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Non celiac Enteropathies : A Clinical and Pathological Insight beyond Serology -An observational study in adults over 18 years in Rajasthan

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Research Article

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The authors declare no competing interests.

We hereby declare that the patients and/or their relatives/guardians gave consent to participate in this study. It is also stated that they have been informed about this study to be of academic nature only and it will not harm them in anyway.

Non celiac Enteropathies: A Clinical and Pathological Insight beyond Serology -An observational study in adults over 18 years in Rajasthan

Abstract: 250 words

Background & objectives: Non celiac enteropathies are a heterogenous group of diseases that mimics celiac disease both clinically and histologically. It encompass a wide range of etiologies. This article aims to provide a comprehensive clinical and pathological insight into non-celiac enteropathies presenting with celiac-like morphology and discordant serology, highlighting the diverse etiologies, diagnostic challenges, and implications for patient care.

Methods: 200 patients with chronic diarrhea (>4 weeks), steatorrhea, documented weight loss (>5% over 3–6 months), unexplained iron deficiency or megaloblastic anemia, hypoalbuminemia without hepatic or renal cause, vitamin deficiencies (including B12 and fat-soluble vitamins), or recurrent abdominal pain associated with diarrhea and systemic features were enrolled. Upper GI endoscopy followed by duodenal biopsy done and sections reported as per proforma and graded as per Modified Marsh system. A diagnostic algorithm followed to interpret endoscopy, biopsy and clinical findings.

Results: Mean age of participants was 37.3 ± 15.1 years, with a male predominance (62.5%). Marsh grade 1, 2, 3a, 3b and 3c were 10%, 9%, 51%, 15% and 15% respectively with negative serology while true celiac disease was seen in 34.5% cases.. The various etiologies found were Alcoholism (10%), NSAID (10%), Olmesartan (9%), H. Pylori (7.5%), Giardiasis (5%), Tropical sprue (1%), HIV (1.5%), azathioprine (1.5%), IBD (1%), peptic duodenitis (4%), Megaloblastic anemia (1.5%), cow milk (2.5%) and soy protein allergy (1.5%).

Interpretation & conclusions: Celiac-like histological features are not disease-specific and may reflect diverse underlying pathologies. So diagnosis should not rely solely on histology or serology but instead require a comprehensive approach incorporating dietary history, medication review, targeted infectious work-up, immunological testing, and, where relevant, therapeutic trials.

Key words: Non-celiac enteropathy (NCE), Celiac like morphology, Duodenal biopsy, Autoimmune enteropathy, Intraepithelial lymphocytosis, Villous atrophy.

Introduction

Non-celiac enteropathies (NCEs) constitute a heterogeneous group of disorders that closely mimic celiac disease (CD) clinically and histopathologically, but lack the hallmark serological and genetic markers of CD[1]. Classical celiac disease is an autoimmune disorder triggered by gluten in genetically predisposed individuals carrying HLA-DQ2 or DQ8, manifesting histologically as villous atrophy, crypt hyperplasia, and intraepithelial lymphocytosis (IELs) on duodenal biopsy, typically supported by positive anti-tissue transglutaminase (anti-TTG IgA) serology[1] and response on gluten free diet.

Non-Celiac Enteropathy (NCE) was diagnosed in adults with histologically confirmed intra-epithelial lymphocytosis with or without crypt hyperplasia and with or without varying degrees of villous atrophy (Marsh 1 to 3) on duodenal biopsy, negative celiac serology (anti-tTG IgA with normal total IgA and/or EMA), exclusion of celiac disease based on lack of serological and clinical response to gluten restriction where applicable. It encompasses a wide spectrum of causes, including infectious agents, drug-induced enteropathies, Immune-mediated conditions and early neoplastic or inflammatory processes including enteropathy-associated T-cell lymphoma (EATL), Crohn's disease, and HIV enteropathy[2-5].

Globally, prevalence of biopsy-proven CD ranges from 0.5% to 1%, the true burden of NCEs remains undefined due to under-recognition, variable diagnostic criteria, and overlapping clinical features[2]. In India, CD prevalence is highest in northern regions such as Punjab, Haryana, Delhi, and Rajasthan—areas with high gluten consumption[3]. In regions like Western Rajasthan, the combination of high gluten intake and endemic parasitic infections results in a considerable proportion of patients displaying celiac-like morphology without fulfilling serological or clinical criteria for CD, highlighting the likelihood of underdiagnosed NCEs[4,].

