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ORIGINAL ARTICLE

Celiac Disease: Confounding Presentations of Jeopardy in Indians

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Background: Celiac disease (CD) (also called gluten-sensitive enteropathy and nontropical sprue) is a known entity since 1888, is a common immune-mediated enteropathy due to allergy to gluten, with a prevalence of approximately 1% worldwide. It has wide spectrum of manifestations ranging from failure to thrive, gastrointestinal symptoms to various autoimmune diseases and malignancies. **Materials and Methods:** The clinical profile of patients diagnosed as CD, presenting at tertiary care hospital of armed forces, was evaluated. The patients were diagnosed as CD as per ESPGHAN guidelines on the basis of symptoms, positive serology, and histological findings (duodenal biopsy). After history and clinical suspicion of CD, IgA anti-tissue transglutaminase antibody was done. Complete history, physical examination, and baseline investigations including complete blood counts, serum glucose, thyroid function tests, etc., were recorded. **Results:** The average age of the cohort was 21.03 years (range 3–75 years). The most common presentation was diarrhea (80.7%) followed by anemia (63.2%) and weight loss (56%). Anemia was found to be second most common presentation after diarrhea and was seen in 63.2%. The prevalence of autoimmune conditions, namely, type-1 diabetes mellitus and thyroiditis were seen in two cases (3.5% each). **Conclusion:** CD is a common immune-mediated condition though typically presenting with gastrointestinal symptoms, atypical manifestations are also not uncommon. Suspicion of this condition and the appropriate investigations should not be delayed in patients presenting with either typical manifestations or uncommon presentations.

Key words: Celiac disease, gluten, autoimmune, diarrhea, anemia

INTRODUCTION

Celiac disease (CD) (also called gluten-sensitive enteropathy and non-tropical sprue) is a known entity since 1888 when first described by Samuel Gee in a report titled "On the Coeliac Affection" although description of a chronic, malabsorptive disorder by Aretaeus from Turkey reaches as far back as the second century AD.[1]

CD is a common immune-mediated enteropathy due to allergy to gluten, with a prevalence of approximately 1% worldwide. The causal relation between consumption of bread and cereals and relapsing diarrhea was first recognized by Dutch pediatrician Willem K Dicke. A similar association was observed during the Second World War when chronic diarrhea patients improved during periods of food shortage in the Second World War as bread was replaced by unconventional, noncereal containing foods.[2,3] Cereals implicated in this disease affliction were wheat, barley, rye, and oats. Dicke *et al.* in their paper postulated the presence of a factor in wheat which was incriminated to be responsible for a deleterious effect on the gut mucosa in susceptible individuals.[3] Subsequently, gluten which is an alcohol-soluble fraction of wheat protein was found to be the agent of interest in CD.[4]

Various gene loci, human leukocyte antigen (HLA), autoantibodies, and other facets of immune system have been implicated in the pathogenesis of CD and also give the clue regarding association of CD with various autoimmune conditions. Genetic predisposition or familial occurrence has shown remarkably close association with the HLA-DQ2 and/or DQ8 gene loci.[5] Estimated association of HLA contribution to the development of CD among siblings is 36%.[5]

With the newer diagnostic modalities and improvement of awareness among clinicians about condition has led to progressively increase in number of patients diagnosed as

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CD. The classic and usually obvious consequences of the enteropathy are malabsorption with diarrhea, weight loss, and nutritional deficiencies.[6] Serologic studies which are used to confirm the diagnosis of CD includes ELISA for IgA antibodies to gliadin and the immunofluorescence test for IgA antibodies to endomysium, which is a structure found in smooth muscle connective tissue. The presence of these antibodies is virtually pathognomonic for celiac disease.[7]

The difficulty in diagnosis is largely due to the silent form of the disease with nonspecific complaints such as fatigue, headaches, and arthralgias which are often ignored by the patients. Patients with celiac disease (and their families) are also more likely to have atopic dermatitis compared with the general population, although the prevalence of other allergies is not increased.[8] It may also present as infertility or amenorrhea in females. Celiac disease is frequently associated with dermatitis herpetiformis, Down syndrome, selective IgA deficiency, and other conditions with autoimmune features such as type 1 diabetes mellitus, thyroid disease, and liver disease.[9]

