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Original article

Environmental factors associated with familial or non-familial forms of Paget's disease of bone

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ABSTRACT

Objectives: The most frequent mutation linked to Paget's disease of bone (PDB), *p.Pro392Leu* within *SQSTM1* gene, leads to phenotypic characteristics of PDB, but this mutation is seemingly insufficient to result in complete pagetic osteoclast phenotype, suggesting that possible environmental factors play a role in PDB pathogenesis. We performed an exploratory study to identify environmental factors potentially associated with familial or non-familial form of PDB in the French-Canadian population.
Methods: We investigated environmental factors through a questionnaire in 176 pagetic patients, including 86 patients with a familial form, and 147 healthy controls. All participants lived in the same geographic area, within a 120 km radius of Quebec City. Associations between environmental factors and familial and non-familial forms of PDB were searched.
Results: In the multivariate model adjusted for intra-familial correlation, PDB was associated with wood fired heating in childhood and/or adolescence (OR = 2.10; 95% CI 1.13–3.90, $P = 0.02$). In the multivariate model without considering correlation for family relatedness, familial form of PDB was associated with residency near a mine (OR = 11.70; 95% CI 2.92–46.80, $P < 0.01$) and hunting (OR = 2.92; 95% CI 1.14–7.47, $P = 0.03$). Wood fired heating during childhood and/or adolescence ($P = 0.02$) was associated with both familial and non-familial forms.
Conclusions: In conclusion, PDB was significantly associated with wood fired heating in childhood and/or adolescence, regardless of the form of PDB, familial or not.

1. Introduction

Paget's disease of bone (PDB) is characterized by an increased bone turnover in which osteoclasts are increased in size, number and nuclearity. This accelerated bone resorption by osteoclasts is coupled with increased osteoblast activity, resulting in a disorganised architecture of new bone, which is weak and subsequently prone to fracture [1]. Although often asymptomatic, PDB can be complicated in around 30% of cases by bone pain, osteoarthritis, shortening and deformation of limbs resulting in walking difficulties, fractures, headache, deafness, cranial nerve palsy and hydrocephalus [2]. Sarcomatous degeneration may happen in 0.3% of patients [2]. Populations originating from North-West Europe are more afflicted by PDB, which advocates for a genetic component. Both prevalence and disease extent have been reported to decrease, whereas the age at PDB diagnosis has increased over recent years [3,4], even in offspring inheriting *SQSTM1* gene mutations [5,6]. Although significant regional differences were reported in several countries [7–10], the decline of PDB prevalence was mostly reported in countries, which previously featured a high prevalence [11,12]. This finding suggests that one or more environmental factors could be involved in PDB pathogenesis [11,12]. The secular declining of both prevalence and severity of PDB in the British population also suggests a role for environmental factors [11,12]. This observation may only be partially explained by the influx of migrants from relative low prevalence regions, such as the Indian subcontinent [13]. The high prevalence of PDB in Lancashire (England) may also be related to environmental factors, such as mining and outdoor air pollution.

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One third of patients have a familial form of PDB, which is transmitted as an autosomal dominant mode of inheritance with high but incomplete penetrance [14]. Each first degree relative has a 50% theoretical risk of being afflicted with PDB [15,16]. Detection of mutations in *Sequestosome1* (*SQSTM1*) gene has put in evidence the strong genetic component of PDB [17]. The *p.Pro392Leu* mutation within *SQSTM1* gene has been initially reported in 46% of familial forms and 16% of sporadic forms of PDB in the French-Canadian population [18]. Few epidemiological studies were performed, but no environmental factor has been clearly identified to date in *p.Pro392Leu* mutation carriers [19]. The hypothesis of a viral etiology remains controversial [20]. In addition, some studies have shown associations with rural lifestyle and animal contact [21–24], but no specific substance has really been identified in epidemiological studies.

We made the assumption that exposure to environmental factors as reported above could be associated with PDB. Using data from our French-Canadian cohort, our exploratory study aimed at identifying potential environmental factors associated with familial or non-familial forms of PDB.

