

Non-infective colitis in infancy: evidence in favour of minor immunodeficiency in its pathogenesis

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Abstract

Forty two infants below the age of 2 years presenting with chronic non-infective diarrhoea and shown to have histologically proved colitis were investigated over a five year period. Allergic colitis was the most common cause of colitis, accounting for 62% of the cases. Other colitides diagnosed included: non-specific colitis, autoimmune enterocolitis, and ulcerative colitis accounting for 10% each; severe combined immunodeficiency 7%, and Crohn's disease 3%. A positive family history and a personal history of atopy were obtained in 48% and 29% of the cases respectively. Serum immunoglobulin A, IgG₂, and IgG₄ were very low in over 50% of the entire cohort of infants with colitis; 66% of those with severe combined immunodeficiency, autoimmune enterocolitis, and ulcerative colitis (n = 11) had low CD3 and CD4 T lymphocytes with an accompanying increase in CD8 in two thirds of those with severe combined immunodeficiency. T lymphocytes were normal in those with allergic colitis. Thus infants with proved non-infective colitis as a group show a high prevalence of IgA, IgG₂, and IgG₄ deficiency. It is likely that this minor deficiency of mucosa associated immunoglobulin production has a role in the pathogenesis of the colitic process.

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Keywords: infants; rectal bleeding; colitis; serum immunoglobulin A; immunoglobulin G subclasses

Colitis in infancy and early childhood comprises a heterogeneous group of conditions¹; while infective colitides are the commonest overall,²⁻⁴ allergic colitis,^{5,6} and other specific and non-specific colitides are described.^{7,8} Food allergy is an important cause of non-infective colitis in the first two years of life.⁹⁻¹¹ Ulcerative colitis and Crohn's disease are uncommon in this age group.¹²

There have been few studies of non-infective infantile colitis and none of immune function in these children.

In this study we discuss the clinical, pathological, and therapeutic findings in a group of infants presenting at less than 2 years of age who had histologically proved colitis. We pay particular attention to their immune function.

Methods

PATIENTS

All children aged less than 2 years referred with recurrent non-infective bloody diarrhoea over the five year period January 1990 to December 1994 were recruited into the study.

All patients had clinical and endoscopic assessment and a histological diagnosis of colitis. The following investigations were routinely performed: full blood count and differential white cell count, serum albumin, serum immunoglobulins and immunoglobulin G subclasses, nitroblue tetrazolium test, barium meal and follow through, technetium white cell scan, and intradermal skin prick test to an assortment of allergens. Stool cultures were negative for parasitic, bacterial, and viral isolates, and tests for *Clostridium difficile* toxin were negative in all cases.

COLONOSCOPY

Colonoscopy with multiple biopsies was performed in all patients using an Olympus PCF-20 colonoscope.

HISTOLOGICAL DIAGNOSTIC CRITERIA

Ulcerative colitis

Diffuse mucosal inflammatory cell infiltration, with crypt architectural distortion, loss of goblet cells, and Paneth cell metaplasia.

Crohn's disease

Evidence of transmural inflammation and focal inflammatory cell aggregation with non-caseating epithelioid granuloma formation.

Allergic colitis

Normal morphology with an increased inflammatory cell infiltrate, containing an increase in eosinophils which clump together, degranulate, and infiltrate the epithelium.

Non-specific colitis

Mixed chronic inflammatory cell infiltrate within the lamina propria with no specific features of ulcerative colitis or Crohn's disease.

Autoimmune enterocolitis

Chronic inflammation consisting almost entirely of plasma cells and lymphocytes with or without focal cryptitis in association with positive serological investigations (positive smooth muscle and gut autoantibodies).

Results

Over the period 1990 to 1994, 42 infants who fulfilled the inclusion criteria of histologically proved non-infective colitis were investigated.

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Table 1 Clinical features of 42 infants at presentation with colitis

Male:female:	26:16			1.6:1		Total	Percentage
	AC	NSC	SC	IBD	AIE		
No of cases	26	4	3	5	4	42	100.0
Age of onset < 6/12	18	3	1	3	3	28	66.7
Signs and symptoms							
Diarrhoea	24	3	3	5	4	39	92.8
Rectal bleeding	20	4	1	5	1	31	73.8
Weight loss	18	2	3	4	3	30	71.4
Abdominal pain	13	2	0	2	0	17	40.5
Anorexia	9	2	2	1	2	16	38.1
Recurrent infections	6	1	3	3	1	14	33.3
Abdominal distention	8	0	1	0	1	10	23.8
Constipation	2	1	0	0	0	3	7.1
Vomiting	10	1	1	1	1	14	33.3
Fever	2	0	3	1	1	7	16.7
Consanguinity	0	1	0	1	2	4	9.5
Family history							
Atopy/asthma	15	1	0	3	1	20	47.6
IBD	3	0	0	1	0	4	9.5
Atopy in patient	9	0	1	1	1	12	28.6
Feeding							
Breast milk only	8	2	1	1	2	14	33.3
Cows' milk formula	8	1	1	1	0	11	28.6
Soya formula	3	0	0	0	0	3	7.1
Mixed	7	1	1	3	1	13	30.9
Weight							
< 3rd centile	15	2	3	3	3	26	61.9
Height							
< 3rd centile	8	1	3	2	1	15	35.7

