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The new entity of adult ultra short coeliac disease: the first international cohort and case-control study

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Background

Ultra-short coeliac disease (USCD) is defined as villous atrophy only present in the duodenal bulb (D1) with concurrent positive coeliac serology. We present the first, multicentre, international study of patients with USCD.

Methods

Patients with USCD were identified from ten tertiary hospitals (six from Europe, two from Asia, one from North America, and one from Australasia) and compared to age and sex matched patients with conventional coeliac disease.

Findings

Patients with USCD (n=137, median age 27 years, IQR: 21-43 years; 73% female) were younger than those with conventional coeliac disease (27 versus 38 years respectively,p<0.001). Immunoglobulin A-tissue transglutaminase (IgA-tTG) titres at index gastroscopy were lower in patients with USCD versus conventional coeliac disease (1.8xULN(IQR:1.1-5.9) vs 12.6xULN(IQR:3.3-18.3),p<0.001).

Patients with USCD had the same number of symptoms overall (median 3 (IQR:2-4) versus 3 (IQR:1-4), p=0.875). Patients with USCD experienced less iron deficiency (41.8% vs 22.4%, p=0.006).

Both USCD and conventional coeliac disease had the same intra-epithelial lymphocytes immunophenotype staining pattern; positive for CD3 and CD8, but not CD4.

At follow up having commenced a gluten free diet (GFD) (median of 1181 days IQR: 440-2160 days) both USCD and the age and sex matched controls experienced a similar reduction in IgA-tTG titres (0.5ULN (IQR:0.2-1.4) versus 0.7ULN (IQR:0.2-2.6), p=0·312). 95.7% of USCD patients reported a clinical improvement in their symptoms.

Interpretation

Patients with USCD are younger, have a similar symptomatic burden and benefit from a GFD. This study endorses the recommendation of D1 sampling as part of the endoscopic coeliac disease diagnostic work-up.

What is already known on this topic

- The first study of ultra-short coeliac disease in adults in 2016 identified patients with villous atrophy confined to the duodenal bulb with positive coeliac serology.
- Systematic review and meta-analyses suggest that taking a duodenal bulb biopsy can increase the diagnostic yield of adult coeliac disease by 8%.
- There are limited further studies and no data on how these patients respond to treatment.

What this study adds

- Our study provides the first international data of patients with ultra-short coeliac disease.
- At presentation adult patients with ultra-short coeliac disease are significantly younger, have a similar symptomatic burden but lower serological titres.
- Adult patients with ultra-short coeliac disease improve both clinically and serologically when on a gluten free diet.

How this study might affect research practice or policy

- Our data supports adherence to undertaking a bulb biopsy.
- Once identified these patients can be treated effectively with a gluten free diet.

Introduction

Coeliac disease is a common autoimmune disorder that affects individuals worldwide, with a global prevalence between 0.7-1.4%.(1) Despite being an increasingly significant global health problem, a significant proportion of individuals with coeliac disease remain undiagnosed (5-76%).(2, 3) There is a global delay in diagnosing coeliac disease which is reported to be between 9.7-13.3 years.(4-6) Furthermore, 5-12.4% of patients have had a previous gastroscopy (where no biopsies were taken) prior to their diagnosis representing a missed opportunity to diagnose coeliac disease.(7, 8) A gluten-free diet (GFD) remains the only treatment, and adherence improves quality of life for the individual and potentially reduces the burden to the health care system.(9, 10)

The conventional form of coeliac disease is characterized by villous atrophy (VA) and crypt hyperplasia in the second part of the duodenal mucosa (D2) with concurrent positive coeliac serology (figure 1).(11) Historical early reports of the value of acquiring biopsies from the duodenal bulb (D1) were disregarded in favour of biopsies from the distal duodenum as it was suggested that histological interpretation was potentially impaired by the presence of Brunner's glands, gastric heterotropia and duodenitis.(12) Ultra-short coeliac disease (USCD) is defined as patients with villous atrophy only present in the duodenal bulb (D1) and concurrent positive coeliac serology (figure 1). This term was coined in 2016 and systematic review and meta-analyses suggest that taking a duodenal bulb biopsy can increase the diagnostic yield of adult coeliac disease by 8%. For paediatric populations, this was shown to be 4% (95% CI: 1 to 9; $P < 0.001$).(12)

