Case Report

A FAMILIAL COELIAC DISEASE FROM TURKEY

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ABSTRACT

A Turkish grandmother, her son and grandson all complaining of diarrhoea were diagnosed as suffering from Coeliac disease on the basis of clinical symptoms, antigliadin antibodies and duodenal biopsy. HLA antigens were also studied on patients to provide the information about relationship between these antigens and Coeliac disease. Therefore we confirm that HLA DR3 and DR7 negative patients who usually DQ2 negative, are DR4 positive may also be true for Turkish patients with Coeliac disease.

Key Words: Coeliac Disease, Familial, In Turkey.

INTRODUCTION

Coeliac disease is a permanent intolerance to gliadin leading to intestinal villous flattening and crypt hyperplasia in susceptible subjects. Immune reactions to gliadin probably play a part in the pathogenesis of the disease although the immunological mechanisms are still poorly understood (1).

Coeliac disease has a markedly variable geographical prevelance throughout the world. Its incidence is highest in Nothern Europe. It is rare in Asians, Africans, Chinese and Japanese (2). Familial predisposition to Coeliac disease is clear but the inheritance does not follow classical Mendelian patterns (3).

HLA typing and Coeliac disease relation have been investigated extensively. In all population studies of Coeliac patients, more than 90% of the patients are DR3 and/or DR7 positive. DQ2 is carried in association with the DR3 and DR7 alleles. Later studies have shown that DR3 and DR7 negative Coeliac patients, usually DQ2 negative, are DR4 positive (4). In Turkey there is no such study that reports the prominent HLA types involved in Coeliac disease with Turkish patients. This study reports a family from three successive generations together with Coeliac disease from Turkey. We tried to identify a clue for HLA typing of Turkish Coeliac patients.

CASE REPORTS

A forty-year old father, who was affected by chronic diarrhoea, had first applied to Hacettepe University Hospital with complaints of bulky, foul smelling stool continuing for 4 years at 10 years of age. The hemoglobin of the patient was 7.5g/dl (N:12-16) and severe iron deficiency anemia was diagnosed. A barium study of the small bowel demonstrated flocculation and mucosal thickening typical for malabsorbtion. The stool examination was negative for the giardiasis and other parasites. The duodenal biopsy was found to be insufficient to establish specific tissue diagnosis. Gluten free diet was tried. After diet trial, the complaints of the patient subsided and he was discharged in good health and prescribed iron supplementation and a gluten free diet. He again applied to hospital with complaints of diarrhoea, severe weight loss and leg edema 30 years later, in May 1994. At this time the patient had discontinued the gluten free diet and malabsorbtion syndrome with all signs and symptoms was evident. Hemoglobin was 10g/dl (N:12-16), hematocrite 30%, Na:136 meq/L (N:132-146), K:3. 0 meq/L (N:3.5-5.5), Ca:8.2 mg/dl (N:8.4-10.2), ALT: 54U/L (N:8-20), AST:53U/L (N:10-30), total protein:5.5g/dl (N:6.4-8.3), albumin: 2.1g/dl (N:3.5-5.0), prothrombin time: 17 sec. (11.2-13.4), INR:1.6 (N:1.12-1.21), serum IgA: 634% (N:90-450), serum IgM:483% (N:60-250), serum IgG:1020% (N:800-1800). Serum immunelectrophoresis was normal. Duodenal biopsy revelead hyperplastic villous

atrophy with hyperplasia of the crypts. The gluten free diet reinstituted; the complaints of the patient, physical signs together with laboratory abnormalities and histological mucosal abnormalities normalized. His HLA typing was HLA A1, A26, B8, B38, DR17, DR4, DQ8, DQ2.

The fifty-eight year old mother of the patient applied to the Gastroenterology Unit of Hacettepe University Hospital with complaints of malaise, weight loss and diarrhoea characteristically similar to her son's in November 1996. Despite being started on iron supplementation years ago, diagnosed as iron deficiency anemia by her physician in her town, she did not benefit from the treatment. Hemoglobin of the patient was 8.8g/dl (N:12-16) and parametres of anemia were similar with iron deficiency anemia. IgA-antigliadin antibody was positive. In the barium study mucosal edema, segmental spasm of the small bowel and flocculation of the barium meal were observed. Small intestinal mucosal biopsy was significant for Coeliac disease. Clinical remission was not achieved because she did not want to take on strict gluten-free diet. Her HLA typing was HLA A1, B8, DR17, DR14, DQ5, DQ2.

