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The hereditary predisposition to hip osteoarthritis and its association with abnormal joint morphology

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SUMMARY

Objective: Genetic factors and abnormalities of joint morphology are important in the aetiology of hip osteoarthritis (OA). The extent to which genetic influences are manifest through joint morphology has undergone limited investigation. Using a cohort with an hereditary predisposition to end-stage hip OA and a control group with no inherited risk, we aimed to identify associations with abnormal joint morphology and clinical features.

Design: One hundred and twenty-three individuals (mean age 52 years) with a family history of total hip arthroplasty (THA) (termed 'sibkids') were compared with 80 spouse controls. Morphology was assessed using standardised radiographs and cam, dysplasia, and pincer deformities defined. Regression modelling described the association of cohort with abnormal joint morphology, adjusting for confounders [age, gender, body mass index (BMI), OA, and osteophyte].

Results: Sibkids had an odds ratio of 2.1 [95%confidence interval (CI) 1.3–3.5] for cam deformity. There were no differences in the prevalence of dysplasia or pincer deformities. In both groups, hips with cam deformities or dysplasia were more likely to have clinical features than normal hips [odds ratio (OR) 4.46 (1.8–11.3), and 4.40 (1.4–14.3) respectively]. Pincer deformity was associated with positive signs in the sibkids but not in the controls (OR 3.0; 1.1–8.2).

Discussion: After adjustment for confounders that cause secondary morphological change, individuals with an hereditary predisposition to end-stage hip OA had a higher prevalence of morphological abnormalities associated with hip OA. Sibkids were more likely to demonstrate clinical features in the presence of pincer deformity, suggesting that the genes are acting not only through abnormal morphology but also through other factors that influence the prevalence of pain.

Introduction

Epidemiological studies indicate that hip osteoarthritis (OA) frequently occurs in the absence of OA in other joints, suggesting that local factors are important in its pathogenesis[1–4].This implies that whilst ultimately similar pathological processes occur within all joints with advanced OA, local factors specific to the hip may be important in the initiation of the process. Drawing on earlier published theories[5,6], Harris[7] suggested that subclinical biomechanical factors were important in the development of hip OA. He rebuked theories that most cases of hip OA were "primary", or "idiopathic", and hypothesised that abnormal hip morphology predates onset of OA and is not secondary to the arthritic process[7]. Several studies[8–14] have since supported the hypothesis that some patients who are destined to develop end-stage OA have a pre-arthritic phase, which has recognisable features and may be amenable to intervention.

Specific abnormalities of hip morphology are recognised as biomechanical risk factors for the development of OA[7–11,15]. The predominant mechanisms are acetabular dysplasia, whereby the shallow acetabulum results in focal loading of articular cartilage beyond its physiological tolerance[10], and femoroacetabular impingement (FAI)[2,15], which occurs as a consequence of abnormal contact between the acetabular rim and femoral head–neck junction, injuring the chondrolabral junction. Together with improved

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understanding of these mechanisms, parameters have been introduced to quantify the deformities and classify patients with early hip disease[5,16–19].

In spite of its clinical heterogeneity and multifactorial nature, the aetiology of hip OA has a significant genetic basis[20]. The increased risk to family members of patients with hip OA is well established[21–26]. Classic twin studies indicate a genetic contribution of 60% in women[22,27]. Linkage studies have identified regions of at least eight chromosomes as harbouring genes involved in the heritability of OA[20].

In light of recent advances in understanding of mechanical factors in pre-arthritic hip disease, and genetic influences in OA, establishing whether the two are linked warrants consideration. Early studies by Wynne-Davis[28] confirmed the importance of genetics in acetabular dysplasia, and Rennie[29] noted that relatives of patients with slipped capital femoral epiphysis (SCFE) had a high prevalence of both the same condition and OA. Although it has been noted that some OA susceptibility genes are active in skeletal development[30], there is no recent literature linking morphological abnormality, assessed using contemporary parameters, with genetic predisposition to hip OA. Investigating whether there is such an association is important as it may enable targeted investigation of the mechanisms by which genetic factors contribute to OA aetiology. Furthermore, morphological abnormalities may be readily screened for, and also can be surgically modified. For these reasons, if an association is proven then this offers great opportunities for identifying and tracking cohorts, and testing and validating biomarkers of early OA.

We hypothesized that the genetic predisposition to hip OA is associated with abnormalities of hip joint morphology. Using a cohort with an hereditary predisposition to hip OA and a control group with no inherited risk, we aimed to identify associations with abnormal joint morphology, and to establish whether morphological abnormalities were associated with the presence of clinical features and OA.

