Frequency of celiac disease and its serological markers in patients with autoimmune hepatitis

Rita Franca[1]
Paulo L Bittencourt[2]
Luiz Antonio Rodrigues de Freitas[3]
Daniel Simões May[1]
Carol F Andrade[1]
Liliane M Cunha[3]
Maria Betania P Toralles[1]
Raymundo Paraná[1]
Luiz Guilherme Lyra[1]
André de Castro Lyra[1]
Daniel R Diniz-Santos[1]
Luciana Rodrigues Silva[1]

Abstract
Transglutaminase (anti-tTG) and anti-endomysial (AEA) antibodies were reported to occur in patients with autoimmune hepatitis (AIH) as well as in subjects with advanced cirrhosis, but the prevalence of celiac disease (CD) in patients with AIH is either negligible or unknown. The frequency of IgA anti-tTG and IgA AEA was determined in 64 patients (54 females, mean age 19[5-67] years) with AIH diagnosed according to international criteria. Patients with positive or intermediate results for those antibodies were submitted to duodenal biopsy and HLA-DQ2 or DQ8 typing. Anti-tTG and AEA were detected in 6 (9%) and one patient (1.6%) with AIH, respectively. Positive and borderline results for IgA anti-tTG were detected, respectively, in two (3%) and four (6%) patients. Only one patient with HLA-DQ2 and IgA anti-tTG and IgA AEA had CD on duodenal biopsy. Two patients with either positive or borderline results for IgA anti-tTG antibody and HLA-DQ2 had normal histology on duodenal biopsy. IgA anti-tTG antibody and/or AEA were observed in 9% of AIH patients, but CD was confirmed in only one of them. The occurrence of IgA anti-tTG antibody in the other patients could be ascribed to the presence of chronic liver disease or to latent or potential CD.

Keywords: Celiac Disease – Autoimmune Hepatitis – Serological Markers.

INTRODUCTION

Celiac disease (CD) is an immune-mediated chronic enteropathy of the small intestine that is triggered by the ingestion of prolamins from wheat, rye and barley in genetically-predisposed individuals sharing either HLA-DQB1*0201 or DQB1*0302.[1] The disease is associated with a spectrum of alterations in the intestinal mucosa that may vary from an increase in the number of

[1] Federal University of Bahia
[2] Portuguese Hospital - Salvador, Bahia;
[3] Oswaldo Cruz Foundation (Gonçalo Moniz Research Center) - Salvador, Bahia.

Correspondência para / Correspondence to:
Rita Franca
Rua Macapá, 461/701 - Ondina
40.170.150 Salvador- BA- Brazil
E-mail: rcfmelo@yahoo.com.br

intra-epithelial Th1 CD4 lymphocytes to architectural damage characterized by crypt hyperplasia and villous atrophy.[1] There is a great geographical heterogeneity in the prevalence of CD. The disease seems to be rarely found in North India and North Africa[2,3] and to be much more frequent in Europe and North-America with prevalence rates ranging from 0,5% to 1% [4], whereas in Brazil, the prevalence of CD is estimated to be 1:681.[5]

The clinical expression of CD is variable. The classical phenotype of CD characterized by diarrhea and growth retardation due to malabsorption is rarely seen. In this respect, population screening studies using serum disease markers, such as anti-transglutaminase (anti-tTG) and anti-endomysium (AEA) antibodies have shown that most of the patients with CD are either entirely asymptomatic or have only subtle and non-specific symptoms.[1] In addition, the occurrence of those antibodies was also shown to precede the clinical and histological presentation of the disease by months or years.[6,7]

Several other immune disorders have been associated with CD, particularly dermatitis herpetiformis, selective IgA deficiency, diabetes mellitus, autoimmune tyrhoiditis as well as primary biliary cirrhosis, primary sclerosing cholangitis and autoimmune hepatitis.[8,9,10,11,12,13,14,15,16]

