

CONCISE REPORT

Paget's disease of bone in early adult life

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Objective: To determine the range and activity of the clinical and biological features of patients aged <40 with Paget's disease of bone.

Methods: A retrospective two centre study of 314 patients with Paget's disease of bone from two university hospitals. The disease was diagnosed by radiological, serum alkaline phosphatase (AP) levels, or clinical features, and bone scintigraphy in most patients. Demographic data, reason for diagnosis, bones affected, disease extent using Coutris' index, complications during progression, and disease activity using Renier's index were assessed. Patients over and under 40 were compared.

Results: 18/314 (5.7%) patients were diagnosed before the age of 40; median (SD) age was 35.4 (5.5) (range 18–40) and AP 555.6 (566.3) IU/l (range 70–1949). Coutris' extension index was 12.8 (10.5) and Renier's activity index 35.9 (31.9). Younger patients had more affected bones ($p < 0.05$) than those aged >40, higher level of extension ($p < 0.05$), higher AP value ($p = 0.05$), and greater incidence of thoracolumbar spine disease. Disease activity did not differ significantly between the groups.

Conclusions: Paget's disease diagnosed before the age of 40 is more extensive but not more active, with higher AP values than in those diagnosed after age 40.

Paget's disease of bone (PDB) is characterised by a focal alteration of bone remodelling, which leads to a bone with an anomalous structure and altered mechanical properties, associated with pain and complications.¹ It varies according to the geographical distribution of the study and the age groups analysed.² In Spain, it is estimated to be 1.5%.³ The number of cases increases with age in such a way that in the majority of cases the median age at diagnosis is between 60 and 70.⁴ PDB is occasionally described in early adult life (≤ 40 years old).^{5–9} The extent of the disease and a familial pattern were the most significant characteristics aiding diagnosis in these young patients.

This study aimed at determining the clinical and biological features of PDB in patients diagnosed before the age of 40 and, especially, the range and activity of the condition.

PATIENTS AND METHODS

This was a retrospective study, in which two university hospitals in Catalonia (Spain) participated. Three hundred and fourteen patients (age range 18–90 years; median (SD) 64.4 (12.6)) diagnosed with PDB of bone were included between 1987 and 2002.¹⁰ Eighteen were under 40 years old. Diagnosis of PDB was made using bone scintigraphy with ⁹⁹Tc polyphosphate in most cases. Retrospective analysis included demographic data, reason for diagnosis, bones affected at diagnosis, complications during disease progression, and total alkaline phosphatase activity in serum (25–120 IU/l).

The extent of the disease, calculated according to the percentage of the skeleton affected, was expressed using Coutris' index.¹¹ The extension coefficient of each bone was weighted according to involvement by bone scintigraphy (the whole bone, two thirds, or one third). The theoretical index ranged from 0 (no bone affected) to 100 (the whole skeleton affected).

The index of activity described by Renier *et al* was used to calculate pagetic bone activity.¹² That author feels that serum alkaline phosphatase (AP) represents the sum of normal and pagetic bone activity according to the following formula:

$$\text{Patients' AP} = (\text{pagetic bone AP} \times \text{Coutris' index}/100) + (\text{normal bone AP} \times (100 - \text{Coutris' index})/100)$$

"Phosphatasic" activity of pagetic bone represents the number of times by which the affected bone is more active than the normal bone.

A comparative study applying the SPSS statistical package was conducted between patients aged under and over 40. The descriptive results are expressed as medians (SD). The following tests were used: χ^2 to compare percentages, Mann-Whitney test to compare the distribution of variables between the two groups, and Spearman's correlation coefficient for correlations. A value of $p < 0.05$ was considered significant.

RESULTS

Of the 314 patients, 18 (5.7%) were diagnosed before the age of 40; nine (50%) were men. Median age at diagnosis was 35.4 (5.5) (range 18–40) with no significant differences between the sexes. Table 1 shows the demographic data of these patients. The follow up period was 3.1 (2.5) years. In most cases diagnosis occurred incidentally: in 8/18 (44%) due to an increase in AP, in 3/18 (17%) as a result of radiological anomalies, in 3/18 (17%) because of bone scintigraphy alterations suggesting the condition, and in 2/18 (11%) as a result of articular pain. In two patients the cause of diagnosis was unknown. APs were normal at the time of diagnosis in four patients, in three of whom diagnosis was made incidentally owing to scintigraphic alterations suggestive of the disease and in one because of joint pain.

A family history was noted in three (17%) patients although questions about this were not asked systematically.

Bone involvement in women was 7.9 (7.1) and in contrast 3.2 (2.5) in men ($p = 0.1$). The median number of bones affected was 5.5 (5.7). Thirteen (72%) patients had polyostotic disease. The number of bones affected in the polyostotic disease was 7.2 (5.8). The disease affected between two and five areas in eight (44%) and more than five bones in five (28%) cases.

Bones affected in order of frequency were pelvis (61%), lumbar spine (50%), skull (45%), thoracic spine (44%), femur (28%), tibia (22%), sacrum (11%), and face bones (11%).

Abbreviations: AP, alkaline phosphatase; PDB, Paget's disease of bone

Table 1 Demographic data of the patients aged <40 at diagnosis

Demographic data	Number	Percentage
Patients	18	
Men	9	50
Women	9	50
Age at diagnosis (years)		
18	1	6
26	1	6
32	1	6
35	2	11
36	4	22
37	2	11
38	2	11
39	2	11
40	3	17
Normal alkaline phosphatases	4	22
Raised alkaline phosphatases	14	78
	Median (SD)	Limits
Age at diagnosis (years)	35.4 (5.5)	18-40
Years of monitoring	3.1 (2.5)	0.5-9

Significant differences were observed between those >40 and <40 for involvement of the lumbar spine (29% v 50%; p<0.05) and the thoracic spine (16% v 44%; p<0.01). For the skull, and despite the variation in percentages (29% compared with 45%), no significant differences were found, probably because of the small number of cases. Locations of the monostotic forms were skull (1), sacrum (1) thoracic vertebra (1) and pelvis (2), with no difference compared with those over 40.

