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## Abstract

A case of a male patient with Kniest dysplasia is reported. The patient's growth and the development and evolution of the patient's abnormalities were tracked for a 30 year period, starting at the patient's birth. The clinical and radiographic features during this period, along with the differential diagnosis of Kniest dysplasia, are discussed. Femoral capital epiphyses and the presence of a cataract in one eye were noted from the early stages of the patient's life. The patient's final height was 165 cm. We believe this to be the first long-term follow up of this condition.

**KEYWORDS:** kniest dysplasia, abnormalities, growth, development

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# Kniest Dysplasia: Patient's Growth Progress and Development — Evolution of Abnormalities, 30 Year Follow Up

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A case of a male patient with Kniest dysplasia is reported. The patient's growth and the development and evolution of the patient's abnormalities were tracked for a 30 year period, starting at the patient's birth. The clinical and radiographic features during this period, along with the differential diagnosis of Kniest dysplasia, are discussed. Femoral capital epiphyses and the presence of a cataract in one eye were noted from the early stages of the patient's life. The patient's final height was 165 cm. We believe this to be the first long-term follow up of this condition.

**Key words:** Kniest dysplasia, abnormalities, growth, development

Kniest dysplasia, named after Wilhelm Kniest (1), who described the first case in 1952, is a rare hereditary condition characterized by an unusual form of short trunk dwarfism which later came to be considered as a variant of metatropic dwarfism (2, 3). Rimoin *et al.* (4) and Siggers *et al.* (5) have classified the Kniest dysplasia as a distinct condition.

The typical major clinical findings include: peculiar facial structure with a flat mid-face and depressed nasal bridge; occasional shallow orbits with protuberant eyes; cleft palate; short trunk dwarfism; kyphosis; accentuated lumbar lordosis; occasional thoracic scoliosis in the later course of the disease; a short and broad thorax with sternal protrusion; short, deformed extremities with prominent joints and limited motion; club feet; occasional severe myopia; retinal detachment; cataracts with later amaurosis; conductive and sensorineural hearing loss; retarded motor development; and normal mental and intellectual development. The major radiographic features include: platyspondyly with anterior wedging of the vertebral bodies (in infancy, occasionally coronal cleft of thoraco-lumbar bodies); low and broad ilia; broad and short femoral necks; short tubular bones with broad metaphyses and large, deformed epiphyses; and retarded ossification of the proximal femora (2-14).

Kniest dysplasia is a dominant autosomic heritable malady of unknown incidence, but both sexes seem equally affected (6, 8, 13). Most reported cases, including Kniest's original case, were sporadic. The etiology is based on mutations in COL2A1, the gene for collagen type II (15-19).

This case report describes a previously unreported male patient with relatively mild Kniest dysplasia, whose growth and development we have been following from his birth to adulthood. To the best of our knowledge, this is the first case of Kniest dysplasia with a 30 year follow up. The purpose of this paper is to contribute to a better understanding of the evolution of abnormalities in Kniest dysplasia.

## Case Report

R. K., a white male, born in 1964, was the first-born of 2 children, the second (a boy) being normal as are the parents. He was born by breech after a 40-week gestation to a gravida 3, para 1, 26-year-old mother who also had two spontaneous abortions. Pregnancy, delivery and neonatal period were normal. The father was 28 years at the birth of infant; there was no consanguinity between the parents. Family history and other past history were unremarkable.

The Apgar scores were 9 (1 min) and 10 (5 min). The infant weighed 3,300 g; crown-to-heel length was 50 cm; head circumference was 39 cm. At birth, the head was large, with decreased anterior-posterior diameter, and flat occiput. The face was slightly edematous with prominent