Autoimmune hepatitis is a chronic autoimmune or immune-mediated liver disorder that leads when untreated to cirrhosis and liver failure.[17,18] The disease usually affects females and is characterized by the presence of circulating autoantibodies such as anti-smooth muscle antibody (SMA), antinuclear antibody (ANA), antiliver kidney microsome type 1 (anti-LKM1), antisoluble liver antigen (SLA) and antiliver cytosol type 1 (anti-LC1) antibodies and by severe interface hepatitis on liver biopsy. The disease is classified in at least two types according to the nature of autoantibodies. The presence of SMA and/or ANA or anti-LKM1 and/or anti-LC1 defines, respectively, AIH types 1 and 2. [19,20]

*Susceptibility to AIH is linked to distinct HLA haplotypes, namely HLA-DRB1*0301 / DQB1*0201; HLA-DRB1*13 / DQB1*0603 and different DRB1*04 alleles.[21,22,23] Concurrent autoimmune disorders (CAID) have been described in up to 50% of the patients with AIH, particularly arthritis, autoimmune thyroiditis, Coombs-positive hemolytic anemia, Graves' disease and ulcerative colitis.[24,25] The frequency of CD in subjects with AIH is thought to be negligible. Only two studies have assessed the prevalence of CD in patients with AIH with reported frequencies ranging from 4% to 6%. [15,16,26,27,28] Recently, a lower prevalence of CAID was reported in Brazilian children with AIH types 1 and 2. [24] The nature of CAID was shown to vary, but the authors have reported no case of CD. However, it is important to mention that neither serological nor histological assessment of CD was performed in the aforementioned study.*

The purpose of the present study was to investigate the frequency of clinical and serological markers of CD in a well defined cohort of patients with AIH from Brazil.

PATIENTS AND METHODS

Subjects

Sixty-four patients (54 females, mean age 19 [5-67] years) from the metropolitan area of Salvador, Bahia, Brazil, who fulfilled the revised diagnostic criteria of AIH [25] have been studied. Forty (63%) of them were children under 16 years of age at disease onset. All patients gave informed consent for participation and the hospital ethical committee approved the study.

Sixty one had AIH-1 and 38 (62%) of them were pediatric AIH. Three had AIH-2 and 2 of them were children. The clinical, laboratory and histological features at presentation and the response to treatment are depicted in Table 1.

In order to look for CD, all patients were clinically evaluated by one of the authors who looked for the presence of signs and symptoms of CAID, in particular gastrointestinal symptoms compatible with CD, such as diarrhea, steatorrhea, flatulence, nausea, vomiting, cow's milk intolerance and abdominal pain.

Laboratory profiles

All patients were negative for hepatitis B surface antigen (ELISA, Abbott Laboratories, North Chicago, IL) and for anti-HCV antibodies (ELISA III, Ortho Diagnostic System, Raritan, New Jersey). All patients were screened at presentation for SMA,

ANA, anti-LKM1 and anti-LC1 antibodies by indirect immunofluorescence on rat liver, kidney and stomach tissue sections and on Hep-2 cells. A titer equal or greater than 1:80 was considered positive.

Determination of serological markers of CD: All serum samples have been tested for IgA AEA by indirect immunofluorescence using 5µm cryostat sections (-20ºC) of human umbilical cord, as previously described.[25] Sera have been obtained from blood samples drawn either at admission (n=14) or after onset of immunossupressive therapy (n=50).

The human umbilical cord was taken after delivery from mothers that gave previous informed consent. The fluorescein isothiocyanate-conjugated (FITC) antihuman IgA (SIGMA) was diluted to 1:100. Sera were tested in 1:5 dilutions and the reaction was considered positive in titers equal or greater than 1:5. Anti-tTG IgA antibodies were tested resolved-time flourimetry using a commercially available kit (Delfia, PerkinElmer Life and Analytical Sciences, Wallac Or, Turku, Finland).[29,30] Blood levels of antibodies were expressed in arbitrary units (AU) and the cut-off level was adopted as suggested by the manufacturer. Levels of less than 8 AU were considered negative; 8-22 AU, borderline and more than 22 AU, positive.

