Arch Jpn Chir 64(1), 3～14, Jan., 1995

臨　　床

Cronkhite-Canada Syndrome: Epidemiological Study of 110 Cases Reported in Japan

Akihiko Goto

Department of Surgery, Hashima City Hospital
Shinseicho 3–246, Hashima City, Gifu, Japan

Received for Publication Oct. 27., 1994

Abstract

One hundred and ten cases of Cronkhite-Canada Syndrome (C-C-S) reported in Japan were reviewed in this epidemiologic study. Seventy-five percent of all C-C-S cases reported in the world in literature have been reported from Japan. There has been no special occupation associated with an increased incidence of C-C-S. Mental and physical stress have been confirmed as among the most important risk factors for this syndrome. Hypogeusia is the dominant initial symptom which usually is followed by diarrhea and ectodermal changes including alopecia, nail dystrophy and skin pigmentation. Gastrointestinal polyposis is closely related to the malabsorption which induced these ectodermal changes. However, there is a small number of cases in which alopecia precedes to the diarrhea in the disease course.

Then, further investigation will be important in establishing the genesis of this syndrome.

I. Introduction

Cronkhite-Canada syndrome (C-C-S)[1] is a rare syndrome characterized by diarrhea, gastrointestinal polyposis, alopecia, onychodystrophy and hyperpigmentation. Despite its increasing incidence in recent years, little is known of regarding its etiology and pathology. The prognosis of this syndrome is generally believed to be poor. A preliminary survey of 80 reported cases in Japan was performed in 1988[2]; approximately one half of these patients were still alive, and many of them had survived many years after its onset. A subsequent study of 110 reported cases in Japan was performed as an epidemiologic investigation, which revealed some environmental factors pertaining to the syndrome. In this report, the result of these studies will be reviewed in details.

Key words: Cronkhite-Canada syndrome, Epidemiologic study.
索引用語: Cronkhite-Canada 症候群
Present address: Department of Surgery, Hashima City Hospital, Shinseicho 3-246, Hashima City, Gifu, Japan.

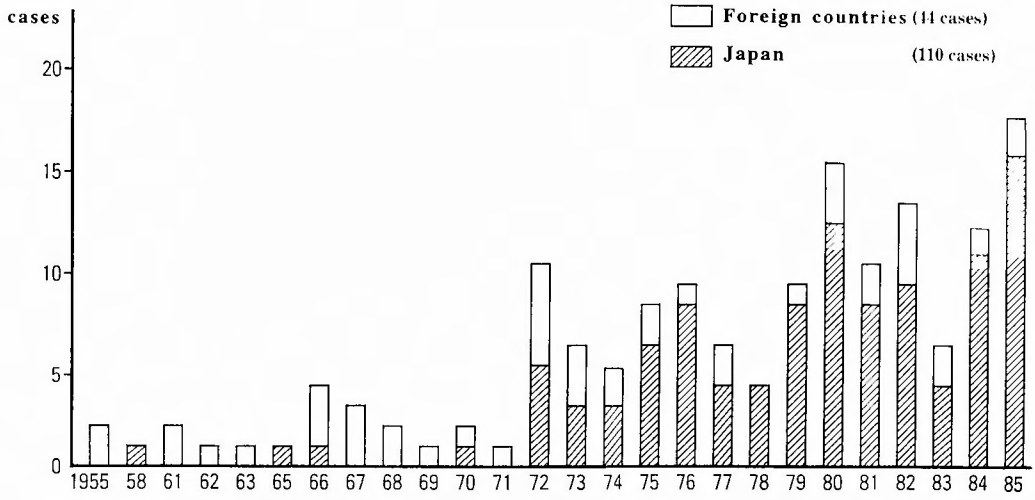

Fig. 1 Cronkhite-Canada Syndrome: 154 cases. Annual reported cases in the world (1955–1985).

	Nation	reported cases	total population ×10,000	rate ×10,000
Asia	Japan	110	12000	1/100
	Singapore	1	250	
	Thailand	1	4900	
North America	U.S.A.	15	23500	1/1560
	Canada	1	2500	
South America	Brazil	1	13000	
	Chile	1	1200	
Australia	Australia	2	1400	1/700
Europe	England	8	5600	1/700
	West Germany	6	6100	1/1000
	East Germany	1	1600	
	Switzerland	1	650	
	Denmark	1	510	
	Spain	1	3800	
	Italy	1	5700	
	Norway	1	410	
	Sweden	1	830	
	USSR	1	7600	

Population status : 1983

Fig. 2 World-wide distribution of Cronkhite-Canada Syndome 154 cases (1955–1985).

