Giardiasis and coeliac disease

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Carswell, F., Gibson, A. A. M., and McAllister, T. A. (1973). *Archives of Disease in Childhood*, 48, 414. **Giardiasis and coeliac disease.** The incidence of *Giardia lamblia* infestation, as shown by examination of the stools, is the same in normal and coeliac children. 93 patients who were suspected of having coeliac disease had upper intestinal biopsies examined for giardia infestation. These patients usually had at least one stool and/or duodenal juice sample examined for *G. lamblia*. 26 patients (14 coeliac, 12 noncoeliac) had giardiasis. Only 13 patients would have been diagnosed if stools alone had been examined. Patients with giardiasis were usually male, younger than the other patients, more likely to have concurrent bacterial infection in the bowel, and more likely to come from a lower socioeconomic group. When the jejunal biopsies of 57 coeliac patients, including those with and without giardiasis, were compared, *G. lamblia* were more commonly found in those patients with less severe histological changes.

Giardia lamblia infestation has been repeatedly suspected of causing malabsorption (Véghelyi, 1939; Cortner, 1959; Court and Anderson, 1959; Hoskins *et al.*, 1967; Morecki and Parker, 1967; Barbieri *et al.*, 1970; Brandborg, 1971). It has also been said to cause mucosal damage (Yardley, Takano, and Hendrix, 1964; Hoskins *et al.*, 1967) and a focal inflammatory lesion has been described (Yardley *et al.*, 1964). Despite this and the wide variation in incidence of giardiasis in some populations, e.g. 40% in institutions in Australia (Court and Stanton, 1959), 1.5 to 50% incidence in the U.S.A. (Nutter, Rodaniche, and Palmer, 1941; Peterson, 1957), there has been little attempt to study the incidence and effect of *G. lamblia* in patients with gluten-sensitive enteropathy. Accordingly, we decided to investigate prospectively the incidence and effect of *G. lamblia* infestation in a population made up of children who were clinically suspected of having coeliac disease. We also compared this incidence with a control population.

Methods

Our control population consisted of inpatients in the Royal Hospital for Sick Children. Patients who were regarded on clinical grounds (including normal stature

and normal bowel movements) as unlikely to have giardiasis or coeliac disease were studied. An attempt was made to collect 1 stool sample from such patients. 52 stool samples out of a possible 65 (80%) were collected. Each stool collected from both populations had three iodine preparations examined for *G. lamblia* cysts and one saline preparation examined for trophozoites (Cruickshank, 1965).

All patients in the test population were initially suspected of having coeliac disease, usually by clinicians other than the authors. Diagnostic assessment included measurement of height and weight, peripheral blood Hb, WBC and film examination, determination of plasma immunoglobulin concentrations by immunodiffusion, serum iron and whole blood folate determinations, x-ray determination of bone age and bone density, barium meal and follow-through, and repeated examination of the stool for parasites and pathogenic microorganisms. In some cases the faecal fat output was estimated. A firm diagnosis of coeliac disease was based on the finding of a flattened upper intestinal mucosa on biopsy when the patient was on a gluten-containing diet, and a clinical response to the withdrawal of gluten from the diet. The patients were usually kept in the wards until the clinical response to gluten withdrawal occurred. 93 test patients were examined and 58 of these were eventually shown to have coeliac disease. The final diagnoses in the 35 patients who did not have coeliac disease are shown in Table I. Most of these 93 patients had three separate stool specimens and one sample of duodenal juice examined for giardia. The duodenal juice was examined

TABLE I

Diagnosis in 35 patients initially suspected of having, but subsequently proven not to have, coeliac disease

Diagnosis	No. of patients
<i>Giardia lamblia</i> infestation	12
Psychosocial diarrhoea*	9
No abnormality detected	7
Low birthweight dwarfism	3
Constitutional dwarfism (small parents)	3
Cystic fibrosis	3
Post-gastroenteritis syndrome	2
Enteropathic coliform infection	1
Iron deficiency malabsorption	1
Hypo- γ -globulinaemia (Bruton type)	1
Milroy's disease with gut involvement	1
Transient gluten intolerance	1
Familial phosphaturic rickets	1
Hypothalamic astrocytoma	1

*This group includes children of small size with a severely disrupted family life and a history of diarrhoea as outpatients. They rapidly gained weight and did not have diarrhoea as inpatients though they not infrequently also had giardiasis.

both fresh for active motile giardia and fixed as air-dried smears by the Giemsa method.