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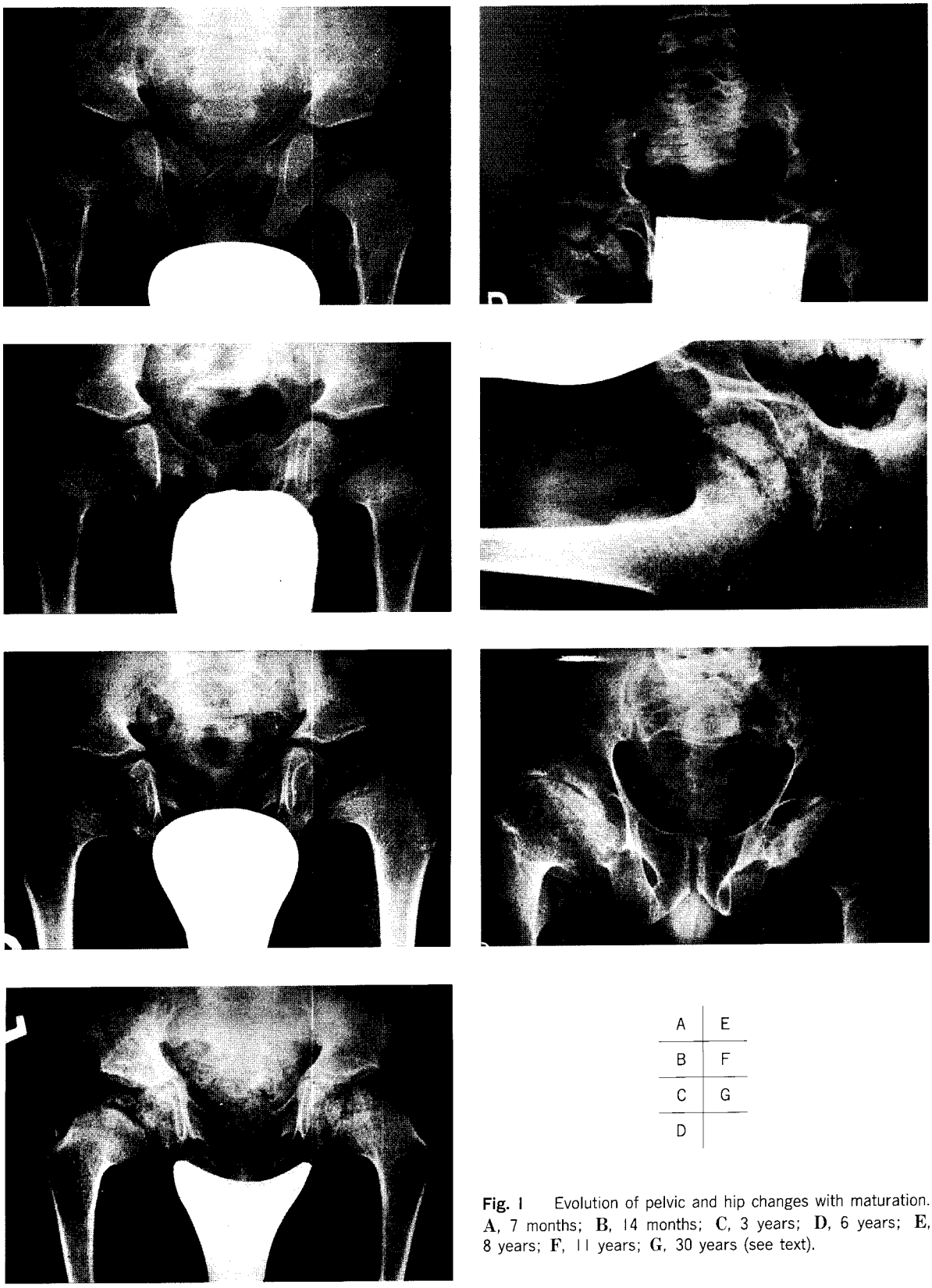

| | |
|---|---|
| A | E |
| B | F |
| C | G |
| D | |

**Fig. 1** Evolution of pelvic and hip changes with maturation. **A**, 7 months; **B**, 14 months; **C**, 3 years; **D**, 6 years; **E**, 8 years; **F**, 11 years; **G**, 30 years (see text).

eyes, epicanthal folds, flat nasal bridge, small and short nose, and relatively long philtrum. Median cleft of the soft palate was not present. The neck and chest were short. The abdomen was protuberant. The upper and lower limbs were slightly internally rotated.

Shortness of the long bones and prominent knees and wrists were noted at the age of 4 months and, at first sight, he was clinically thought to be an example of metatropic dwarfism. At that time, abduction of the hips was limited to 60 degrees. X-rays of the pelvis and hips, at the age of 7 and subsequently at 14 months, showed broad metaphyses in the proximal femora and retardation and irregularity in the ossification of the epiphyses (Fig. 1A, B).

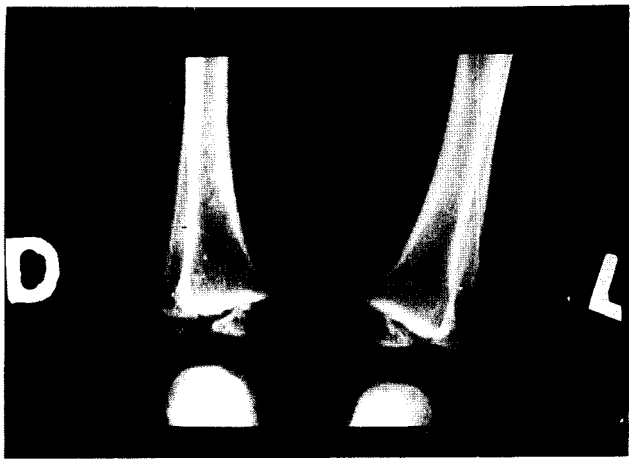


**Fig. 2** Ankle X-ray at 18 months of age illustrating metaphyseal irregularity, fragmentation, and deformity.

At the age of 9 months, he was able to sit unsupported. He did fairly well at home and seemed alert and playful to his parents. He made somewhat slow progress in his milestones, including walking and speech. The boy walked later than average (walking was always difficult).

