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ORIGINAL PAPERS

Coeliac disease: clinical features in adult populations

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ABSTRACT

Introduction: coeliac disease (CD) is a chronic disease of the small intestine, which is caused by gluten intolerance, producing malabsorption of nutrients and vitamins. Clinical manifestations of CD in adults are highly variable, including intestinal and extra-intestinal symptoms. The disease may also occur in individuals who are asymptomatic.

Objective: our objective is to describe the incidence and clinical manifestations of CD in adults.

Material and methods: a retrospective study was carried out in patients diagnosed of CD between January 1990 and December 2008. Diagnosis was based on serologic tests and duodenal biopsy, which were compatible with CD in all of them.

Results: sixty eight adult patients were diagnosed of CD in this period. Mean age was 33 (18-65) years and 50 (74%) were women. The clinical manifestations were diarrhoea in 38 (55%), abdominal pain in 27 (40%), loss of weight in 15 (22%), dyspepsia in 13 (19%). Analytical results showed a slight increase of transaminases in 26 (38%), ferropenic anaemia in 33 (48.5%) cases, sub-clinical hypothyroidism in 3 (4.5%) patients, and folic acid deficiency in 16 (23.5%) cases. Almost all patients were diagnosed between 2000 and 2008: 60 (87%). Population-based incidence of CD in adults had increased from 0.7-2/100,000 per year in the nineties to 3.5-10.3/100,000 in the last years.

Conclusions: CD can appear at any age and with a wide manifestation spectrum, which can be atypical in some cases. Patients with ferropenic anaemia and a negative response to treatment or those with an unexplained increase in transaminases should be screening for CD. Atypical manifestations and low suspect index can delay diagnosis even during years. There is a marked increase in the incidence-rates of CD in adults over time.

Key words: Coeliac disease. Incidence. Anti-transglutaminase antibodies. Gluten-free diet. Autoimmune disorders.

RESUMEN

Introducción: la enfermedad celiaca (EC) es una enfermedad crónica que afecta al intestino delgado, causada por intolerancia al gluten cuyas manifestaciones clínicas son muy variables incluyendo síntomas extraintestinales y formas asintomáticas.

Objetivo: nuestro objetivo es describir la incidencia y manifestaciones clínicas de la EC del adulto.

Métodos: estudio retrospectivo de los pacientes mayores de 18 años diagnosticados de EC entre enero-1990 y diciembre-2008 mediante test serológicos y biopsia duodenal.

Resultados: se incluyeron 68 pacientes con una mediana de edad de 33 años (18-65); 50 (74%) mujeres. Las manifestaciones clínicas fueron: diarrea en 38 (55%), dolor abdominal en 27 (40%), pérdida de peso en 15 (22%), dispepsia en 13 (19%) y 3 dermatitis herpetiforme. Los principales datos analíticos fueron: aumento de transaminasas en 26 (38%), anemia ferropénica en 33 (48,5%), hipotiroidismo subclínico en 3 (4,5%) y déficit de ácido fólico en 16 (23,5%) casos. Casi todos los pacientes han sido diagnosticados entre los años 2000 y 2008: 60 (87%). La incidencia de EC en adultos ha aumentado desde 0,7-2/100.000 habitantes por año en la década de los 90 hasta 10,3/100.000 habitantes por año en 2008.

Conclusiones: la EC puede aparecer a cualquier edad con un amplio espectro de manifestaciones clínicas, las cuales pueden ser atípicas en muchos casos. En aquellos pacientes con anemia ferropénica y respuesta negativa al tratamiento o con elevación inexplicable de transaminasas se debe realizar cribado para EC. Las manifestaciones atípicas y un bajo índice de sospecha, pueden retrasar el diagnóstico durante años. Existe un aumento marcado en la incidencia de EC en los adultos en los últimos años.

Palabras clave: Enfermedad celiaca. Incidencia. Anticuerpos antitransglutaminasa. Dieta sin gluten. Enfermedades autoinmunes.

