Acta Medica Okayama

Volume 13, *Issue* 3 1959 *Article* 5

OCTOBER 1959

Statistical study of aca-talasemia, a review of thirty-eight cases appearing in the literatures

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Abstract

1. With a view to grasp more simply and clearly the characteristics of this disease and in order to find a clue for prompt discovery of cases when encountered in future, the authors undertook a statistical study of the cases already reported by various authors. 2. The cases reported so far amount to 17 familial groups which consisted of 38 acatalasemic cases. These groups were distributed widely throughout Japan. The disease seemed to be prevalent in the rural communities where adherence to the custom of consanguineous marriage occurs. As yet, we have not heard of the occurrence of this disease in other countries. 3. The disease has equal distribution in both sexes. About one half of patients showed a peculiar oral gangrene (Takahara's disease). The great majority of these were noted in those less than 10 years of age. 4. The great majority of them were children whose parents were united in consanguineous marriage and have siblings with acatalasemia. 5. As for the treatment of oral lesions in this disease, extraction of tooth at the site of the lesions, removal of the diseased tissues en masse by resection, and penicillin treatment given concomitantly are effective. The course and the length of time required in healing of the wound due to the operation are about the same as in the case of normal persons. 6. The authors wish to call special attention to the phenomenon peculiar to the acatalasemic blood. The blood of acatalasemic individuals changes to brownish-black color in the absence of foaming or bubble formation upon the application of hydrogen peroxide to blood.

Acta Med. Okayama 13, 209—219 (1959)

STATISTICAL STUDY OF ACATALASEMIA, A REVIEW OF THIRTY-EIGHT CASES APPEARING IN THE LITERATURE

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Received for publication, April 22, 1959

INTRODUCTION

Since the first report of acatalasemia in 1947 by Takahara, seventeen additional familial groups constituting 38 cases of acatalasemia have been reported in Japan as of December 31, 1958. For the purpose of surveying the statistical data of these reported cases, we prepared a list shown in Table 1 with the co-operation of physicians who previously had contributed to the case reports. Based on this list we analyzed such problems as related to institutions where the disease was discovered, sex difference, date of discovery, the age at the time of discovery, age at the onset of the disease, presence or absence of oral lesions, hereditary factors, and the method of discovery.

STATISTICAL CONSIDERATION

The institutions where the disease was discovered : Institutions of discovery and the number of patients discovered at each institution are as follows. Five familial groups of 12 cases at Okayama University ; 5 familial groups of 10 cases at Tokyo Medical-Dental College ; 1 familial group of 3 cases at Sapporo Medical College ; 1 familial group of 2 cases at Kyushu Dental College ; 1 familial group of 1 case at Mie University ; 1 familial group of 2 cases at Shinshu University Medical School ; 1 familial group of 2 cases at Kyushu University Medical School ; 1 familial group of 3 cases at the Toyama-ken Takaoka Agricultural Co-operative Assoc. Hospital ; and 1 familial group of 3 cases from a dental practitioner at Kumamoto.

As is clear from the above, this disease is widely distributed from Hokkaido to the north and Kyushu to the south. In every locality there is an indication that the incidence of the disease is more prevalent in the rural than in the urban communities, and this fact appears to be closely associated with hereditary factors to be discussed later. Moreover, we have not as yet heard of its occurrence in any other foreign country. Eight familial groups with a total of 19 cases (50%) were observed by oto-rhino-

laryngologists ; 8 familial groups of 18 cases (47%) were reported by oral surgeons ; and 1 familial group of 1 case (3%) by a general surgeon.

Frequency of discovery : Since Takahara discovered 1 familial group of 4 acatalasemic cases in December 1946, there appeared successively, 1 familial group of 1 case in 1949 ; 1 familial group of 2 cases in 1950 ; 2 familial groups of 6 cases in 1951 ; 1 familial group of 3 cases in 1952 ; 3 familial groups of 5 cases in 1953 ; 2 familial groups of 4 cases in 1955 ; 1 familial group of 2 cases in 1956 ; 2 familial groups of 4 cases in 1957 ; and 2 familial groups of 4 cases in 1958 as of December 31th 1958. Consequently, the disease is being recognized more and more each year.

Sex difference : There are 19 male cases (50%) and 19 female cases (50%) ; thus there seems to be no unusual prevalence of the disease in either sex.