At 18 months, he was not yet able to walk. X-rays of the ankles taken at the time demonstrated widening of the distal tibial and fibular metaphyses (Fig. 2).

At about 2 years, he began to walk alone and could say a few words (with no significant speech). He demonstrated a stiff, waddling gait since the start of walking. Though the legs appeared bowed during walking, the knees could be brought together when standing. Physical examination showed valgus ankles. There was ligamentous instability of both knees, and bilateral instability of the ankles. Leg pains were present as early as the start of walking. Discomfort varied from transient muscular aching of the legs to severe bone pain in the tibia or localized at the knee or ankle. Pain decreased with age, ceasing during adolescence. No chest pains or symptoms localized in the upper extremities were detected. At the

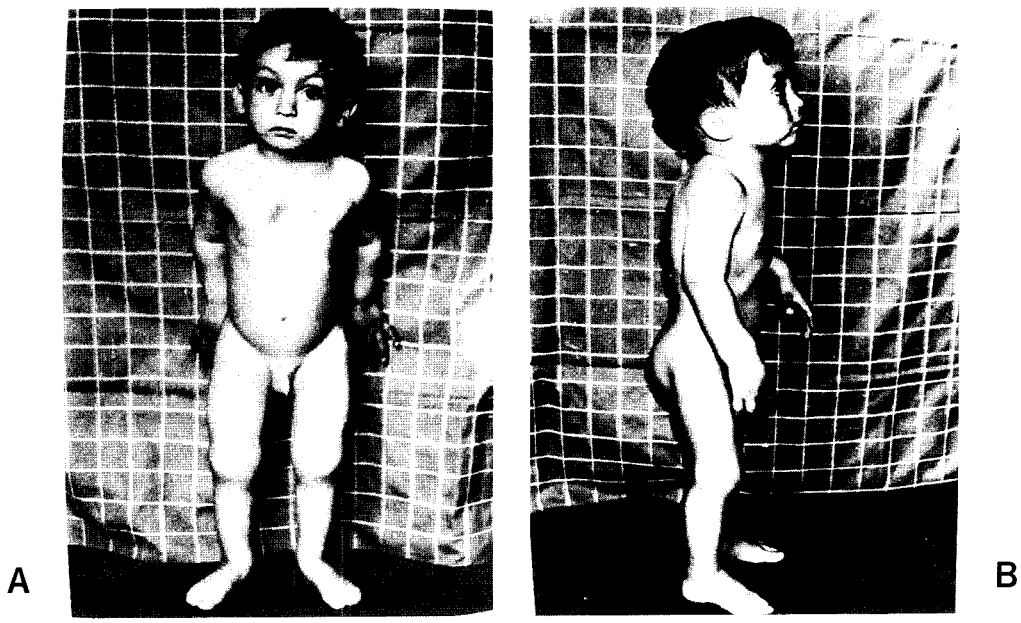


**Fig. 3** The patient's views at the age of 3 years. **A**, front view; **B**, lateral view. Note flat face and short proximal segments of the upper limbs.

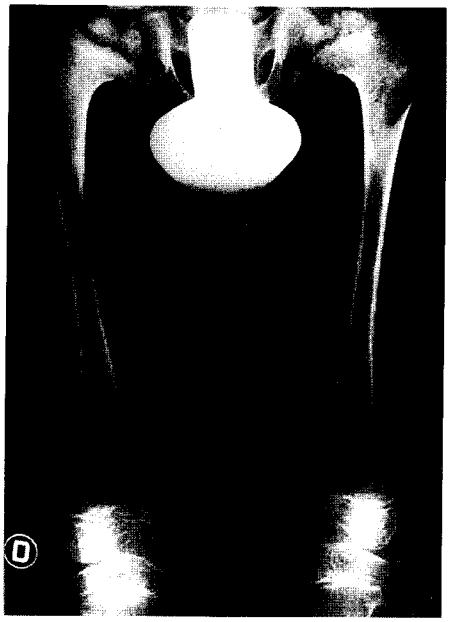

Fig. 4

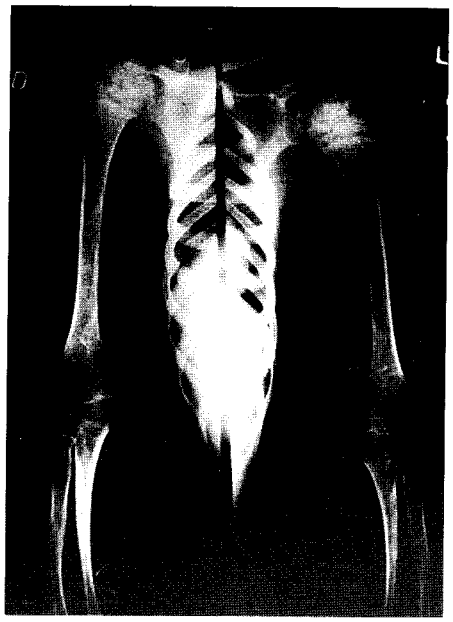

Fig. 5

**Fig. 4** X-ray of the lower limbs at 6 years of age. The tubular bones are short with broad metaphyses. The epiphyses in the heads of the femurs are large and deformed with irregularity in the ossification.