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INTRODUCTION

Coeliac disease (CD) is an autoimmune process that arises from permanent intolerance to food gluten –a substance present in common cereals such as wheat, barley and rye. It appears in genetically predisposed persons (HLA-DQ2 and HLA-DQ8), and produces a chronic inflammation of the small-intestine mucosa, thus altering absorption of some nutrients. The estimated global prevalence is approximately 1-3% of the general population. However, only a few years ago, CD was considered to be an infrequent disease that was normally diagnosed in childhood, where it presented itself with a classical triad of diarrhoea, abdominal bloating and growth retardation (1,2).

The spectrum of clinical features in adults is quite variable and extends from completely asymptomatic forms to several complex and widely differential clinical features such as persistent anaemia due to iron, folic acid or vitamin B12 deficiency, gastrointestinal symptoms (diarrhoea, abdominal pain, dyspepsia, constipation), hypertransaminasemia, osteoporosis, neurological symptoms (epilepsy, ataxia), hypoproteinemia, hypocalcaemia, dermatitis herpetiformis, recurrent cankers, infertility and repeat abortions (1,2). Treatment consists of a gluten-free diet, which usually resolves clinical symptoms and normalizes analytical alterations. The recent increase in number of diagnosed cases in adults is due to better knowledge of the disease and a higher index of suspicion.

There therefore arises a need for revising the incidence and clinical features of CD in our environment.

METHODS

An observational, descriptive, retrospective study was carried out in the sanitary department of Hospital POVISA (Vigo, Spain), which treats a population of almost 145,000 adults. Patients recruited belonged to the +18 year old group and were diagnosed of CD through serologic (antigliadine, antiendomysium or antitransglutaminase antibodies) and histological tests, between January 1985 and December 2008. IgA antigliadine antibodies were measured using an immunoanalysis technique and IgA and IgG antiendomysium antibodies was measured using an immunofluorescence technique; both were the methods used during the eighties and nineties. Tissue transglutamniase antibodies was measured (both IgA and IgG) using a quantitative enzymelinked immunosorbent assay, and became the reference method in the last decade. In cases with histology compatible with CD but with negative antibodies, the diagnosis was confirmed means by HLA-DQ2 o HLA-DQ8 analysis. Histological specimens were graded according to the Marsh classification. Patients diagnosed during childhood or less than 18 years of age were excluded from the study. Data on the following was collected: sex, age at diagnosis, family history for CD, autoimmune diseases, tumours, and reason for initial consultation, symptom evolution time, and clinical manifestations to diagnosis, service in which it was diagnosed and most relevant clinical data. In cases with increased analytical serum transaminases, a conventional study was carried out to discard other pathologies (hepatitis B and C virus serology, autoantibodies –antinuclear, antimitochondrial, anti-smooth muscle and anti-LKM–, ferric metabolism, alpha-1 antitrypsin and ceruloplasmin), irrespective of whether it was the motive for consultation or not.

RESULTS

A total of 68 patients fulfilled entry criteria. Average mediana age at diagnosis was 36 years (range: 18-65), of which 50 were females (74%) and 18 were males (26%). Most patients (97%) were positive for at least some of the antibodies (antigliadine, antiendomysium or antitransglutaminase); while the two patients (3%) with negative antibodies were subject to HLA-DQ2, which turned out to be positive. All patients presented a compatible histology for CD. Most of the patients presented villous atrophy; 21 patients (30%) were classified as grade Marsh IIIb, 21 (30%) as Marsh IIIc and 16 (24%) as Marsh IIIa. Five patients (8%) were graded as Marsh II, four patients (6%) as Marsh I, and only 1 patient as grade IV.

