Epidemiological Survey on Chronic Inflammatory Bowel Disease Developed during Childhood in Japan, and a Case-Control Study on Nutrition during Infancy

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An epidemiological survey was performed from 1979 to 1993 on Japanese patients who developed ulcerative colitis (UC) or Crohn's disease (CD) during childhood. A case-control study was also conducted concurrently in order to assess whether artificial feeding during infancy (up to 4 months after birth) could be a risk factor for these diseases. The cumulative number of patients until 1993 was 578 cases for UC (sex ratio, 1.1:1.0) and 260 cases for CD (sex ratio, 1.4:1.0). There was almost no change in the number of new cases of UC and CD per year after 1978, showing cases of around 32 (mean $\pm$ SD; 32.1 ± 6.8) per year for UC and 16 (15.7 ± 6.3) per year for CD. A case-control study was performed on 133 cases of UC and 42 cases of CD. The 2×2 contingency tables were prepared to calculate the odds ratio, significance and 95% confidence interval. Comparison between the group fed exclusively by breast milk or mixed, and the group fed by artificial (bottle) feeding alone for the development of inflammatory bowel disease, showed the following results: in UC, the odds ratio was 0.53 and the 95% confidence interval was 0.31 to 0.89; and in CD, the odds ratio was 0.30 and the 95% confidence interval was 0.13 to 0.70. These results indicated that breast feeding during infancy until postnatal 4 months might decrease the development of chronic inflammatory bowel disease.

Key words: case-control study; Crohn's disease; feeding during infancy; inflammatory bowel disease; ulcerative colitis

Ulcerative colitis (UC) and Crohn's disease (CD), which are referred to as chronic inflammatory bowel disease (IBD), are chronic intestinal inflammatory diseases of which the pathogenesis and pathologic state are still largely unknown. Compared to Western countries, the incidence of IBD is less frequent in Japan. IBD often develops in adults at the age of around 20 years and therefore, has been regarded as rare in Japanese children.

Cooperating with the Research Committee of Inflammatory Bowel Disease of the Ministry of Health and Welfare of Japan, we conducted a nationwide epidemiological survey using a questionnaire from 1979 for the purpose of clarifying the development and substantial state of IBD in Japanese children. The cumulative num-ber of patients during a 15-year period, from 1979 until 1993, was 578 cases for UC and 260 cses for CD.

Here we present the results of our study on the epidemiological tendency of childhood IBD development in Japan and the results of a concurrently conducted case-control study on feeding during infancy until postnatal 4 months and the development of IBD.

Materials and Methods

Nationwide epidemiological survey

The survey was conducted by mailing a questionnaire to a total of 344 institutions through-

Abbreviations: CD, Crohn's disease; IBD, inflammatory bowel disease; UC, ulcerative colitis

Table 1. Diagnostic criteria for UC

Answer **a** and one of the items under **b**.

a   Present or past history of persistent or recurrent mucous and bloody stool or melena.

b i)   Endoscopy shows 1) fragile rough or granular mucosa with liability of hemorrhage (contact hemorrhage) and mucous, bloody and purulent secretion on mucousa, and 2) multiple erosions/ulcers or pseudopolyposis.

ii)   Biopsy shows inflammatory response mainly on the mucosa often with erosion, crypt abscess, bizarre arrangement of the glands and transformation of the epithelium.

iii)   Barium enema shows 1) transformed mucosa whose surface is rough or granular and 2) multiple erosions/ulcers or 3) pseudopolyposis, sometimes with intestinal stenosis or shortening.

iv)   Surgical resection or autopsy shows typical macroscopic and histological findings of UC. However, infectious colitis such as bacillary dysentery, amebic dysentery, and schistosoma japonicum and tuberculous colitis as well as radiation colitis, ischemic colitis and granulomatous colitis must be excluded.

Note 1.   Keep in mind that some patients do not notice blood in their stool.
Note 2.   When it is difficult to make a definite diagnosis because of "unclear" findings, the case should be classified as "suspect"; then a definite diagnosis should be made if distinctive findings are noticed in recurrent attacks.