Subsequently, the American College of Gastroenterology and British Society of Gastroenterology (BSG) now recommend bulb biopsy as standard practice when an upper endoscopy is undertaken to assess for "suspected coeliac disease/ malabsorption". However, adherence to biopsy protocols is low (37.0-39.5%).(13-16) One reason for this may be a perceived increase in cost or alternatively a perception that a patient with histological changes confined to the bulb may not benefit from a GFD.(7) The value of taking D1 biopsies remains controversial and there is only a single centre study of 26 adult patients from the UK describing the clinical presentation of VA confined to D1.(13, 15-18)

Understanding the phenotype and therapeutic outcomes of patients with USCD is crucial for optimizing diagnostic approaches and treatment strategies, as well as improving overall patient care and long-term health outcomes. There is a paucity of data regarding the phenotype of patients with USCD by comparison to conventional coeliac disease. Furthermore, there is limited data on the benefit of a GFD in patients with USCD. To address this, we present the first, multicentre, international study of patients with USCD.

Methods

The study was proposed after the 19th International Society for the Study of Celiac Disease Conference, Sorrento, October 2022, as an international, multicentre, observational cohort study enrolling all patients with USCD between 2009-2022. Patient data was collected from hospital databases that prospectively record information about patients with coeliac disease. One centre collected information retrospectively from hospital records based on positive histological findings. Ten tertiary coeliac disease centres participated in the study: Sheffield, UK; Caceres, Spain; New York City, USA; Palmerston North, New Zealand; Ankara, Turkey; Bologna, Pavia, Milan and Salerno, Italy; Tehran, Iran.

Patients

Group One: For this cohort study, adult (≥16 years) patients were identified from ten tertiary hospitals between January 2009 and December 2022. Patients were defined as having USCD if they had a combination of positive serological markers (immunoglobulin A-tissue transglutaminase (IgA-tTG) or immunoglobulin A-endomysial antibody (IgA-EMA)) and histologically confirmed VA confined to D1 while on a gluten containing diet. D2 biopsies were architecturally non-diagnostic of coeliac disease (Marsh grade 0-2) and diagnoses were made locally by gastroenterologists with expertise in coeliac disease.

Group Two: For the age and sex matched case-control study, controls were identified from databases of adult patients with coeliac disease diagnosed in each centre. Each age and sex matched control was from the same centre as the patient with USCD. Age and sex matched adult coeliac disease controls were then randomly selected using IBM SPSS Version 27.0 (IBM Corp, New York) case control matching function.

Both USCD and age and sex matched controls had D1 and D2 biopsies.

Data was collected following assessment by a clinician with a special interest in coeliac disease at each centre. Data was reviewed in case notes, endoscopy records and the referral. Data was collected on presenting symptoms, serology at time of presentation (including haemoglobin, vitamin B12, folate, iron, vitamin D, IgA-tTG and IgA-EMA), human leukocyte antigen (HLA) typing and histology of duodenal biopsies. Patients with USCD and the case-control patients were then followed up to determine the effects of a GFD on their serological markers and symptoms. All patients were assessed for commonly occurring symptoms in coeliac disease both at presentation and follow up.

In order to assess for any potential differences between USCD and conventional coeliac disease when specifically considering age and sex at presentation, a further analysis was undertaken comparing all patients with USCD (n=137) to those with conventional coeliac disease from the Sheffield, UK coeliac database (n=434).

Serology

IgA-tTG antibody levels were measured by different ELISA kits (Aeskulisa Diagnostics (Wendelsheim, Germany), ELiA Celikey (Thermo Fisher, Freiburg, Germany), ARUP Laboratories (Utah, USA), QuantaLite (Inova Diagnostics, San Diego, California), Eu-tTG (Eurospital, Italy) and Euroimmune (Luebeck, Germany)). Therefore, levels were standardised using the upper limit of normal (ULN) based on the manufacturer's supplied reference ranges. IgA-EMA was detected by immunofluorescence on primate oesophagus sections (Binding Site, Birmingham, UK). The normal ranges of blood tests differed by centre and therefore to allow for direct comparison, the lower limit of normal (LLN) was used for ferritin, vitamin B12, folic acid and vitamin D based on the manufacturer's supplied reference ranges of each test. All blood tests were complete prior to endoscopy as part of the referral process.

HLA typing was performed for HLA-DQ2 and DQ8 at six centres and full genomic HLA typing at three. One centre did not perform HLA typing (table 1).