Accurate differentiation between CD and NCEs is clinically critical, as misclassification can lead to inappropriate long-term gluten-free diets and delay targeted treatment for infectious, drug-

induced, or immune-mediated enteropathies[5]. Hence, we need a systematic evaluation of seronegative villous atrophy in Indian adults to delineate the etiological spectrum of NCEs.

This article aims to provide a comprehensive clinical and pathological insight into non-celiac enteropathies presenting with celiac-like morphology and discordant serology, highlighting the diverse etiologies, diagnostic challenges, and implications for patient care.

Methods

Adults (>18 years) presenting with clinical features suggestive of small intestinal pathology were included, such as chronic diarrhea (>4 weeks), steatorrhea, documented weight loss (>5% over 3–6 months), unexplained iron deficiency or megaloblastic anemia, hypoalbuminemia without hepatic or renal cause, vitamin deficiencies (including B12 and fat-soluble vitamins), or recurrent abdominal pain associated with diarrhea and systemic features. Patients also required endoscopic suspicion of small bowel mucosal abnormality, histologically confirmed intra-epithelial lymphocytosis, with or without crypt hyperplasia with or without villous atrophy on duodenal biopsy, and negative celiac serology (anti-tTG IgA with normal total IgA where applicable) were included. Patients of age <18 years, inadequate or poorly preserved biopsy specimens, neoplastic lesions on histology, or endoscopic villous scalloping without histological atrophy were excluded from the study. A sequential sampling technique was employed, and all eligible patients were consecutively enrolled until the target sample size was achieved. Study was conducted from December 2024 to October 2025.

This was a hospital-based observational descriptive study. All consecutive adult patients (>18 years) fulfilling the predefined inclusion criteria during the study period were included. No formal sample size calculation was performed, as the study aimed to describe the clinicopathological spectrum of non-celiac enteropathies rather than estimate population prevalence.

All procedures were performed using the Olympus 190 UGI endoscope, with patients kept nil by mouth for 6 hours. Lignocaine spray used for local anesthesia. At the time of endoscopy, most patients were provisionally evaluated for suspected malabsorption syndrome or possible celiac disease based on clinical presentation. On upper gastrointestinal endoscopy, the predominant finding was scalloping of folds in the second part of the duodenum (D2). No other consistent macroscopic abnormalities were documented. Biopsies were obtained from the second part of the duodenum (D2) and, where villous atrophy was suspected, additional samples were taken from the duodenal bulb (D1) at the 9 and 12 o'clock positions. At least four well-oriented fragments were collected whenever possible to maximize histological accuracy[6].

Algorithm followed and basic investigations done are mentioned in flow diag.

Sections from formalin fixed paraffin embedded tissue were cut at 4 μm to ensure reliable intraepithelial lymphocyte (IEL) counts. Well-oriented mucosal fragments defined as 3–4 consecutive villi aligned perpendicularly over muscularis mucosae, with clearly visible villi from base to tip were used for reporting. Fragments with transversely sectioned crypts were avoided for interpretation. Only biopsy specimens deemed adequate for histopathological assessment (minimum four well-oriented mucosal fragments) were included. Inadequate or non-diagnostic biopsies were not entered into the study dataset and were therefore not included in screening or analysis. IELs were counted in at least 5 oriented villi, counting started from tip of villous and then going down on both side, focusing on the upper one-third of the villous, (10 enterocytes per side), yielding IELs per 20 ECs and then followed same for at least five villi and calculated per 100 enterocytes. The cutoff of ≥30 IELs/100 enterocytes was taken to minimize over-diagnosis in infection-prone populations[7]. Histological grading of duodenal biopsies was performed according to the Modified Marsh classification. Marsh 0 indicates normal mucosa; Marsh 1 shows increased intraepithelial lymphocytes (>30 per 100 enterocytes); Marsh 2 includes crypt hyperplasia in addition to intraepithelial lymphocytosis; and Marsh 3 denotes varying degrees of villous atrophy in terms of Crypt-to-villous height ratio.