The eight year old grandson along with his grandmother applied to the hospital. He also had chronic, foul smelling, bulky diarrhoea from three years of age. His weight was 20 kg (10 percentile), and his height was 120 cm (25-50 percentile). Physical examination was normal. IgA-antigliadin antibody of the child was also positive. Relief of all symptoms of the disease occurred with strict gluten-free diet. His HLA antigens were also studied and found that HLA A3, A26, B38, B60; DR4, DR11, DQ7, DQ8 positive. While the typical association of HLA DR3, HLA B8 and HLA DQ2 with Coeliac disease was detected on the grandmother and her son, the tissue antigen typing of the grandson revealed HLA DR4 association but not HLA DR3, HLA B8 or HLA DQ2.

DISCUSSION

Coeliac disease has been traditionally considered to be disease of childhood and early adult life characterised by malabsorbtion, diarrhoea, weight loss and failure to thrive. The disease can, however, be found at any age and in many cases is devoid of any of these typical features, but it is detected as a result of investigation of heamatological abnormalities such as anemia, macrocytosis and folate deficiency (5). It is also recognised that there are a significant number of subjects with villous atrophy who are completely asymptomatic. These include 10-15% of first-degree relatives of known Coeliac disease patients (6). It is therefore possible that a large number of people perhaps the majority, remain undiagnosed and only the tip of the iceberg of cases are recognised. Some of these will have non-specific but significant symptoms, which would benefit from treatment with a gluten-free diet. Even in those who are asymptomatic there is evidence that they have significant bone problems and are at increased risk of developing malignancies, particularly of gastrointestinal tract. Treatment with a gluten-free diet reduces the risk of lymphoma in Coeliac disease and seems to produce improvement in bone mineralisation (7).

At present, a small bowel biopsy is the only definitive test for Coeliac disease. A reliable, less invasive test would facilitate screening of much larger numbers of people. A number of serological tests have been used as a pointer to diagnosis and include antireticulin antibody (ARA), antiendomysial antibodies (EMA), antigliadin antibodies (AGA), but their sensitivities and specificities have varied with assay methodology, the antibody isotype detected, and the patient group studied. IgA class AGA and EMA seem to give the best diagnostic performance and this combination has been suggested to be useful for population screening, by first testing for AGA and then confirmation with a positive IgA EMA (8).

Coeliac disease is associated with the HLA Class II extended haplotypes DR3-DQ2 or DR5/7-DQ2. A small minority of the Coeliac disease patients have the haplotype DR4-DQ8. Most Coeliac disease patients carry the risk alleles encoding the DQ2, but this is also the case in about 20% of the general population. Therefore it is probable that other genes outside the HLA region are involved in Coeliac disease susceptibilty. One of the future targets for Coeliac disease research is to identify other susceptibility genes and their functions (9).

Several major hypothesis regarding the nature of the primary host defect in Coeliac disease have been proposed during the past decades, namely: the missing enzyme theory, the immunological hypothesis, the membrane glycoprotein defect, and the mucosal permiability defect. The immunological theory is the one most widely accepted. HLA Class II molecules on antigen presenting cells expose processed peptides to immunocompetent T cells thus initiating the disease mechanism. The major environmental trigger is ingested gluten but adenovirus infection has also been suggested to play some part. Gliadin specific, DQ2 restricted T cells have been isolated from the intestinal mucosa of patients (10).

In this study, we confirm the familial nature of Coeliac disease for Turkish people. We also confirm the HLA typing same as other countries. But our major aims should be to investigate the prevelance of gluten

sensitivity in Turkish population and to prevent the ill health because of underdiagnosis of Coeliac disease. Non-invasive serological screening tests may be useful for this clinical purpose. For the present, they may be used to screen of selected groups such as first-degree relatives of Coeliac patients.

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