II. Materials and Methods

Of the 110 cases of C-C-S that have been reported in Japan, 71 cases were reported in the literature and 39 were reported only in an abstract. Requests for the additional clinical material were sent to the authors or their relatives to confirm clinical features associated with C-C-S. A response for questionnaire was obtained in all 110 cases. The criteria of C-C-S included: gastrointestinal polyposis (confirmation of juvenile polyp-type polyposis by radiography, endoscopy, or histopathologic findings), alopecia, onychodystrophy and hyperpigmentation of the skin (based on slides, or photographs of the head and fingers).

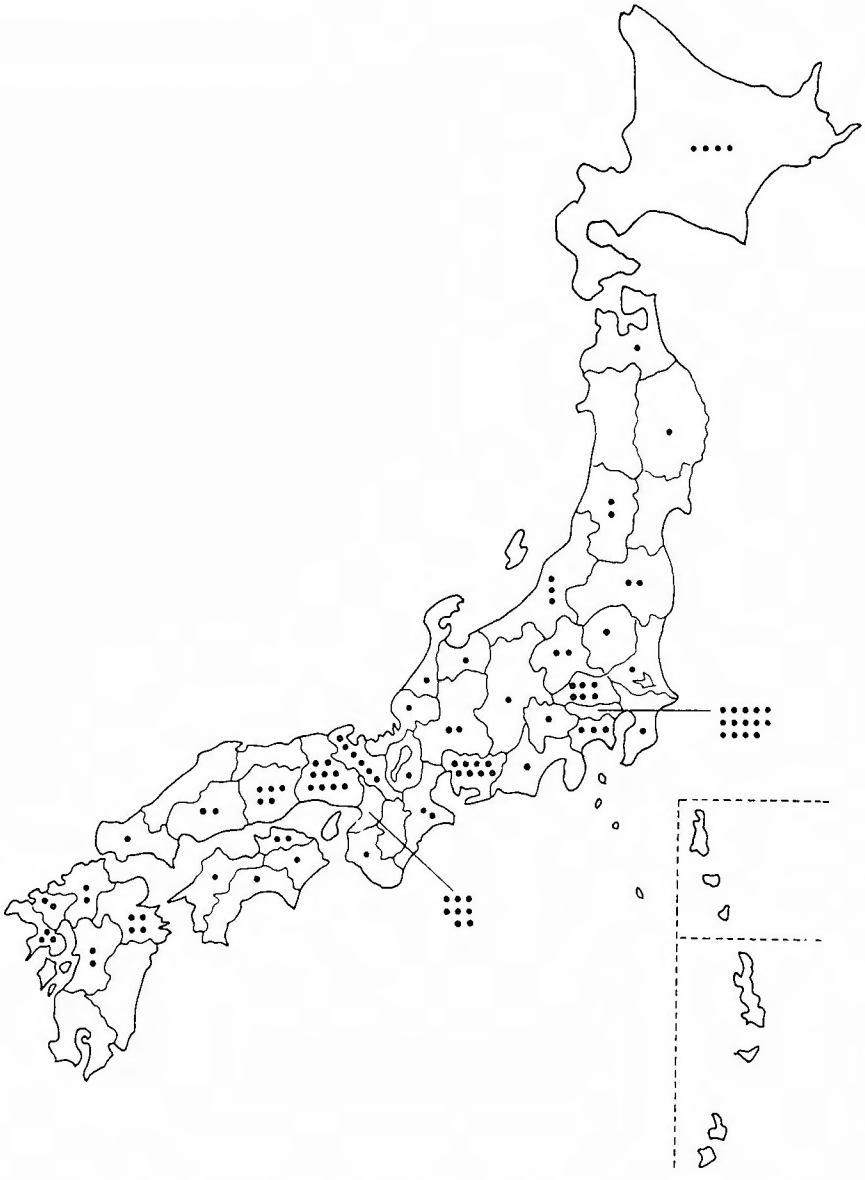

Fig. 3 Cronkhite-Canada Syndrome: Distribution of 110 cases in Japan.

III. Results

Few cases of C-C-S were reported in the world literature after the first report of in 1955. However, since 1972, the number of reported cases has been increasing at an annual rate of 8 to 15 cases, with those reported in Japan accounting for approximately two thirds of all the cases (Fig. 1).

The world-wide distribution of C-C-S is shown in Fig 2. The highest incidence of C-C-S occurs in Japan with the U.S.A. as the next most frequent country. The number of cases of C-C-S in England and Germany has been surpassed by the two former countries. Most other countries have reported only isolated cases (Fig. 2).

