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Original Article

Characteristics of Paget's disease in Spain. Data from the National Paget's Register

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ABSTRACT

Objectives: To describe the clinical and epidemiological characteristics of patients included in the National Register of Paget's disease.
Methods: A Register of patients with Paget disease (PD), radiologically confirmed, and pertaining to 25 hospitals was analyzed. Clinical and epidemiological data were collected, including age, sex, date, and presentations at time of diagnosis, treatment, quality of life (QL) (EuroQol 5D) and perceived health, environmental factors (profession, history of measles, contact with animals, dairy consumption, housing conditions, place of birth and address) and family history (PD history, origin of the ancestors, number of children). We conducted a statistical description of the data.
Results: The register included 602 patients with an average age of 62 (11) years and a predominance of male (55%). Of the patients included, 79% showed symptoms at the time of diagnosis, mainly pain (83%); 82% had received treatment, mainly bisphosphonates (47% more than one drug). Despite treatment, a significant proportion had limitations in their QL, especially related to pain (64%), mobility (47%), and anxiety/depression (33%). Most of the patients had been exposed to situations which were considered as risk factors. Of the patients included, 14% had family history of PD and 1.5% had children with PD. The ancestors of the familial cases came more frequently from Ávila, Salamanca, La Coruña, and Málaga.
Conclusions: The pain and the limitation of mobility decrease the QL of patients with PD despite treatment. Frequently, patients have a history of exposure to risk factors

Características de la enfermedad ósea de Paget en España. Datos del Registro Nacional de Paget

Palabras clave:
Enfermedad de Paget
Registro nacional
Características de los sujetos

RESUMEN

Objetivo: Describir las características clínicas y epidemiológicas de los sujetos incluidos en el Registro Nacional de Paget.
Sujetos y método: Registro de pacientes con enfermedad ósea de Paget (EOP), confirmada radiológicamente, de 25 centros participantes. Se recogieron datos clinicoepidemiológicos (edad, sexo, fecha y manifestaciones al diagnóstico y tratamientos), calidad de vida (CV) (cuestionario EuroQol de 5 dimensiones), estado de salud, factores ambientales (profesión, antecedentes de sarampión, contacto con animales, consumo de lácteos, condiciones de la vivienda, lugar de nacimiento y domicilio) y familiares (historia de EOP, procedencia de los ascendientes y número de hijos). Se realizó una descripción estadística de los datos.

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Resultados: El registro incluyó a 602 sujetos con edad media de 62 (11) años con predominio de varones (55%). El 79% de los sujetos presentaba síntomas en el momento del diagnóstico, fundamentalmente dolor (83%). El 82% de los sujetos había recibido tratamiento, principalmente bisfosfonatos, con más de un fármaco en el 47% de los casos. A pesar del tratamiento, una proporción importante tenía limitación de la CV, especialmente relacionada con dolor (64%), movilidad (47%) y ansiedad junto con malestar (33%). La mayor parte de los sujetos habían estado expuestos a situaciones que se consideran factores de riesgo. El 14% de los sujetos tenía historia familiar de EOP y el 1,5% de los sujetos tenía hijos con EOP. Los ascendientes de los casos familiares procedían con más frecuencia de Ávila, Salamanca, Málaga y La Coruña.
Conclusiones: El dolor y la limitación de la movilidad disminuyen la CV del sujeto con EOP a pesar del tratamiento. Son frecuentes los antecedentes de exposición a factores de riesgo.

Introduction

Paget's bone disease (PBD) is a focal alteration of the bones that is generally diagnosed after 50 years of age. Prevalence in Spain is 0.7% to 1.3%[1,2] and its geographical distribution is irregular, with zones of high prevalence.[3] The affected bone is deformed, increasing the risk of complications, such as fractures in weight bearing areas, Pagetic arthropathy, or compromise of nervous system structures. As a consequence, many subjects have pain and limitation of movement that reduce their health related quality of life (QL).[4] On rare occasions, PBD degenerates into osteosarcoma.

The main lesion consists in a proliferation and an activation of osteoclasts of the affected bone areas with a notable increase in bone exchange. The result is a plexiform bone, of a larger size, deformable and fragile, associated to hypervascularization and peritrabecular fibrosis. The lesion affects one or several bones (without a tendency for metastasis), while the rest of the bone tissue remains unchanged in its structure or metabolism.

