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OXANDROLONE THERAPY IN SKELETAL DYSPLASIA*

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Three patients with short stature and different forms of skeletal dysplasia were treated with oxandrolone, 1.25 mg/day. All patients had a normal growth hormone response (10 ng/ml) to the insulin-induced hypoglycemia test (ITT). After one year of follow-up, it was noted that the pretreatment growth rate which was 2.5 cm/yr in the patient with spondyloepiphyseal dysplasia congenita (chronological age, 13 4/12 yr) had increased to 6.7 cm/yr after one year of treatment, while the pretreatment growth rate of the patient with hypochrondroplasia (chronological age, 12 7/12 yr) which was recorded at 2 cm/yr had risen to 5.3 cm/yr. The patient with multiple epiphyseal dysplasia (chronological age, 9 5/12 yr) had a pretreatment growth rate of 1.5 cm/yr which had risen to 8 cm/yr after the same period of treatment. An increase was noted in the height standard deviation score for chronological age and in the height standard deviation score for bone age in all patients. After one year of therapy, all patients were observed to still be in the prepubertal stage.

Oxandrolone therapy seems to be useful in the treatment of short stature seen in skeletal dysplasia.

However, a more lengthy study is needed in order to assess the efficacy of treatment with regard to adult height prognosis and to determine the optimal dosing required.
Key words: skeletal dysplasia, growth, oxandrolone therapy.

Human skeletal dysplasias are a heterogenous group of disorders that result in disproportionate short stature. While individually rare these developmental defects of the skeleton give rise to a significant proportion of children with moderate to severe short stature. The understanding and appreciation of the heterogeneity within the skeletal dysplasias led to a systematic description of over 100 different forms which have been primarily classified on the basis of clinical and radiographic changes[1,2].

The aim of this study was to evaluate the use of oxandrolone a non-aromatizable androgen in the treatment of three different types of skeletal dysplasias which manifest short stature spondyloepiphyseal dysplasia congenita, hypochondroplasia and multiple epiphyseal dysplasia and to ascertain the effect of the drug on the growth of these children.

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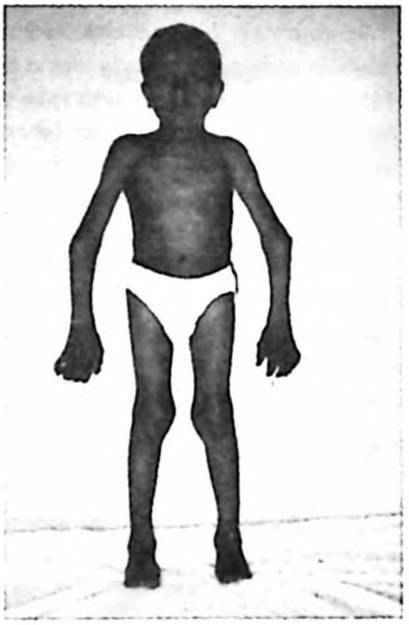
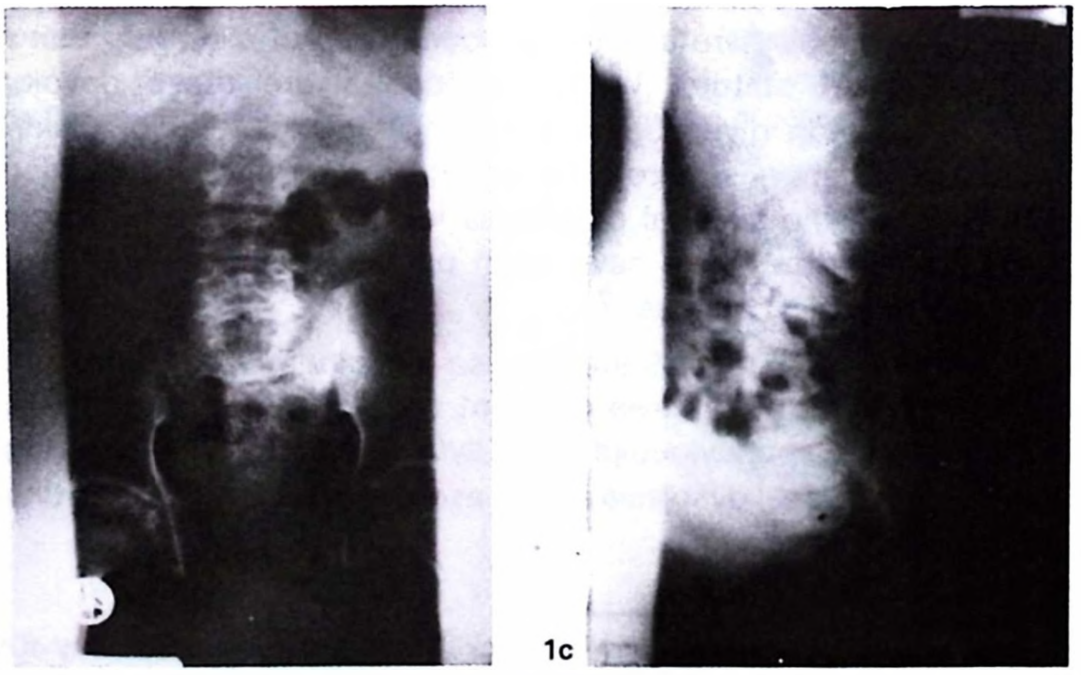
Material and Methods

