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HLA in migraine and coeliac children

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Abstract The linkage between HLA antigens and disease susceptibility has been investigated in several diseases. Two different mechanisms are known to act in the relation between the HLA system and headache: linkage and association of alleles. Among neurological disorders associated with coeliac disease (CD) we focussed on headache in 1997. From a group of 70 coeliac children, we studied 10 children with headache (3 boys and 7 girls). For each subject we evaluated clinical history and HLA antigens. The incidence of headache was not different with respect to the prevalence of headache in the general population. The HLA setting is not different between the 2 groups examined. However, we highlight 2 cases for the particular HLA setting.

Key words Coeliac disease • Headache • Children • HLA antigens

Introduction

In the last few years, increasing attention has been given to the study of the association between diseases with familial clustering and antigens of the major histocompatibility complex [1–3]. Genetic and segregation studies have shown that migraines are polygenic, multifactorial diseases [2, 3].

Recent findings obtained with the application of molecular biological techniques to the study of candidate genes have confirmed the association of migraine with a genetic pathogenesis [2].

Familial hemiplegic migraine is an autosomal dominant disease linked to chromosomes 1 and 19, as phenotypical variants [2, 3].

A recent Italian study [4] indicated that the two types of migraine (MWA and MwoA) have multifactorial inheritance, but several genetic and environmental factors are still largely unknown. We support the hypothesis of a protective role of DR2 antigen in MWA and provide additional basis for the proposed difference within MwoA and MWA.

Now several authors are studying the comorbidity of migraine [1, 2, 4].

There is a non-coincidental association with other neurological and autoimmune disorders [5–7].

The polymorphisms of antigens of the HLA system are potentially responsible for HLA associations in disease [7].

Among neurological disorders associated with coeliac disease we focussed on headache in 1997 [8]. Particularly, we proposed to verify if the headache presented by the group of coeliac children was secondary to the malabsorption syndrome or was a primary disease coexisting with coeliac disease.

There is strong genetic influence on the susceptibility to coeliac disease illustrated by a high prevalence rate among first-degree relatives of probands, and by high concordance

rate among monozygotic twins. The concordance rate among HLA is about 40% [9, 10].

A typical feature of genes in the HLA complex is linkage disequilibrium. Some genes occur more often together on haplotypes.

Coeliac disease was first found to be associated with the HLA class I molecule B8. Later, a stronger association with the class II molecule DR3 was found and, particularly, it was found to be associated with DR3 only when this allele was carried on the B8-D3 haplotype.

It has provided evidence for a stronger association HLA-DQ2 in linkage disequilibrium with both DR3 and DR7/DR5 [9, 10].

The linkage analysis shows cis-encoded genes in DQ2-DR3 association, but these genes are located in trans in DR5/DR7 heterozygous individuals [9, 10].

Coeliac disease and autoimmune-associated disorders may be linked with HLA genes and other genetic factors [2–4, 7].

The aim of the present study was to examine, in children, the linkage between headache and coeliac disease.

Study population and methods

From a starting population of 70 coeliac children, we examined 10, including 3 boys and 7 girls affected by recurrent headache. For each subject we evaluated clinical history and allelic frequencies.

Serological tissue typing for class I (loci A, B, Cw) and II (DR, DQ loci) was performed with the standard microcytotoxicity assay, according to Terasaki and McClelland [11].

Genomic DNA was extracted from peripheral blood leucocytes and submitted to polymerase chain reaction (PCR) of the second exons of DQ-A1 and DQ-B1 genes. The DNA was amplified by using sequence-specific primers (PCR-SSP), according to Sasazuki and Kimura [12].

The diagnosis of coeliac disease was made according to the European Society of Paediatric Gastroenterology and Nutrition (ESPGAN) criteria [13]. Headache was confirmed according to International Headache Society (IHS) criteria [14].

Table 1 Clinical history of 10 children with coeliac disease and headache. *MWA*, migraine with aura; *TTA*, tension-type headache; *MwoA*, migraine without aura; *OE*, occipital epilepsy

Patient	Age at diagnosis (years)	Headache	
		Type	Age at onset, years
1	9.02	MWA	7.0
2	12.02	TTH	14.0
3	11.5	MwoA	16.0
4	7.5	TTH+MwoA	6.0
5	8.10	MwoA	7.5
6	8.0	MWA+OE	10.0
7	6.0	MWA	6.0
8	2.0	MwoA	6.0
9	10.0	TTH	14.0
10	4.0	MwoA	10.0

Results

Three children were affected by MWA, 4 by MwoA, 1 by MWA and occipital epilepsy, and 2 by tension-type headache (Table 1). No patient presented cerebral calcifications.

Four children showed neurological symptoms after diagnosis of coeliac disease and when they were put on a gluten-free diet.

