HLA and duodenal ulcer

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SUMMARY. One hundred and one white patients, consisting of 78 men and 23 women, with duodenal ulcer were HLA typed. An association was found between duodenal ulcer and HLA-B12.

The aetiology of duodenal ulcer is unknown. That genetic factors play some part has been accepted since the recognition of the familial aggregation of peptic ulcer (Doll and Buch, 1950) and the independent segregation of gastric and duodenal ulcer (Doll and Kellock, 1951). An association between duodenal ulcer, blood group O, and non-secretor status is well established (McConnell, 1966), although less well recognised is the increased frequency of urinary pepsinogen phenotype A and duodenal ulcer (Samloff and Cole, 1975). Polygenic inheritance has been suggested to explain the lack of a simple mode of inheritance (Cowan, 1973).

The possibility of genetic heterogeneity has also to be considered—for example, some families contain individuals with duodenal ulcer, associated with a high serum Gp.I pepsinogen level, this being inherited in an autosomal dominant fashion (Rotter *et al.*, 1976). Furthermore, duodenal ulcer may be associated with gastrinomas in the autosomal dominant multiple endocrine adenomatosis syndrome (Rotter *et al.*, 1977a).

In a recent study of a group of 54 white males, there was reported an increased frequency of the HLA antigen B5 compared with a control group (Rotter *et al.*, 1977b). This present study was carried out to try to confirm this last observation in a larger group of white males and white females.

Methods

One hundred and one white patients were studied, 78 males (age range 19–76 years, mean 44 years) and 23 females (age range 34–67 years, mean 49 years). The majority of the patients were referred for investigation to the Gastroenterology Unit at Broadgreen Hospital, the remainder being seen at the Gastroenterology Unit at Walton Hospital,

Liverpool. Duodenal ulcer was diagnosed endoscopically and/or at operation during previous or subsequent surgery. Patients with combined duodenal and prepyloric ulcer were excluded.

HLA typing was carried out for 26 antigens in the A and B series using a modified microlymphocytotoxicity test (Terasaki and McClelland, 1964). The control series consisted of 500 blood donors, medical students, and members of staff from the same geographical area.

Results

The Table shows the frequency of the various HLA antigens in the patients and in controls. The only notable difference between the two series is in respect of HLA B12, which was present in 46.5% of patients and in 29.2% of controls ($\chi^2=11.58$, $P=0.001$). As 26 comparisons were made, an approximate correction for this P value is obtained by multiplying by 26 (Svejgaard *et al.*, 1974), giving $P=0.026$. The relative risk (Haldane, 1955) for B12 positive individuals of developing duodenal ulcer is 2.1, with 95% confidence limits of 1.4–3.3. Of the 78 male patients, 38 were B12 positive (48.7%) and eight were B5 positive (10.3%). Analysis of these results for male patients alone gives results differing very little from the total series.

Sixty-four out of 98 patients with duodenal ulcer who had their ABO blood groups tested were group O positive (65.3%) compared with 48.9% in controls. The frequency of blood group O was not significantly different between B12 positive and B12 negative patients (66% and 64.7% respectively).

Discussion

This study shows what appears to be a significantly increased liability of HLA B12 positive individuals to develop duodenal ulcer with a relative risk of 2.1. A previous study of male Caucasian patients with duodenal ulcer showed an increased risk for B5 but

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Table HLA antigens in patients and controls

Antigen	Duodenal ulcer (101)		Controls (500)*		χ^2	P
	Positive		Positive			
	(no.)	(%)	(no.)	(%)		
A1	40	39.6	169	33.8	1.25	0.32
A2	50	49.5	219	43.8	1.11	0.35
A3	28	27.7	142	28.4	0.02	0.99
A9	10	9.9	98	19.6	5.36	0.03
A10	7	6.9	46	9.2	0.54	0.59
A11	11	10.9	67	13.4	0.47	0.60
A28	9	8.9	26/451	5.8	1.38	0.34
A29	12	11.9	33/463	7.1	2.55	0.16
Aw30/31	2	2.0	25/440	5.7	2.37	0.20
Aw32	8	7.9	31/458	6.8	0.17	0.84
B5	12	11.9	48	9.6	0.49	0.61
B7	22	21.8	149	29.8	2.65	0.13
B8	25	24.8	139	27.8	0.39	0.61
B12	47	46.5	146	29.2	11.58	0.001
B13	1	1.0	24	4.8	3.06	0.14
B14	15	14.9	34	6.8	7.27	0.01
B15	7	6.9	53	10.6	1.26	0.35
B16	5	5.0	3/136	2.2	1.34	0.43
B17	10	9.9	45	9.0	0.08	0.92
B18	8	7.9	30	6.0	0.52	0.62
B21	2	2.0	3/54	5.6	1.44	0.47
B22	7	6.9	26	5.2	0.49	0.65
B27	6	5.9	43	8.6	0.79	0.50
B35	11	10.9	57	11.4	0.02	1.00
B37	0	0	5/195	2.6	2.63	0.25
B40	13	12.9	57	11.4	0.18	0.80

*In the case of some antigens not all the controls were tested and the relevant numbers involved are given in each instance.

no increased risk for B12. The data from the two studies can be combined by the methods of Woolf (1955). For B12 the combined relative risk is 1.61 ($\chi^2=6.95$, $P=0.008$) and P for heterogeneity=0.03. There is thus evidence of the two studies not being homogeneous in regard to the association with B12. For B5 the combined risk is 2.0, $\chi^2=9.22$, $P=0.002$, P for heterogeneity=0.08.

In this situation it is important to consider the possibility that there have been important differences in the way patients have been selected for study. The diagnosis of duodenal ulcer in the present study was based on macroscopical evidence—that is, the ulcer was seen at endoscopy or surgery. Furthermore, cases of combined duodenal and gastric ulcer were excluded because there is evidence that there may be important differences in aetiology in this group from that for patients with either duodenal or gastric ulcer alone (Doll and Kellock, 1951). In addition, patients on long-term ulcerogenic drugs were also excluded. Rotter *et al.* do not state their criteria for the diagnosis of duodenal ulcer in their patients. It is important that the way in which patients are ascertained for inclusion in studies of this type is clearly stated.

The reasons for the differing findings in these two studies are at present not obvious. Clearly, it would be useful if additional studies using well-defined

clinical criteria were carried out, the results being compared and combined with the two studies analysed here.

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