

Associations with autoimmune disorders and HLA class I and II antigens in inclusion body myositis

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Abstract—Whether autoimmune mechanisms play a role in the pathogenesis of inclusion body myositis (IBM) is unknown. Human leukocyte antigen (HLA) analysis in 52 patients, including 17 with autoimmune disorders (AIDs), showed that patients were more likely to have antigens from the autoimmune-prone HLA-B8-DR3 ancestral haplotype than healthy control subjects, irrespective of the presence of AIDs. Patients lacked the apparently protective HLA-DR53 antigen. The results provide further support for an autoimmune basis in IBM.

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Inclusion body myositis (IBM) is a slowly progressive inflammatory myopathy with a male predominance and preferential weakness onset in the quadriceps muscles, finger flexors, or pharyngeal muscles. In general, immunosuppressive treatment has no beneficial effect.¹ Whether autoimmune mechanisms play a role in the pathogenesis has not yet been established.

IBM is histologically characterized by signs of an ongoing degenerative process and inflammation with invasion of major histocompatibility complex (MHC) I-expressing muscle fibers by CD8⁺ T cells with a restricted T-cell receptor gene usage. The MHC region on chromosome 6 has a key function in the presentation of short pathogen-derived peptides to T cells. Genetic susceptibility for many autoimmune disorders (AIDs) has been linked with the MHC. To determine whether the MHC predisposes subjects to IBM and other AIDs, we investigated 1) the frequency of AIDs in IBM, 2) human leukocyte antigen (HLA) class I and II antigen associations in Dutch patients, and 3) relations between associated HLA antigens and clinical features.

Patients and methods. Between March 1996 and September 1999, 86 patients with IBM were known to be living in the Netherlands. The recruitment process of these patients has been reported.² Five patients could not be located, 6 died prior to assessment, 12 refused participation, and 11 could not be included for logistical reasons. The remaining 52 patients, 47 with definite and 5 with probable IBM,² all Caucasian, were included. All pa-

tients gave informed consent. The local ethics board approved the study.

Patients and spouses (if available) were questioned by one investigator, paying particular attention to age and symptoms at onset and presence of AIDs. Reports of AIDs were verified by information from the treating physicians.

Typing of HLA class I and II antigens was performed by a complement-dependent lymphocytotoxicity technique using locally prepared sets of anti-HLA allosera and monoclonal antibodies. A panel of randomly selected, serologically typed, healthy Dutch blood donors (n = 2,440) served as a control population.³ A few patients were also typed using DNA-based methods.

The antigen frequencies of patients and controls were compared using the χ^2 test. Odds ratios were calculated using the Woolf-Haldane method. Relations between HLA antigens and age at onset were investigated by forward multiple linear regression analysis. Antigens linked with IBM were related to gender, site of onset, and presence of AIDs using the χ^2 test or Fisher exact test as appropriate and corrected for multiple comparisons using the Bonferroni method. Data are presented as means \pm SD.

Results. The mean age of the 52 examined patients was 67 ± 8 years for men (n = 36) and 71 ± 10 years for women (n = 16) with a mean age at symptom onset of 58 ± 8 years for men and 56 ± 9 years for women. Mean duration of symptoms was 9 ± 5 years for men and 15 ± 7 years for women. The studied patient group was representative for the Dutch IBM population cohort with respect to age and sex distribution.

Seventeen patients (33%) had AIDs, including three patients with multiple disorders. These were autoimmune thyroid disease (n = 6), rheumatoid arthritis (n = 4), type I diabetes mellitus (n = 2), Sjögren disease (n = 2), psoriasis (n = 2), vitiligo, sarcoidosis, celiac disease, and ulcerative colitis (all n = 1).

HLA class I B8 and class II antigens DR3, DR52, and DQ2 were more likely to be found in patients with IBM than in control subjects (table; see also table E-1 on the *Neurology* Web site at www.neurology.org). The B8-DR3-

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*See the Appendix on page 2398 for a list of Group members.

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Table Frequencies of HLA class I and II antigens in IBM patients and controls

HLA antigen	IBM, n (%)	Controls, n (%)	OR	95% CI	<i>p</i> value	<i>p_c</i> value
A1	25 (48)	747 (31)	2.1	1.2–3.6	0.01	0.44
B8	36 (69)	554 (23)	7.5	4.2–13.6	<10 ⁻⁵	<10 ^{-5*}
DR1	18 (35)	473 (20)	2.2	1.2–3.9	0.01	0.55
DR3	41 (79)	599 (25)	10.8	5.6–20.9	<10 ⁻⁵	<10 ^{-5*}
DR4	3 (6)	679 (28)	0.2	0.1–0.5	<10 ⁻⁴	0.007*
DR7	2 (4)	459 (19)	0.2	0.1–0.7	0.003	0.19
DR8	0 (0)	128 (5)	0.2	0.0–2.7	0.11	0.1
DR9	1 (2)	58 (2)	1.2	0.2–6.0	1.00	1.00
DR10	0 (0)	100 (4)	0.2	0.0–3.6	0.27	1.00
DR11	5 (10)	340 (14)	0.7	0.3–1.7	0.42	1.00
DR12	0 (0)	108 (5)	0.2	0.0–3.2	0.17	1.00
DR13	17 (33)	669 (28)	1.2	0.7–2.2	0.53	1.00
DR14	0 (0)	127 (5)	0.2	0.0–2.7	0.11	1.0
DR15	10 (19)	414 (26)	0.7	0.4–1.4	0.34	1.00
DR16	4 (8)	43 (2)	4.9	1.8–13.4	0.02	0.67
DR52	47 (90)	1641 (67)	4.2	1.7–10.2	0.0002	0.01*
DR53	4 (8)	1088 (45)	0.1	0.0–0.3	<10 ⁻⁵	<10 ^{-5*}
DQ2	41 (79)	881 (37)	6.1	3.1–11.7	<10 ⁻⁵	<10 ^{-5*}
DQ4	0 (0)	29 (3)	0.3	0.0–4.7	0.40	1.00
DQ5	22 (42)	300 (35)	1.4	0.8–2.4	0.3	1.00
DQ6	26 (51)	453 (50)	1.0	0.6–1.8	1.00	1.00
DQ7	9 (18)	652 (28)	0.6	0.3–1.2	0.12	1.0
DQ8	0 (0)	184 (20)	0.0	0.0–0.6	<10 ⁻⁵	0.001*
DQ9	2 (4)	71 (8)	0.6	0.2–2.2	0.42	1.00