In those aged <40 disease extension was 12.8 (10.5) (15.8 (12.6) in men; 10.7 (7.2) in women; p not significant). In the monostotic forms it was 4.5 (2.5) and in polyostotic forms 15.9 (10.7) (p<0.05). Renier's activity index was 35.9 (31.9) (range 1-107.3) The skull was the most active bone in the monostotic forms, with a Renier index of 107.

Seventy three per cent of patients presented complications during progression of the disease. The most common were cranial symptoms: headache, deafness, vertigo, tinnitus, facial pain, increased skull (56%); vertebral symptoms (39%); and bone deformity (27%). Bone pain and joint limitations were less common. Sarcomatous degeneration was not found in any case.

The disease was active at the time of diagnosis in 77% of patients. Median AP was 555.6 (566.3) IU/l (70-1949). AP in the monostotic forms was 267 (330) IU/l (84-856) and in the polyostotic form 675 (610) IU/l (70-1949). AP significantly correlated with the Coutris extension index (p<0.01), number of locations (p<0.01), and Renier's activity index (p<0.01). Table 2 shows the clinical and analytical data.

In the comparative study (table 3) younger patients had more affected bones than older patients (5.5 (5.7) v 3.1 (3);

Table 3 Comparative study results

	Under 40	Over 40
Number of patients	18	296
Number of bones affected*	5.5 (5.7)*	3.1 (3)
Alkaline phosphates (IU/l)*	555.6 (566.3)*	377 (493)
Coutris' extension index*	12.8 (10.5)*	8.7 (6.5)
Renier's activity index	35.9 (31.9)	35.2 (46.3)

Results are shown as median (SD).
*p<0.05.

p<0.05), a higher Coutris extension index (12.8 (10.5) v 8.7 (6.5); p<0.05), a higher AP value (555.6 (566.3) v 377 (493); p = 0.05), and greater frequency of thoracolumbar spine involvement (p<0.03). However, the Renier index was not significantly different (35.9 (31.9) v 35.2 (46.3); p not significant).

DISCUSSION

PDB is diagnosed relatively often among the adult population and its prevalence increases with age. It has been reported on few occasions in subjects aged under 40. In this study, 5.7% of the patients were diagnosed before the age of 40 years. A percentage which is similar to the seminal work of Dickson *et al* (8.1%).⁹ Juvenile Paget's disease (familial idiopathic hyperphosphatasia) should be differentiated.¹³ Its aetiopathogenicity is unknown, although hereditary and environmental factors may have a role. Thirteen to fifteen per cent of patients have a family history of the disease and it is estimated that the risk of incurring the disease is seven times greater in those with a familial history.⁴ These patients usually have an earlier onset and a greater prevalence of deformity. In this study, five (28%) had bone deformity, and a family history was noted in three (17%) patients. Various observations suggest that PDB may result from a bone infection by a slow virus with a subclinical period,¹⁴ which may explain why the disease manifests itself in the fifth or sixth decades of life. This theory does not explain the appearance of cases at early ages.

Renier and Audran estimated the progression of pagetic lesions over the years.¹⁵ They suggested that in 70 patients diagnosed with this disease at 70, bone lesions would have started before the age of 30 in 45 (64%), although diagnosis was made at a young age in only three. Those authors conclude that PDB probably starts in youth but is not diagnosed until later.

As in other studies, diagnosis occurred coincidentally. The increase in complementary tests in clinical practice has highlighted subclinical cases of PDB and this may be one of the reasons why they were diagnosed at a younger age. The particular interest in this condition of one of the hospitals taking part in the study may be another reason for the early diagnosis.

Table 2 Clinical and analytical data of the young patients in the study

	All patients	Monostotic	Polyostotic	Women	Men
Number of bones affected	5.5 (5.7)	1	7.2 (5.8)	7.9 (7.1)	3.2 (2.5)
1	5	5			
2-5	8		8		
>5	5		5		
AP Value (IU/l)	555.6 (566.3)	267 (330)	675 (610)	709.2 (639.8)	421.5 (469.4)
Coutris' extension index	12.8 (10.5)	4.5 (2.5)*	15.9 (10.7)*	10.7 (7.3)	15.8 (12.6)
Renier's activity index	35.9 (31.9)	31.4 (43.3)	37.8 (28.1)	45.3 (32.6)	27.2 (31)

Results are shown as median (SD).
*p<0.05.

The patients in the study presented more extensive disease as shown by the predominance of polyostotic forms and a higher Coutris extension index. The location in the lumbar and thoracic spine may also have favoured diagnosis owing to the relative frequency with which radiography is performed on these areas. In this study patients with cranial involvement had higher AP levels. AP levels were normal at the time of diagnosis in only four patients (22%), a figure similar to that described in a previous study (21.9%).¹² The high percentage of young people with PDB located in the skull may explain the high AP levels and thus the early diagnosis. Although a notable difference is seen between men and women there is no statistical difference, possibly owing to the small number of patients.

PDB in young people is rare and occurs in an extensive form in most cases. It should be taken into consideration, despite age, in patients with a family history of the disease and an increase in serum AP levels. Early treatment of these patients may affect the progression of the disease.

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