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Bilateral hereditary micro-epiphyseal dysplasia: Further delineation of the phenotype with 40 years follow-up

Accepted: 22 January 2002 / Published online: 16 April 2002
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Abstract Bilateral hereditary micro-epiphyseal dysplasia (BHMED) is a distinct skeletal dysplasia with specific clinical and radiological findings. It was first published in 1959. We have re-examined the original family for further delineation of the phenotype.

Résumé La dysplasie micro – épiphysaire héréditaire bilatérale (BHMED) est une dysplasie squelettique distincte avec des aspects clinique et radiologique spécifiques. La première publication date de 1959. Nous avons examiné de nouveau la famille originaire pour mieux définir le phénotype.

Presented at the SICOT Conference, Paris, France, 2001

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Introduction

Bilateral hereditary micro-epiphyseal dysplasia (BHMED) is a rare, usually symmetrical skeletal dysplasia first reported by Elsbach [4] in 1959. In the family he described, several members complained mainly of pain in hips and knees from early childhood. Because of the radiological finding of small epiphyses in the hip and knee joint, Elsbach designated the disorder “bilateral hereditary micro-epiphyseal dysplasia”. BHMED should be differentiated from multiple epiphyseal dysplasia (MED), in which the epiphyses have a (relatively) normal size.

Recently, several members of the original family were referred to the department of orthopaedic surgery in Delft with questions about the genetic background and the recurrence risk of the disease. We re-examined the extended family to evaluate diagnostic criteria, and the clinical course to determine the clinical spectrum, so as to provide tools for the diagnosis of possibly affected persons with only partial expression of the disease.

Patients and methods

Clinical examination

The pedigree was updated and contained 54 subjects in six generations (Fig. 1). Thirty-two members of the family and 12 spouses were examined by the first author (A.K.M.). A full medical history was taken according to a standardised questionnaire. Physical examination was performed according to a standard protocol. The range of motion of hip, knee, and shoulder joints was measured according to guidelines of the American Medical Association [4]. Total body height (TBH), sitting height, leg length, and span width were measured and compared with reference data from the Dutch population [2].

Prior and additional radiographs of first- and second-degree family members were evaluated by one of the authors (P.F.D.). In some cases results of laboratory tests of serum calcium, phosphate, and alkaline phosphatase levels were available and collected.

Diagnostic criteria

All subjects over 4 years old were classified clinically and radiologically as affected, unaffected, or inconclusive (included not known).

Fig. 1 Revised pedigree of the bilateral hereditary micro-epiphyseal dysplasia family. Identification numbers between brackets represent identification numbers in the pedigree originally published by Elsbach (1959) [4]

Fig. 2 AP-radiograph of the pelvis and hips of a bilateral hereditary micro-epiphyseal dysplasia patient (IV-15)

Clinical classification

The original clinical description by Elsbach [4] was used as the basis for the clinical diagnosis of BHMED. Diagnostic criteria for clinical affection status were bilateral simultaneous onset of pain in hip and knee joints, short stature, waddling gait, and restricted range of motion of the hip. Patients and relatives who fulfilled all clinical diagnostic criteria were categorised as affected (group I). Subjects who did not fulfil all diagnostic criteria, or who were not examined or only incompletely examined, were categorised as inconclusive with respect to clinical affection status (group II). Patients who showed no clinical signs were categorised as unaffected (group III).

Radiological classification

All radiographs were reviewed by a radiologist specialised in skeletal dysplasias (P.F.D.), without knowledge of the clinical evaluation or the a priori risk for the condition. The diagnostic criteria for radiological affection status were (a) a hip characterised by valgus angle of the femoral neck [7], which is short and thickened [16]; (b) flattening of the head of the femur, especially at the medial part, and dysplasia of the acetabulum by an apparently abnormal teardrop configuration of the medial acetabular wall (Fig. 2); (c) small epiphyses of proximal and distal femur and proximal tibia with or without flattened condyles of the knees, and a shallow intercondylar notch; and (d) a symmetrical distribution of abnormalities. Subjects fulfilling the first, second, and fourth criterion (minimal diagnostic criteria) were regarded as radiologically affected. Patients not fulfilling these criteria were classified as radiologically unaffected.

Table 1 Summary of radiological versus clinical affection status

^a Patients with radiographs previously published by Elsbach (1959) [4] but without clinical re-examination in the current study
^b Inconclusive is divided into doubtful and not known

Radiological affection status	Clinical affection status				Total
	Affected	Unaffected	Doubtful	Unknown	
Affected	13	–	–	2 ^a	15
Unaffected	1	9	–	–	10
Doubtful ^b	–	–	1	–	1
Unknown ^b	–	1	1	–	2
Total	14	10	2	2	28

One of the two index patients of the publication by Elsbach had died before the re-examination (Fig. 1, IV-26). This was the only patient we regarded as affected on the basis of the clinical and radiological description by Elsbach only. The updated case history of the second patient (Fig. 1, IV-28) is described in the results.

