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Cold weather and Kashin-Beck disease

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Abstract

Kashin-Beck disease (KBD) is an endemic osteoarthropathy. Its distribution region covers a long and narrow belt on the Pacific side and belongs to continental climate with short summer, long frost period, and large temperature differences between day and night. In particular, KBD patients are typically scattered in the rural areas with seasonal features such as cold winters and rainy autumns. Etiological studies have demonstrated that the carrier of pathogenic factors is the grains produced in endemic areas. Risk factors for KBD include fungal contamination of grains due to poor storage conditions associated with cold weather. The epidemiological characteristics of KBD include agricultural area, early age of onset, gender equality, family aggregation, regional differences, and annual fluctuations. A series of preventive measures have been successfully taken in the past decades. National surveillance data indicate that the annual incidence of KBD is gradually declining.

Keywords

Kashin-Beck disease; epidemiology; etiology; national surveillance; fungal contamination of grain; unbalanced dietary protein intake

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1 Introduction

Historically, Kashin-Beck disease (KBD) was first described in 1849 and recorded in Russian literature[1]. The name Kashin-Beck comes from two physicians Nicolai Ivanowich Kashin (1825-1872) and Eugene V Beck (1885-1916) to commemorate their outstanding contributions to the disease. In China, the earliest documentation on KBD can be traced back to 1908. Not until the founding of new China in 1949, has the comprehensive study of KBD begun. So far, a great achievement has been made in the prevention and control of KBD. As a degenerative osteoarthritis, KBD is characterized by multiple, symmetrical articular cartilage injury in endemic areas[2]. Pathologically, KBD is manifested by joint swelling, degeneration, hyaline cartilage necrosis and inflammatory hyperplasia, leading to joint deformation and secondary injury[3-4]. Serious sequelae, such as limbs deformity and short stature, cause growth disorder in children and physical disabilities in adulthood. Experimental studies have demonstrated certain pathological changes similar to KBD in patients can be duplicated in dogs, monkeys, and chickens[1,5]. Pathological studies illustrated the ultrastructural characteristics of cartilage injury, laid the imaging basis of X-ray examination, and clarified the early biochemical changes of KBD. In clinical, most patients have no obvious symptoms at the initial stage of KBD. In contrast, the X-ray imaging of the fingers can reflect the severity of the pathological changes of KBD. In epidemiological investigation, children's right hand (including wrist) X-ray photographs are often taken for diagnosis of KBD[4].

2 The epidemiology of KBD

Epidemiological research includes classic contents such as pathogenic factors, transmission route, and susceptible population. The geographical distribution of endemic KBD covers a long and narrow zone, which is related to the features of regional environment[1,6-7]. Cold weather as a natural condition affects residents' lifestyle in local area. Cold and rainy weather influence the composition ratio of moldy diet ingredients linked to the poor storage conditions of grains in endemic areas. The causative factor of KBD is transmitted through food, especially through wheat, barley, and maize but not *via* rice or rarely millet. The occurrence of KBD is closely associated with the mycotoxin contamination of grains produced in the epidemic area, which suggests that KDB is not due to short of something but is more similar to poisoning. It should be noted that cold weather is not an etiological factor, but it is a necessary condition for the activation of the pathogenic factors and the amplification of their detrimental effects. This theory has been verified by epidemiological and experimental studies on the grain mildew[8]. KBD areas are scattered in a wide space characterized by cold and rainy season during the grain harvest. Epidemiological field