Autoantigen contained within the endomysium is tissue transglutaminase (tTG). These IgA-antibodies against endomysium and the endomysialautoantigen tissue transglutaminase are found to be highly sensitive and specific for diagnosis of celiac disease.[10] Some studies also revealed a high sensitivity and specificity for IgG antibodies against deamidated gluten peptides, almost reaching that of IgA anti-transglutaminase antibodies.[11]

Patients with typical gastrointestinal symptoms such as diarrhea and weight loss may just reflect the tip of the iceberg, hence early identification becomes imperative to treat the symptoms, deranged biochemical parameters, or associated auto-immune condition, and to avoid long-term complication including malignancies. The potential advantages of screening for asymptomatic CD in population includes a reduction in risk for enteropathy-associated T-cell lymphoma, a reversal of unrecognized nutritional deficiency states, resolution of mild or ignored intestinal symptoms, avoidance of other autoimmune disorders, an improvement in general well-being, and a possible reduction in mortality which is achieved by timely intervention and initiation of gluten-free diet.[4] Patients start showing symptomatic improvement within weeks after initiation on gluten-free diet. Hematological and biochemical picture also starts resolving subsequently. Serological resolution of raised antibody titers can be used to broadly monitor compliance to gluten-free diet.

Main management strategy for CD remains adherence to gluten free diet.[12] Gluten rechallenge not necessary according to a consensus statement issued by the National Institutes of Health and ESPGAN, in patients with good improvement in symptoms, histology, and a decline in the titer of antiendomysial antibodies.[12] Patient education regarding the condition is important. In practice, motivating CD patient for gluten-free diet for lifetime remains a tedious task and entails regular counseling during each clinical visit. Professional dietician consultation for educating patient regarding various gluten-free dietary options available as per customary dietary options according to ethnicity of the individual is an important part of management. The patient should be thoroughly investigated for associated nutritional deficiencies and associated autoimmune conditions and should be treated accordingly.

This study is aimed to evaluate the profile of CD at a tertiary level hospital in Northern India and its association with autoimmune disorders.

Aims and objectives

1. To evaluate the presentations and clinical profile of patients of CD presenting at a tertiary level hospital
2. To study the prevalence of associated conditions, which have an increased association with celiac disease, such as type 1 diabetes mellitus, autoimmune thyroid disease, liver disease, etc.

MATERIALS AND METHODS

The study was conducted at Army Hospital (Research and Referral), Delhi, after approval from the Hospital's Ethical Committee. Written and informed consent from all patients were obtained.

The patients were diagnosed as CD as per ESPGHAN guidelines on the basis of symptoms, positive serology, and histological findings (duodenal biopsy). After the history and clinical suspicion of CD, IgA anti-tTG antibody was done. All patients underwent upper gastrointestinal endoscopy and duodenal biopsies (from first and second part of duodenum). For patients with IgA deficiency, IgG antigliadin antibodies were planned as test for serological evaluation. For biopsy to be characteristic, the Marsh Criteria of CD were utilized.

Inclusion criteria

Only patients with a confirmed diagnosis of CD were included in the study.

Exclusion criteria

Any patient not meeting the criteria of CD (Biopsy negative or IgA tTG negative) was excluded. Any patient who was unwilling for an endoscopy was also excluded from the study.

A written informed consent of patients was taken the pro forma of which is attached as Appx "A." A detailed history (including family history) and clinical examination of all the patients presenting with symptoms of CD was done. On clinical examination height, weight, and body mass index (BMI) were recorded. Patients were examined for

cutaneous manifestations of CD (mouth ulcers, pallor, and dermatitis herpetiformis), nutritional deficiencies, features of thyroid disorders, and features of chromosomal disorders such as Down syndrome or Turners syndrome.

Baseline evaluation

The following investigations were done in the patients.

a. Hemoglobin (Hb), total leukocyte count, differential leukocyte count, and platelet count
b. Peripheral blood smears
c. Liver function tests including serum bilirubin, alanine aminotransferase, aspartate aminotransferase and alkaline phosphatase, gamma glutamyltranspeptidase
d. Serum calcium, serum phosphate
e. Serum iron, total iron binding capacity (TIBC), serum ferritin
f. Blood sugar fasting and postprandial, hemoglobin A1c
g. T3, T4, thyroid-stimulating hormone, Antithyroid peroxidase antibodies
h. Bone mass densitometry in adults
i. Additional tests as indicated.

