Abnormalities of the Small Bowel in Chronic Non-Infective Diarrhea: A Histopathological Study

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ABSTRACT

Background: The incidence of chronic non-infectious diarrhea cases is increasing in line with the developments of medical technology and science. The objective of this study was to uncover the histopathologic abnormalities of the small bowel in cases of chronic non-infectious diarrhea.

Materials and Methods: All chronic non-infectious diarrhea patients in Cipto Mangunkusumo Hospital from 1996 until 2000 were included in this study. For the control group, we used 37 endoscopically-normal patients with functional dyspepia with the same characteristics (sex and age). All of the patients underwent gastroduodeno-jejunoscopic and ileocolonoscopic examinations. Patients with infection were excluded from this study. Biopsies were taken from the duodenal bulb, descending duodenum, jejunum near the Treitz ligament, terminal ileum, and colon. Histopathological tests were performed on all of the biopsies.

Result: Histopathological examination was carried out on 31 patients and 37 control patients. In the duodenal bulb, the width of villi, lymphocyte infiltration, eosinophil infiltration, stage of inflammation, and polymorphonuclear cells infiltration were all lower in the chronic non-infectious diarrhea group than in the control group ($p < 0.01$). In the descending part of duodenum and jejunum, lymphocyte infiltration, the stage of inflammation, and polymorphonuclear cell infiltration were found to be higher in the chronic non-infectious diarrhea group than in the control group ($p< 0.01$). Within the terminal ileum, lymphocyte infiltration, the stage of inflammation and lymphoid follicle hyperplasia were found to be higher in the chronic non-infectious diarrhea group than in the control group ($p< 0.01$).

Conclusion: Histopathologically, increased lymphocyte infiltration, inflammation and lymphoid follicle hyperplasia were discovered in specified areas of small intestine in chronic non-infectious diarrhea patients.

***Keywords**: Histopathological examination, chronic non-infectious diarrhea, lymphocyte infiltration, mucosal inflammation, lymphoid follicle hyperplasia*

INTRODUCTION

Chronic diarrhea is common in Indonesia.[1,2] The incidence of chronic non-infectious diarrhea cases is increasing in line with advances in medical technology and science.[1,2,3]

There are many etiologies of chronic non-infectious diarrhea, such as drugs, hormones/neurotransmitters, metabolic disturbances, disturbance of electrolyte transport in the enterocyte, malabsorption, post surgery abnormalities, ischemic bowel disease, radiation enteritis, inflammatory, tumor, functional (idiopathic) etc.[1,2,3,4,5,6,7]

The purpose of this study was to elucidate histopathological abnormalities of the small bowel in chronic non-infectious diarrhea.

MATERIALS AND METHODS

All chronic non-infectious diarrhea patients in the out-patient clinic or the in-patient ward in the Division Gastroenterology, Department of Internal Medicine, Cipto Mangunkusumo Hospital from 1996 until 2000 were recruited in this study. The control group consisted of 37 endoscopically normal functional dyspeptic patients with the same characteristics (sex, age). All of the chronic non-infectious diarrhea patients underwent blood tests, including biochemistry, haematology test, liver function test, pancreatic function test using the serum amylase-lipase, and thyroid function test. They also underwent stool tests (routine, parasite, bacterial culture etc.). Gastroduodeno-jejunoscopic and ileocolonoscopic examination were performed on the patients. All infectious patients were excluded from this study.

