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## Microscopic Enteritis; clinical features and correlations with symptoms

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### ABSTRACT

**Aim:** To assess the clinical characteristic of CD as well as correlation of symptoms and the degrees of intestinal mucosal lesions in Iranian children.

**Background:** Microscopic Enteritis (Marsh 0-II) is associated with malabsorption.

**Patients and methods:** From August 2005 to September 2009, 111 cases with malabsorption and classical gastrointestinal symptoms were evaluated.

**Results:** The mean ( $\pm$ SD) age of children with CD was  $4.9 \pm 3.5$  years (range, 6 month - 16 years) and the mean duration of symptoms was  $8 \pm 20.5$  months. 50 cases (45%) were female and 61 cases (55%) were male. The most common clinical presentation was failure to thrive in 72%, chronic diarrhea in 65.8% and Iron deficiency anemia in 59.5%. Sensitivity of EMA was 100% in patients with Marsh IIIb and Marsh IIIc. EMA was also positive in 77% of cases with Marsh 0, 18% in Marsh I, 44% in Marsh II and 81.8% in patients with Marsh IIIa.

**Conclusion:** Histopathology did not reflect the severity of gluten sensitivity. This would suggest that the degree of intestinal mucosal damage might not be a reliable prognostic factor. Significant symptoms can be present with minor histological change on biopsy.

**Keywords:** Coeliac disease, Serology, Histology, Macroscopic enteritis.

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### Introduction

Microscopic enteritis (ME) is the stage of microscopic and sub-microscopic changes

(Marsh 0-II) associated with the symptoms of micronutrient deficiencies. It is characterized by subtle mucosal abnormalities without prominent inflammation, villous effacement, erosions or ulcerations on conventional light microscopy (1).

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Classical coeliac disease (CD) with diarrhea, abdominal distension and failure to thrive is uncommon in western studies, and atypical forms (2) are more frequently found (3). The literature lacks data on CD in cohorts with severe malabsorption. Serological tests are often used as a powerful screening tool for CD and they proved to have a superior value compared to milder enteropathy (4-6). In developing countries many individuals with even classical CD may still remain undiagnosed due to poor access to intestinal biopsy and serology (7, 8). This lack of access to investigations may contribute to patients presenting with overt malabsorption. Evidence shows that coeliac disease develops gradually from small bowel mucosal inflammation to crypt hyperplasia and only a few patients might develop overt villous atrophy. Milder enteropathy like microscopic enteritis (1) seems to be a common presentation form of CD. Progress has been made toward the hypothesis that a form of gluten intolerance exists that's different from CD, defined as non-coeliac gluten sensitivity (NCGS) (9, 10), and it is estimated that for every person who has CD, there are at least six or seven people who have GS. Therefore, wheat allergy, CD, and GS combined together may affect about 10% of the general population. Whether CD or NCGS, unfortunately milder enteropathy is usually ignored and under-reported by pathologists (11). In developing countries the problem is even worse as CD with borderline enteropathy is not routinely considered as a likely diagnosis because some etiologies such as post-infectious diarrhea, malnutrition and parasitosis are more obvious causes (12). However, ruling out other etiologies would not make the diagnostic procedures much easier as milder enteropathy has a non-specific nature. In recent years emphasis has shifted away from CD in the context of being a treatable entity only when associated with severe mucosal damages. This is because recognizing the atypical presentation of CD and recently described non-

coeliac gluten sensitivity has introduced a new insight in treatment strategy. It is still not sufficiently clear why some patients present with diarrhea and others may be subclinical (13, 14). The pathologic spectrum of the mucosal abnormalities seen on small intestinal biopsies, range from microscopic enteritis (Marsh 0-II) to macroscopic form (Marsh IIIa-c) (1) but mostly uncorrelated with symptoms. The term of macroscopic enteritis points to the macro-endoscopic characteristic of Marsh III-a-c lesions that could be visualized by endoscope (15). Despite the fact that microscopic enteritis (Marsh 0-II) represent the most common presentation form of CD, treatment of this condition is still based on severe mucosal damages like Marsh III (1, 16, 17). There are little data concerning this issue in Iranian children. A better understanding of the pathology behind the symptoms will diminish the role of histology (18) for diagnosis of CD. This will open a new prospect for the treatment of symptomatic patients with milder enteropathy. The aim of this study was to assess the clinical characteristic of CD patients as well as relationship between symptoms and the severity of intestinal mucosal lesions.

