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Kashin-Beck disease: a historical overview

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Abstract In 1919, the first report on Kashin-Beck disease (KBD) made by a Japanese doctor described an endemic occurrence in the northern district of Korea. In the 1930s, Dr. Takamori and his colleagues at Manchuria Medical College produced a series of reports on its epidemiology, clinical and roentgenological findings observed in the north-eastern district of China. In 1940s, a Tokyo University group led by Dr. Ogata found that the salivary glands of KBD patients were markedly degenerated. Administration of the condensed water taken from the endemic area into experimental rats produced degeneration of the salivary glands and changes in bones and joints similar to those of KBD. Thus, they proposed parotin deficiency theory as the etiology of KBD, and they recommended parotin therapy for KBD in its early stage. In the 1950s, Dr. Takizawa and his colleagues at Chiba University demonstrated that ferulic acid and *p*-hydroxycinnamic acid, found in the drinking water in the endemic area, caused degeneration of the salivary gland in rats. They recommended boiling the drinking water or using activated charcoal for the prevention of KBD. In the 1970s, the Japanese Ministry of Health and Welfare made a nationwide survey for the incidence of KBD in Japan. They concluded that there was no case of KBD in Japan with the exception of a few patients who had been brought up in the northeastern district of China and later had moved to Japan.

Résumé En 1919, la première observation faite par un médecin japonais sur la maladie de Kashin-Beck (KBD) décrit la présence endémique de la maladie dans une région du nord de la Corée. Au cours des années 30, le Dr. Takamori et ses collègues de la Faculté de Médecine de Manchurie présentent une série de communications sur l'épidémiologie, la clinique et la radiologie du KBD étudiée au nord de la Chine. Dans les années 40, une équipe de l'Université de Tokyo dirigée par le Dr Ogata décou-

vre une dégénérescence des glandes salivaires chez les patients atteints de KBD et montre que l'administration de l'eau recueillie dans les régions endémiques produit chez le rat une dégénérescence des glandes salivaires et une modification des os et des articulations semblables au KBD. Ils proposent comme étiologie du KBD une insuffisance parotidienne et recommandent un traitement de "parotine" pour les stades précoces du KBD. Dans les années 50, le Dr Takizawa et ses collègues de l'Université de Chiba démontrent que l'acide ferulic et l'acide *p*-hydroxy-cinnamic présent dans l'eau des régions endémiques provoque la dégénérescence des glandes salivaires du rat et recommandent soit de faire bouillir l'eau potable ou soit d'utiliser du charbon de bois activé pour prévenir du KBD. Dans les années 70, le Ministère Japonais de la santé a réalisé une enquête nationale sur l'incidence du KBD au Japon qui a conclu son absence au Japon à l'exception de quelques cas qui ont séjourné dans la région du nord-est de la Chine et sont retournés ultérieurement au Japon.

Introduction

This paper presents a historical overview of studies on Kashin-Beck disease (KBD) carried out by Japanese researchers. In 1919 a Japanese army doctor, T. Okano [29], first reported on an endemic condition of progressive polyarthritis found in the northern district of the Korean Peninsula where the altitude above sea level is 1000 m.

Professor Tokio Takamori and his colleagues from Manchuria Medical College made the first discovery of the endemic occurrence of KBD in the northeastern China in the early 1930s. They reported on its clinical features, epidemiology, radiology and pathological anatomy at the General Congress of the Japanese Society of Internal Medicine in 1934 [33]. From that time, Takamori and his colleagues kept reporting on various aspects of KBD basing on their own surveys and pathological analyses until the end of World War II [32, 34, 35, 36, 37, 38, 39]. Takamori called the condition dysostosis enchondralis

