X linked spondyloepiphyseal dysplasia: a clinical, radiological, and molecular study of a large kindred


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Abstract

X linked spondyloepiphyseal dysplasia (SED) is a rare disorder characterised by disproportionate short stature and degenerative changes in the spine and hips. We report a large kindred with 11 affected males and 17 obligate carrier females. We examined clinically and radiographically the seven living affected males and obtained detailed historical information on the four dead. The natural history was characterised by normal growth until late childhood. Decreased growth velocity was the earliest detectable abnormality. In adulthood, four subjects required hip replacements but disability was minimal. Clinical examinations showed a characteristic habitus with short stature (>2 SD below the mean) and a decreased upper segment to lower segment ratio (>1 SD below the mean) in all affected subjects. Also noted were scoliosis (6/7), limitation of hip rotation (6/7), and decreased range of movement of the lumbar spine (4/7). Radiographic evaluations were available on nine subjects. Radiographic changes were evident in two patients in childhood; findings in adulthood included narrow disc spaces (8/9), platyspondyly (7/9), the characteristic central and posterior hump of the vertebral bodies (6/9), bony spurs (7/8), and pelvic abnormalities (7/9). We also systematically evaluated eight obligate carrier females. They could not be distinguished from the general population on clinical and radiographic findings. Linkage analysis showed significant linkage with markers on Xp22, as previously reported. A recombinant event between DXS43 and DXS207 places the locus distal to DXS43.

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Key words: osteochondrodysplasia; X linked inheritance; linkage analysis; X linked spondyloepiphyseal dysplasia.

X linked spondyloepiphyseal dysplasia (SED), with a reported incidence of 1.7 per million, is a rare, progressive skeletal dysplasia. It usually presents as disproportionate short stature with onset between 5 and 10 years of age. Owing to impaired growth of the spine, affected males have a characteristic habitus with a short neck and trunk and a barrel chest. Degenerative changes in the spine and hips lead to symptoms of secondary osteoarthritis such as pain and stiffness in the late thirties or early forties and often result in hip replacement before the age of 50. Radiological manifestations, usually recognisable by adolescence, most characteristically include platyspondyly with anterior wedging, a central and posterior hump of the vertebral bodies, and narrow and irregular intervertebral disc spaces. Kyphosis, lordosis, or scoliosis are often present. The pelvis tends to be narrow and deep, the femoral necks short, and the femoral heads flattened. Mild dysplastic changes consisting of narrow clefts and flattening of the articulating surfaces in other large joints may also be seen. Significant variability of expression may occur, but, in general, X linked SED has a mild phenotype; affected subjects lead relatively active lives and have a normal lifespan.

A small number of obligate female carriers of this disorder have been investigated and most have been found to be clinically and radiologically indistinguishable from the general population. However, one such female has been documented to have had arthritis since the age of 33 and by 66 to have had complete fusion of both sacroiliac joints and of the apophyseal joints of the lower cervical vertebrae, and hip abnormalities requiring surgery. Another carrier female was reported to have flattening of the intercondylar notches of the femora on frontal x ray of the knees. The gene for X linked SEDT, termed SEDL, was localised to the short arm of the X chromosome by Szpiro-Tapia et al in 1988. This localisation has been most recently refined by the same group to a 1-2 Mb interval on Xp22.

We document the spectrum and further define the natural history of X linked SED in 11 affected males belonging to a large kindred, the largest reported to our knowledge since 1971. In addition, we present the results of a systematic evaluation of eight obligate female carriers in an attempt to establish definitively whether heterozygote manifestations are likely to occur in this condition. Finally, we present the results of linkage analysis using polymorphic loci flanking the SEDL locus.

Methods

CLINICAL EVALUATIONS

Our proband (V.11) initially presented at 12 years of age for evaluation of disproportionate...
short stature. Physical examination showed a short trunk with a broad chest and radiographs showed a narrow pelvis. The family history was remarkable for at least 10 other males with a similar habitus in a pattern consistent with X linked inheritance. A diagnosis of X linked SEDT was made. The family was subsequently approached by the mother of the proband for their participation in this study.

Thirty-six members of this large family of British descent were included in the study (fig 1). Fourteen at risk males were evaluated clinically, with medical records and selected radiographs reviewed when necessary, to establish the diagnosis. Seven of them were confirmed to be affected (III.8, 11, 15, and V.5, 6, 7, 11), and six unaffected (III.2, 14, IV.3, 7, and V.1, 9). One boy aged 4 years (V.12) was too young for a definitive diagnosis. In addition, from history provided by family members, we identified four affected males who had died (III.1, 3, 5, 13); medical records (n = 3), x rays (n = 2), or family photographs (n = 4) were examined to confirm the diagnosis. Among the 18 female participants we identified by pedigree analysis nine obligate carriers, one non-carrier, and eight of unknown status.