All 93 patients had an upper small bowel biopsy performed. The biopsies were taken from the third or fourth part of the duodenum or within the first foot of the jejunum after fluorescent screening of the Crosby-Kugler capsule's position. The biopsies were orientated and mounted on stiff paper before fixing in 10% formal-saline. Serial paraffin-embedded sections were routinely examined with haematoxylin and eosin, periodic acid Schiff, and Giemsa staining techniques. All biopsies were examined for giardia (Fig. 1). After examination of multiple well-orientated sections, the biopsies were graded after the manner of Rubin and Dobbins (1965) into 5 grades. Grade 0 showed normal leaf and finger villi with uniform columnar epithelial cells, well-marked brush border, and no increased cellularity of the lamina propria. The grades 1 to 4 reflect increasing pathological change. They approximately correspond with Shiner and Doniach's (1960) classification so that 0 to 1 was 'normal'; 2 was 'partial villous atrophy'; 3 to 4 was 'subtotal villous atrophy'. In each histological grading the following features were considered in order of importance: villous structure, reduction in enterocyte height as measured in well-orientated sections at the villous tips, absence of the brush border, cellular infiltration, and vascularity of the epithelial cell layer and lamina propria. Thus, grade 4 had no detectable villous structure, but cuboidal epithelial cells with absence of the brush border, extensive cellular infiltration of the enterocytes and lamina propria, and increased vascularity.

The histological grading was carried out by A.A.M.G. without knowledge of the clinical features. The dissecting microscope was used to assess the villous structure in an equivalent 0 to 4 grading system. If the independent dissecting microscope and histological

FIG. 1.—*G. lamblia* on surface of duodenal mucosa. (Giemsa. $\times 530$.)

assessments disagreed by more than one grade, the histological sections were reassessed. Independent histological assessments by two observers (A.A.M.G. and F.C.) showed a high reproducibility of the histological grading system and a good correlation of this with the dissecting microscope grading.

Results

Patients with giardiasis. 26 of the 93 test patients had giardiasis.

Stools. 9 out of 52 control subjects (17%) had *G. lamblia* in the single stool sample tested. The test population had a total of 205 stools examined for cysts. In the patients who were eventually shown to have coeliac disease, 5 out of 32 (16%) had *G. lamblia* in the first stool examined. In the test patients who were shown not to have coeliac disease, 4 out of 23 (17%) were shown to have *G. lamblia* in the first stool examined. Clearly there is no difference in the incidence of positive stool tests for giardiasis between the control, noncoeliac, and coeliac groups. In the test group when multiple stools were examined, 9 patients had *G. lamblia* in the first stool. A further 4 patients had *G. lamblia* detected on subsequent stool examination. 13 patients who would not have been diagnosed as having *G. lamblia* infestation on the basis of stool examination were diagnosed on examination of the biopsy or duodenal juice.

Duodenal juice. In 15 of the 26 test patients with giardiasis, the parasites were found in the duodenal juice. In 8 of these patients giardia were detected in the juice but not in the stool.

In 10 of the 15 patients *G. lamblia* were also seen in the biopsy.

Biopsy. This showed *G. lamblia* in 15 out of the 26 test patients who had giardiasis. In 3 of these 15 patients, *G. lamblia* were not detected when the stool was examined.

Age and sex. Tables II and III show the age and sex incidence of the patients studied. There was a preponderance ($P < 0.002$) of males in the patients with giardiasis. None of the other differences shown is statistically significant.

