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Celiac disease in childhood: analysis of 41 cases

Çocukluk çağında Çölyak hastalığı: 41 vakanın analizi

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ÖZET: *Bu çalışmada Ocak 1982 ve aralık 1995 tarihleri arasında tanımlanan çölyak hastalıklı 41 çocuk retrospektif olarak incelenmiştir. Yirmi ikisi kız, 19'u erkek olan hastaların ortalama yaşları 6± 6.8 yıl (13 ay-18 yıl arası) idi. En sık başvuru yakınmalaı persistan veya tekrarlayan diyare (%85), kısa boy (% 68), karın şişliği (%39), büyüme geriliği (%29)olan hastaların bazılarında eşlik eden diğer hastalıklar mevcuttu; iki hastada gecikmiş puberte, iki kronik karaciğer hastalığı ve/veya portal hipertansiyon, iki büyüme geriliği, iki hipotiroidizm, bir tip 1 diyabet, bir diyabet insipit, bir jüvenil romatoid artrit. Histopatolojik bulgular 33 hastada çölyak hastalığı ile uyumlu iken, nonspesifik mukozal değişiklikler tanımlanan 8 hasta serolojik belirteçler ve glutensiz diyete cevaplarıyla çölyak hastalığı kabul edildi. Hastalara tamamen glutensiz diyet önerildi ve ikinci ince barsak biyopsisi yapılan 9 hastada histolojik olarak da düzelme gözlendi.*

Anahtar Kelimeler: **Çölyak hastalığı, çocukluk, ince barsak biyopsisi**

SUMMARY: *In this study, 41 children with celiac disease diagnosed between January 1982 and December 1995 were evaluated retrospectively. Twenty-two of the patients (54%) were males and 19 (46%) females. The mean age was 6 ± 6,8 years (range, 13 months to 18 years) and the most common presenting symptoms were persistent or recurrent diarrhea (85%), short stature (68%), abdominal distention (%39), failure to thrive (29%). Some of the patients had coexisting diseases; two (5%) patients had delayed puberty, two (5%) chronic liver disease and/or portal hypertension, two (5%) growth retardation, two (5%) hypothyroidism, one (2.4%) type I diabetes mellitus, one (2.4%) diabetes insipidus and one (2.4%) juvenile rheumatoid arthritis. Histopathologic findings of 33 patients were compatible with celiac disease. Eight patients who had non-specific mucosal changes were also considered as celiac disease by the serologic markers and with the extremely good clinical response to gluten-free diet. The patients have been recommended a strict gluten-free diet, 9 patients had a second small bowel biopsy which showed histological improvement.*

Key Words: **Celiac disease, childhood, small bowel biopsy**

CELIAC disease (CD) or gluten sensitive enteropathy is a common and important disease related with ingestion of cereal grains such as wheat, barley or rye and is a striking example of an illness that results from the interaction of genes with the environment (1). The entity was first described by Samuel Gee in 1888 by the name of "Coeliac affection" (2). Since the report of Weijers et al (3), we have known that the prolamins from different cereals are toxic to the intestinal wall of the patients with CD. CD is related with several genetic and environmental factors. Falchuk et al.(4) demonstrated a markedly increased frequency of the class I antigen HLA-B8 in patients with CD compared with controls.

The recommended criteria for a diagnosis of CD have evolved over the years since small intestinal biopsy was introduced. An early diagnostic definition suggested for children required a small bowel biopsy demonstrating villous atrophy, a second biopsy demonstrating mucosal recovery on a gluten-free diet and recurrence of the lesion after a gluten challenge according to the ESPGAN criteria (5), but according to revised criteria, the initial diagnosis is based firstly on the appearance of hyperplastic villous atrophy and secondly on full clinical remission after withdrawal of gluten from the diet. The finding of circulating antibodies at time of diagnosis and the disappearance when the patient is taking a gluten free diet adds weight to the argument (6).

