The use of imaging in epidemiological studies: Developmental dysplasia of the hip

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ABSTRACT

During the last three decades technical advances and the introduction of new, radiation free modalities have allowed a less restrictive use of imaging. Combining different low- or no radiation modalities as appropriate affords a unique opportunity to undertake large-scale, population based longitudinal research examining the prevalence, natural history and the effectiveness of treatment for a variety of diseases. In this paper we address the use of imaging in epidemiological studies of developmental hip dysplasia (DDH) based on work performed at Haukeland University Hospital since 1987, and since 2006 in collaboration with MRC Centre of Epidemiology for Child Health, UCL Institute of Child Health, London. This life-course approach to investigating phenotypes for, risk factors for, and outcomes of DDH is novel (1).

DEVELOPMENTAL HIP DYSPLASIA (DDH)

Prevalence and aetiology

DDH is the most common musculoskeletal disorder in infancy, with a reported prevalence from 0.5% to 4% according to age, ethnicity and method of ascertainment. The term DDH refers to a spectrum of pathology, which includes the dislocatable newborn hip with a normal or dysplastic socket ascertained on clinical screening, the stable but dysplastic newborn hip detected on ultrasound screening and the dysplastic and dislocated hip identified in later infancy and early childhood (late DDH).

The median birth prevalence of persistent and clinically diagnosed DDH was estimated to be 1.3 per 1000 (range 0.8 to 1.5) based on a review of studies from 44 unscreened populations of predominantly northwest European ancestry (2). By contrast, the prevalence of neonatal hip instability, ascertained through clinical examination, is higher, ranging from 1.6 to 28.5 per 1000. The sonographic prevalence of DDH is higher again, between 2 and 4% (3). DDH affects both hips in approximately 30-40% of the cases (4,5). In cases of unilateral disease, the left hip is more often affected than the right (4,5). More girls are affected than boys: for example, neonatal hip instability is about 3-4 times more common in girls than in boys (5,6) while for DDH presenting in later childhood, the ratio of girls to boys is approximately 5:1 (4,7,8). Similarly, DDH detected on ultrasound is also more common in girls, affecting 5.7% of all girls compared with 1.2% of boys (3).

The extensive literature on the aetiology of DDH has hitherto comprised two largely opposing themes of 'biological' (mainly genetic) versus environmental (mainly intrauterine and early postnatal) determinants. Most of the risk factors are believed to fall into two groups, one associated with decreases in resistance of the hip to dislocation (shallow acetabulum, connective tissue laxity, female gender) and the other with external constraints (oligohydramnios, breech presentation, primipara, tight clothing) (2). Previous twin and family studies indicate a high heritability, consistent with a strong genetic susceptibly to disease *onset* but not necessarily to progression or severity (9,10). In a recent study from the Norwegian Twin Registry, Kramer reported the prevalence odds ratio for DDH to be much higher for mothers than for siblings, fathers, and offspring, suggesting a maternal effect (11). Familial joint laxity, associated with joint hypermobility, has been identified as a risk factor for DDH, and Hakim et al. have recently estimated the heritability of joint hypermobility to be 70% in female adult twins (12).

It has been proposed that there are two components to the genetic mechanisms underlying DDH, namely connective tissue laxity with a polygenic or monogenic autosomal dominant inheritance, and a primary acetabular dysplasia with a presumed polygenic inheritance. The degree of interaction between these two components remains unknown. Wynne-Davies reinforced this hypothesis in her research, suggesting two DDH phenotypes – a "joint laxity" type and an "acetabular dysplasia" type. Czeizel, on the other hand, found that the age at diagnosis in these two types did not differ, suggesting that neonatal and late DDH are not different entities (13). The results of recent work using a complex segregation analysis has, however, favoured a two-locus model (14), in which the accepted segregation model at the major locus was compatible with recessive transmission, with a gene frequency of the deleterious allele of around 0.20. These findings

provide some support for the earlier proposed two-gene model, with one gene system related to dysplasia and the other controlling the capsule.

