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ORIGINAL ARTICLE

The differential diagnoses for severe enteropathy or severely damaged small intestinal mucosa

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ABSTRACT

Aim: The aim of this study was to explore the aetiology of severe duodenal mucosal abnormality in consecutive patients who underwent gastroscopy and duodenal biopsy over the past 10 years.
Background: A range of differential diagnoses have been reported for severe duodenal architectural distortion.
Methods: Clinical and laboratory data of all the patients with severe duodenal architectural distortion diagnosed at MidCentral District Health Board (DHB), New Zealand were collected and statistically analysed. Ninety-five percent confidence intervals (CI) are shown.
Results: Between September 2009 and April 2019, 229 patients were diagnosed with severe enteropathy. The median patient age was 41 years (range 6-83 years). Two hundred and twenty-four of these patients (97.8%, 95.0-99.3%) were diagnosed with coeliac disease (CeD), with one of these patients having gluten induced T-cell lymphoma. From the remaining five patients, one had a diagnosis of tropical sprue and four did not have a clear aetiology. There were 180 patients from 191 (94.2%, 89.9-97.1%) with at least one positive coeliac marker, all with a diagnosis of CeD. Eleven patients (5.8% of 191, 2.9-10.1%) had negative markers for both tissue transglutaminase IgA (tTG-IgA) and IgA-endomysial antibodies (EMA-IgA) with six having a diagnosis of seronegative CeD.
Conclusion: Although the spectrum of histological changes in CeD may range from normal to a flat mucosa, severe duodenal architectural distortion seems to occur mainly in CeD. Idiopathic enteropathy was recorded as the second but by far less frequent presentation of severe enteropathy. This study highlights that infection and other aetiologies are rarely implicated in severe enteropathy, with one case (0.4%) of refractory CeD/T-cell lymphoma.

Keywords: Coeliac disease, Differentials, Severe enteropathy, Histology.

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Introduction

The mucosal changes seen in coeliac disease (CeD) are a result of the intestinal immune reaction to the gliadin and glutenin proteins (1). There is infiltration of the lamina propria and epithelium with chronic inflammatory cells resulting in a spectrum of mucosal changes from mild to severe enteropathy with complete loss of villi, enhanced epithelial apoptosis, and crypt hyperplasia. Endoscopic features of CeD include flattening of mucosa with loss of duodenal folds, visible fissures, nodularity, scalloping, and prominent submucosal vascularity (2). One or two biopsies from first part and four from second part of the duodenum are recommended to confirm a CeD diagnosis. There is a gradient of decreasing histological changes seen from the proximal to distal small intestine (3, 4). The histological changes can be graded using the Marsh classification (5, 6). It is important to note that the degree of histological changes does not necessarily correlate with the severity of symptoms or degree of malabsorption (7).

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A diagnosis of CeD can be made based on positive serological and histological changes ranging from Marsh 0 to III (8). Diagnosis without a biopsy can be considered for children and a subgroup of young adults with a very high tissue transglutaminase IgA (tTG-IgA) (10 times the upper limit of normal) and symptoms of CeD (9, 10).

The histological findings seen in CeD can often be confused with other pathologies, including food allergies such as cow's milk allergy, inflammatory bowel disease, tropical sprue, eosinophilic duodenitis, and drugs (angiotensin receptor blockers, chemotherapy), as outlined in the Paris consensus (11).

There are primary enteropathies of the newborn which can also mimic CeD. These include microvillous inclusion disease, tufting enteropathy, IPEX (immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome) syndrome, dyskeratosis congenita, trichohepatoenteric syndrome 1, tetratricopeptide repeat domain 7A (TTC7A) deficiency, Unc-45 myosin chaperone A (UNC45A) deficiency, and neonatal inflammatory skin and bowel disease-1 (NISBD1) (12).

Infections can also be responsible for the histological changes; these include viral gastroenteritis, giardiasis, Whipple's disease, and opportunistic infections in HIV patients such as microsporidiosis, cyclopsporidiosis, isosporiasis, cryptosporidiosis, Mycobacterium and Cytomegalovirus infection, cryptococcosis, and visceral leishmaniasis (13-17). The spectrum of diseases less commonly responsible for these histological changes include AIDS enteropathy, common variable immunodeficiency, autoimmune enteropathy, enteropathy-type intestinal T-cell lymphoma, immunoproliferative small intestine disease, and CD4 T-cell lymphoproliferative disorders (13-17). These differential diagnoses are summarised below in Table 1.