MATERIAL AND METHODS

The forty-one children enrolled into this study we-

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Table 1. Mode of presentation of CD in the patients (n=41)

	n	%
Persistent or recurrent diarrhea	35	85
Abdominal distention	16	39
Failure to thrive	12	29
Weight loss	9	22
Vomiting	7	17
Malaise	7	17
Anorexia	6	15
Abdominal pain	6	15
Geophagia	2	5
Constipation	1	2

Table 2. Mode of presentation of CD in the patients (n=41)

Diseases	*n*	%
Delayed puberty of no apparent cause	3	7.3
Chronic liver disease and/or portal hypertension	2	5
Growth retardation of no apparent cause	2	5
Hypothyroidism	2	5
Iron deficiency anemia	2	5
Type I diabetes mellitus	1	2.4
Diabetes insipidus	1	2.4
Juvenile rheumatoid arthritis	1	2.4

re diagnosed as CD between January 1982 and December 1995. We used small intestinal biopsy, antigliadin antibody (AGA), and response to gluten free diet as the diagnostic markers for CD. Twenty-two of these patients (54%) were male and 19 (46%) were females. The mean age on first admission was 6±6.8 years (median 6 years, range 13 months to 18 years), and these patients had been followed up for a duration of 24±46 months (range, 3 months to 8 years).

All the patients height, weight and weight for height measures had been recorded carefully during their follow-up, as were the presence of signs of malabsorption or associated diseases. The investigative procedure for these patients included an initial clinical assessment followed by routine hematological and biochemical analyses. D-Xylose absorption test was performed on all patients. After an overnight fasting, 5 g of D-xylose dissolved in 50 ml of water was given to the patients. Serum samples were obtained after one hour and D-xylose concentration measured. The values below 20 mg/dl were accepted as abnormal (7). After obtaining informed consent, the children were fasted an overnight, sedated and a proximal small intestinal mucosal biopsy specimen was obtained using a pediatric Karl Storz biopsy capsule. Histologically, subtotal villous atrophy, crypt hyperplasia and intraepithelial lymphocyte infiltration were compatible with CD.

AGA IgG and IgA were determined in 32 and 18 patients, respectively. The determination of AGA was done by using commercial kits (Labmaster-ELISA test, Labmaster diagnostics, Turcu-Finland)(8). After the diagnosis of CD, the patients were informed about the disease and recommended a gluten-free diet. A Small intestinal biopsy was repeated on 9 patients after a mean follow-up period of 8 months.

RESULTS

The presenting symptoms and signs on first admission were; persistent or recurrent diarrhea in 35 patients (85%), abdominal distention in 16 (39%), failure to thrive in 12 (29%) (4 without any gastrointestinal system symptoms), weight loss in 9 (22%), vomiting in 7 (17%), malaise in 7 (17%), anorexia in 6 (15%), abdominal pain in 6 (15 %), geophagia in 2 (5%), pallor without any other symptoms in 2 (5%), and constipation in 1 (2%) (Table I). The onset of the symptoms varied from 6 months to 12 years of age (median 1.5 years).

Before they had been diagnosed as having celiac disease, some patients had been under medical care with a different diagnosis. Three of them (7.3%) were being followed up as being in delayed puberty, 2 (5%) as having chronic liver disease and/or portal hypertension, 2 (5%) growth retardation, 2 (5%) with hypothyroidism, one (2.4%) type I diabetes mellitus, one with (2.4%) with diabetes insipidus, one (2.4%) with juvenile rheumatoid arthritis and one (2.4%) with Meckel's diverticulum (Table II).

Twelve patients (29.2%) had parental relations. One patient had a sister with CD, and another had father and grand mother with CD.

