Original Clinical Article

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Orthopaedic manifestations of pseudoachondroplasia

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Abstract

Purpose In 1959, Maroteaux and Lamy initially designated pseudoachondroplasia as a distinct dysplasia different from achondroplasia the most common form of skeletal dysplasia. Pseudoachondroplasia is caused by a mutation in the collagen oligomeric matrix protein gene (COMP) gene on chromosome 19p13.1-p12 encoding the COMP. The COMP gene mutations result in rendering the articular and growth plate cartilages incapable of withstanding routine biomechanical loads with resultant deformity of the joints. The purpose of the study was to characterize the typical orthopaedic findings in pseudoachondroplasia.

Methods The charts and radiographs of 141 patients with pseudoachondroplasia were analyzed. This cohort, to our knowledge, represents the largest group of patients describing the typical orthopaedic manifestations of pseudoachondroplasia.

Results Patients with pseudoachondroplasia have normal craniofacial appearance with normal intelligence. Short stature is not present at birth and generally appears by two to four years of age. The condition is a form of spondyloepiphyseal dysplasia and the long bones are characterized by dysplastic changes in the epiphysis, metaphysis and vertebral bodies. Radiographically the long bones have altered the appearance and structure of the epiphyses with small irregularly formed or fragmented epiphyses or flattening. The metaphyseal regions of the long bones show flaring, widening or 'trumpeting'. The cervical (89%) and thoracic and lumbar vertebrae show either platyspondyly, ovoid, 'cod-fish' deformity or anterior 'beaking'. Kyphosis (28%), scoliosis (58%) and lumbar lordosis (100%) are commonly seen. The femoral head and acetabulum are severely dysplastic (100%). The knees show either genu valgum (22%), genu varum (56%) or 'windswept' deformity (22%).

Conclusion Most commonly these distortions of the appendicular and the axial skeleton lead to premature arthritis particularly of the hips and often the knees not uncommonly in the 20- to 30-year-old age group.

Level of Evidence: III

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Keywords: Pseudoachondroplasia; skeletal dysplasia; genetics; dwarfism

Introduction

Pseudoachondroplasia was initially described by Maroteaux and Lamy in1959[1] and characterized as a distinct skeletal dysplasia separate from achondroplasia. Achondroplasia is the most common form of skeletal dysplasia of the approximate 450 cases that have been well described in the literature. Pseudoachondroplasia is the second-most common form of skeletal dysplasia, and it is characterized by a rare short-limb, short-trunk disproportionate dwarfing type condition inherited in a dominant autosomal pattern. The condition involves a dysplasia of the epiphyses and metaphyses of long bones and results in architectural deformations of the axial and appendicular skeleton. Pseudoachondroplasia is caused by a mutation in the collagen oligomeric matrix protein (COMP) gene located on chromosome 19p13.1—p12.[2-11] COMP accumulates in the rough endoplasmic reticulum of the matrix and leads to premature chondrocyte cell death and impaired endochondral bone formation.[2-11] Subsequent abnormal bone growth seen in pseudoachondroplasia appears directly related to the COMP gene.[2-11] Although a number of articles in the past have dealt with the overall features in non-orthopaedic journals, the opportunity to collect a large amount of information in a large cohort of patients with pseudoachondroplasia has led us to pursue identification of the orthopaedic manifestations in the orthopaedic literature.

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Patients with pseudoachondroplasia have a normal craniofacial appearance and have significant affectation of both the axial and appendicular skeleton.[12,13] The hips, knees and spine are nearly always affected and architectural deformities often lead to premature osteoarthritis.[12,13] Diagnosis is generally accomplished by a combination of clinical findings, radiographs and genetic testing for the COMP gene mutation. The diagnosis of pseudoachondroplasia is not established at birth and generally occurs between ages of two to four years of age when patients are walking.[12-14] The usual initial characteristic findings are abnormalities in gait such as 'waddling' and overall short stature with disproportionate shortening of the limbs.[2,12-14] Further clinical and radiographic definition generally occurs as patients grow and vary progressively from early age to skeletal maturity. Adult height usually ranges between three feet five inches to four feet three inches[12-14] (Fig. 1).