The disease has an unknown origin, although it presents a hereditary component on which external factors would act; probably paramixovirus.[5] The genetic and family studies support the theory of a dominant autosomic transmission with variable penetrance. Mutations of the sequestosome-1 (SQSTM1) gene have been described in subjects with PBD.[6] SQSTM1, also known as p62, is a ubiquitin binding protein that acts on RANK receptor activation (NF-kB receptor activator) through activated transduction signals mediated by the tumor necrosis factor (TNF) and interlekin-1, through TRAF6 (TNF receptor associated factor 6).[7] Numerous authors have mentioned the importance of a hereditary factor that can affect RANK signal in osteoclasts, both in family cases as in sporadic ones.

The clinical and epidemiological knowledge of PBD in Spain has increased and even surpassed that of other European countries. In addition, there is information available on its frequency and the existence of high-prevalence areas in central regions (Ávila, Madrid, Salamanca, and Zamora).[8–11] There is also data on the frequency of familiar cases.[12–14] There are less published series with clinical and prognostic data[15] and no information is available on the influence of treatment on the diseases natural progression, because the therapeutic response is measured fundamentally by the descent in the bone exchange.[16]

Patient registries are useful to know the epidemiological and clinical characteristics of a disease.[17] The National Paget Registry was created with the idea of obtaining data of subjects with PBD to analyze their characteristics and serve as tools in future research. This registry includes data of subjects previously diagnosed and attended by the health centers interested in the study of this disease. These characteristics make the population and geographical distribution uneven. From this data, the evaluation of the disease profile, determining their distribution and geographical and compare these results with that of other countries that possess similar registries. Although their conclusions are not applicable to the whole of the Spanish population, the knowledge of the impact of the disease, the variability in its expression and the response to treatment would allow for the planning of diverse actions.

The objective of this work is to describe the clinical and epidemiological characteristics of subjects included in the National Paget Registry.

Subjects and methods

We carried out a transversal registry of the disease. Included subjects were previously diagnosed and therefore it was not necessary to perform a radiologic survey of asymptomatic subjects in order to look for cases. The inclusion criteria were the diagnosis of PBD confirmed by radiology and the signing of informed consent. Subjects that invited to participate were included in administrative databases or in research bases of the participating centers. Although some of the data was obtained from the clinical history (date of diagnosis, initial signs and symptoms and corroboration of treatment), most of the information was recovered directly from the subjects through the mail or in person. For the data retrieval, a web questionnaire was designed and its access were limited through the use of a username and password.

Identifying data of the subjects was not included, which only the attending physician knew, something that was extended to maintaining confidentiality and safety of the data through adequate support type strategies.

The study was performed according to the principles of the Declaration of Helsinki in its last review[18] and according to the recommendations of the Spanish Society of Rheumatology[19]; and the Ethics committee of the Hospital Clínic of Barcelona reviewed and approved it.

The information recovered was based on the Paget Registry of New England[17] and was divided in several parts:

1) Clinico-demographic: data on gender, date of birth, date of diagnosis, year at the beginning of symptoms, type of symptoms (pain, deformity, deafness, fractures, and an increase of the total alkaline phosphatase) and treatments received.
2) QL: the 5 dimension EuroQol questionnaire (movement, personal care, daily activities, pain and malaise and anxiety and depression)[20] in addition to one question on the perception of the subject with respect to their current health status, measured through a visual analog scale (VAS) scored from 0 (worse health status imaginable) to 100 (best possible health).
3) Environmental: the objective of this part was to identify the exposure to possible risk factors, especially infectious in origin. Information on the locality, province and nation of birth, weight at birth, number of brothers, place among the brothers, history of measles, common contact with animals (dogs, cats, birds, rodents,

amphibians, simians, horses, cows, sheep among others), history of consumption of unpasteurized milk, conditions of the home during infancy, places of residence in the year prior and current employment situation.

4) Family: the family history of PBD, the number of children, the number of children, the exposure of the children to measles, vaccination for the virus and the presence of PBD in the children. In cases with the family history, data was obtained on the place of origin of the paternal and maternal ascendants (locality, province, and country).

Statistical analysis

In first place, a process of database clearance, resolution of possible inconsistencies, and creation of new variables. In second place, a description of the sample obtained was performed through the use of central tendency measures (means and medians) and dispersion measures (standard deviation and interval) in the case of the quantitative variables, and percentage distribution in the case of qualitative variables. In addition, summary variables were created in the case of multiple response questions. The analysis was performed with Stata 10.0 (StataCorp, College Station, TX).

