Eur Arch Otorhinolaryngol (1996) 253 : 501–503

BRIEF COMMUNICATION

T. Miyazawa · C. Tago · H. Ueda · H. Niwa
N. Yanagita

HLA associations in otosclerosis in Japanese patients

Received: 13 December 1995 / Accepted: 27 February 1996

Abstract Otosclerosis is a disease of the otic capsule that is caused by abnormal resorption and redeposition of bony tissue. Sixty-two unrelated Japanese patients exhibiting clinical otosclerosis were typed for HLA-A, -B, -C antigens. Twenty-one of the patients were also typed for DR antigens. The frequency of HLA-Aw33 was significantly higher in otosclerosis patients than in the control group (24.2% vs 9.5%). This finding suggests that the presence of HLA-Aw33 antigens may be related to an increased susceptibility to otosclerosis or to its clinical outcome.

Key words Deafness · Otosclerosis · HLA antigens

Introduction

Otosclerosis is a disease of the otic capsule that is caused by abnormal resorption and redeposition of bony tissue. The most common location for a focus is anterior to the oval window. Otosclerotic changes may gradually invade the annular ligament and stapes, causing bony ankylosis of the stapes and conductive deafness (clinical otosclerosis).

Morphological features of the pathological process are well known, but the etiology remains controversial. Otosclerosis is now considered to be an inherited disorder, with most studies indicating an autosomal dominant mode of inheritance with incomplete penetrance of about 40% [7, 13]. These findings suggesting hereditary factors are believed to play a significant role in expression of the disease [14].

T. Miyazawa (✉) · C. Tago · H. Ueda · N. Yanagita
Department of Otorhinolaryngology, School of Medicine, Nagoya University, 65 Tsurumai-cho, Showa-ku, Nagoya, 466, Japan

H. Niwa
Clinic of Otorhinolaryngology, National Nagoya Hospital, 4-1-1, Sannomaru, Naka-ku, Nagoya, 460, Japan

Various genetic markers have been investigated to identify hereditary factors associated with otosclerosis. A number of studies have also tried to establish an association with HLA antigens [4, 5, 8, 10, 15]. A further purpose of determining an association between HLA and disease is to define populations that are more susceptible or resistant to disease in order to study pathogenesis. In the present study, we investigated the frequencies of HLA antigens in 62 Japanese patients exhibiting clinical otosclerosis.

Materials and methods

The study group comprised 62 unrelated Japanese patients who had a diagnosis of otosclerosis clinically confirmed by both audiometric and surgical findings during stapes surgery. Twenty-nine were men (aged 18–60 years; mean 36, SD 11 years), and the remaining 33 were women (aged 15–62 years; mean 41, SD 13 years). All patients were admitted to the otorhinolaryngology clinics of Nagoya University Hospital or National Nagoya Hospital and underwent surgery for otosclerosis between 1991 and 1995. Four hundred and seventy-two unrelated healthy Japanese [1] served as controls. Neither the patients nor the controls were born in a specific region of Japan. Phenotyping for HLA-A, -B, -C (62 patients) and HLA-DR (21 patients) was performed on venous blood samples using the standard United States National Institutes of Health (NIH) complement-dependent microlymphocytotoxic technique [19]. HLA antigen frequencies in the patients with otosclerosis and controls were compared for significant differences by means of χ^2 analysis with Yate's correction when necessary. P values were corrected for purposes of comparison and given as Pc (corrected P): $Pc = 1-(1-P)^n$, where P was the uncorrected value, and n the number of comparisons [6, 17]. A Pc value of less than 0.05 was accepted as being statistically significant. Relative risk was also calculated according to Svejgaard et al. [18].