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Fig. 1 Map drawn by Takamori indicating the endemic area of KBD and goiter in 1940

endemica based on its pathological and endemiological findings. Figure 1 illustrates a map drawn by Takamori indicating the endemic area of KBD and goiter in the northeastern region of China in about 1940. Takamori classified KBD into three stages based on roentgenological analyses of 116 KBD patients and comparing them with 500 healthy people living in the nonendemic areas in China. He described that, in addition to various grade of deformity and swelling of joints and retarded growth, roentgenological findings of the hand in the first stage of KBD include uneven epiphyseal cartilage, particularly of the proximal phalanx. In the second-stage, ossification in the epiphyseal cartilage, a funnel-shaped defect in the metaphysis and flattened and deformed head of the phalangeal bones was seen. In the third stage, abnormally widened metaphysis, narrowed joint space, advanced osteoporosis of phalangeal bones, and no epiphyseal line were seen on the roentgenogram. Kubo, Aiso, Kako and Hiyeda were among those at Manchuria Medical College who worked with Professor Takamori in studying KBD very intensively in north-eastern China in the 1930s. Kubo et al. [14, 15, 16, 17, 18, 19, 20], Aiso et al. [1, 2] and Kako [10, 11, 12] all produced a series of reports on KBD. Hiyeda et al. [4, 5, 6, 7] found that the concentration of iron ions in the blood of KBD patients was higher than that of the normal control subjects, and they proposed the iron intoxication theory as etiology of KBD in 1936 and 1937.

In the 1940s, a Tokyo University group began studying the etiology of KBD. Noguchi et al. [21, 22] reported in 1943 and 1944 that the KMnO_4 concentration in drinking water in the endemic area was much higher than that in the nonendemic area. Ide et al. [8] reported in 1951 that administration of the condensed water taken from the endemic area into rats produced degeneration of the salivary gland and changes in bones and joints similar to those of KBD. Professor Tomosaburo Ogata and his colleagues [23] from Tokyo University reported in 1942 that the salivary glands of KBD patients histologically show marked degeneration and that, therefore, their endocrine function must be impaired. Ogata and Takizawa [23, 24, 25, 26, 27, 28] produced experimental aptyalistic rats by excising the salivary glands, and they demonstrated degeneration of the articular cartilage and atrophy of the subchondral bone in these animals. From these facts, Ogata and Takizawa considered that parotin deficiency caused by some exogenous factors might be the cause for KBD. Thus, Ogata and Takizawa proposed parotin deficiency theory as the etiology for KBD. They stated that organic substances contained in the drinking water in the endemic area caused the degeneration of the salivary gland and the gland's endocrine dysfunction induced osteochondrodysplasia. They recommended "parotin treatment" for KBD in its early stage. A series of their studies on experimental aptyalism in rats and its influences on the

metabolism of bone and cartilage were reported between 1943 and 1952.

In 1959, Professor Enjiro Takizawa and his colleagues in Chiba University started to study exogenous factors that may cause degeneration of the salivary gland in KBD patients. They demonstrated that ferulic acid and *p*-hydroxy-cinnamic acid, which are in the drinking water, deriving from decayed plants, cause degeneration of the salivary gland in rat. Thus, they proposed these organic substances as causative agents for KBD and recommended boiling the drinking water for more than 30 min or using activated charcoal to render the organic substances ineffective so as to prevent the development of KBD. Results of their study were reported annually between 1959 and 1968. At the same time, Takizawa and his colleagues [40, 41] carried out a nationwide survey for KBD in Japan from 1956 to 1968 based on their own roentgenological criteria and palpation findings of the salivary gland. They reported that an average of 13.7% of school children in Japan are subclinically suffering from KBD and that the incidence was particularly high in the countryside of Hokkaido. The Japanese Ministry of Health and Welfare was panic-stricken by this report, although other KBD researchers, including Professor Takamori, did not accept Takizawa's roentgenological criteria for the diagnosis of early stage of KBD.