Centre	Country	N	Total cohort size	Prevalence (%)	Biopsy policy if suspected coeliac disease		HLA typing	Data storage	Immuno-histochemistry staining		
					D1 biopsy	D2 biopsy			CD3	CD4	CD8
Ankara	Turkey	11	255	4.3	Taken since 2016	Taken	Full genomic	Prospectively collected coeliac database	Yes	No	No
Bologna	Italy	4	100	4.0	Taken since 2015	Taken	DQ2 and DQ8	Prospectively collected coeliac database	Yes	Yes	Yes
Caceres	Spain	9	117	7.7	Taken since 2018	Taken	DQ2 and DQ8	Prospectively collected coeliac database	No	No	No
Columbia	United States of America	9	~650	1.4	Taken since 2010	Taken	Not done	Prospectively collected coeliac database	No	No	No
Milan	Italy	9	~420	2.1	Taken since 2016	Taken	DQ2 and DQ8	Prospectively collected coeliac database	Yes	No	No
Pavia	Italy	4	~480	0.8	Depending on endoscopic appearance	Taken	Full genomic	Prospectively collected coeliac database	Yes	No	Yes
Palmerston North	New Zealand	3	34	8.8	Taken since 2018	Taken	DQ2 and DQ8	Retrospective data collection	No	No	No
Salerno	Italy	3	420	0.7	Depending on endoscopic appearance	Taken	DQ2 and DQ8	Prospectively collected coeliac database	Yes	*	*
Sheffield	United Kingdom	81	1526	5.3	Taken (on dedicated list) since	Taken	Full genomic	Prospectively collected coeliac	Yes	Yes	Yes

					2009			database			
Tehran	Iran	4	2000	0.2	If clinical suspicion	Taken	DQ2 and DQ8	Prospectively collected coeliac database	No	No	No

Table 1: Number of cases of ultra short coeliac disease from each centre
* Denotes staining complete if complicated case ~denotes approximate value

Biopsies and histology

Multiple biopsies were taken in D1 and quadrantic biopsies in D2 and the most severe histological findings used for diagnosis and analysis. The biopsy specimens were first preserved in formalin and then embedded in paraffin wax. Afterwards, they were thinly sliced into sections measuring 3µm in thickness. These sections were subsequently stained using haematoxylin and eosin. Duodenal biopsies were assessed by experienced histopathologists with an interest in gastroenterology. The biopsies were all orientated by experienced biomedical scientists in the histopathology laboratory and three levels were cut from each specimen. This ensured that in at least some of the levels there was full length villi present and the interpreting histopathologists looked for the longest villi that were present in all three levels. Grading was complete using the Modified Marsh criteria: Marsh 1 lesions demonstrated increased intraepithelial lymphocytes (IEL), Marsh 2 lesions demonstrated crypt hyperplasia and Marsh 3 lesions demonstrated villous atrophy.(19)

CD3 antibody was measured using Streptavidin Biotin peroxidase method by automated Ventana Benchmark XT system (Roche, Ventana Medical Systems Inc., Tucson), Clone:LN10: Leica Concentrate and immunohistochemistry anti-human Cd3 Dako or GenScript. CD8 antibody was measured with clone: C8/44B; Dako RTU Link and CD4 with clone:4B12; Dako RTU Link. An average of 2 biopsies were tested for both D1 and D2.

Follow up

Follow up data was collected in each centre based on clinical improvement (Likert scale) divided into four categories: “symptoms worse", “symptoms the same”, “symptoms improved” and “symptoms completely resolved” after clinical assessment as part of routine care. Serological follow up was complete using the blood tests as described above. The length of follow up varied based on the time the patient was known to the centre.

Ethics

All clinical data was anonymised prior to analysis. Patients underwent clinical tests and assessments as part of their routine care. The Sheffield UK Coeliac Research Database was approved by the Yorkshire and the Humber Sheffield Research Ethics Committee,

under registration number 14/YH/1216 renewed 19/YH/0095. The database is used to identify efficiently and comprehensively patients eligible for a specific healthcare intervention in order to help recruitment into trials, and for using routine clinical data to study the course of disease and effectiveness of healthcare used in daily coeliac clinical practice. Where necessary, all data collection was approved locally by research and development/audit departments within the country of collection. The study protocol was approved by the ethical committee of the Research Institute for Gastroenterology and Liver Disease, Shahid Beheshti University of Medical Science Tehran (protocol IR.SBMU.RIGLD.REC.1395.87), the local research committee at Palmerston North Hospital, the Columbia University Irving Medical Center Institutional Review Board (protocol IRB-AAAB0960), the local Institution Review Board of Caceres or the Ethics Committee of IRCCS Pavia, ICS Maugeri, Pavia, Italy (protocol number CE2381).

