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Radiographic features of hand osteoarthritis in adult Kashin-Beck Disease (KBD): the Yongshou KBD study

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SUMMARY

Objective: Kashin-Beck Disease (KBD) is a rare and severe osteoarthropathy endemic to China. We evaluated the frequency and patterns of hand radiographic osteoarthritis (rOA) in adults with and without KBD.

Methods: Han Chinese ($N = 438$) from Yongshou County of central China underwent right hand radiography for determining case status. Presence of KBD was based on characteristic radiographic deformities of articular ends of bones including articular surface depression, carpal crowding, any subchondral bone deformities in the proximal end of phalanges or first metacarpal bone, or the distal ends of metacarpal bones 2–5, and any bony enlargement with deformity of the distal ends of phalanges. Hand rOA severity was determined by osteophyte (OST), joint space narrowing (JSN), and Kellgren and Lawrence (KL) grades.

Results: This study included 127 KBD and 311 non-KBD adults of similar mean age (39 years) and body mass index (BMI) (21 kg/m^2). Inter- and intra-rater reliability for radiographic determination of case status and rOA features was high (kappa 0.72–0.96). Compared to non-KBD, KBD adults had significantly more severe hand rOA of the thumb, distal interphalangeal (DIP), proximal interphalangeal (PIP) and metacarpophalangeal (MCP) joints. Only KBD adults had end-stage carpometacapal (CMC) disease. In KBD, DIPs and PIPs were more affected than MCPs and the frequency of OSTs was significantly higher in PIPs than DIPs.

Conclusions: Compared with age-matched adults from the same area and farming occupation, KBD hand rOA was more widespread and severe, particularly of PIPs and CMCs. The ability to differentiate adult KBD from non-KBD hand rOA will facilitate genetic analyses of the vast majority of affected individuals.

Introduction

Kashin-Beck Disease (KBD) is a rare and severe progressive osteoarthropathy endemic to China[1]. According to the 2013 Chinese Health Statistics document issued by the Chinese Ministry of Health, KBD is still a threat to 38,071,000 people living in KBD endemic areas of China; 16,826 of a total 644,994 KBD affected individuals are children under 13 years old[2]. Geographically, KBD is endemic in a region extending from north-eastern China to the southwest and encompasses 14 of the 34 provinces and regions[3]. Pathologically, KBD affects the epiphyseal cartilage of multiple

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joints and causes cartilage necrosis of the epiphyseal hypertrophic zone adjacent to subchondral bone; this likely explains the occurrence of severe joint deformities during development in young people with KBD[4]. Radiographic abnormalities associated with KBD can be observed as early as 5 years of age[5]. These radiographic abnormalities reflect secondary repair and remodeling of the adjacent bone and cartilage of the metaphyses and epiphyses in response to cartilage necrosis[6].

After years of persistent research, the pathogenesis of KBD is still unclear. Various causes have been suggested, including: selenium (Se) deficiency alone or in combination with iodine deficiency[7,8]; ingesting of grains with mycotoxins[4]; and excess of fulvic acid, but none of the proposed explanations is entirely satisfactory[9]. In recent years, more attention has been paid to potential genetic etiologies of KBD[10–12]. The Yongshou KBD study was designed to assess potential genetic etiologies of KBD. The success of genetic studies relies heavily on careful phenotyping of individuals to ascertain their affection status. To date, a standardized and evidence-based system of KBD joint disease evaluation has only been developed for children, as described below, but not adults.

Various Chinese diagnostic criteria for KBD have been available for 16 years[13]. The latest version of the Chinese national diagnostic criteria for KBD[14] was released in 2010. According to these criteria ("Diagnosis of Kashin-Beck Disease", WS/T 207-2010), a diagnosis of KBD is typically based upon a history of living in a KBD area, clinical symptoms, and hand radiographic changes. Based on these criteria, it is generally easy to diagnose KBD in childhood or adolescence. In contrast, it can be difficult to distinguish KBD, particularly mild KBD, from osteoarthritis (OA) in adults. For this reason, some researchers consider the national criteria unsuitable for use in diagnosing adult KBD[15]. The purpose of this study was to define KBD case status based upon hand radiographs and to evaluate the patterns of radiographic features of hand radiographic osteoarthritis (rOA) in a moderately large sample of KBD and non-KBD adults of similar age and occupation.