AC = allergic colitis; NSC = non-specific colitis; SC = severe combined immunodeficiency; IBD = inflammatory bowel disease (ulcerative colitis and Crohn's disease); AIE = autoimmune enterocolitis.

Table 2 Site of macroscopic colonic abnormality in 42 infants undergoing endoscopy. All were confirmed on histological examination to have a colitis. Total colonic examination was achieved at endoscopy in 35/42 (83%)

	No	Percentage
Rectosigmoid	13	30.9
Pancolitis	15	35.7
Normal	7	16.7
Rectum to hepatic flexure	5	11.9
Others	2	4.8
Total	42	100

Table 3 Histological diagnoses in 42 consecutive cases of non-infective colitis in children aged < 2 years at presentation

	No	Percentage
Allergic colitis	26	61.9
Non-specific colitis	4	9.5
Autoimmune enterocolitis	4	9.5
Ulcerative colitis	4	9.5
Combined immunodeficiency	3	7.1
Crohn's disease	1	2.8
Total	42	100

Males were more common than females (ratio 1.7 to 1). Diarrhoea, bloody stools, and weight loss were the most common presenting symptoms. Abdominal pain, anorexia, and vomiting occurred in 41%, 39%, and 33% of the cases respectively (table 1). In 66% of infants the symptoms started before the age of 6 months, and the duration of the symptoms before presentation ranged from two weeks to 14 months (mean duration 3.5 months).

A personal history of atopy was present in 29% overall. This was commonest in those with allergic colitis (35%) being found in 20% of those with specific inflammatory bowel disease and 12% of those with autoimmune related colitis.

A positive family history of atopy/asthma was found in 48% of all the cases. Over 60% of the atopic relatives were grandparents, uncles and

aunts, and cousins. A quarter of the infants themselves had a personal history of atopy or asthma or both. Thirty three per cent of the cases were exclusively fed on breast milk at the onset of the symptoms and another 31% were on breast and artificial milk. Recurrent upper respiratory infections were recorded in 33% of the cases.

Sixty two per cent of the cases had a weight less than the third centile for age and sex at presentation, and 36% a height less than the third centile.

All infants underwent colonoscopy and a total colonoscopic examination was achieved in 83% (35/42). Table 2 shows that during the endoscopic examination, macroscopic abnormalities of the intestine were evident in 83% of the patients. A pancolitis was found in 36% and inflammatory changes confined to the recto-sigmoid 31%. The rectum was macroscopically abnormal in 78% of cases. The endoscopy was macroscopically normal in 17% of the cases, and all of these had allergic colitis on histology.

Allergic colitis accounted for 62% of cases of colitis in the infants, while non-specific colitis, autoimmune enteropathy, and ulcerative colitis each accounted for 10% of the cases. Crohn's colitis was seen in only one male infant who was 18 months old (table 3).

Anaemia (haemoglobin < 105 g/l) was observed in 36% of the cases at presentation, with a mean haemoglobin concentration of 98 g/l. Thrombocytosis, increased erythrocyte sedimentation rate, and low albumin concentrations were observed in 56%, 49%, and 55% respectively, and eosinophilia in six cases (14%) (table 4). The nitroblue tetrazolium test and skin prick tests were normal in all the infants.

