Reumatol Clin. 2017;xxx(xx):xxx–xxx

Sociedad Española de Reumatología - Colegio Mexicano de Reumatología

Reumatología Clínica

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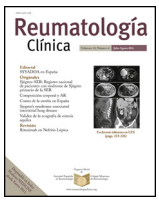

Special Article

Paget's Disease of Bone: Approach to Its Historical Origins☆

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ARTICLE INFO

Article history:
Received 14 September 2015
Accepted 17 February 2016
Available online xxx

Keywords:
Osteitis deformans
Historic
Paleopathology
Roman
Epidemiology

ABSTRACT

Paget's disease of bone is the second most common bone disease after osteoporosis. It is characterized by focal regions of highly exaggerated bone remodeling, with abnormalities in all phases of the remodeling process. This study aims to investigate the hypothesis of a possible British origin of Paget's disease of bone by studying the worldwide geographic distribution of cases identified in ancient skeletons excavated from archeological sites. The methodology consists in reviewing cases of Paget's disease of bone described in the literature.

Enfermedad ósea de Paget: aproximación a sus orígenes históricos

Palabras clave:
Osteítis deformante
Histórico
Paleopatología
Romano
Epidemiología

RESUMEN

La enfermedad ósea de Paget es la segunda enfermedad ósea más común después de la osteoporosis. Se caracteriza por la aparición de regiones focales que presentan una remodelación ósea muy exagerada, con anormalidades en todas las fases del proceso. Este estudio tiene como objetivo investigar la hipótesis del posible origen británico de esta enfermedad estudiando su distribución geográfica mundial en esqueletos antiguos excavados en yacimientos arqueológicos. La metodología utilizada consiste en una revisión de la literatura que presenta diagnóstico de la enfermedad ósea de Paget.

Characterization of Paget's Disease of Bone

Paget's disease of bone is a chronic disorder of unknown origin. It was described for the first time by Sir James Paget in 1877. It was initially referred to as *osteitis deformans*, as it was considered to be chronic inflammation of the bone. At the present time, it is regarded a chronic bone remodeling process in the absence of an inflammatory component. Thus, some authors suggest that a more suitable term would be *osteodystrophia deformans*.[1]

Paget's disease of bone involves a disorganization in focal bone remodeling. There is an increase in osteoclast activity, which results in greater bone resorption, the clinical expression of which is the development of lytic bone lesions observed in conventional radiography.[2–4] In response, there is accelerated and chaotic bone formation, which results in sclerotic bone that is functionally weaker than normal bone, without the characteristically laminar pattern. The clinical signs are usually expressed years later with the onset of bone deformity, accompanied by pain, osteoarthritis and pathological fractures.[2,5–7] The most frequently affected bones are the pelvis, femur, spine, skull and tibia. Other less common clinical manifestations are entrapment neuropathy, sensorineural hearing loss, high-output heart failure and malignant transformation with the development of osteosarcoma.[2,3,6,8–14]

The disease is usually detected in individuals over the age of 55 years. It becomes more frequent as individuals get older, and there is a slight predominance of men. The most common clinical signs

☆ Please cite this article as: Menéndez-Bueyes LR, Soler Fernández MC. Enfermedad ósea de Paget: aproximación a sus orígenes históricos. Reumatol Clin. 2015. http://dx.doi.org/10.1016/j.reuma.2016.02.008

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are bone pain, osteoarthritis and bone fracture. It is frequently diagnosed incidentally on the basis of a compatible radiological image taken during an examination for some other medical concern, given that it can develop without being detected for years. For this reason, the disorder is considered to be underdiagnosed in the general population.[8]

The geographic distribution is irregular. In epidemiological studies performed over the past 30 years, the prevalence of Paget's disease has been seen to be high in northwestern European populations. It is markedly more frequent in Great Britain (3%–5% of the population over 55 years of age) and in areas to which this population has emigrated, such as Australia, New Zealand and the United States. Other regions in which the rate is high are France and Spain (0.7%–1.3%). Moreover, within these countries, there are foci in which the disease burden is even greater. The most widely known of these is Lancashire, in England, where the prevalence is 6.3% of the population over 55 years of age with respect to 4.3% in the remainder of the areas studied, focusing on the population of the same age.[15,16] In Spain, the Sierra de la Cabrera in the Community of Madrid and the region of Vitigudino in Salamanca, in the western region of the country, are also areas of high prevalence.[17] There are more cases in the interior than along the coastline. The disease is less frequent in Scandinavian countries and Asia, where the rate is less than 1%.[17–19]

