

Diagnostic Utility of Coeliac Disease: A Descriptive Study in a Tertiary Care Hospital, Oman

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Abstract

Objectives: The prevalence of coeliac disease in Oman is unknown. We aim to estimate the prevalence of coeliac disease in at-risk subjects, describe the clinical characteristics and laboratory findings associated with coeliac disease and the validity of serological testing for coeliac disease at the Royal Hospital, Oman over a period of three years.

Methods: This is a retrospective case finding study. The medical and laboratory records were reviewed for patients for whom serum antiendomysium IgA antibodies were requested at the Royal Hospital during a 3-year period (1st Jan 2006-31st Dec 2008). The data were extracted in order to assess the following: a) Prevalence rate of coeliac disease among at-risk subjects; b) Clinical characteristics in patients with coeliac disease and clinical manifestations for which the requesting clinicians considered coeliac disease as a possible diagnosis, including their specialties; c) Laboratory tests results in patients with coeliac disease; and d) Validity of antiendomysium antibodies testing in comparison with histopathology of jejunal biopsies for diagnosing coeliac disease.

Results: The study included 431 patients (250 females, 181 males) who were suspected of having (or screened for) coeliac disease. The median of age was 15 years (range: 9 months-74 years) with mean \pm SD 18.95 \pm 14.1 years. Of these, 15 (3.5%) patients (10 females, 5 males) with a median age of 19 years and mean 21.4 \pm 13.0 years (range: 2.5-38 years), had positive antiendomysium antibodies results with median (range) of 160 (40-320) IU/L and mean \pm SD 204.5 \pm 160 IU/L. Of these 15 patients, 13 had positive jejunal histopathological changes indicative of coeliac disease; the remaining 2 patients had no biopsy examination. Of the 44 patients with negative antiendomysium antibodies <10 IU/L who had jejunal biopsy, 41 were negative and 3 had histopathological changes suggestive of mild coeliac disease. All the 3 patients had serum

total IgA levels within the reference range. The calculated validity indicators for antiendomysium antibodies were: sensitivity 81.3%, specificity 100%, positive predictive value 100%, negative predictive value 93.2% and efficiency 94.7%. The most common mode of presentation in patients with coeliac disease was gastrointestinal features, type 1 diabetes mellitus, anemia, short stature and hypothyroidism. The seropositivity in type 1 diabetics was 4.9%. Investigations for coeliac disease were most frequently made by endocrinologists (pediatric and adult) who accounted for 53.8% followed by gastroenterologists (pediatric and adult) with 40.6% with less consideration by the other clinicians (5.6%).

Conclusion: The availability of highly specific and sensitive serological test and increased awareness for coeliac disease among some medical specialties has increased the number of diagnosed cases of coeliac disease. The requesting for serological test is being made mainly by endocrinologists and gastroenterologists.

Keywords: Coeliac disease; Antiendomysium antibodies; Prevalence; Oman.

Introduction

Coeliac disease (CD), formerly named nontropical sprue or coeliac sprue (from the Dutch word sprue) is an immune-mediated intolerance to gluten (from wheat, barley, or rye) in genetically susceptible individuals.^{1,2} Although patients with CD were previously known to be presented with severe diarrhea, malabsorption, stomatitis and weight loss; a wide range of clinical manifestations of systemic involvements however, may develop during the course of the disease.³ Also, although CD was originally considered a disease of infants and children with malabsorption, it is now considered to affect all ages including the elderly.⁴

The diagnostic criteria for CD are usually based on the histological changes in jejunal biopsies of patients, while they are on and off gluten diet as per guidelines of the European Society of Pediatric Gastroenterology and Nutrition (ESPGAN). The characteristic findings include intraepithelial lymphocytosis, crypts hyperplasia and villous atrophy with improved response to gluten free diet.⁵ From 1990, the ESPGAN criteria added value

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on the finding of positive circulating antibodies (IgA gliadin, antireticulin and antiendomysium) at the time of diagnosis and their disappearance together with the improvement of symptoms when the patients are on gluten free diet.^{6,7} The sensitivity of serological tests, particularly antiendomysium or antitissue transglutaminase antibodies is greater than 90%, and tests for either markers is considered to be the best means for CD screening.⁸ The National Institute of Clinical Excellence (NICE) has also recently recommended the use of serological testing for these antibodies as a first-line test for patients with suspected CD.⁹