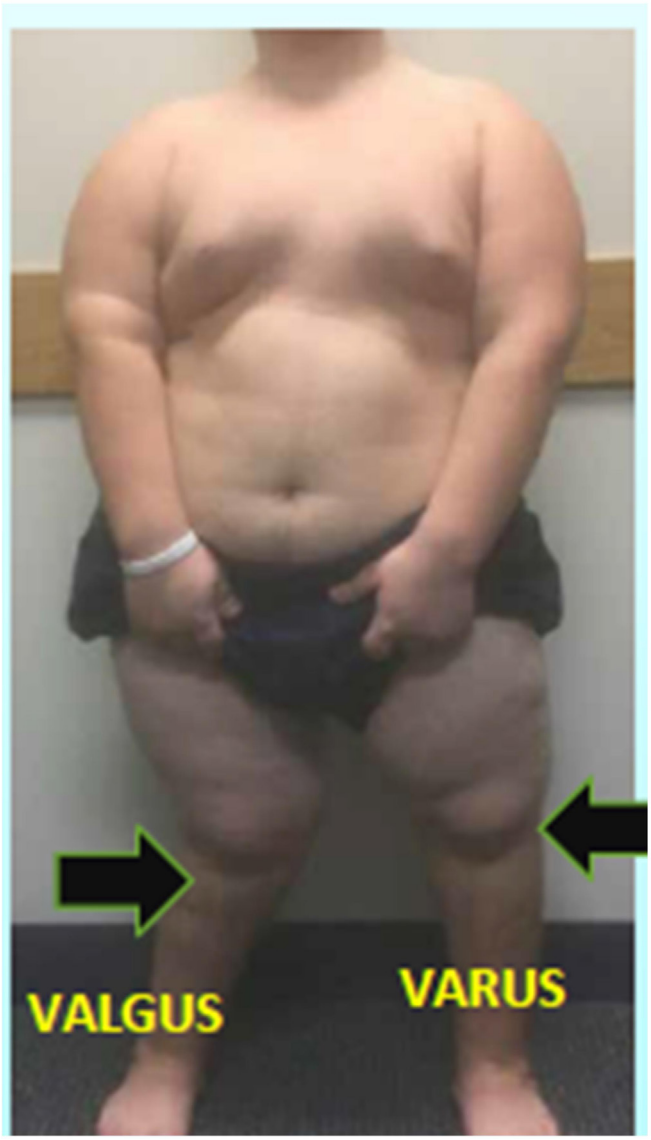

Fig. 1 Clinical photo of 16-year-old-patient with pseudoachondroplasia. Note short 'stubby' fingers, hands, trunk and 'windswept' knees.

Patients and Methods

After institutional review board approval, records and radiographs from a large cohort of patients with the diagnosis of pseudoachondroplasia were reviewed. The cohort consists of 141 patients with charts and radiographs (or a 'mixture' of both). All records and radiographs were scrutinized and interpreted by a senior paediatric orthopaedic surgeon (DSW) and a fourth-year medical student (JG). Typical findings are represented as the number of positive findings compared with the overall number of charts or radiographs that were available. Clinical and radiographic findings were analyzed by areas of the body; hand and wrist, forearm and elbow, upper arm and shoulder, cervical spine, thoracic and lumbar spine, pelvis and hips, knees, ankles and feet. Likewise, it is to be noted that patients with pseudoachondroplasia have normal intelligence and normal lifespan.

Results

Clinical findings

Results were classified by clinical findings and radiographic findings and recorded as typical (50% or above), common (25 to 50%) and occasional (below 25%) (Table 1). The cohort was composed of 71 male and 69 female patients. Ages ranged from 16 months to 55 years with a mean age of nine years (Fig. 2).

It is to be consistently noted that in all cases (100%) there were no abnormal craniofacial changes, and this finding constitutes a differentiator from many other skeletal dysplasias.

The fingers are short and typically 'stubby' in appearance with short phalanges, short metacarpals, marked laxity of the metacarpophalangeal joints, marked laxity of the wrists, ulnar deviation of the wrist and prominent distal radius and ulna (100%).

The forearms are typically short. There is usually an increased valgus carrying angle at the elbow (cubitus valgus) and prominent distal humeral condyles. Diminished range of movement is commonly observed (100%).

The upper arm is typically short (100%) and occasionally bowed. The shoulders commonly have a restricted range of movement (53%).