From each patient, two biopsy specimens were taken from the duodenal bulb, 2 specimens from the descending portion of the duodenum, 2 specimens from the jejunum near the Treitz ligament, 2 specimens from the terminal ileum and 6 specimens from the colon. A small caliber pediatric colonoscope (an Olympus PCF-10) was used to perform the gastroduodeno-jejunoscopy, while an Olympus Evis CF-200 colonoscope was used to perform the ileocolonoscopy. The endoscopical gradation (overall grade of damage) of the small intestine was made according to the Indonesian system and OMED[8] as follows: 0 (normal), + (mild), ++ (moderate) and +++ (severe). The grade was established as mild if there was mild hyperemia and/or mild erosion; moderate if there was moderate hyperemia and/or moderate erosion; severe if there was severe hyperemia and/or severe erosion and/or ulcer; hyperemia if there was increased vascularity and redness of the mucosa; or erosive if there was a superficial mucosal defect, flat lesion covered with exudate. Ulcer implies to a benign defect of the gastro intestinal mucosa larger and deeper than erosion. The results and the histopathological specimens which had already been stained were also examined at the Academic Medical Center University of Amsterdam. The histopathological specimens were stained with Giemsa or Haematoxyllin-Eosin.[9,10] The height, width of the villous mucosa and intervillous space were measured with the measurement on the microscope (micrometer) objective lens 10 x 10, with a magnification of 10x : 1 U = 10 micron. The Inflammatory cells were examined with objective lens 40x10 and 100x10. Haematoxyllin-Eosin was used for the staining. The following scoring system for inflammatory cells (lymphocytes, plasma cells, eosinophils and polymorphonucelar cells) was used: 0 (negative), +, ++ +++. The score was established as + if the histology showed that the distance between 2 cells was larger than the diameter of the cells; ++ if the histology showed that the distance between 2 inflammatory cells was smaller than the diameter of the cells; or +++ if the inflammatory cells were touching each other. Inflammation grading was established as 0 (normal), + (mild), ++ (moderate), or +++ (severe). The grade was established as mild if the number of inflammatory cells was +; moderate if the number of inflammatory cells was ++; or severe if the number of inflammatory cells was +++. The number of goblet cells per 100 mm was counted in all specimens.

RESULTS

Thirty-three patients with chronic diarrhea were included in this study. The most frequent characteristics of the patients were as follows: male (66,7%), with a mean age 40.15 $\pm$ 14.20 years old, good-to-average economic status (97%), non-bloody and non-steatorrhea (72.7%), and more than 24 weeks of diarrhea (39.3%).

The characteristics of the patients can be seen in table 1.

During endoscopic examination, we found the descending part of duodenum to be normal in all patients (100%); inflammation in the duodenal bulb in 6% of the patients; lymphoid follicle hyperplasia of the jejunum in 9% of the patients and lymphoid follicle hyperplasia of the terminal ileum in 21% of the patients; inflammation of the terminal ileum in 36.4% of the patients (table 2).

Table 1. Characteristics of The Patients

Characteristics	Frequency	Percent (%)
Sex		
Male	22	66.7
Female	11	33.3
Mean age (yo)	40.15 ± 14.20	
Socio-economical status		
Good-average	32	97.0
Bad	1	3.0
Stool form		
Bloody diarrhea	7	21.2
Soft nobloody-nonsteatorrhea	24	72.7
Watery	2	6.1
Duration of diarrhea (weeks)		
3-4	6	18.2
>4-12	9	27.3
>12-24	5	15.2
>24	13	39.3

Table 2. Endoscopical Examination of The Patient

Small Intestine	Hyperemia	Erosian	Ulcer	Overall Grade of Damage	Other
Duodenal bulb:					
0	32 (97%)	32 (97%)	32 (97%)	31 (94%)	
+	1(3%)	1(3%)	1(3%)	1(3%)	
++	0	0	0	1(3%)	
Descending part of duodenum					
0	33(100%)	33(100%)	33(100%)	33(100%)	
+/++	0	0	0	0	
Jejunum					
0	33(100%)	33(100%)	33(100%)	33(100%)	LFH=3(9%)
+/++	0	0	0	0	
Terminal ileum					
0	21(63.6%)	24(72.7%)	32(97%)	21(63.6%)	LFH=6(18%)
+	10(30.3%)	8(24.2%)	1(3%)	10(30.3%)	TI=1(3%)
++	2(6.1%)	1(3%)	0	2(6.1%)	TI+LFH=1(3%)

Note : 0 = Normal/negative ;= mild ; ++= moderate ; +++ = severe
LFH = lymphoid focllicle hyperplasia ; TI = terminal iletis

Histopathological examination of the duodenal bulb showed differences in the width of the villi, lymphocyte infiltration, eosinophilic infiltration, grade of inflammation between the chronic non-infectious diarrhea group and the control group. Due to technical problems, the histopathological examination was performed in only 31 cases (table 3).