Diagnosis

Universal clinical newborn screening with the Barlow/Ortolani tests was introduced in most European countries during the late 1950's and early 1960's, and radiographic imaging of the 10-14% infants considered at risk of DDH during the early 1980's, with the aim of reducing the requirement for surgery through early diagnosis and non-surgical treatment. However despite clinical screening, the prevalence of surgery for DDH in early childhood has not decreased significantly in either the Scandinavian countries or the UK (15-17). This has led some countries to introduce ultrasound as a primary screening test for detecting DDH and extend its use as a diagnostic test. Ultrasound screening is offered to newborns and very young infants but can also be used diagnostically up to the age of 4-5 months, when radiographs become diagnostic. Following a few early publications on its feasibility (18-20), Graf suggested a grading system for DDH based on sonographic appearances (21) and implemented universal ultrasound screening throughout Austria in 1990. He has reported a subsequent decrease in the rate of late diagnosed DDH (after one month of age) as compared to the pre-ultrasound screening period (22,23), but at the cost of very much higher treatment rates in infants who have sonographic appearances of uncertain significance and who are unlikely to have derived any benefits from screening and treatment. Similar findings have been reported from subsequent observational studies (22,24) and also from the only two randomised controlled trials of hip screening performed worldwide (25,26) although the findings of the trials were not statistically significant.

Outcomes

Protocols for the management and follow-up of children diagnosed with DDH through screening vary widely according to the criteria used to define clinical or radiological normality. Reliable data on longer term outcomes is lacking, in part reflecting biases in follow up as, in many centres, most newborns treated with abduction splinting are only followed until the age of 6-12 months or walking age, with longer term follow-up confined to those with most severe DDH. This is reflected in the few reports of small selected case series that provide data on adult outcomes (27,28).

Further, reported outcomes of early treatment are difficult to interpret in the absence of control groups as well as of age-related radiographic standards. For girls aged one month to seven years, the standards for acetabular inclination (AI) as reported by Tönnis and Brunken are commonly used (29). These are based on radiographs from 2,294 girls with normal or potentially abnormal right hips, and significant biases in assessment cannot be excluded. Reference data for older age groups are sparse.

In an observational study of 332 babies treated with a Pavlik harness, 5% of those treated required surgery, with 2.5% of treated hips showing significant dysplasia by five years of age, and 1% of hips signs of avascular necrosis (30). These estimates are comparable to other case series reviewed in a recent decision analysis (31).

Long term outcome of DDH can also be assessed by the contribution of DDH to population requirements for total hip replacement, particularly in young adults where radiological evidence for DDH has not yet become obscured by secondary degenerative change. However such findings may in part reflect access to health care and need to be interpreted cautiously.

THE BERGEN HIP-STUDY

Sonographic hip phenotypes in an unselected newborn population

Due to a relatively high rate of late DDH in Bergen and the surrounding suburbs during the period 1983 to 1987 (2.6 per 1000 live births), a study was designed to examine the effect of ultrasound screening on the treatment and follow-up rates as well as on the rates of late DDH. According to Thornsbury's model for radiological research we first undertook a pilot study of 1507 newborns at the maternity unit, Haukeland University Hospital, addressing basic key factors for a worthwhile screening test, i.e. feasibility, repeatability and construct validity (32). The hip assessment at the maternity unit was well organised with up to 20 scans performed hourly, and was well tolerated among caregivers, personnel and colleagues.

Informed by the initial results we refined Graf's original hip-classification, reducing the number of hip categories from 13 to three by ascertaining hip morphology and stability separately (Figure 1) (33). The modified system proved to be robust, with a moderate to high intra and inter-observer variability (34).

Next a study comprising all newborns delivered at Haukeland University Hospital in Bergen between 1/1/1988 to 30/6/1990 was performed. Over this period, 11925 newborn infants (>99.5% white) were enrolled in a clinical trial designed to evaluate the effectiveness of three different screening strategies for DDH: universal ultrasound screening (n=3613), selective ultrasound screening (n=4388) and clinical screening alone (n=3925). All infants received a detailed newborn clinical examination, including assessments of joint laxity and hip stability, and known risk factors for DDH were elicited and noted. Approximately two fifths were also examined by hip ultrasound performed in a standardized manner by a single observer (KR). Follow-up clinical and radiological data on those diagnosed to have DDH or other hip disorders were collected on subjects at all ages. This is one of only