Table 1 Chart depicting frequency of radiographic findings in pseudoachondroplasia

	Radiographic manifestation	Percentage occurrence (n/total)	Frequency
Hand and wrist	Wrist epimetaphyseal dysplasia (EMD)	*64* (64/100)	Typical
	EMD of metacarpals and phalanges	*100* (100/100)	Typical
	EMD of elbows	*63* (56/88)	Typical
	Radial head subluxation	*17* (15/88)	Occasional
Upper arm and shoulder	EMD of shoulder and proximal humerus	*73* (68/93)	Typical
	Hatchet shaped humeral head	*53* (36/68)	Typical
	Humeral head subluxation	*34* (32/93)	Common
Cervical spine	Cervical spine dysplasia	*89* (53/59)	Typical
	Cone-shaped odontoid	*17* (10/59)	Occasional
	C1/C2 instability	*12* (7/59)	Occasional
Thoracic and lumbar spine	Thoracolumbar vertebral EMD	*100* (121/121)	Typical
	Anterior beaking - thoracic	*49* (59/121)	Common
	Anterior beaking - lumbar	*48* (58/121)	Common
	Codfish - thoracic	*34* (41/121)	Common
	Codfish - lumbar	*36* (43/121)	Common
	Platyspondyly - thoracic	*59* (71/121)	Typical
	platyspondyly - lumbar	*53* (64/121)	Typical
	Scoliosis - thoracic	*58* (70/121)	Typical
	Scoliosis - lumbar	*45* (54/121)	Common
	Kyphosis - thoracic	*28* (34/121)	Common
	Kyphosis - lumbar	*18* (22/121)	Occasional
Pelvis and hips	Acetabular dysplasia	*100* (129/129)	Typical
	Coxa vara	*30* (39/129)	Common
	Femoral head dysplasia	*100* (129/129)	Typical
	Mushroom shaped femoral head	*69* (89/129)	Typical
Femur and knee	EMD of distal femur	*100* (159/159)	Typical
	Genu varum	*56* (89/159)	Typical
	Genu valgum	*22* (35/159)	Occasional
	Windswept appearance	*22* (35/159)	Occasional
	Proximal tibial EMD	*100* (159/159)	Typical
	Proximal fibular dysplasia	*100* (159/159)	Typical
	Fibular overgrowth	*36* (20/56)	Common
Ankle and foot	Ankle EMD	*79* (53/67)	Typical

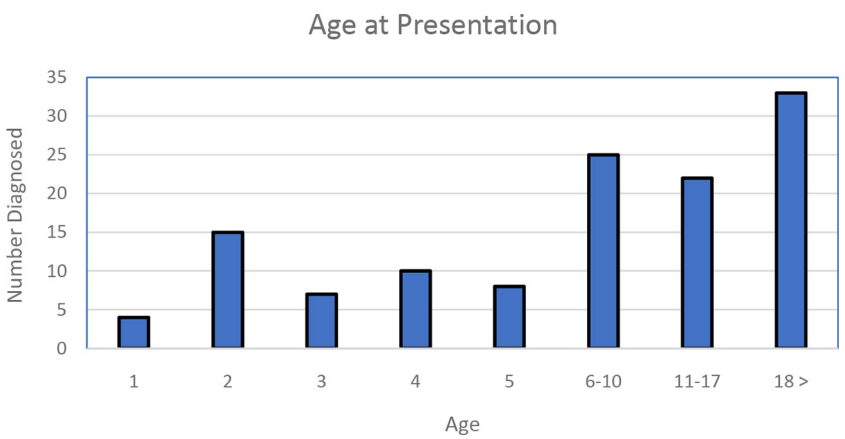

Fig. 2 Bar graph depicting age distribution of patients in the cohort.

Typically there is no restriction of movement in the cervical spine (100%).

The thoracic spine may commonly present with scoliosis (58%) or kyphosis (28%) or both and typically with an increased lumbar lordosis (100%).

Typically there is a waddling gait with a positive Trendelenburg sign (> 50%). The thigh is short and may have angular or rotational deformity. Hip movement may well be restricted particularly in abduction and typically in skeletally mature patients.

Typically, the knees will be angularly deformed and be positioned in genu valgum (22%) or genu varum (56%) or a combination of both termed 'windswept deformity' (22%). There is marked laxity of the knee in all patients in both medial-lateral and anteroposterior directions (100%). The femur is always shortened and often bowed in shape.

Although the distal tibia may be tilted into varus or valgus, the marked laxity at the ankles allow for the ankle and foot to be positioned in a valgus pronated position. All feet and toes were short and stubby.