investigations have proved that the decisive factors of KBD are agriculture and self-produced grains[9]. The soil in the KBD area is suitable for the growth of Fusarium that can infect the grains growing on the land. Poor storage condition facilitates the proliferation of Fusarium. The milling process is equivalent to inoculation, which is conducive to fusarium contamination of grains. Fusarium produces pathogenic substances as represented by mycotoxins in flour[10]. Once ingested by children, the contaminated flour may cause inflammatory necrosis in cartilage and further induce the development of KBD. A lot of research data indicate that the pathogenic factor is dependent on various conditions such as the environment, soil, grain, agricultural technology, agricultural production methods, and food processing methods in the endemic area[2]. The occurrence of KBD relates to distinct risk factors, among which the weather is the most uncontrollable[11]. In recent years, due to changes in the conditions such as land contracting and mechanization, the harvest period has been significantly shortened, which has significantly improved the quality of grains. However, these innovations are unable to radically eliminate the threat from rainy and cold weather. When the environmental conditions of endemic areas are appropriate, KBD is still able to take its prevalence within a certain range[12]. The pathogenic factors of KBD basically act on the epiphyseal cartilage, epiphyseal plate cartilage and articular cartilage of developing children. Cartilage damage is induced by chemical substances that enter the human body through dietary intake. However, the origination and spread of the pathogenic factors can be mediated by different modulators such as occupations, soil, cold weather, and harvest methods. Also, KBD can be reversed by blocking the pathogenic factors and appropriate treatment in the early stage of the disease. Once the early stage of disease is not controlled in time, it will further develop into a destructive stage, leading to joint deformation and dysfunction. Hence, the prevention of KBD should be taken as an initiative measure to obstruct the transmission route of pathogenic factors and control the occurrence of new cases. The onset age of KBD is commonly in children aged 7-13 years old. If the appropriate treatment is taken during this period, most cases can be cured. Therefore, the attention must be paid to the early detection and treatment of children's cases. The life expectancy of KBD patients is similar to that of non-endemic areas.

3 The geographical distribution of KBD

Globally, the geographical distribution of KBD ranges from the Tibetan Plateau in Southwest China to the narrow zone in Northeast China, covering eastern Siberia of Russia and partial region of Northern Korea. There has not been any case reported in other countries. KBD in the endemic areas of the Far East of Russia has been eradicated in the 1960s. The epidemic situation of KBD in North Korea is unknown. In China, KBD is distributed in Heilongjiang Province, Jilin Province, Liaoning Province, Hebei Province, Shandong Province, Henan Province, Inner Mongolia Autonomous Region, Shanxi Province, Shaanxi Province, Gansu Province, Sichuan Province, Qinghai Province, and Tibet Autonomous Region. The endemic distribution of KBD has several characteristics.

3.1 The endemic area of KBD is related to climate and topography

The geographical areas of KBD belong to continental climate, which is characterized by short summer, long frost period, and large temperature differences between day and night[1,12]. Endemic areas are located at the junction of warm and humid monsoon regions in southeast coast as well as arid and cold inland regions in northwest China. In the Loess Plateau of Northwest China, the disease is more serious in the gully area. In Northeast China, the terrain of the disease area is mostly shallow mountains and hills, among which river valley, grassy marshland, intermountain valley, and other low-lying humid areas are the most serious ones for KBD. However, the relationship between the disease and the terrain is relative. The endemic KBD also is pandemic in the Northeastern plain region, such as Songnen Plain and Songliao Plain.

3.2 In the endemic area, sick villages are presented with focal or patchy distribution

Although KBD is a typical endemic disease, the sick area can be adjacent to or alternated with the non-sick area. Within the same administrative division, not all places have the disease, and they often crisscross with each other. In a large area of sick villages, one or several "healthy islands" can appear, whereas in a large area of non-sick villages, one or several "sick islands" can occur. Sick or non-sick villages are distributed in a focal or mosaic pattern, or connected intermittently into a patch, or in a strip along the foothills or valleys.

3.3 Variability and the relative stability of endemic KBD

The endemic or non-endemic areas of KBD may alternate. Non-endemic areas can become sick areas. New patients can reoccur in some old endemic areas. These old areas may naturally disappear and become the historical areas of KBD. In terms of spatial distribution, KBD is obviously different from infectious diseases, with rare case of spreading from place A to place B. Once KBD has occurred in certain villages of an endemic area, therein new cases will unlikely reappear thereafter within a short time. Yet, it is possible that new cases may arise intermittently

or continuously over several years or even decades in the same endemic area, but they will not "spread" to the adjacent non-sick areas.

