Turkish Journal of Endocrinology and Metabolism, (2000) 4 : 143-146 **ORIGINAL ARTICLE**

HLA Typing in Turkish Patients with Paget's Disease of Bone

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Paget's disease of bone is a disorder of bone, primarily affecting elderly population. The disease causes a structural disorganisation of of bone tissue in affected sites. The etiology is unknown. Microrganisms and/or genetic tendecy are clamied to play role in the etiopathogenesis. Evidence exists to support the genetic etiologies such as familial clustering and HLA linkage or chromosomal abnormalities. To demonstrat e the genetic linkage we performed HLA typing of 15 patients with Paget's disease of bone and 60 control subjects. A total of seventyone antigens were studied in various loci (Class I antigens: 53, Class II antigens: 18). Statistical analysis revealed that the HLA Q8 was a more prominent antigen in patients (χ^2 test; p:0.02).

Our findings did not support previous studies where HLA DR2 was addressed as the responsible antigen, however, did reveal an antigen which belongs to Class II HLA loci which harbors the HLA-DR2, DR6 antigens, previously shown to play role in etiopathogenesis of the disease. Our results must be confirmed by larger samples.

Key words : Paget's disease of bone, etiology, HLA typing

Introduction

Paget's disease of bone is a disorder of bone remodelling, characterized by an increase of bone resorption and compensatory new bone formation. The disease causes a structural disorganisation of bone tissue of affected sites. The etiology of Paget's disease is unknown. Recent progress in Paget's disease research includes new data regarding the etiology of this disorder and the ongoing development of more effective therapies.

Osteoclasts in this condition contain intranuclear and cytoplasmic structures that are thought to be viral nucleocapsids of the Family Paramyxoviridae (1). However, this finding may not be specific to Paget's disease, because viral-like inclusions have been noted in other skeletal disorders, e.g., giant-cell tumors (2), pycnodysostosis (3) and osteopetrosis (4); thus their relevance to Paget's disease remains controversial.

Genetic factors may play an important role in the pathogenesis of Paget's disease. Between 14 and 25 percent of family members of patients with Paget's disease eventually contract the disease (5,6). Familial aggregation studies indicate that first degree relatives of patients with Paget's disease have a sevenfold increase in risk of developing the condition (6-9). An increased frequency of particular HLA DQ and DR antigens was found in patients with Paget's disease (10). In families with apparent autosomal dominant inheritance of Paget's disease, there may be a susceptibility locus on chromosome 18 (11).

Because of the mass amounts of evidence supporting the linkage of HLA to Paget's disease of bone in the present study we aimed to demonstrate whether there is a linkage between Paget's disease of bone and HLA.

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Materials and Methods

15 unrelated, untreated, patients (10 women, 5 men) who attended to osteoporosis research clinic at this institution in Izmir, were studied. There were no exclusion criteria. The diagnosis of Paget's disease of bone was based on typical roentgenographic features and a positive bone scan. Serum alkaline phosphatase was elevated in all patients. The control group consisted of 60 (22 men and 38 women), healthy, unrelated, organ donators. They all had normal serum alkaline phosphatase activity and no clinical signs of Paget's disease. Control subjects belonged to the age group similar to that of patients (58,53 ± 6.47 vs 56,53 ± 5.71).

All patients and control subjects were studied for the serologically defined HLA class I (A,B, and C) and class II (DR and DQ) antigens. The number of antigens tested at the various loci was 71 (Class I antigens: 53, Class II antigens: 18). Tissue typing for HLA-A, -B, -C was performed using the standard two-stage microcytotoxicity assay. HLA-DR and DQ determination was done on T-cell-depleted, B-cell-enriched lymphocytes by extended incubation microcytotoxicity testing (12).

Statistical analysis

HLA antigen frequencies in patients and control subjects were compared using χ^2 2x2 two-tail test and odd's ratio. For odd's ratio, confidence intervals containing "1" and for χ^2, **p** values less than 0.05 were accepted statistically significant. Program used for statistical analysis was SPSS 6.0 for Windows.

Results

An increased frequency of several antigens was found in patients compared with control subjects (Table 1). The most striking finding was the increased frequency of HLA-DQ8 in patients compared with control subjects (%26.7 vs %5).

Table 1. Increased HLA Frequencies in Askhenazi Patients with Paget's disease of bone compared to control subjects.

Antigens	patients (%)	controls (%)	odd's ratio	χ^2	p
HLA- DQ8	26.7	5	6.909	6.65	0.02

Discussion

There are questions in Paget's disease of bone awaiting to be answered regarding the type of hereditary transmission, and the manifestation at old age, and discordance of HLA results in Paget's disease of bone.

Some studies hypothesize viral and bacterial infections as a cause of the Paget's disease of bone and one of the most prevelant amongst these viruses in USA is measles virus and in England is Canine Distemper Virus (13-16). However many recent studies could not confirm the viral association (17,18), hence viruses associated with Pagetic osteoclasts could be opportunistic rather than causative.

Several studies in 1970's failed to find an association between Paget's disease of bone and histocompability antigens of the A and B loci (19-21). On the other hand, studies of several families with multiple cases of Paget's disease of bone suggested a possible genetic linkage with HLA class I loci (22,23). Later studies that extended to the Class II antigens demonstrated a possible linkage to DR antigens, especially DR2 antigen (24,25) and in one study DR6 (26). Some authors could not demonstrate HLA linkage (27), yet opposition is rare. Recently chromosome 18q has been suggested to involve in the etiolopathology of Paget's disease of bone (28-31), however several authors do not support this finding (32,33).

Our results displayed that DQ8 antigen was more frequently expressed in Paget's disease patients than control subjects. In the literature, HLA-DQ8 is addressed to increase the susceptibility to romatoid arthritis and type 1 diabetes mellitus (34-37). So far no study has suggested the HLA DQ8 antigen as an etiologic factor for Paget's disease of bone, still the antigen belongs to Class II HLA loci which was previously shown to harbor antigens possibly associating with Paget's disease; HLA-DR2, -DR6. Possibly due to small number of patients tested we are not able to confirm the correlations between HLA antigens and Paget's disease which has been reported in the literature (HLA-A1, HLA-DR2, -DR6) or the difference in our findings could be explained on the ethnical grounds.

In conclusion, the data from the present study suggest that HLA-D-linked abnormalities may be associated with predisposition to Paget's disease of bone. The increase in HLA-DQ8 antigen should be confirmed by a larger number of samples in order to prove the strict correlation of these antigens to

the disease and their involvement with its etiopathogenesis.

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