At diagnosis, the weight was below the 3rd centile in 25 (61%) patients, below the 10th centile in 34 (83%) patients. Only two patients were above 50th centile with regard to weight standards. With gluten free diet, all patients started to gain weight appropriately and only 5 (12.2%) patients remained below the 3rd centile, but those had

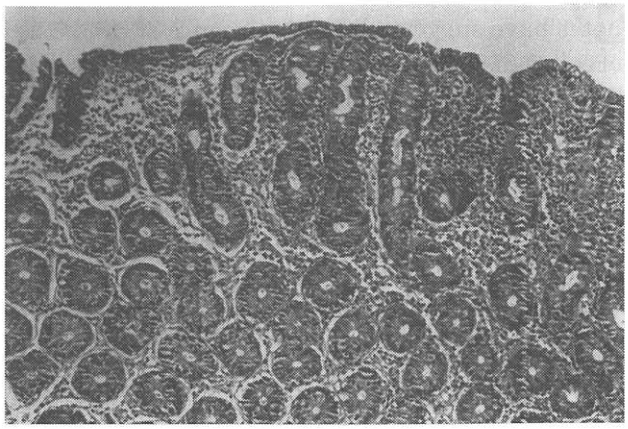

Figure 1. *A small bowel biopsy demonstrating villous atrophy with shortening of the villi and crypt hyperplasia (Hematoxylin-Eosinx33)*

been treated for less than 6 months.

The height was below the 3rd centile in 28 of 41 patients (68%), and only two patients (5%) were over the 50th centile. With gluten free diet, the height remained below 3rd centile in 12 (42.8%) of these 28 patients, all of whom were treated less than 6 months. Ten out of 28 (35.7%) patients reached 50th centile. Eight out of 12 patients (66.6%) who remained below the 3rd centile were older than 9 years on diagnosis. Weight for height at the time of diagnosis was above 90% of the standards in 22 patients (54%). With gluten-free diet, 39 of the patients (95%) were over 90% of the standards.

Twenty-six patients (63%) were anemic; 23 had iron deficiency anemia which was the only sinificant symptom in two ,and 3 had megaloblastic anemia with vitamin B12 and folate deficiencies. D-xylose test was abnormal in 38 patients (93%). Serum transaminases were measured in 30 patients. AST was abnormal in 12 (40%), and ALT in 9 (30%). Sixteen out of 35 patients (46%) were hypoalbuminemic and 23 out of 33 patients (69%) were hypocalcemic. Reducing substance in stool and steatocrite were negative in all patients. Serum carotene, vitamin A and zinc levels, which were measured in 25 patients, were found below the normal limits in 23 (92%), 20 (80%) and 13 (52%) patients, respectively.

AGA IgG was found positive in 30 patients (94%), whereas it was AGA IgA in 13 patients (72%). Contrast studies of the small intestine were performed on 17 patients. Seven of them indicated malabsorption.

A small intestinal biopsy was performed on all 41 patients. Thirty-three of them (80.5%) had typical lesions for celiac disease (Figure 1), and histopathological findings of the remaining 8 patients (19.5%) whose presenting symptoms were chronic diarrhea and abdominal distention, were not specific. Three of them with a normal biopsy were considered as latent celiac patients (9), three others had increased intraepithelial lymphocytes and were classified as type I CD. The remaining two patients were accepted as type II CD with increased intraepithelial lymphocytes and enlarged crypts (10). Serum AGA levels and D-xylose tests were abnormal in these eight patients and they clinically improved remarkably with a gluten-free diet.

After a mean of 8 months (range 6 to 11 months) of strict gluten-free diet, a second biopsy was performed on 9 patients, and histological findings were found to be normal in all.

DISCUSSION

Celiac disease, characterized by an inflammatory enteropathy of the upper small intestine causing malabsorption and failure to thrive, is a permanent intolerance to dietary gluten in susceptible children. Treatment with a gluten-free diet results in clinical and mucosal recovery and subsequent gluten challenge provokes a clinical and mucosal relapse (5).

Celiac disease is most commonly encountered in northwest Europe with the prevalence of 33 to 203 per 100.000 persons (11). Several reports had pointed out that there is a female predominance in adults. In childhood, sex difference, is less marked although there is still a slight female predominance (11). In our study, the males composed 54% of the population.