Results

The National Paget Registry was maintained open for more than 15 months and closed in September 2007. Six hundred two cases of PBD were included from 25 centers (Table 1), all of them with a radiologically confirmed diagnosis.

Clinico-demographic questionnaire (Table 2)

In the distribution according to gender there was a predominance of males (55%) over females (45%). The mean age of the subjects was 62 (11) years (median, 63; interval, 28-92).

The most frequent initial symptoms was pain (65%) followed by deformity (19%), and the most infrequent symptom was fracture (5%). At the moment of registry entry, 21% of the subjects was asymptomatic, while 56% of the subjects presented a symptom, 19% presented 2 symptoms, and 4% had 3 of the investigated symptoms.

Most of the subjects had received treatment for PBD (82%), mainly risedronate (55%), calcitonin (32%), tiludronate (19%), and alendronate (19%). Nineteen percent of the subjects had not received treatment, 35% of the subjects had received 1 drug and 47% of them had received 2 or more drugs. A temporal difference in the use of these was observed, because before the year 1995, the most used was calcitonin (61% of subjects) while after the year 2000, only 11% used calcitonin.

Quality of life questionnaire (Table 3)

Each one of the dimensions of the 5 dimension EuroQol questionnaire had 3 response categories: no problems, moderate problems, and severe problems. In order to dispose of the percentage of subjects with moderate or severe problems, the 2 last response options were regrouped. Pain and malaise were the dimension which was associated to a moderate or severe limitation with more frequency (64% of subjects) followed by mobility (47% of subjects). The dimension corresponding to anxiety and malaise reached 33%. In the evaluation of the current health status, a mean VAS score of 65 (21) (median, 67 points).

Table 1
Distribution of the subjects according to the participating center

Center	Province [a]	No.	%
Hospital General Universitario de Elche	Alicante	18	3.0
Hospital Nuestra Señora de Sonsoles	Ávila	48	8.0
Hospital Clínic i Provincial	Barcelona	28	4.6
Hospital de Viladecans	Barcelona	17	2.8
Hospital Germans Trias i Pujol	Barcelona	10	1.7
Hospital de la Santa Creu i San Pau	Barcelona	30	5.0
Instituto Municipal de Asistencia Sanitaria	Barcelona	50	8.3
Hospital General de Granollers	Barcelona	24	4.0
Hospital Universitario Puerta del Mar	Cádiz	24	4.0
Hospital Universitario Reina Sofía	Córdoba	22	3.6
Hospital Universitario de Guadalajara	Guadalajara	18	3.0
Hospital General San Jorge	Huesca	18	3.0
Hospital Arquitecto Marcide	La Coruña	25	4.1
Hospital del Bierzo	León	13	2.1
Hospital Arnau de Vilanova	Lérida	20	3.3
Hospital Universitario La Paz	Madrid	41	6.8
Hospital Ramón y Cajal	Madrid	17	2.8
Hospital General Carlos Haya	Málaga	32	5.3
Hospital Clínico Virgen de la Victoria	Málaga	14	2.3
Hospital Virgen de la Arrixaca	Murcia	5	0.8
Hospital Universitario Virgen de la Vega	Salamanca	25	4.1
Hospital Virgen de la Salud	Toledo	40	6.6
Hospital de Basurto	Vizcaya	41	6.8
Hospital Universitario Miguel Servet	Zaragoza	22	3.6

[a] In alphabetical order.

Table 2
Descriptive analysis of the clinico-demographic questionnaire

Variable	No.	%
Radiological diagnosis	602	100
Gender		
Male	329	54.6
Female	273	45.3
Initial signs and symptoms (multiresponse)		
Pain	391	64.9
Deformity	114	18.9
Deafness	68	11.3
Fractures	29	4.8
Total increase in alkaline phosphatase	32	5.3
Distribution of the number of symptoms and signs		
0	129	21.4
1	337	56.0
2	112	18.6
3	23	3.8
4	1	0.2
Treatment for Paget	495	82.2
Risedronate	329	54.6
Calcitonin	192	31.9
Tiludronate	116	19.3
Alendronate	114	18.9
Etidronate	106	17.6
Zoledronate	37	6.1
Pamidronate	36	6.0
Chlodronate	28	3.0
Other drugs	16	2.7
Year of diagnosis		
Before 1995	195	33.4
Between 1995 and 2000	183	30.4
2001 and after 2001	224	37.2
Distribution of the number of drugs received		
0	107	17.8
1	213	35.4
2	148	24.6
3	93	15.4
4	30	5.0
5	10	1.7
6	1	0.2

Environmental questionnaire

Of the 602 individuals in the sample, 594 were born in Spain (98.7%). The provinces of origin with a greater frequency of the disease were Barcelona (11%), Ávila (10%), Toledo (7%), and Salamanca (5%).