Table 1 - Clinical and laboratory features of patients with autoimmune hepatitis types 1 and 2

Clinical features	AIH (n°=64)
Mean age (years)	19 [5-67]
Age less than 16 years n (%)	40 (63)
Female gender n (%)	54 (84)
Concurrent autoimmune diseases n (%)	11 (17)
Laboratory Findings	
ALT * IU/L (x upper normal limit)	13 [0,5-81]
AST** IU/L (x upper normal limit)	26 [0.8-129]
Albumin g/dl (normal 3.5 -5.0)	3.4 [1.0-5,0]
Globulin g/dl (normal:)	4,45 [1.8-8,7]
Histologic al features n (%)	
Severe activity	21 (33)
Cirrhosis	30 (47)
AIH score	
Probable diagnosis	20 (31)
Definite diagnosis	44 (69)

Nota: * ALT= alanine aminotranspherase; ** AST= aspartate aminotranspherase

In order to evaluate the presence of IgA deficiency, total IgA was measured in all patients by radial immunodifusion (Biocientífica S.A- Argentina). In case of occurrence of concurrent IgA deficiency, serum samples were also screened for IgG AEA using a commercially available conjugated antihuman IgG (IMMCO- USA).

*HLA-DQB1*02 and DQB1*0302 determination: HLA typing was performed in patients who tested positive for IgA AEA or with either positive or borderline results for anti-tTG using a commercially available kit for assessment of HLA-DRB1*02 and DQB1*0302 (Delfia® Celiac Disease Hybridization Assay).*

Histological evaluation

Upper digestive endoscopy have been performed in all patients who tested positive for IgA AEA or with either positive or borderline results for IgA anti-tTG, except in one patient who had died before endoscopy. Five fragments from the second portion of the duodenum were obtained from each patient and were fixed in 10% formalin. Analysis was performed by one pathologist well-trained in the histological diagnosis of CD and graded accorded to the modified Marsh classification.[31,32,33]

Statistical analysis

All data were analysed with SPSS statistical software, version 9.0 (SPSS, Chicago, IL). Quantitative variables were expressed as mean values and range. Clinical and laboratory are expressed in text and tables as percentages or mean and range.

RESULTS

Past history of gastrointestinal symptoms was reported from 47 (73,4%) patients with AIH. Episodes of diarrhea and flatulence were described by 22 (34,4%) and 21 (30,4%) patients, respectively. Seventeen (26,6%) complained of past symptoms of nausea and vomiting, whereas episodes of abdominal pain, cow´s milk intolerance and steatorrhea were referred by 15 (23,4%), 15 (23,4%) and 9 (14%) patients, respectively. Ten patients described the occurrence of those symptoms at least one week before clinical evaluation.

Table 2 - Clinical and laboratory findings of 6 AIH patients with celiac antibody pattern

#	Age(yr): Sex	IgA tTG (AU)	AEA	CD–related symptoms	Autoimmune conditions	HLA-DQ	Duodenal Biopsy (Marsh 's criteria)
1*	10:F	8.4	-	-	None	-	Type 0
2	31:F	81.5	-	+	Hashimoto	DQ2	Type 0
3*	6:F	8.3	-	+	None	-	Type 0
4*	13:F	9.6	-	-	None	DQ2	Not performed
5*	10:F	12.9	-	+	Type 1 diabetes	DQ2	Type 0
6*	15:F	49.3	+	+	None	DQ2	Type 3 b

Notas: *Patients who had sera collected before starting immunosuppressive therapy; [-] negative; [+] positive

Two (3%) patients tested positive for IgA anti-tTG and had past history of gastrointestinal symptoms, including one IgA AEA-positive subject, who presented severe steatorrhea at admission and had serum samples collected before immunossupressive treatment. Those patients with the aforementioned markers for CD were females with AIH-1. Two subjects had concurrent autoimmune disorders, namely thyroiditis and type 1 diabetes (TABLE 2).