RESULTS

The study was conducted at Army Hospital (Research and Referral) for assessing the clinical profile and response to gluten-free diet in a cohort of celiac disease. A total of 57 CD patients were included in study during the period from October 2013 to March 2015. Patients were diagnosed as per inclusion criteria which required IgA tTG positivity in addition to the histological changes characteristic of the disease. The patients were followed up on monthly basis after diagnosis and initiation of gluten-free diet.

Age and sex distribution

The average age of the cohort was 21.03 years (range 3–75 years). The age-wise distribution is depicted in Figure 1. In our study, about 71% cases were below 30 years of age. Out of 57 patients, 28 (49.1%) were female with a male-to-female ratio of 1.036. A male preponderance was noted in the younger age groups while in the older age groups the reverse was observed.

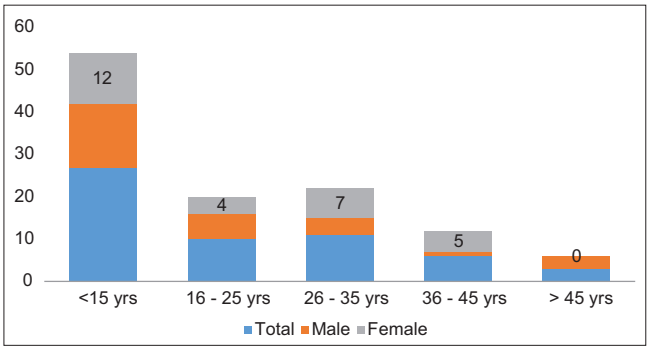

Figure 1: Age and sex distribution

Baseline parameters

The patients were questioned regarding the symptomatology and the responses recorded. The various baseline parameters that were recorded are shown in Table 1. Investigations were also carried out at baseline to assess the impact of the illness on the metabolic and hematological parameters. These investigations are summarized in Table 1.

Chronic diarrhea, weight loss, and other symptoms

Chronic diarrhea was the most common symptom noted. It was the presenting symptom in 46 (81%) of the patients. Similarly, symptoms of weight loss were also frequently reported. It was present in 32 (56%) patients. Other commonly reported symptoms were bloating of the abdomen (38.6%), generalized weakness (40.4%), and failure to thrive (36.8%). The less common symptoms that were present were recurrent oral ulcerations (5.3%) and symptoms of lactose intolerance (8.8%). Two patients (3.5%) reported a history of multiple fractures in the past [Figure 2].

Failure to thrive was one of the most prominent presenting symptoms, especially in younger age group patients. Where

Table 1: Baseline parameters

Parameters	Present, *n* (%)	Absent, *n* (%)
Diarrhea	46 (80.7)	11 (19.3)
Weight loss	32 (56.1)	25 (43.9)
Bloating	22 (38.6)	35 (61.4)
Lactose intolerance	5 (8.8)	52 (91.2)
Weakness	23 (40.4)	34 (59.6)
Failure to thrive	21 (36.8)	36 (63.2)
Pallor	36 (63.6)	21 (36.4)
Recurrent mouth ulcers	3 (5.3)	54 (94.7)
Fractures	2 (3.5)	55 (96.5)
Underweight (low BMI)	35 (61.4)	22 (38.6)
Body fat content (under)	23 (40.4)	34 (59.6)
Anemia*	36 (63.2)	21 (36.8)
Iron deficiency[#]	14 (24.6)	43 (75.4)
Low Albumin[$]	20 (35.1)	37 (64.9)

*Hb <13.5 g% in males and <12.5 g% in females was defined as anemia; [#]Iron deficiency was defined as serum iron level 40 mcg/dL; [$]Low albumin was defined as serum albumin <3.5 g/L. Hb=Hemoglobin; BMI=Body mass index

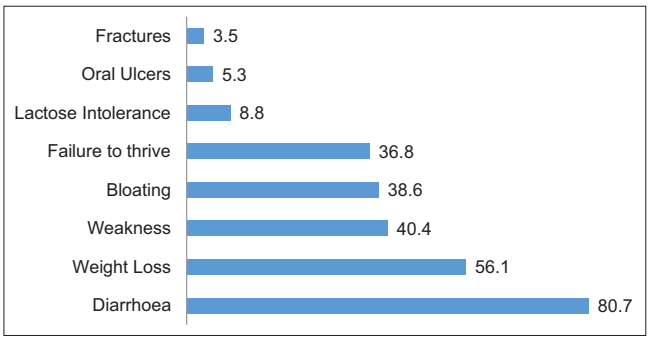

Figure 2: Prevalence (%) of various baseline presentations ($n = 57$)

it was found that overall failure to thrive was present in 21 (36.8%) patients, among the patients less than 15 years of age ($n = 27$), it was present in 11 (41%) cases.