Crypt-to-villous height ratios (Cd:Vh) were assessed on 4–5 axes, and villous atrophy was graded using modified Marsh criteria. Grade 3a: Vh < normal but still > Cd (Cd:Vh <1:3 but >1:1); Grade 3b: Cd = Vh (Cd:Vh = 1:1); Grade 3c: Cd > Vh (Cd:Vh ≥ 1:1). In healthy Indian

adults, the normal Cd:Vh ratio is approximately 1:3 to 1:5. Distribution of IEL's was called "Crescendo" if IEL's were present predominantly at villous tip, while "Decrescendo pattern" if IEL's were concentrated at the base of villous. Additional features such as lamina propria inflammation, eosinophilia, basement membrane thickening, and parasites when present were also noted[8-9].

In patients with negative anti-tTG IgA but significant villous atrophy, total serum IgA levels were evaluated to exclude selective IgA deficiency (Fig 1). In cases of low IgA, alternative serological assessment like EMA (Anti endomysial antibody), DGP (IgG) (Deamidated gliadin peptide antibodies, and anti-tTG IgG were done and detailed clinicopathological correlation were undertaken before excluding celiac disease. The possibility of overlapping or dual etiologies was also considered during final diagnostic classification.

Histology was reported using a structured proforma.(Annexure 1) Data were compiled in Microsoft Excel and analyzed with IBM SPSS Statistics version 26 (IBM Corp., Armonk, NY, USA). Continuous variables were summarized as means/medians, categorical variables as percentages. Associations were tested using Chi-square or Fisher's exact test, with $p < 0.05$ considered significant.

In patients with villous atrophy and negative celiac serology, a supervised trial of gluten-free diet was advised and follow-up assessment was performed after initiation of etiology specific treatment to evaluate symptomatic response before final categorization.

The study was approved by the Institutional Ethics Committee of Dr. S.N. Medical College, Jodhpur (IEC No. SNMC/IEC/2024/989). Archival biopsy samples and anonymized clinical data were used to maintain patient confidentiality.

Results

This cross-sectional study included 200 adults from Western Rajasthan who underwent duodenal biopsy for celiac-like symptoms. The aim was to evaluate the spectrum of Non-celiac enteropathies (NCEs) presenting with celiac-like morphology (CLM).

The mean age of participants was 37.3 ± 15.1 years, with a male predominance (62.5%). Patients presentation and symptoms frequencies mentioned in Table 1. These findings highlight the systemic, non-classical presentation of duodenal mucosal injury in this cohort.

All biopsies demonstrated increased intraepithelial lymphocytes, while crypt hyperplasia was observed in 90%. Villous atrophy was present in 81% of cases: partial (Marsh 3a) in 51%, subtotal (3b) (Fig 2) in 15%, and total (3c) (Fig 3) in 15% (Table 1). Earlier stages—Marsh 1 (10%) and Marsh 2 (9%)—were less common, suggesting that most patients presented with advanced mucosal damage.

Mean hemoglobin levels declined progressively with worsening Marsh grade ($p < 0.001$). Hb was highest in Marsh 1 (11.8 ± 1.4 g/dL) and lowest in Marsh 3c (10.1 ± 0.5 g/dL), consistent with worsening malabsorption and micronutrient deficiency in advanced disease (Table 1).

Anti-TTG antibodies were positive in 69 patients (34.5%). These cases were labelled as Celiac disease and were excluded from further statistical analysis as this study aims to talk about Non-celiac enteropathies. Seropositivity correlated strongly with higher Marsh grades ($p < 0.013$), being most frequent in Marsh 3c (30/30) followed by 3b (20/30). In contrast, the majority of Marsh 3a and lower grades were seronegative, underscoring the diagnostic limitations of serology in early or atypical presentations (Table 2).

Overall, an etiological diagnosis was established in 163 of 200 patients (81.5%). Among the 131 seronegative patients, 94 (71.8%) had alternative causes. In 27 patients (13.5%), no specific or definite etiology could be identified despite extensive evaluation, representing unexplained NCEs (Table 3). These cases showed only mildly increased chronic inflammatory infiltrate in lamina.