Materials and methods

Ethics approval

The Yongshou KBD study is an international collaborative study conducted by permission (document [2007]017) of the Management Office of the Human Genetic Resource Council of the Chinese State. Institutional Review Board (IRB) approval was obtained from Xi'an Jiaotong University (China). In anticipation of sharing samples and clinical data with collaborators, IRB approval was also obtained from Duke University (USA) and the University of North Carolina at Chapel Hill (USA). Written informed consent was obtained from each participant.

Participants

The Yongshou KBD study was conducted in Yongshou County of Shaanxi Province in central China. The selection of participants occurred in three steps. First, the study region (Yongshou County) was selected on the basis of a high KBD prevalence, estimated to be 2.7% according to a government survey conducted in 1979–1982[5]. Second, to identify a subset of individuals with the most homogeneous environmental exposures for purposes of a future genetic analysis of KBD, one of the 67 villages of Yongshou County (Shangqiu) was selected randomly and every available adult in this village was invited in 2007 to participate in this study; a total of 125 individuals from this village agreed to participate. Permission (document [2007]017) of the Management Office of the Human Genetic Resource Council of the Chinese State was obtained to cover genetic analyses of these 125 individuals. Third, to obtain county-wide data on the hand radiographic presentation of KBD, a total of 1200 adult subjects were selected randomly from among ~60,000 individuals from the remaining 66 villages of Yongshou County. With the assistance of the village leaders, attempts were made to contact all 1200 individuals face to face in 2011; a total of 333 individuals agreed to participate. These participants were aged 10–12 years at the time of the original government survey.

A total of 458 individuals were enrolled in the study; right hand radiographs could be obtained on 438 (122 from Shangqiu and 316 from all the other 66 villages) and these served as the total sample for these analyses. For both men and women, a total of 96.8% of participants were farmers (98.4% of participants form Shangqiu and 95.6% of the remaining participants).

Radiographs and case definition

Posterior–anterior radiographs of the right hand and wrist were taken using a JF-10 portable X-ray unit (Xianwei Ltd. Co. Shanghai, China). Case status was determined on the basis of radiographic features considered characteristic of KBD (Fig. 1). These features were derived from several sources[6] and included four main categories of bone and joint abnormalities: (1) articular surface depressions. These articular depressions appeared both in the absence of other findings of OA but sometimes accompanied them; (2) "carpal crowding," as described by Wang *et al.*[6] was a feature considered representative of KBD and not OA; (3) any subchondral bone deformities in the proximal end of phalanges or first metacarpal bone, or the distal ends of metacarpal bones 2–5, such as an irregular subchondral bone surfaces with/without sclerosis, discontinuity or appearance of fragmentation; (4) bony enlargement with deformities of the distal ends of phalanges was considered especially characteristic of KBD. Subjects matching any one of the four criteria were classified as KBD. On the basis of these criteria, 127 of the 438 individuals were classified as KBD, 279 had some hand rOA but did not meet the case definition for KBD, and 32 had no evidence for hand rOA.

All radiographs were scored for osteophyte (OST) (0–3) and joint space narrowing (JSN) (0–3) using the standardized "the Osteoarthritis Research Society International (OARSI) Atlas (2007)"[16], and Kellgren and Lawrence (KL) grade (0–4)[17]. Radiographic scoring (blinded to the age, gender and other characteristics of the subjects) was completed for fifteen joints of the right hand and wrist: four distal interphalangeal joints (DIPs), four proximal interphalangeal joints (PIPs), five metacarpophalangeal joints (MCPs), the thumb interphalangeal (IP) joint, and the first carpometacapal (CMC) joint.

A musculoskeletal researcher (QF) was trained by an expert musculoskeletal radiologists (JBR) to read the hand radiographs for KBD features to determine case status, and radiographic features of hand rOA (OST, JSN and KL grade). Inter-rater reliability for case status determination was made by blinded reading of 50 radiographs by the expert radiologist and the musculoskeletal researcher. Intra-rater reliability for case status determination was made by blinded readings of 100 radiographs by the musculoskeletal researcher on two occasions at least 1½ months apart. Intra-rater reliability of scoring of OA features was made by blinded readings of 30 radiographs (900 OST readings, 450 JSN and KL readings) by the musculoskeletal researcher on two occasions at least 1 ½ months apart. Reliability was assessed by kappa (κ) statistic[18].

Statistical analysis

Hand rOA was defined as OST $\geq$ 1, JSN $\geq$ 1 or KL grade $\geq$ 2. The primary analysis consisted of comparing the mean and standard