Other investigations at baseline

The patients on enrollment underwent detailed evaluation to ascertain their hematological and biochemical state. Totally 36 patients (63.2%) had anemia (which was defined as Hb <12.5% in males and <11.5 g% in women). The serum albumin which was utilized to ascertain the nutritional state of the patients was, however, normal in 37 (64.9%) of patients. On further investigation 14 (24.6%), anemic patients demonstrated to be having an iron deficient state (diagnosed by low serum iron, low ferritin, and high TIBC).

Bone mineral density was done to evaluate the presence of metabolic bone disease at baseline presentation. As the test is not standardized <16 years of age, only patients >16 years of age underwent this test. Out of total 27 patients who were tested, 1 patient was found to have osteopenia making its prevalence 3.7% in the studied subgroup.

Body composition analysis was done on patients at the time of inclusion in the study to have baseline fat percentage and to evaluate the percentage of CD patients presenting with low body fat percentage. It revealed that 38% CD cases had body fat percentage below normal, majority (34 out of 57, i.e. 60%) had normal body fat percentage. Only 1 patient had fat percentage above normal.

Atypical presentations

Although diarrhea was presenting symptom in majority of the patients, it was not seen in 11 (19.2%) of the 57 patients. Of these 11 patients, 7 patients presented with anemia. 5 patients presented with failure to thrive out of which 2 patients had both anemia and failure to thrive. 5 patients had history of abdominal bloating out of which 1 also had lactose intolerance. In these patients 1 presented with type-1 diabetes mellitus.

DISCUSSION

Celiac disease (CD) is a chronic and immunologically determined form of enteropathy affecting the small intestine in genetically predisposed children and adults. It is precipitated by the ingestion of gluten-containing foods. Gluten is present in wheat, rye, and barley and gives the dough the desired baking properties. It is widely used as an ingredient in food processing, hence, dietary modification with gluten-free diet remains the mainstay in the management of CD. The prevalence of CD in the adult population varies roughly from one in 100 to one in 300 in most parts of the world.

Indian studies of CD have shown a male preponderance.[13,14] In a retrospective study conducted at All India Institute of Medical Sciences sex ratio (M: F) was found to be 1.17.[13] In another 5-year prospective study conducted at PGI Chandigarh in 300 celiac patients of pediatric age group sex ratio was found to be 1.5.[14] However, this ratio has shown female preponderance (1:2–1:3) in western studies and has been found commensurating with the prevalence of autoimmune diseases in females.[15] In our study, calculated M: F ratio was 1.036 showing slight male preponderance. The difference may be attributed to relatively lesser number of female patients presenting to the hospital due to ignorance by husband or parents for generally innocuous symptomatology in CD, giving a skewed impression of sex distribution.

Chronic diarrhea is one of the most common presenting symptoms in celiac disease. As per ESPGHAN guidelines,[16] prevalence has been studied between 13% and 51%. In a prospective case–control study at PGI which has studied presentation of CD in pediatric age group, diarrhea was found as presenting complaint in 84% cases ($n = 300$) against 52% in control with $P < 0.001$.[14] In another Indian studies, it is noted to be one of the chief presenting complaints in about 44% cases.[13] In other western studies, diarrhea has been noted in less than 50% cases.[17] In our study, 80.7% cases presented with symptoms of persistent diarrhea, which fairly corroborates with the various previous studies.

Abdominal bloating is a common presenting symptom in CD patients. Patients of CD presenting with abdominal distention as presentation has been estimated around 48% in same case–control study at PGI Chandigarh.[14] Studies included in ESPGHAN guidelines suggest the prevalence of 28%–36% in children and about 10% in adults.[16] Abdominal bloating is a vague and nonspecific symptom, hence differences in between the studies is inevitable. In western countries, pooled prevalence of abdominal bloating has been estimates about 38%. In our study, total 22 out of 57 studied patients presented with abdominal bloating as one of the presenting complaint, i.e. 38.6%. This fairly corroborates with the prevailing patterns.