Four patients had borderline results for IgA anti-tTG. One subject was asymptomatic and the other had gastrointestinal symptoms, previous namely bouts of diarrhea and steatorrhea (TABLE 2). The patient with IgA AEA and three out of the six patients with positive IgA tTG or borderline IgA tTG carried HLA-DQB1*02.

IgA deficiency was observed in five (7,8%) patients. All tested negative subsequently for IgG anti-AEA.

Only one patient (1,6%), who was positive for anti-tTG and AEA and had exuberant symptoms of malabsorption, had histopathological evidence of CD. He had subtotal villous atrophy on duodenal biopsy compatible with type 3 b lesion according to modified Marsh classification.

DISCUSSION

Several autoimmune or immune mediated diseases have been associated with AIH. In this regard, concurrent extrahepatic autoimmune disorders have been reported in 30% to 50% of adults and 16% to 25% of the children with AIH types 1 and 2. [20,22,23,24] ***Celiac disease has been previously associated with AIH, PBC and PSC as well as to liver dysfunction characterized mainly by mild lobular and portal inflammation reversible on a gluten-free diet.*** [14,15,34]

In the present study, we have screened Brazilian patients with AIH for CD, using anti-tTG and AEA and we have found the occurrence of the disease in only one (1,6%) patient with AIH-1. The affected subject was a 15-year old girl with anti-tTG and AEA. In addition, IgA anti-tTG antibodies were either positive (n=1) or borderline (n=4) in four other patients without known histological evidence of CD. To date, two studies from Italy have been published concerning the prevalence of CD in patients with AIH. Volta and others [15] ***have screened 157 patients with AIH-1, 24 with AIH-2, 62 with PBC and 110 with chronic viral hepatitis with anti-gliadin antibody and AEA. The authors have found the occurrence of AEA in 4% of the patients with AIH-1 and in 8% of the subjects with AIH-2. All subjects with AEA were adults and only two had gastrointestinal symptoms. Five of them were submitted to duodenal biopsy that revealed subtotal villous atrophy consistent with the diagnosis of celiac disease. Villalta and others*** [16] ***have determined the prevalence of IgA and IgG anti-tTG antibodies in 47 patients with AIH, 100 subjects with hepatitis C and 120 healthy controls. The authors***

have found IgA and IgG anti-tTG antibodies in three (6.4%) subjects with AIH. All had duodenal biopsies compatible with CD. None of the patients and controls had IgG anti-tTG antibody and only one subject with hepatitis C had IgA anti-tTG.

When compared to those two aforementioned studies, our results showed a lower frequency of CD in subjects with AIH. However, it is worth to mention that more than half of our patients were children. The frequency of concurrent autoimmune disorders in patients with AIH is reported to be lower in children, when compared to adults.[22,23,24] Even though, some case reports have disclosed HAI in children with DC[27,28], all subjects with AIH that were reported to have CD upon screening were adults.[15,16] Thus it is possible that older age could also favor the development of CD in subjects with AIH.

*Conversely, we cannot entirely rule out the possibility of false-negative results in some of our subjects, due to the fact that only fourteen patients in our cohort had their sera collected before the start of immunosuppressive therapy. It is well acknowledged that corticosteroids and azathioprine can better the histopathological lesions of CD[35,36], but their effect on the circulating titers of anti-tTG and AEA is less known. In this regard, two patients with either positive or borderline results for IgA anti-tTG antibody and HLA-DQ2 had normal histology on duodenal biopsy. Therefore, we cannot entirely exclude CD in those HLA-DQ2-positive patients under immunossupression with anti-tTG antibody and normal duodenal histology. On the other hand, it is also possible to ascribe the occurrence of IgA anti-tTG antibody in those subjects with AIH but without CD. In this respect, it has to be highlighted that IgA and IgG anti-tTG antibodies have been reported in different chronic liver diseases[37] and that their specificity for the diagnosis of CD is significantly impaired in subjects with cirrhosis.[38] On the contrary, the occurrence of these antibodies altogether with the findings of one of HLA susceptibly alleles for CD, namely HLA-DQB1*02 or HLA-DQB1*0302, has been associated with enhanced predisposition to overt CD, since their appearance has been reported to precede disease occurrence and mucosal inflammation by months or years.[6,7]*