The clinical presentation of celiac disease is very variable. The main symptom is prolonged diarrhea. Celiac disease should be suspected in all infants and small children having the combination of prolonged diarrhea which started after beginning the gluten containing diet and failure to thrive (12,13). In addition, these children may have other signs of severe enteropathy and malabsorption, such as dehydration, hypoproteinemia, hypokalemia, hypoprothrombinemia and hypocalcemic rickets. It has been known for years, however, that the presence of celiac disease in older children may be completely different (14). As in our two patients, iron deficiency anemia may be the only present manifestation . Thus, the diagnosis of celiac disease can not be based on the

symptomatology. The first requirement for the diagnosis of celiac disease is the finding of a characteristic small intestinal mucosal abnormality on histological examination of a biopsy specimen. In our study, the first small intestinal biopsies were compatible in the majority of the patients with CD. It has also been shown that there is a spectrum of structural features of CD from an infiltrative pattern to flat mucosa (10). Jejunal biopsies of our three patients revealed type I and two type II CD according to this spectrum. Our three patients were accepted as latent celiac patients with a normal jejunal biopsy. These patients might show severe changes of mucosal architecture during a lifetime without gluten free diet. The presence of circulating antibodies (AGA, antireticulin and antiendomysium) at diagnosis and their disappearance when the patient is under gluten free diet add weight to the diagnosis (6). They are usually used for screening.

In children and adolescents with celiac disease, growth retardation is a dominant feature(15). In some patients, short stature is the only symptom of CD and short stature of unknown cause is considered an indication for further investigation, including serological tests and a jejunal biopsy (16,17). In our study, 68 % of the patients had short stature at first admission, and short stature was the main complaint without gastrointestinal symptoms in 4 (9%) of them. As a result of malabsorption, malnutrition is a frequent symptom in celiac patients.

Two of our patients had another family member with CD. Family studies have revealed high frequency of the disorder in the first degree relatives of patients suggesting that genetic factors might influence susceptibility to CD (10).

There is an association between CD and certain other well-defined diseases, the pathogenesis of which is immunological. The most important of these is type I diabetes mellitus. About 2 to 4 percent of patients suffering from this disease also develop celiac disease (18). We had only one patient (2.4%) with type 1 DM and CD coincidentally.

Retrospective studies based on the review of case notes have suggested that between 2.7% and 5.8% of celiac disease patients had hypothyroidism (19). The association of CD and hypothyroidism has clinical importance. Both diseases can present with lethargy, macrocytic anemia, bowel disturbance, and malabsorption. Failure to recognize and treat both may, therefore, result in an apparent, lack of response to treatment (19). In our study, 5% of the patients had hypothyroidism. One of our patients was being followed up as diabetes insipidus (DI) before the diagnosis of CD. The coincidence of DI and CD is not defined in literature. There is a case report about a patient who had congenital hypothyroidism, DI and CD, but the relationships among them could not be established (20).

Biochemical evidence of liver dysfunction has been found in 39 % of adults and up to 57 % of children with celiac disease (21). Vajro et al (22) reported six children with elevated serum transaminase activity as an early manifestation CD. Hepatic damage may be an atypical manifestation and resolve after gluten free diet. Hepatosplenomegaly was also reported in childhood CD with or without liver dysfunction (23). In our study, elevated serum transaminase levels were found in up to 40% of the patients.

Dietary compliance is well correlated with histological improvements. In all the patients who had abandoned their gluten free diet, clinical improvement was not noticed. It may take one to 16 years to have a relapse after abandoning the diet (24).

Owing to the absence of any characteristic features, many subclinical cases of CD could not be detected. Celiac disease should be noted in any patients with chronic/recurrent diarrhea, anemia, failure to thrive or growth retardation. Clinical and histopathological findings are variable. As the disease is treatable, screening is useful in patients at risk, and diagnosis should be done in all susceptible patients by using all diagnostic tests. A Gluten-free diet is very important for patients especially for for the appropriate growth of children.

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