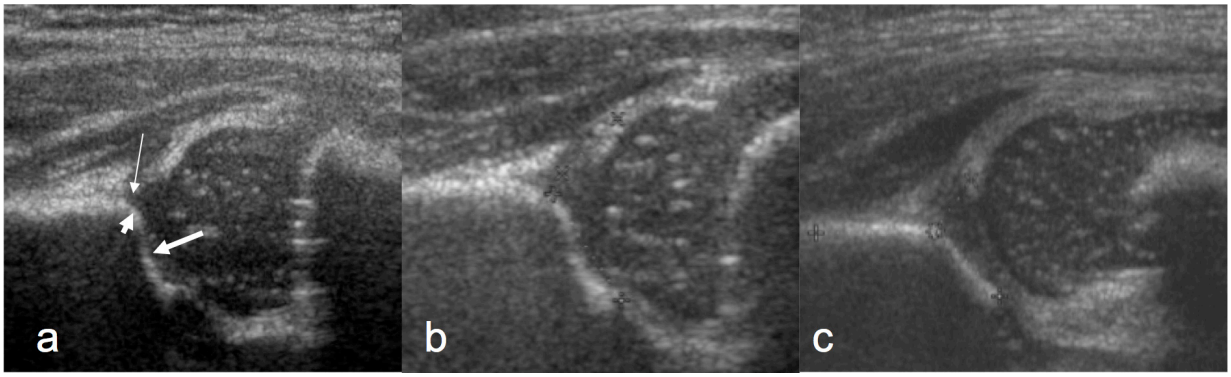

Figure 1. Rosendahl's modification of Graf hip types: Type I is a normal hip with a good bony modelling (large arrow), a sharp bony rim (arrowhead) and a narrow, covering cartilage roof triangle (small arrow) (a), Type II embraces physiologically immature hips (b) while type Type III hips are dysplastic (mild or significant) with deficient bony modelling, rounded/flattened bony rim and displaced cartilage roof (c). The images are obtained during the first postnatal day in three different newborns.

two such trials world-wide with such extensive prospective sonographic documentation of neonatal hip morphology and clinical features (25,26).

Although on average the rates of late DDH was lower for those receiving universal or selective ultrasound screening compared to those receiving clinical screening alone (0.3, 0.7 and 1.3 per 1000, respectively), the differences were not statistically significant (25). This may reflect in part a fall in the number of later diagnoses of DDH cases seen in the clinically screened group as compared to the pre-trial period (1.3 vs. 2.6 per 1000). These findings were concordant with those from a recent extensive systematic review (35). In our study, universal ultrasound screening also resulted in a relatively high treatment rate of 3.4% vs. 1.7% in the group receiving clinical screening. The reason for this was that the pre-specified treatment protocol required that newborns with stable but mildly dysplastic hips as shown on ultrasound (1.3% of all newborns) were to be treated from birth. However more recent research suggests that active sonographic surveillance of this group reduces the number requiring treatment with similar results at follow-up (36,37).

The percentage of newborns with normal, immature, mildly dysplastic and severely dysplastic hips in the universally screened group, i.e. an unselected newborn population, was 83.6%, 13.0%, 2.7% and 0.7%, respectively (3). There was a strong association between hip morphology and stability in that 100% of the severely dysplastic, and 65% of the mildly dysplastic hips were dislocatable or dislocated. For immature and normal hips the corresponding figures were 0.6% and 0.1%, respectively. On follow-up 97% of newborns with stable, immature hips normalised spontaneously during the first 3 months, while the natural history for those presenting with dysplastic hips with or without instability is unknown since all received treatment from birth in accordance with the study protocol. Although early complications of treatment, i.e. avascular necrosis of the femoral head commonly reported to affect 1-3% of those treated, were not seen during the follow-up period of 27-57 months, the development of pre-pubertal growth disturbances of the proximal femur with secondary degenerative change was not assessed.

Radiographic hip phenotypes at skeletal maturity

Since February 2007 and with ethical approval, peer review and funding from the UK Arthritis Research Campaign, the University of Bergen and Helse-Vest we have been inviting all cohort members for their consent to attend for a clinical and radiological examination for the first time in *adult* life at age 18/19 years. Specifically, this allows *all* those born in 1989 (n=5050) as well as those born in 1988 and 1990 and in whom neonatal sonographic abnormalities were detected (n=550) to be followed, giving a sample of 5570. Follow up of this cohort will provide a unique population-based longitudinal 'phenobank' of high quality standardised hip images in the newborn period and at skeletal maturity together with anthropometric measurements obtained at the end of puberty. To meet the appropriate standards for imaging, all radiographs are being obtained by one radiographer and reported by a single radiologist, whilst all the measurements are being performed by two researchers (38,39).