Due to the availability of such accurate and practical non-invasive serological tests for CD, as well as increased medical awareness about its existence, CD has shifted from what was thought to be a rare disease to a common one. During the last two decades, there has been an increase in the reported prevalence of CD, particularly in the Caucasian population with a prevalence of around 1% in the UK and European populations.¹⁰⁻¹² The high prevalence is also attributed to the inclusion of Marsh I-II in the definition of CD, often termed as gluten-sensitive enteropathy (GSE).

This study aims to estimate the prevalence of CD in at-risk subjects, describe the clinical characteristics and laboratory findings associated with CD and the validity of serological testing for CD at the Royal Hospital, Oman during a period of three years.

Methods

This retrospective audit case finding study was conducted at a tertiary care hospital, the Royal Hospital in Muscat, Oman. Ethical approval for conducting this work was obtained from the Research and Ethical Review Committee, Directorate of Research and Studies, Royal Hospital, on 10/4/2012.

The medical and laboratory records of the patients for whom serum antiendomysium IgA antibodies (EMA) test, a serological marker of CD, was requested during the three years period (1st Jan 2006-31st Dec 2008) were reviewed. The results of EMA were compared with the results of histology of the jejunal biopsies (when available). The laboratory, clinical and demographic characteristics were extracted for all the patients for whom investigations for CD were considered, in order to assess the followings:

- Prevalence rate of CD among at-risk subjects
- Clinical characteristics including main manifestations of CD, presence of other associated diseases, and clinical manifestations for which the requesting clinicians considered CD as a possible diagnosis, including the specialty of the requesting clinician.
- Laboratory tests result particularly, in relation to the biochemical and hematological indicators of anemia, vitamin deficiency, liver function and bone profile.
- Validity indicators of EMA testing in comparison with histopathology of jejunal biopsies for diagnosing or excluding CD.

The diagnosis of CD was made on the basis of results of jejunal biopsy histopathology examination and EMA testing, as well as response to gluten-free diet. At the time of study, serum specimens for EMA assay were referred to Biomnis Laboratory, France, (EMA

positive cut-off at titre >10 IU/L). The jejunal histopathological examinations were done at the Histopathology Laboratory, Royal Hospital. The features consistent with CD included: hyperplasia of crypts, atrophy of villous, and increase of intraepithelial lymphocytes.

The data collected included patient demographics, presenting symptoms, other associated clinical manifestations or diseases, and specialty of the requesting clinicians. The results of the laboratory tests (where available) included: CBC (including mainly: hemoglobin concentration, MCV, MCH, RDW), ferritin, transferrin saturation, vitamin B12, folate, bone profile, liver function test, total IgA, EMA and jejunal histopathology.

The data were analysed using SPSS statistical software. Descriptive statistical data were presented to summarise the study variables as number, percentage, mean \pm SD or median (range) as appropriate. The prevalence rate of CD among at-risk subjects was calculated by dividing the number of patients with proven CD during the study period by the population size in whom the disease was screened. The validity indicators (sensitivity, specificity, positive predictive value, negative predictive value and efficiency) were calculated for the test (EMA) in comparison with the gold standard (biopsy).

Results

During the three years study period (1st Jan 2006-31st Dec 2008), EMA testing was requested for 431 patients who were suspected by the requesting clinician of having CD. There were 250 females and 181 males, with median age of 15 years (mean \pm SD: 18.95 \pm 14.1 years) and a range of 9 months-74 years. Of these, 15 (3.5%) patients (10 females, 5 males) had positive EMA with concentrations of 204.5 \pm 160 IU/L and median (range) of 160 (40-320) IU/L. The median age in these 15 patients was 19 years and mean 21.4 \pm 13.0 years (range: 2.5-38 years). Of these 15 patients, 13 patients had jejunal biopsy which all showed positive histopathological changes indicative of CD. The remaining 2 patients had no biopsy examination; both had type 1 diabetes mellitus (DM) and were aged 9 months and 28 years with EMA results of 80 and 70 IU/L, respectively. Forty-four patients with negative EMA <10 IU/L had jejunal biopsy, of whom 41 patients were negative for CD changes and 3 patients had histopathological changes (Marsh I), suggestive of mild CD. All the 3 patients had serum total IgA levels within the reference range with results of 3.0, 2.4 and 3.5 g/L (NR 0.5-3.7 g/L). Taking these results into consideration and that the two patients with negative EMA and Marsh I changes as being GSE or possibly early CD, the calculated validity indicators of EMA for the diagnosis of CD are: sensitivity 81.3%, specificity 100%, positive predictive value 100%, negative predictive value 93.2% and efficiency 94.7%.