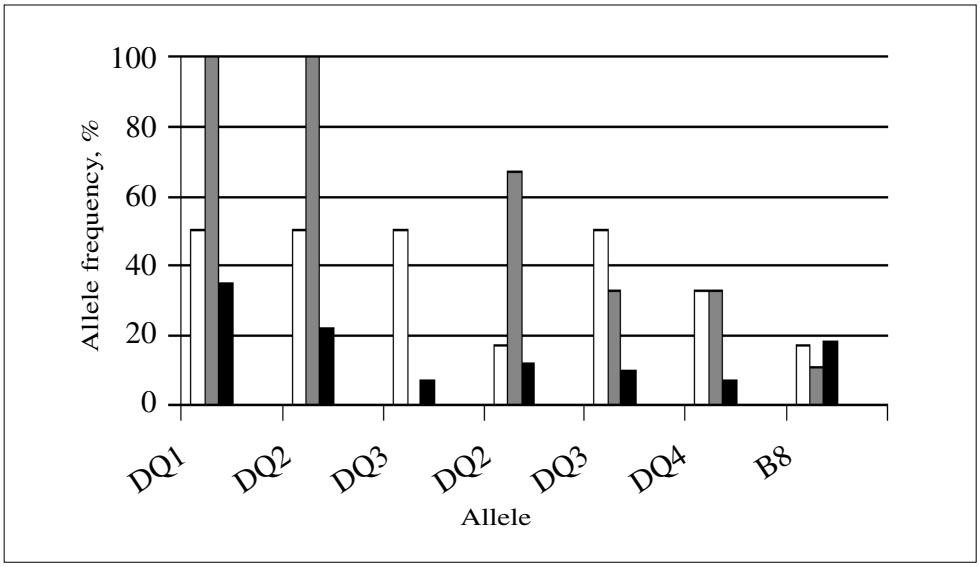

Fig. 1 HLA typing of study group and comparison to the Italian population. □ Children with coeliac disease and headache (n = 10). ■ Children with coeliac disease (n = 60). ■ Italian population [17]

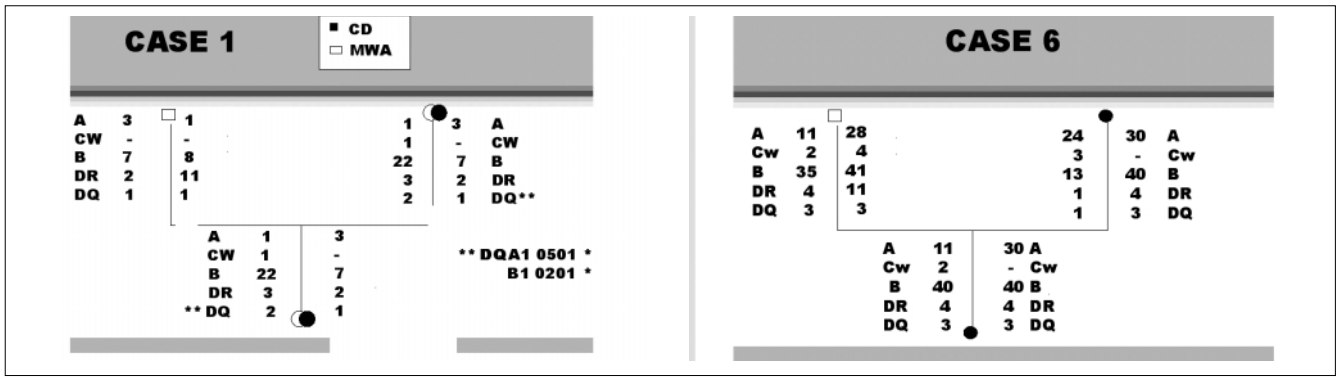

Fig. 2 Familial HLA segregation in case 1 (MWA) and case 6 (MWA and occipital epilepsy)

The HLA typing is summarized in Fig 1. The allelic distribution is not significantly different between coeliac children with and without headache.

The cases examined are few, but we underline 2 cases.

In case 1 (Fig.2a), mother and daughter had the diseases: coeliac disease and MWA and same HLA typing. DQ2 is in cis with DR3 and is coexistent with DR2.

In case 6 (Fig.2), DR4 allele is in a homozygous condition because it is present in both parents.

The incidence of headache in this group (17.4%) was not different with respect to the general population.

Discussion

Coeliac disease and migraine are frequent diseases with an onset in childhood and they are both associated with other diseases with autoimmune pathogeneses. Migraine is a complex disease and comorbidity is an important aspect of its pathogenesis.

Migraine is a chronic illness with a variety of clinical symptoms in different patients. Genetic determinants are certainly at the basis of some migraine forms.

Screening for coeliac disease is valid [15], and discovering associated diseases allows a better understanding of pathogenesis.

The results of our study do not clarify the pathogenesis of migraines associated with coeliac disease. However the first case reported clearly shows the possibility of a linkage between these two diseases when the same HLA is present.

In epilepsies and particularly in occipital epilepsy, we already look for coeliac disease as a silent disease according to Gobbi et al. [16]. Therefore we believe coeliac disease screening to be useful both in migrainous and epileptic children for a true comprehension of the linkage between the diseases observed.

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