The T cell lymphocyte subset population showed a low CD3 and CD4 in two thirds of those with severe combined immunodeficiency (SCID) and three quarters of those with

Table 4 Laboratory findings at presentation in 42 infants with histologically proved colitis

	No (total)	Percentage
Anaemia (Hb < 105 g/l)	15 (42)	35.7
Eosinophilia (> 800 abs)	6 (42)	14.3
Thrombocytosis (> 4 × 10 ¹¹)	23 (41)	56.1
Raised ESR	18 (37)	48.6
Albumin (< 35 g/l)	23 (42)	54.8
NBT test normal	12 (12)	100
RAST negative	32 (32)	100
Positive autoantibodies		
Smooth muscles	2 (26)	7.7
Gut	3 (26)	11.5
Others	0 (26)	0.0
T lymphocytes		
Low CD3 and CD4	6 (13)	46.1
Abnormal PHA response	3 (9)	33.3
Immunoglobulins		
IgG (< 3.1 g/l)	10 (38)	26.3
IgA (< 0.3 g/l)	18 (38)	47.3
IgE (> 22 IU/ml)	3 (22)	13.6
IgG ₂ (< 35 mg/dl)	16 (27)	59.2
IgG ₄ (< 4.8 mg/dl)	13 (27)	48.1

Others = antinuclear, mitochondrial, reticulin, and gastric parietal cell antibodies; ESR = erythrocyte sedimentation rate; Hb = haemoglobin; PHA = phytohaemagglutinin.

autoimmune enterocolitis, with a raised CD8 in two of the three patients with SCID who had graft versus host disease. An abnormal phytohaemagglutinin (PHA) response was observed in all the patients with autoimmune enterocolitis, and one third of patients with SCID. Both the T cell lymphocyte subsets and the PHA response were normal in those with allergic colitis and non-specific colitis. Immunoglobulin G concentrations were below the age related minima (< 3.1 g/l) in 26% of the infants, and low IgA concentrations (< 0.3 g/l) were found in 47%. Low IgG₂ (< 35 mg/dl) and IgG₄ (< 4.8 mg/dl) subclasses were observed in 59% and 48% of the infants studied respectively. This was due to a high prevalence in those with allergic colitis, where 71% had low IgG₂ and 50% low IgG₄, and in ulcerative colitis where three quarters of the cases had low IgG₂ and IgG₄ (table 5).

RESPONSE TO TREATMENT

Table 6 shows that 77% of the infants with allergic colitis had remission of their symptoms and started gaining weight on dietary manipulation within the first three months of treatment, while only 20% of those with specific inflammatory bowel disease (ulcerative colitis and Crohn's disease) who were on steroids, salazopyrine, and dietary management went into remission in the first three months of treatment. Those with severe combined immunodeficiency and autoimmune enterocolitis responded to immunomodulation slowly, with only a quarter having a remission of the symptoms within six months of the start of treatment.

Table 5 Percentage of each group of infants with colitis with low circulating concentrations of IgA, IgG₂ and IgG₄ subclasses and with abnormal T cell subset counts

	AC	NSC	AIE	UC	SCID
Immunoglobulins					
Low IgA	(23) 47.8%	(3) 66.6%	(4) 50.0%	(4) 50.0%	(3) 33.3%
Low IgG ₂	(14) 71.4%	(2) 100.0%	(4) 100.0%	(4) 75.0%	(2) 50.0%
Low IgG ₄	(14) 50.0%	(2) 50.0%	(4) 0.0%	(4) 75.0%	(2) 100.0%
T lymphocyte					
Low CD3 and CD4	(3) 0.0%	—	(4) 75.0%	(2) 50.0%	(3) 66.6%
Abnormal PHA	(3) 0.0%	—	(2) 100.0%	(1) 0.0%	(3) 66.6%

The figures in parentheses are the numbers of patients tested.

AC = allergic colitis; NSC = non-specific colitis; AIE = autoimmune enterocolitis; UC = ulcerative colitis; SCID = severe combined immunodeficiency; PHA = phytohaemagglutinin.

Discussion

This study showed that evidence of minor immunodeficiency is common in infants with non-infective colitis. In agreement with previous studies we have confirmed that in this age group the commonest cause of non-infective colitis is allergic colitis.^{1 5 6 9 11 14 15} Ulcerative colitis, non-specific colitis, autoimmune enterocolitis, and severe combined immunodeficiency accounted for only approximately one third of the cases, occurring with the same frequency.

Serum IgG₂ and IgG₄ deficiency commonly coexisted with deficiencies of IgA, raised IgE or both in this group of infants with colitis.^{16 17} These immunoglobulins have a role in health in protecting the individual against the uncontrolled absorption of whole proteins and complex antigens from the gastrointestinal lumen. Previous work has shown that the formation of immune complexes, particularly IgA specific immune complexes, may contribute to the release of goblet cell mucus onto the intestinal surface, thus preventing the penetration of antigens or the adherence of infectious agents.¹⁸ A deficiency of the serum immunoglobulins may lead to failure of antigen-immunoglobulin complex formation, resulting in intact antigen absorption and sensitisation of the individual. With re-exposure to dietary antigen, minute quantities of allergen may be absorbed and result in allergic symptoms. A vicious cycle of allergic reaction with increased allergen uptake across a disrupted mucosal surface may ensue. Uptake of non-specific intestinal antigen can in turn evoke an IgG mediated reaction which may predispose to chronic disease.¹⁹