The age at the time of discovery : The age at the time of discovery of this disease covers all age range from the oldest 55 years to the youngest one year old ; namely, 1 case at 55 ; 1 at 53 ; 1 at 42 ; 2 at 38 ; 1 at 36 ; 1 at 32 ; 1 at 31 ; 1 at 27 ; 1 at 26 ; 1 at 25 ; 1 at 21 ; 1 at 19 ; 1 at 18 ; 4 at 17 ; 2 at 15 ; 4 at 13 ; 1 at 12 ; 1 at 11 ; 1 at 10 ; 2 at 9 ; 1 at 8 ; 3 at 6 ; 1 at 5 ; 2 at 3 ; 1 at 2 ; and 1 at one year old. The mean age is 18 years, and the majority of them (26 cases-68%) is under 20 years at the time of discovery of the disease. Those who were under 10 years old numbered 12 cases (32%).

Presence or absence of oral lesions : Acatalasemia is essentially a congenital and constitutional abnormality, and among them, especially among the young ones, a certain peculiar progressive gangrene (Takahara's disease) is instigated in the oral cavity. This disease may manifest in varying forms of severity. Some show lesions which begin with a tooth and develop into gangrene of maxilla or mandible, while others may be minimal and simply assume alveolar pyorrhea-like lesions. Rarely the gangrenous lesion originates from the tonsil. Out of 38 cases, 21 (55%) had such oral lesions, and in contrast to these there were 16 cases (42%) showing none. In the latter no symptoms were noted but absence of catalase in the blood was detected. In one case no clinical description was given.

The classification of patients who had oral lesions at the time of discovery in accordance with the degree of severity is as follows : 5 cases (24%) minimal type, presenting advanced alveolar pyorrhea-like lesions and ulcerations of the dental alveolus ; 9 cases (43%) moderately severe type, showing atrophy and retraction of the gums as well as spontaneous loss of teeth due to gangrene of the dental alveolus ; 5 cases (24%) severe type

with progressive gangrene in upper or lower jaw ; and 1 uncertain case (10%). Tonsillar gangrene originating from the tonsillar lacunae was found in two cases among the severe type.

Following the first two symptomless cases (out of 4 acatalasemia) discovered at Okayama University in 1951, 14 additional cases of symptomless acatalasemia have been reported by other investigators (HAYASHI, SHIRABE, TAKEUCHI, OGURA, YONEMARU, ONISHI and IMAGAWA). These symptomless cases were discovered while checking the blood of siblings of acatalasemia cases or during surgical procedures in which the application of hydrogen peroxide was made.

With the advent of antibiotics and sulfa drugs there is a marked decrease in the number of advanced oral gangrene cases as compared to the number encountered during a period from 1946 to 1950. In consequence we would expect, hereafter, a proportionate increase of the symptomless type.

Age at the onset of oral disease : The majority of oral gangrene (Takahara's disease) occurs under 10 years of age. Now, separating the 21 cases according to different age groups, we find 1 case (5%) to be 20 years old ; 1 case (5%) 13 yrs., 1 case (5%) 10 yrs., 4 cases (19%) 9 yrs., 1 (5%) 6 yrs., 1 (5%) 4 yrs., 2 (10%) 3 yrs., 3 (14%) 2—3 yrs., 2 (10%) 2 yrs., 3 (14%) among infants ; and 2 uncertain cases (10%). Therefore, it is advisable to examine by using the hydrogen peroxide droplet test and determine the blood catalase activity when alveolar pyorrhea which is difficult to cure is encountered in children under ten years of age. If early and adequate treatment is given, residual lesions which are observable in this disease such as severe difficulty in opening the mouth (Case Nos. 10, 12), difficulty in mastication due to retraction of the gums (Case No. 16), and tissue destruction due to gangrene (Case Nos. 1, 2, 5) can be prevented to a certain degree.

Hereditary relationship : Practically all instances of this disease are observed in families with close consanguineous marriage. Out of 17 familial groups, 13 families consisting of 26 cases(68%) are noted in those whose parents are first cousins. Next, there are 2 familial groups of 7 cases (18%) whose parents are first cousins once removed ; 1 familial group of 2 cases (5%) whose great-great grand parents had a close consanguineous marriage; and 1 familial group of 3 cases (8%) whose parentage is uncertain because their family emigrated to Hokkaido four generations ago and all relatives are now dead.