The mean weight at birth was 3511 g (656) g (median, 3500 g; interval, 1000-4700). The mean number of brothers was 4 (2.6) and 50% of individuals occupied the second place among the brothers.

In relation with the exposure to possible risk factors, 65% of the patients had had measles, although 29% were unaware of the fact. Eighty percent of the subjects had had contact with at least one domestic animal, most frequently dogs (70%), cats (48%), and birds (38%). Seventy-five percent of the registry participants had consumed unpasteurized milk in the past.

In relation with the employment status, 53% of the subjects were retired, while only 13% of the subjects were active in their employment (Table 4).

With respect to the living conditions during infancy, subjects shared a home with a mean 6.3 (2.4) persons (median, 6; interval, 1-14); the mean number of rooms at their home was 3.6 (1.7) (median, 3; interval, 0-11) and 50% did not have a bathroom in their home with a mean 0.5 (0.6) (median, 0; interval, 0-3).

Family questionnaire

Forteen percent of the subjects in the registry had a family history of PBD. Twenty were identified in Ávila, 10 in Salamanca, 7 in Málaga, and 6 in La Coruña. The most common origin of the maternal ascendants was Ávila (29%), Salamanca (15%), and Málaga (10%) for the grandmother; and Ávila (31%), Salamanca (15%), and La Coruña (9%) for the grandfather. In the case of the paternal ascendants, the most common provinces were Ávila (31%), Salamanca (15%), and Málaga (9%) for the grandmother; and Ávila (31%), Salamanca (17%), and La Coruña (9%) for the grandfather.

Eighty-nine percent of the subjects had children, in a mean number of 2.7 (1.5) (median, 2; interval, 1-13). Eighty-eight percent of the children of Paget patients had been exposed to measles and 64% had been vaccinated against it. The disease was also present in 1.5% of children of those on the registry who had descendants.

Table 4
Exposure to situations considered as risk factors

Factor	No.	%
Measles		
No	35	5.8
Yes	390	65.2
Unknown	173	28.9
Contact with animals (multiresponse)		
Dogs	367	70.0
Cats	292	48.5
Simians	2	0.3
Birds	229	38.0
Rodents	67	11.1
Horses	159	26.4
Sheep	150	24.9
Other animals	78	13.0
Distribution of the number of animals		
0	123	20.4
1	132	21.9
2	72	12.0
3	103	17.1
4	52	8.6
5	51	8.5
6	32	5.3
7	27	4.5
8	10	1.7
Consumption of unpasteurized milk	451	75.5
Current employment status		
Job activity	81	13.6
Employed	78	13.1
Unemployed	2	0.3
Retired	315	52.8
Retired, before work	80	13.4
Retired without a job	36	6.0
Retired with a job	5	0.8

Discussion

In this article, data of subjects with PBD included in the first phase of the National Paget Registry is described, data gathered in a multicentric transversal study formed by 602 subjects with PBD. This data corresponds to the largest series ever published in Spain and exceeds that of the best registry to date on PBD.[21] Data referring to distribution by gender and age is similar to that of other series, with a discreet male predominance.[20–23]

On numerous occasions the subjects were asymptomatic at the moment of diagnosis,[24] situation that is observed in up to 50% of some series.[25] Only a little over 20% of these subjects was in this situation. Bone pain is important in PBD and appears in 2 of every 3 subjects and increases with age.[17] In this study, pain was the most frequent symptom at diagnosis. Although pain is commonly characterized as originated from the bone, it must be considered to be related to bone deformity and have a joint or neurological origin. An elevated percentage of subjects has associated joint alterations, osteoarthritis or a Pagetic arthropathy which can be the cause of pain in up to 56% of subjects.[25,26] This type of pain is less susceptible of modification with antiresorptive therapy. Other manifestations, such as deformity, deafness or fracture, were present in less than 20%.