2. Methods

2.1. Recruitment of participants

The present study was approved by the CHU de Quebec-Université Laval Ethics Committee. After information on the study, all participants signed a consent form before recruitment. We performed a case-control study, including French-Canadian patients recruited at the rheumatology clinic of our university hospital, the CHU de Quebec, or via their relatives. More specifically, patients with a familial form of PDB and their affected relatives, unrelated affected individuals (non-familial form), and controls were recruited. Controls were unrelated healthy adults without personal or familial history of PDB and with normal total serum alkaline phosphatase levels at inclusion. None of the controls carried any mutation in *SQSTM1* gene. Controls were not matched for age and sex with PDB patients. All participants lived in the same geographic area within a 120 km radius of Quebec City. For all affected participants, the status for the *p.Pro392Leu* mutation, age at diagnosis, duration of disease and number of affected bones if applicable, were known at the time of recruitment [14,18], in addition to Renier's index for PDB extent estimate [25]. A complete assessment of bone health, including measurement of total serum alkaline phosphatase level, radiographs of the pelvis and skull, and a whole-body bone scan was performed for each affected participant. An affected participant was diagnosed with PDB if at least two of the following criteria were satisfied:

- an increase in total serum alkaline phosphatase level and/or;
- a typical aspect of PDB on bone radiographs and/or;
- an abnormal whole-body bone scan, as previously reported [18,26].

2.2. Evaluation of exposure to environmental factors through a questionnaire

We enrolled affected participants and controls from June to September 2011, and investigated environmental factors through a telephone interview questionnaire. The questionnaire was administered by two interviewers (JD, MCA) between August 2011 and May 2012 and included the following sections: sociodemographics (gender, date of birth, education), physical characteristics (weight, height, eye color, weight loss), childhood sickness and vaccines (chickenpox, measles, mumps, whooping cough, rubella), tobacco exposure, diet (wheat, unpasteurized dairy products, spinach, mushroom, fish, shellfish, raw meat, wild meat, offal), drink (origin of drinking water, alcohol), residency (birth place, place of residence, wood fired heating, proximity (< 1 km) of a farm or a mine), work, leisure and animal contact. Exposure to environmental factors was defined either during childhood/adolescence or adulthood.

2.3. Statistical analyses

We first searched for associations between environmental factors and PDB by comparing 176 affected participants, including both familial and non-familial forms, and 147 healthy unrelated controls. Analyses adjusted for gender with and without correlation for familial relatedness were performed for each environmental factor, and odds ratio (OR) and their 95% confidence intervals (95% CI) were calculated. All factors with a P-value < 0.10 were included in a multivariate logistic mixed model. A backward algorithm was then performed and factors with a P-value < 0.05 were retained in the final model.

Associations between environmental factors and familial or non-familial forms were also searched by comparing 86 individuals with a familial form, 88 participants with a non-familial form and 147 unrelated healthy controls. Multinomial analyses adjusted for gender were first performed, and odds ratio (OR) and their 95% confidence intervals (95% CI) were calculated. A final multivariate multinomial model was then constructed including factors with a gender-adjusted P-value < 0.10 and using a backward algorithm to retain those with a P-value < 0.05. For this analysis, models without correlation for familial relatedness were performed since controls and individuals with the non-familial form of PDB have no relatives, thus leading to no variation in the random effect associated to family for these individuals. However, an analysis with correlation for familial relatedness including only individuals with the familial form of PDB and controls was performed to validate that results observed with the previous model without correlation are consistent with those obtained when correlation is taken into account.

2.4. Role of the funding source

The funding source has supported the salary of the interviewer as well as office expenses.

3. Results

We contacted 617 individuals. Three hundred and firty of them consented to participate in the study. Among those participants, 323 completed the questionnaire, including 176 affected participants (86 with a familial form and 88 with a non-familial form) and 147 healthy controls (Fig. 1). General characteristics of affected participants are reported in Table 1 and Tables S1–S2 [See the supplementary material associated with this article online]. The proportion of males was higher in affected participants with familial (41.9%) and non-familial form (60.2%) of PDB than the unrelated healthy controls (23.8%). The mean age of affected participants was not significantly different from controls, 73.3 ± 8.4 versus 71.9 ± 10.1 years (Table S3). The *p.Pro392Leu* mutation was present in 27.3% of affected individuals and in 81.3% of patients with a familial form of the disease (data not shown).

3.1. Association study of environmental factors with PDB

In the gender-adjusted analyses with correlation for familial relatedness, PDB was associated with many of the investigated environmental factors (Table S3). For instance, PDB was significantly associated with rural residency during childhood and