Medical history and results of a detailed musculoskeletal examination including ranges of movement were recorded for all seven living affected males and eight obligate carrier females. Radiological investigation of affected males consisted of a full skeletal survey; obligate carrier females had only x rays of the spine and hips performed. Additional clinical data and previous radiographs from affected males were obtained from a preliminary study performed by the late Dr H Little in 1968.

LINKAGE ANALYSIS

Blood samples from relevant participants were obtained for linkage analysis (n = 36) including seven affected males, six unaffected males, eight obligate carrier females, nine females of uncertain status, and six spouses. Blood was also collected from a male of uncertain status (V.12) but he was not used for linkage calculation. This includes all living people in the pedigree (fig 1) except for IV.10, an obligate carrier who consented to physical examination and radiographs only. DNA was successfully extracted from paraffin embedded blocks of tissue from one patient (III.5).

Genomic DNA was extracted from whole blood using a nucleic acid extractor (ABI) and from paraffin embedded tissue blocks using the method of Wright and Manos. It was then resuspended in TBE pH 8.0 and the concentration measured by fluorimetry. RFLP and microsatellite repeat markers were used to determine the haplotype of all family members using standard techniques.

Southern blotting was performed for the loci DXS9, DXS41, and DXS28. For the microsatellites at loci DXS1224, DXS16, DXS987, DXS207, and DXS43, the reverse PCR primer was endlabelled with 32P-gamma ATP. An aliquot of the amplification reaction was run on a 6% polyacrylamide sequence gel which was then dried and exposed to Kodak x ray films. For MP1 the PCR product was run on a non-denaturing 10% polyacrylamide gel which was then stained with ethidium bromide and photographed on a UV transilluminator.

Pairwise lod scores were calculated using MLINK and ILINK of the LINKAGE 5.1 package of computer programs. Multipoint lod scores were calculated with the FA-STLINK versions of LINKMAP. When performing multipoint analysis, highly polymorphic markers were recorded as penta- or tetra-allelic, in order to facilitate analysis. Recombination fractions were converted into map distances using the Haldane mapping function. The mode of inheritance of SEDT was assumed to be X linked recessive, with a penetrance of 1.0 and an allele frequency of 0.00001. While the allele frequency probably represents an overestimate of the actual allele frequency, it is conservative in terms of gen-
X linked spondyloepiphyseal dysplasia

Results

Of the seven living affected males (aged 16, 28, 32, 34, 62, 73, and 77 years), none had been previously diagnosed with SEDT except the proband. All reported the onset of short stature to have been in early adolescence. Two subjects (V.6, V.7), who were 32 and 28 years of age respectively, had no limitation of activity or symptoms attributable to SEDT. However, the remainder reported that they limited their activities to some extent because of hip or back stiffness or pain. In general, patients reported a progression of symptoms which correlated with their age. Hip replacements had been done on three subjects (III.5, III.11, III.13) originally at 33, 37, and 44 with all requiring more than one procedure. During the study period, our oldest patient (III.8) aged 77 also underwent hip replacement. Despite symptoms, however, affected males were able to perform without impairment of function in the work place. None, other than at times of surgery, had had to stop working. Occupations included a construction worker, a carpenter, a cab driver, and a mechanic.

All affected males had disproportionate short stature with a short trunk and a barrel chest configuration. This habitus was confirmed in the photographs and descriptions of the dead males. In the seven affected subjects available for examination, upper segment to lower segment ratios ranged from 0.82 to 0.94 (>1 SD below the mean) with a median of 0.88. They all had an increased arm span compared to height (>6 cm difference). Adult heights ranged from 152 to 159 cm with a mean of 156 cm (>2 SD below the mean). Some older males reported decrease in adult height of several inches with age but documentation of previous heights could not be obtained. Our proband had a height of 152 cm at 16 years of age and inspection of his growth chart (fig 2) showed a decline in growth velocity which began in early childhood and levelled off at less than the 3rd centile at 14 years.

Musculoskeletal examination showed decreased ranges of movement which were, in general, positively correlated with age. Limitation of movement of the hip, usually involving internal and external rotation, was present in all patients except the 16 year old proband (V.II) and was significant even in the 34 year old (V.5). Some limitation of movement of the cervical spine was noted in the older people, but was not a pronounced feature of the disorder. Decreased range of movement of the lumbar spine was evident in the oldest four patients who had minimal ability to perform forward flexion and decreased ability to perform extension, side flexion, and side rotation. Three older males complained of some stiffness and had some limitation of movement of their shoulders but the degree of discomfort was quite mild compared to that of their spine and hips. Six patients had scoliosis. No extraskeletal manifestations were noted.