* Frequency difference significant, *p_c* < 0.05.

HLA = human leukocyte antigen; IBM = inclusion body myositis; *p_c* = *p* value corrected for 61 split and 61 broad informative comparisons.

DR52-DQ2 haplotype was found in 35 patients (67%). In the remaining 17 patients, the distribution was as follows: Six (12%) had DR3-DR52-DQ2, one patient had B8-DR52, five patients (10%) had DR52, whereas in five patients, none of the antigens was found. Of the five “probable IBM” patients, three had the complete haplotype associated with the disorder, one had part, and one none of the associated antigens. The B8-DR3-DR52-DQ2 haplotype was present in 11 of 17 patients (65%) with AIDs and in 24 of 35 patients (69%) without AIDs.

As HLA-A1 is known to be in positive linkage disequilibrium with the above-mentioned haplotype, its frequency was the subject of further study. In the group with the B8-DR3-DR52-DQ2 haplotype, 22 of 35 were HLA-A1 positive and 13 of 35 were A1 negative, whereas in the group of 17 with the incomplete associated haplotype, 3 patients had A1 (*p* = 0.003 for frequency difference). None of the other linked antigens was found in these three patients.

The presence of HLA-DR4, HLA-DR53, and HLA-DQ8 in patients was significantly less frequent than in control subjects.

As the results indicated a preference for the A1-B8-DR3-DR52-DQ2 haplotype, we investigated the possibility of associations between these HLA antigens and clinical features. Presence of HLA-A1 was associated with an ear-

lier onset (*p* = 0.017, adjusted *R*² = 0.09, *B* = -5.4, 95% CI for *B* = -9.8 to -1.0). The mean age at onset in HLA-A1-positive patients was 54.3 ± 8.4 years and in A1-negative patients 59.7 ± 7.5 years. The individual associated antigens did not relate to gender, a preferential site of onset (i.e., pharyngeal, quadriceps, or finger flexor weakness or other type of weakness), or presence of AIDs.

The HLA-DR53 antigen was present in only four patients, none of whom showed overt clinical differences compared with HLA-DR53-negative patients.

Discussion. In this study of a large cohort of IBM patients, we found an increased frequency of HLA-B8 and HLA-DR3 antigens in patients compared with control subjects. The B8-DR3 haplotype has been associated with AIDs such as myasthenia gravis, Lambert–Eaton myasthenic syndrome (LEMS), type I diabetes mellitus, sarcoidosis, celiac disease, and Graves disease. Our results confirm previously described associations of IBM with HLA-B8 and HLA-DR3 in Australians⁴ and with HLA-DR3 and HLA-DR52 in Americans.⁵ Our findings are also in accordance with an American DNA-based study.⁶ In our patients, the B8-DR3 haplotype

also included HLA-DR52 and HLA-DQ2 and indirectly HLA-A1, which are known to be in linkage disequilibrium.

HLA-A1 was associated with an earlier onset. Similarly, HLA-B8 has been related to earlier disease onset in LEMS and myasthenia gravis.⁷ The concept that this autoimmune-prone haplotype is implicated in the development of IBM is certainly quite feasible. Interestingly, the MHC did not provide any indication of why there is a male predominance in IBM.

Our patients had a high frequency of AIDs, but their presence did not influence the frequency of the B8-DR3-DR52-DQ2 haplotype in the IBM cohort. We found no preference for target-specific AIDs or for AIDs with a suspected T-cell-mediated pathogenesis. Compared with Dutch patients with LEMS, an antibody-mediated AID studied using comparable methods, patients with IBM had a similar frequency of additional AIDs.⁷ The fact that we paid particular attention to AIDs may have resulted in a higher frequency than the 3 to 15% reported in retrospective studies.⁸⁻¹⁰

It is obvious that the increased frequency of the HLA-B8-DR3 haplotype did not lead to a proportional lowering of other common haplotypes such as those of HLA-DR1 and HLA-DR2 antigens. HLA-DR53 was uncommon in IBM as were HLA-DR4, HLA-DQ8, and, to a lesser extent, HLA-DR7. As HLA-DR53 was the shared denominator in the common haplotypes of these antigens, the negative association could be attributed to a low frequency of DR53. Hence, the increased risk for IBM could also be ascribed to an absence of HLA-DR53.

The high frequency of AIDs, the very strong association with the extended HLA-DR3 haplotype linked to many of these AIDs, the protective effect of HLA-DR53, the influence of HLA-A1 on the age at onset, and the similarities between regionally different Caucasian populations all point to an important

immunogenetic role of the MHC in the predisposition for developing IBM. These findings also support the inflammatory histopathologic arguments for characterizing IBM as an AID.

Appendix

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