Amongst relevant histories, 6 (9%) patients had next of kin diagnosed with CD, 2 suffered from thyroid disorders (autoimmune thyroiditis), 2 had been previously diagnosed with irritable bowel syndrome, and 3 had been diagnosed with other autoimmune pathologies (diabetes mellitus type 1, pernicious anaemia, and Sjögren syndrome). Reasons for consultation were as follows: ferropenia in 20 (30%), diarrhoea in 18 (26%), abdominal pain in 11 (16%), hypertransaminasemia in 6 (9%), family history in 3 (4.5%), cutaneous lesions compatible with dermatitis herpetiformis in 3 (4.5%), loss of weight in 3 (4.5%), neurological symptoms in 2, nausea in 1 and dyspepsia in 1. Symptoms present at diagnosis are shown in table I.

Eleven (16%) patients were asymptomatic at the time of diagnosis: 8 had been under study for ferropenia and 3 for hypertransaminasemia. All cases remitted due to first-degree family history presented abdominal symptomatology: diarrhoea and abdominal pain. The average evolution period from start of symptoms to diagnostics was 37.5 months (range: 1-180). Evolution period was not included in the study for 9 patients (13.2%) either because it was not recorded in the history or the patient was unable to precise dates due to

Table I. Symptoms at the time of diagnosis

Symptoms at the time of diagnosis	*No. (%)*
Diarrhoea	38 (55)
Abdominal pain	27 (40)
Weight loss	15 (22)
Dyspepsia	13 (19)
Loss of appetite	4 (6)
Vomiting	3 (5)
Dermatitis herpetiformis	3 (5)
Hypocalcaemia	3 (5)
Neurological symptoms	3 (5)
Osteoporosis (diagnosed by bone mineral density scan)	2 (3)
Constipation	2 (3)

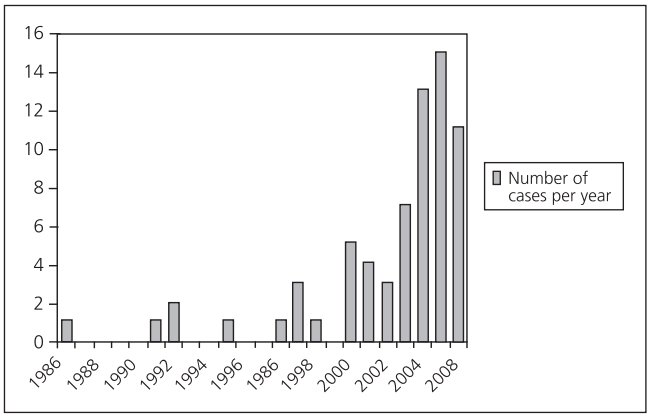

Fig. 1. Number of cases of CD in adults per year.

symptoms persisting over years. Most patients (61.7%) were diagnosed by the Gastroenterology Department. Diagnosis breakdown for the rest of the patients was as follows: 16 (23.5%) by Internal Medicine, 5 (7.3%) by Haematology, 3 (4.4%) by Dermatology, 1 (1.4%) by Endocrinology, 1 (1.4%) by Neurology and 1 (1.4%) by General Surgery.

The most relevant analytical data was as follows: 33 (48.5%) patients presented ferropenic anaemia at the time of diagnosis, 26 (38%) had slight increase of transaminases, and 16 (23.5%) had folic acid deficiency. Other significant analytical data are shown in table II.

There has been an increasing trend over the past years of patients diagnosed for this condition. Only 8 patients had been diagnosed between 1985 and 1999 but numbers have progressively increased since then up to a sum total of 68 cases (Fig. 1). Therefore, the estimated incidence for the 1990s is 0.7-2/100,000 inhabitants/year. Such incidence increased considerably after 2002 to reach 3.5-10.3/100,000 inhabitants/year.