3.4 The Urban/rural distribution of KBD

The occurrence of KBD shows no differences in gender, race, and education, but significant differences in occupation and habitat[2]. There are clear boundaries between urban and rural areas. New cases never occur in the urban area. Non-agricultural residents in cities, towns, railways, forest areas, and mines are almost free of the disease. Epidemiological investigation demonstrated that the distribution of the condition is related to the source of rations. In endemic area, the disease occurs in farmer family, but not in urban residents. The children from farmer families in the endemic areas suffer from the disease, some of whom can be very serious. Moreover, the disease can spread to the residential areas of urbanized farms. Some agricultural production teams lived in seriously sick villages, but they witnessed down trend of the malady after their home-grown rations had been substituted with state-owned warehouse grains. Interestingly, KBD could occur if urban residents bought or traded for more flour or corn from endemic villages. Therefore, the essence of occupational differences is derived from the distinct sources of staple food.

4 The chronological distribution of KBD

4.1 The annual fluctuations of KBD

The incidence rates of KBD are different every year. For example, the X-ray detection rate of children (metaphysis) in Shangzhi County of Heilongjiang Province from 1979 to 1982 was 53.5%, 14.4%, 41.2% and 59.3%, respectively. The X-ray detection rate of children in the Olunchun Autonomous Banner of Inner Mongolia Autonomous Region was 41.1% in 1990, 22.1% in 1991 and 61.6% in 1992, respectively. Generally, KBD occurs in the following year with early frost and heavily rainy autumn. The appearance of fluctuation depends on the active degree of pathogenic factors. In China, the incidence rate of KBD had roughly two peaks, one occurred in 1955-1956 after the agricultural cooperation, and the other in 1969-1970 when autumn floods were widespread. After the national implementation of economic reform and opening-up policy in 1984, the living standard of the people has improved and the incidence of KBD has significantly reduced[2].

4.2 The seasonal changes of KBD

The occurrence of KBD presents an obvious seasonal tendency, especially in winter and spring. This feature is consistent with the biological characteristics of crops harvested in rainy autumn, improper storage in cold weather, fungal contamination of grain, resulting in the onset of disease in winter and spring. It should be noticed that cold and humidity are the basic conditions for mycotoxin production, and such environmental conditions only exist in certain areas, which are the prerequisite for endemic KBD to develop. In contrast, when the causative factors of KBD are overly active or weak in some areas, it is difficult to find seasonal fluctuations.

5 The population distribution of KBD

5.1 Age of onset

KBD mostly occurs in adolescents but rarely in adults. In severe areas, the age of onset may be two or three years old. The youngest age recorded is a 97-day-old baby. Children are susceptible to KBD, which is the reason that the epidemiological surveillance of KBD has been carried out in children. In mild areas, the onset age is more than ten years old. In the early stage of the disease, there are only X-ray changes, and clinical examination cannot detect any obvious signs. If the patients stay in the epidemic environment during this period, the condition will gradually deteriorate. One or two years later, some patients can appear early epiphyseal closure, serious bone destruction and other changes, but some patients still have no obvious signs in clinical examination. The abnormality of epiphyseal development results in short finger deformity or dwarfism in adulthood.

5.2 Relationship between KBD and the source of rations

There is a close relationship between the types of staple food and KBD. Wheat and corn are the staple food in the endemic areas. KBD does not occur in the residents who eat rice in endemic areas, which is a special phenomenon[13]. Ethnic Korean residents living in the seriously sick area grow rice in paddy field. They rely on rice as their staple food and do not suffer from KBD. If ethnic Korean residents grow corn in dry field, they eat corn as the staple food and likewise suffer from KBD. Moreover, the incidence of KBD of ethnic Korean residents is the same as that of Han residents. In the endemic areas, when the Han residents plant rice, there are almost no new cases of KBD. After the dry field was changed to paddy field and rice was used as the staple food, KBD gradually disappeared in the originally serious villages. In some places, there were more paddy fields but no disease; however, the disease quickly appeared when these places became sick areas several years after paddy field were converted to dry field and corn as the staple food[2].

5.3 Genetic susceptibility of KBD

KBD has no ethnic susceptibility. All ethnic groups that conform to the same lifestyle and habits can be affected. In China, ethnic groups such as Han, Manchu, Hui, Mongolian, Tibetan, Daur and Korean people are all known to be susceptible to KBD. Epidemiological surveys have shown that the prevalence rate of the people who moved from the non-disease area to the disease area can reach a disease rate similar to or slightly higher than that of the local population. People living in the same family have almost the same chance of contacting pathogenic factors. Therefore, the occurrence of KBD shows family aggregation to a large extent.