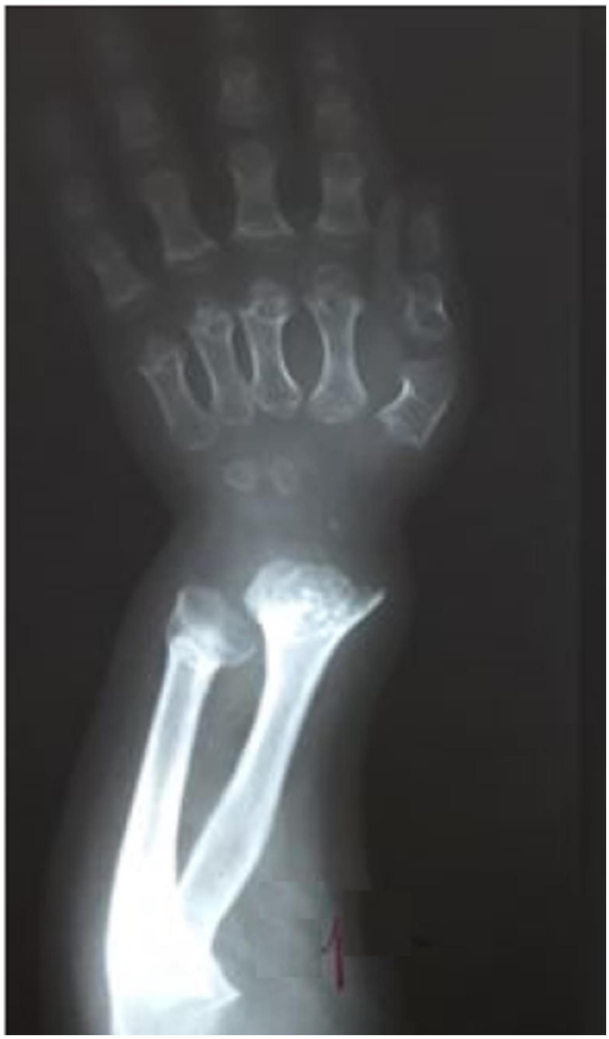

Fig. 3 Typical epimetaphyseal changes in the wrist and hand.

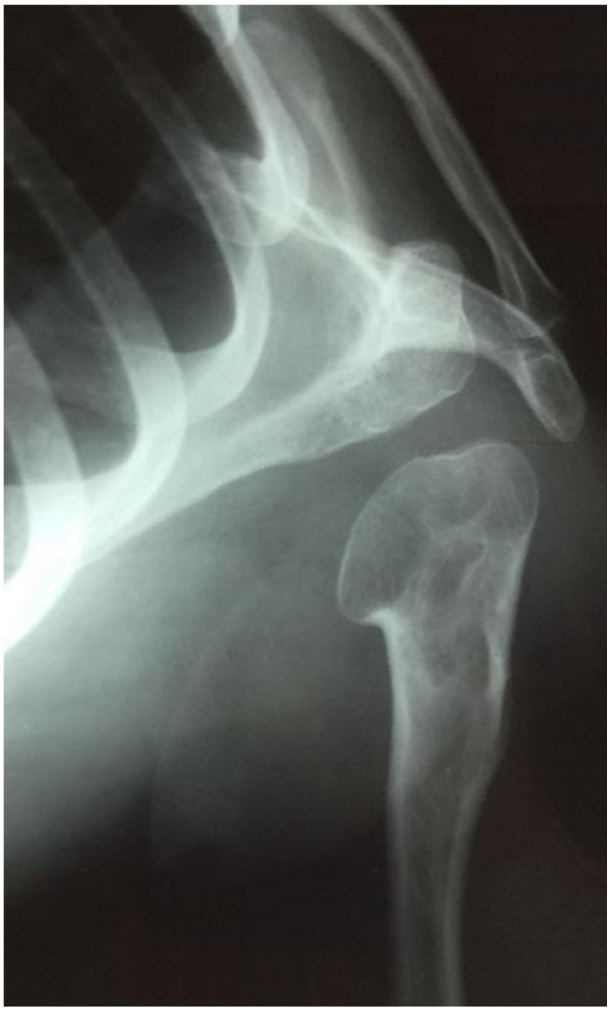

Fig. 4 'Hatchet-shaped' deformity of the humeral head.

Radiographic findings

All radiographic craniofacial features are normal.