Results

The frequencies of HLA I and II antigens in the otosclerosis patients and the control group are listed in Tables 1 and 2. The frequency of HLA-Aw33 was significantly higher in otosclerosis patients than in the control group (24.2% vs 9.5%; $P = 0.0006$, $Pc = 0.019$, relative risk =

Table 1 HLA class I antigens in patients with otosclerosis compared with controls (*RR* relative risk)

	Controls ($n = 472$)	Patients ($n = 62$)		RR
	%	*n*	%	
A2	40.7	22	35.5	
A11	17.2	12	19.4	
A24	68.4	33	53.2	0.53*
A26	21.2	12	19.4	
A31	12.5	13	21.0	
Aw33	9.5	15	24.2	3.01**;***
B7	12.9	9	14.5	
B13	3.8	2	3.2	
B15	17.2	2	3.2	0.16**
B17	0.6	1	1.6	
B35	15.5	8	12.9	
B37	1.4	1	1.6	
B39	7.2	4	6.5	
B44	10.8	12	19.4	
Bw46	10.1	4	6.5	
Bw48	4.6	2	3.2	
B51	14.2	10	16.1	
Bw52	23.5	17	27.4	
Bw54	14.0	9	14.5	
Bw55	3.8	2	3.2	
Bw56	1.3	4	6.5	5.36*
Bw59	7.0	2	3.2	
Bw60	10.6	6	9.7	
Bw61	23.6	13	21.0	
Bw62	15.5	6	9.7	
Bw67	1.1	3	4.8	
Bw70	1.8	1	1.6	
Cw1	27.6	15	24.2	
Cww3	49.4	27	43.5	
Cww4	7.2	7	11.3	
Cw6	1.9	1	1.6	
Cw7	23.8	16	25.8	

* $P < 0.05$, ** $P < 0.01$, *** Pc (corrected P) < 0.05

Table 2 HLA class II antigens in patients with otosclerosis compared with controls

	Controls ($n = 472$)	Patients ($n = 62$)		RR
	%	*n*	%	
DR1	12.4	4	19.0	
DR2	34.3	6	28.6	
DR3	0.0	1	4.8	
DR4	41.6	7	33.3	
DRw6	16.1	6	28.6	
DRw8	24.8	3	14.3	
DR9	26.1	11	52.4	3.12**
DRw12	7.6	1	4.8	
DRw14	5.5	1	4.8	

** $P < 0.01$

3.01). Frequencies of HLA-Bw56 and -DR9 were also increased but not significant. Decreases of HLA-A24 and -B15 frequencies were observed, but the corrected probabilities were not significant.

Discussion

Although numerous reports on the subject have been published, the exact mechanism of pathogenesis in otosclerosis has not been clarified. Current etiological theories include a systemic connective tissue disorder, a possible disturbance in calcitonin metabolism at the cellular receptor level, autoimmunity to type II collagen, and an inflammatory vascular reaction initiated by a viral infection [16]. Hereditary factors have also been widely considered, which might account for an enhanced affinity for certain viruses by cells or tissues and cellular components that may be lacking in immunological stability [2, 14]. Recently, it has been suggested that otosclerosis may represent a host's ongoing immunological response to measles or other viral antigens [9, 11, 12].

The correlation of specific diseases with HLA antigens has recently received considerable attention. For most HLA-associated diseases, there has been evidence that tissue damage is mediated by autoimmune mechanisms. In these cases class I and II antigens of the major histocompatibility complex (MHC) may act directly as disease susceptibility agents. It is generally accepted that the biological role of MHC molecules is to present exogenous antigen to T lymphocytes. Class I molecules present essentially viral antigens to cytotoxic CD8-positive T cells capable of lysing virus-infected target cells.

A number of previous studies have tried to establish an association between HLA antigens and otosclerosis. However, these associations have not proven to be consistently reproducible. Different ethnic groups may also have different frequencies of HLA antigens and patterns of linkage disequilibrium [3]. However, some associations between HLA antigens and disease are consistent irrespective of race, e.g. HLA-B27 and ankylosing spondylitis, implicating the antigen itself.