6 The dynamic trend of KBD

Based on the systematic analysis of national KBD data, the dynamics of the disease can be summarized with the following trends.

6.1 Long-term downward trend

When tracking historical records, the disease has been rapidly and steadily declining to a level of comprehensive control. Wenzhigou Village in Liaoning Province is the best representative village with preserved X-ray hand films. The detection rates of children in this village were 47.6% (1956), 38.8% (1964), 1.69% (1979) and 0.87% (1984). The disease dynamics of other areas are basically synchronized with this trend[2].

6.2 Differences among endemic areas

From the late 1970s to the early 1980s, the second group of rapidly declining areas appeared, including Sichuan Province, Shanxi Province, Hebei Province, Henan Province, Shandong Province, Eastern Gansu Province and shallow mountain areas in Shaanxi Province. The X-ray positive rates of children aged 7-12 years old were lower than 10% in some endemic areas, including Songpan County (6.3%), Wangcang County (2.9%), Zhengning County (8.7%), Xia County (1.8%), Manchu Autonomous County of Fengning (3.3%) and Weichang County (6.3%). It is assumed that the drops was attributable to the improved living conditions in these places during the 10-year monitoring period. In 1999, the X-ray positive rates of children aged 7-12 were 3.0% in Songpan County, 0 in Wangcang County, 0 in Zhengning County, 0 in Xia County, 1.0% in Manchu Autonomous County of Fengning and1.6% in Weichang County.

6.3 The fluctuation of the epidemic disease

Some active areas were mostly distributed in alpine regions of Shaanxi Province, Inner Mongolia Autonomous Region, and Heilongjiang Province. The two monitoring points in Shaanxi Province, Cuimu Town in Linyou County and Caomiao Town in Lintong County, are about 1 300 meters above sea level. Wushen County and Olunchun Autonomous Banner in Inner Mongolia Autonomous Region, and Fuyu County in Heilongjiang Province are cold and high latitude areas. In 1990, the X-ray positive rates of children aged 7-12 were 45.7% in Cuimu Town of Linyou County, 68.6% in Caomiao Town of Lintong County, 28.2% in Wushen County of Inner Mongolia Autonomous Region, and 59.6% in Olunchun Autonomous Banner. The monitoring results acquired in 1994 were 17.5%, 19.4%, 28.1% and 26.0%, respectively. Despite the continuing decline, the rates remained at a high level. This fact argues that the disease risk has not been fully controlled and the natural pathogenic factors are still active.

6.4 Deterioration of prevalence trend

In a large range, some newly emerged severe areas have appeared in the locations where there had never been any patients, and some areas which were originally mild have later become active and severe. The X-ray films of children in Yulin City of Northern Shaanxi Province were taken in 1994, with positive rates at age of 7-12 being 38.9% in Mangkeng Village and 17.8% in Gaojiahuochang Village. There has no prior KBD case report in Mangkeng Village and Gaojiahuochang Village. These districts should be regarded as new active and severe areas.

6.5 The recent trends of KBD

From 1990 to 1999, the overall trend of disease dynamics was declining year by year, although there were some specific circumstances. In 2000, the expert group revised the monitoring strategy by switching the fixed-point monitoring to the moving-point monitoring; as such, the most severe point in the monitoring province was set as the yearly monitoring point to reflect the provincial disease condition. Similar to the previous years, the overall trend of disease dynamics from 2000 to 2007 also declined annually. Since 2008, the detection rate of new cases in children has gradually dropped to less than 1%. In recent years, the national disease level control has reached the elimination standard.

6.6 The current situation of KBD

In addition to individual villages and towns, a few new cases of KBD are found in all monitored points or areas. However, patients with sequelae of KBD cover more than a dozen provinces and autonomous regions. The number of diagnosed KBD patients are presently close to 180 000. Their life and work are seriously affected. Numerous patients hinder the economic development

of endemic regions. These patients are the key target of national poverty-alleviation program.

