RAPID

PUBLICATIONS

High Frequency of Histocompatibility Antigens HLA-DR3 and DR4 in Herpes Gestationis

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ABSTRACT Herpes gestationis (HG) is a rare, autoimmune, vesiculobullous disease of pregnancy or the puerperium characterized by the deposition of complement (and occasionally immunoglobulin) within the lamina lucida of the cutaneous basement membrane zone. We have studied 23 patients with a history of HG, 20 of whom had typical immunofluorescence findings during the active phase of their disease. HLA typing showed HLA-DR3 in 61% of patients (controls 22%, Pc < 0.005) and the combination of DR3, DR4 in 43% (controls 3%, Pc < 0.00001). The most striking finding of this study was that the greatest risk of HG is associated with the concurrent presence of two specific histocompatibility leukocyte antigen (HLA)-DR antigens.

INTRODUCTION

Herpes gestationis (HG)[1] is a rare, intensely pruritic, vesiculobullous disease of pregnancy. It usually begins during the second or third trimester, though it occasionally appears in the postpartum period. It may not develop until after multiple normal pregnancies, but once it appears it tends to occur earlier and to be more severe in subsequent pregnancies.

The immunopathologic hallmark of HG is the linear deposition of complement (C′) along the dermal-epidermal junction (1, 2). Immunoglobulin G (IgG) is only occasionally seen using standard direct immunofluorescence testing, but a serum IgG antibody capable of avid C′ binding is often demonstrable along the basement membrane zone (BMZ) by special indirect immunofluorescence techniques (2–4). This antibody can be passively transferred to the fetus and may then be demonstrated in cord blood or bound to the infant's skin (2, 4). 5–10% of the infants develop cutaneous lesions compatible with HG (5). A larger proportion may show C′ deposition in skin specimens even in the absence of clinical disease (4).

In 1978 Harrington and Bleenan (6) performed tissue typing on 11 patients with HG and found no consistent pattern of histocompatibility leukocyte antigens (HLA) type. Holmes and Black (7) recently described three patients with HG and hypothyroidism, all of whom had HLA-A1 and B8. HLA-DR typing was not done in either study. In the present report, we have investigated the HLA-A, B, C, and DR antigens in 23 patients with a history of HG.

METHODS

Patient identification. Patients were identified by surveying immunofluorescence laboratories, the heads of various dermatology training centers, the practicing dermatologists in the Dallas area, and the authors of previous articles on HG. Patients were accepted as having had HG if they had (*a*) a clinically compatible eruption during pregnancy or the puerperium and (*b*) a positive direct or indirect immunofluorescence (IF) test. Three patients had their disease before IF testing became generally available but were accepted because they had typical clinical features and supporting histopathologic findings. 23 patients were thus available for tissue typing.

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[1] *Abbreviations used in this paper*: BMZ, basement membrane zone; C′, complement; HG, Herpes gestationis; IF, immunofluorescence; Pc, corrected P value.

HLA typing. HLA-A, B, and C typing was performed by a standard microcytotoxicity method (8). DR typing was done on purified B cells separated by nylon wool adherence (9). Typing sera were obtained from local donors and by exchange with other investigators. Patients were tested for 17 HLA-A antigens, 27 HLA-B antigens, 8 HLA-C antigens, and 10 HLA-DR antigens. Normal control individuals were Caucasian residents of the greater Dallas-Fort Worth area, typed in our laboratory using the same reagents.

The data were analyzed for statistical significance by the chi-square test with Yates' correction. *P* values were corrected for the number of antigens tested at each locus. Relative risks were calculated according to the formula of Woolf or Haldane as appropriate.

RESULTS

A complete listing of our HLA data is presented in Table I. Only significant *P* values are noted on the table. The major finding was the high frequency of the simultaneous presence of HLA-DR3 and DR4. 43% of HG patients had this phenotype, compared with 3% of normal controls. The difference is statistically significant whether corrected for the number of DR antigens ($Pc < 0.00001$) or for the total number of A, B, C, and DR antigens investigated ($Pc < 0.0006$). The frequency of the combined phenotypes was significantly greater than that which would be expected on the basis of the gene frequencies of HLA-DR3 and HLA-DR4 in the HG group, as calculated by the Hardy-Weinberg formula. Further, the expected and observed frequencies for all possible combinations of DR antigens were calculated. For combinations observed more than a single time, only the combination of DR3 and DR4 remained significant.

HLA-DR3 alone was also significantly associated with the development of HG ($Pc < 0.005$). HLA-A1, B8 and DR3 are in linkage disequilibrium in Caucasian populations. The small increase in HLA-B8 seen in our group is probably related to this fact. HLA-DR4 was also increased, but not significantly so. HLA-Cw3 is in linkage disequilibrium with DR4. The (statistically insignificant) increase in Cw3 appears to be due to this association.