Hand and wrist radiographs were collected from 100 patients. All of these of patients, (100/100) had short stubby fingers and epimetaphyseal dysplasia of the metacarpals and phalanges and widening flared metaphysis. Wrist epimetaphyseal dysplasia was noted in 64% (64/100) of patients on plain radiographs. At the hands, the metacarpals are short, the phalanges are short, there is evidence of epimetaphyseal dysplasia as reflected delayed appearance, small irregular flattened epiphyses and widened and flared metaphyses. The carpal bones are delayed in appearance and/or small irregularly shaped. At the wrists epimetaphyseal dysplasia of the distal radius and ulna are present as well as ulnar deviation of the wrist (Fig. 3).

Elbow radiographs from 88 patients showed 63% (56/88) to have epimetaphyseal dysplasia of the elbows as reflected in absent or small irregular epiphyses and widened and flared metaphyses. Of those, 17% (15/88) had radial head subluxation identified on plain radiographs. The forearms are short. The distal radius and ulna are prominent. At the elbow level there is cubitus valgus, short radius and ulna, occasional radial head dysplasia, epimetaphyseal dysplasia of the proximal radius and ulna and flared metaphyseal distal humerus.

We collected data from 93 patients with radiographic evidence of shoulder dysplasia. Epimetaphyseal dysplasia of the shoulder and proximal humerus was identified in 68 patients. (Absent or small irregular epiphyses and widened flattened metaphyses.) Of those with shoulder epimetaphyseal dysplasia, 53% (36/68) displayed a 'hatchet-shaped' deformity of the humeral head. Humeral head inferior subluxation was noted on 34% (32/93) of patient radiographs. In the upper arm the humerus is short (Fig. 4).

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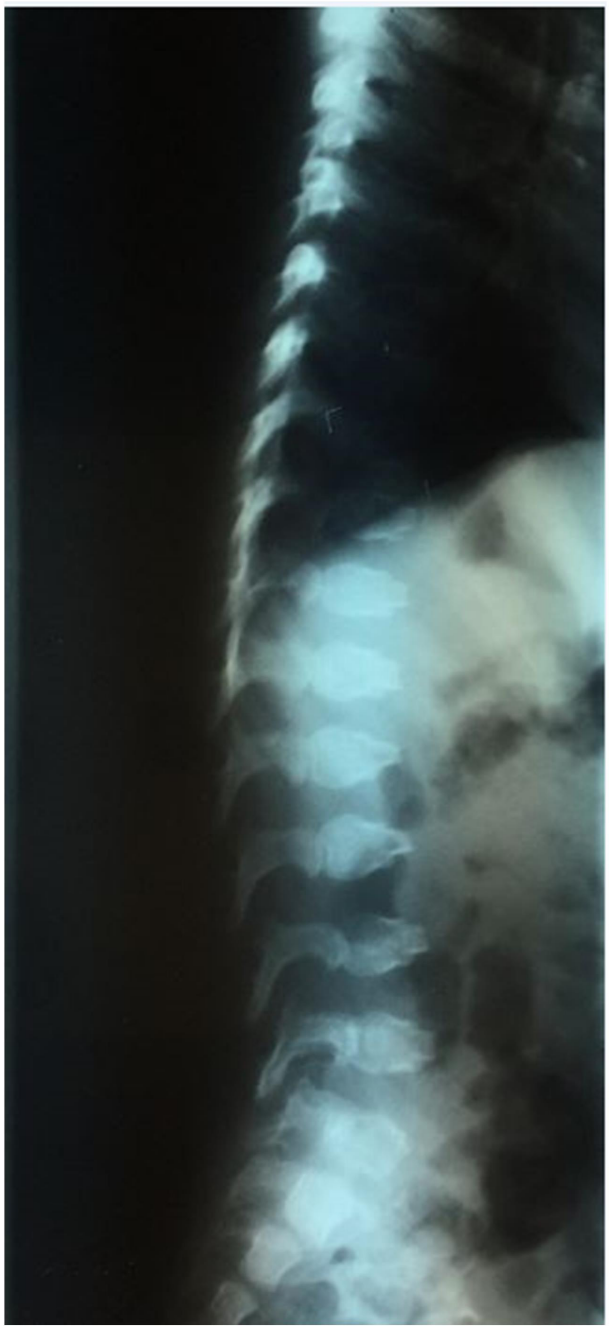

Fig. 5 Typical 'beaking' and platyspondyly seen in spine.