7 Prevention and control of KBD

In the 1990s, the prevention and control strategy of KBD based on "Grain Exchange" was formed and implemented. The core content of KBD control strategy is not to eat the grains produced in the endemic area. The relevant measures include changing dry land to paddy field in the endemic area where water source conditions permit, promoting scientific grain storage, so as to reduce grain pollution. The popularization of paddy field has made in Jilin, Liaoning, and Heilongjiang Provinces, achieving the control standard of KBD as early as in the 1990s. The disease in Tibet and Qinghai has slowly declined as well, especially after having implemented the policy of "Free program for Food, Housing and Tuition" in school-age children. Tibet and Qinghai achieved the goal of elimination in 2017, reinforcing that "Grain Exchange" is an important measure for the elimination of KBD. Collectively, preventive measures are summarized as follows. (1) Where the water sources permit, the dry land should be converted to paddy field and rice should be consumed as the staple food; where the water source is not available, millet, sorghum and other grain food should be chosen as the staple food; (2) In areas with convenient transportation or near to cities and towns, vegetables or other high value-added crops can be planted, and staple food can be purchased from the market; (3) Returning farmland to forest or animal husbandry in remote mountainous areas to avoid eating self-produced grains; (4) To improve the methods of grain harvest, transportation, and storage; to reduce the opportunities of fungal pollution and toxin production; to enhance the quality of food hygiene and safety. In view of the monotonous dietary structure of the residents in the endemic areas, it is important to change the grain planting structure and advocate the diversity of crops and grains; (5) Moving out or relocation. It is necessary to move residents out of the sick area with poor natural environment to the non-sick area. Local school-age children are collectively transferred to boarding schools in epidemic-free areas; (6) Comprehensive preventive measures. According to the actual situation of the epidemic areas, the above-mentioned preventive measures can be integrated to form a combination of comprehensive measures; and (7) Government increases financial investment and implements comprehensive preventive measures for the prevention and control of KBD.

8 The etiology of KBD

8.1 Mycotoxin contamination

In terms of the etiology of KBD, the chondrocyte necrosis of deep cartilage is thought to be caused by environmental factors[14-15]. Nearly 50 suspected pathogenic theories have been proposed, including genetics, radiotoxicity, vitamin deficiency, infectious theory, endocrine imbalance, over-limited lead in water, chronic iron intake excess, calcium deficiency, fungal poisoning, biogeochemical theory, *etc.* Of various environmental risk factors, some are the main factors, and the others may be auxiliary factors. Certain theories have been eliminated following extensive and in-depth research. For example, virus infection in the etiology of KBD has been invalidated; the genetic hypothesis has been discarded. In recent years, modern biotechnology has been used to investigate the effects of food mycotoxins in the pathogenesis of KBD. From 1932 to 1945, Ex-Soviet scholar Sergievsky and colleagues recognized that the grains in the disease area was the carrier of pathogenic factors. Grains can be polluted by fungi in the process of harvesting, threshing, drying, and storage. The humid conditions in endemic area are conducive to breeding fungi and producing fungal toxin. Furthermore, they proposed that KBD is a food-borne poisoning disease (food mycotoxicosis or food mycotoxic enchondral osteodystrophy) caused by Fusarium oxysporum and mycotoxins. The main arguments include: (1) There are suitable conditions for the growth of food fungi. The distribution of the disease areas in the former Soviet Union and China belongs to continental climate that is characterized by short summer, long frost period, large temperature differences between day and night, and grain harvest in the rainy season; (2) A variety of dominant fungi can be detected in grains from KBD area, such as Fusarlum Sporotrichiella.Var. Poae in Chita of the former Soviet Union, Fusarium graminearum and Fusarium moniliforme in Shaanxi province, and Fusarlum moniliforme in Gansu province; (3) Mycotoxins such as Butenolide (BUT), Alternariol methyl ether (AME), Deoxynivalenol (DON), 15-DON, 3-DON and nivalenol (NIV) were readily detected with higher concentrations in the grains from the disease area than those from the non-disease area; (4) The *in vitro* culture of chondrocytes revealed that mycotoxins such as BUT, DON and NIV could induce the dedifferentiation and apoptosis of chondrocytes, inhibit DNA synthesis and proliferation, and cause membrane damage to chondrocytes, resulting in the biochemical and metabolic disorders of cartilage. Rats and puppies fed with extracts from Fusarium cladosporium, Fusarium pyriformis and Fusarium oxysporum could suffer from cartilage damage similar to KBD; and (5) The trial of "Grain Exchange" was carried out in Shuangyashan City (1972-1980) and Fusong County (1958-1965). A field trial on the prevention of KBD was conducted with rice grown in paddy fields in Shangzhi County (1970-1988). The above-mentioned series of projects have achieved satisfactory results in KBD control.