Gregoriadis et al. [8] studied 68 Greek patients with otosclerosis and reported a significantly higher frequency of HLA antigen Bw35, B14. His group also found a higher frequency of A11 in patients with otosclerosis. Dahlqvist et al. [5] studied 74 otosclerosis patients and uncovered a significantly lower frequency of B40 HLA antigen than among controls. They did not, however, find a significant increase in any of the A or B antigens. In contrast, Chobaut et al. [4], Majsky et al. [10], and Pedersen et al. [15] found no association between HLA types and otosclerosis.

In the present study, a significantly increased frequency of antigen Aw33 was found in our patients with otosclerosis. This finding suggests that HLA-Aw33 anti-

gens may represent an increased susceptibility to otosclerosis or its clinical outcome. Since reports of associations between otosclerosis and specific HLA types have been highly variable, susceptibility to otosclerosis in the different races may well be controlled by a number of predisposing factors, including HLA. Further investigations on larger series of patients in different races should be performed to confirm a true association between HLA antigens and otosclerosis.

References

1. Aizawa M (1986) HLA in Asia-Oceania. The Proceedings of the 3rd Asia-Oceania Histocompatibility Workshop Conference. Hokkaido University Press, Sapporo, Japan
2. Arnold W, Friedmann I (1988) Otosclerosis–an inflammatory disease of the otic capsule of viral aetiology? J Laryngol Otol 102:865–871
3. Batchelor JR, McMichael AJ (1987) Progress in understanding HLA and disease associations. Br Med Bull 43:156–183
4. Chobaut JC, Bertrand D, Raffoux C, Wayoff M (1982) HLA antigens in otosclerosis. Am J Otol 3:241–242
5. Dahlqvist A, Diamant H, Dahlqvist SR, Cedergren B (1985) HLA antigens in patients with otosclerosis. Acta Otolaryngol (Stockh) 100:33–35
6. Edwards JH (1974) HLA and disease. The detection of associations. J Immunogenet 1:249–257
7. Gordon MA (1989) The genetics of otosclerosis: a review. Am J Otol 10:426–438
8. Gregoriadis S, Zervas J, Varletzidis E, Toubis M, Pantazopoulous P, Fessas P (1982) HLA antigens and otosclerosis. Arch Otolaryngol 108:769–771
9. Harris JP, Keithley EM (1993) Inner ear inflammation and round window otosclerosis. Am J Otol 14:109–112
10. Majsky A, Novotny Z, Fajstavr Y (1982) HLA and otosclerosis. Tissue Antigens 20:306–307
11. McKenna MJ, Mills BG (1989) Immunohistochemical evidence of measles virus antigens in active otosclerosis. Otolaryngol Head Neck Surg 101:415–421
12. McKenna MJ, Mills BG (1990) Ultrastructural and immunohistochemical evidence of measles virus in active otosclerosis. Acta Otolaryngol (Stockh) [Suppl] 470:130–140
13. Morrison AW (1967) Genetic factors in otosclerosis. Ann R Coll Surg (Engl) 41:202–237
14. Niedermeyer H, Arnold W, Neubert WJ, Hofler H (1994) Evidence of measles virus RNA in otosclerotic tissue. ORL 56:130–132
15. Pedersen U, Madsen M, Lamm LU, Elbroud O (1983) HLA-A,-B,-C antigens in otosclerosis. J Laryngol Otol 97:1095–1097
16. Roald B, Storvold G, Mair IWS, Mjoen S (1992) Respiratory tract viruses in otosclerotic lesions. Acta Otolaryngol (Stockh) 112:334–338
17. Svejgaard A, Ryder LP (1994) HLA and disease associations: detecting the strongest association. Tissue Antigens 43:18–27
18. Svejgaard A, Platz P, Ryde LP (1983) HLA and disease 1982: a survey. Immunol Rev 70:193–218
19. Terasaki PI, Bernoco D, Park MS, Gungor O, Iwaki Y (1978) Microdroplet testing for HLA-A, B, C, and D antigens. Am J Clin Pathol 69:103–120