**Fig. 5** X-ray of the upper limbs at 6 years of age. Note short humeri and deformed epiphyses.

time, both the height and weight were below the third percentile. The height was 80 cm and the weight 10.5 kg.

At the age of 3 years, he was admitted to hospital for the investigation of short stature and restricted joint mobility. He was noted to have a disproportionately large head; he had a round, flat face with a flattened nasal bridge and kyphoscoliosis. The proximal segments of the upper limbs were especially short (Fig. 3A, B). Abduction of the hips was limited to 50 degrees. X-rays of the pelvis and hips, taken at the time, showed pronounced retardation and irregularity in the proximal femora (Fig. 1C).

Routine blood analysis and urinalysis were normal. Detailed qualitative and quantitative studies of urinary mucopolysaccharides failed to reveal any abnormality. The amino acid excretion pattern was normal, as was his karyotype.

His eyesight was probably defective from early infancy, but no details are available before he reached the age of 4 years, when he was examined by an ophthalmologist on account of suspicion of poor visual acuity. Myopia with a refractive error of 7 dioptres in the right and 6.5 dioptres in the left eye was first noted. A posterior polar cataract was detected in the left eye from an early stage but this never appeared in the right.

His hearing soon became suspect. He responded to low-pitched sounds at low intensity, but his response to high-pitched sounds was much less clear. There was moderately severe bilateral hearing loss of sensory-neural origin in the left ear and mixed sensory-neural and conductive origin on the right. In the next two years, his hearing somewhat deteriorated and a hearing aid was provided. With the hearing aid, his hearing was effective and his speech was clear. Significant deterioration of hearing wasn't noted later in the rest of his life.

At the age of 6 years, he had orthopaedic treatment because of difficulty in walking with his valgoid feet. The distal femora, proximal and distal tibias, and distal radii were broad.

At the time, several series of skeletal x-rays were available for examination. They showed shortening of the shafts of the long bones with broad metaphyses, especially in the proximal femora, and large and deformed epiphyses with retardation and irregularity in ossification of the epiphyses in the heads of the femurs and humeri (Figs. 4, 5). Abnormalities on both the epiphyseal and metaphyseal sides of the growth plate were identifiable. The ends of the long bones were osteoporotic. There was a relative increase in bone density adjacent to the growth plates on both the epiphyseal and metaphyseal sides. The

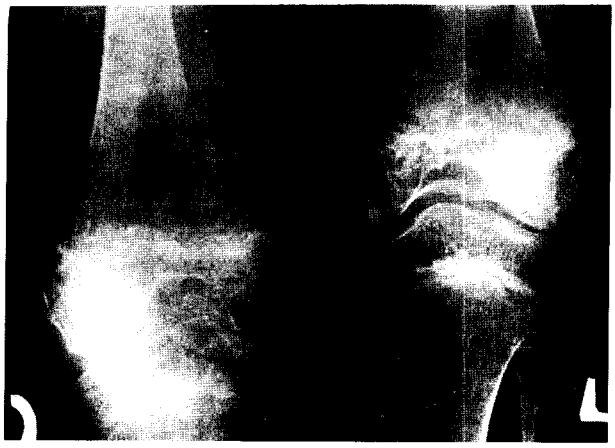

**Fig. 6** X-ray of the knees at 6 years of age showing increased density adjacent to the growth plates on both of the epiphyseal and metaphyseal sides. The epiphyses and metaphyses are osteoporotic and wide. The proximal tibial metaphysis and growth plate are dome-shaped with corresponding central thinning of the epiphyseal ossification center.

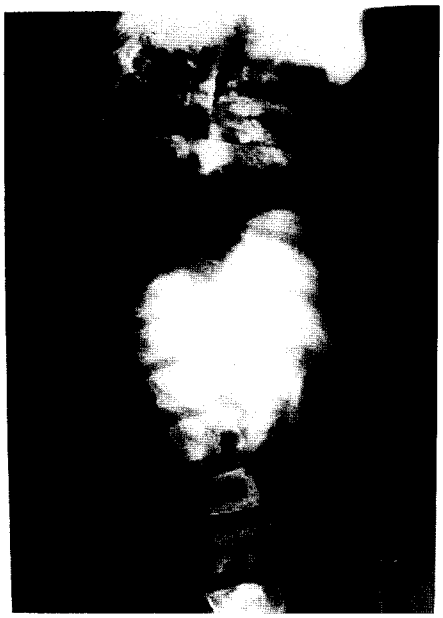

**Fig. 7** Lateral view of the mid and lower thoracic and lumbar spine at the age of 6 years. The vertebral bodies are flattened and irregular with mild anterior wedging in the lower thoracic and upper lumbar spine.