The geographical distribution of this syndrome in Japan was analyzed using the addresses of patients obtained at the time of their first medical examination. The occurrences of C-C-S were broadly scattered over the country from Hokkaido to Kyushu, with the highest incidences in Tokyo, Aichi, Osaka and Hyogo. This is probably because the incidense is somewhat proportional to the relative population density (Fig. 3).

The age distribution of the patients ranged from 31 to 85 years, although most patients were in their fifties. By sex, the population included 73 males and 37 females with a male-to-female ratio 2 : 1 (Fig. 4).

Occupationally, the largest group of patients were out of work, and the majority of these patients were housewives. Elderly individuals (60 years) accounted for 74% of patients. The next most frequent occupatients of the patients were farming and office work. There was no remarkable difference in the incidence of this syndrome between individuals who performed primarily physical

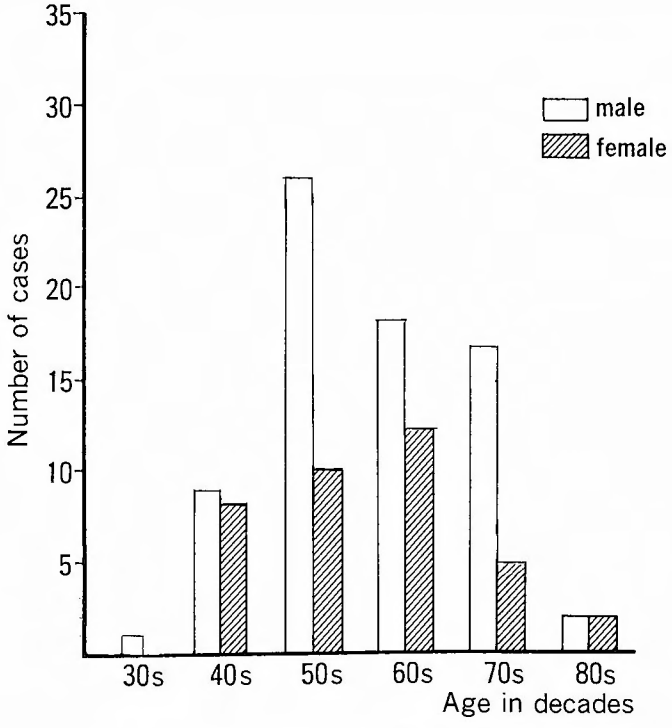

Fig. 4 Cronkhite-Canada Syndrome: 110 cases reported in Japan from 1958 to 1985 by age and sex.

or mental work (Fig. 5).

Previous and co-existing diseases are shown in Fig 6. Gastric or duodenal ulcer were the most frequent disorders, followed by hypertension. Patients with articular rheumatism, diabetes mellitus, typhoid fever, psychosis, or bronchial asthma all demonstrated a higher incidence. In a few patients, autoimmune disease such as scleroderma or Systemic lupus erythemtousus (SLE) complicated in the C-C-S (Fig. 6).

Mental stress, such as mental suffering or family problems was the most frequent precipitating factors for C-C-S. Physical fatigue was the next most important risk factor. The longterm intake of drugs, such as Chinese medicines, or analgesic' was observed to be a precipitating factor for this syndrome. Surgical stress, traveling abroad, and overeating or excessive drinking also were found to correlate with the occurrence of this syndrome (Fig. 7).

The most frequent initial symptom was a taste disorder (Hypogeusia) (34%), followed by diarrhea and anorexia. Diarrhea often was found concurrently with abdominal pain and epigastric

