A retrospective audit of endoscopic duodenal biopsies to uncover undetected Coeliac disease in Malaysian patients

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ABSTRACT

Background: Coeliac disease, an autoimmune enteropathy related to gluten sensitivity was hitherto thought to be rare in Asia. Recent data however suggests that Celiac disease may be under-diagnosed in Asia.

Objective: The aim of this audit was to determine the frequency of histological changes compatible with Coeliac disease among patients undergoing elective diagnostic oesaphago-gastro-duodenoscopy (OGDS) under the care of a single practitioner in a Malaysian hospital.

Materials and methods: The archived endoscopically obtained duodenal biopsy specimens of 241 consecutive Malaysian subjects undergoing elective diagnostic (OGDS) were reviewed by a pathologist blinded to the clinical data. Based on intra-epithelial lymphocyte counts, crypt hyperplasia and villous atrophy, each subject was assigned to one of the categories of the Modified Marsh classification for the histological diagnosis of Coeliac disease. The clinical charts of all subjects were reviewed by a single gastroenterologist blinded to the findings of the histological review.

Results: Of the 241 study subjects, 132 (54.8%) were females. There were 56 (23.2%) Malays, 90 (37.3%) Chinese, 88 (36.5%) Indians and seven (2.9%) from the other category. The median age of the study sample was 49 years (range 15-88 years). The OGDS was done as part of screening in 15(6.2%) subjects while in the remaining it was part of the investigation of a clinical problem. Based on histological findings, none of the subjects could be assigned to a modified Marsh class of >1. The prevalence of histological changes compatible with Coeliac disease in the study was 0% (binomial exact one-sided 97.5 % confidence interval 0-1.52%).

Conclusion: In conclusion, this audit provides no evidence that active Coeliac disease is significantly under-detected among symptomatic patients presenting for diagnostic OGDS. The possibility that a significant number may have potential coeliac disease cannot be excluded.

KEYWORDS:
Coeliac disease, prevalence, Malaysia

INTRODUCTION

Coeliac disease is an autoimmune enteropathy with systemic and gastrointestinal manifestations.[1] The primary mechanism is an immune mediated reaction to fractions of wheat protein in genetically predisposed individuals.[1] The condition is diagnosed on the basis of clinical features, serology and small intestinal biopsy. The condition has traditionally been thought to be rare in Asia and indeed that is the prevailing perception among gastroenterologists in Malaysia. Recent data however suggests that Coeliac disease may be under-diagnosed, and placed the global pooled prevalence of serologically determined and biopsy proven Coeliac disease in the general population at 1.4% and 0.7% respectively.[2] A recent seroprevalence study among healthy young adults in Malaysia determined the prevalence of Coeliac disease at 1.25%.[3] There has however been no published histological study on Coeliac disease in Malaysia. Our study essentially reports the results of an audit of all duodenal biopsies undertaken at diagnostic oesaphago-gastro-duodenoscopy (OGDS) by a single gastroenterologist in Pantai Hospital Kuala Lumpur (PHKL), Kuala Lumpur, Malaysia. The objective was to determine the prevalence of histological abnormalities compatible with Coeliac disease in the study sample with a view to test the hypothesis that Coeliac disease is under-diagnosed.

MATERIALS AND METHODS

It was the personal routine practice of the gastroenterologist in PHKL to take mucosal biopsies of the second part of the duodenum in all patients undergoing elective diagnostic oesophago-gastro-duodenoscopy. The rationale for this was that non-specific gastrointestinal symptoms are sometimes due to small intestinal mucosal disease and the availability of a biopsy eliminates the necessity for repeat endoscopy if small intestinal disease was considered a diagnostic possibility at a later stage in the clinical evaluation. Biopsies were not routinely taken if the endoscopy was undertaken as an emergency, if the indication was primarily therapeutic or if the patient was on anticoagulant or antiplatelet drugs. The archived histology slides of the duodenal biopsy specimens of 289 such patients who underwent diagnostic oesophago-gastro-duodenoscopy in 2019 were retrieved and re-examined by a single experienced pathologist who was blinded to the clinical data of the subjects. Two hundred and forty-one of these patients who were Malaysian nationals

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Table I: Frequency of symptoms and anaemia among study subjects.