Gastrointestinal (GI) symptoms were observed in the majority of our patients with AIH. However, only 10 (15%) subjects had symptoms at least one week before inclusion in the study. One of those patients had CD. The others were not investigated due to symptom remission (data not shown). These findings are in accordance with the high frequency of gastrointestinal disturbances reported in children and adults in the general population.[39,40]

In summary, IgA anti-tTG antibody and/or AEA were observed in 6 (9,4%) patients with AIH, but CD was confirmed in only one children with AIH-1. The occurrence of IgA anti-tTG antibody in the other patients with AIH can be ascribed either to the presence of chronic liver disease or to latent or potential CD.

Freqüência da doença celáaca e seus marcadores sorológicos em pacientes com hepatite auto-imune

Resumo

Anticorpos antitransglutaminase (anti-TGt) e antiendomísio (AAE) são identificados em pacientes com hepatite auto-imune (HAI), assim como em pacientes com cirrose avançada. Contudo, a prevalência de doença celíaca (DC) em pacientes de HAI é desconhecida. A freqüência de anti-TGt IgA e AAE IgA foi determinada em 64 pacientes (54 mulheres,com media de idade de 19 anos [5-67]) com diagnóstico de HAI definido pelos critérios internacionais de HAI. Os pacientes anti-TGt IgA positive ou indeterminado e (ou) AAE IgA positivo foram submetidos à biópsia duodenal e determinou-se o tipo de HLA-DQ2 ou DQ8. Os anticorpos anti-TGt IgA e AAE IgA foram observados em 6 (9%) pacientes e em um paciente (1,6%) com HAI, respectivamente. Resultados positivos e borderline para anti-TGt IgA foram encontra-

dos, respectivamente, em dois pacientes (3%) e quatro pacientes (6%). A DC foi confirmada pela biópsia duodenal (Marsh 3b) em um paciente com HLA-DQ2, anti-TGt IgA e AAE IgA. Outros dois pacientes apresentaram anti-TGt positivo ou bordeline e HLA DQ2 e a histologia duodenal mostrou-se sem alterações. Positividade para anticorpos anti-TGt IgA e (ou) AAE IgA foi observada em 9% dos pacientes com hepatite auto-imune, porém o diagnóstico foi confirmado em apenas um dos pacientes (1,6%). A ocorrência de anticorpo anti-TGt IgA nos outros pacientes pode ser atribuída à presença de doença hepática crônica, ou, ainda,a uma DC latente ou um paciente com potencial para DC.

Palavras-chave: doença celíaca; hepatite auto-imune; marcadores sorológicos.

REFERENCES

1 HILL, I.D. et al. Celiac disease: Working Group Report of The First World of Pediatric Gastroenterology, Hepatology and Nutrition. J. Pediatr. Gastroenterol. Nutr., Philadelphia, v.35, p.S78-88, 2002.

2 BDIOUI, F. et al. Prevalence of celiac disease in Tunisian blood donors. Gastroenterol. Clin. Biol., Paris, v.30, n.1, p.33-36, 2006.

3 SACHDEV, A. et al. Adult onset celiac disease in north India. Trop. Gastroenterol., New Delhi, v.23, n.3, p.117-119, 2002.

4 FASANO, A. et al. Prevalence of celiac disease in at-risk and not-at-risk groups in the United States: a large multicenter study. Arch. Intern. Med., Chicago, v.163, p.286-292, 2003.