Table II. Analytical data

Analytical data	*No. (%)*
Ferropenic anaemia	33 (48.5%)
Hypertransaminasemia	26 (38%)
Folic acid deficiency	16 (23.5%)
Increased C-reactive protein	11 (16%)
Hypoproteinemia	9 (13.2%)
Hypoalbuminemia	8 (11.7%)
Increased ESR	6 (9%)
IGA deficiency	3 (4.5%)
Coagulation alterations	3 (4.5%)
Thyroid dysfunction (subclinical hypothyroidism)	3 (4.5%)
Hypocalcaemia	2 (3%)

DISCUSSION

Results obtained by our study describe the clinical CD characteristics in adults at the time of diagnosis. Both mean age at diagnosis and predominance in females (2.7:1) coincide with results obtained in large series (3-6). Adult CD is normally classified according to its mode of presentation: "classical" where the predominant symptom is diarrhoea as a sign of intestinal malabsorption, generally associated with villous atrophy; "atypical" where patients with little to no gastrointestinal symptoms are included and diagnosis is made during iron deficiency or infertility study; and "silent" which include asymptomatic patients detected in a screening programs or during the performance of an endoscopy (7). Chronic diarrhoea is the most frequent manifestation and literature cites it in almost 85% of the cases (5). This symptom is also the most common in our series and affects more than half of the patients.

However, a progressive lesser presence of diarrhoea (8) and a progressive increase of patients diagnosed with non-digestive or atypical manifestations are observed. This is the so-called invisible "iceberg" part of the disease and affects a high number of cases (9). The "silent" or "atypical" manifestations can account for almost half the number of cases (10,11), as in the case of data for patients from our area.

Ferropenic anaemia is described as a frequent manifestation (5,6) where percentages fluctuate between 8 and 22%. On the other hand, CD could explain 2.8% of the hidden ferropenic anaemia cases in 50+ year old adults (12). One third of our patients were diagnosed within the context of an unknown ferropenic anaemia study, where more than 50% of the cases presented ferropenia in analytical results. This means a higher prevalence than that shown in literature data. Furthermore, a sizeable percentage (25%) of these patients was completely asymptomatic. It has been described

that a third of the patients (1 of 4 patients in our series) can present folic acid deficiency (6), which could lead to worsening of any pre-existing ferropenic anaemia condition.

Amongst the frequently detected analytical alterations in atypical forms, unexplained high hepatic enzyme levels account for up to 20-40% of the cases at the time of diagnoses (6,13,14). Our series shows a very high frequency of increased hepatic enzymes levels in agreement with the highest prevalence described in literature. The mechanism for such analytical alterations in CD is unknown although there are speculations towards an autoimmune origin due to findings of chronic inflammatory infiltrates in hepatic biopsies (15). Other theories propose an increased intestinal permeability to toxins or antigens within the context of intestinal inflammation (14). Hypertransaminasemia is usually less significant and patient recovers quickly after a gluten-free diet. However, there are cases of more serious hepatic disease described, even severe hepatic dysfunctions that could lead to transplants, where a good response to diet was obtained (16,17). The high prevalence of CD in the general adult population and the frequency with which such patients can present alterations in hepatic function tests have led to the inclusion of CD screening in hypertransaminasemia study protocols, especially in young women without any specific digestive manifestations or any previous history of elevated transaminases (18,19).

Amongst the atypical presentation forms, mention must be made of the association with neurological pathology (20,21) such as peripheral neuropathies and ataxia. The series we present describes 3 cases, including one ataxia and another peripheral mononeuritis. The pathogenesis of such alterations is linked with nutritional factors and sometimes, the rapid introduction of a gluten-free diet brings about an adequate response (22). Other factors associated with development of neurological symptoms within the CD context are either genetic (HLA region of chromosome 6) or immunological.

Loss of bony mass is frequent (7%) in adult patients diagnosed with CD (23), due to malabsorption of calcium and vitamin D, and is associated with an increased risk of fractures (24). Data collected in our area show a lower incidence of osteoporosis, which is probably due to use of strict definition criteria for loss of bony mass, > 2.5 standard deviation in densitometry. It is important to highlight that this complication can appear in earlier age groups; one of the patients was just 32 years old at the time of diagnosis.