In this long term follow-up we aim to create standards for radiological indices of hip dysplasia at skeletal maturity, estimate the prevalence of radiologically defined hip dysplasia at skeletal maturity and report the frequency of four longitudinal dysplasia phenotypes based on sonographic assessments in the newborn and radiological assessments at skeletal maturity (Figure 2).

We also aim to investigate associations between these different dysplasia phenotypes with clinically assessed hip joint mobility and hypermobility, weight, height and body mass index (BMI) at age 18/19 years,

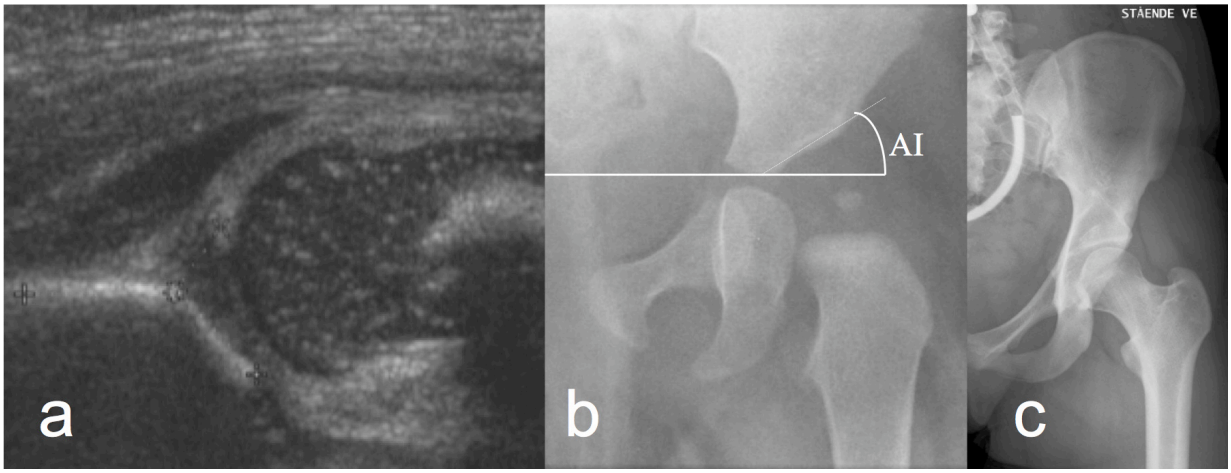

Figure 2. Ultrasound left hip in a newborn girl, showing a mildly dysplastic hip (a). A follow-up radiograph at four months of age shows a dysplastic acetabulum with a high acetabular index (AI) (b), while a pelvic radiograph at 18 years of age shows residual dysplasia (c).

and with prepubertal weight, height and BMI trajectories using data from child health records, taking into account first degree family history of hip dysplasia with or without hip arthroplasty, perinatal factors, including breech delivery, and birth weight, obtained from the National Birth Registry. We will examine associations between radiographic measures of osteoarthritis (including minimum joint space and acetabular depth ratio) and reported hip pain at ages 18/19 years. Finally we are establishing a genetic biobank for this cohort by obtaining and archiving salivary DNA samples, for which the overall aim is to establish a resource for future genetic epidemiological research on DDH.

Future follow-up of cohort members through adult life will add invaluable and unique information on childhood hip disorders and their long term outcomes. The linked national registries in Norway provide an important and unique opportunity to trace and follow members over this time period. This will require longer term storage of images in an accessible format. In recognition of this the UK Medical Research Council stipulates that research records relating to clinical or public health studies should be retained for at least 20 years to provide scope for longer follow-up if necessary [MRC guidelines on Personal Information in Medical Research].

CONCLUSION

We have described the rationale for, and the establishment and unique potential of, this longitudinal, population based hip "phenobank", which includes standardised ultrasound examinations of the newborn hip and radiographs at skeletal maturity. Research based on this 'phenobank' will improve our understanding of the causes, natural history and outcome of DDH as well as future strategies for treatment and follow-up of DDH. High standards for image quality are an essential component of that endeavour and modern radiological methods with low dose exposure provide a safe and ethically approved approach to enhancing our objective assessments of hip development in whole populations.

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