There was no apparent relationship between HLA type and clinical disease activity, number of pregnancies before the onset of HG, duration of disease, or the tendency or severity of recurrence. There was no relationship between HLA type and the presence or absence of IgG along the BMZ by direct IF.

Exclusion of the three patients in whom the diagnosis was not confirmed by IF did not alter the statistical validity of our findings. The Pc after exclusion of these three patients is still <0.00001.

The relative risks associated with the antigens found to be increased in HG patients are also shown in Table I. The most striking relative risk (23.5) was seen in those with the combination of DR3 and DR4.

DISCUSSION

Several studies have drawn attention to associations between HLA B8, DR3, and various disease states, but no correlations have been noted with HG. There

TABLE I
HLA Antigens in 23 Patients with a History of Herpes Gestationis

HLA antigen	Normal controls (n = 134)*		HG patients (n = 23)	
	n	%	n	%
A1	40	30	09	39
A2	65	49	10	43
A3	39	29	07	30
A11	16	12	03	13
Aw24	24	18	03	13
A26	05	04	01	04
Aw30	06	04	01	04
Aw31	07	05	03	13
Aw32	09	07	01	04
B5	11‡	08	04	13
B7	37	28	03	13
B8	29	22	10	43 $P < 0.05$ RR§ = 2.79‡
B12	33	25	01	04
B14	11	08	04	13
B15	11‡	08	04	13
B18	09	07	01	04
Bw21	02	01	01	04
Bw22	01	01	02	09
B27	11	08	01	04
Bw35	20	15	03	13
Bw39	04	03	01	04
B40	08‡	06	04	13
Bw41	01	01	01	04
Bw44	33	25	03	13
Cw1	08‡	06	01	04
Cw2	14‡	11	01	04
Cw3	25‡	19	08	35
Cw4	25‡	19	03	13
Cw5	17‡	13	01	04
DR1	30‡	24	02	09
DR2	31‡	25	03	13
DR3	28‡	22	14	61 $P < 0.0005$ RR = 5.44
DR4	42‡	33	12	52
DRw6	16‡	13	06	26
DR7	25‡	20	02	09
DRw9	03‡	03	01	04
DR3, DR4	04	03	10	43 $P < 0.00001$ RR = 23.5

* Only significant uncorrected *P* values are listed.
‡ The number of normal controls was less than 134 for some antigens: B5 = 131, B15 = 130, B40 = 128, Cw1–Cw5 = 133, DR1–DR7 = 126, DRw9 = 100.
§ RR = relative risk.

was no history of other "autoimmune" diseases in any of our patients, excluding the possibility that our results are due to coexistent disease. A possible explanation for the association of HLA-DR3 with apparently dissimilar diseases might be that the presence of HLA-B8, DR3 somehow contributes to a heightened state of immune responsiveness to either self or foreign antigenic stimuli.

The most interesting result of our study is the strong association of HG with the simultaneous presence of HLA-DR3 and DR4. Similar findings have also been associated with insulin-dependent diabetes mellitus (10), but the combined occurrence there results from an increase in either antigen independently. None of our patients had a history of diabetes. There was no evidence of blood or urine glucose elevation even though many patients were being treated with systemic steroids for control of their blistering disease. All infants born to women in our group had birth weights in or below the expected normal range. Thus, we feel that we can confidently exclude the possibility of diabetes in all the members of our group.

It is important to stress that the presence of HLA-DR3, HLA-DR4, or the combination of the two is neither required nor sufficient to produce disease. HLA type does not appear to be related to the clinical parameters of patients with HG. Yet the association of HG with the combined expression of HLA-DR3 and DR4 is firmly established.

The results of our study suggest that the immunologic abnormalities of HG are under the control of genes located in or near the HLA D/DR region. C′ components C_2, C_4, and factor B are known to be encoded by genes between the HLA-D and HLA-B loci. Abnormalities of C′ components or of control of the C′ cascade genetically linked to the HLA D/DR region might explain why C′ is usually deposited without demonstrable IgG in the skin of patients with HG. The recent report by Grimwood et al. (11) of C_3 nephritic factor (an antibody directed at the alternative pathway C_3 convertase, C_3bBb) in the serum of a patient with HG provides support for such a proposal.

Finally, it is possible that gene complementation of the type observed in some immune responses in mice (12) is related to the increased risk for the development of this condition. According to this hypothesis, each DR locus would code for polypeptide chains, the interaction of which would somehow confer susceptibility to this disease. Such interactions have recently been reported in mice (13) but have not yet been observed in humans.

HG appears to be an immunologically mediated disease where both genetic predisposition (HLA type) and environmental factors (pregnancy) seem to be involved. Further study of this condition may shed light on the mechanisms behind the HLA association in this and other immunologically mediated diseases.

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