5 GANDOLFI, L. Prevalence of celiac disease among blood donors in Brazil. Am. J. Gastroenterol., New York, v.95, p.689-692, 2000.

6 COLLIN, P. et al. Follow-up of patients positive in reticulin and gliadin antibody tests with normal small-bowel biopsy findings. Scand. J. Gastroenterol., Oslo, v.28, p.595-598, 1993.

7 NIVELONI, S. et al. The natural history of gluten sensitivity: report of two new celiac disease patients resulting from a long-term follow-up of nonatrophic, first-degree relatives. Am. J. Gastroenterol., New York, v.95, p.463-468, 2000.

8 SUGAI, E. et al. Celiac disease serology in dermatitis herpetiformis: which is the best option for detecting gluten sensitivity? Acta. Gastroenterol. Latinoam., Buenos Aires, v.36, n.4, p.197-201, 2006.

9 CATALDO, F. et al. Prevalence and clinical features of selective immunoglobulin A deficiency in coeliac disease: an Italian multicentre study: Italian Society of Paediatric Gastroenterology and Hepatology (SIGEP) and "Club del Tenue" Working Groups on Coeliac Disease. Gut, London, v.42, p.362-365, 1998.

10 KAUKINEN, K. et al. Celiac disease and autoimmune endocrinologic disorders. Dig. Dis. Sci., New York, v.44, p.1428-1433, 1999.

11 PERETTI, N. et al. The temporal relationship between the onset of type 1 diabetes and celiac disease: a study based on immunoglobulin an antitransglutaminase screening. Pediatrics, Elk Grove Village, v.113, p.e418-422, 2004.

12 VALENTINO, R. et al. Prevalence of coeliac disease in patients with thyroid autoimmunity. Horm. Res., Basel, v.51, n.3, p.124-127, 1999.

13 VOLTA, U. et al. Coeliac disease in patients with autoimmune thyroiditis. Digestion, Basel, v.64, p.61-65, 2001.

14 VOLTA, U. et al. Celiac disease in autoimmune cholestatic liver disorders. Am. J. Gastroenterol., New York, v.97, p.2609-2613, 2002.

15 VOLTA, V. et al. Frequency and significance of anti-gliadin and anti-endomysial antibodies in autoimmune hepatitis. Dig. Dis. Sci., New York, v.43, p.2190-2195, 1998.

16 VILLALTA, D. et al. High prevalence of celiac disease in autoimmune hepatitis detected by anti-tissue transglutaminase autoantibodies. J. Clin. Lab. Anal., New York, v.19, n.1, p.6-10, 2005.

17 MANNS, M.P.; VOGEL, A. Autoimmune hepatitis, from mechanisms to therapy. Hepatology, Baltimore, v.43, p.S132-144, 2006.

18 KRAWITT, E.L. Autoimmune hepatitis. N. Engl. J. Med., Boston, v.354, p.54-66, 2006.

19 GOLDBERG, A.C. et al. Analysis of HLA haplotypes in autoimmune hepatitis type 1: identifying the major susceptibility locus. Hum. Immunol., New York, v.62, p.165-169, 2001.

20 GOLDBERG, A.C. et al. Autoimmune hepatitis in Brazil: an overview. Scand. J. Immunol., Oxford, v.66, n.2/3, p.208-216, 2007.

21 BITTENCOURT, P.L. et al. Genetic heterogeneity in susceptibility to autoimmune hepatitis types 1 and 2. Am. J. Gastroenterol., New York, v.94, p.1906-1913, 1999.

22 GREGORIO, G.V. et al. Autoimmune hepatitis in childhood: a 20-year experience. Hepatology, Baltimore, v.25, p.541-547, 1997.

23 CZAJA, A.J. et al. Genetic predispositions for the immunological features of chronic active hepatitis. Hepatology, Baltimore, v.18, p.816-822, 1993.