Table 3. Results of Histopathological Examination on The Duodenal Bulb

Duodenal Bulb	Chronic Non Infective Diarrhea (n=31)	Control (n=37)	p value
Height of villi (μm)	306.70 ± 87.71	265.00 ± 81.99	NS
Height of crypt (μm)	204.11 ± 66.02	196.67 ± 56.01	NS
Width of villi (μm)	113.01 ± 27.50	96.00 ± 27.46	0.014
Crypt: Villous ratio	0.70 ± 0.32	0.80 ± 0.26	NS
Goblet cells number per 100 μm villi	3.36 ± 1.34	2.95 ± 1.41	NS
Intervillous space (μm)	54.61 ± 28.72	59.14 ± 74.14	NS
Inflammatory cells: Lymphocyte			
0	2	0	0.002
+	17	8	
++	12	29	
Intraepithelial lymphocyte			
+	28	31	NS
++	2	6	
+++	1	0	
Plasma cell			
0	1	0	NS
+	31	37	
Eosinophil			
0	18	9	0.006
+	12	28	
++	1	0	
Polymorphonuclear cells			
0	8	3	NS
+	22	34	
Grade of inflammation:			
0	1	0	0.007
+ (mild)	17	8	
++ (moderate)	13	29	
LFH			
0	30	35	NS
+	0	2	

LFH = lymphoid focllicle hyperplasia ; NS = not significant

The histopathological findings from the pars descendens duodenum showed differences in lymphocyte infiltration, grade of inflammation, and polymorphonuclear cell infiltration (table 4).

Table 4. Result of Histopathologic Test on The Descending Part of Duodenum

Pars Descendens Duodenum	Chronic Non Infective Diarrhea (n=31)	Control (n=37)	p-value
Height of villi (μm)	319.60 ± 73.12	317.27 ± 99.66	NS
Height of crypt (μm)	194.81 ± 59.74	218.79 ± 84.66	NS
Width of villi (μm)	112.01 ± 23.61	125.76 ± 35.88	NS
Crypt: Villous ratio	0.62 ± 0.23	0.74 ± 0.34	NS
Goblet cells number per 100 μm villi	3.53 ± 1.24	3.80 ± 2.01	NS
Intervillous space (μm)	40.31 ± 19.02	30.91 ± 34.58	NS
Inflammantory cells: Lymphocyte			
0	1	0	<0.001
+	16	36	
++	14	0	
Intraepithelial lymphocyte			
+	30	32	NS
++	1	5	
Plasma cell			
0	1	1	NS
+	30	35	
Eosinophil			
0	19	18	NS
+	11	18	
++	1	0	
Polymorphonuclear cells			
0	9	31	< 0.001
+	21	5	
Grade of inflammation:			
0	1	0	< 0.001
+ (mild)	15	36	
++ (moderate)	15	0	
LFH			
0	30	36	NS
+	0	0	

LFH = lymphoid focllicle hyperplasia ; NS = not significant

The results of the histopathological test of the jejunum showed that there were differences in the width of villi, intervillous space, lymphocyte infiltration, grade of inflammation, and polymorphonuclear cell infiltration (table 5).