## Patients and Methods

### *Study design and inclusion criteria*

From August 2005 to September 2009, 111 subjects with malabsorption and classical gastrointestinal symptoms were evaluated in three Pediatric Gastroenterology units in Iran. (see flow chart) Patients were referred because of gastrointestinal symptoms (failure to thrive, chronic diarrhea, abdominal pain, bloating and constipation) or extraintestinal reasons (iron deficiency anemia, abnormal transaminase level and short stature). Diarrhea that persists for more than 2 weeks was considered chronic. Iron deficiency anemia and failure to thrive was defined

**Table 1.** Histological classification for coeliac disease

Classification	Histology	IEL/100 enterocytes	Crypts	Villi	Endoscopy
Normal mucosa	Marsh 0 Normal	<25/100 EC	Normal	N	Normal
Microscopic Enteritis	Marsh 0 SME (Microenteropathy)	<25/100 EC	Normal	N	Normal
	Marsh I Lymphocytic enteritis	>25/100 EC	Normal	N	Normal
	Marsh II Hyperplastic stage	>25/100 EC	Hyperplastic	N	Normal
Macroscopic Enteritis	Marsh IIIa	>25/100 EC	Hyperplastic	PVA	Abnormal
	Marsh IIIb	>25/100 EC	Hyperplastic	STVA	Abnormal
	Marsh IIIc	>25/100 EC	Hyperplastic	TVA	Abnormal
	Marsh IV	<25/100 EC	NCD, HP	TVA	Abnormal

SME= sub-microscopic enteritis, N= normal, EC= enterocytes, PVA= Partial villous atrophy, STVA= Subtotal Villous atrophy, TVA= Total villous atrophy, NCD, HP= Normal crypt depth, but hypoplasia

according to CDC criteria and Global Database on Child Growth and Malnutrition (19, 20).

The following clinical variables were collected through a questionnaire: age and gender, duration of symptoms, clinical findings, growth parameters (height and weight Z scores) laboratory and intestinal biopsy findings. Before referral, most of these cases were treated with multiple courses of anti-parasitic drugs, a common practice for the treatment of chronic diarrhea and failure to thrive in Iran by general physicians. All of subjects had at least a three -month period of previous ingestion of gluten. All findings were recorded on a database sheet designed for the study.

#### **Exclusion criteria**

The children with irregular follow up, bloody diarrhea, missing data, or chromosomal disorder were excluded from study.

#### **Investigation**

The study group underwent investigations including blood tests, coeliac serology and gastroscopy with duodenal biopsy (GD2). All serum samples were collected at the time of diagnosis when the patients were receiving a normal diet without any restrictions. Routine

hematology, biochemical and serology tests [endomysial antibody (EMA)] were performed. In order to exclude selective IgA deficiency, total IgA level by immunodiffusion method was determined in all 111 patients who underwent UGIE. IgA deficiency was ruled out in all cases.

#### **Ethical approval and consent**

The study was approved by Ethical and Research Center for Children and Adolescents Health at Zahedan University of Medical Sciences. Informed consent from the parents of all subjects who agreed to participate in this study was obtained before collecting samples and endoscopy.

