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CELIAC DISEASE IN FIRST DEGREE RELATIVES OF CELIAC CHILDREN

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ABSTRACT – ***Context*** - The first degree relatives of celiac patients represent a high risk group for the development of this disorder, so their screening may be crucial in the prevention of long-term complications. ***Objective*** - In order to determine the prevalence of celiac disease in a group of first degree relatives of children with proven gluten intolerance, we conducted a prospective study that consisted in the screening of celiac disease, using a capillary immunoassay rapid test that allows a qualitative detection of IgA antibody to human recombinant tissue transglutaminase (IgA-TTG). ***Methods*** - When the screening test was positive subjects were advised to proceed with further investigation. The screening test was performed in 268 first degree relatives (143 mothers, 89 fathers, 36 siblings) corresponding to 163 children with celiac disease. ***Results*** - Screening test was positive in 12 relatives (4.5%), of which 1 refused to continue the investigation. In the remaining 11 relatives celiac disease was diagnosed in 7 cases (2.6%, 5 mothers, 2 fathers) who had a median age of 39 years (27-56 years), mild gastrointestinal symptoms, high titre of IgA-TTG and histology abnormalities confirming the diagnosis. All these patients are currently on a gluten-free diet. ***Conclusion*** - The prevalence of celiac disease among first degree relatives (2.6%) was 5 times higher than that in the general population. Although the recommendations for screening asymptomatic high risk groups, such as first degree relatives, are not unanimous the early diagnosis is crucial in preventing complications, including nutritional deficiency and cancer.

HEADINGS – Celiac disease. Family. Child.

INTRODUCTION

Celiac disease (CD) is an immune-mediated enteropathy triggered by the ingestion of gluten in genetically susceptible individuals. Epidemiological studies have shown that the prevalence of CD in Europe and in the United States of America vary from 0.5% to 1% in the general population[10, 12]. A study involving a population of adolescents in Portugal proposed an estimated prevalence of 0.7%[2].

In recent years the epidemiological knowledge of CD has grown significantly due to the identification of the wide variety of clinical manifestations of this disease, coupled with the advent of more sensitive and specific serological markers, and the recognition of genetic susceptibility. Thus, it has been possible to identify asymptomatic individuals with CD (silent form) that represent the higher portion of the submerged "celiac iceberg". Individuals with silent form of CD, although asymptomatic, have intestinal villous lesions, susceptibility to complications and benefit from starting a gluten-free diet[13]. Measurement of quantitative serum IgA and antibody to human recombinant tissue transglutaminase (IgA-TTG) are recommended for initial testing for CD. Identification of anti-endomysium antibodies, although more sensitive and specific, is observer dependent and therefore more subject to interpretation error and added cost. Confirmation of the diagnosis of CD requires an intestinal biopsy from the second or more distal part of the duodenum[10].

Based on the current evidence it is recommended to screen individuals who belong to groups at higher risk such as first-degree relatives of celiac patients and those affected by conditions associated with CD (type 1 diabetes mellitus, autoimmune thyroiditis, Down syndrome, Turner syndrome, Williams syndrome and selective IgA deficiency)[10]. A higher prevalence of CD among relatives of celiac patients has been demonstrated by several studies varying from 2.8% to 9.5%[1, 3, 5, 7, 9, 15, 16].

In order to clarify the current situation in Portugal, we conducted a study to determine the prevalence of CD in first degree relatives of a group of celiac Portuguese children.

MATERIALS

Population and design

This prospective study consisted in screening the

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first degree relatives of celiac children (diagnosed according to the criteria of the European Society for Gastroenterology, Hepatology and Nutrition) for CD, using a capillary immunoassay rapid test. From January 2009 to July 2010 all first degree relatives of CD patients attending a Pediatric Gastroenterology outpatient's clinic at a University Hospital were invited to participate in the study and extra-time was available to screen all those that accepted. Subjects were asked about their medical past history, including gastrointestinal and nongastrointestinal manifestations; none was under gluten-free diet or had a prior diagnosis of CD.

The study was approved by the Hospital Ethics Committee and sponsored by a grant from the Unit of Research of São João Hospital, Porto, Portugal (contract 2008-019). All subjects provided informed consent and were informed of the possible need of small intestinal biopsy to confirm diagnosis.

Screening test

The capillary immunochromatographic rapid test used for the screening (BIOCARD™ celiac test) allows a qualitative detection of IgA and IgA-TTG from a capillary blood sample (10 microliters), providing a result within 10 minutes. This test has been used in several studies, particularly in children of preschool age in Hungary showing sensitivity near 80% with high specificity (100%) for a final diagnosis of celiac disease by biopsy. The positive predictive value of rapid testing was 100% and the negative predictive value was 99.4%[11].