UC, ulcerative colitis.

out Japan, including pediatric clinics and pediatric surgical departments at university hospitals, pediatric hospitals and pediatric clinics at general hospitals with over 390 beds. The questionnaire included questions on the age at onset, extent of the disease, symptoms and feeding during infancy.

The subjects of the present survey were patients aged under 15 years who consulted any of the above-listed institutions to which the questionnaire was sent, and were newly diagnosed as having UC or CD according to the diagnostic criteria shown in Table 1 (The Research Committee of Ulcerative Colitis of The Japanese Ministry of Health and Welfare, Diagnostic Criteria Section, 1975) and Table 2 (Crohn's Disease Study Committee of the Japanese Society of Gastroenteology, 1976), determined by the Specific Disease Intractable Bowel Disturbance Survey and Research Group of the Japanese Ministry of Health and Welfare or the Japanese Society of Gastroenterology Crohn's Disease Study Committee.

The survey was conducted annually from 1979 to 1993 by mailing a questionnaire in order to accumulate cases.

Case-control study on feeding during infancy and the onset of IBD

Patients
IBD children who were diagnosed and reported from 1978 to 1988 included 334 cases of UC (male; 174, female; 160) and 135 cases of CD (male; 75, female; 60). Among these, those whose feeding until postnatal 4 months was recorded on the questionnaire were studied.

UC: 264 cases (male; 130, female; 134), with a mean age of 10 years and 6 months (range from 2 months to 15 years and 10 months).

CD: 94 cases (male; 56, female; 38), with a mean age of 11 years and 3 months (range from 2 months to 15 years and 9 months).

Controls
Since the number of cases of both UC and CD is rather small, the study required 2 controls for each UC patient and 3 controls for each CD patient for statistical analysis.

Table 2. Diagnostic criteria of CD

A case having **i)** to **iii)** of the following morbid states which fulfill the clinical and pathological conditions for CD is classified as "suspect."

A case having **i)** to **iii)** plus one out of **iv)** to **vi)** is classified as "definite."

When a case has **iv)** and two out of **i)** to **iii)** however, it can also be regarded as "definite."

Intestinal tuberculosis, ulcerative colitis, ischemic enteritis/colitis, radiation enteritis/colitis, intestinal Behçet disease, non-specific intestinal ulcer, non-specific multiple small intestinal ulcer, and acute terminal ileitis must first be excluded as possible problems.

  i)   Skipping or regional morbidity
  ii)   Cobble stone appearance or longitudinal ulcer
  iii) Full thickness inflammatory reaction (tumor or stenosis)
  iv)   Non-caseous sarcoid-like granuloma
  v)   Fissure or fistula
  vi)   Affected anal region (intractable ulcer, atypical anal fistula, or anal fissure)

Note 1. This disease is classified according to the affected region. Example: CD of the ileum, CD of the ileum and colon, CD of the colon.
Note 2. Regional colitis (grenulomatous colitis) is regarded as CD.
Note 3. Histological examination of the regional lymph nodes is recommended in surgical patients to differentiate CD from intestinal tuberculosis.
CD, Crohn's disease.

The hospitals at which the IBD children were examined or the collaborating institutions of the Intractable Inflammatory Bowel Disturbance Survey and Research Group of the Japanese Ministry of Health and Welfare were requested to select the controls and to administer the questionnaire.

They were instructed to choose controls in a randomized manner from healthy individuals or outpatients excluding chronic disease patients matched for age, sex and block of birth (all Japan was divided into 7 blocks), because there are differences in the number of IBD patients due to sex, age and block of birth (Urashima et al., 1996). The questionnaire was filled out by selecting one applicable answer from the below-mentioned i) to iii) concerning feeding during infancy (until 4 months of age) in each selected control: i) breast feeding only, ii) mixed feeding and iii) artificial feeding only.

Analysis

For the data analysis, 2 × 2 contingency tables were prepared for i) breast feeding only or mix-ed feeding versus artificial feeding only, ii) mixed feeding or artificial feeding only versus breast feeding only; the odds ratio and 95% confidence interval were calculated for each group.