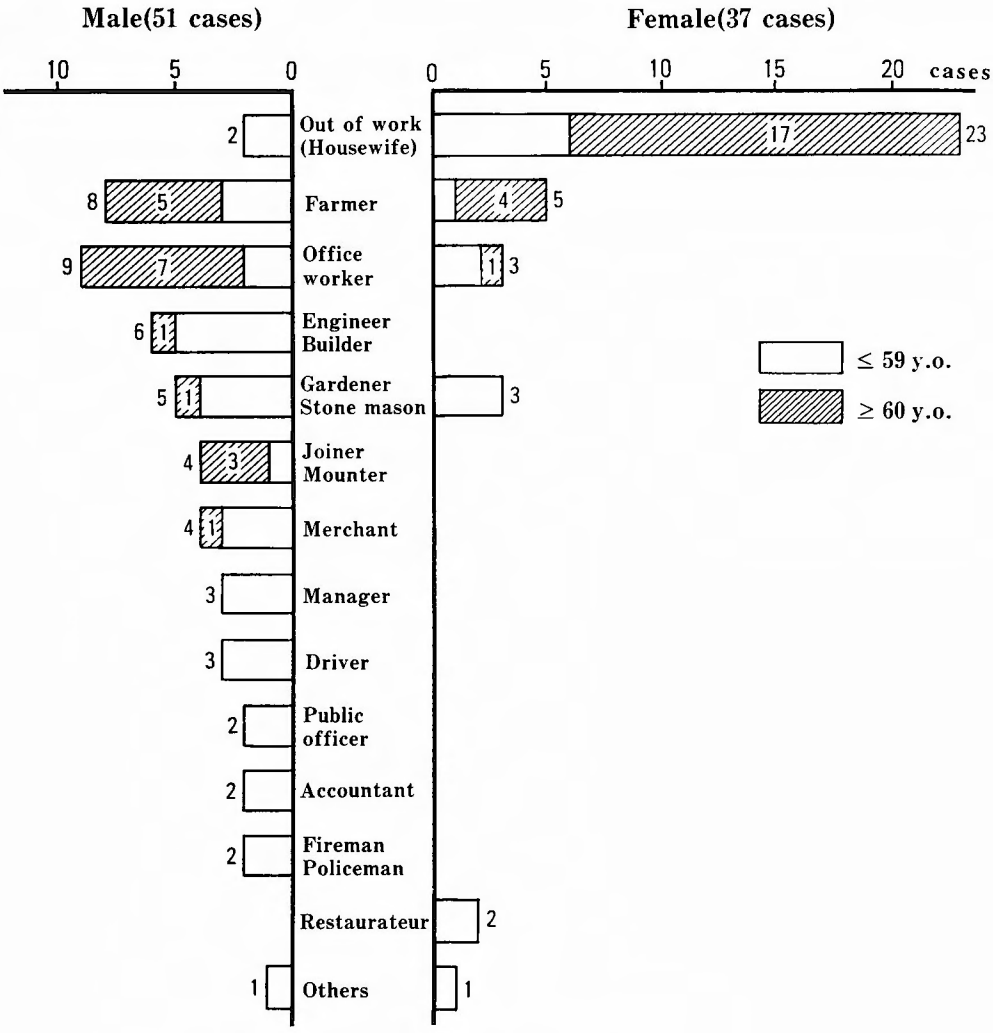

Fig. 5 Classification of Occupation.

discomfort. Hypogeusia and the sensation of a dry mouth (Xerostomia) occurred solely in many cases (Fig. 8).

The most frequent cardinal symptom was diarrhea (84%), followed by hypogeusia, anorexia, weight loss, abdominal pain and general malaise. Xerostomia and or strange sensation in the mouth were found in a few patients. With regard to cutaneous findings, onychomadesis and onchychodystrophy both were found in 91% of the patients and pigmentation in 79%. Edema, anemia and glossitis were the next most common findings (Fig. 9).

The courses of development of these symptoms could be classified into five types. Type I: Diarrhea was the initial symptom (39 cases). In 22 of these patients, the order of development of subsequent symptoms was diarrhea, pigmentation, onychodystrophy, and alopecia. Hypogeusia was included in the course of six patients. Type II: Hypogeusia preceded all other symptoms (45 cases). In these patients, this symptom was followed by diarrhea in 32 patients and onychopathy in 10. Diarrhea, alopecia, pigmentation were the next most common symptoms after hypogeusia. In this group, 13 cases were not seen diarrhea in all course. Type III: A strange sensation in the mouth or a dry mouth (xerostomia) was the initial symptom (7 cases) and was followed by diarrhea, alopecia, pigmentation, and onychodystrophy. Type IV: Abdominal pain was the initial symptom (10 cases),

Disease	Cases
Gastric or Duodenal Ulcer	8
Hypertension	7
Diabetes Mellitus	3
Typhoid fever	3
Psychosis	3
Articular rheumatism	4
Bronchial asthma	3
Hypothyroidism	2
Drug induced anaphylaxis	2
Scleroderma	1
SLE	1
Metabolic myopathy	1
Pulmonary tuberculosis	1
Colon carcinoma	1
Laryngeal carcinoma	1
Ileus	1
Anemia	1
Total	43

SLE:systemic lupus erythematosus

Fig. 6 Previous and co-existent diseases.

which was followed by ectodermal changes such as alopecia, pigmentation, and onychodystrophy. Type V: Alopecia was the initial symptom (9 cases), and was followed by cutaneous symptoms such as pigmentation, and onychotrophy with or without diarrhea (Fig. 10).