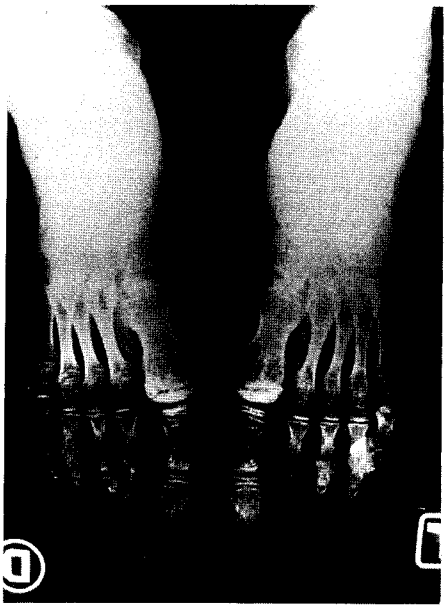

**Fig. 8** Anteroposterior view of the feet at the age of 6 years. There is mild thinning of the shafts of the second through the fifth metatarsals.

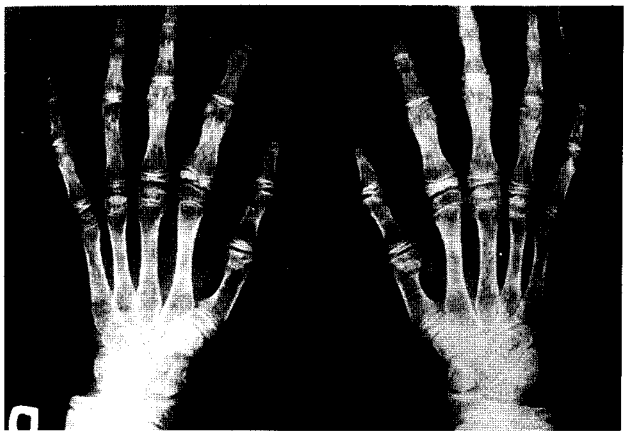

**Fig. 9** The hands at the age of 11 years showing a mild narrowing of joint spaces. The metacarpals, proximal and middle phalanges are wide at both ends. The dome-shaped distal radial metaphysis protrudes into the center of the epiphysis.

proximal tibial metaphyses were dome-shaped with corresponding central thinning of the epiphyseal ossification centers. The epiphyses at the knees were large (Fig. 6). There was generalized platyspondyly with anterior wedging primarily involving the thoracic spine and irregularity of the superior and inferior surfaces of the vertebral bodies. There was thoracic kyphosis (Fig. 7). The iliac, pubic, and ischial bones were hypoplastic. The iliac bones had a square configuration (Fig. 1D). The shafts of the second through the fifth metatarsals were abnormally thin

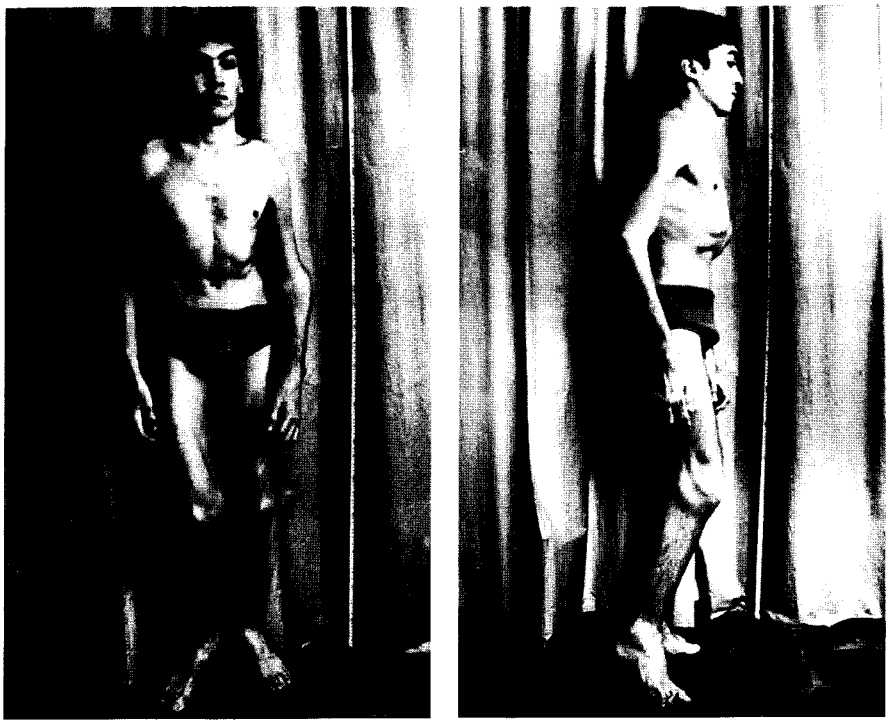


**Fig. 10** The patient's views at the age of 18 years. **A**, front view; **B**, lateral view. Note marked thoracic kyphosis and flexion contractures of the joints. Both the large and small joints of the extremities are enlarged.