Statistical analysis

Data handling was complete using Microsoft Excel (2016); statistical analysis was conducted in IBM SPSS Version 27.0 (IBM Corp, New York).

The prevalence of each presenting symptom was compared between cohorts using Chi squared test of two proportions where there was adequate sample size and if not, Fisher's exact test was used.(20) Shapiro-Wilk test was used to assess for Gaussian distribution of continuous data such as age and IgA-tTG titre. Where normally distributed and no outliers, a t-test was used, otherwise the Mann Whitney-U test used. A p value of <0.05 was considered statistically significant.

Role of the funding source

No funding was acquired to complete this study.

Results

When comparing age and sex between individuals diagnosed with conventional coeliac disease (n=434), and USCD, it was observed that those with USCD presented at a younger age (27 years (IQR:21-43 years) versus 38 years (IQR:26-53 years), $p<0.001$) but no difference in sex ratio (66.6% versus 73·7% females respectively, $p=0.12$).

For other comparisons group one patients with USCD (n=137) were compared to group two patients with conventional coeliac disease (n=137) (table 1). Group one patients were referred from primary care, were self-referring, referred from other departments within the same hospital (with symptoms or positive coeliac disease serology) or referred from other hospitals (68%, 19%, 10%, 3% respectively).

Patients with USCD (Group 1) when compared to age and sex matched conventional coeliac disease (Group 2) had the same number of symptoms overall (median 3 (IQR:2-4) versus 3 (IQR:1-4), $p=0.875$).

The most common presenting symptoms for patients with USCD were abdominal pain, diarrhoea and bloating (Table 2). When compared to age and sex matched patients with conventional coeliac disease, patients with USCD had more flatulence (13.1% versus 5.1%, p=0.021). Patients with conventional coeliac disease also demonstrated more iron deficiency (41.8% vs 22.4%, p=0.006). Patients with USCD had higher index ferritin levels than age and sex matched patients with conventional coeliac disease (2.5xLLN (IQR: 1.0x-5.8xLLN) versus 1.2xLLN (IQR: 0.6x-2.7xLLN), p<0.001) though there was no difference in iron deficiency anaemia (p=0.181).

In total, 65.3% of patients had HLA typing complete. More patients with USCD were HLA-DQ2 homozygous than patients with conventional coeliac disease(40.4% versus 25.8%, p=0.038) (Table 2). Patients with USCD also had lower IgA-tTG titres compared to patients with conventional coeliac disease (1.8xULN (IQR:1.1-5.9) versus 12.6xULN (IQR:3.3-18.3), p<0.001). Similarly, a lower proportion of patients with USCD tested positive for IgA-EMA (76.5% versus 89.2%, p=0.043) (Figure 2).

Presenting characteristic	**USCD (n=137)**	**Age & Sex matched (n=137)**	**P value**
Female	73.7%	73.7%	1
Age	27 (IQR:21-43)	27 (IQR:21-43)	1
Abdominal pain	41.6%	32.8%	0.134
Diarrhoea	34.3%	28.5%	0.298
Bloating	34.3%	30.7%	0.519
Fatigue	29.2%	35.8%	0.246
Iron deficiency anaemia	24.8%	32.1%	0.181
Irritable bowel syndrome	17.5%	24.8%	0.139
Constipation	16.1%	8.8%	0.067
Weight loss	13.9%	13.9%	1
Flatulence	13.1%	5.1%	0.021*
Asymptomatic	13.1%	19.9%	0.135
Folate deficiency anaemia	12.4%	17.6%	0.226
Positive family history	10.9%	17.5%	0.12
Nausea	10.9%	8.0%	0.41
Heartburn	10.2%	8.0%	0.529
Low Vitamin D	7.3%	12.4%	0.156
B12 deficiency anaemia	7.3%	11.0%	0.285
Alternating bowel habit	7.3%	4.4%	0.303
Dyspepsia	5.8%	12.4%	0.059
Urgency	4.4%	3.6%	0.758
Osteopenia	3.6%	1.5%	0.224