Table 3
Quality of life: subjects with moderate or severe problems

5 dimension EuroQol questionnaire	No.	%
Movement	284	47.4
Personal care	141	23.7
Daily activities	141	23.8
Pain and malaise	383	63.9
Anxiety and depression	194	32.7
VAS score, mean (SD)	64.9 (21.4)	

Abbreviations: SD, standard deviation; VAS, visual analog scale.

The finding of a suspicious radiological lesion or the elevation of alkaline phosphatase can be the method of establishing the diagnosis in asymptomatic patients. According to data from the registry, radiology has been the most commonly employed method of detection in asymptomatic patients, while laboratory data is used with a much lesser frequency (less than 5%).

Most of the subjects has received pharmacologic treatment, 47% with more than one drug. The most commonly employed drugs were mainly risedronate and tiludronate. However, in a good amount of patients, other biphosphonates have been used which do not have an indication in the treatment of PBD. In addition, the use of salmon calcitonin in 32% of subjects is noticeable, because it is considered to be a second line drug by the PBD treatment guidelines.[27] Most of the subjects received treatment before 1995, but their use was noticeably reduced after the introduction of the newer generations of biphosphonates in the treatment of PBD.

The disease is the cause in a reduction in the QL.[20] Several authors have approached this subject through the use of different instruments, mainly the SF-36 (36-items Short-Form self-questionnaire) and the 5 dimension EuroQol,[4,20,25] and point to the fact that the pain and the movement are the most affected variables, which coincides with what has been observed in these subjects. However, it is necessary to take into account that most of the subjects had received treatment,

including several drugs which are considered effective. Even when efficacy is usually measured in terms of the reduction in bone exchange, it has been proven through clinical trials that treatment with oral and intravenous biphosphonates reduce pain and improve QL.[16] However, Langston et al found results similar to those in this study in the PRISM clinical trial.[20] This can be due to the fact that treatment is reserved for symptomatic patients and therefore, to phases in which complications have less possibilities to respond. There is no data on the usefulness of treatment in the initial phases of PBD, at which time complications have not appeared.

Anxiety and depression produce an important deterioration of the QL of these subjects in some studies,[20] but not in all.[21,25] These variables affect the QL of 32% of our patients. However, the significance of this relationship has not been studied.

Many patients were exposed to situations that are considered as risk factors for PBD due to its relation to paramixovirus, as well as a history of measles and domestic animals.[28] Other possible vehicles of an exogenous agent which leads to PBD are the consumption of contaminated water or food,[29] which happened in 75% of subjects.

An important part of the patients comes from high prevalence zones.[3] The percentage of subjects born in other places such as Barcelona, Toledo, or Málaga, must be taken with prudence although it could be related to high prevalence areas, it could also be influenced by the higher proportion of centers and subjects included in the registry that corresponded to these zones.

The proportion of children that presented PBD was less than those that had a family history, but in this circumstance it must not be interpreted as a reduction in the frequency of PBD because the age at appearance is late and the pattern of inheritance has a variable penetrance. Because of this, children of patients with PBD can benefit from a timelier diagnostic measures and early treatment plan.

This study has some limitations derived mainly from its nature, by including a non random sample and, therefore, my not be representative nor generalizable to the Spanish population. In addition, and because it still is an initial stage in the registry, no information can be extracted on the natural progression of the disease. Lastly, the geographical distribution must be considered because the sample is more related to the participation of centers interested in PBD than with the population density (Table 1), obliging us to be cautious when evaluating the results of the origin of patients and their ancestors.

In spite of all of this, the study has a large series of patients with trustworthy data and results from different parts of the country, which will allow in the future to plan more precise research on the clinical behavior and epidemiological pattern.

In summary, this is a transversal, multicentric study that collects clinical data, the health related QL and the environmental and familiar factors of an ample series of subjects with PBD in Spain. Although some cases are asymptomatic, pain and movement limitation are frequent and cause a reduction in the QL, in spite of having received treatment, fundamentally with biphosphonates. The exposure to environmental factors related to paramixovirus is common. This data corresponds to an initial phase of the National Paget Registry that must be completed after a follow-up phase to evaluate the progression of PBD. It must also be the basis of the study that allow us to know the frequency, family history and the existence of high-prevalence areas.

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Apendix

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