(Fig. 8). A diagnosis of metatropic dwarfism with some superimposed rickets was subsequently modified to dysplasia spondyloepiphysaria congenita, but, in fact, he has neither of these conditions. In an effort to improve ossification, a daily dosage of 100,000 I.U. vitamin D was started.

At 7 years, extensive ballooned inferior retinal detachments were seen in both eyes which showed about 6 dioptres of myopia. In the next several years, the detachment slowly progressed to a certain degree and the patient was treated surgically. The operation was fairly successful.

His intelligence was unimpaired; indeed, taking into account the visual and auditory disabilities, it was probably above average. Disability was not present to a significant degree. He started at the local school at the normal age.

X-rays of the pelvis and hips, taken at 8 and 11 years of age, showed narrowing of the hip joint spaces and bilateral coxae varae with short, thick femoral necks. The femoral capital epiphyses were flat and wide. The changes were more pronounced with age (Fig. 1E, F). X-rays of the hands and wrists taken at the time showed: the metacarpals, proximal and middle phalanges were wide at both ends; the distal phalanges were flared at the proximal ends; the first metacarpal was shortened, the epiphyseal ossification centers were large, the growth plates of both radii had the shape of an inverted V. Mild narrowing of joint spaces was present. Periarticular areas of the phalanges were osteoporotic (Fig. 9).

At 15 years, the patient's height was about the third percentile (153 cm), and the weight was about the tenth (43 kg).

At 18 years of age, the height was 159 cm and the span was 164 cm. The upper-lower segment ratio was 0.90. There was marked thoracic kyphosis, and the lower ribs were flared laterally. Both the large and small joints of the extremities were enlarged, and joint motion was limited (Fig. 10A, B). The limitation was more pronounced with age. He suffered stiffness in the morning. Three years later, he developed pain in the left hip.

At the time of the last survey, at age 30, he had severe hip pain bilaterally with marked limitation of motion. X-rays, taken at the time, showed pronounced degenerative changes of the hips, including joint space narrowing, deformed femoral heads, and big osteophytes

(Fig. 1G). Bilateral total hip replacement was indicated. The final height was 165 cm.

He had still sufficient visual acuity to go through life independently. In the period from age 15 to 30 (the latter half of our follow up), the patient's condition was stable. His hearing was unchanged and adequate for him to dispense with a hearing aid. He was able to drive a car and make a long trip. At that time, he was just about to finish his study of computers.

## Discussion

Kniest dysplasia often has been confused with metatropic dwarfism (1, 2), and has been referred to as pseudometatropic dwarfism (20) and metatropic dwarfism, Type II (21). The confusion arises primarily because of the presence of dumbbell-shaped, short tubular bones and platyspondyly in both conditions. Metatropic dwarfism in the newborn period is characterized by a long and narrow chest, prominent metaphyseal flaring, severe platyspondyly, and marked supra-acetabular notches, whereas Kniest dysplasia is characterized by a short, broad chest, less severe metaphyseal flaring, milder platyspondyly with typical vertical clefting of the vertebral bodies, and slight notching of the lateral margins of small iliac bones. These differences are considered significant enough to differentiate these two conditions (8, 9, 22).

Spondyloepiphyseal dysplasia congenita (SEC) in the newborn period can be confused with Kniest dysplasia. In SEC, pubic and ischial bones are severely hypoplastic and dumbbell-shaped femora and vertical clefting of the vertebral bodies are absent.

Morquio's disease, diastrophic dwarfism, and pseudodiastrophic dwarfism should be included in a differential diagnosis. However, there should be no difficulty in distinguishing these disorders from Kniest dysplasia, because of the distinctive changes of the spine and the pelvis in the latter condition. Skeletal abnormalities are present at birth in Kniest dysplasia but do not appear until early childhood in Morquio's disease (23).

Weissenbacher-Zweymüller syndrome is said to have rhizomelic micromelia with flared, dumbbell-shaped metaphyses. This chondrodysplasia is characterized by better prognosis, micrognathia and coronal cleft vertebrae, but platyspondyly is absent (24, 25).