The reason for this irregular expression of the disease is not well known. A number of theories, including an autoimmune process, an endocrine disorder, an infectious disease and a neoplastic condition, have been proposed. The origin remains unclear, although it is evident that there is a marked familial aggregation that suggests an underlying genetic factor. Study findings support the existence of autosomal dominant inheritance, with variable penetrance and the implication of specific mutations, particularly that involving the *sequestosome-1* gene (*SQSTM1*). This mutation has been related to the most aggressive expression of Paget's disease of bone.[20] This hereditary component would be subjected to environmental influences that would trigger the disease. Several exogenous factors have been proposed, including paramyxovirus infection, consumption of untreated water and unpasteurized milk, and vitamin D deficiency during childhood. We consider the findings of a study conducted in the Sierra de la Cabrera in Madrid, one of the Spanish foci in which the disease is highly prevalent, to be especially interesting. The conclusion was that the possible causative agent would not be a canine virus, but the consumption of bovid meat without monitoring by health authorities. The result was the ingestion of the infectious agent from the tissues of infected animals (as occurs in Creutzfeldt-Jakob disease). The development of a slow-acting agent is consistent with the advanced age of the patients and their infection during childhood and adolescence, when health monitoring of livestock in Spain was limited or nonexistent.[21] On the other hand, the Lancashire focus was related to a high arsenic concentration in the pesticides used in the cotton industry, which was eliminated by means of the rivers. However, none of the studies performed has demonstrated solid evidence of the role of any of them in the development of the disease.[22]

In recent years, there has been evidence of a decrease in the incidence of the disease and of the severity of the clinical manifestations. This may be due to changes in the ethnic composition of the populations because of migration and to improved hygienic conditions introduced as public health measures (vaccination programs and reduced exposure to zoonosis).[5]

The diagnosis in symptomatic patients is based mainly on clinical findings, supported by laboratory tests and radiological images. There is an increase in bone formation and resorption markers. The marker of choice for diagnosis is serum total alkaline phosphatase, the level of which is usually increased. In the radiological study, there is generally local enlargement of the bone with cortical thickening, changes in the trabecular pattern and the coexistence of lytic and blastic lesions. Management of the active disease is based on bisphosphonates, the most widely utilized being zoledronic acid. It is an effective treatment that relieves pain and improves quality of life. Normalization of alkaline phosphatase levels is a useful marker for monitoring the response to treatment. Orthopedic surgery is also utilized to repair fractures.[2,8]

Historical Notes on the Origin of Paget's Disease of Bone

Data concerning the origin of Paget's disease of bone, like anything that has to do with this disorder, are unclear and ill-defined.[6,7,23] It gets to the point in which key sourcebooks on paleopathology do not coincide in its classification, presenting it as a metabolic disease,[24–28] whereas other authors are not so clear, including it in a miscellaneous section.[29–31]

We find that the prevalence rates of the disease are currently high in the British Isles, which is exactly where the most abundant paleopathological evidence is discovered. Moreover, different studies seem to indicate the existence of a higher predisposition of Europeans to develop the disease, leading to the establishment of the hypothesis that the origin of Paget's disease of bone can be found among the populations of northwestern Europe.[32] In any case, the prevalence and severity now appear to be decreasing.[33–35]

This theory was endorsed in a recent work by Mays[36] who presents evidence from the paleopathological study of Paget's disease of bone, confirming that, with a marked difference, the greatest number of documented cases (up to 94%) corresponded to the British Isles. In fact, the disease has a strong genetic component.[37] For example, there is evidence that an optineurin (*OPTN*) gene variant affects the susceptibility of developing Paget's disease of bone and interacts with the TNFRSF11A polymorphism to produce a greater severity of the disease in sporadic cases.[38] The presence of certain mutations may lead to other complications like dementia.[9] Paget's disease of bone has also been seen to share a common molecular mechanism with multiple myeloma, represented by the receptor activator of the nuclear factor-kappa B ligand (RANKL)/osteoprotegerin, and the 2 diseases can occur simultaneously.[10]

According to Mays,[36] some of these factors could have led to the recent extension of the disease to other parts of the world with the arrival of residents of Britain due to colonial conquests.[39] This would explain its existence with prevalences similar to those found in Europe in the United States[11] and New Zealand.[12]

However, we consider that there are two elements of the study that can bias the result and, thus, the conclusions. First, it includes only those cases in which the findings are double-checked by means of a radiological study, in addition to a histological study, which is considered to be essential for the diagnosis of the disease[35]; the current clinical diagnosis is normally radiographic, based on a wide range of changes, and bone biopsy is little utilized.[3,4,13,14] Second, there is a certain publication bias with regard to the paleopathological evidence in Mediterranean countries which, to a large extent, is caused by the existence of something of a lag in the methodological approach to the paleopathological analysis in these areas, as there is no consolidated tradition for performing those studies and publishing the findings. There is also a systematic lack of knowledge about those studies that are not written in English.

As a consequence, although double-checking the evidence is important, we consider that not every case in which that condition is not met should be rejected, especially if a radiological study has been performed.[28,30,31,40] If we extend the search with this criterion, we may find that the total of cases increases, both in number and in geographic regions, including those outside the European continent. Hence, the thesis of the British origin of the disease would come to be seriously debatable.[26]