X rays were reviewed by a radiologist experienced in skeletal dysplasias (PB) and compared to previous films where available. Two males had evidence of spinal and pelvic changes of SEDT in early to mid childhood. The proband (V.II) had had steep acetabula at the age of 3 and another patient (V.5) had had flattening and anterior wedging of the vertebrae and a narrow pelvis with a thick, short femoral neck at the age of 8. On the most recent radiographs, findings in the spine included narrow disc spaces (8/9), bony spurs (7/8), flattened vertebral bodies (7/9), anterior wedging (7/8), and the characteristic central and posterior hump (6/9). Of interest, the 77 year old man (III.8) had had the classical central and posterior hump of the vertebral bodies on radiographs done at 51 years of age but not on recent radiographs because of the extensive degenerative changes which had occurred in the interim. The 62 year old (III.15), however, had neither platyspondyly nor the central and posterior hump on radiographs done at 36, 58, and 62 years of age, although a narrow disc space and bony spurs were already evident at the age of 36 years. Scoliosis was confirmed in six of the seven living subjects. Other findings included a narrow pelvis (5/9), steep acetabula (3/7), and a thick, short femoral neck or a flattened femoral head or both (6/8). Radiographic findings are illustrated in figs 3 and 4.

Eight obligate carrier females were available for examination (IV.1, 9, 10, 12, 14, 15, 16, 17). They were aged 40, 52, 45, 43, 42, 40, 27, and 28 years respectively. Their heights were normal, ranging from 150 to 170 cm with a mean of 161 cm. As a group they were not found to be disproportionate. Six had normal upper segment to lower segment ratios and the other two (IV.10, IV.16) had ratios of 0.79 and 0.86, values more than 2 SD below the mean. Six had a normal arm span compared to height (<6 cm difference). The arm span was greater than height by 10.5 cm in IV.9 and by 11.0 cm in IV.14. Five subjects indicated that they suffered from occasional mild back or hip pain but in only one case did it necessitate a lim-
Radiographs of the lumbosacral spine, lateral views, showing progressive changes with age. Subject V.5 is shown at 12 (A), 22 (B), and 35 years (C). Note the increasing platyspondyly and development of the characteristic central and posterior hump. His grandfather at the age of 77 years (D) has obliterated intervertebral spaces. The typical hump present at 51 years of age is no longer apparent.

Radiographs of the pelvis, anteroposterior view, of an affected male (V.5) aged 35 years (A) and his mother (IV.9) aged 52 years (B). Note the narrow pelvis and the short femoral neck in the male. The female has a similar pelvic configuration.

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with X linked spondyloepiphysyal dysplasia tarda. Clinical findings are consistent with the previously defined spectrum of the disorder and include disproportionate short stature with a short trunk and barrel chest and symptoms of musculoskeletal pain and limitation of movement. Onset occurred in late childhood and progressed, often resulting in reduction of activity and the early requirement for a hip replacement. None of our patients was significantly debilitated; all were able to carry out activities of daily living without assistance into their senior years. Reported cases have had a wide spectrum of severity; some are so disabled by arthritis as to be unable to work while others lead normal, active lives despite rigidity in the back and hips. The relatively mild clinical course of our patients fits with this latter group. The variability described suggests that there might be different mutations at the same locus.

Radiographic findings were also consistent with those previously reported. We noted, however, as illustrated by our 62 year old patient, that platyspondyly and the central and posterior hump of the vertebral bodies are, although pathognomonic when present, not universal findings. Secondly, the fact that our oldest patient had had the characteristic central and posterior hump of the vertebral bodies at the age of 51 but no longer at 77 suggested to us that within the progressive course of SEDT there may be a window of time in which this classical feature is present.

As the vast majority of patients with X linked SEDT do not come to medical attention until they are symptomatic or until short stature is evident, the natural history of the condition in early childhood has not been well described. Subtle radiographic features have been reported in a small number of children, including two of our cases at ages 3 and 8, but it remains unclear whether such changes can be consistently identified before early adolescence. Clinical features are generally detected earlier. Kyphosis, lordosis, scoliosis, and knee and back pain have been reported in childhood. The most consistently reported early manifestation is growth failure, but no data exist on the growth pattern of affected males. Of particular interest was our proband’s growth pattern; his growth charts from infancy and early childhood suggest that a decline in growth velocity occurred within the first few years of life (fig 2). This may prove to be the earliest detectable manifestation of X linked SEDT and may be a useful clinical marker of the disorder in an at risk male. It would be of interest to follow other at risk males from infancy to establish whether this finding is universal.

Systematic evaluation of eight obligate carrier females for possible manifestations of X linked SEDT showed no consistent findings. Although radiographic investigations showed a pelvis subjectively similar in appearance to that of the affected males, these subjects were not radiographically distinguishable from the general population by available objective measures.

The most recent report on the refinement of the SEDL gene locus predicts it to be within the 1-2 Mb interval defined by DXS16 and DXS987 on Xp22. Our findings are in agreement with these reports. Analysis of our kindred with polymorphic markers in this region yielded a recombinant which localised the SEDL gene distal to DXS43. The region between DXS16, previously defined as the distal boundary, and DXS43 is approximately 3-4 Mb and spans the interval reported.

No specific biochemical abnormality has been identified in X linked SEDT. The nature of the condition points to an abnormality in one of the components of the extracellular matrix of articular cartilage but no candidate genes have been identified in the relevant region of Xp22. Given the size of the genetic interval, an analysis of additional families will be necessary to refine the localisation before iden-
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