The aim of this study was to assess the aetiology of severe architectural distortion in small bowel mucosa.

Methods

The main hospital in MidCentral District Health Board (DHB), Manawatu, New Zealand is Palmerston North Hospital. This is a secondary care hospital with 350 beds which serves an urban population of 75,000 and a total catchment population of 172,000, increasing to 500,000 for the delivery of some tertiary services, including coeliac disease. This study was approved by the research committee at MidCentral DHB.

Medlab Central (the pathology laboratory providing services to MidCentral DHB) performed a database search of all duodenal histology results available from 1 July 2009 to 26 May 2019. This identified 229 patients with Marsh III histology who constituted the study subjects. We performed a retrospective review of their medical records using Central Region Clinical Portal (created by Orion Health, in use since 2011) and Eclair (version 7.5.1 created by Sysmex, for histology predating 2011). Inclusion criteria were male or female patients of any age with duodenal biopsy reports available demonstrating Marsh III histology with an assigned diagnosis. Exclusion criteria were histology less severe than Marsh III, abnormal histology without a diagnosis and absence of antibodies; there were eleven such patients. Two additional patients were removed as no data was available leaving a total of 229 in the study.

Data was collected for each individual where available for demographics, symptoms, diagnosis, year of diagnosis, serological markers (albumin, C-reactive protein (CRP), ferritin, folate, vitamin B12, bilirubin, alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), IgA anti-endomysial antibodies (EMA-IgA), tTG-IgA, endoscopic appearance of the stomach and duodenum, and histology report. The histology, was assessed according to the original Marsh classification (I-III) (18). We calculated 95% confidence intervals for the data using R version 4.2.0.

Results

Demographics

There were 229 patients in the study, 153 (66.8%) were female and 76 (33.2%) were male (see Table 2). The median age of the patients was 41 years (range 6-83 years). Eight patients (3.5%, 1.5-6.8%) had biopsies under the age of 10, 94 patients (41.1%, 34.6-47.7%) were biopsied between age 10 and 40, and 127 patients (55.5%, 48.8-62.0%) were biopsied at age 40 or above.

Table 1. Supporting features for the differential diagnoses of villous flattening.

Differential diagnosis	Increased intraepithelial T-lymphocytes	Flat intestinal villi	Supporting features
Infectious diseases			
Parasitic infections (e.g. *Giardia*)	Rare	Rare	Identification of parasite Clinical response to course of antibiotics and anthelmintics Increased eosinophils in lamina propria
Tropical sprue	Yes	Mild degree	Travel history to tropical countries (especially South Asia, Southeast Asia, Africa and South America falling within the tropics) for at least 2 months in poor hygienic conditions
Bacterial overgrowth	Yes	Variable degree	Positive H2-glucose breath test, duodenal or jejunal aspirate and culture
Whipple disease	Rare	Yes	PAS-positive macrophages in lamina propria Positive PCR for *Tropheryma whipplei*
Viral gastroenteritis	Yes	Variable degree	Mucosal recovery after infection resolved
Opportunistic infections in HIV* patients (microsporidiosis, cyclopsporidiosis, isosporiasis, cryptosporidiosis, *Mycobacterium*, *Cytomegalovirus*, *Cryptococcosis*, and visceral leishmaniasis)	Possible	Variable degree	Known history of HIV/AIDS Identification of causative organism
Medications			
ARBs† e.g. Olmersartan	Possible	Variable degree	Neutrophilic infiltration in lamina propria; deposition of subepithelial collagen; crypt apoptosis
Chemotherapy agents	Rare	Possible	Suggestive oncological history Crypt architectural distortion; neutrophilic infiltration in lamina propria; crypt apoptosis; involvement of other gastrointestinal tracts
Other more common causes			
Collagenous sprue	Possible	Yes	Subepithelial collagen deposition (usually >20μm)
Crohn's disease and ulcerative colitis	Rare	Rare, patchy	Ulcerations, neutrophilic inflammation; crypt distortion; microgranulomas; basal plasmacytosis; ileal and colonic involvement
Eosinophilic gastroenteritis and food allergies	Possible	Mild degree	History of atopy and allergies Eosinophilic infiltration in lamina propria; involvement of other gastrointestinal tracts
Rare causes			
Autoimmune enteropathy	Possible	Variable degree	IgA/IgG positive enterocyte antibodies of jejunum History of associated autoimmune conditions Clinical response to immunosuppression Deep crypt lymphocytosis and/or plasma cell infiltrate, neutrophilic cryptitis +/- crypt micro-abscesses and reduced Paneth cells on duodenal histology
Common variable immunodeficiency	Yes	Variable degree	Diagnosis of primary common variable immunodeficiency Exclusion of Giardia lamblia infection
AIDS‡ enteropathy	Yes	Variable degree	Known history of AIDS, presence of opportunistic infections Duodenal biopsies show reduced $CD4^+$ T cells and increased $CD8^+$ T cells
Enteropathy-type intestinal T-cell lymphoma	Yes	Variable degree	Aberrant T cell population on immunohistochemistry or flow cytometry with TCR monoclonality on PCR
Immunoproliferative small intestine disease	Yes	Variable degree	Plasmacytic infiltrate of $CD20^+$ B cells and plasma cells expressing alpha heavy chain but no light chains
$CD4^+$ T-cell lymphoproliferative disorders	Yes	Variable degree	Immunohistochemistry showing diffuse infiltration of the epithelium/lamina propria by small/medium $CD3^+CD4^+$ T cells and presence of monoclonal rearrangement for beta-TCR and/or gamma-TCR on duodenal biopsies or increased presence on flow cytometry