Table 5. Result of Histopathologic Test on The Jejunum

Jejunum	Chronic Non Infective Diarrhea (n=31)	Control (n=37)	p-value
Height of villi (μm)	314.11 ± 59.70	341.76 ± 76.06	NS
Height of crypt (μm)	180.01 ± 42.82	189.41 ± 58.15	NS
Width of villi (μm)	103.01 ± 17.81	125.59 ± 40.76	0.007
Crypt: Villous ratio	0.57 ± 0.16	0.57 ± 0.23	NS
Goblet cells number per 100 μm villi	4.31 ± 2.18	4.29 ± 1.53	NS
Intervillous space (μm)	43.60 ± 19.01	24.12 ± 11.58	<0.001
Inflammantory cells: Lymphocyte			
0	1	0	<0.001
+	21	36	
++	9	0	
Intraepithelial lymphocyte			
+	30	36	NS
++	1	1	
Plasma cell			
0	3	1	NS
+	28	35	
Eosinophil			
0	20	20	NS
+	10	15	
++	1	1	
Polymorphonuclear cells			
0	13	36	<0.001
+	17	0	
Grade of inflammation:			
0	1	0	0.002
+ (mild)	20	35	
++ (moderate)	10	1	
LFH			
0	27	36	NS
+	3	0	

LFH = lymphoid focllicle hyperplasia ; NS = not significant

The results of the histopathological tests of the terminal ileum showed differences in the Crypt/villous ratio, goblet cells number per 100 μm of villi, lymphocyte infiltration, grade of inflammation, and mucosal lymphoid follicle hyperplasia (table 6).

Table 6. Result of Histopathologic Test on The Terminal Ileum

Terminal Ileum	Chronic Non Infective Diarrhea (n=31)	Control (n=37)	p-value
Height of villi (μm)	287.71 ± 90.80	235.41 ± 73.32	0.013
Height of crypt (μm)	161.41± 47.62	186.22 ± 64.09	NS
Width of villi (μm)	119.63 ± 22.31	114.59 ± 34.20	NS
Crypt: Villous ratio	0.59 ± 0.21	0.88 ± 0.54	0.011
Goblet cells number per 100 μm villi	12.19 ± 4.39	14.99 ± 4.96	0.029
Intervillous space (μm)	46.90 ± 25.22	53.51 ± 25.19	NS
Inflammantory cells: Lymphocyte			
+	19	35	0.003
++	8	1	
Intraepithelial lymphocyte			
+	31	35	NS
++	0	2	
Plasma cell			
0	0	1	NS
+	27	35	
Eosinophil			
0	1	0	NS
+	15	15	
++	10	20	
+++	1	1	
Polymorphonuclear cells			NS
0	14	26	
+	12	10	
Grade of inflammation:			
0	1	0	0.006
+ (mild)	17	34	
++ (moderate)	9	2	
LFH			
0	9	33	<0.001
+	17	4	

LFH = lymphoid focllicle hyperplasia ; NS = not significant

The overall causes of chronic diarrhea in these patients were idiopathic/ nonspecific ileocolitis (48.5%), Irritable Bowel Syndrome (IBS) (18.2%), Crohn's disease (12.1%) etc. (table 7).

The presence of abnormalities in the small intestines coincided with that in the large intestines in 12 (36%) chronic non-infectious patients (table 8).

Table 8. The presence of abnormalities in the small and large intestines

Table 7. The Causes of Chronic Non-infectious Diarrhea

Causes	Frequency	Percent (%)
Idiopathic/non-specific duodeno-jejuno-ileo-colitis	16	48.5
Irritable bowel syndrome	6	18.2
Crohn's disease	4	12.1
Colon Polyp	2	6.1
Ulcerative colitis	2	6.1
Normal duodenojejuno-ileocolon	2	6.1
Eosinophilic duodenojejuno-ileocolitis	1	3.0

Table 8. The Presence of Abnormalities in the Small and Large Intestines

Abnormality of the small intestines	Abnormality of the large intestines +(%)	-(%)	Total (%)
+	12 (36)	8	20
-	6	7	13
Total	18(55)	15(45)	33(100%)

DISCUSSION

Most patients in the study were male. This finding was consistent with another study.[11] The mean age of the patients in this study was older than in another study on bloody diarrhea, which had a mean age of 30 years, but was consistent with a Korean study[11,12,13]. Most patients were economically well-to-do. This fits with the general observation that infectious causes of chronic diarrhea are more frequent in patients from lower socioeconomic classes.

