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Lack of association of mannose binding lectin variant alleles with systemic lupus erythematosus

T Momot, K Ahmadi-Simab, A Gause, W L Gross, E Gromnica-Ihle, H H Peter, K Manger, H Zeidler, R E Schmidt, T Witte

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Mannose binding lectin (MBL) is a member of the collectin family, is structurally related to the complement component C1q, and is involved in the innate immune response.¹ So far, three mutations of MBL have been described in codons 54, 57, and 52 (termed variant alleles B, C, and D or 0 alleles) that are associated with dysfunctional formation of the molecule.^{2–3} Homozygous combinations of variant alleles of MBL have been found in about 1–10% of Europeans and are associated with increased incidence of infections in childhood, subsets of adults, and possibly those with systemic lupus erythematosus (SLE).⁴

In a recent prospective study of 91 patients with SLE, MBL deficiency was a risk factor for “arterial thrombosis”, in particular, with myocardial infarction.⁵ We have now examined in a multicentre study 287 white German patients with SLE for MBL deficiency as a risk factor for myocardial and cerebral infarction.

DNA of these patients has been collected since 1999 in a German multicentre study on the genetics of connective tissue diseases⁶ after receiving written consent. All patients were white German subjects and fulfilled the American College of Rheumatology criteria for the classification of SLE.⁷ Of the patients with SLE, 263/287 (91.6%) were female, with a mean (SD) age at inclusion of 48 (14.5) years, and median duration of SLE at the time of inclusion of 15 years. DNA from 120 white German blood donors and from 61 patients with Sjögren's syndrome (classified according to ESG criteria⁸) was obtained as control.

MBL alleles were defined using a restriction fragment length polymorphism analysis as described previously.⁹ To control the quality of the method, 50 samples were analysed twice and gave identical results on retesting.

Homozygous combinations of 0 alleles of MBL were present in 20/287 (7%) and heterozygous 0 alleles in 103/

287 (36%) patients with SLE, in 6/61 (10%) and 16/61 (26%) patients with Sjögren's syndrome, and in 12/120 (10%) and 60/120 (50%) controls, respectively (not shown). The homozygous combination of 0 alleles was not associated with SLE.

Data on the prevalence of previous myocardial or cerebral infarction was reviewed from the charts of all patients with SLE, where possible, and could be collected from 14/20 patients with and 160/267 patients without homozygous MBL 0 alleles. Myocardial infarction had occurred in 1/14 (7.1%) and cerebral infarction in 0/14 (0%) patients with homozygous MBL 0 alleles compared with 13/160 (8.1%) and 12/160 (7.5%) patients without homozygous MBL 0 alleles (table 1).

Since then, 8/20 patients with SLE with homozygous MBL 0 alleles have been followed up for 4 years and myocardial and cerebral infarction have not occurred (not shown).

Inconsistent results were obtained from several studies, as to whether MBL is a risk factor for coronary artery disease. In a recent publication on 91 Danish white patients with SLE, 4/7 patients with homozygous MBL variant alleles developed myocardial infarction.⁵ Those patients have been followed up prospectively for up to 8 years. In our retrospective study on white German patients with SLE there was, however, no association of the prevalence of arterial thrombosis, myocardial or cerebral infarction, or leg embolus with MBL variant alleles.

Patients in our study were significantly older than those in the Danish study. The possibility cannot be ruled out that patients with homozygous MBL 0 alleles die at a younger age of arterial thrombosis or infections, the most common causes of death in patients with SLE¹⁰ and may be underrepresented in our study.

However, reports of MBL alleles as risk factors for myocardial infarction in SLE cannot be confirmed at present.

Table 1 Prevalence of previous myocardial and cerebral infarction and leg embolus in patients with SLE typed for MBL alleles

	A/A	A/O	O/O
Myocardial infarction	7/102 (7)	6/58 (10)	1/14 (7)
Cerebral infarction	8/102 (8)	4/58 (7)	0/14 (0)
Leg embolus	3/102 (3)	0/58 (0)	0/14 (0)

Results are shown as No (%).