Previously TAKAHARA, SATO, MIHARA and DOI studied the genetic relationships of this disease by making detailed pedigree charts of 3 families

List of Cases of Acatalasemia

Family No.	Pt. No.	Patient Name	Sex	Institution	Reporter	Date & Age of Discovery	Intraoral Disease Yes Time of Onset
1 a‡ b c d e f g	1	NAKAYAMA Taeko	F	Okayama Univ.	TAKAHARA Shigeo	Dec. 1946 11 yrs	+ 9 yrs
	2	NAKAYAMA Sumio	M	〃	〃	Dec. 1946 13 yrs	+ 9 yrs
	3	NAKAYAMA Kaoru	F	〃	〃	Dec. 1946 9 yrs	+ 9 yrs
	4	NAKAYAMA Ikuko	F	〃	〃	Dec. 1946 3 yrs	+ 2 yrs
2 c‡ d f g	5	FUKUTAKE Jun-ichi	M	〃	〃	Feb. 1949 13 yrs	+ 3 yrs
3 c‡ d f	6	ABE Yoshiichiro	M	〃	〃	Jan. 1951 53 yrs	+ Childhood
	7	ABE Sadako	F	〃	〃	Jan. 1951 42 yrs	+ Childhood
	8	ABE Tomiko	F	〃	〃	Jan. 1951 38 yrs	—
	9	ABE Takashi	M	〃	〃	Jan. 1951 36 yrs	—
4 h‡ i	10	YOSHIKAWA	F	Tokyo Medical-Dental Coll.	YOSHIYA Masaru	Mar. 1950 18 yrs	+ 2—3 yrs
	11	YOSHIKAWA	M	〃	〃	Mar. 1950 9 yrs	+ 2—3 yrs
5 h‡ i	12	KANEKO	F	〃	〃	May. 1950 17 yrs	+ 2—3 yrs
	13	KANEKO	F	〃	〃	May. 1950 3 yrs	+ 2 yrs
6 j‡	14	SAITO	M	〃	YOSHIYA Masaru MUKAI Takeo	Feb, 1955 55 yrs	+ 20 yrs
	15	SAITO	M	〃	〃	Feb. 1953 Died at 25 of age	+ Childhood
7 k‡	16	KANAZAWA Kazue	F	Sapporo Med. Coll.	HAYASHI Hajime OZAKI Seiichi ISHIZUKA Takeshi UEDA Seihachiro	June 1952 17 yrs	+ 9 yrs
	17	KANAZAWA	M	〃	〃	June 1952 15 yrs	—
	18	KANAZAWA	F	〃	〃	June 1952 6 yrs	—

‡ indicates references shown in the last column

Occasion of Discovery	Hereditary Relation	References
Intraoral disease	Consanguin. marriage first cousins once removed (parents)	a. 56th Chugoku District Assembly of Japan Oto-Rhino-Laryng. Soc., July 11, 1947. (J. of Oto-Rhino-Laryng. Soc. of Japan, 51, 163, 1948.) 49 th General Assembly of Japan Oto-Rhino-Laryng. Soc., April 4, 1948. (J. of Oto-Rhino-Laryng. Soc. of Japan, 52, 46, 1949.) b. "Jibiinkoka" (Oto Laryngology, Tokyo) 21, 53, 1949. c. "Okayama Igakkai Zasshi" (J. of Okayama Med. Soc., Japan.), Vol. 63, No. 1, 1951. d. Proceedings of the Japan Academy, I. Vol. 27, No. 6, p. 295, 1951. II. Vol. 28, No. 7, p. 383, 1952. III. Vol. 28, No. 10, p. 585, 1952. e. "Okayama Igakkai Zasshi" (J. of Okayama Med. Soc. Japan.), Vol. 64, No. 4, 1952. f. Lancet, Dec. 6, p. 1101, 1952. g. Laryngoscope, Vol. 64, No. 8, p. 685, 1954.
Family inquiry	〃	
〃	〃	
〃	〃	
Intraoral disease	cousins (parents)	
Trauma	cousins (parents)	
Family inquiry	〃	
〃	〃	
〃	〃	
Intraoral disease	cousins (parent)	h. "Kōkubyogakkai Zasshi" (J. of the Oral Disease Society, Japan) Vol. 19, No. 1, p. 18, 1952. i. "Sogo Igaku" (General Med. Science, Japan) Vol. 12, No. 12, p. 915, 1955.
〃	〃	
〃	cousins (parents)	
〃	〃	
〃	cousios (parents)	j. "Kōkubyogakkai Zasshi" (J. of the Oral Disease Soc. Japan) Vol. 20, No. 4. p. 277, 1953.
Family inquiry	〃	
Intraoral disease	Investigation incapable	k, "Nihon Kōkukagakkai Zasshi" (J. of the Japan Oral Disease Soc.) Vol. 3, No. 4, p. 254, 1954.
Family inquiry	〃	
〃	〃	