Vomiting	2.2%	4.4%	0.25
Osteoporosis	2.2%	2.9%	0.5
Dysphagia	0.0%	2.9%	0.061
Median number of symptoms	3 (IQR 2-4)	3 (IQR 1-4)	0.875
HLA-DQ2 heterozygous	53.9%	48.3%	0.453
HLA-DQ2 homozygous	25.8%	40.4%	0.038*
HLA-DQ2/DQ8 heterozygous	7.9%	9.0%	0.787
HLA-DQ8 heterozygous	3.4%	2.2%	0.655
HLA-DQ8 homozygous	5.6%	0.0%	0.059
Other coeliac associated HLA types	3.4%	0.0%	0.246

Table 2: Presentation of patients with ultrashort coeliac disease (USCD) and age and sex matched patients with conventional coeliac disease
*Denotes significance at p<0.05

Biopsy findings

Patients with USCD had a similar number of biopsies taken compared to patients with conventional coeliac disease from D2 (4 (IQR: 4-4) vs 4 (IQR: 4-4), p=0.870) and D1 (2 (IQR: 1-2) vs 2 (IQR: 1-2), p=0.164). In total, 16.8% of patients with USCD had had a previous gastroscopy of which only 45.5% had had a previous D1 biopsy taken. In patients diagnosed with USCD, biopsies from D2 were: histologically normal in 41.6% of cases, Marsh grade 1 in 41.6% of cases and Marsh grade 2 in 16.8% of cases. In the age and sex matched controls, 94.6% had villous atrophy in D1.

The immunophenotype of the intra-epithelial lymphocytes was the same in both D1 and D2 with all the intra-epithelial lymphocytes staining with CD3 and CD8, but not with CD4 (Figure 3).

Follow up

Serological and clinical assessment occurred after a median of 1181 days (IQR: 440-2160 days). Following recommendation of a gluten free diet patients with both USCD and the age and sex matched controls experienced a similar reduction in IgA-tTG titres (0.5ULN (IQR:0.2-1.4) versus 0.7ULN (IQR:0.2-2.6), p=0·312) and similar levels of IgA-EMA positivity (26.9% vs 23.1%, p=0.598) (Figure 2). Levels of vitamin B12, iron, folate and vitamin D all improved after undertaking a gluten free diet (Figure 2). Symptomatic improvement occurred in both patients with USCD and in the age and sex matched controls (95.7% vs 89.1%, p=0.115). In total, 16.1% of patients with USCD had complete resolution of their symptoms, 79.6% reported a partial improvement, 3.2%

reported no change in their symptoms and 1.1% reported symptoms to be worse after following a GFD.

Discussion

This is the first multi-centre international study of USCD. We have demonstrated that patients with USCD are younger than those with conventional coeliac disease and have lower IgA-tTG titres. Despite only having villous atrophy in the duodenal bulb patients with USCD are both symptomatic and derive benefit from a GFD. This study endorses the recommendation of taking samples from D1 as a mandatory component of coeliac disease diagnostic work-up.

A single centre study (n=26) from our centre previously identified patients with USCD as younger and having lower IgA-tTG titres. Furthermore, this work demonstrated that an additional D1 biopsy can increase the diagnostic yield by 9.7%.(17) Despite endorsement from the American College of Gastroenterology and British Society of Gastroenterology the adherence to biopsy protocols in general remains low (37.0-39.5%).(13-16) As a result there remains a global delay in diagnosing coeliac disease between 9.7-13.3 years.(4-6) Of the patients with USCD, 41.6% and 16.8% had Marsh 1 and Marsh 2 lesions in D2 respectively, therefore if only D2 biopsies were taken, these patients may have been incorrectly diagnosed as having potential coeliac disease.(13) The implications for both the patient and the clinical recommendation to follow a GFD are different in 'real world' practice when faced with a patient with potential coeliac disease by comparison to villous atrophy (Marsh 3) confirmed coeliac disease. The BSG guidelines have made no recommendation for the role of a GFD in patients with 'potential coeliac disease'.

Conversely in a prospective randomised controlled study of 23 patients with potential coeliac disease (Marsh grade 1-2, raised intraepithelial lymphocytes only or raised intraepithelial lymphocytes and crypt hyperplasia but no villous atrophy) individuals that were randomised to commence a GFD showed both symptomatic benefit and a reduction in their tTG titres.(21) In this historical study from 2003-2008 none of the patients had a duodenal bulb biopsy. It could be suggested that these patients may have had USCD.