Failure to thrive is an important presentation in pediatric age group CD patients. In case–control study done at PGI Chandigarh, the prevalence of failure to thrive was found to be 91%.[14] As per studies included in ESPGHAN guidelines[16] short stature and growth failure was found in 20%–30% in pediatric age group patient and about 19% in adult population. In same guidelines, failure to thrive has been noticed in 48%–89% in various countries. In our study, it has been estimated to be 60% in pediatric age group. Cases presented with weight loss as one of the presenting complaints in our study were 56.1%. Failure to thrive was found in 36.8%. In our study, we have included patients from all age group and included 57 CD cases only, which has contributed to a varied result. The difference in data may be attributed to study design in which we have included both pediatric and adult age groups as well as the clientele under study belongs to Armed forces, where nutrition is well catered centrally, in the form of regular rations. In addition, studies have shown to significantly improve the weight in CD patients, once they are started on gluten-free diet.[14] Same has been depicted well in our study group also.

Mean prevalence of type-1diabetes mellitus has been estimated to be 4% in western studies.[16] Indian studies have shown prevalence of diabetes mellitus to be about 2.2.[13] In our study, out of 57 CD patients, 2 had diabetes mellitus (i.e. prevalence of 3.5%). The estimated prevalence is indicative of the trend noted in previous studies.

Anemia is one of the important associate of celiac disease. Majority of cases of anemia are secondary to iron deficiency. In western studies, overall prevalence of anemia at the time of diagnosis of CD has been estimated between 12% and 69%.[18] In studies included in ESPGHAN guidelines,[16] overall prevalence found was between 16% and 23%. In Indian studies, it is found in 10%–31% cases.[13,14] In our study, anemia was found in 63.2% cases at the time of presentation. As the incidence of nutritional anemia is endemic in India by virtue of it being a developing country, where concept of balanced diet is vague in the general population, incidence of anemia in CD is accepted to be high. Hence, our results corroborates with the overall extensively studied pattern of presentation of anemia in patients of celiac disease.

Metabolic bone disease is a common long-term associate of celiac disease. It generally manifests as bony pains or fractures to trivial trauma. Western studies have corroborated its presence in about 26% CD patients.[19] In Indian studies, its prevalence has been estimated in 1%–4.4%.[13,14] In our study, out of total 27 patients (all above age of 16 years) evaluated by DEXA scan, 1 showed osteopenia, i.e. 3.7%. In addition, total 2 out of 57 CD patients, presented with a history of fracture to low intensity trauma making prevalence of 3.5%. Hence, overall presentation of metabolic bone disease in the study group commensurate with the previous studies.

As per ESPGHAN guideline,[16] studies liver transaminitis has been found in total 5% of cases. Other Western meta-analysis has estimated its prevalence around 27%.[20] In our study group, total 12 patients presented with raised serum glutamate oxaloacetate transaminase (SGOT) and 11 patients had raised serum glutamic pyruvic transaminase (SGPT) with total 8 (14%) patients with elevation of both the transaminases with 15.7% in terms of SGOT and 10.5% for SGPT. The liver transaminitis has shown a regressing trend on follow-up on gluten-free regime though statistical significance could not be established. Criteria followed for transaminitis in the study were SGOT >41 IU/L and SGPT >63 IU/L.

The prevalence of auto-immune thyroiditis has been about 3% in the studies included in ESPGHAN guidelines.[16] Other western studies have shown prevalence ranging 2%–7.8% (average, 4.1%).[21] In our study, total 2 patients out of 57 were found to have autoimmune thyroiditis making its prevalence 3.5%.