Statistical significance was assessed by statistical volume χ (chi) which is a modification of the square root of chi-square value and the 95% confidence interval performed by Miettinen's test.

Results

Nationwide epidemiological survey

The cumulative number of cases until 1993 was 578 cases for UC and 260 cases for CD. There was almost no change in the number of new cases of UC and CD per year after 1978 until 1993, showing a number of around 32 cases (mean ± SD; 32.1 ± 6.8) per year for UC and around 16 cases (15.7 ± 6.3) per year for CD (Figs. 1 and 2). The incidence rate per 100,000 children in the population shows a recent tendency toward an increase; the proportion was
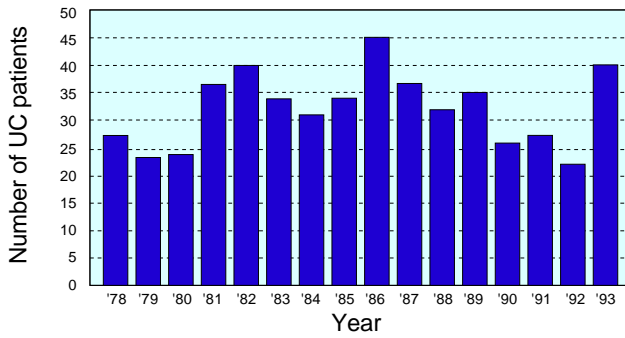
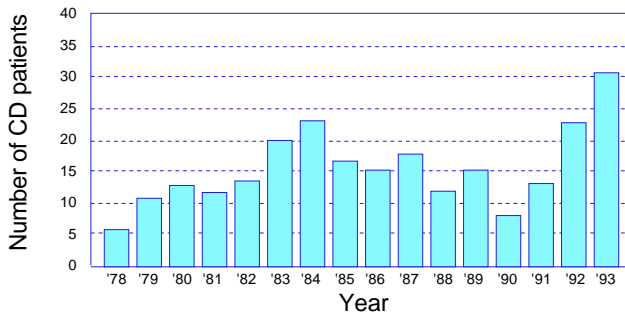**Fig. 1.** The annual number of UC patients.

Fig. 2. The annual number of CD patients.

0.18 for UC and 0.13 for CD in 1993 according to our survey. The male to female ratio was 1.1:1.0 for UC and 1.4:1.0 for CD, showing a slight predominance for boys in both diseases.

The predominant initial symptoms of UC were diarrhea (58.3%), bloody stool (47.6%) and abdominal pain (33.9%); pancolitis occurred in the majority of patients. On the other hand, the predominant initial symptoms of CD were abdominal pain (74.2%), diarrhea (58.9%) and fever (56.3%) (Figs. 3 and 4). Most CD patients had a lesion in the lower ileum, transverse colon or ascending colon.
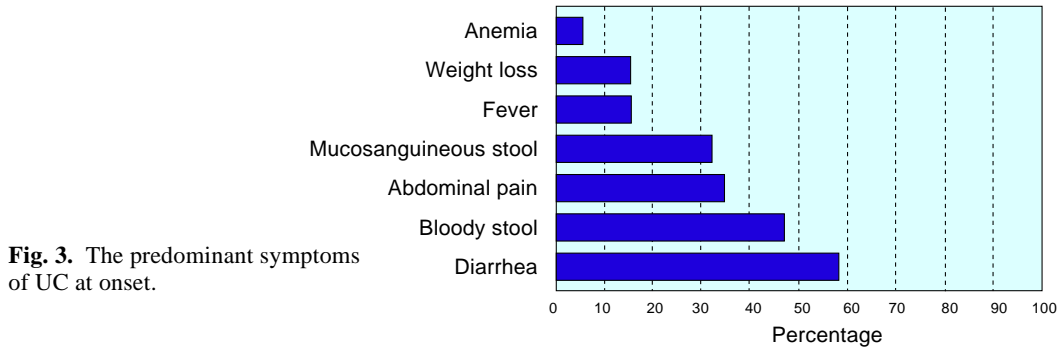

