

Atopic Manifestations Are More Common in Patients with Crohn Disease Than in the General Population

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Background: The role of TNF- α in Crohn disease is now well established and anti-TNF- α is frequently used as a second- or third-line treatment. Tumor necrosis factor- α (TNF- α) is traditionally associated with macrophages but has recently also been found in mast cells of the ileal wall in patients with Crohn disease. As it is well known that mast cells and TNF- α play important roles in atopic manifestations like asthma, allergic rhinitis, and eczema the aim of this study was to investigate whether these are seen more commonly in Crohn patients than in the general population. **Methods:** Patients with Crohn disease ($n = 308$), aged 18–50 years, living in the Linköping region in southeast Sweden, were asked to answer a questionnaire regarding the presence of any kind of atopic manifestations. The questionnaire was also sent to 930 controls collected from the Southeastern Region Population Registry. The controls were matched according to age, sex, and place of residence. **Results:** The response rate among the Crohn patients was 91% (280/308) and among controls 84% (779/930). Eczema was a significantly more frequent manifestation, being almost twice as common in Crohn patients (27%) as in the general population (16%). Adjustment by logistic regression for place of residence, gender, age and coexistence of any other atopic manifestation did not change the odds ratios significantly. **Conclusion:** Atopic manifestations as a group, and eczema as a single manifestation, are significantly more frequent in Crohn patients than in the general population.

Key words: Atopic disorders; Crohn disease; IBD; mast cells; TNF- α

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The etiology and pathogenesis of Crohn disease (CD) is complex and multifactorial, and includes environmental factors, disordered immune system, and luminal factors as well as genetics. Today we know there are mutations in specified genes (1–3). Some of these hereditary factors involve different types of cytokines, e.g. tumor necrosis factor- α (TNF- α) (4), which is known to take an important part in the pathogenesis of CD (5). This knowledge has recently led to the use of anti-TNF- α as a second- or third-line treatment for CD and it is now being used for maintenance treatment as well (6).

TNF- α is traditionally associated with macrophages (7, 8) but has recently also been found in mast cells of the ileal wall in Crohn patients (9, 10). It is well-known that mast cells and TNF- α play an important part in atopic manifestations like asthma, allergic rhinitis, and eczema (11). Earlier, there has been a discussion concerning atopic diseases and their possible concurrent prevalence with inflammatory bowel disease (IBD) and some series have shown an increased prevalence of atopic disease while others have not (12, 13).

The aim of this study was to investigate whether atopic manifestations such as asthma, allergic rhinitis, and eczema are more common in CD patients than in the general population.

Materials and Methods

Patients

Three hundred and eight patients with CD, aged 18 to 50 years and living in the southeastern region of Sweden (the county of Östergötland, the northern county of Jönköping and the southern county of Kalmar with a total population of approximately 680,000) were asked to complete a questionnaire regarding the presence of atopic diseases. In all patients the diagnosis was based on standard clinical, radiological, endoscopical, and histological criteria. No account was taken of whether the patients had ileal, colonic, or ileocolonic disease.

A total of 930 healthy subjects, in the same age range and

Table I.

Questionnaire	
1. Have You ever been in contact with a physician because of asthma?	Yes/No/Do not know
2. If the answer to the question above is Yes, did You during the past three years take any medication against asthma?	Yes/No
3. Do You have any siblings?	
4. Do You have any children?	
5. Have any of the following relatives ever been in contact with a physician because of asthma?	
Parents	Yes/No/Do not know
Siblings	Yes/No/Do not know
Children	Yes/No/Do not know
6. Have You ever been in contact with a physician because of allergic rhinitis?	Yes/No/Do not know
7. If the answer to the question above is Yes, did You during the past three years take any medication against allergic rhinitis?	Yes/No
8. Have any of the following relatives ever been in contact with a physician because of allergic rhinitis?	
Parents	Yes/No/Do not know
Siblings	Yes/No/Do not know
Children	Yes/No/Do not know
9. Have You ever been in contact with a physician because of atopic eczema?	Yes/No/Do not know
10. If the answer to the question above is Yes, did You during the past three years take any medication against atopic eczema?	Yes/No
11. Have any of the following relatives ever been in contact with a physician because of atopic eczema?	
Parents	Yes/No/Do not know
Siblings	Yes/No/Do not know
Children	Yes/No/Do not know

from the same cities as the cases, were randomly selected from the Southeastern Region Population Registry.

Questionnaire

Each subject enrolled in the study was asked to complete a questionnaire (Table I) regarding the presence of asthma, allergic rhinitis, and eczema among themselves and their 1st-degree relatives. They were also asked to register any medication they had received for any of these conditions during the past 3 years. The questionnaire was sent by mail in March 2000 and all subjects who did not answer within the period of 3 weeks were sent a reminder at that time.