Risk Factor	case
Mental stress	38
Mental suffering	18
Family problems	6
Leaving the family	2
Nursing a family member	4
Family member accident	2
Business troubles	6
Physical fatigue	23
Long-term drug use	11
Surgical colectomy	3
Travel abroad	3
Excessive drinking or eating	3
Radiation therapy	1
Drug poisoning	1
Not confirmed	27
Total	110

Fig. 7 Precipitating Factors.

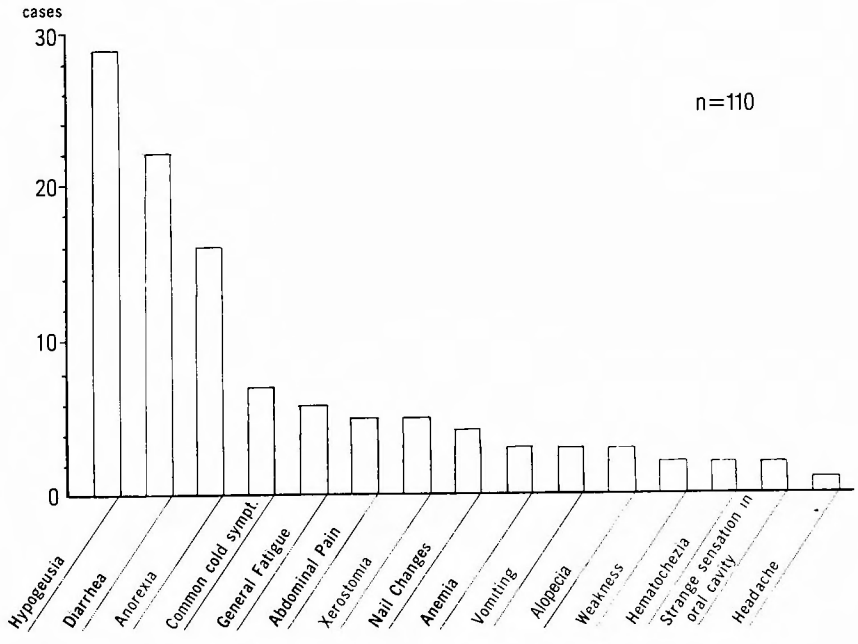

Fig. 8 Cronkhite-Canada Syndrome: Initial Symptom.

IV. Discussion

1. Frequency distribution of C-C-S

Since the first report of Cronkhite-Canada Syndrome in 1955[1], there were only 21 reported cases of this syndrome, until after 1971 of which those reported in Japan accounted for 38% (8) of these cases. Since 1972, however, the unmber of cases in Japan has rapidly increased. Thus, of the 110 cases reported since 1972, 81 of these cases or (75%) were those reported in Japan. While this point has been raised by KAMAGAMI[3] and DANIEL[4], the reason for this increase remains unknown. The comparatively high standard of medical care in Japan, and the high rate of health examinations performed due to the nation-wide health insurance system, may be among the causes; however, it appears that other factors (e.g. environmental or ethnic) are also at work.