It is perceived that a bulb biopsy strategy may increase healthcare utilisation costs. This may be due to the use of a second histopathology pot (for the bulb biopsy), processing costs and increased pathology reporting time. This may explain some of the reluctance to take biopsies, however adequate duodenal biopsy strategies potentially avoid diagnostic delays for patients with undiagnosed adult coeliac disease and are a cost effective approach in improving the quality adjusted life years of patients with coeliac disease.(22, 23)

It may be possible to place D1 and D2 biopsy samples in the same histopathology pot. A historical paediatric study (n=198) found that 'intraepithelial lymphocytosis was easily recognized in bulb biopsies, and that although the normal villous-to-crypt ratio is lower in the bulb than in the more distal duodenum, significant villous atrophy was usually apparent'. When samples were reviewed by experienced histopathologists, the changes of coeliac disease were still identifiable and the risk of inter-observer variability was low.(24)

We found that patients with conventional coeliac disease were more likely to have iron deficiency than those with USCD, which may correlate with more extensive mucosal inflammation and impaired absorptive capacity of the duodenum in the former. Interestingly, there was no difference in iron deficiency anaemia.

When considering the paediatric population, in a study of 834 paediatric patients diagnosed with coeliac disease, 11% were diagnosed with USCD, these USCD paediatric patients were also found to have lower tissue transglutaminase antibody titres and less iron deficiency than patients with conventional coeliac disease.(25) This suggests that the paediatric and adult USCD cases are similar. This is corroborated by capsule endoscopy studies that demonstrate an association between iron deficiency anaemia, increased age and extent of disease in conventional coeliac disease.(26)

Our study demonstrates that HLA DQ2 homozygosity is more common in conventional CD by comparison to USCD (40.4% versus 25.8% p=0.038). This could suggest that the HLA genotype may have a quantitative relationship between the DQ heterodimer and phenotype. Supporting this a study of seven patients with USCD that found the HLA-DQ2 haplotype to be less common in patients with USCD and no difference in HLA-DQ8 haplotype. (27) However, all these findings are based on small sample sizes and further investigation is required to determine the significance of a possible different HLA haplotype in USCD.

A limitation of this study is that histology samples could be affected by inter-individual variability between histopathologists, however as all histopathologists have a specialist interest in coeliac disease the risk of this is reduced. It is uncertain how this would translate to 'real world' clinical practice beyond centres with an interest in coeliac disease.

Another limitation is the lack of a central reference lab so there was no standardisation between IgA-tTG assays; to address this, the results were evaluated in relation to the upper limit of normal as stated by the manufacturer for each assay. Centres involved have a special interest in coeliac disease and therefore there may be a referral bias.

In conclusion, this is the first multi-centre international study to evaluate the new entity of USCD. Patients with USCD are younger than those with conventional coeliac disease and have lower serological markers of coeliac disease. Despite only having villous atrophy in the duodenal bulb patients with USCD are both symptomatic and

derive benefit from a GFD. This study endorses the recommendation of taking samples from D1 as a mandatory component of coeliac disease diagnostic work-up.

Figure 1: Sub-types of coeliac disease divided by extent of villous atrophy

Figure 2: Comparison of serological markers in coeliac disease at baseline and follow up.

Serological comparisons made between patients with ultra short coeliac disease and age and sex matched controls at baseline and follow up for: (A) Immunoglobulin A – tissue transglutaminase titre, (B) Ferritin, (C) Folate, (D) Vitamin B12, (E) Vitamin D, (F) Immunoglobulin A – endomysial antibody.

Figure 3: Biopsies of D2 and D1 from a patient with ultra short coeliac disease

In the H&E stained sections of D2 (a) there is a normal villous height, no significant crypt hyperplasia but there is an increased number of intra-epithelial lymphocytes. In the H&E stained sections of D1 (e) there is complete villous atrophy, gross crypt hyperplasia and an increased number of intra-epithelial lymphocytes. The immunophenotype of the intra-epithelial lymphocytes is the same in both sites with all the intra-epithelial lymphocytes staining with CD3 (b and f) and CD8 (d and h) but none of them stain with CD4 (c and g)

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