#### **Intestinal biopsy and pathology**

Upper gastrointestinal endoscopy (UGIE) by a pediatric fiberoptic endoscope was performed in 111 symptomatic patients with negative tests for parasitic illnesses. During the procedure, 4 biopsies from different part of duodenum were obtained and correctly oriented on acetate filters. The tissue obtained by biopsy was examined by expert pathologists who were not aware of clinical findings. Biopsy specimens were evaluated according to Marsh classification 1992, as revised

by Rostami et al (21, 22). (Table 1) Serology was performed after Endoscopy

**Diagnosis and treatment:** The diagnosis was made based on clinical symptoms, serology including total serum IgA, IgA EMA and duodenal biopsy. All patients were given a dietary chart form including written information about foods to be avoided (wheat, barley, rye, oat) and received iron and multivitamin as a supplementation. The importance of compliance with a GFD was repeatedly explained to the parents and the child. Gluten-free diet (GFD) (23) was recommended for all children with Macroscopic enteritis (Marsh IIIa-c) and those with Microscopic enteritis (Marsh I-II) with positive serology (Figure 1).

All serum samples were collected at the time of diagnosis when the patients were receiving a normal diet without any restrictions. Routine hematology, biochemical and serology tests endomysial antibody (EMA) were performed. In order to exclude selective IgA deficiency, total IgA level by immunodiffusion method was determined in all 111 patients who underwent UGIE. IgA deficiency was ruled out in all cases.

#### **Statistical analysis**

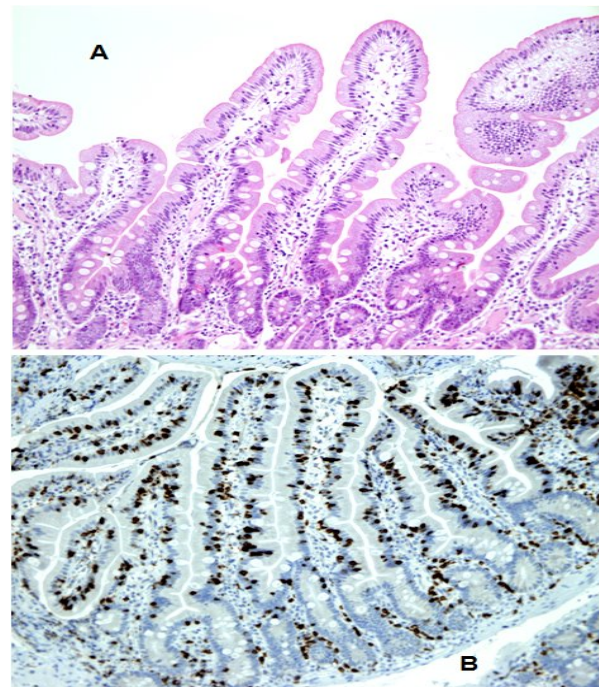
We calculated frequencies and percentages for qualitative variables and means, medians and standards deviations for quantitative variables. The links between qualitative variables were assessed using Chi square test. P value <0.05 were considered significant. Data are expressed as mean  $\pm$  SD.

## **Results**

#### **Data analysis**

From 111 symptomatic patients with negative screening for parasites, 84 cases fulfilled the diagnostic criteria for having CD. This included all symptomatic patients with enteropathy (Marsh I-IIIc) and positive serology. Those patients with macroscopic enteritis (Marsh IIIa) and negative serology were also considered as CD. However, patients with microscopic enteritis (Marsh 0-II)

and negative serology were not diagnosed as CD. Those patients with milder enteropathy (27/111) and negative serology could have been NCGS (24) and will be followed up under the test of time strategy. Summary of data analysis has shown in table 2.



**Figure 1 . Microscopic Enteritis (Marsh I and Marsh II);** Normal villi with pathological increase of T Lymphocytes (A) with cript hyperplasia (B); **A** H&E x 10 **B** CD3 x10. This form of mucosal abnormality is overlooked by many pathologists.