Certain differences were observed between true celiac disease and Non-Celiac Enteropathies (NCE). Clinically, patients with NCE more frequently presented with chronic diarrhea without classical features of nutritional deficiency, and some had identifiable secondary causes such as infection or drug exposure. Histologically, although celiac-like morphology was noted, NCE cases often showed patchy villous blunting, variable intraepithelial lymphocytosis,

absence of uniform crypt hyperplasia in some cases, and additional features such as neutrophilic infiltration or granulomatous inflammation depending on the underlying etiology.

DISCUSSION:

The present study evaluated non-celiac enteropathies (NCEs) presenting with celiac-like morphology (CLM) on duodenal biopsy. The objective was to identify alternative etiologies mimicking celiac disease and to highlight the limitations of anti-TTG serology in diagnosis. By integrating histopathological, serological, and clinical data, the study emphasizes the diagnostic challenges in differentiating true celiac disease from its mimickers.

Celiac disease is an autoimmune disease characterized by sensitivity to gluten, which in genetically susceptible individual (HLA-DQ2 & HLA-DQ8 positive) triggers an inflammatory response which results in Intra-epithelial and lamina inflammation and varying degrees of villous atrophy[10]. Adults with the disease present with abdominal pain and diarrhea, sometimes with extra-intestinal features like iron deficiency anemia and metabolic bone disease[10]. Upper GI endoscopy followed by duodenal biopsy should be taken in all adult patients if serology for celiac disease is positive, or negative but strong suspicion of celiac disease.

There are numerous clinical mimickers of celiac disease like Irritable bowel syndrome, Functional diarrhoea, Small intestinal bacterial overgrowth, Autoimmune and/or inflammatory conditions like Inflammatory bowel disease, microscopic colitis, thyroid disorders, or even adrenal insufficiency, infectious causes like bacterial and viral gastroenteritis, giardiasis (Fig 4), tropical sprue, drugs, Whipple's disease etc.

There are various histological mimickers of celiac disease. Kamboj et al have divided these into Early and Late mimickers[11].

Early mimickers are defined as those conditions causing increased IEL's with no villous atrophy and crypts with minimal to no hyperplasia.

Isolated intraepithelial lymphocytosis with or without crypt hyperplasia or Marsh grade 2 and 1 lesion respectively, also known as lymphocytic duodenitis with or without crypt hyperplasia is associated with number of clinical conditions. In our study we had 20 (10%) cases. In one large single centre study 15,839 duodenal biopsies over 2000 to 2010 in adult patient revealed 7% cases belonging to Marsh grade 1/2 category[12]. There are other smaller studies with (n=14-100) reported the etiology for Marsh type 1/2 lesion in the duodenum to be Celiac disease (9-21%), Inflammatory bowel disease (2-12%), Non-steroidal anti-inflammatory drug induced changes (14 -21%) and small intestinal bacterial over growth SIBO (5-9%), autoimmune conditions (4-14%) and other unexplained conditions ranging from 7 to 34% of cases[12-14]. NSAID's comprised of 20(10%) cases in our study. Symptoms resolved upon discontinuation of drug. The possible cause may be due to direct toxic effect of drug itself or its metabolites which are excreted in bile or may be hypersensitivity reaction to drug[15]. Various retrospective studies have reported NSAID as a cause of Marsh type 1/2 lesion ranging from 14-20% of cases[12,14]. Inflammatory bowel disease has also been implicated for Type 1/2 lesion in duodenum. The various histologic clues that type 1/2 lesion is as a part of IBD are endoscopic erosions, neutrophilic infiltration, edema, crypt abscess and rare granulomas and a non-tip dominance of IEL. In our study IBD comprised of 2(1%) cases while Patterson ER has reported 7.2% of cases in his study where Crohn's disease was the main etiology among IBD[16]. This may be due to the fact that simultaneous upper and lower GI biopsies are not taken in our setting. In our study marsh 1 and marsh 2 cases were clinically mild and presented as abdominal pain and discomfort.