Increased intestinal permeability, which is a genetically expressed defect that predisposes to the development of inflammatory bowel disease, has been reported.²⁰ One of the genetic defects reported here is probably a deficiency of immunoglobulin A, IgG₂, and IgG₄ subclasses which predisposes individuals to the absorption of whole antigens, an IgE mediated immunological response, and the release of inflammatory mediators, resulting in an enterocolitis. The inflamed intestinal epithelium allows more antigens to cross the mucosa and the vicious cycle continues.

Anaphylatoxins stimulate macrophages to release prostaglandin E₂, thromboxane B₂, and leukotriene B₄,²¹ thus initiating and maintaining the inflammatory and tissue damaging process (type 2 and 3 hypersensitivity).

IgG₁ secreting plasma cells are the immunocyte class showing by far the greatest expansion

Table 6 Time to clinical remission in 42 children aged < 2 years with non-infective colitis treated as follows: allergic colitis, dietary exclusion(s) with/without sodium cromoglycate; autoimmune enterocolitis (AIE), immunosuppression; non-specific colitis (NSC), ulcerative colitis, and Crohn's disease (IBD), immunosuppression and dietary manipulation

	No	< 3 months	3-6 months	> 6 months
Total	42	47.6%	23.8%	28.6%
Allergic	26	76.9%	15.4%	7.7%
AIE	4	—	25.0%	75.0%
NSC	4	—	75.0%	25.0%
IBD	5	—	20.0%	80.0%
SCID	3	—	33.3%	66.6%

in specific inflammatory disease.²² The upregulation of IgG₁ is probably a compensatory mechanism that can occur when the other subclasses are low, as seen in these infants.

A family history of atopy is very common in infants with colitis in this and other studies.^{9-11 14 23} These infants are prone to recurrent infections of the upper respiratory tract, which may be due to the IgG₂ and IgG₄ subclass deficiency¹⁶ as seen in our patients. The finding of a negative intradermal skin prick test in our patients is not unusual, since infants have a poor response to such tests.²⁵

In this series, the T cell function was abnormal in patients with severe combined immunodeficiency, autoimmune enterocolitis, and ulcerative colitis, but largely normal in those with allergic and non-specific colitis. The low CD3 and CD4 T lymphocyte subset population with a raised CD8 in those with SCID probably reflects graft versus host disease (GVHD) due to immunocompetent lymphocytes from the mother. The endoscopic and histological findings in two of these patients were in keeping with GVHD. Those with autoimmune enterocolitis had plasma cell plus lymphocytic infiltration of the lamina propria and the mucosa, with positive smooth muscle and gut autoantibodies.

A third of the infants in this study were exclusively breast fed when they developed colitis. Previous studies in infants fed cows' milk based formulas from birth have suggested that this group may be at a higher risk of developing allergic colitis. The condition is, however, described in children fed other whole protein milk formulas (soybean) and in infants fed on breast milk.^{14 24} In this latter group, exclusion of cows' milk, egg, and soybean products from the maternal diet may alleviate the infant's symptoms.

The outcome of treatment with exclusion diet alone was excellent in the children in this study with allergic colitis. Infants with other causes of colitis took longer to go into remission, requiring immunosuppression. This group frequently relapsed when intercurrent infections occurred. No case of non-specific colitis went on to develop specific inflammatory bowel disease during follow up within the time course of this study.

We have shown that infants with non-infective colitis commonly have an associated minor immunodeficiency. We suggest that in allergic colitis low levels of IgA, IgG₂, and IgG₄ might impair the function of mucosal defences against macromolecular passage across the mucosal barrier, thus predisposing to an aller-

gic inflammatory response and mucosal injury. In ulcerative colitis it seems more likely that the minor immunodeficiency alluded to here is a result of an underlying immunodysregulation, although the findings of specific IgE reagent antibodies to cow's milk in as many as 30% of children with ulcerative colitis implies that loss of barrier function in these children might also predispose to allergic responses.

In this study population—as in others previously—allergic colitis was the commonest cause of non-infective colitis in infancy and this responded excellently to exclusion diet alone. A positive family and personal history of atopy was common in infants with allergic colitis and in this group the rectum was invariably affected. Macroscopic appearance at endoscopy did not discriminate between normality and allergic colitis, and for this reason mucosal biopsy is considered mandatory to make the diagnosis.

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