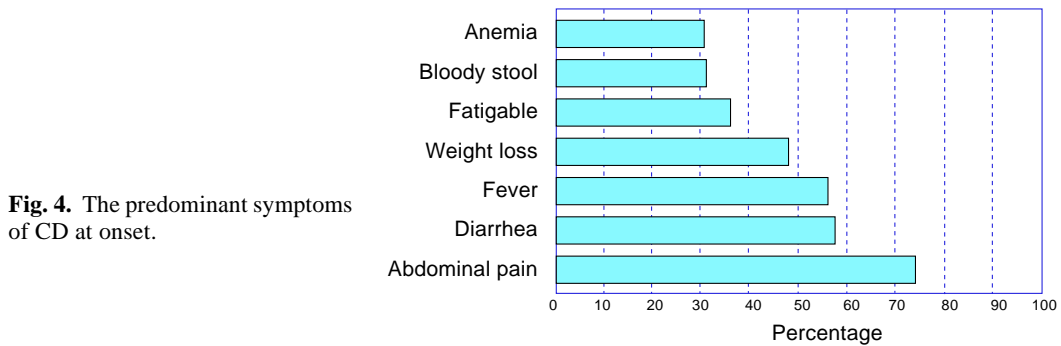**Fig. 3.** The predominant symptoms of UC at onset.

Fig. 4. The predominant symptoms of CD at onset.

Table 3a. The kind of feedings during early infancy in UC patients and controls

| | Number | | |
	UC patients	Controls	Total
Breast feeding	35	93	128
Mixed	61	128	189
Artificial feeding	37	45	82
Total	133	266	399

UC, ulcerative colitis.
Age: mean, 10 years and 4 months; range, 4 months to 15 years and 3 months.

Table 3b. The kind of feedings during early infancy in CD patients and controls

| | Number | | |
	CD patients	Controls	Total
Breast feeding	10	51	61
Mixed	17	57	74
Artificial feeding	15	18	33
Total	42	126	168

CD, Crohn's disease.
age: mean, 11 years and 6 months; range, 11 months to 15 years and 1 month.

Case-control study on feeding during infancy and onset of IBD

Reports on 133 UC cases (male; 66, female; 67) with 266 controls and 42 CD cases (male; 23, female; 19) with 126 controls were collected. The return rate was 48.2% for UC and 44.7% for CD (Tables 3a and b).

Analysis based on the above reports gave the following results concerning breast feeding only or mixed feeding versus artificial feeding only: in UC, the odds ratio was 0.53, and the 95% confidence interval was 0.31 to 0.89 (Table 4a); and in CD, the odds ratio was 0.30, and the 95% confidence interval was 0.13 to 0.70 (Table 4b).

Table 4a. Analysis of UC

| | Number | | Total |
	UC patients	Controls	
Artificial feeding only or mixed	98	173	271
Breast feeding only	35	93	128
Total	133	266	399
Odds ratio	1.51		
95% Confidence interval	2.46–0.92		

| | Number | | Total |
	UC patients	Controls	
Breast feeding only or mixed	96	221	317
Artificial feeding only	37	45	82
Total	133	266	399
Odds ratio	0.53		
95% Confidence interval	0.31–0.89		

UC, ulcerative colitis.

Table 4b. Analysis of CD

| | Number | | Total |
	CD patients	Controls	
Artificial feeding only or mixed	32	75	107
Breast feeding only	10	51	61
Total	42	126	168
Odds ratio	2.18		
95% Confidence interval	5.19–0.91		

| | Number | | Total |
	CD patients	Controls	
Breast feeding only or mixed	27	108	135
Artificial feeding only	15	18	33
Total	42	126	168
Odds ratio	0.30		
95% Confidence interval	0.13–0.70		

CD, Crohn's disease.

The above analytical results indicated that breast feeding during infancy may decrease the development of UC and CD.

Discussion

UC and CD are chronic intestinal inflammatory diseases. There are many similarities between these two diseases which are collectively called idiopathic inflammatory bowel disease.