Serologic markers and small bowel histology

When the screening test was positive, subjects were advised to proceed with further investigation, which consisted in the confirmation of IgA-TTG determined by ELISA in venous blood, complete blood count and biochemical profile, as well as endoscopic duodenal biopsy. Serum IgA-TTG levels above 10 U/mL were considered positive. Histological classification of intestinal biopsies was performed by an experienced pathologist and classified according to Marsh-Oberhuber classification[4]. When IgA deficiency was suspected in the capillary test subjects were referred to their general practitioner with advice to measure total serum IgA and IgG human recombinant antitransglutaminase antibody. The diagnosis of CD was established if serum IgA-TTG was above 10U/mL (without IgA deficiency) and Marsh type 3 lesion (villous atrophy) on duodenal biopsy.

RESULTS

During the study period 163 children with CD were observed; 232 parents (143 mothers and 89 fathers, aged 22-64 years, median 38 years) and 36 siblings (11 sisters and 25 brothers, aged 12 months to 28 years, median 10 years) accepted to participate in the screening test for CD.

In 82 celiac children (50.3%) more than one relative participated in the study, two relatives per celiac child in 61 cases, three relatives per child in 19, and four relatives per child in 2 cases.

The screening test was positive in 4.5% of the first degree relatives (nine mothers, two fathers, one brother) and 1.1% of tests (two fathers, one brother) was suggestive of IgA deficiency. One mother with a positive screening test refused to pursue further investigation. The remaining relatives with positive screening test (n = 11) underwent additional investigation with the determination of the serum IgA-TTG and endoscopic duodenal biopsy.

After the additional investigation CD was diagnosed in 7 of the 11 relatives, corresponding to a CD prevalence of 2.6% (7:268). These relatives with CD (5 mothers, 2 fathers) had a mean age of 39 years (27-56 years), and the majority had mild symptoms (frequent diarrhea = 2, constipation = 1, heartburn = 1, epigastric pain = 1), high titre of IgA-TTG and histopathological findings on the duodenal biopsy (Table 1).

The additional investigation did not confirm the diagnosis of CD in four relatives with positive screening test (three mothers, one brother). These relatives were asymptomatic, titre of venous IgA-TTG was negative (0.3-1.4 U/mL) and histopathological findings on the duodenal biopsy were unremarkable.

All the newly diagnosed celiacs started a gluten-free diet and were referred to the adult Gastroenterology clinic for further follow-up.

TABLE 1. Characteristics of the first-degree relatives diagnosed with celiac disease

Test	Age / kinship	Symptoms	Hemoglobin (g/dL)	M.C.V.y (fL)	IgA-TTG(U/mL)*	Biopsy (Marsh-Oberhuber)
29	32 / Father	Frequent diarrhea	15.2	81.8	127	IIIb
34	40 / Father	Heartburn	14.7	89.3	33	IIIa
47	56 / Mother	Constipation	14.3	87.5	558	IIIa
62	50 / Mother	Frequent diarrhea	14.7	86.8	317	IIIb
68	27 / Mother	Epigastric pain	12.1	83.1	304	IIIb
229	36 / Mother	Asymptomatic	12.1	85.7	497	IIIb
273	39 / Mother	Asymptomatic	NA	NA	306	IIIb

[y] M.C.V.: Mean corpuscular volume

*IgA-TTG considered positive if serum IgA-TTG was above 10 U/mL

NA = not available

TABLE 2. Studies of the prevalence of the celiac disease among the first degree relatives

Study (author, year, location)	Index case (n)	First degree relatives (n)	CD Prevalence * (%)
Fasano et al. 2003, USA [5]	9019**	4508	4.5%
Almeida et al. 2008, Brazil [6]	72	188	4.8%
Grover et al. 2007, India [7]	53***	169	8.2%
Srivastava et al. 2009, India [8]	30	91	4.4%
Bonamico et al. 2006, Italy [9]	208***	441	9.5%
Dolinsek et al. 2004, Slovenia [11]	45	105	4.7%
Esteve et al. 2006, Spain [13]	82	221	4.9%
Vitoria et al. 1994, Spain [10]	210	642	2.8%
Present study, 2009, Portugal	163	268	2.6%

* Diagnosis performed by serological assay and histology of intestinal biopsy

** Index cases consisting of high-risk group that included patients with CD or individuals with suggestive symptoms or conditions associated with CD

*** Index cases formed by children and adults with CD

DISCUSSION

In this study the prevalence of CD in the first degree relatives of celiac children was 2.6% (approximately 1:38 relatives). This prevalence is similar to one of the first European studies conducted in Spain by Victoria et al.[16] that revealed 2.8% among 642 first degree relatives. This is 4 times higher than the proposed prevalence among the general Portuguese population (0.7%)[2]. A wider national investigation, a screening program involving 1655 children and adolescents (6-18 years old) in six districts of Portugal for diagnosis of CD, through determination of IgA-TTG (ELISA) in peripheral blood and duodenal endoscopic biopsy, showed a prevalence of CD of 0.5%*, which is considerably lower than the present results and highlights the risk of first-degree relatives for CD in contrast to general population.