8 l‡	19	YANAGIDA	M	Kyushu Dental Coll.	KUHARA Katsuyuki YAMADA Chokei	Mar. 1953 17 yrs	+ 13 yrs
	20	YANAGIDA	F	〃	〃	Mar. 1953 6 yrs	+ 5—6 yrs
9 m‡	21	MOMODA	F	Kyushu Univ.	SHIRABE Ken-ya	Mar. 1955 19 yrs	—
	22	MOMODA	M	〃	〃	Mar. 1955 15 yrs	—
10 n‡	23	ISHII Mizuko	F	Mie Univ.	KITAJIRI Kinzaburo KUWAHARA Masaya	June. 1953 21 yrs	+ 3 yrs
11 o‡	24	MIYAZAWA	M	Shinshu Univ.	TAKEUCHI Kazuo	Mar. 1956 13 yrs	—
	25	MIYAZAWA	M	〃	〃	Mar. 1956 10 yrs	—
12 p‡	26	NAGASE Haruo	M	Okayama Univ.	OGURA Yoshio KIKUCHI Hiroshi DOI Katsu-saburo	Oct. 1955 8 yrs	—
	27	NAGASE Kumiko	F	〃	〃	Oct. 1955 5 yrs	-
13 q‡	28	MIYAMOTO	M	Takaoka Agricul. Co-operat. Assoc. Hospital, Toyama Pref.	TOYOTA Bun-ichi YONEMARU Toshiya SANNO Isamu	July. 1957 31 yrs	—
	29	MIYAMOTO	M	〃	〃	July. 1957 6 yrs	—
	30	MIYAMOTO Akira	M	〃	〃	July. 1957 1 yrs	—
14 r‡	31	KANZAKI	M	Okayama Univ.	ONISHI Chosho NISHIMOTO Shigeharu	Aug. 1957 2 yrs	—
15	32	HAYASHI	M	Tokyo Medical-Dental Coll.	IMAGAWA Yoso ONISHI Masao	1958 26 yrs	+ 4 yrs
	33	HAYASHI	M	〃	〃	1958 13 yrs	+ Unknown
16	34	YOSHIKAWA Shige	F	〃	〃	1958 38 yrs	—
	35	YOSHIKAWA Kiyoko	F	〃	〃	1958 32 yrs	—
17 s‡ t	36	SAKA	F	Dentist's Office in Kumamoto	TOCHIHARA Yoshito	Oct. 1957 12 yrs	+
	37	SAKA	F	〃	〃	1957 27 yrs	+ Unknown
	38	SAKA	F	〃	〃	1957 17 yrs	—

‡ indicates references shown in the last column

Intraoral disease Family inquiry	Cousins (parents) 〃	l. "Rinsho Shika" (Clinical Dentistry, Japan) No. 205, p. 12, 1954.
Operation on ear Family inquiry	Cousins (parents) 〃	m. "Jibiinkoka" (Oto-Laryngology, Tokyo), Vol. 28. No. 2, p. 57, 1956.
Operation on tonsil	Cousins (parents) 〃	n. J. of Oto-Rhino-Laryng. Soc. of Japan, Vol. 57, No. 1, p. 97, 1954.
Operation for paranasal sinusitis Family inquiry	Consanguin. marriage 4 generat. previously 〃	o. "Jibiinkoka" (Oto-Laryngology, Tokyo), Vol. 29, No. 2. p. 121, 1957.
Operation on ear Family inquiry	Cousins (parents) 〃	p. "Jibiinkoka" (Oto-Laryngology, Tokyo), Vol. 30, No. 1, p. 20, 1958.
Operation for paranasal sinusitis Family inquiry 〃	Cousins (parents) Child between ♯28 and unrelated mother 〃	q. "Juzen Igakkai Zasshi" (J. of Kanazawa Med. Soc., Japan), Vol. 60, No. 3, p. 572, 1958.
Treatment for pustule	Cousins (parents)	r. "Chiryo" (Trearment, Japan), Vol. 41, No. 6, p. 771, 1959.
Panphlet inquiry & Field investigation 〃	Cousins (parents) 〃	unpublished
〃 〃	Cousins (parents) 〃	unpublished
Intraoral disease Family inquiry 〃	First cousins once removed (parents) 〃 〃	s. "Saikai-Iho" (Kumamoto Medical News, Japan), No. 119, p. 3, 1958. t. "Shika-Gakuho" (Dentists' Monthly, Japan), Vol. 58, p. 401, 1958.

with acatalasemia. They concluded that the etiological factor is of the mendelian recessive monogenic character. In any event, there is little doubt that this disease is caused by unusually close consanguineous marriages.