Ethics

The study was approved by the Ethics Committee of the Faculty of Health Sciences of Linköping University.

Statistical analysis

Values are expressed as odds ratio (OR) and 95% confidence interval (CI) unless otherwise stated. The chi-squared test and logistic regression adjusted for age, gender,

place of residence, and coexistence of any other atopic manifestation were used when comparing cases and controls. Significance was set at a *P* value of less than 0.05. Calculations were performed with SPSS 11.0, SPSS Inc., Ill., USA.

Results

The response rate among the CD patients was 91% (280/308) and among the controls 84% (779/930) distributed locally according to Table II. In CD patients, we received answers from 145 women (51.8%) and 135 men (48.2%) and in the controls 413 (53.0%) women and 366 men (47.0%). Out of a total of 179 subjects who did not answer the questionnaire, 2 subjects returned a blank questionnaire and 4 letters were returned because the addressee was unknown (Table II).

Both patients and controls answered the questions in almost all cases but 2 subjects did not answer whether they had been in contact with a physician because of asthma, 13 because of allergic rhinitis and 9 because of atopic eczema. Atopic disease as a group was significantly more common among

Table II. Response rates among enrolled patients and controls

	Enrolled CD patients	Answering CD patients	Enrolled controls	Answering controls
Southern Kalmar County	25	23 (92%)	75	62 (83%)
Northern Jönköping County	61	55 (90%)	180	144 (80%)
Östergötland County	222	202 (91%)	675	573 (85%)
Total	308	280 (91%)	930	779 (84%)

CD = Crohn disease.

Table IIIA. Subjects in contact with physician

	CD patients	Controls	Odds ratio CD (95% CI)
Asthma <i>n</i> = 1052	40 (15%)	90 (12%)	1.36 (0.91–2.04) <i>P</i> = 0.14
Allergic rhinitis <i>n</i> = 1031	54 (20%)	143 (19%)	1.11 (0.78–1.58) <i>P</i> = 0.57
Eczema <i>n</i> = 1016	72 (27%)	121 (16%)	1.98 (1.41–2.77) <i>P</i> = 0.0001
Any atopic disease <i>n</i> = 1057	122 (44%)	259 (33%)	1.61 (1.21–2.14) <i>P</i> = 0.001

Table IIIB. Subjects with medication among those in contact with physician

	CD patients	Controls	Odds ratio CD (95% CI)
Asthma <i>n</i> = 126	25 (68%)	49 (55%)	1.49 (0.61–3.60) <i>P</i> = 0.38
Allergic rhinitis <i>n</i> = 195	41 (77%)	104 (73%)	1.23 (0.56–2.66) <i>P</i> = 0.61
Eczema <i>n</i> = 191	35 (50%)	74 (61%)	0.69 (0.37–1.30) <i>P</i> = 0.26
Any atopic disease <i>n</i> = 375	79 (68%)	180 (70%)	0.86 (0.54–1.41) <i>P</i> = 0.57

Table IIIC. Subjects with medication (incl. prescription free medication)

	CD patients	Controls	Odds ratio CD (95% CI)
Asthma <i>n</i> = 1055	41 (12%)	92 (12%)	1.30 (0.87–1.66) <i>P</i> = 0.20
Allergic rhinitis <i>n</i> = 1035	57 (21%)	143 (19%)	1.18 (0.84–1.66) <i>P</i> = 0.35
Eczema <i>n</i> = 1026	75 (28%)	123 (16%)	2.02 (1.45–2.81) <i>P</i> < 0.0001
Any atopic disease <i>n</i> = 1057	128 (46%)	261 (34%)	1.69 (1.28–2.24) <i>P</i> < 0.0001

CD = Crohn disease.

patients with CD ($P = 0.001$) and atopic eczema was almost twice as common among CD patients compared with the controls ($P = 0.0001$, Table IIIa). When comparing medication for the atopic disorders, as a marker of more severe symptoms, we found no differences between the CD patients and the controls that had been in contact with a physician (Table IIIB). However, when all patients taking prescription free-medications were included, we again found a difference between the two groups (Table IIIC). Medication for any atopic disease was more common ($P < 0.0001$) as well as for atopic eczema ($P < 0.0001$), where it was twice as common among the CD patients.