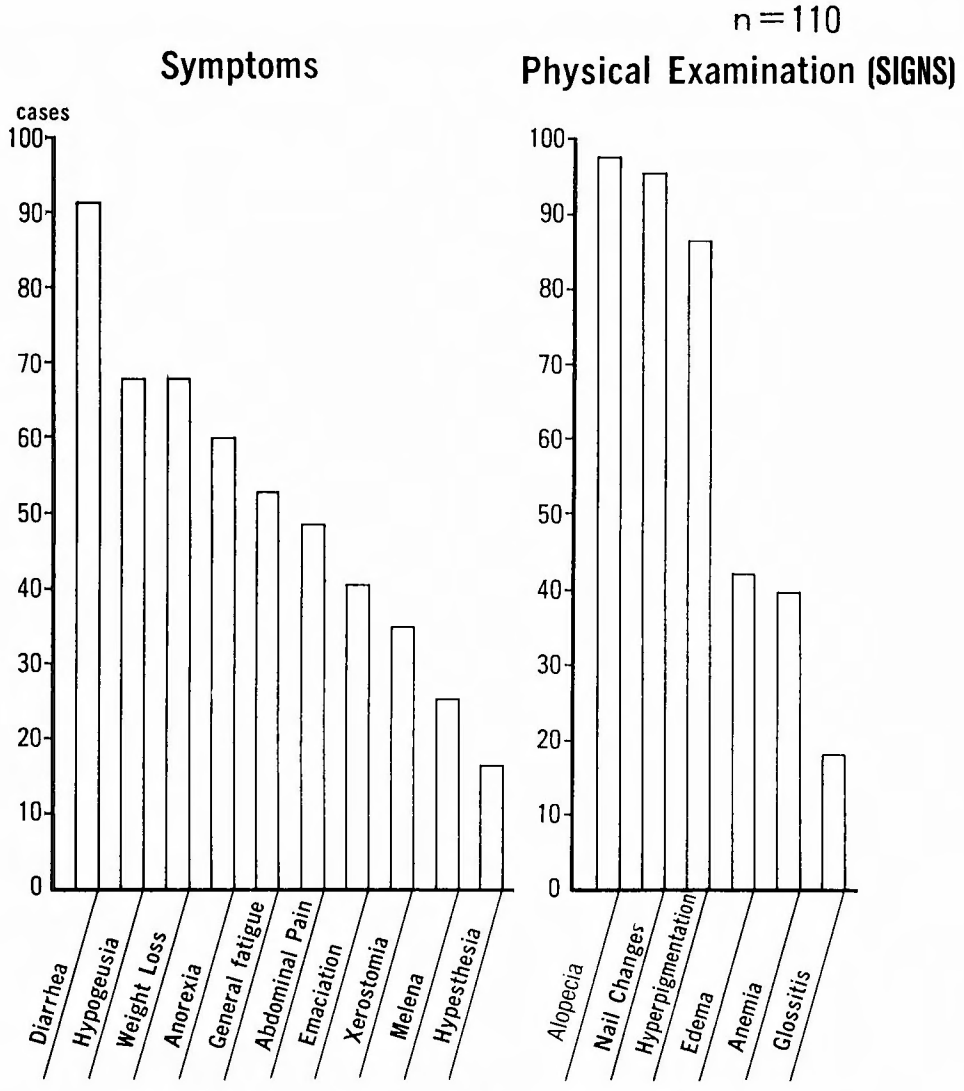

Fig. 9 Clinical Sings and Symptoms in Patients with Cronkhite-Canada Syndrome.

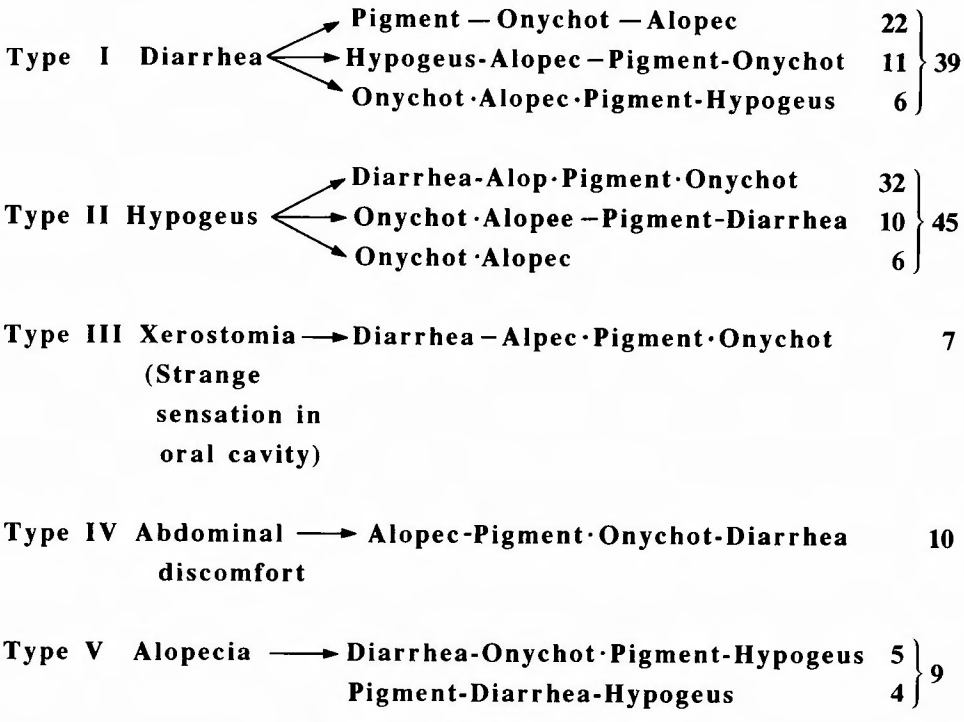

Fig. 10 Five Clinical Courses of C-C-S.

2. Past history, concurrent illnesses and risk factors

To investigate the epidemiologic conditions of related to this syndrome, the patient's past medical history, concurrent illnesses, living environment, and risk factors were surveyed in detail. Although the gamut of occupations ranged from the university professor to construction worker, none of them were considered specific to the onset of this syndrome. Rather, the patient's activity of daily living, attitudes, and work load were apparent triggers for this syndrome.