Fibrochondrogenesis needs to be distinguished from Kniest dysplasia, because micromelia, widening of the metaphyses of the long bones, and platyspondyly are seen in both. Micromelia and platyspondyly are more severe in fibrochondrogenesis. In addition, the patients have small hook-like protrusions of the medial acetabulum. The characteristic histopathologic finding is fibrosis of the cartilage (26).

The patient had most of the clinical and X-ray findings of the previously reported patients with Kniest dysplasia (Tables 1, 2). The manifestations of this patient in the newborn period are similar to those of Case 1 of Langer *et al.* (27). Both had a large head, midfacial hypoplasia, with a flat nasal bridge, small and short nose, relative micrognathia, short neck, and mildly bowed limbs. Roentgenographic findings in the later period include generalized osteoporosis, bulbous ends of long bones, irregular trabecular structure with increased density on both sides of the region of the growth plate, vertebral flattening and irregularity, and hypoplastic pelvis.

Several differences from the previously reported cases were noted. To our knowledge, our patient is unique in the following ways:

a) It is known that the final height ranges between 106 cm and 145 cm (13, 28). Our patient attained a rather good adult height (165 cm). The father's height was 179 cm and the mother's 163 cm. We have described herein a relatively mild case of Kniest dysplasia and this height could be a manifestation thereof.

b) The femoral capital epiphyses, usually absent throughout childhood in Kniest dysplasia, were present in our patient from the early stages of life, although very flat.

c) The ocular manifestations are similar to those of Case 2 of Kagotani *et al.* (29). However, posterior polar cataract was described in our patient in the left eye from an early age. In spite of ocular complications during childhood, he still had sufficient visual acuity to go through life independently.

The literature on vitreoretinal degeneration such as Wagner's disease or Stickler syndrome may indicate the relation of Kniest dysplasia to similar diseases.

Platyspondyly and cloudy calcification across the epiphyseal plate in our case were less marked than usually seen in the syndrome (4, 6, 8, 9). Cleft palate was absent. Upper cervical spine instability was not noted in our case, although Merill and Schmidt (30) have described a 41-month-old child with occipitoatlantal instability in Kniest dysplasia.

Thus, in conclusion, Kniest dysplasia is only one of a large number of genetically determined associations of skeletal, visual and hearing defects, many of which await

**Table I** Clinical findings of the previously reported patients with Kniest dysplasia[a]

| Clinical findings | Kniest (1) | Rimoin (4) | Siggers (5) | Brill (6) | Kim (8) | Lachman (9) | Spranger (13) | Merrill (30) | Kozlowski (31) | Frayha (32) |
|---|---|---|---|---|---|---|---|---|---|---|
| Normal head circumference | + | + | + | | | | | | + | |
| Face round with central depression | + | + | + | + | + | + | + | + | + | + |
| Prominent forehead | | | | | | + | | | + | |
| Broad mouth | | + | | | | + | | | | + |
| Cleft palate | − | + | + | − | + | + | + | + | − | − |
| Prominent eyes | + | + | + | + | + | + | + | | | + |
| Epicanthal folds | | | | + | + | | | | | |
| Wide-set eyes | | + | | | | | | | + | |
| Low set, large ears | | | | | | | | | + | |
| Short neck | | | | | | | | | + | |
| Short trunk | + | + | + | | + | + | + | + | + | + |
| Bell-shaped chest | + | | + | + | + | + | + | | + | + |
| Sternal protrusion | | | | | | | + | | | |
| Prominent costochondral junctions | | | | | | | | | + | |
| Scoliosis | + | | + | | | | | | | |
| Kyphoscoliosis | − | + | | | + | | + | | | |
| Thoracic kyphosis | | | | + | | + | | + | | + |
| Lumbar hyper lordosis | + | + | + | | | | + | | + | |
| Lower ribs flared laterally | | | | + | | | | | | |
| Shortening of the extremities | + | + | + | | | + | + | | + | + |
| Enlargement and stiffness of joints | + | + | + | + | + | + | + | + | + | + |
| Long and knobby fingers | | + | | | | + | | | + | + |
| Contractures of fingers | + | + | + | | + | + | | | | + |
| Congenital dislocation of hips | + | | + | | | | | | | |
| Tibial bowing | − | + | + | | + | | | | + | + |
| Clubfeet | | | | | | | + | | + | |
| Flat, out-turned feet | | | | | + | + | | | | + |
| Myopia | | + | + | + | + | + | + | | + | − |
| Retinal detachment | − | + | + | | | + | + | | | |
| Cataract | | | | + | | | | | + | |
| Nuclear cataract | | | | | + | | | | | |
| Vitreous strands | | | + | | | | | | | |
| Lattice degeneration | | | + | | | | | | | |
| Corneal clouding | | | | | | | | | + | |
| Deafness | − | + | + | + | + | + | | + | | + |
| Recurrent otitis media | − | + | + | | + | + | | + | | − |
| Recurrent respiratory infections | − | | + | | + | + | | | + | − |
| Respiratory distress | − | + | + | | | | | | | |
| Tracheomalacia | − | + | + | | | | | | | |
| Cor pulmonale | | | | | | | | + | | |
| Inguinal hernia | + | + | + | | | | | | | |
| Umbilical hernia | − | + | + | | | | | | | |
| Retarded motor milestones | + | + | + | | + | + | + | + | + | − |
| Retarded mental development | − | − | | − | − | − | | | + | − |
| Delayed speech | + | + | + | | | | | + | | |

[a]: Blank space: not mentioned.