Data about parents were received in 237 out of 280 (85%) of the CD patients and in 692 out of 779 (89%) controls, including 1 subject in each group who was excluded because of adoption. In parents of CD patients, atopic disease was just as common as it was among parents of controls (Table IV). In this group, allergic rhinitis as a single manifestation seemed to

Table IV. Parents in contact with physician

	CD patients	Controls	Odds ratio CD (95% CI)
Asthma <i>n</i> = 946	43 (18%)	99 (14%)	1.33 (0.90–1.97) <i>P</i> = 0.16
Allergic rhinitis <i>n</i> = 948	41 (17%)	92 (13%)	1.46 (0.97–2.20) <i>P</i> = 0.067
Eczema <i>n</i> = 939	55 (23%)	133 (19%)	1.28 (0.89–1.84) <i>P</i> = 0.19
Any atopic disease <i>n</i> = 1049	95 (34%)	231 (30%)	1.25 (0.93–1.68) <i>P</i> = 0.14

CD = Crohn disease.

Table V. Siblings in contact with physician

	CD patients	Controls	Odds ratio CD (95% CI)
Asthma <i>n</i> = 967	39 (15%)	99 (14%)	1.12 (0.75–1.69) <i>P</i> = 0.57
Allergic rhinitis <i>n</i> = 983	49 (19%)	116 (16%)	1.27 (0.87–1.85) <i>P</i> = 0.23
Eczema <i>n</i> = 965	61 (24%)	135 (19%)	1.51 (1.05–2.16) <i>P</i> = 0.027
Any atopic disease <i>n</i> = 971	101 (39%)	242 (34%)	1.27 (0.94–1.71) <i>P</i> = 0.11

CD = Crohn disease.

be more common in parents of CD patients, but this did not reach statistical significance ($P = 0.067$).

Of the CD patients, 258 out of 280 (92%) answered the questions about their siblings, and among the controls 713 out of 779 (92%) responded. In the non-respondents we included 22 of the CD patients and 66 of the controls that did not have any siblings or were adopted. As well as in CD patients and controls, atopic eczema was more common ($P = 0.027$) among siblings of the CD patients than among siblings of the controls. It was, however, not more common with any of the other atopic manifestations or atopic disease in general (Table V).

Among CD patients, 153 (55%) had children at the time of the study, while 456 (59%) of the controls had children (ns). Of the CD patients, 139 out of 153 (91%) completed the questionnaire regarding their children and among the controls 433 out of 456 (95%). The children of both the CD patients

Table VI. Children in contact with physician

	CD patients	Controls	Odds ratio CD (95% CI)
Asthma <i>n</i> = 610	27 (18%)	69 (15%)	1.21 (0.74–1.99) <i>P</i> = 0.44
Allergic rhinitis <i>n</i> = 598	28 (18%)	53 (12%)	1.83 (1.10–3.04) <i>P</i> = 0.019
Eczema <i>n</i> = 608	56 (37%)	137 (30%)	1.39 (0.93–2.05) <i>P</i> = 0.10
Any atopic disease <i>n</i> = 589	68 (44%)	175 (38%)	1.24 (0.85–1.82) <i>P</i> = 0.26

CD = Crohn disease.

Table VII. All first-grade relatives in contact with physician

	CD patients	Controls	Odds ratio CD (95% CI)
Asthma <i>n</i> = 1052	83 (30%)	217 (28%)	1.10 (0.81–1.48) <i>P</i> = 0.77
Allergic rhinitis <i>n</i> = 1050	91 (33%)	209 (27%)	1.35 (1.00–1.82) <i>P</i> = 0.054
Eczema <i>n</i> = 1053	125 (45%)	310 (40%)	1.24 (0.93–1.64) <i>P</i> = 0.14
Any atopic disease <i>n</i> = 1059	171 (61%)	437 (56%)	1.25 (0.94–1.65) <i>P</i> = 0.13

CD = Crohn disease.

and controls showed a similarity to their grandparents regarding allergic rhinitis ($P = 0.019$), which appeared more often in the CD families than was expected (Table VI).

When the 1st-degree relatives were studied as a single group, we found that there were no significant differences between the two groups (Table VII). There was, however, a tendency towards a higher risk of atopic diseases among 1st-degree relatives of CD patients, and especially allergic rhinitis as a single manifestation ($P = 0.054$).

Discussion

Our results showed that atopic diseases were more common among patients with CD and their 1st-degree relatives than in a control group of healthy individuals and their 1st-degree relatives. These data did not change when corrected for gender, age, place of residence, and concurrent atopic manifestations in logistic regression.

The cases themselves showed almost twice the risk of having eczema and also a higher risk of suffering from some other kind of atopic disease, as well as a need for treatment. These data were similar among siblings of the cases, while among parents and children of the patients with CD, there was a higher frequency of allergic rhinitis than expected. There was also a distinct tendency towards a higher frequency of allergic rhinitis in all 1st-degree relatives of the CD patients. The frequency figures for the controls are difficult to compare with those of earlier studies in Sweden, since most studies are conducted on children. However, these studies (14, 15), as well as some of the few studies on adults (16–19), are well in line with the figures found in our study.