Methods

Cohorts

Subjects were enrolled from a prospective longitudinal study[25,26] of a cohort at risk of hip OA, and their spouse controls. These cohorts have been reviewed at baseline[25] and 5[26] years, and this report is based solely on data acquired from those participating at the 5-year review. The study had Institutional Review Board (IRB) approval and all subjects consented to participation. The reader is referred to our previous publication[26] for a detailed description of the construction of the cohorts. In summary, individuals from families in which two female siblings in the previous generation had undergone total hip arthroplasty (THA) for idiopathic end-stage OA were recruited. This group was termed the 'sibkid' cohort. Exclusion criteria for enrolment included significant trauma (hip injury requiring consultation with General Practitioner of Emergency department), or any history of predisposing factors to hip OA, such as developmental dysplasia, SCFE, and Perthes. No cases were excluded on these grounds.

Clinical assessment

All subjects underwent clinical and radiographic assessment. Clinical assessment was performed by a single experienced orthopaedic fellow (TCBP). A proforma, completed by a research nurse, documented the findings in a standardised manner. Height and weight were recorded to calculate body mass index (BMI). All subjects were asked whether they had had surgery on either hip. The presence of symptoms was defined by pain (suggestive of degenerative change) or clicking (suggestive of labral pathology) in either groin in the last 2 years necessitating investigation or treatment. A routine examination of the hips was performed and the presence of clinical signs defined by irritability on passive movement (groin pain on hip flexion, or on rotation at 90° of flexion) or a positive anterior impingement sign[31], recorded as binary outcomes. Observer reliability of the clinical assessment was good[26]. Because the orthopaedic fellow that performed the clinical assessment also arranged the clinic appointments, it was not possible to blind him to the participant's sibkid or spouse status; however the clinical assessment was observed and documented independently by a research nurse, and was performed before radiographs were obtained.

Radiographic assessment

Radiographic technique

All participants underwent a standardised supine anteroposterior (AP) pelvis radiograph to identify features of OA and evaluate acetabular morphology[26]. Feet positioning and centering of the beam was as recommended[32]. A 20 mm calibration ball was secured to the skin overlying the greater trochanter. In order to avoid rotated AP radiographs, the radiographer repeated the radiograph if necessary to ensure that the obturator foramen index was within 0.7–1.4[33]. In order to evaluate proximal femoral morphology, cross-table lateral radiographs of each hip were taken in 15° internal rotation[32,34,35], using a 15° wedge placed beneath the femoral condyles to standardise rotation.

Grading of OA

All radiographs were scored by consensus[36,37] opinion of two experienced readers (a Consultant Musculoskeletal Radiologist, EGM, and an Orthopaedic Fellow, TCBP), as described elsewhere[26]. An overall OA grade was assigned using the Kellgren & Lawrence (K&L) system[26,37]. The repeatability for the minimum joint space width and osteophyte grading[38] was good[26].

Assessment of joint morphology

Continuous variables

Proximal femoral morphology was assessed from the lateral radiograph. The alpha angle[18,19,32,39] and anterior offset ratios (AOR)[19,32,34] were measured. Acetabular morphology was determined from the AP pelvis radiograph. The lateral centre-edge angle (CEA)[5,32], acetabular index (AI)[32], and acetabular depth:width ratio (ADWR)[10] were measured. These measurements were made using a custom software program, validated in previous studies[8,19].

Categorical variables

To classify the morphology of each hip, reference ranges were applied to the continuous morphology measurements. A cam deformity was defined as an alpha angle $> 62.5°$ or an AOR < 0.135[19]. Acetabular dysplasia is apparent when the femoral head is uncovered, the acetabulum shallow or the sourcil slopes excessively. Dysplasia was defined as a CEA $< 19.7°$, or an AI $> 11.6°$, or an ADWR < 0.40 (males) or <0.42 (females). Global over-coverage (pincer deformity) was defined as a CEA $> 39.9°$, or an AI $< -4.9°$, or an ADWR of >0.57 (males) or >0.65 (females). These acetabular thresholds were derived from the same cohort as the proximal femoral parameters[19], and are consistent with thresholds published elsewhere[32,40]. Focal over-coverage, which is a sub-type of pincer deformity caused by acetabular retroversion, was diagnosed by the presence of a cross-over sign[32]. Because of its