HLA AW19, B12 in immunoproliferative small intestinal disease

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SUMMARY A group of 21 patients with immunoproliferative small intestinal disease (IPSID), 10 with alpha heavy chain paraproteinaemia and 11 without it, were HLA typed. The results were compared with 35 disease controls and 120 normal controls. A significant increase of Aw19 and B12 antigens was noted among the patients compared with the control subjects. The high rate of association of both AW19 and B12 antigens in patients as compared with controls suggests a possible haplotype (Aw19, B12) association with IPSID.

The so-called 'Mediterranean' abdominal lymphoma now referred to as immunoproliferative small intestinal disease (IPSID) (WHO, 1975) is a disease of the young with a geographical distribution which shows that the overwhelming majority of cases reported have been of Mediterranean or Middle Eastern origin (Ramot *et al.*, 1965; Eidelman *et al.*, 1966; Rappaport *et al.*, 1972; Shahid *et al.*, 1975; Nasr *et al.*, 1976; Zarrabi and Rosner, 1976). It is usually characterised by the cardinal symptoms and signs of chronic watery diarrhoea and steatorrhoea with abdominal pain and weight loss. Clubbing of fingers and toes is common. Small intestinal biopsy usually reveals villous atrophy and diffuse, massive plasmolymphocytic infiltration of the lamina propria together with involvement of mesenteric lymph nodes.

Analysis of the patient's serum and jejunal juice frequently demonstrates a fast-moving heterogeneous paraprotein essentially composed of an incomplete heavy-chain of IgA. Many cases do not conform to this pattern, however, and our series is marked by a considerable clinical and pathological heterogeneity.

The suggestion that a potentially reversible, pre-malignant stage of the disease exists (Ramot *et al.*, 1965; Rogé *et al.*, 1970) which, if untreated may rapidly progress to a malignant phase with a fatal outcome, makes early detection of the disease in susceptible population groups highly desirable. This, together with the peculiar geographical

distribution of the disease, warrants a search for disease-associated environmental and genetic factors.

To our knowledge, no report on the relationship between HLA and IPSID has hitherto appeared in the literature. In the present study, which started about two years ago as part of a larger prospective project, 21 patients suffering from IPSID were HLA typed together with 35 disease and 120 healthy controls in order to discover any particular association that might exist.

Methods

PATIENTS

Fifty-six patients suffering from malabsorption syndrome or chronic diarrhoea along with 120 healthy controls were studied for the A, B, C antigens of the HLA system. The patients were typed blindly without any knowledge regarding aetiology of their malabsorption or diarrhoea. Out of these 56 cases, 21 were found to have IPSID either with alpha-chain protein in their sera (group I, 10 patients), or without it (group II, 11 patients). The remaining 35 cases of malabsorption due to other causes served as disease controls (group III) and 120 voluntary blood donors were used as healthy controls (group IV). Disease controls were all subjected to peroral jejunal biopsy and serum analysis (by radial immunoselection) in order to exclude IPSID.

TECHNIQUES

Using standard NIH lymphocytotoxicity test, 14 antigens for the A locus, 15 for the B locus, and

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five for the C locus were detected on the peripheral blood lymphocytes.

The antisera used were monospecific and mostly of local origin, although well-defined antisera from NIH and some from Eurotransplant were also used. At least three antisera were used for detection of each specificity.

Results

As shown in the Table, groups I and II both exhibited a significant increase in AW19 from the A-locus compared with control groups III and IV ($P < 0.001$). The former groups (I and II) also showed an increase in B12 from the B-locus compared with controls III and IV ($P < 0.001$). A relative increase in B17 in group II patients compared with all other groups was also noted.

The most significant finding, however, was the simultaneous presence of both AW19 and B12

antigens in patients compared with controls, which is suggestive of a haplotype association

The immediate family members of one patient from group I were also studied (Figure). The patient's 11 year old sister, and 54 year old mother shared high risk HLA antigens with her. Both were symptom-free, however, with no alpha-chain protein in their sera. Nevertheless, the patient's sister is still below the usual age of onset (15 to 30 years) and is being followed up.

Discussion

IPSID occurs relatively frequently in the Middle Eastern countries and the Mediterranean basin (Ramot *et al.*, 1965; Eidelman *et al.*, 1966; Rappaport *et al.*, 1972; Shahid *et al.*, 1975; Nasr *et al.*, 1976; Zarrabi *et al.*, 1976). However, our own studies on over 50 patients diagnosed during the past two years at Taj Pahlavi Cancer Institute, Tehran, have not

Table Distribution of HLA antigens observed more frequently in IPSID than in control groups

HLA specificities	Patients						Controls				χ^2	P	RR
	Group I (10 cases)		Group II (11 cases)		Group I + II (21 cases)		Group III (35 cases)		Group IV (120 cases)				
	(no.)	(%)	(no.)	(%)	(no.)	(%)	(no.)	(%)	(no.)	(%)			
AW19	3	30	4	36.3	7	33.3	2	6	4	3.3	22.36	< 0.0001	15
B12	4	40	3	27.2	7	33.3	2	6	13	10.8	7.43	< 0.001	4
Aw19 + B12	3	30	3	27.2	6	28.5	0	0	1	0.8	28.39	< 0.0001	48

χ^2 : Chi-square (comparison of groups I + II with groups III + IV).
RR: Relative risk.

Figure Pedigree of the family of a patient suffering from small intestinal lymphoma and alpha-heavy chain disease. The patient is marked by a black circle, and other members sharing the same haplotype are shown by striped circles.

shown a clustering of cases in any one particular region of the country (Banisadre, 1978). This makes population surveys for early detection of new cases difficult and unproductive, and, clearly, a search for factors associated with susceptibility to IPSID is highly desirable. Factors such as disease-associated HLA antigens may help identify individuals at high risk, particularly among immediate family members of patients. Those who appear to be at risk can then be followed up closely for development of early signs of the disease, which may still be potentially reversible (Report of a WHO Meeting of Investigators, 1976; Rogé *et al.*, 1970). In this regard, a review of the literature revealed two reports of the familial incidence of IPSID. The first one, from Iran (Banihashemi *et al.*, 1973), described three families with lymphoma in multiple family members. One of the families included a 22 year old girl and her 28 year old brother who developed IPSID within six months of each other, even though they had lived far apart. The second report (Maurer *et al.*, 1976) described four brothers (all children between 2 and 7 years old) who all developed IPSID within a span of seven years. These findings raise the possibility of a genetic predisposition or immune deficiency which may pave the way for mutagenic or oncogenic stimuli in the environment.

In one family studied by us two members showed 'high risk' HLA antigens in common with the patient, and these members are being closely followed up.

The importance of association between HLA haplotype and disease has been emphasised before (Terasaki and Mickey, 1975). Our data and the family study of one of our patients in which the inheritance of AW19, B12 as haplotype was shown are suggestive of a significant association between HLA haplotype AW19, B12, and IPSID. Unfortunately, we still have insufficient data concerning lymphatic malignancies other than IPSID, although this is being collected and the findings will be re-

ported later on. It remains to be established whether our findings are significant in terms of susceptibility to the disease or its course.

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