The most frequent stool form was soft, non-bloody, non-steatorrhea (72.7%). This was in line with the findings of a previous study[12]. The most frequent duration of diarrhea of >24 weeks was different compared to other studies, which showed a duration of 1-240 months.[11]

An endoscopically abnormal duodenal bulb was found in only 2 (6%) patients, and an abnormal terminal ileum was found in only 12 (36.4%) patients. The abnormalities were best discovered with histopathology examination. In this study, we found normal endoscopic findings in 21 specimens from the terminal ileum, 31 specimens from the dudenal bulb, and 33 specimens from the descending part of duodenum or jejunum. However, histopathologically we found only 8 patients with normal small intestine, where as the rest had abnormalities. This finding shows the importance of histopathological examination in establishing a definite diagnosis, as has been reported in other studies.[14,15,16] Some reports have suggested that small and large intestinal biopsies should be routinely obtained from the endoscopy of patients with normal appearing mucosa with chronic lower GI tract symptoms.[14,17,18] It has also been recognized that biopsies from macroscopically normal mucosa in patients with Crohn's disease can demonstrate diagnostic abnormalities.[19,20]

We found lymphoid follicle hyperplasia in the jejunum, which may be due to inflammation. Lymphoid hyperplasia in the duodenum and jejunum is usually abnormal and is always associated with changes of duodenitis or jejunitis.[9] Through endoscopic examination, we also found lymphoid follicle hyperplasia in the terminal ileum. However, this finding still requires thorough evaluation in order to differentiate normal and pathological (infected or inflamed) tissue. In a normal terminal ileum, we can usually find lymphoid follicle hyperplasia containing lymphoid aggregates and IgG subclass-containing cells.[21,22,23] The prevalence of follicle lymphoid hyperplasia in this study was 3 out 30, or 10%, in the jejunum, and 17 out of 26, or 65.38%, in the terminal ileum. Such frequency was higher than findings from other studies, which showed lymphoid hyperplasia in 3% of 1000 consecutive autopsies[24,25]. Lymph folliculitis and lymphoid hyperplasia of the appendix and colon in ulcerative colitis have recently been reported.[26] Lymph folliculitis and/or lymphoid hyperplasia were supposed to be early lesions of ulcerative colitis.

Histopathologically, the villous width of the duodenal bulb of chronic diarrhea patients was longer than in the control group, but this was questionable.

Histopathologically, the lymphocyte and eosinophil

infiltration and grade of inflammation of the duodenal bulb in the chronic diarrhea group were lower than in the control group. To define whether this was caused by a mechanism other than inflammation, these findings will have to be studied more intensively.

In the pars descendens of the duodenum, based on histopathological examination, lymphocyte infiltration and the stage of inflammation and polymorphonuclear cells were much greater than in the control group. These findings differed from the results of other studies.[27,28,29.30]

In the jejunum, based on the histopathological examination, lymphocyte infiltration and the grade of inflammation and polymorphonuclear cells were higher than in the control group. These findings were also different from the results of the other studies.[27,28,29,30]

In the terminal ileum, the histopathological examination revealed that lymphocyte infiltration, grade of inflammation, polymorphonuclear cells and lymphoid follicle hyperplasia were greater than in the control group. These findings were also varied in literature.[27,28,29,30,31,32.33,34]

The most frequent cause was idiopathic/non-specific duodenojejunoileo-colitis. This finding was in line with another study, which reported the most frequent histological finding was nonspecific inflammation in chronic diarrhea patients.[11]

All of the 4 patients with Crohn's disease had terminal ileitis and colitis. This finding was in line with statements in the literature that Crohn's disease can affect both the small intestine and large intestine.[33,35] In two patients with ulcerative colitis, there were no small intestinal abnormalities, only colon abnormalities, and these findings were the same as in other literature.[36]

CONCLUSION

Through histopathological examination, we found increased lymphocyte infiltration, inflammation and lymphoid follicle hyperplasia in specified areas of small intestine in chronic non-infectious diarrhea patients. The histopathological appearance should be classified according to the disease.

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