Late histologic mimickers are those which show Marsh 3 lesion on duodenal biopsy. In our study, out of 162(81%) Marsh grade 3 lesions, 3a were 102(51%), 3b and 3c each 30(15%). Out of these 162, only 67(41.3%) were seropositive and responded to gluten free diet while rest were Celiac mimickers and their etiologies comprised of giardiasis, tropical sprue, medications, megaloblastic anemia, gastric metaplasia and cow milk and soy sensitivity. Out of 131 seronegative cases 27(20.6%) no definitive cause could be assigned to celiac like morphology. In a study by Green PHR et al done on 72 adults patients with villous atrophy and seronegative celiac like morphology, various etiologies reported were Seronegative CD in 28%, medications

in 26%, unclassified sprue in 14%, CVID in 16%, autoimmune enteropathy, giardiasis, tropical sprue, small intestinal T cell lymphoma, SIBO each in 4%, collagenous sprue in 3%, enteropathy associated T cell lymphoma, crohn's disease and extensive gastric metaplasia each in 1%[17].

In our study 18 (9%) cases showed association with Olmesartan as a cause for celiac like morphology where histology reverted to almost normal after discontinuation of drug. Rubio-Tapia et al in their study reported villous atrophy in all 22 patients while 15 out of 22 showed neutrophilic infiltarion and 7 showed excess collagen deposition additionally[18]. Two other studies done in French and Spanish population separately reported Olmesartan associated enteropathy in 36 and 11 patients respectively[19,20]. They recommended that older age at onset, prominent collagen deposition and neutrophilic infiltration in a seronegative enteropathy should always be search for drug history even if drug was started many years back. Other medicines like Ipilimumab, Colchicine, Mycophenolate, Methotraxate, and azathioprine are implicated in causation of celiac like morphology in seronegative patients. In our study we had 3(1.5%) cases of Azathioprine associated seronegative celiac like morphology in patient of atopic dermatitis not responding to topicals and oral anti-histaminics. In the present study 10 (13.5%) cases show villous atrophy morphologically corroborating as marsh (3a) with negative serology but with history of chronic alcoholism. Similar findings have also been reported by Sjölund K, Persson Jet al[21]. In our study we couldn't find any case of collagenous sprue, may be that we had interpretated collagen deposition just as a part of chronic inflammatory reaction. Collagenous sprue shows a thick (>5u), irregular band wrapping around capillaries. Our studies finds H.pylori as a cause of celiac like morphology in 15(7.5%) cases. Similar findings are reported by Mohmmed N. Hilmi et al which showed villous broadening and flattening with chronic inflammation in lamina[22]. Cow milk allergy associated enteropathy is seen in 5(2.5%) and soy protein allergy in 3(1.5%) cases in this study which is supported by Fontaine JL[23] which showed Marsh 2, 3a and 3b lesions with increased number of eosinophils due to cow milk allergy and Shah N et al[24] which showed isolated increase in lamina eosinophils with villous broadening due to inflammatory infiltrate. Three cases (1.5%) of megaloblastic anemia were seen in our study where Serum B12 level was reduced and diagnosis made on peripheral blood and bone marrow smears, showed celiac like changes on duodenal biopsy. This finding corroborated with Nasrin NN et al where they reported 7.2% cases showed Marsh type 1 lesion and others showed Villous atrophy[25].

Anti-TTG antibodies, although considered highly sensitive and specific, were positive in only 34.5% of patients, predominantly among those with advanced villous atrophy (Marsh 3). A significant correlation was noted between antibody positivity and the degree of mucosal injury ($p < 0.013$). These findings reinforce the phenomenon of **seronegative celiac disease**, often explained by IgA deficiency, minimal gluten exposure, or immunosuppression[26]. Importantly, the presence of villous atrophy in seronegative patients highlights the need to consider other causes such as infections, drug-induced injury, immune-mediated enteropathies, and malignancies.

These findings reaffirm that **celiac-like histological features are not disease-specific** and may reflect diverse underlying pathologies. In such cases, diagnosis should not rely solely on histology or serology but instead require a **comprehensive approach** incorporating dietary history, medication review, targeted infectious work-up, immunological testing, and, where relevant, therapeutic trials.

This study highlights the importance of maintaining a broad differential diagnosis, particularly in tropical and resource-limited settings. A multidisciplinary diagnostic strategy is essential to avoid misdiagnosis, ensure appropriate therapy, and improve patient outcomes.