Familial groups of siblings with multiple occurrence of acatalasemia : On investigating the multiple occurrence of this disease in a single family line, 2 familial groups (12%) had 4 patients ; 3 familial groups (18%) 3 patients ; 9 familial groups (53%) 2 patients ; and 3 familial groups (18%) had 1 patient each. Of the two familial groups with 4 patients each, the Nakayamas had 4 patients out of 7 siblings, namely, the ratio of 4/7, while in the Abes it was 4/10 ; and in the Kanazawas with 3 patients it was 3/5 ; in the Yoshikawas with 2 patients (4th Familial Group) it was 2/7 ; in the Kanekos, 2/6 ; in the Saitos, 2/8; in the Yanagidas, 2/6 ; in the Momodas, 2/6 ; in the Miyazawas, 2/3 ; in the Nagases, 2/5 ; in the Hayashis, 2/6 ; in the Kikkawas (16th Familial Group), 2/4. Of the groups with 1 patient each, in the Miyamotos, 1/9 ; in the Fukudas, 1/1 ; in the Ishikawas, 1/2 ; and in the Kanzakis, 1/2. From these it is clear that more than 80% of families have two or more patients among their siblings.

Methods of treatment and their efficacy : As already mentioned by Takahara, in the treatment of oral gangrene occurring in acatalasemic cases, the extraction of tooth or teeth causing the gangrene and the radical excision of diseased tissues in cases where the gangrene progressed as far as the bone, are most effective. Moreover, the concurrent use of penicillin is recommended. Of those who had oral gangrene, the methods of treatment are described in 16 cases. In 7 cases, from 3 familial groups, at Okayama University, for the far advanced type with progressive osseous gangrene, removal of the diseased tissues (partial resection of the maxilla), extraction of teeth, and penicillin injections were carried out. For those mildly advanced cases, the extraction of teeth and penicillin injections were given. Every case was successfully cured. Those with minimal lesions recovered spontaneously without treatment or with conservative treatment. Of the severe cases, two had complication of tonsillar gangrene, but they were cured by tonsillectomy. At Tokyo Medical-Dental College, 3 familial groups consisting of 6 cases were cured by extracting teeth and penicillin injections, but two of them developed scars which made it impossible to open the mouth and thus required further plastic operations. One case at Sapporo Medical College had teeth extractions and penicillin injections. In this case also, a plastic operation was necessary to correct a defect resulting in difficulty of mastication due to the retraction of the gums. In one case at Kyushu Dental College teeth were extracted and a

synechia of the lower lip was cured by plastic surgery. One case at Mie University was treated by extraction of teeth and other treatments, thus resulting in a cure. In all foregoing cases, the course and the length taken in healing of the wound showed no significant difference from those observed in persons who do not have acatalasemia.

Clues to the discovery of acatalasemic cases : As for clues leading to the discovery of this disease, the majority of them are discovered at the time of operative treatment or during other prophylactic measures such as extraction of tooth, when the blood turns black and there is no foaming upon the application of hydrogen peroxide to the open wound. Also when a patient is thus discovered, the members of the family are usually examined and consequently other acatalasemic patients are often discovered among the siblings. In order to fully understand the etiology of this unusual disease, we wish to make a plea to the general public and physicians to be aware of the disease. We must wait for further information and observations on additional cases before the etiologic and genetic factors can be more clearly determined.

CONCLUSIONS

1. With a view to grasp more simply and clearly the characteristics of this disease and in order to find a clue for prompt discovery of cases when encountered in future, the authors undertook a statistical study of the cases already reported by various authors.

2. The cases reported so far amount to 17 familial groups which consisted of 38 acatalasemic cases. These groups were distributed widely throughout Japan. The disease seemed to be prevalent in the rural communities where adherence to the custom of consanguineous marriage occurs. As yet, we have not heard of the occurrence of this disease in other countries.

3. The disease has equal distribution in both sexes. About one half of patients showed a peculiar oral gangrene (Takahara's disease). The great majority of these were noted in those less than 10 years of age.

4. The great majority of them were children whose parents were united in consanguineous marriage and have siblings with acatalasemia.

5. As for the treatment of oral lesions in this disease, extraction of tooth at the site of the lesions, removal of the diseased tissues en masse by resection, and penicillin treatment given concomitantly are effective. The course and the length of time required in healing of the wound due to the operation are about the same as in the case of normal persons.

6. The authors wish to call special attention to the phenomenon peculiar to the acatalasemic blood. The blood of acatalasemic individuals changes to brownish-black color in the absence of foaming or bubble formation upon the application of hydrogen peroxide to blood.

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