The manifestation spectrum for adult CD in its silent forms includes dermatitis herpetiformis in 15-25% of the cases (25). This is a cutaneous, pruriginous disease of the papulovesicular type, where lesions affect extensive surfaces (elbows, knees, buttocks, back and scalp). Cutaneous biopsy shows granular IgA deposits in the papillary dermis and in the basal membrane of epidermis. Establishment of a gluten-free diet resolves lesions and pruritus. An increasing appearance of autoimmune diseases is also described, amongst which are type 1 diabetes, psoriasis, and thyroid disorders. Up to 30% of the patients may present some of these manifestations (26) as against 3% of the general population (27). There is likewise an increased relative risk (1.29; IC 95% 1.06-1.55) of suffering from neoplasia in CD patients as compared to the general population (28). Other atypical gastrointestinal manifestations include the development of ascites (29) and acute pancreatitis and even relapsing pancreatitis (30-32).

Moreover, in addition to the previous symptoms and complications described, patients with CD present a marked impairment in health-related quality of life, which improves and reaches results similar to those in the general population when on a gluten-free diet (33).

Between 5-15% of the first generation kin of patients with CD would typically present serology and histology compatible for the disease (4), and familial-cases association of 57% have been described (34) and therefore it is considered as an adequate group for carrying out screening programs, especially in kinfolk with symptomatology (2).

The estimated prevalence of CD is 1-3% (2,35) at the world level, although with slight differences amongst countries. Such differences are conditioned by the many risks of developing CD and also due to varying study designs, diagnostic criteria and screening strategies. Data available for Spain report prevalence of 1:389 for the general population (36) and of 1:370 in a study carried out on blood donors (37). The estimated incidence of adult CD varies between 2-13/100,000 inhabitants/year (38). There is a progressive increase of incidence (increase by 10 points between 1950-2001) and prevalence, up to the point where the figure gets doubled in the last two decades (39). Such increment is related to improvements in diagnostic tests (greater sensitivity and specificity of antitransglutaminase antibodies in relation to antiendomysium and antigliadine), better knowledge of the disease by clinicians and a greater index of suspicion to silent forms of the disease (2). Such increased incidence is parallel to other autoimmune diseases (diabetes mellitus type 1, multiple sclerosis, Crohn's disease) and seems to be related with environmental factors. Moreover, according to the hygienist hypothesis, any reduction in exposure to infectious agents during childhood is related to alterations of intestinal microbiota, which is considered as one of the pathogenic factors involved in the development of CD.

Another pathological factor that is probably involved is the increasing presence of gluten in post-infancy diets (39). Incidence rates presented in this study clearly show a progressive increase, where figures during the past years have increased ten-fold with respect

to their values in the 1990s. Incidence data, although high, are slightly lower than in other series. This is probably due to stricter inclusion criteria in our series, where only patients with positive serology and compatible biopsy were included. In cases with negative antibodies, a positivity for HLA-DQ2 or DQ-8 was required. Prevalence was not determined because the sanitary area of Hospital POVISA does not include patients from paediatric age groups or < 18 year old patients.

In conclusion, despite being one of the most common genetic disease, and even with the progressive improvement in the detection of new cases, physicians are encouraged to obtain a higher knowledge and interest about this procedure to obtain a greater number of diagnosis, nearly to the expected prevalence. Atypical presentation forms are related with a sizeable delay in adult CD diagnosis, where average delay was up to 3 years even in high prevalence areas (6). Persistence of symptoms prior to diagnosis in some cases is sometimes unacceptably prolonged. It is fundamental to have a high index of suspicion for the disease, when patients manifest any of the previously described characteristics. Early detection of CD is very important because it helps establish treatment in early stages and therefore not only does it lead to disappearance of symptomatology (classical and atypical) but also prevents development of complications over time. Performance of unnecessary invasive explorations such as endoscopies and hepatic biopsies are thus avoided.

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