TABLE II

Mean age (mth) of patients with (G+) or without (G-) *Giardia lamblia* infestation

	G+ve	G-ve
Coeliac patients	35	56
Noncoeliac patients	36	48
All population	35	53

TABLE III

Sex of patients (% males) with (G+) and without (G-) *Giardia lamblia* infestation

	G+ve	G-ve
Coeliac	79	48
Noncoeliac	75	39
All population	77	45

Associations of giardia infestation. Giardiasis is very common in immune deficiency (Heremans *et. al.*, 1966). Only 2 out of the 93 patients studied had an immune deficiency; both had giardiasis. 1 was a coeliac patient with an isolated absence of IgA from the plasma and 1 was a non-coeliac patient who had Bruton-type hypo- γ -globulinaemia.

G. lamblia infestation is said to be more common in persons living in unhygienic and overcrowded conditions or in institutions (Court and Stanton, 1959; Brandborg, 1971). In our series the distribution of patients by the social class of the father is shown in Fig. 2. It will be noted that in none of the patients with giardiasis was the social class of the father above 3, whereas 14% of the patients who did not have giardiasis had fathers of social class 1 or 2. In addition, approximately 40% of the patients with giardiasis came from severely disrupted homes. 1 child with giardiasis came

FIG. 2.—Distribution of patients by social class. (Classification of Occupations, 1970.) Above, 21 patients with giardiasis; below, 60 patients without giardiasis.

from a family of 9 children in which the father was unemployed and the family lived in one room and kitchen with an outside water closet. Several other children with giardiasis came from 1 parent families living in poor social conditions. Perhaps associated with the poor social circumstances of these children was the finding that 12% of children with giardiasis had an additional bowel infection (*Esch. coli* O127 in the stool of a 19-month-old child; *Shigella flexneri* and *Shigella sonnei* in 2 other children's stools), whereas only 2% of the children who did not have giardiasis had an additional bowel infection (*Esch. coli* 005 found in the duodenal juice). This differing incidence of infection is probably significant ($P < 0.05$ by 't' test; < 0.06 by the Fisher-Irwin test).

Effect of giardia infestation on small bowel biopsy. Fig. 3 shows the distribution of biopsy grades between the coeliac and noncoeliac population. The noncoeliac population was not a homogeneous group and perhaps it is not surprising that no significant difference was found in the severity of mucosal damage in those with and without giardiasis. There was a higher incidence ($P < 0.05$) of severe mucosal abnormality (grade 4 lesion) in those coeliac patients who did not have giardiasis as compared with those who did.

There was no significant difference in the incidence of other findings suggestive of malabsorption in the two groups of patients with coeliac disease (see Table IV). We did not observe any of the

FIG. 3.—Distribution of small bowel biopsy grades in (above) 57 coeliac patients (14 with giardiasis) and (below) 30 noncoeliac patients (11 with giardiasis). Patients with giardiasis are indicated by $\blacksquare$ and without giardiasis by $\blacksquare$.

acute focal inflammatory lesions which were described by Yardley *et al.* (1964) but not confirmed by Morecki and Parker (1967) or Brandborg (1971). Only in occasional cases did we observe possible penetration of the mucosa by the *G. lamblia* which were usually distributed along the surface of the villi (Fig. 1).

Discussion

It is apparent that infestation with *G. lamblia* may well be missed if only the stools are examined (Cortner, 1959; Yardley *et al.*, 1964). As the

TABLE IV

Comparison of incidence (%) of dwarfing,* low whole blood folate (<60 ng/ml), and jejunal dilatation and delay in passage of barium meal in patients with (G+) and without (G-) giardiasis

	Coeliac		Noncoeliac	
	G+ve	G-ve	G+ve	G-ve
Low whole blood folate	72	62	58	33
Dwarfing	73	67	70	57
Jejunal dilatation	85	78	50	72
Delay in passage of barium meal	46	47	11	39

*Height <10th centile on Tanner-Whitehouse chart.

incidence of positive results does not increase sharply with repeated stool sampling it seems unnecessary to examine more than 2 stools. Thereafter, upper intestinal biopsy and examination of the juice should establish or refute the diagnosis of giardiasis.