Studies analyzing the diagnosis of CD in the first degree relatives of celiac children have shown variable results (Table 2), which may be explained by several factors: variation in the number (1:1, 1:2 or 1:3) and type of first-degree relatives (parents, siblings or offsprings) that are studied for each celiac child (index case), studies with exclusively pediatric celiac patients compared to others that included adult celiacs, absence of histological confirmation in the index cases and the use of different screening methods that reflects the natural evolution of serological markers[8].

The recognition that first-degree relatives belong to a group at higher risk for the development of CD is particularly important concerning the siblings and the cluster of relatives with more than one index case. In this study, the real prevalence of CD in the first degree relatives may have been undervalued due to the fact that there was no more than one index case per family. On the other hand, the fact that more than one first degree relative was screened only in half (50.3%) of the patients, may have induced some bias in the results.

We found some false positive results that might be attributed to overestimation of very faint colouring of the test. However when performing screening procedures, some false-positives that may be confirmed by simple tests like IgA-TTG in venous blood may be acceptable in order not to miss any patients. Unlike automated readings on ELISA method, the capillary test relies on visual inspection and subjective decision on positivity. Therefore, confirmation of the diagnosis by venous blood serology and, if appropriate, intestinal biopsy is important to validate the preliminary screening test.

According to one recent study[14], the diagnosis of CD in the individuals at high risk for this disease is extremely important because delayed diagnosis and treatment seems to be related to the increase of about 4 times in the mortality due to CD. Screening for CD in the first-degree relatives of celiac children yields a high probability of identifying new patients and allows the prevention of complications associated with the disease.

CONCLUSION

The risk of CD is elevated in the first degree relatives of celiac patients, so they should be advised to be screened by measurement of quantitative serum of IgA and of IgA-TTG. The use of the rapid screening test may be useful but should be done by experienced observers trained to avoid technical errors that can induce misenterpretation of the result. The presence of digestive signs or symptoms should not influence the decision to screen as these do not show high predictive value. Confirmation of the diagnosis upon positive screening should follow current recommendations with intestinal biopsy.

* Trindade E, et al. (2004) – unpublished data

Oliveira A, Trindade E, Tavares M, Lima R, Terra M, Dias JA. Doença celíaca nos familiares em primeiro grau de crianças celíacas. Arq Gastroenterol. 2012,49(3):204-7.

RESUMO – ***Contexto*** - Os familiares em primeiro grau de doentes celíacos pertencem a um grupo de alto risco para desenvolver esta patologia, pelo que o seu rastreio poderá ser determinante na prevenção de complicações a longo prazo. ***Objetivo*** - No sentido de determinar a prevalência da doença celíaca num grupo de familiares em primeiro grau de crianças celíacas, foi realizado um estudo prospectivo que consistiu no rastreio da doença celíaca através de um teste rápido capilar imunocromatográfico para a detecção qualitativa de anticorpos IgA antitransglutaminase (IgA-TTG). ***Resultados*** - Nos casos em que este teste de rastreio foi positivo, os familiares foram aconselhados a prosseguir com investigação adicional. Realizou-se o rastreio a 268 familiares em primeiro grau (143 mães, 89 pais, 36 irmãos) correspondentes a 163 crianças com doença celíaca. O teste de rastreio foi positivo em 12 familiares (4,5%), um dos quais recusou prosseguir a investigação. Entre os restantes 11 familiares com teste positivo, diagnosticou-se doença celíaca em sete casos (2,6%, 5 mães, 2 pais), apresentando idade mediana de 39 anos (27–56), sintomas digestivos associados a título elevado de IgA-TTG e alterações histológicas diagnósticas. Todos os familiares diagnosticados estão sob dieta isenta de glúten. ***Conclusões*** - A prevalência da doença celíaca nos familiares em primeiro grau (2,6%) foi 5 vezes superior à verificada na população em geral. Embora as recomendações para o rastreio de indivíduos assintomáticos dos grupos de alto risco, como os familiares em primeiro grau, não sejam unânimes, o diagnóstico é importante para a prevenção das complicações, nomeadamente os deficits nutricionais e neoplasia.

DESCRITORES – Doença celíaca. Família. Crianças.

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