Regarding the patients past medical history, adult disease such as gastric ulcer, hypertension and diabetes mellitus were prominent. Risk for this syndrome, such as mental stresses associated with familial misfortunes, poor human relations in the office, business failures and lawsuits accounted for 38 of the cases (46% of confirmed cases). Physical fatigue also was reported in 23 cases (28%). In addition, in some cases the onset of this syndrome was associated with the long-term administration of drugs, surgery or radiotherapy. The importance of stressors, which could also cause gastric and/or duodenal ulcer, was noted. Considering that this syndrome occurred in patients with a history of ulcer, the factors contributing to these ulcers were also presumed to be related to C-C-S. So far, the involvement of psychologic factors has been emphasized in ulcerative colitis and it is well known that mental and physical stresses aggravate symptom in ulcerative colitis patients. The finding that such stress is involved in the induction of C-C-S suggests some similarity between these two disorders.

3. Clinical manifestations and gastrointestinal malabsorption

The main symptoms of Cronkhite-Canada syndrome are diarrhea, alopecia, onychodystorphy and hyperpigmentation. These symptoms have been ascribed to gastrointestinal polyposis and bacterial infection which have been mentioned as a supervening factors, although the mechanism of

their onset remains unknown[5-8]. The present epidemiologic investigation of 110 Japanese cases revealed polyps resembling the juvenile type polyp in all of the patients, as well as cutaneous disorders such as onychodystrophy, alopecia, and hyperpigmentation. However, the mode of onset was not uniform throughout the cases. As stated in the first report of CRONKHITE and CANADA[1], diarrhea is the most frequent first symptom and is followed by cutaneous symptoms such as alopecia, onychotrophy and pigmentation. The clinical course of patients 39 (35.4%) of the 110 patients met this clinical profile. The most frequent cause of the cutaneous symptoms in these patients were protein loss and the malabsorption of vitamins and trace elements secondary to diarrhea due to polyps in the gastrointestinal tract. However, there were 28 patients (35%) in which the complaint of a taste disorder (Hypogeusia) preceded all other symptoms. Although attention to this symptom has not been heeded thus far, it may play an important role in the sequence of symptoms. Many patients with C-C-S have hypocalcemia as well, and there is a report associating C-C-S with hypoparathyroidism. However, there are few cases in which the onset of a taste disorder has coincided with any severe hypocalcemic symptoms such as tetany. While the etiology of hypocalcemia remains unknown, it has recently been reported that a decrease in serum zinc is responsible[9, 10]. Following this report, decrease in serum zinc were reported in some patients and a disturbance of zinc absorption secondary to gastrointestinal polyps has been suggested. However, there are only a few confirmed cases. Incidentally, among the 40 cases reported in foreign countries, a taste disorder has been demonstrated only in 6.

4. Etiology

Despite many previous reports, the eiology of this syndrome remains unknown. Unlike familial polyposis and Peutz-Jaghers syndrome, there is no report demonstrating a hereditary basis. Since malabsorption was not present in some cases of C-C-S, JARNUM[8] has hypothesized that the alopecia, onychopathy, and pigmentation are congenital. NELSON[11] has demonstrated an aberration on chromosome 21 in children with a protein-losing gastroenteropathy. On the otherhand, ALI [12] has reported that no chromosomal aberration is demonstrable in adults with this syndrome, and has denied the involvement of factors at the chromosomal level.

Although this syndrome is characterized by gastrointestinal polyposis and ectodermal changes, there have been few cases in which a causal relation of these clinical findings could be established. However, as confirmed in the present investigation, the existence of digestive tract polyposis has been suggested in all but a few cases, even prior to the onset of gastrointestinal symptoms, a taste disorder or ectodermal changes. Moreover, some intrinsic factors, (e.g. mental and physical stress), has been identified in the course of this study as background factors which apparently had not attracted previous attention. It is likely that these stresses act on the gastrointestinal mucosa to elicit a local inflammatory reactions and that the countereaction of the body to such changes assumes the specific form of the juvenile type polyp which characterizes this syndrome. The fact that this specific counteraction may occur anywhere along the length of the digestive tract suggests the presence of a certain congenital abnormality such as a substratum. The above-mentioned stressors act as triggers on this substratum, causing the polyps. When this assumption is taken together with the fact that ulcerative colitis (whose etiology also is unknown) may relapse or be exacerbated due to mental and physical stress, we may assume the existence of a common etiologic factor for these two disorders. It is an established theory that polyps in this syndrome (unlike adenomas and adenomatous polyps,) are inflammatory polyps. KENNEDY[13] reported in 1961 that this type of polyp is reversible. So far it has been believed that the prognosis of this syndrome is poor, and that even if transient improvement oc-

curs, death ensues in many cases. However, we have previously reported that many patients with this syndrome experience long survival[2]. The above-mentioned inflammation theory is clinically supported by the fact that steroids and antiplasmins agents provide remarkably effective treatment in some cases.