In the 15 patients with CD, the most common mode of presentation was gastrointestinal, accounting for 7/15 patients and comprising of diarrhea (6), abdominal pain (4), weight loss (1): followed by type 1 DM (5/15), clinical anemia (5/15), short stature

or failure to thrive (4/15) and hypothyroidism (2/15), one patient had both type 1 DM and hypothyroidism, Table 1. Screening for CD is usually considered in the work-up assessment for type 1 diabetics, and in this study, 102 patients were screened for CD and 5 were found to be EMA seropositive making the prevalence of EMA seropositivity indicative of CD in type 1 diabetics to be 4.9% in Oman.

Table 1: Main Clinical manifestations at presentation in patients with Coeliac Disease (n= 15).

Clinical Manifestations	Diagnosed CD	
	Number	%
Gastrointestinal	7	46.7%
Type 1 Diabetes Mellitus	5	33.3%
Anemia (clinical)	5	33.3%
Short stature / Failure to Thrive	4	26.7%
Hypothyroidism	2	13.3%

For the clinical manifestations for which diagnostic suspicion of CD was considered, screening for CD in type 1 DM was the commonest indication for requesting EMA, followed by the presence of gastrointestinal symptoms, short stature, anemia and thyroid disease, Table 2. For the specialties of the clinicians requesting EMA, the test was most frequently requested by both pediatric and adult endocrinologists (53.8%) and similarly both pediatric and adult gastroenterologists (40.6) with less being requested by other physicians, surgeons and gynecologists (all 5.6%), Table 3. The results of the different laboratory tests for the 15 patients with CD are presented in Table 4. Twelve patients showed low ferritin (<12 µg/L in females, <18 µg/L in males) and low transferrin saturation (<10%) indicative of iron deficiency anemia.

Table 2: Clinical presentation and diagnosis of 431 patients for whom serum EMA testing was requested.

Clinical Feature / Manifestation	No.	%
Type 1 diabetes mellitus	102	23.7%
Gastrointestinal	96	22.3%
Failure to Thrive/Short Stature	76	17.6%
Anemia (Clinical/Laboratory)	59	13.7%
Hypothyroidism/Hyperthyroidism	23; 10	5.3%; 2.3%
Osteomalacia/Osteoporosis	10; 8	2.3%; 1.9%
Neurological	12	2.8%
Liver disease	11	2.6%
Hypopituitarism	6	1.4%
Musculoskeletal	6	1.4%
Delayed puberty	4	0.9%
Gonadal Dysgenesis	3	0.7%
Down syndrome	3	0.7%
Hemoglobinopathy	3	0.7%
Polyglandular syndrome	2	0.5%
Chronic renal failure	2	0.5%
Hypoparathyroidism	2	0.5%

Table 3: Specialty of clinicians who requested serum EMA for the 431 patients .

Specialty of Requesting Clinician	Requested Tests	
	No.	%
Endocrinologists (Adult)	117	27.1%
Endocrinologists (Paed)	104	24.1%
Gastroenterologists (Adult)	89	20.6%
Gastroenterologists (Paed)	78	18.1%
Rheumatologists (Adult)	15	3.5%
Pediatricians	8	1.9%
Hematologist	8	1.9%
Neurologists	5	1.2%
Internal Medicine	6	1.4%
Gynecologists	1	0.2%
Total	431	100%

Table 4: Results of laboratory tests for patients with Coeliac Disease (n=15).