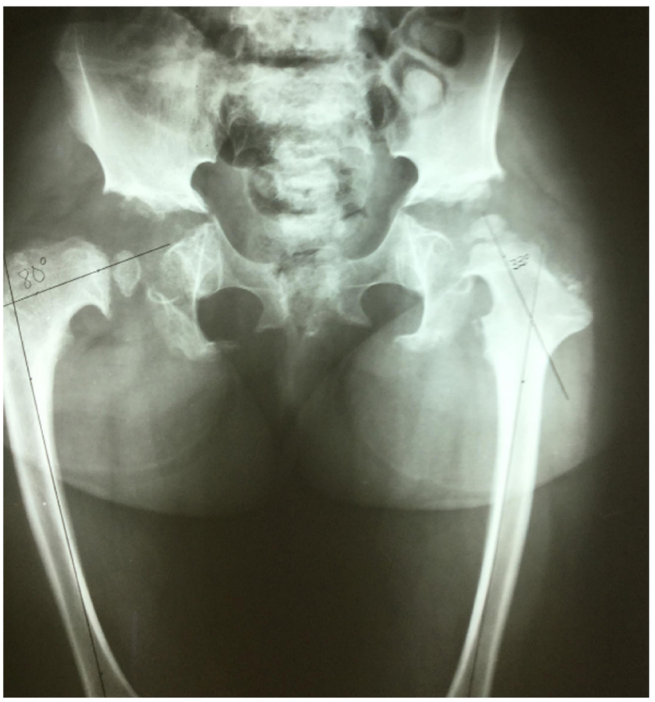

Fig. 6 Typical changes of small irregular epiphyseal ossification centre, acetabular dysplasia and metaphyseal flaring in young patient. Left hip post-osteotomy. Right hip coxa vara.

Of the 59 patients with available data, 53 of them (89%) (53/59) showed cervical spine dysplasia including but not limited to cervical platyspondyly or trapezoidal flattening, and other dysplastic changes (irregular misshaped). A cone-shaped odontoid was seen with cervical instability of which 17% (10/59) presented with a cone-shaped odontoid while 12% (7/59) had C1/C2 instability.

Data on thoracic and lumbar spinal abnormalities were combined into one category. Of 121 patients with vertebral radiographs, 100% (121/121) had varying degrees of changes in thoracolumbar vertebral architectural geometry. These dysplastic changes included anterior vertebral 'beaking', vertebral 'codfish' or ovoid shape and platyspondyly. Thoracic and lumbar anterior 'beaking' occurred in 49% (59/121) thoracic and 48% (58/121) lumbar of patients, respectively. Thoracic and lumbar platyspondyly occurred in 59% (71/121) thoracic and 53% (64/121) lumbar of patients, respectively. Thoracic and lumbar scoliosis was noted in 58% (70/121) thoracic and 45% (54/121) lumbar of individuals, respectively. Thoracic and lumbar kyphosis was noted in 28% (34/121) thoracic and 18% (22/121) lumbar of individuals, respectively (Fig. 5).

Hip epimetaphyseal dysplasia was always seen and reflected in delayed ossification small irregular flat epiphyses and wide flared metaphyses. All patients affected, 129, showed acetabular dysplasia with distorted acetabular shape. Of these 129, 30% (39/129) showed coxa vara deformity, either bilateral or unilateral. Femoral head dysplasia was noted in 100% (129/129) of patients. Of these, 69% (89/129) showed a mushroom shape deformity of the femoral head. Early in life the femoral head ossification centre may be absent, delayed in appearance, small, irregular, fragmented and later flattened with age. Distortion of the acetabulum often leads to improper femoral pelvic congruence (Figs 6 and 7).