Complications of autoimmune diseases such as hypothyroidism, scleroderma and SLE have indicated the involvement of immune mechanisms in the onset of this syndrome. However, to further establish investigations at the genetic level may be required.

V. Conclusion

This epidemiologic investigation was conducted on 110 cases of Cronkhite-Canada syndrome reported in Japan. As reported above, this syndrome occurs frequently in Japan and its main symptoms are due to the polyps generated in the gastrointestinal tract. These polyps are closely related to the malabsorption which, in turn, is the cause of ectodermal changes such as alopecia, onychopathy and chromatosis. It has also been suggested that mental and physical stress are involved in the onset of this syndrome, and there also are findings suggestive of the involvement of immune mechanisms.

Acknowledgment

This epidemiologic study of Cronkhite-Canada syndrome was conducted under the grant from Malabsorption Investigation Group of the Ministry of Health and Welfare. The author is much indebted to the doctors who had cooperated for this work.

References

1) Cronkhite LW Jr, Canada WJ: Generalized gastrointestinal polyposis: An unusual syndrome of polyposis, pigmentation, alopecia and onychotrophia. N Eng J Med 252: 1011–1015, 1955.
2) Goto A, Mimoto H, Shibuya C, et al: Cronkhite-Canada syndrome: An analysis of clinical features and follow-up studies of 80 cases reported in Japan. Arch Jpn Chir 57: 506–526, 1988.
3) Kamagami T, Nakamura T, et al: A case of Cronkhite-Canada syndrome. Teikyo Med J 5: 149–154, 1982.
4) Daniel ES, Ludwig SL, Lewin KJ, et al: The Cronkhite-Canada syndrome: An analysis of clinical and pathologic features and therapy in 55 patients. Medicine 61: 293–309, 1982.
5) Johnson GK, Soergel K, Hensley GT, et al: Cronkhite-Canada syndrome: Gastrointestinal pathophysiology and morphology. Gastroenterology 63: 140–152, 1972.
6) Gualdi NC: La sindrome di Cronkhite et Canada Minerva Med 66: 1308–1312, 1975.
7) Ohkita H, Okuno Z, Nakashima I: A case of gastrointestinal polyposis with melanosis. Nihon Rinsho 16: 1486–1491, 1958.
8) Jarnum S, Jensen H: Diffuse gastrointestinal polyposis with ectodermal changes. Gastroenterology 50: 107–118, 1966.
9) Seshimo Y, Takayasau S: Cronkhite-Canada syndrome. Hifu 25: 925–926, 1983.
10) Henken RL, Schecter PJ, Friedewald WT, et al: A double blind study of the effects of zinc sulfate on taste and smell dysfunction. Am J Med Sci 272: 285–289, 1976.
11) Nelson R: Long-arm depretion of chromosome with protein losing enteropathy. Proc Roy Soc Med 65: 1081–1083, 1972.
12) Ali M, Weinstein J, Biempica A, et al: Cronkhite-Canada syndrome: Report of a case with bacteriologic immunologic and electron microscopic studies. Gastroenterology 79: 731–736, 1980.
13) Kennedy JA and Hirson C: A transient syndrome with Peutz-Jeghers features and ectodermal change. Proc Roy

Soc Med 54: 234–235, 1951.

和文抄録

Cronkhite-Canada 症候群：本邦報告110例の疫学的検討

羽島市民病院 外科
後藤 明彦

Cronkhite-Canada 症候群の本邦報告110例について疫学的調査を中心に検討した．本邦では本症候群の報告は世界の報告例の75％を占めている．本症候群の発症については職業的な特異性は認めなかった．しかし，精神的及び肉体的ストレスが本症候群の発症に重要な因子であることが判明した．

味覚異常は初発症状の中，最も重要であり，ついで，下痢および脱毛，爪甲異常，皮膚色素沈着などの皮膚症状がみられた．消化管ポリポーシスは消化管よりの吸収障害を来すものとされ，皮膚症状の出現と密接な関係を持つものと考えられる．しかし，下痢の発生する以前に脱毛をきたす症例も少数に認められる．

本症候群の成因はいまだに不明であるが，本症候群のポリープには可逆性の認められることより，炎症性ポリープが示唆され，免疫学的機序が示唆される．