Test	No.	Mean ± SD	Median (Range)
Hemoglobin Con. (g/dL)	15	10.1 ± 2.55	10.0 (6.1-14.0)
RDW (× 10 ¹² /L)	15	17.7 ± 4.9	17.4 (12-28)
MCV (fl)	15	64.4 ± 9.8	65.3 (43.7-79.9)
MCH (pg)	15	20.5 ± 4.7	19.6 (11.9-28.3)
Ferritin (µg/L)	15	10.9 ± 14.6	4.0 (2.0-48)
Transferrin Saturation (%)	15	6.2 ± 3.2	5.5 (3.1-11.0)
Vitamin B12 (pmol/L)	10	375.7 ± 236.9	270 (218-888)
Folate (nmol/L)	10	25.7 ± 8.9	28 (12.9-37.8)
EMA.A (IU/L)	15	205 ± 116.9	160 (40-320)

Discussion

This study revealed that 15 cases (10 females, 5 males) were diagnosed to have CD from a total of 431 patients who were investigated for this disease at the Royal Hospital, Oman during a period of three years (2006-2008). Giving a prevalence rate for CD of 3.5% that was reported for at-risk patients with manifestations or diseases suggestive to be present or associated with CD. The median (range) of age for the patients with CD was 19 years (2.5-38 years) and for patients who underwent EMA testing was 15 years (9 months-74 years). The broad age range reflects the clinicians' awareness about CD occurrence among all age groups and not only children as what was previously thought for CD as being a childhood disease.¹³ It also appears that CD prevalence is increasing in our region with figures approaching those in developed countries.

In comparison with other studies, Hin et al.¹¹ reported 30 cases of CD among 1000 high-risk hospital patients, giving a CD prevalence of 3%, which is comparable to the prevalence of 3.5% observed in the current case finding study. In Eastern Saudi Arabia,

in clinically CD suspected patients, the seropositivity was 7.6% with histology confirmed CD at 4%.¹⁴ Also, the prevalence of CD in a healthy adult Saudi population who volunteered in a prospective study at a blood donation centre in Jeddah, Saudi Arabia was 1.5%.¹⁵ This prevalence rate seems to be approaching the high rates reported in Caucasian populations.^{10-12,16} Concerning age, the age range of patients with CD in a series by Sanders et al.¹² was 1-82 years. It has been recognized that about 25% of patients with CD are diagnosed in patients above the age of 60 years.¹⁷ Few studies related to CD have been conducted in Oman. Fraser et al.¹⁸ reported a 3.3% prevalence rate of CD among 51 patients with unexplained iron deficiency anemia. While Akinbami et al.¹⁹ reported CD in 13% of 62 children presented with chronic diarrhea in their 7 year prospective study. Also, recently Al-Lawati et al.²⁰ reported 9 children with CD with mean age of 7.1 years at diagnosis in their 6 year search at Royal Hospital.

Coeliac disease is an immune-mediated disorder that may affect different organs in the body with a variety of clinical and laboratory manifestations. Our study observed a wide spectrum of clinical presentations that might be considered to be as a result of CD by the requesting clinicians. These clinicians ordered EMA with further consideration of jejunal biopsy examination for patients with different clinical features including gastrointestinal, endocrinological, hematological, musculoskeletal, as well as other signs and symptoms. It was interesting to note that the majority of EMA requests were made by the endocrinologists (adult 27.1%, pediatric 24.1%) and by gastroenterologists (adult 20.6%, pediatric 18.1%). This points to the increasing awareness among the endocrinologists, besides the gastroenterologists for considering CD in the differential diagnosis, including the work-up investigations in type 1 DM. However, the requesting rate is still less for the other specialties, since much less requests were made by rheumatologists (3.5%), pediatricians (1.9%), hematologists (1.9%), internists (1.4%), neurologists (1.2%) and gynecologists (0.2%). No request was made by other clinicians including Surgeons.