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Flow Diagramme (Fig 1)

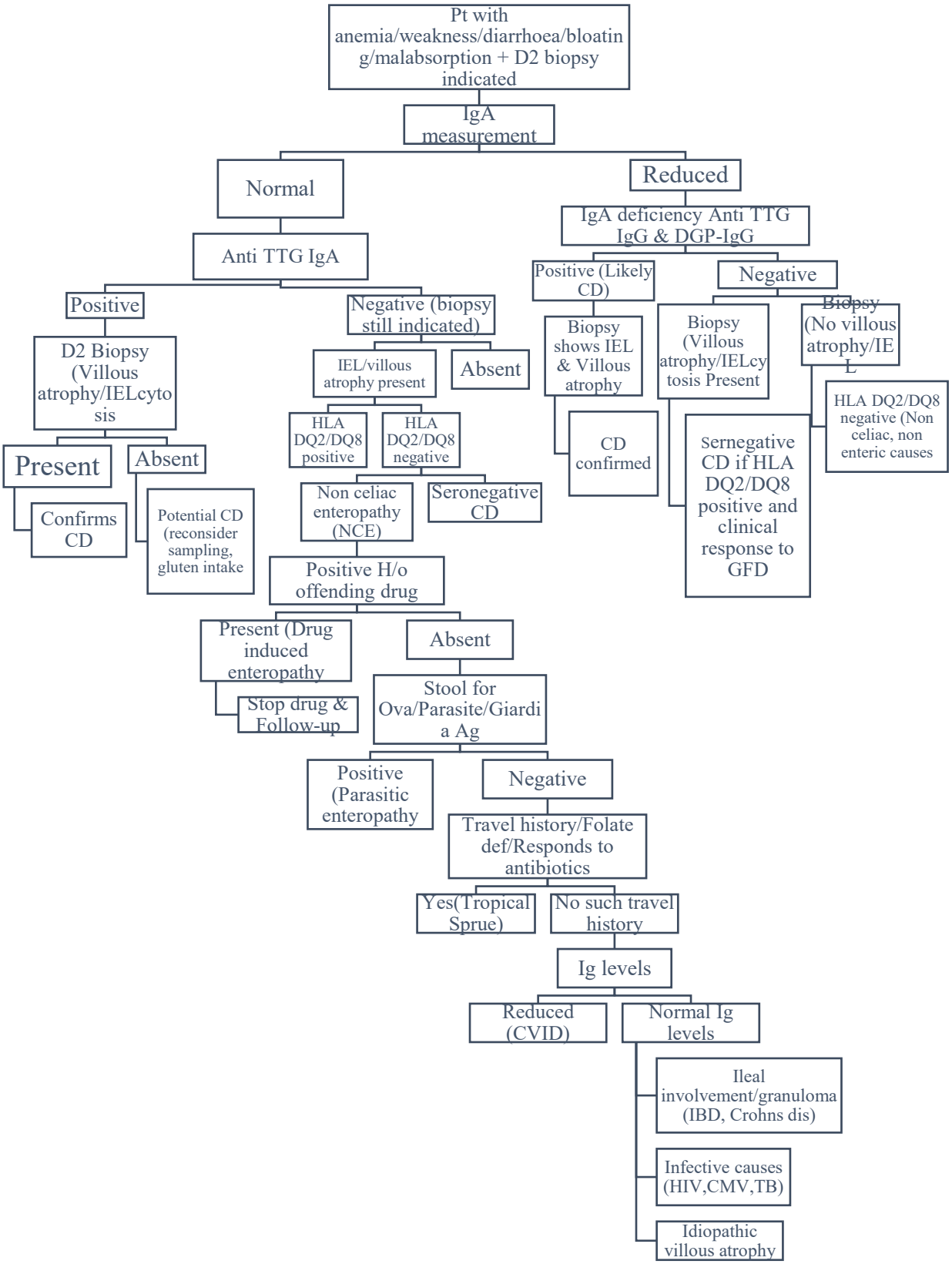

Pt with anemia/weakness/diarrhoea/bloating/malabsorption + D2 biopsy indicated
IgA measurement
Normal
Reduced
Anti TTG IgA
IgA deficiency Anti TTG IgG & DGP-IgG
Positive
Negative (biopsy still indicated)
Positive (Likely CD)
Negative
D2 Biopsy (Villous atrophy/IELcytosis
IEL/villous atrophy present
Absent
Biopsy shows IEL & Villous atrophy
Biopsy (Villous atrophy/IELcytosis Present
Biopsy (No villous atrophy/IEL
Present
Absent
HLA DQ2/DQ8 positive
HLA DQ2/DQ8 negative
CD confirmed
HLA DQ2/DQ8 negative (Non celiac, non enteric causes
Confirms CD
Potential CD (reconsider sampling, gluten intake
Non celiac enteropathy (NCE)
Seronegative CD
Sernegative CD if HLA DQ2/DQ8 positive and clinical response to GFD
Positive H/o offending drug
Present (Drug induced enteropathy
Absent
Stop drug & Follow-up
Stool for Ova/Parasite/Giardia Ag
Positive (Parasitic enteropathy
Negative
Travel history/Folate def/Responds to antibiotics
Yes(Tropical Sprue)
No such travel history
Ig levels
Reduced (CVID)
Normal Ig levels
Ileal involvement/granuloma (IBD, Crohns dis)
Infective causes (HIV,CMV,TB)
Idiopathic villous atrophy

Table 1: Demographic, clinical and Histological profile and Mean Hemoglobin (HB) Across Marsh Types

Variable	Category	Number of cases= n(%)		
Gender	Male	125(62.5%)		
	Female	75 (37.5%)		
Symptoms	Anemia	192(95.4%)		
	Weakness	192(95.4%)		
	Chronic diarrhoea	35(17.5%)		
	Burning/Bloating	15(7.5%)		
	Post prandial fullness	14(7%)		
	Abdominal Pain	7(3.5%)		