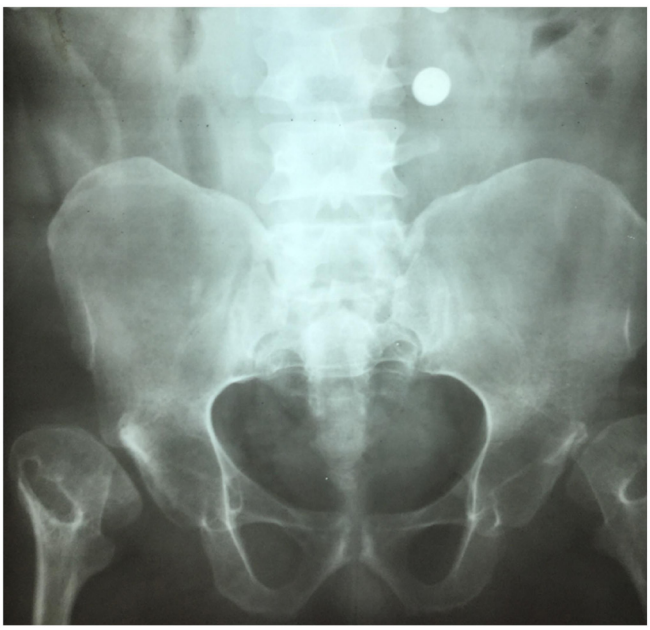

Fig. 7 Older patient with typical epimetaphyseal changes at the hip.

All patients (159/159), had epimetaphyseal dysplasia of the distal femur characterized by absent or delayed small irregular flattened epiphyses and wide flared metaphyses. All of the patients available for evaluation of the knees had angulated deformity, 56% (89/159) demonstrated genu varum, 22% (35/159) demonstrated genu valgum and 22% (35/159) demonstrated a 'windswept' appearance (one varus and one valgus). All findings seen in the distal femoral epiphyseal and metaphyseal were likewise seen in the proximal tibial epiphyses and metaphyses. Proximal tibial epimetaphyseal dysplasia was noted in all (159/159) patients with available radiographic evidence. Fibular epimetaphyseal dysplasia also occurred in all 159 patients. Fibular overgrowth relative to the shorter tibia occurred in 36% (20/56) patients out of 56 patients available for radiographic examination who had genu varum (Fig. 8).

Radiographs show short metatarsal and phalanges with epimetaphyseal dysplasia and distal tibial epimetaphyseal dysplasia in 79% (53/67) patients. At the ankle and foot, the changes may lead to ankle varus or valgus paralleling the type of knee abnormality (varus or valgus). The ankle and foot are in a pronated position due to the increased joint laxity. The tarsal bones are late appearing and often small and irregular in shape (Fig. 9).

Discussion

It is clear that the mutation in the COMP gene accounts for all of the clinical and radiographic findings seen in pseudoachondroplasia. The accumulation of COMP in the rough endoplasmic reticulum directly affects chondrocyte maturation and leads to premature cell death.[2-11] This alteration affects cartilage in all areas of the axial and appendicular skeleton and results in deformities in alignment, in sagittal and coronal planes.[9,13] The resulting deformity of the joint surfaces directly leads to premature arthritis from the opposing deformed and irregular joint surfaces.[10,12,14,15] The cartilage is less resilient and less capable of resisting daily routine loads of ordinary living. Shetty et al[16] discussed issues of cervical spine instability which occurred in 22% of our cohort (7/59).

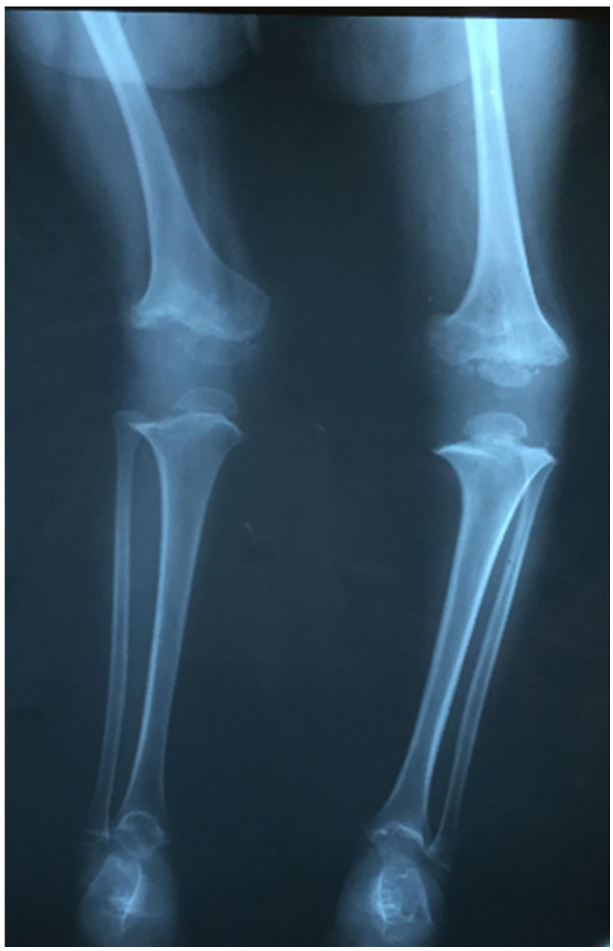

Fig. 8 Typical epimetaphyseal changes at knees and patient with 'windswept' knees.