Then, in 1968, the Japanese Ministry of Health and Welfare organized a survey team for KBD to follow up those children who had been diagnosed as having subclinical KBD by Takizawa's group about 10 years previously. The survey team led by Dr. Itsuzo Shigematsu [31] from the National Institute for Public Health concluded in 1972 that there was no KBD case among these children who had reached adulthood by the time of the follow-up. Thus, Takizawa's roentgenological criteria for the early diagnosis of KBD were denied in Japan, and at the same time, Ogata-Takizawa's parotin deficiency theory as the etiology for KBD lost its attraction. Kawamura et al. [13] reported that 37 children, who in 1962 were diagnosed as subclinically suffering from KBD, were examined again 12 years later, and none showed clinical or roentgenological signs of KBD. Kawamura et al. concluded that Takizawa's criteria for early detection of KBD was based on a faulty interpretation of roentgenological findings of normal variations of the hands in growing children. This was the reason for the wrong diagnosis.

In 1981, Egashira and Kawamura [3] were asked by the World Health Organization (WHO) to visit Heilongjiang Province and Liaoning Province in northeastern China to survey the incidence of KBD. After an extensive survey, they found that no people fed on rice during childhood suffered from KBD. Changing sources of the drinking water had little influence on the incidence of KBD. Fusarium infection of grains is five times higher in the endemic area than in the nonendemic area, and serum-Se levels are significantly lower among those living in the endemic area than those in the nonendemic area. Presently in Japan, only little research work is being car-

Table 1 Number of cases reported with KBD in Japan between 1984 and 1997

Year	1984	1985	1987	1988	1990	1991	1997
Women	4	—	1	4	2	2	3
Men	—	3	—	1	2	2	1
Total	4	3	1	5	4	4	4

ried out with regard to the etiology of KBD. Iwata et al. [9] reported in 1991 that on electron microscopy numerous vacuoles were observed in chondrocytes of KBD patients, and measurement of glycosaminoglycan in the urine of the patients suggested the existence of abnormal metabolism of the cartilage. Sasaki et al. [30] reported in 1994 that rats fed on a low Se diet showed a decrease in bone mineral density and degeneration of nuclei and endoplasmic reticular ballooning of chondrocytes in the deep layer, but changes were not as marked as those observed in KBD patients.

Table 1 summarizes the cases of KBD reported in Japan between 1984 and 1997. One to five cases are reported almost each year. There is no significant difference in the number of cases between females and males. Racially, all of them are Japanese, born from Japanese parents in Heilongjing Province during World War II and brought up there, except for one individual who was brought up in Liaoning Province. They returned to Japan after having lived in these provinces for about 50–60 years. This fact clearly indicates that KBD is an endemic condition that affects both Chinese and Japanese born and brought up in the endemic area.

In Japan today, the etiology of KBD is understood to be multifactorial based on various combinations of Se and iodine deficiency in the soil, a high concentration of organic substances in the drinking water, and severe contamination of grains by fungi produced mycotoxin. Furthermore, the mechanism of osteochondral necrosis in KBD is now presumed to be as follows; Se deficiency can be a predisposing factor for KBD, because Se deficiency would induce latent impairment of the antioxidant system of the body. Exogenous free radical carriers such as organic substances derived from decayed plants and mycotoxin derived from fungi contamination may promote lipid peroxidation of chondrocytes. In addition, the oxidation process is accelerated by the deficiency of Se, which has an inhibitory effect on the toxicity of mycotoxin by reducing lipid peroxidation of chondrocytes. Such accelerated oxidation processes of chondrocytes result in degeneration of the cartilage and disturbance of enchondral ossification. Iodine deficiency, which is often associated with Se deficiency in the endemic area, is considered likely to impair subchondral bone repair. Assuming such a mechanism of osteochondral necrosis in KBD, the author [42] has proposed some preventive measures for KBD as follows:

1. Construction of a controlled water supply system in the endemic area

2. Introduction of methods of prevention for grain infection by fungi
3. Establishment of the examination network for early diagnosis
4. Children in the endemic area are fed on rice that is sent from outside, during the growing period

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