#### **General characteristics**

The mean  $\pm$  SD age of children with CD was  $4.9 \pm 3.5$  years (range, 6 month - 16 years) and the mean duration of symptoms was  $8 \pm 20.5$  months. 50/111 cases (45%) were female and 61/111 cases (55%) were male. The most common clinical presentation was failure to thrive in 80/111(72%) cases, chronic diarrhea in 73/111(65.8%) and iron deficiency anemia in 66/111(59.5%) cases followed by abdominal pain in 62/111(55.9%), fatty stool and abdominal distension in 54/111(48.6%) (Table 3). An association with a family history of diabetes, hypothyroidism and CD was found in 4, 7 and 13 cases respectively.

**Table 2.** Histology and serology in 111 patients with enteropathy according to Modified Marsh classification

Histology	Marsh 0 N=13(11.7%)	Marsh I n=11 (9.9%)	Marsh II n=27 (24.3%)	Marsh IIIa n=44 (39.6%)	Marsh IIIb n=10 (9%)	Marsh IIIc n=6 (5.4%)	Total
EMA +ve	10/13(76.9%)	2/11 (18%)	12/27 (44.4%)	36/44 (81.8%)	10/10 (100%)	6/6 (100%)	76/111 (68.5%)
EMA -ve	3/13(23%)	9/11 (82%)	15/27(55.5%)	8/44(18%)	0	0	35/111 (31.5%)
	Mic.E*	Mic.E	Mic.E	Mac.E**	Mac.E	Mac.E	

\* Microscopic Enteritis

\*\* Macroscopic Enteritis

**Table 3.** Comparing clinical findings between Marsh I-II and Marsh IIIa-c in 111 patients with malabsorption syndrome and abnormal histology

Variable	Marsh 0 N=13/111	Marsh I N=11/111	Marsh II N=27/111	Marsh IIIa-c N=60/111	p-value
chronic diarrhea	3 (23%)	9(82%)	18(66.6%)	43 (71.7%)	0.005
Failure to thrive	7(53.8%)	9(81.8%)	20(74%)	44(73.3%)	0.43
Short stature	7(53.8%)	7(63.6%)	15 (70.3%)	33(55%)	0.96
Abdominal pain	5(38.5%)	4(36.4%)	17(63%)	36(60%)	0.24
Abdominal distension	4(30.8%)	5(45.5%)	15(55.5%)	30(50%)	0.52
Fatty stool	1(7.7%)	4(36.4%)	10(37%)	39(65%)	0.001
Decreased appetite	4(30.8%)	4(36.4%)	10(37%)	30(50%)	0.56
constipation	3(23%)	4(36.4%)	6(22.2%)	3 (5%)	0.01
vomiting	2(15.4%)	4(36.4%)	5(22.7%)	21(35%)	0.27
rickets	0	0	3(11.1%)	11(18.3%)	0.16
Tibial edema	0	0	1(3.7%)	6(10%)	0.54
Anemia	3(23%)	4(36.4%)	13(48.1%)	46(76.7%)	0.001
EMA	10(79.9%)	2(18.2%)	12(44.4%)	52(86.7%)	0.001

Among subjects with coeliac disease, 2 cases of hypothyroidism, 1 case of cirrhosis and diabetes were found. Chronic diarrhea, constipation failure to thrive, and short stature were significantly more prevalent in patients with Marsh I compared to those with Marsh III (Figure 2).