	Growth Retardation	1(0.5%)		
Histological findings	Increased IEL's	200(100%)		
	Crypt Hyperplasia	180(90%)		
	Villous Atrophy	Partial(3a) 102(51%)		
		Subtotal (3b) 30(15%)		
		Total (3c) 30(15%)		
Modified Marsh Grade	**Type of Lesion**	**n (%)**	**Hb(g/dl) (Mean ± SD)**	**P value**
	1 (Infiltrative)	20(10%)	11.80 ± 1.37	**<0.001**
	2 (Hyperplastic)	18(9%)	10.86 ± 0.46	
	3a (Partial Atrophy)	102(51%)	10.66 ± 0.91	
	3b (Subtotal Atrophy)	30(15%)	10.44 ± 0.87	
	3c (Total Atrophy)	30(15%)	10.10 ± 0.54	

Table 2: Association Between Anti-TTG Positivity and Modified Marsh Classification

Modified Marsh Grade	TTG Negative (n=131)	TTG Positive (n=69)	Total (n=200)	P value
1	19	1	20	**<0.013**
2	17	1	18	
3a	85	17	102	
3b	10	20	30	
3c	0	30	30	

Table 3: Spectrum of Diagnoses Underlying Celiac-like Duodenal Morphology

Variable	Category	N(%)
Celiac like Morphology with no known cause(Seronegative)	No specific cause could be identified	37(18.5%)
Celiac like Morphology with known cause (Seronegative)	Alcohol intake	10 (5%)
	Giardiasis	10 (5%)
	Tropical sprue	2 (1%)
	HIV-associated enteropathy	3 (1.5%)
	Drug-induced (Olmesartan)	18 (9%)
	Drug-induced (Azathioprine/Hypo-immunomeds)	3 (1.5%)
	Drug-induced (NSAIDs)	20 (10%)
	Eosinophilic gastroenteritis	2 (1%)
	Small intestinal Crohn‘s disease	2 (1%)
	H. pylori-associated duodenitis	15 (7.5%)
	Peptic duodenitis (Foveolar metaplasia)	8 (4%)
	Megaloblastic anemia	3 (1.5%)
	Cow‘s milk sensitivity	5 (2.5%)
	Soy sensitivity	3 (1.5%)
Celiac Disease	Seropositive (Celiac disease)	69 (34.5%)

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table1.docx
- Table3.docx