Earlier studies, using family and personal history and/or cutaneous prick tests, have shown conflicting results regarding a possible association between IBD and allergic diseases (12, 13, 20–26). Troncone et al. conducted prick tests with common inhalant allergens on 122 patients affected by CD or ulcerative colitis (UC) and did not find any differences compared to a control group chosen from the hospital staff and patients undergoing minor surgery (13). Mee et al. did not find any overall differences in prick test response in their relatively small study but found a significant difference in a higher response to food allergens among patients with IBD

(22). Furthermore, Desreumeaux et al. have shown an airway-like inflammation of the gut in patients with type-2 mediated disease, like atopy and asthma (27), as well as an increased intestinal permeability in patients with bronchial asthma (28). Gilat et al. performed a study in Israel on children with IBD where they noted a high frequency of recurrent respiratory infections (29), which could be a sign of a more sensitive epithelium both in the airways and in the intestine in IBD patients. In the same manner, Herrlinger et al. found that IBD patients show significantly decreased pulmonary function in comparison to healthy controls, an impairment that persisted during remission but was more pronounced during active disease (30).

An interesting finding is that various manifestations show differences in prevalence among different generations. In parents as well as in children of CD patients, allergic rhinitis was the most common manifestation, while in CD patients and controls, as well as in their siblings, atopic eczema was almost twice as common as in the controls. Similar experiences regarding the family pattern in atopic disease have not been seen in epidemiological studies (31). The finding that atopic eczema is more common in CD was reported earlier by Pugh et al. (12) in 200 patients, while all kinds of atopic diseases were more common in patients with UC ($n = 300$). In the study by Gilat et al. (29) a significantly higher prevalence of eczema was found in CD patients, as well as in their 1st-degree relatives. In stool samples from patients with IBD, especially in patients with active mucosal inflammation, an elevated level of eosinophil cationic protein (ECP) has been found (32). In infants and children with atopic eczema and food allergy, an increase in ECP and TNF- α in stool has been shown after oral challenge with cow's milk, indicating an association with intestinal inflammation (33, 34). Furthermore, there are several interesting similarities between atopic eczema and CD. Both are diseases in a barrier system towards various environmental factors, to some extent they have a genetic predisposition to environmental trigger factors and sometimes the inflammation leads to severe fibrosis. There are, however, some differences regarding the role of T-helper lymphocytes (Th) and the pathophysiology. CD is generally considered to be mediated by a Th-1 response, while atopic disease is mediated by a Th-2 response (35). According to this paradigm of competing responses between Th-1 and Th-2, it is difficult to explain our findings. There are, however, similar difficulties regarding other extraintestinal manifestations in IBD, such as primary sclerosing cholangitis (PSC), which is considered a Th-1 disorder (35) but is seen in UC, a Th-2-mediated disease (36, 37). Another finding opposing the classical Th-1/Th-2 paradigm is that memory cells belonging to both Th-1 and Th-2 cells can coexist (38).

One possible confounding factor in our study could be smoking, since it is known that as many as 50% of CD patients are smokers (39, 40) and there is also an elevated frequency of smokers in families with CD (41). Smoking has also been shown to give rise to earlier relapse after induced

remission (42,43), as well as smoking cessation being favorable in CD (44). Maternal and early tobacco exposure has been considered to be important in the development of asthma in the early years (45). It has not been shown that tobacco smoking causes asthma more frequently, but may rather be associated with more severe asthmatic symptoms (46). Early exposure to tobacco smoke seems to be of less importance in other atopic diseases (47), and in a recent large Swedish study an association was found between current tobacco-smoke exposure and a low risk for atopic disorders, in smokers as well as their offspring (48).

A relative over-diagnosis of other disorders among patients with CD is possible, as a result of proximity to the medical profession. However, the contrary might be possible as well, as patients suffering from a chronic disease might hesitate to seek medical attention for disorders that might seem to be relatively minor compared to CD. Neither of these suppositions has, to our knowledge, been shown to be true. The diagnosis of the different atopic disorders were not verified by a specialist, nor do we know whether the physician contacted in the questionnaire was a general practitioner or a specialist in allergology or dermatology. However, any diagnostic errors would most likely occur in a similar manner in both groups.

When conducting multiple analyses of this kind on a limited material, there is always a risk of finding significant differences by chance. However, our findings stand firm even if we change the limits of significance to a *P* value of less than 0.01, and this refutes the suggestion of these being just random findings.

In conclusion, our data show that atopic disease, as a group, and atopic eczema as a single manifestation are more common in patients with CD than in a control group from the general population. It seems that there is an association between atopic eczema and CD and we propose further investigation of the mast cell and responses to the intestinal flora in the pathogenesis of IBD.

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