Although IBD has been regarded as a rare pathologic condition in Japan compared with Western countries, the number of patients with UC or CD increased significantly in adults from 1965 to 1970. The annual occurrence of these diseases in children did not show any significant changes; about 32 cases for UC and about 16 cases for CD. However, the incidence rate per 100,000 children in the population of children might demonstrate a tendency toward an increase recently due to a decrease in the population of children. The possible causes of such an increase may be westernization of Japanese dietary habits, which is assumed to be a risk factor for developing these diseases, changes in living environments and progress in diagnostic technology.

Similar to adults, the predominant symptoms in children are diarrhea, bloody stool and abdominal pain in the case of UC and abdominal pain and diarrhea in the case of CD. Growth disturbance is also a characteristic childhood symptom.

Infection (Bargen, 1924; Crohn et al., 1932; William and Fradkin, 1937), immune abnormality (Kraft and Kirsner, 1971), hereditary factors (Asakura et al., 1982; Mitake et al., 1992) and neural and endocrine abnormality (Kubota et al., 1992; Watanabe et al., 1992, 1997) have long been regarded as factors that are involved in the development of IBD. Recently, the possible roles of monokines, cytokines and macrophages have been drawing attention as being causes of IBD.

Dietary and living habits have also been considered as causative factors. People who have milk allergy (Glassman and Newman, 1990), those who eat more bread, margarine, cheese and ham, and those who eat less vegetables and fruits are considered to have a higher risk for developing UC. On the other hand, the risk of developing CD is reported to be higher in people who eat more carbohydrates, especially sugar (Persson et al., 1987). Some reports have suggested that people who eat a large amount of fast foods, such as hamburgers and fried chicken, are exposed to a higher risk of developing IBD. With respect to smoking, it is reported that nonsmokers have a higher risk of developing UC. By contrast, smoking appears to be a factor causing CD to worsen (Benoni and Nilsson, 1987).

There are few reports on the dietary and living habits of children in relation to the development of IBD. Gilat and colleagues (1987) conducted a large scale case-control study on the causes of childhood IBD at 14 institutions in 9 countries, including Western and Middle-Eastern countries. Their study failed to demonstrate a significant difference between the patients and controls with respect to the frequency and period of breast feeding during infancy. They reported that the type and times of artificial feeding during infancy, the addition of sugar to milk or artificial feeding and the timing of initiating mixed feeding probably do not play any role in the onset of IBD (Gilat et al., 1987). On the other hand, Bergstrand and Heller (1983) reported that artificial feeding is a significant pathogenic factor of CD. Accordingly, a definitive conclusion has not yet been reached. The case-control study which we conducted this time showed one result, namely that the incidence of IBD is significantly lower among breast-fed Japanese children.

In a report on a case-control study similar to ours, Kono and colleagues (1993) described that artificial feeding during infancy was not considered as a risk factor for the development of IBD in Japanese adults. This might indicate a smaller influence of nutrition during infancy on the development of IBD in adults. From this, the discrepancy between our results and those of Gilat and colleagues (1987) may derive from the difference in the subject's age of the

start of the disease (under 20 years in Gilat and colleagues' population and under 16 years in our population).

Artificial feeding lacks IgA defense and has a higher risk of bacterial contamination compared with breast feeding, which facilitates the development of transient mucosal injury. Mucosal injury causes antigens to be absorbed more readily in artificial-fed children. As a result, these children are likely to be sensitized by a dietary antigen such as that in milk and often develop milk allergy, compared with breast-fed children. Glassman and Newman (1990) reported that patients who had a past history of milk allergy during childhood developed IBD at a significantly early stage. Their report may indicate that the incidence rate of childhood IBD is higher for artificial-fed children than for breast-fed children. Furthermore, the growth of enterobacterium has been considered to differ between breast-fed and artificial-fed children. This difference might have some association with nutrition during infancy and the development of IBD.

The proportion of breast-fed infants is currently increasing in Japan. We intend to pay further attention to the increase and decrease of the incidence of childhood IBD.

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