* Human immunodeficiency virus
† Angiotensin II receptor blockers
‡ Acquired immune deficiency syndrome

Continued			
Enteropathies of the newborn			
Microvillous inclusion disease	No	Yes	Microvillous inclusions in enterocytes and colonocytes on transmission electron microscopy; positive CD10/villin stain
Tufting enteropathy	Possible	Variable	Presence of focal epithelial "tufts" made of closely packed enterocytes with rounding of the apical plasma membrane; positive MOC31 stain
IPEX syndrome	Yes	Yes	Forkhead box P3 (FOXP3) gene mutation
Dyskeratosis congenita	Yes	Yes	Pathogenic gene variant of telomere
Trichohepatoenteric syndrome 1	No	Yes	Liver disease, immune defects, facial dysmorphism, abnormal hair
TTC7A deficiency	No	Yes	Intestinal atresia, underlying severe combined immunodeficiency
UNC45A deficiency	No	Yes	Impaired hearing, bone fragility Microvillous inclusions on electron microscopy; positive CD10/villin stain
Neonatal inflammatory skin and bowel disease-1 (NISBD1)	No	Yes	Neonatal onset of severe skin rash, diarrhoea and recurrent infections

Table 2. Characteristics of patients undergoing endoscopy and duodenal biopsy.

	Number	Percent (95% CI)
Sex		
Males	76	33.2
Females	153	66.8
Age (years)		
Median	41	
Range	6-83	
<10	8	3.5
10-40	94	41.1
≥40	127	55.5
Indication		
Abdominal pain	58	33.3 (26.4-40.9)
Diarrhoea	43	24.7 (18.5-31.8)
Anaemia	27	15.5 (10.5-21.8)
Bloating	12	6.9 (3.6-11.7)
Weight loss or poor weight gain	11	6.3 (3.2-11.0)
Constipation	10	5.8 (2.8-10.3)
Other*	9	5.2 (2.4-9.6)
Fatigue	4	2.3 (0.6-5.8)

* Includes rash, erythema nodosum, dysphagia, gastrointestinal bleeding.

Symptoms profile

Forty-three patients (24.7%, 18.5-31.8%) presented for endoscopic biopsy due to diarrhoea while ten patients (5.8%, 2.8-10.3%) had constipation. Fifty-eight patients (33.3%, 26.4-40.9%) were suffering from abdominal pain with a further 12 patients (6.9%, 3.6-11.7%) experiencing bloating. Four patients (2.3%, 0.6-5.8%) were troubled by fatigue while weight loss or poor weight gain was the presenting symptom in 11 patients (6.3%, 3.2-11.0%). Twenty-seven patients (15.5%, 10.5-21.8%) experienced anaemia prior to endoscopic biopsy. Nine patients (5.2%, 2.4-9.6%) had other reasons for being offered an endoscopy, these included four patients suspected for inflammatory bowel disease and a rash, erythema nodosum, one patient experiencing dysphagia and three patients having had gastrointestinal bleeding.