#### Laboratory and Histopathology findings

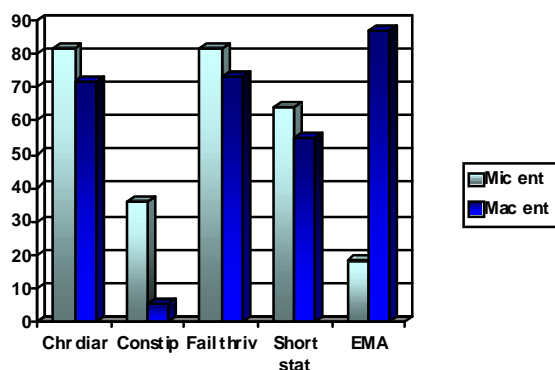
IgA EMA was positive in 68/98 of subjects. Histology revealed Marsh 0 in 13 cases (11.7%), Marsh I in 11 cases (9.9%), Marsh II in 27 cases (24.3%), Marsh IIIa in 44 cases (39.6 %), Marsh IIIb in 10 cases (9 %) and Marsh IIIc in 6 cases (5.4 %) of

patients, respectively. Positive EMA were found in 10/13(76.9%) of patients with Marsh 0, 2/11 (18%) of patients with Marsh I, 12/27 (44.4%) in Marsh II and 36/44 (81.8%) with Marsh IIIa. Sensitivity of EMA was 100% in patients with Marsh IIIb and Marsh IIIc (Table 2). Chronic diarrhea, constipation failure to thrive, and short stature were significantly more prevalent in patients with Marsh I compared to those with Marsh III (Table 3).

#### Discussion

The present study demonstrates that Microscopic Enteritis (ME) is the most common

histological presentation of CD. A high percentage of patients with marsh I had diarrhea and other clinical symptoms of overt malabsorption but without evidence of mucosal atrophy. This may suggest that histology doesn't reflect the severity of disease and the degree of damages in intestinal mucosa might not be a reliable prognostic factor. This study also highlights that sensitivity of EMA may be increased by grade of histopathology. Despite the limitation of sensitivity of serology, EMA was positive in a significant number of patients with ME. This may suggest that serology is a far more reliable marker for CD compared to histology with milder enteropathy.

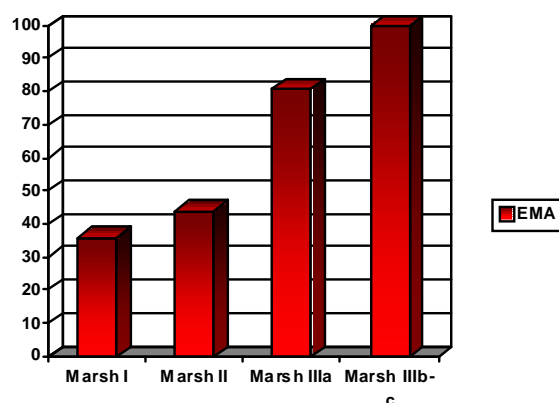


**Figure 2.** Clinical presentation in microscopic enteritis (Mi ent, Marsh I) compared to macroscopic enteritis (Mac ent, Marsh IIIa-c) in percentage. Chronic diarrhea, constipation, failure to thrive, short status

Conflicting reports exist on the distribution of lesions in CD along the small bowel mucosa and the relationship between symptoms and the length of lesions. However, despite the previously belief, symptomatology in CD does not seem to be related to the degree or length of affected bowel (5, 25). Some studies that have attempted to correlate the degree of villous atrophy with the mode of clinical presentation suggest patients with mild enteropathy of any kind with positive antibodies may experience clear gluten-induced symptoms (17, 25), and the severity of CD doesn't

reflect in the dept or the length of mucosal abnormalities (26, 27).

The lack of relationship between pathology and symptoms was impressively supported by our data. We show that the percentage of patients with diarrhea, constipation and failure to thrive was even higher in Marsh I patients compared to marsh III. Anemia and positivity for autoantibodies were the only parameters that significantly correlated with the macroscopic lesions (Marsh III) in this study. Although we are not quite sure why sensitivity of serology is co-relating so closely with the degrees of mucosal abnormalities (22, 28-31) (Fig 3) small bowel inflammation is not reported only as severe (Marsh III) in anemic patients in other studies (27, 32).



