Immunoglobulin allotypes are not associated with HLA-antigens, autoantibodies and clinical symptoms in systemic lupus erythematosus


Universities of Hannover1, Freiburg2, Erlangen3, Düsseldorf4, Bielefeld, Bonn, Mainz, München (Federal Republic of Germany), Bern (Switzerland), Ancona (Italy);
Central Laboratory of the Netherlands Red Cross Blood Transfusion Service and Laboratory of Experimental and Clinical Immunology, University of Amsterdam5 (The Netherlands)

Received April 22, 1991/Accepted May 28, 1991

Summary. Immunoglobulin heavy chain (G1m, G2m, G3m, A2m) and kappa light chain (Km) allotype and phenotype frequencies of 323 central European Caucasian patients with systemic lupus erythematosus (SLE) were examined and correlated with various genetic, serologic and clinical markers of SLE. No significant associations were found between immunoglobulin allotypes or phenotypes and all 20 parameters tested (nephritis, vasculitis, arthralgias, photosensitivity, discoid lesions, central nervous system disease, Raynaud’s phenomenon, sex, anti-Ro, anti-La, anti-nRNP, HLA-DR1-DR7, HLA phenotypes B8-DR3, B7-DR2). It could therefore be assumed that Gm, A2m and Km allotypes were not associated with HLA-antigens and had no influence on the serologic and clinical expression of SLE.

Key words: Immunoglobulin allotypes – Systemic lupus erythematosus – Genetics – Gm – Km – HLA-antigens – Autoantibodies – Clinical symptoms

Introduction

Systemic lupus erythematosus (SLE) is commonly regarded as the prototype of a non organ-specific autoimmune disease, the etiology of which is still unknown. Various genetic factors have been implicated in the pathogenesis of SLE [1-3]. Among other genetic markers, immunoglobulin allotypes have been proposed as being associated with SLE [4, 5]. While the results of previous studies in Caucasians have been controversial [6, 7], we have not found any association between immunoglobulin allotypes or phenotypes and the disease SLE as such [8].

* To whom offprint requests should be sent at: Abteilung Immunologie und Transfusionsmedizin, Medizinische Hochschule Hannover, Konstanty-Gutschow-Strasse 8, W-3000 Hannover 61, Federal Republic of Germany


It has also been proposed that immunoglobulin allotypes, while not being markers for the disease itself, are associated with the presence of certain clinical symptoms, mainly nephritis in SLE [7], and Whittingham et al. have reported a strong association between the Km1 allotype and the presence of La antibody in patients with autoimmune diseases [9]. Furthermore, it has been suggested that a higher risk of developing SLE is conferred by an interplay of HLA antigens and Gm phenotypes [4, 7] but others have failed to confirm these observations [6]. We therefore extended our previous studies investigating whether immunoglobulin allotypes and phenotypes are associated with MHC markers, autoantibodies and clinical symptoms in SLE patients.

Patients and methods

A total of 323 Caucasian patients with SLE were recruited from the outpatient clinics of four collaborating German centers (Hannover, Düsseldorf, Erlangen, Freiburg). All patients fulfilled the 1982 revised ARA criteria for the classification of SLE [10]. Patients with overlap syndromes were carefully excluded.

Patient's histories were retrospectively analyzed for clinical symptoms at any time during the course of their disease. Seven major clinical symptoms were selected for investigating possible associations with immunoglobulin allotypes (the percentage of patients who were positive for the symptom is given in brackets after each symptom): nephritis (39%), photosensitivity (47%), discoid lesions (14%), arthralgia (94%), central nervous system disease (psychosis and/or cramps; 27%), vasculitis (24%), and Raynaud’s phenomenon (44%). Associations between immunoglobulin allotypes and clinical symptoms were determined in a total of 275 patients. Furthermore, in all 323 patients, a calculation for the association of sex with immunoglobulin allotypes and phenotypes was performed.

In 254 patients, Ro (32%), La (12%) and nRNP (8%) antibodies were determined by counterimmunoelectrophoresis. HLA-B and -DR antigens were determined in 269 patients, and associations were sought for the presence of the following class II antigens: DR1, DR2, DR3, DR4, DR5, DR6, DR7, and the phenotypes B7-DR2 and B8-DR3. HLA typing was performed using a standard complement-dependent microcytotoxicity assay [11].