Diagnosis

Two hundred and twenty-four patients (97.8%, 95.0-99.3%) out of the 229 had a diagnosis of CeD (including six with seronegative CeD), with one of these patients having gluten induced T-cell lymphoma. Of the five patients with non-coeliac enteropathy, one had a diagnosis of tropical sprue whilst the remaining four did not have a clear aetiology.

Serological markers and histology

Not all cases had available data (Table 3). One hundred and eighty (94.2% of 191, 88.9-97.1%) cases with available data had at least one coeliac marker testing positive and were all diagnosed with CeD. Eleven (5.8% of 191, 2.9-10.1%) had negative markers for both tTG-IgA and EMA-IgA with six having a diagnosis of seronegative CeD, one tropical sprue and four with unclear diagnoses. None of the 11 patients with negative markers were tested for HLA DQ2 or DQ8. Three cases with markers (1.5%, 0.3-4.4%) had a negative tTG-IgA but no record of EMA-IgA and 35 (15.3% of all cases, 10.9-20.6%) had neither coeliac marker tested.

Ferritin was found to be low in 92 patients (50.6% of 182, 43.0-58.0%), all had CeD. Another 90 patients (49.5% of 182, 42.0-57.0%) had normal ferritin levels and 47 patients (20.5%) had no ferritin recorded. Folate was found to be low in fourteen patients (12.7% of 110, 7.1-20.4%), all had CeD. Another 96 patients (87.3% of 110, 79.6-92.9%) had normal folate levels and 119 patients (52.0%) had no folate recorded. Fourteen patients (9.8% of 143, 5.5-15.9%) had low vitamin B12, all had CeD. Vitamin B12 levels were normal in 129 patients (90.2% of 143, 84.1-94.5%) and 86 patients (37.6%) had no vitamin B12 recorded. Five patients (3.0% of 165, 1.0-6.9%) had a low albumin, all had CeD. A further 160 patients (97.0% of 165, 93.1-99.0%) had normal albumin and 64 patients (38.8%) had no albumin recorded. Twenty-four patients (17.8% of 135, 11.7-25.3%) had an elevated CRP, all had CeD. There were 111 patients (82.2% of 135, 74.7-88.3%) with normal CRP and 94 patients (41.0%) had no CRP recorded. Fifty-three patients (30.8% of 172, 24.0-38.3%) had an elevated ALT or AST, all were CeD apart from two with an unclear diagnosis. One hundred and nineteen patients (69.2% of 172, 61.7-76.0%) had normal enzymes while 57 patients (33.1%) had no liver enzymes recorded. Table 3 further details the comparison between CeD and non-CeD for these serologies.

All two hundred and twenty-nine patients had Marsh III histology. Two hundred and twenty-four of these patients (97.8%, 95.0-99.3%) were diagnosed with CeD, with one of these patients having gluten induced T-cell lymphoma. From the remaining five patients, one had a diagnosis of tropical sprue and four did not have a clear aetiology.

Table 3. Serological abnormalities seen in coeliac disease compared with non-coeliac disease.

	Coeliac disease (N = 224)		Non-Coeliac disease (N = 5)		Total (N = 229)	
Abnormality	Data available	Abnormal (%, 95% CI)	Data available	Abnormal (%, 95% CI)	Data available	Abnormal (%, 95% CI)
Coeliac marker (tTG-IgA or EMA-IgA)	186	180 (96.8, 93.1-98.8)*	5	0 (0-52.2)	191	180 (94.2, 89.9-97.1)
Iron	178	92 (51.7, 44.1-59.2)	4	0 (0, 0-60.2)	182	92 (50.5, 43.1-58.0)
Folate	105	14 (13.3, 7.5-21.4)	5	0 (0, 0-52.2)	110	14 (12.7, 7.1-20.4)
Vitamin B12	138	14 (10.1, 5.7-16.4)	5	0 (0, 0-52.2)	143	14 (9.8, 5.5-15.9)
Albumin	160	5 (3.1, 1.0-7.1)	5	0 (0, 0-52.2)	165	5 (3.0, 1.0-6.9)
CRP	133	24 (18.1, 11.9-25.7)	2	0 (0, 0-84.2)	135	24 (17.8, 11.7-25.3)
ALT/AST	167	51 (30.5, 23.7-38.1)	5	2 (40.0, 5.3-85.3)	172	53 (30.8, 24.0-38.3)

* Excludes the six patients with seronegative CeD.