8.2 T-2 toxin

Since the 1990s, Fusariotoxin T-2 (T-2 toxin) has been proposed as the causative substance of KBD[6,16-17]. The primary

evidence includes: (1) The supernormal concentration of T-2 toxin, ranging 2.0-1549.4 ng/g, in wheat and corn of KBD-endemic areas. T-2 toxin was detected from the food flour of patient households in KBD area and the content of T-2 toxin was higher than that of commercial market flour in the non-sick areas. Accordingly, the T-2 toxin of grains in the disease area below 100 μg/kg or at least below 300 μg/kg is a measure to block the occurrence of KBD; (2) Feeding chicks with 100 ng/kg·day of pure T-2 toxin in the feed for 3-5 weeks could cause pathological changes analogous to human KBD, resembling the result of using Fusarium bacteria mixed with chicken feed at a ratio of 1/10; (3) T-2 toxin could apparently inhibit the proliferation of chondrocytes in a dose-dependent manner[18]; (4) T-2 toxin could induce apoptosis and dedifferentiation of chondrocytes *in vitro*; (5) The effects of mycotoxins on the cartilage as well as peripheral blood of patients with KBD. There are differences in the expression profiles of T-2 toxin, deoxynivalenol, aflatoxin B1, zearalenone, fumonisin B1 and ochratoxin related genes in peripheral blood monocytes, which are mainly involved in apoptosis, collagen synthesis, cartilage growth, and development. Therefore, the environmental factors deserve further study to determine whether a single gene or a gene in conjunction with mycotoxin specifically causes the initial damage of chondrocytes in KBD. In any cases, still some questions need to be answered: (1) How to explain the focal distribution of the disease area in epidemiology? T-2 toxin and other mycotoxins are widespread in other countries, but no KBD has been identified; (2) The strains isolated from different endemic areas are inconsistent. T-2 toxin theory still needs to be further investigated. Collectively, the hypothesis of mycotoxin has been tested through epidemiological and experimental studies. The pathogenic factors of KBD enter the human body *via* locally produced grains. The grains in the disease area are polluted by mycotoxin or fungal metabolites to form heat-resistant toxic substances. The KBD is a food-sourced osteoarthropathy, which excludes other theories such as water pollution, soil pollution, genetic factor, *etc.* Mycotoxins in food play a decisive role in the process of inflammatory necrosis of articular cartilage. Unbalanced dietary protein intake, gene sensitivity and perhaps other factors participate in and affect the pathological progression as well.

In summary, the geographical distribution of endemic KBD covers a special zone on the Pacific side, which belongs to continental climate characterized by short summer, long frost period, and large daily temperature differences. KBD is initiated by environmental factors. The pathogenic factors of KBD enter the human body upon consumption of self-produced grains in the endemic areas. Grains are polluted by fungi in the process of harvesting, threshing, drying, and storage. Particularly, the role T-2 toxin in pathogenesis of KBD is worthy of further study. In recent years, KBD-related research has advanced to elucidating the expression profiles of susceptible genes and the molecular mechanisms of cartilage damage. The rapid development of modern biotechnology has made it possible to decipher the etiology of KBD in the near future.

Author contributions

Sun D J and Wang K W conceived and designed the manuscript. Yu J, Wang K W and Sun D J provided data analysis and interpretation. Wang K W wrote the first draft that was revised by Yu J and Sun D J. All authors contributed to the scientific completeness and accuracy of the article's content.

Conflicts of interests

All authors declare no competing interests.

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