Genetic examination

We used all members of the family for whom DNA was available.

Results

Pedigree

The updated pedigree (Fig. 1) shows only those subjects of whom information about the phenotype was available.

In six successive generations, 15 subjects were clinically or radiologically affected, or both. The male/female ratio among patients was close to one. This pattern of familial occurrence, and possibly one male-to-male transmission (II-1 → III-2), suggests an autosomal dominant mode of inheritance. All subjects with an affected parent and at least one affected child, and who had been examined clinically and radiologically, showed clinical expression, suggesting that at adult age the penetrance of the gene defect is high.

Clinical findings

Six men – five according to the clinical criteria and one on the basis of Elsbach's description [4] – and eight women were classified as clinically affected (group I); for one male and one female at 50% prior risk the clinical affection status was inconclusive (group II), whereas in two men and eight women at 50% prior risk the diagnosis of BHMED was clinically excluded (group III).

The clinically affected subjects (group I) clearly showed reduced femur abduction (limited with an average of 15°) and internal rotation (limited with an average of 25°) as compared to group III (unaffected), whereas group II (inconclusive) is too small and heterogeneous for meaningful comparison. There was no loss of knee mobility among patients of group I, although all persons classified clinically as affected suffered from knee complaints. The mobility of the shoulders was unlimited, even at older age, although they were painful above the age of 50 in group I. The hands showed no malforma-

Fig. 3 Radiographs of the right knee of a bilateral hereditary micro-epiphyseal dysplasia patient (III-2). **a** AP-view, **b** lateral view

tions. However, a shortening of the metacarpals (MC), especially of MC IV and V, became more apparent upon clenching of the fists.

Radiological findings

The six men and eight women who were classified as affected according to clinical criteria (group I) were also classified as affected according to radiological criteria, except one. This woman fulfilled the clinical diagnostic criteria but the radiographs were considered normal (Table 1). The remaining three men and nine women were radiologically classified as unaffected or inconclusive.

The hip joint showed a valgus angle of the femoral neck, which is short and thickened; flattening of the head of the femur, especially at the medial part; and a dysplasia of the acetabulum by an apparently abnormal tear-drop configuration of the medial acetabular wall (Fig. 2).

Additional radiographic features observed more than once among persons classified as radiologically affected were a shallow intercondylar notch on the AP view (Fig. 3a) and small epiphyses and flattened condyles on the lateral view of the knee (Fig. 3b). In a few cases the lateral femoral condyle showed a focus of osteochondritis dissecans or an ulcer. Radiographs of the wrist from affected relatives showed an 'ulna plus' ($n=10/14$) with slight radial drift of the carpus and flattening of the ulnar part of the radial epiphysis (Fig. 4). The spine showed signs of lumbar spondylosis, whereas the cervical and thoracic part of the spine was normal. Flattened verte-

Fig. 4 AP radiograph of the wrist (IV-3) with an 'ulna plus' with slight radial drift of the carpus and flattening of the ulnar part of the radial epiphysis

brae, such as occur in, e.g., spondylo-epiphyseal dysplasia [5], were not observed.

Body measurements

Patients who were classified as clinically and radiologically affected had a lower mean TBH in comparison with

Table 2 Body measurements in bilateral hereditary micro-epiphyseal dysplasia patients compared with controls and reference population (values in centimetres) SD standard deviation

Group	Num- ber	Total body height			Sitting height			Leg length			Span width		
		Mean	SD	Range	Mean	SD	Range	Mean	SD	Range	Mean	SD	Range
				Min. Max.			Min. Max.			Min. Max.			Min. Max.
Men													
Affected men	5	164	7	154	171	87	4	81	91	76	3	73	80
Unaffected first-degree male relatives	2	165	3	163	167	86	2	84	87	80	1	79	80
Male spouses of affected women	5	168	5	160	173	90	4	84	93	78	6	72	89
Male spouses of unaffected women	4	178	3	175	182	95	3	91	98	83	3	79	87
Control men (outpatient clinic)	21	178	10	160	195	92	11	58	106	86	10	72	120
Control men (Dutch population)	10,843	179.7	10.4	—	—	—	—	—	—	—	—	—	—
Women													
Affected women	8	154	4	148	159	81	2	78	84	83	3	79	87
Unaffected first-degree female relatives	7	165	5	155	172	85	3	80	90	80	4	75	85
Female spouses of affected men	2	162	0	162	162	89	1	88	89	74	1	73	74
Female spouses of unaffected men	—	—	—	—	—	—	—	—	—	—	—	—	—
Control women (outpatient clinic)	31	166	7	155	188	90	5	82	101	75	5	64	87
Control women (Dutch population)	11,178	167.2	10.6	—	—	—	—	—	—	—	—	—	—

unaffected first-degree relatives (Table 2). However, the difference was larger when the affected persons were compared with controls from the outpatient clinic or with the reference population. Compared to controls, the unaffected first-degree relatives of BHMED patients also showed a lower TBH. Among men, a similar trend was observed for sitting height and span width.