A number of other skeletal dysplasias possess clinical or radiographic findings that are similar to pseudoachondroplasia. Achondroplasia from which pseudoachondroplasia was originally separated has marked variation from pseudoachondroplasia and is recognized at, before, or shortly after birth.[2-11] There are typical craniofacial changes, marked rhizomelic shortening, no evidence of epimetaphyseal dysplasia and a completely different gene mutation in the FGFR3 receptor.[2-11] The COMP gene also is involved in the causation of multiple epiphyseal dysplasia, a condition

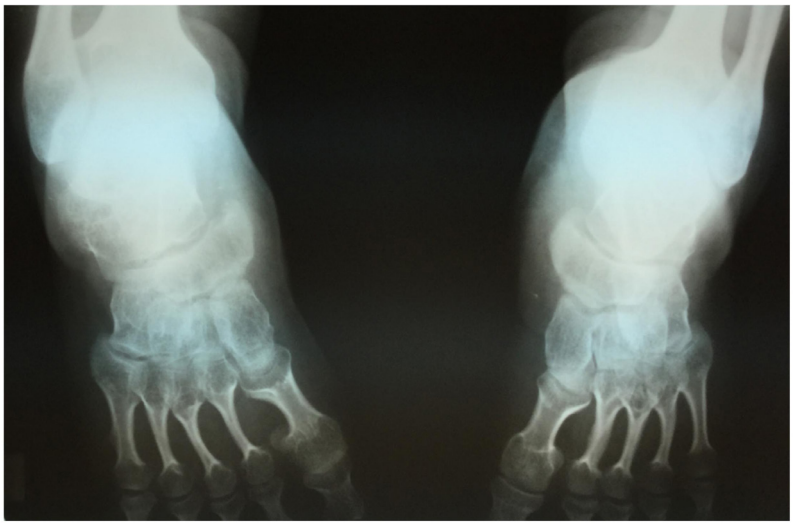

Fig. 9 Anteroposterior radiographs of feet demonstrating short metatarsals with epimetaphyseal dysplasia.

of short stature and multiple epiphyseal dysplastic changes but without spinal abnormalities.[2-11] Morquio-Brailsford disease has several characteristics that mimic pseudoachondroplasia. There are usually craniofacial changes associated with Morquio, although patients with Morquio commonly have spinal deformities, significant genu valgum, hip dysplasia and atlantoaxial instability.[2-11] Molecular testing helps differentiate this lysosomal storage disease from the COMP mutation. Extraskeletal involvement in the heart and lungs and other viscera may be present in Morquio.

The end results of the COMP gene mutation render the articular cartilage incapable of withstanding routine biomechanical loads with resultant deformation of the joints particularly manifest in the lower extremities.[2-11] These alterations result in premature arthritis and a higher likelihood of total joint replacement.[2-11] At the time of this review, we are aware of nine total hip replacements, two total knee replacements and five extensive knee realignments in the cohort with many others likely to follow a similar course.

Conclusion

The COMP mutation resulting in pseudoachondroplasia produces a myriad of structural and functional alterations in the axial and appendicular skeleton, with a predilection for premature arthritis particularly of the hips and knees.

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COMPLIANCE WITH ETHICAL STANDARDS

FUNDING STATEMENT

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

ETHICAL STATEMENT

Ethical approval: This retrospective study involved human participants and study was performed in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: This study was reviewed and approved by our institutional review board who determined that formal consent was not required.

ICMJE CONFLICT OF INTEREST STATEMENT

ST reports personal fees from Regeneron Pharmaceuticals, outside the submitted work.

The other authors declare no conflict of interest.

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AUTHOR CONTRIBUTIONS

DSW, JG, MM: Study design, Data collections, Data analysis, Manuscript preparation and review, Final manuscript approval.

ST, LS: Data collections, Data analysis, Manuscript review, Final manuscript approval.

DM: Study design, Manuscript review, Final manuscript approval.

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