In our study, the clinical manifestations (in decreasing order) in the fifteen patients with CD were gastrointestinal, type 1 DM, anemia, short stature or/and failure to thrive and hypothyroidism. Iron deficiency anemia was evident in 80% of our CD cases as evidenced from serum ferritin and transferrin saturation as well as hematological indices (hemoglobin concentration, MCV, MCH, RDW). In their review of 264 patients with CD Sender et al.¹² found that 28.4% of patients had gastrointestinal symptoms, 20.1% had iron deficiency anemia, and 52.7% were diagnosed by gastroenterologists. Hin et al.¹¹ in their 30 cases of CD who were diagnosed during screening 1000 high-risk subjects at nine clinics using EMA in 1997 found that 15/30 patients had anaemia and 25/30 had non-gastrointestinal symptoms. Also in our study, the small number of cases might have limited the reporting of other features which are expected to be found in CD. In addition, screening for CD is part of the work-up investigations for patients with type 1 DM, and of the 102 type 1 diabetics who were screened for CD in our study, 5 (4.9%) were EMA seropositive. The prevalence rate

of CD in type 1 DM varies in the literature with a range of 1-19% (mean 4.5%) as reviewed in 26 reports by Holmes.²¹

Our study revealed high predictive values for serum EMA in diagnosing CD with sensitivity 81.3%, specificity 100%, positive predictive value 100%, negative predictive value 93.2% and efficiency 94.7%. There was a very good agreement with the histological findings. Serological tests have been used as surrogate markers of CD for more than 20 years with an increasing interest in their use in the diagnosis of CD.²² The IgA class EMA and anti-tissue transglutaminase (anti-tTG) ELISA assays are considered to be reliable tests for diagnosing CD.^{8,20} Patients with negative serology (in the absence of IgA deficiency) and gluten-dependent enteropathy together with minimal histological changes are considered to have CD-like enteropathy (or GSE).^{8,23-25} When IgA deficiency exists, serological testing using IgG class EMA and anti-tTG are recommended to be measured. IgA deficiency, defined as serum IgA <0.1 g/L may occur at a prevalence of one in approximately 500, being less common in Asian population with variable reports of its occurrence in patients with CD of one in 39 patients in one study and one in 131 in another study.²⁶⁻²⁹ Screening or testing for CD may therefore aid the detection or diagnosis of IgA deficiency or hypogammaglobulinemia.³⁰ No patient with IgA deficiency was reported in our patient series in this study. In patients with IgA deficiency, testing for CD IgG EMA and anti-tTG serology is recommended. Recently, newer assays incorporating synthetic deamidated gliadin-related peptide (DGPs) or other tTG isoenzymes or antigens have been described.^{31,32} These assays are available as kits for combined detection of IgA- and IgG- class antibodies to DGP (DGP dual) and for IgA and IgG antibodies to both tTG and DGP (tTG/DGP screen). These tTG/DGP screen and DGP Dual assays may represent useful tools to confirm gluten sensitivity in IgA anti tTG-seronegative patients (whether IgA deficient or not) who are suspected to have CD. However, further experience in their utilization is required before justifying their practical advantages.³²⁻³⁵ Currently in our laboratory, testing for IgA class anti-tTG and total IgA is performed as a CD screening panel. This in-house test availability, together with increased awareness of CD following the introduction of new guidelines in 2009 on the indications of CD testing,⁹ has resulted in increased requests at our laboratory for serological screening of CD.

Our study has some limitations, namely; The study reported the prevalence of CD among at-risk subjects with symptoms or diseases suspected of the disease. Assessment of prevalence of CD among healthy subjects such as blood donors or those contributing in screening programs is recommended. In addition, the serological diagnosis was based only on IgA class EMA. It is worth to study the validity of other serological tests which have been used as surrogate markers of CD such as anti-tTG and DGPs, including their combined detection of IgA- and IgG- class antibodies (tTG/DGP screen and DGP dual). Also, longitudinal studies for the prevalence of CD among patients with metabolic associates of CD such as diabetes mellitus, iron deficiency anemia, osteoporosis, and failure to thrive is worth much consideration.

Conclusion

The availability of serological tests and increased medical awareness has increased requests for the diagnosis of CD. The results showed that serum antiendomysium IgA antibodies is a highly sensitive and specific test for diagnosing CD and that the diagnosis is made mainly by the endocrinologists and gastroenterologists (pediatric or adult), but to a lesser extent by other clinicians. Furthermore, the disease was found to be associated mainly with anemia, gastrointestinal features, type 1 diabetes mellitus, failure to thrive or hypothyroidism and serum EMA.

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