24 BITTENCOURT, P.L. et al. Frequency of concurrent autoimmune disorders in patients with autoimmune hepatitis: effect of age, gender and genetic background.J. Clin. Gastroenterol., New York, 2007. No prelo.

25 VOLTA, U. et al. IgA anti-endomysial antibodies on human umbilical cord tissue for celiac disease screening: save both money and monkeys. Dig. Dis. Sci., New York, v.40, p.1902-1905, 1995.

26 BRIDOUX-HENNO, L. et al. A case of celiac disease presenting with autoimmune hepatitis and erythroblastopenia. J. Pediatr. Gastroenterol. Nutr., Philadelphia, v.33, p.616-619, 2001.

27 LEONARDI, S. et al. Autoimmune hepatitis associated with celiac disease in childhood: report of two cases. J. Gastroenterol. Hepatol., Melbourne, v.18, n.11, p.1324-1327, 2003.

28 ARVOLA, T. et al. Celiac disease, thyrotoxicosis and autoimmune hepatitis in child. J. Pediatr. Gastroenterol. Nutr., Philadelphia, v.35, p.90-92, 2002.

29 SOINI, E.; KOJOLA, H. Time resolved fluorometer for lanthanide chelates: a new generation of nonisotopic immunoassays. Clin. Chem., Washington, DC, v.29, p.65-68, 1983.

30 MENJÍVAR, M. et al. Comparison of the DELFIA and RIA methods for measuring luteinizing and follicle stimulating hormones in serum. R. Invest. Clin., Mexico, DF, v.45, n.6, p.579-584, 1993.

31 MARSH, M.N. Gluten, major histocompatibility complex, and the small intestine: a molecular and immunobiologic approach to the spectrum of gluten sensitivity ('celiac sprue'). Gastroenterology, Philadelphia, v.102, p.330-354, 1992.

32 ROSTAMI, K. et al. Sensitivity of antiendomysium and antigliadin antibodies in untreated celiac disease: disappointing in clinical practice. Am. J. Gastroenterol., New York, v.94, p.888-894, 1999.

33 KAUKINEN, K. et al. Celiac disease without villous atrophy: revision of criteria called for. Dig. Dis. Sci., New York, v.46, p.879-887, 2001.

34 MAGGIORE, G.; CAPRAI, S. The liver in celiac disease. J. Pediatr. Gastroenterol. Nutr., Philadelphia, v.37, p.117-119, 2003.

35 KATZ, A.J. et al. Gluten-sensitive enteropaty: inhibition by cortisol of the effect of gluten protein in vitro. N. Engl. J. Med., Boston, v.295, p.131-135, 1976.

36 ROSTOM, A.; MURRAY, J.A.; KAGNOFF, MF. American Gastroenterological Association (AGA) Institute technical review on the diagnosis and management of celiac disease. Gastroenterology, Philadelphia, v.131, p.1981-2002, 2006.

37 KAUKINEN, K. et al. Celiac disease in

patients with severe liver disease: gluten-free diet may reverse hepatic failure. Gastroenterology, Philadelphia, v.122, p.881-888, 2002.

38 VECCHI, M. et al. High rate of positive anti-tissue transglutaminase antibodies in chronic liver disease: role of liver descompensation and of the antigen source. Scand. J. Gastroenterol., Oslo, v.38, p.50-54, 2003.

39 SOBRAL, D.T.; VIDIGAL, K.S.; FARIAS E SILVA, K. Sintomas digestivos em jovens: inquérito em estudantes de medicina. Arq. Gastroenterol., São Paulo, v.28, n.1, p.27-32, 1991.

40 BERN, C. et al. The magnitude of the global problem of diarrhoeal disease: a ten-year update. Bull. World Health Organ., Geneva, v.70, n.6, p.705-714, 1992.

Recebido em / ***Received***: 25/06/2007
Aceito em / ***Accepted***: 25/08/2007