these the causal variant remains to be discovered. More studies are still required to determine the association of the different genes, as well as the importance of environmental factors which influence the development of PDB with these genetic alterations¹¹⁻¹⁶.

Some mutations of SQSTM1 may act as predisposing factors but are not sufficient to induce PDB, with additional factors (genetic or environmental) possibly being necessary^{10-12,17,18}. Mutations of this gene are the most common cause of familial PDB. Transverse studies indicate that 80% of the carriers of SQSTM1 mutations develop PDB in the eighth decade of their lives. There are data which show that the age of onset of the disease in families with PDB in the current generation, in those with SQSTM1 mutation, is delayed in comparison with their parents' generation^{10-12,15}. This emphasises the importance of environmental factors in triggering the disease.

To date, the precise molecular mechanisms which lead to the development of pagetic lesions in carriers of the SQSTM1 mutation have not yet been defined. On the other hand, recent experimental data suggest that one or a number of environmental factors may be required to induce the complete pagetic phenotype in the presence of the SQSTM1 mutation. Since environmental factors, some of them toxic, play a significant role in the development of PDB, and as the response to these factors is genetically conditioned, presented

in this number is a work by Dr Usategui-Martín et al.¹⁹, designed to determine whether the variability of some of the genes involved in the metabolism of exogenous toxins are related to the risk of developing PDB.

Bibliography

1. Paget J. On a form of chronic inflammation of bones (osteitis deformans). *Med Chir Trans* 1877;60:37-63.
2. Mankin HJ, Hornicek FJ. Paget's sarcoma: A historical and outcome review. *Clin Orthop Relat Res* 2005;438:97-102.
3. Hansen MF, Seton M, Merchant A. Osteosarcoma in Paget's disease of bone. *J Bone Miner Res* 2006;21 (Suppl 2):P58-63.
4. Ralston SH. Clinical practice. Paget's disease of bone. *N Engl J Med* 2013;368:644-50.
5. Del Pino J, Corral L, Miron JA, Morales A. Enfermedad de Paget: epidemiología y fisiopatología. En: Torrijos Eslava A, coordinador. Enfermedad Ósea de Paget. Madrid: Medea;2001.p.11-42.
6. Del Pino J, Rodríguez M. Epidemiología: consideraciones actuales. En: Guañabens Gay N, coordinadora. Enfermedad Ósea de Paget. Barcelona: SCM;2006.p.3-12.
7. Guañabens N, Garrido J, Gobbo M, Morales Piga A, Del Pino J, Torrijos A, et al. On behalf of the PAGET Study Group. Prevalence of Paget's disease of bone in Spain. *Bone* 2008;43:1006-9.
8. Poor G, Donath J, Fornet B, Cooper C. Epidemiology of Paget's disease in Europe: the prevalence is decreasing. *J Bone Miner Res* 2006;21:1545-9.
9. Cundy HR, Gamble G, Wattie D, Rutland M, Cundy T. Paget's disease of bone in New Zealand: continued decline in disease severity. *Calcif Tissue Int* 2004;75:358-64.
10. Bolland MJ, Tong PC, Naot D, Callon KE, Wattie DJ, Gamble GD, et al. Delayed development of Paget's Disease in offspring inheriting SQSTM1 mutations. *J Bone Miner Res* 2007;22:411-5.
11. Ralston SH, Albagha OME, Genetics of Paget's Disease of Bone. *Curr Osteoporos Rep* 2014;12:263-71.
12. Gennari L, Merlotti D, Rendina D, Gianfrancesco F, Esposito T, Ranuccio N. Paget's disease of bone: epidemiology, pathogenesis and pharmacotherapy. *Expert Opin Orphan Drugs* 2014;2:591-603.
13. Morissette J, Laurin N, Brown JP. Sequestosome 1: mutation frequencies, haplotypes, and phenotypes in familial Paget's Disease of bone. *J Bone Miner Res* 2006;21(Suppl 2):38-44.
14. Albagha OM, Visconti MR, Alonso N, Wani S, Goodman K, Fraser WD, et al. Common susceptibility alleles and SQSTM1 mutations predict disease extent and severity in a multinational study of patients with Paget's disease. *J Bone Miner Res* 2013;28:2238-46.
15. Visconti MR, Langston AL, Alonso N, Goodman K, Selby PL, Fraser WD, et al. Mutations of SQSTM1 are associated with severity and clinical outcome in Paget's disease of bone. *J Bone Miner Res* 2010;25:2368-73.
16. Albagha OME, Wani S, Visconti MR, Alonso N, Goodman K, Cundy T, et al. Genome-wide association identifies three new susceptibility loci for Paget's disease of bone. *Nat Genet* 2011;43:685-9.
17. Laurin N, Brown JP, Morissette J, Raymond V. Recurrent mutation of the gene encoding sequestosome 1 (SQSTM1/p62) in Paget Disease of bone. *Am J Hum Genet* 2002;70:1582-8.
18. Hocking IJ, Lucas GJA, Daroszewska A, Mangion J, Olavesen M, Nicholson GC, et al. Domain specific mutations in Sequestosome 1 (SQSTM1) cause familial and sporadic Paget's disease. *Hum Mol Genet* 2002;11:2735-9.
19. Usategui-Martín R, Corral E, Alonso M, Calero-Paniagua I, Carranco-Medina TE, Quesada-Moreno A, et al. Estudio de las deleciones de los genes GSTM1 y GSTT1 y del polimorfismo Ile105Val del gen GSTP1 en pacientes con enfermedad ósea de Paget. *Rev Osteoporos Metab Miner* 2014 6;4:83-8.