Clinical feature	Frequency (%)
Abdominal pain, discomfort or dyspepsia.	180 (74.7)
Chronic diarrhoea.	20 (8.3)
Altered bowel pattern not attributable to a specific cause.	25 (10.4)
Symptoms fulfilling criteria for irritable bowel syndrome.	17 (7.1)
Weight loss.	23 (9.5)
Anaemia.	38 (15.8)
Chronic iron deficiency.	10(4.1)

and constituted the study subjects. The subjects were predominantly from in and around the city of Kuala Lumpur. None of the subjects had a prior diagnosis of Coeliac disease nor had any of the subject been given previous instructions to be on a gluten free diet. Endoscopic biopsies were taken using standard pinch biopsy forceps and stored in formalin overnight. The biopsy specimens were embedded in paraffin wax, microtomed and stained with haematoxylin and eosin. The biopsies were scrutinised methodically for intraepithelial lymphocytes (IEL) counts, crypt hyperplasia and villous atrophy. The clinical records were reviewed for details on demographic data, symptom profile and the eventual diagnoses in the study cohort. IEL counts were expressed as more than 30 per 100 enterocytes or less than or equal to 30 per 100 enterocytes. Based on the IEL counts, crypt hyperplasia and villous atrophy each subject was assigned to one of the categories of the Modified Marsh classification for the histological diagnosis of Coeliac disease.[4]

The binomial exact confidence interval for the prevalence of histological features compatible with Coeliac disease was determined using an online statistical calculator (sampsize.sourceforge.net © Phillipe Glaziou 2003-2005). This retrospective observational study was approved by the Hospital Research and Ethics committee.

RESULTS

Of the 241 study subjects, 132 (54.8%) were females. With regard to ethnicity, 56 (23.2%) were Malays, 90 (37.3%) were Chinese, 88 (36.5%) were Indians and seven (2.9%) were others. The median age of the study sample was 49 years (range 15-88 years). The symptom profile and frequency of anaemia in the group is shown in table I. In 6.2% (15/241) of the subjects, OGDS was undertaken as part of screening while in the rest OGDS was undertaken as part of the investigation of a clinical problem.

Only one patient had an IEL count of more than 30 per 100 enterocytes but crypt hyperplasia or villous atrophy was not observed in this particular case. This case was a fifteen-year-old female patient admitted with clinical features suggestive of acute enteritis coupled with a background of recurrent abdominal discomfort and an iron deficiency anaemia. The clinical features were not typical of Coeliac disease and she was negative for anti-tissue transglutaminase and anti-endomysial antibodies. All other patients had an IEL count of less than 30 per 100 enterocytes. One patient had mild villous atrophy with an IEL of less than 30 per 100 enterocytes. This particular patient had a definitive diagnosis of chemotherapy induced acute enterocolitis. Seven other patients had focal crypt hyperplasia with an IEL of less than 30 per 100 enterocytes and no villous atrophy. None of the subjects could therefore be assigned to a modified Marsh class of greater than one. The prevalence of histological changes compatible with Coeliac disease in the sample study was therefore 0% (binomial exact one-sided 97.5 % confidence interval 0-1.52%).