Authors' affiliations

T Momot, K Ahmadi-Simab, A Gause, W L Gross, E Gromnica-Ihle, H H Peter, K Manger, H Zeidler, R E Schmidt, T Witte, Abteilung Klinische Immunologie, Medizinische Hochschule Hannover, Carl-Neuberg-Str 1, 30625 Hannover, Germany

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Correspondence to: Dr T Witte, witte.torsten@mh-hannover.de

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Decreased levels of serum soluble HLA class I antigens in HLA-B27 positive spondyloarthropathies

É Toussiroto, P Saas, J Pariset, J Chabod, P Tiberghien, D Wendling

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Human leucocyte class I antigens (HLA-I) are expressed on the surface of all nucleated cells but can also be found in soluble forms. These soluble HLA-I (sHLA-I) molecules can be produced by either membrane shedding, proteolysis of the intact heavy chain, or by alternative splicing.¹ They have been implicated in regulatory functions and have immunomodulatory properties.² Increased levels of sHLA-I were found during graft rejections, in various infectious (cytomegalovirus, hepatitis B or C, HIV infection, active tuberculosis) and autoimmune diseases.^{3–6} In systemic lupus erythematosus and rheumatoid arthritis, levels of sHLA-I antigens correlate with disease activity.^{4,6} Spondyloarthropathies (SpA) are conditions closely linked to HLA-B27, a class I antigen. Thus, in this study, we evaluated the serum concentrations of sHLA-I antigens in a large cohort of patients with SpA.

One hundred and twenty three patients who met the European Spondylarthropathy Study Group criteria for SpA⁷ were assessed (table 1). Disease activity was evaluated by the Bath Ankylosing Spondylitis Disease Activity Index and laboratory measures of inflammation (erythrocyte sedimentation rate and serum C reactive protein). The control group comprised 102 healthy subjects (63 male; mean (SD) age 39.5 (3.4)) and included 23 HLA-B27 positive subjects. Determination of sHLA-I antigens was done by a sandwich enzyme linked immunosorbent assay (ELISA; using W6/32 and an anti-β₂-microglobulin polyclonal antibody; Bouts Laboratories, Milan, Italy).

Patients with SpA had decreased sHLA-I serum levels in comparison with healthy controls (mean (SD) 0.86 (0.6) v 1.18 (0.5) µg/ml; p = 0.0003) (fig 1). HLA-B27 positive SpA showed decreased sHLA-I concentrations in comparison with HLA-B27 negative SpA (0.79 (0.26) v 1.17 (0.7) µg/ml; p = 0.007), while there was no difference between HLA-B27 positive and HLA-B27 negative controls (1.24 (0.5) v 1.17 (0.5) µg/ml; p > 0.05). Furthermore, there was no significant difference in sHLA-I concentrations between HLA-B27 negative patients with SpA and HLA-B27 negative controls

(1.17 (0.7) v 1.17 (0.5) µg/ml p > 0.05), while HLA-B27 positive SpA still had decreased sHLA-I values in comparison with HLA-B27 positive controls (0.79 (0.26) v 1.24 (0.5) µg/ml; p = 0.006). We found no correlation between serum sHLA-I concentration and any of the laboratory and clinical indexes of disease activity (regression analysis, p > 0.05).

The significance and role of the sHLA-I antigens still remain unclear. They are present in several body fluids⁸ and in synovial fluid from various arthropathies.⁹ sHLA-I antigens can bind antigenic peptides and they probably have immunoregulatory functions by the inhibition of cytotoxic T lymphocytes and natural killer cells.^{1,2} Previous studies have suggested that sHLA-I might be used as marker of disease activity or as prognostic factor in autoimmune diseases.^{4,6} On the contrary, in our series of patients with SpA we observed decreased values of sHLA-I. These results were particularly evident in HLA-B27 positive patients with SpA while HLA-B27 did not influence the level of sHLA-I in controls. Thus, both the disease and the HLA-B27 antigen

Table 1 Clinical and biological characteristics of 123 patients with spondyloarthropathies (80 ankylosing spondylitis, 8 reactive arthritis, 4 psoriatic arthritis, 10 enteropathic arthritis and 21 undifferentiated SpA)

Age (years)	41.8 (1.3)
Sex (M/F)	80/43
Disease duration (years)	8.2 (7.7)
ESR (mm/1st h)	25.0 (26.1)
CRP (mg/l)	23.1 (41.7)
HLA-B27 (+/-/ND)	99/21/3
BASDAI (0–10)	4.9 (2.0)
Extra-articular manifestations, No (%)	47/123 (38)
Peripheral disease, No (%)	42/123 (34)

Results are shown as mean (SD), unless indicated otherwise. ESR, erythrocyte sedimentation rate; CRP, C reactive protein; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; ND, not determined.