**Figure 3.** Sensitivity of serology (%) in patients with different degrees of mucosal abnormalities

Interestingly 10/13 symptomatic patients with Marsh 0 had positive EMA. It is very unlikely that these symptomatic cases with malabsorption who were extensively investigated for other conditions to be false positive. As the depth, length or degrees of the mucosal abnormality do not seem to correlate with the severity of symptoms, should there be a different explanation for malabsorption syndrome in all cases with normal, mild and severe enteropathy? Accumulated evidence suggest that the gluten-sensitized lymphocytes in

the mucosa (33) have the crucial role in the pathogenesis and they give real aspect of what CD means, irrespective of mucosal damages. In other words it seems that the sensitized mucosal lymphocytes even when within normal range (26, 27), or something that correlates closely with that state of sensitivity are the key factors not only in pathogenesis but also in the genesis of the symptoms.

This hypothesis was proved with the range of severe symptoms of our patients presenting with ME. Low specificity would be other explanation but not for EMA as this auto-antibody are extremely specific for CD. Even in absence of mucosal abnormalities subtle systemic and local inflammatory factors are implicated in the genesis of anemia and suggest that pro-inflammatory cytokine TNF $\alpha$  inhibits at the level of the enterocytes affects the uptake of the micronutrients like iron (34, 35) or phosphate (36) in patients with microenteropathy. It seems that malabsorption in CD is secondary to inflammation and cytokines stimulation. This theory would perhaps explain why our Marsh 0-II patients with non-coeliac gluten sensitivity may behave like full blown CD (24). Focusing on symptomatology in choosing the candidate for therapy seems to be a better strategy than concentrating on the degrees of the mucosal abnormalities. The lack of significant severity of disease in patients with Marsh III compared to Marsh I in our study would be in favor of such a strategy. Similar to other studies (26, 37) children in both groups presented with classical picture of coeliac disease and the extent of visible enteropathy did not explain differences in clinical presentation. Our patients had typical symptoms like growth impairment with positive or negative antibodies and anemia. We clearly experienced that the degrees of intestinal mucosal abnormalities alone are not reliable predictors of disease behavior. The quality of life of the symptomatic cases with Marsh I and

II with CD or NCGS could be dramatically improved by introducing a gluten-free diet (32, 38, 39). The overall aim should be treating the symptoms whether full blown CD or NCGS rather than treating the medical terms like villous atrophy. The question for the future agenda would be how far symptomatic, (40) NCGS with Marsh 0-II would benefit from a gluten free diet after exclusion of other causes for their microenteropathy.

Although the size of our study was small but nonetheless our results are adding solid evidence to the existing literature to emphasize the superiority of serology compared to milder histology like ME in diagnosing CD. The other limitation of our study was the lack of possibility of follow up of our patients and implementing a GFD in NCGS as the study was performed before description of this new entity. But again this would not prevent us to suggest that treatment of gluten sensitive cases should not be based on villous atrophy as histology does not always reflect the severity of CD.

The lack of awareness between clinicians is one of the main reasons for delaying the diagnosis and treatment of NCGS and CD cases with microenteropathy.

It is time to acknowledge, believe and act to shift the paradigm from villous atrophy to the sole presentation form of CD and NCGS in order to make a difference in life quality of symptomatic patients with or without milder enteropathy. As a consequence it is necessary, today, to motivate the pathologists to look at new morphological aspects of this precocious forms of the disease, for example a re-evaluation of the value of 25/100 epithelial cells of T lymphocytes as the barrier of normality strictly depending on the number and quality of the biopsies and the experience of the pathologist. It is important to keep in mind that the biopsy is a photograph of a moment in the history of disease and today with the concept of

microscopic enteritis, the sensation is that everything starts with T cells stimulations that start the inflammation process in the lower part of the mucosa and then progressively in the surface epithelium. This is the natural history of pre-macroscopic lesions implicated in malabsorption related symptoms with no management place in the current guidelines. A larger scale study would be required to assess further the pathological modalities, the clinical characteristics/implications and long term complications.

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