DISCUSSION

The key finding of the current study is that the prevalence of histological changes compatible with Coeliac disease in this sample of Malaysian subjects who underwent diagnostic OGDS for a variety of reasons was 0% with a Binomial exact one tailed 97.5% confidence interval of 0 to 1.52%. It is acknowledged at the outset that there are a number of limitations to this study. The sample size was limited and the demographic profile of the sample reflected the local referral pattern rather than being representative of the general Malaysian population. Furthermore, in the majority of subjects only one or two endoscopic biopsies was taken from the second part of the duodenum. Nonetheless when taken into context with other data, it does permit some insight into the likelihood of Coeliac disease being under-diagnosed locally. The study sample consisted of a symptomatic population that included patients with dyspepsia or abdominal discomfort, weight loss, chronic diarrhoea, and anaemia. Screening for Coeliac among patients with dyspepsia,[5] symptoms of irritable bowel syndrome[6] or iron deficiency anaemia[7] has shown prevalence rates higher than among control subjects. Furthermore, surveys of patients with established Coeliac disease have revealed that between 35 and 77% of patients have at least one gastrointestinal symptom including abdominal discomfort.[8,9] It is therefore not unreasonable to presume that the frequency of histologically defined Coeliac disease in a symptomatic population would be higher than in the general population. This makes the 0% prevalence rate of in the current study all the more significant. The rate in our study is lower than the rates of Coeliac disease reported in similar studies among selected and unselected patients undergoing OGDS and duodenal biopsy in a number of other countries including Canada (2.2%),[10] Romania (2.2%),[11] Northern Ireland (5%),[12] Spain (2.2%),[13] Australia (1.4%),[14] the US (1.8%)[15] and the Netherlands (1.0%).[16] Given the confidence interval of the observed prevalence in our study, it would seem that histologically proven Coeliac disease among our subjects is truly lower than similar studies from elsewhere in the world.

It cannot be discounted that the rate of Coeliac disease in our sample may have been underestimated because only 1-2 biopsies were taken in most subjects as opposed to the

minimum of four biopsies recommended to maximise the detection rate of Coeliac disease.[17] However this limitation was mitigated to some extent by the careful scrutiny for elevated counts of IEL during the histological audit; raised IEL being recognised as a sensitive albeit non-specific marker of Coeliac disease. To put this into perspective, the odds ratio of detecting an elevated IEL count when ≥4 biopsies are taken as opposed to fewer biopsies has been shown to be in the order of 1.24 (95% confidence interval, 95%CI: 1.09, 1.40).[17] Furthermore entirely normal findings have been reported to be unlikely in patients with Coeliac disease.[18] Clearly, larger multicentre prospective studies in which ≥4 duodenal biopsies are taken with concurrent serological testing would be optimum to establish the incidence of Coeliac disease unequivocally.

The limitations of our study notwithstanding, the results do not provide any evidence that Coeliac disease is significantly under-diagnosed at least PHKL. Indeed, the failure to detect any cases is compatible with the general clinical experience of most gastroenterologists in Malaysia who rarely encounter newly diagnosed cases of Coeliac disease among Malaysian subjects. However, the possibility that Coeliac disease is underdiagnosed even by gastroenterologists in Malaysia cannot be entirely excluded as duodenal biopsies and serological markers for Coeliac may be underutilised.

An important question that needs to be addressed is how our results can be reconciled with the relatively high Coeliac seroprevalence rate of 1.25% reported among young healthy Malaysian adults.[3] One explanation is that there may be a significant number of subjects with potential Coeliac in the Malaysian population who do not manifest either the clinical or histological features of Coeliac disease because of insufficient exposure to wheat in their diet. Potential Coeliac disease refers to the condition whereby the subject is seropositive for Coeliac antibodies and HLA DQ2 or DQ8 but does not have either the clinical features or histological features of Coeliac disease.[1] An insight into the possible cause of this discordance between the seroprevalence and histological rates of Coeliac disease can be gained by examining the results of the study by Ramakrishna et al., from India[19] who reported marked differences in the prevalence of Coeliac disease between the North and South of India despite no perceptible regional differences in genetic susceptibility to the condition. The difference in Coeliac disease between the North and South of India was attributed largely to differences in wheat consumption between the regions.[19]

It is also notable that in the recently reported Malaysian seroprevalence study there was no association between seropositivity and gastrointestinal symptoms.[3] The only symptom that was found to be associated with seropositivity was chronic fatigue. This is therefore concordant with the absence of histologically active Coeliac disease in our own cohort of patients with predominantly gastrointestinal symptoms. The implication of our findings taken in conjunction with the previous seroprevalence study is that active case finding of Coeliac disease in Malaysians may have to focus on patients with non-localising symptoms such as chronic fatigue.

In conclusion this audit of duodenal biopsies provides no evidence that active Coeliac disease is being significantly under detected in symptomatic patients presenting for diagnostic oesaphago-gastro-duodenoscopy.

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