**Table 2** X-ray findings of the previously reported patients with Kniest dysplaia[a]

| X-ray findings | Kniest (1) | Rimoin (4) | Siggers (5) | Brill (6) | Kim (8) | Lachman (9) | Spranger (13) | Merrill (30) | Kozlowski (31) | Frayha (32) |
|---|---|---|---|---|---|---|---|---|---|---|
| Generalized osteopenia | + | + | + | + | | + | | | | + |
| **Skull** | | | | | | | | | | |
| Normal circumference | | | + | + | | | | | | |
| Occipital flattening | | | + | | | | | | | |
| Wide sella turcica | − | | + | − | − | | | | | |
| Small sella turcica | + | | | + | + | | | | | |
| Prominent forehead | | | + | | | | | | | |
| Hypoplastic midface | | | + | | | | | | | |
| **Chest** | | | | | | | | | | |
| Bell-shaped thorax | + | + | + | + | + | | | | + | |
| Wide anterior ribs | | + | | + | + | | | | + | |
| Narrow intercostal spaces | | | + | | | | | | | |
| Short clavicles | | + | + | | | | | | | |
| Deformed, hypoplastic scapulae | | | + | + | | | | | | |
| **Vertebrae** | | | | | | | | | | |
| Platyspondyly | + | + | + | + | + | + | + | | + | + |
| Elongeted vert. bodies | | | | | | + | | | | + |
| Coronal clefts | + | + | | | | + | + | | | + |
| Anterior wedging (v. bodies) | | | | + | + | + | + | | | |
| Cloudlike radiodensity effect | | + | + | + | | + | | | | |
| Narrowed intervert. disk spaces | | + | + | + | | | | | | |
| Odontoid broad and short | | + | + | +/− | | | | | | |
| Ununited odontoid | | | | | | + | | | | |
| Hypoplastic odontoid | | | | | | | | + | | |
| Atlantooccipital instability | | | | | | | | + | | |
| Caudal narrowing of interpedic. distances | | | | + | + | + | | | | |
| Coccyx unusually large | | | | + | | | | | | |
| **Pelvis** | | | | | | | | | | |
| Hypoplastic pelvis | | + | | + | + | + | + | | | + |
| Rectangular ilia | | | + | + | | | | | + | |
| Increased acetabular angles | | | | | | + | | | | |
| Shallow acetabula | | | + | | | + | | | | |
| Narrow sacrosciatic notches | | | | | | + | | | | + |
| Delayed ossif. of the pubic bones | | | + | | | | | | | |
| **Long bones** | | | | | | | | | | |
| Dumbbell shaped | + | + | | | | + | | | | |
| Shortened diaphyses | + | + | + | | | + | + | | + | |
| Flared metaphyses | + | + | + | + | + | + | + | + | + | + |
| Large irregular epiphyses | + | + | + | + | + | + | + | + | + | + |
| Femoral heads markedly delayed in ossification | + | + | + | − | | + | + | | + | |
| Wide and short necks | | | + | + | + | + | + | + | | |
| Prominent trochanters | | | + | | | | | | | |
| Cloudlike radiodensities on both sides of the epiphy. plates | | + | | + | + | + | | | | |
| Cyst-like lucencies in distal femur | | | | + | | | | | | |
| **Hands** | | | | | | | | | | |
| Delayed epiphy. ossification | | + | | | | + | | | | + |
| Narrowed joint spaces | | + | + | + | + | + | | | | + |
| MCP joints flat and squared | | + | | | + | | | | | + |
| Flattening of metacarpal heads | | | | + | | + | | | + | + |
| Prox. phalanges-fragmented accessory centers | | + | | | | + | | | | + |
| Carpal centers-unsual size and shape | | + | + | + | + | + | | | | + |
| **Ankles** | | | | | | | | | | |
| Varus deformity | | | + | | | | | | | |
| **Feet** | | | | | | | | | | |
| Shafts of metatarsals abnormally thin (II–V) | | | | + | + | | | | + | |
| Fourth metatarsal shortened | | | | + | + | | | | | |
| Early arthroses | | | | + | + | | | | | |

[a]: Blank space: not mentioned.

better definition. This and further long-term follow up studies of such conditions may well provide insight into the evolution of the abnormalities in Kniest dysplasia.

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