In turn, unaffected first-degree relatives of patients also showed a reduced TBH as compared to the general population matched for age and gender.

Laboratory data

Available results from additional laboratory measurements including calcium, phosphate, and alkaline phosphatase levels in serum were within the normal ranges.

Discussion

In this study we analysed the clinical and radiological features of a skeletal dysplasia previously described by Elsbach in 1959. Elsbach allocated the name “bilateral hereditary micro-epiphyseal dysplasia” to this condition [4]. Some authors [1, 11] argued that this family might be classified as a type of MED. Others [12] classified it as a form of osteopetrosis with precocious manifestations. We found the clinical picture in this family, and especially the radiological features, consistently different from MED and to be unique in its presentation. The onset of complaints in this family was at about 4 years of age as compared to at about 10 years in MED. In both disorders complaints stabilise during adolescence. In adulthood, complaints in BHMED worsen due to early-onset osteoarthritis. In the Elsbach family mainly the hip and knee joint were bilaterally affected and harmful, whereas in MED the elbow and ankle are involved also [14]. Affected BHMED-individuals had a small TBH but with an apparently proportionate build. The gait was waddling. The affected individuals had a smaller TBH than unaffected first-degree relatives. In turn, these unaffected relatives showed a smaller TBH than controls. In addition, the TBH of spouses of affected subjects was remarkably reduced compared to the control group and the reference population. Thus, this indicates that the short stature of offspring of affected patients cannot only be attributed to the putative dominant mutation causing BHMED, but might also be the result of (epi-)genetic factors that play a role through height-related partner selection [8, 15]. Furthermore, it shows that TBH is not a distinctive inclusion criterion when defining the affection status in a skeletal dysplasia with mild-to-moderate effect on final adult height.

Both BHMED and MED show an autosomal dominant mode of inheritance with a gender ratio of about one. Radiographically in people with BHMED the epiphyses of the proximal and distal femur and proximal (and distal) tibia appear rather late in comparison with their

peers, with subsequent flattening in the following years. Initially, during childhood, the epiphyses of the knee are irregular. In adolescence the knee epiphyses show a more continuous aspect without irregularities, and only the joint surface is flattened, especially at the lateral condyle. Fairbank described MED in 1935 [5] and gave a further delineation in 1947 [6]. In some cases the disease was familial. Short hands with brachydactyly, characteristic for MED [10, 14], were not reported in BHMED. In the family described here we found shortening of MC IV and V. In children with MED a deficiency of the lateral part of the distal ossification centre of the tibia is observed, evolving into in a sloping end of the tibia at adulthood [10]. In contrast, in BHMED the distal tibia epiphysis is only small in size.

Other conditions with partial resemblance of epiphyseal ossification disturbances are mucopolysaccharidosis IV (M. Morquio-Brailsford, MPS-IV) and disorders characterised by punctuated chondrodysplasia. In BHMED some stippling on the periphery of the epiphyses (a sign of multiple ossification centres) may be observed, but never as prominently as in chondrodysplasia punctata [13]. In MPS-IV epiphyseal dystrophy is found, with typical changes in the spinal column and in most centres of ossification – especially of the hip. In contrast with BHMED the acetabula are enlarged [9]. Furthermore, the mode of inheritance for both chondrodysplasia punctata and MPS-IV is autosomal recessive, which clearly differentiates these conditions from BHMED.

The patient with radiological signs of a bilateral epiphysiolysis of the hip (III-5), was a coincidental finding without signs of BHMED.

The clinical features in this family with BHMED represent a consistent and distinct phenotype with multiple differences in comparison with MED. Therefore, BHMED possibly represents a specific skeletal dysplasia due to a unique genetic defect. Future linkage analysis and characterisation of the molecular defect causing this disorder will clarify whether it is indeed allelic to other skeletal dysplasias, like MED, or due to a mutation of a novel gene. This study demonstrates that BHMED is a distinct entity to be separated from classical MED. A dysfunction of the epiphyseal chondrocyte with subsequent delayed

and irregular ossification might be the pathogenic basis of BHMED. Epiphyseal irregularity, together with the morphoplastic influence of both articular surfaces, probably accounts for the discongruence and secondary osteoarthritis.

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