In view of the difficulty of correctly diagnosing the presence of *G. lamblia* infestation, it is perhaps worth reviewing the positions taken with regard to giardiasis, mucosal damage, and malabsorption. Brandborg *et al.* (1967), Morecki and Parker (1967), Barbieri *et al.* (1970), and Brandborg (1971) suggested that upper small bowel biopsy is normal or nearly normal on routine histological examination. Da Silva *et al.* (1964), Yardley *et al.* (1964), Yardley and Bayless (1967), and Hoskins *et al.* (1967) all found that a mild partial villous atrophy was commonly present in giardiasis, and Hoskins *et al.* (1967) found that there was some reversal of the mucosal appearance towards normal on repeat biopsy after treatment. On electron microscopy some reports have described damage to the microvilli (Takano and Yardley, 1965; Hoskins *et al.*, 1967; Barbieri *et al.*, 1970), whereas Morecki and Parker (1967), admittedly in a single patient, did not find evidence of damage to microvilli. In all these studies there are few data on examination of control samples and little emphasis on comparison with similar groups. In this study it has been shown that in coeliac disease *G. lamblia* are more likely to be present in those cases with less severe histological changes. It seems unlikely that this is due to more rapid passage of the damaging gluten through the upper small bowel in patients with coeliac disease and giardiasis, since Table IV does not show any evidence of more rapid passage of barium in coeliac patients with giardiasis.

Conflicting reports also occur in the literature as to the ability of *G. lamblia* to produce malabsorption. Cortner (1959) reported 4 cases of malabsorption and associated giardiasis, but did not offer a convincing exclusion of coeliac disease or of the effects of other treatment started simultaneously with the quinacrine used to eradicate the giardiasis. Kotcher *et al.* (1966) measured faecal fat excretion before and after treatment of giardiasis. They also measured xylose absorption in 4 patients with untreated giardiasis and failed to show malabsorption. Morecki and Parker (1967) described a patient who had a normal jejunal mucosa and had steatorrhoea which was absent after a course of mepacrine. Barbieri *et al.* (1970) reviewed 11 asymptomatic children with giardiasis. They showed that whereas only 2 out of 11 patients had normal lipiodol absorption before treatment

of the giardiasis, 6 had normal lipiodol absorption after eradication of giardiasis. Similarly, 3 out of 11 patients who had abnormal D-xylose absorptions before treatment had normal results after treatment with metronidazole.

The predilection of giardiasis for male children is interesting, and has not been previously reported. The present series has confirmed that giardiasis is commoner in patients living in poor social circumstances. The finding of increased incidence of bowel infections in giardiasis is consistent with the theory that overcrowding and neglect predispose to infestation. Both increased and reduced incidences of bacterial and other parasitic infections have previously been reported in giardiasis (see Dogiel, 1964, for a review). It may be that some of the conflicting evidence with regard to the effect of *G. lamblia* arises because the effects noted are due to the interaction of infection, infestation, disruption of bowel flora, and malnutrition (Yardley and Bayless, 1967). The fact that *G. lamblia* and the signs under review disappear after therapy (e.g. mepacrine or metronidazole) does not prove that the two are causally related since both these drugs affect organisms other than *G. lamblia*. It is of interest in this context to quote León-Barua and Lumbreras-Cruz (1968) who found that in most cases of diarrhoea 'due' to giardiasis, tetracyclines given in low doses suppress the diarrhoea, though parasites continue to be found in the stool. Furthermore, in cases of diarrhoea that persisted after eradication of the parasites, tetracyclines in low oral doses appear to be effective in eliminating the diarrhoea. More detailed studies of all the operating pathogenic factors are required.

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