Discussion

Severe enteropathy has been a matter of debate with a range of differential diagnoses in current literature. Despite a broad range of differential diagnoses for severe distortion in small intestinal architecture, in this retrospective study we demonstrate that CeD is the underlying condition in most patients (224 of 229 patients, 97.8%, 95.0-99.3%) with severe enteropathy. The patient with dual pathology of CeD and T-cell lymphoma was a 65-year-old male who had an endoscopy for gastrointestinal bleeding. The gluten induced T-cell lymphoma diagnosis was based on histological markers. This finding reassuringly suggests that malignant transformation in CeD is rare and the prevalence of refractory CeD/T-cell lymphoma was only 1/229 (0.4%), one of 224 CeD cases with severe enteropathy.

Of the five remaining patients, a 50-year-old male had a diagnosis of tropical sprue and four had idiopathic enteropathy with negative serology. The patient with tropical sprue had negative coeliac serology and received an endoscopy to investigate abdominal pain and the histology improved following antibiotic treatment. If tropical sprue causes severe enteropathy, one may argue that similar degrees of enteropathy may occur in other small bowel infections like in cases with H. pylori, Giardia or small intestinal bacterial overgrowth. However, severe enteropathy is rarely seen in these patients.

Our findings from this study are consistent with most reported studies in existing literature. For instance, an Italian study by Schiepatti et al found that 94.9% of patients with flat villi had underlying CeD. The remaining 5.1% of patients were found to have common variable immunodeficiency, intestinal lymphoma, unclassified sprue, and Olmesartan-associated enteropathy (19). In contrast, few studies report non-coeliac enteropathies could cause a similar degree of architectural distortion in the small intestine as seen in CeD. The rarity of these non-coeliac enteropathies means that CeD is by far the most common aetiology behind the severe enteropathy (20). Having said that, the degrees of enteropathy rarely have a major clinical significance as often it is not correlated with clinical presentation (7). Nevertheless, we are unsure about the mechanism behind the variable histological spectrum in different conditions. Gluten induced enteropathy is triggered by immune reaction and chronic inflammation that may affect the microstructure of intestinal villi long-term and infection usually affects the lamina propria with involvement in full thickness of small bowel only on occasion. This is a possible explanation that might explain the variable changes in small intestine in infection versus inflammation.

A study conducted by DeGaetani et al over a ten-year period found seronegative CeD to be the most common explanation for idiopathic enteropathy with negative serology. This was followed by medication-induced enteropathy and unclassified sprue (21). The majority of patients with unclassified sprue reported symptomatic improvement with immunosuppressive therapy. Our study had six patients with seronegative CeD, all having Marsh III histology. There were a further four patients with idiopathic enteropathy with negative serology, none of which were tested for HLA DQ2/8 alleles.

Primary enteropathy of newborns encompass a broad range of diseases. None of the diseases identified in Table 1 were thought to be responsible for the histology seen in the younger patients from this study. It would be interesting to review the records more thoroughly for the younger patients to ascertain whether there was a response to a gluten-free diet.

There were some potential limitations to our study, in addition to those that are standard for retrospective studies. First, this study is limited by selection bias due to patients having incomplete data available for analysis with some missing multiple variables. Second, HLA DQ2/8 gene testing was not available for the four patients with idiopathic enteropathy with negative serology.

Conclusion

In conclusion, this study has shown that CeD is by far the most common aetiology behind severely damaged small intestinal mucosal changes. In most susceptible individuals, CeD causes Marsh III histological changes and other differential diagnosis for severe enteropathy were rare in our retrospective experience. Finally, it was important to note that CeD is for most a benign condition with refractory or malignant transformation being rare (0.4%) in patients

with severe enteropathy. We however acknowledge that we did not investigate the prevalence of refractory CeD in milder degrees of enteropathy.

Conflict of interests

The authors declare that there is no conflict of interest.

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