CONCLUSION

We have evaluated 57 patients with celiac disease, who presented to tertiary care hospital of armed forces. While chronic diarrhea was the most common presentation, there were other atypical presentations such as anemia in the absence of diarrhea, weight loss, or abdominal symptoms. The associated auto-immune conditions seen in our patients were type-1 diabetes mellitus and auto-immune thyroiditis with a prevalence of 3.5% each. Suspicion of this condition and the appropriate investigations should not be delayed in patients presenting with either typical manifestations or uncommon presentations.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Paveley WF. From aretaeus to crosby: A history of coeliac disease. BMJ 1988;297:1646-9.
2. Dicke WK. Simple dietary treatment for the syndrome of Ghee Herter. Ned Tijdschr Geneeskd 1941;85:1715.
3. Dicke WK, Weijers HA, Van DE Kamer JH. Coeliac disease. II. The presence in wheat of a factor having

a deleterious effect in cases of coeliac disease. Acta Paediatr 1953;42:34-42.
4. Van DE Kamer JH, Weijers HA, Dicke WK. Coeliac disease. IV. An investigation into the injurious constituents of wheat in connection with their action on patients with coeliac disease. Acta Paediatr 1953;42:223-31.
5. Petronzelli F, Bonamico M, Ferrante P, Grillo R, Mora B, Mariani P, *et al.* Genetic contribution of the HLA region to the familial clustering of coeliac disease. Ann Hum Genet 1997;61:307-17.
6. Pittschieler K, Ladinser B. Coeliac disease: Screened by a new strategy. Acta Paediatr Suppl 1996;412:42-5.
7. Volta U, Granito A, Parisi C, Fabbri A, Fiorini E, Piscaglia M, *et al.* Deamidated gliadin peptide antibodies as a routine test for celiac disease: A prospective analysis. J Clin Gastroenterol 2010;44:186-90.
8. Ciacci C, Cavallaro R, Iovino P, Sabbatini F, Palumbo A, Amoruso D, *et al.* Allergy prevalence in adult celiac disease. J Allergy Clin Immunol 2004;113:1199-203.
9. Seissler J, Schott M, Boms S, Wohlrab U, Ostendorf B, Morgenthaler NG, *et al.* Autoantibodies to human tissue transgutaminase identify silent coeliac disease in type I diabetes. Diabetologia 1999;42:1440-1.
10. Gale L, Wimalaratna H, Brotodiharjo A, Duggan JM. Down's syndrome is strongly associated with coeliac disease. Gut 1997;40:492-6.
11. Grodzinsky E, Hed J, Skogh T. IgA antiendomysium antibodies have a high positive predictive value for celiac disease in asymptomatic patients. Allergy 1994;49:593-7.
12. National Institutes of Health Consensus Development Conference Statement. Celiac Disease 2004;128 (4 Suppl 1). DOI: 10.1053/j.gastro.2005.02.007.
13. Makharia GK, Baba CS, Khadgawat R, Lal S, Tevatia MS, Madan K, *et al.* Celiac disease: Variations of presentations in adults. Indian J Gastroenterol 2007;26:162-6.
14. Poddar U, Thapa BR, Singh K. Clinical features of celiac disease in Indian children: Are they different from the West? J Pediatr Gastroenterol Nutr 2006;43:313-7.
15. Jacobson DL, Gange SJ, Rose NR, Graham NM. Epidemiology and estimated population burden of selected autoimmune diseases in the United States. Clin Immunol Immunopathol 1997;84:223-43.
16. Husby S, Koletzko S, Korponay-Szabó IR, Mearin ML, Phillips A, Shamir R, *et al.* European society for pediatric gastroenterology, hepatology, and nutrition guidelines for the diagnosis of coeliac disease. J Pediatr Gastroenterol Nutr 2012;54:136-60.
17. Rampertab SD, Pooran N, Brar P, Singh P, Green PH. Trends in the presentation of celiac disease. Am J Med 2006;119:355.e9-14.
18. Hin H, Bird G, Fisher P, Mahy N, Jewell D. Coeliac disease in primary care: Case finding study. BMJ 1999;318:164-7.
19. Bottaro G, Cataldo F, Rotolo N, Spina M, Corazza GR. The clinical pattern of subclinical/silent celiac disease: An analysis on 1026 consecutive cases. Am J Gastroenterol 1999;94:691-6.
20. Sainsbury A, Sanders DS, Ford AC. Meta-analysis: Coeliac disease and hypertransaminasaemia. Aliment Pharmacol Ther 2011;34:33-40.
21. Ch'ng CL, Jones MK, Kingham JG. Celiac disease and autoimmune thyroid disease. Clin Med Res 2007;5:184-92.