Immunoglobulin allotyping. The following Gm, A2m, and Km allotypes were detected by haemagglutination inhibition assay [12]:

---


Rheumatology
Clinical and Experimental Investigations
© Springer-Verlag 1991
Number of Patients

Allotypes

Number of Patients

Phenotypes

Hom. - /Het. - Phenotypes

G1m (z, a, x, f), G2m (n), G3m (g, b0, b1, b3, b5, c3, c5, s, t), A2m (1, 2) and Km [1, 3]. As G3m (b0, b1, b3, b5) usually occur together in Caucasians, these allotypes were summarized as G3m (b). These allotypes were correlated with the symptoms, antibodies and HLA antigens stated above, as well as with the following Gm phenotypes: fnb, zafngb, zaxfnfgb, zafgb, fnb, zaxg, zafmgb, zafgb, zaf, gb-heterozygous, za-homozygous, za-g-homozygous, fnb-homozygous.

Statistical analysis. The Chi-square test was used to test for associations of allotypes and phenotypes with HLA antigens, clinical symptoms and autoantibodies. Altogether 460 tests were performed (11 allotypes and 12 phenotypes vs. sex, 7 clinical symptoms, 3 autoantibodies and 9 HLA phenotypes). Uncorrected P values were reported, but have to be judged considering the total number of tests performed.

Results

The overwhelming majority of tests did not show any associations between immunoglobulin allotypes/phenotypes and clinical symptoms, autoantibodies or HLA antigens. Figure 1a shows the distribution of immunoglobulin allotypes in patients with nephritis; no significant associations were observed. The distribution of phenotypes is shown in Fig. 1b, c. Here, an association was found between the presence of nephritis and the phenotypes zaxg (P = 0.0028) and za-g-hom (P = 0.012).

For all other clinical symptoms, HLA phenotypes and autoantibodies tested, significant (P < 0.01) associations with any of the 23 immunoglobulin allotypes and phenotypes could not be detected. A weak association between the phenotype zaxf;gb and HLA-DR4 [7 out of 39 DR4 positives (18%) were zaxf;gb, versus 9 out of 214 zaxf;gb positives (4%) without DR4; P = 0.010] was not considered relevant for SLE since DR4 does not constitute an important genetic marker in SLE [3].

Discussion

Immunogenetic markers such as T-cell receptor genes, MHC gene products and immunoglobulin allotypes have not only been implicated as factors predisposing to the development of SLE [4, 13–15], but have also been found to be associated with the formation of autoantibodies and clinical symptoms in SLE [9, 16–23]. While the association of HLA-B8 and HLA-DR3 with Ro and La antibodies and the association of HLA-DR3 and Ro and La antibodies with cutaneous symptoms of SLE have repeatedly been confirmed [24–26], reports on associations of immunoglobulin allotypes with SLE have been sporadic and controversial. The initial report of Whittingham et al. in 1983, comprising 53 SLE patients, described an additive effect of the presence of HLA-B8 and Gm heterozygosity on the susceptibility to SLE, but no apparent interaction between these genetic loci [4]. Schur et al. who examined 104 patients, have observed increased frequencies of the phenotype za;gb in SLE [6], but found no associations of Gm and Km allotypes and phenotypes with various clinical symptoms, serological parameters including La antibodies, and indicators for SLE nephritis (urinary abnormalities, elevated blood urea nitrogen). Stenszky et al. did not find any increase of Gm allotype or phenotype frequencies in SLE, but have reported an additive effect of HLA-B8 and Gm f;b homozgyosity on the risk of developing SLE-related nephropathy [7]. Associations of Gm allo- or phenotypes with other clinical symptoms of SLE have not been reported. Recently, Whittingham has reported an association between the anti-La antibody response and Km-1 in a group of 26 patients with autoimmune disease, mainly Sjögren’s syndrome [9]. Genth et al. however, did not find any associations between Gm allotypes/phenotypes and HLA antigens or autoantibodies [27].

In a total of 323 SLE patients we have recently shown that no single immunoglobulin allotype or phenotype is associated with SLE [8]. Our results presented here also