C.K., a 13 4/12-year-old boy was referred to our hospital for evaluation of short stature. His height was 128.5 cm (below the third percentile) and trunk/lower extremity ratio was 61/67.5 cm. His arm span was 133 cm, and the skeletal age was determined at 15 years. The testicular volume was 3 × 3 ml, and he was classified as being in Tanner's Pubic Hair Stage 1[3]. He was the second male child born to parents who were first degree relatives (Fig. 1a). Radiographic studies revealed spondyloepiphyseal dysplasia congenita (Figs. 1b, c).

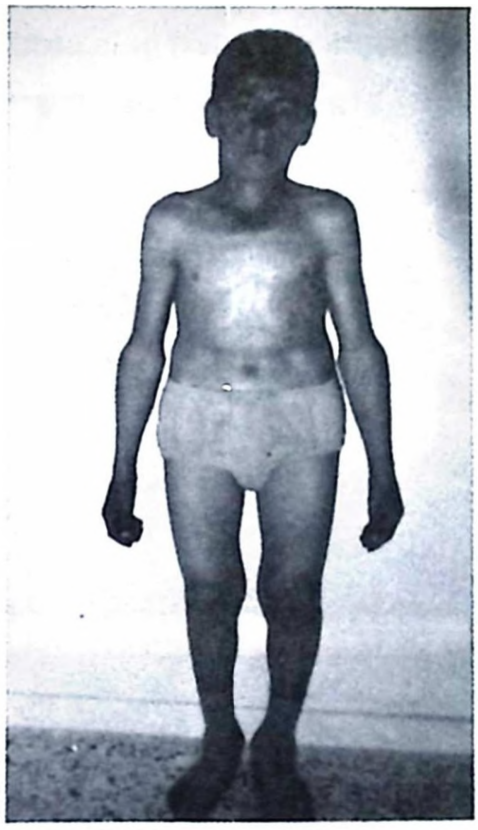




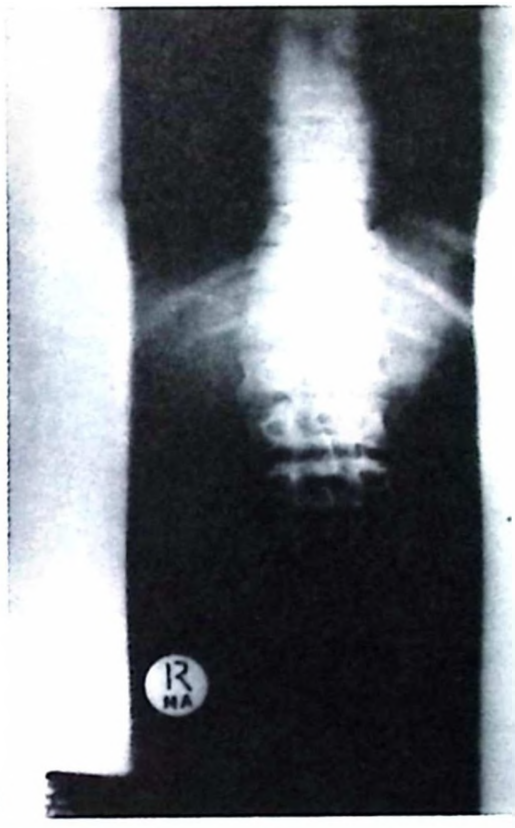
1b 1c

Fig. 1a, 1b, 1c: Spondyloepiphyseal dysplasia congenita patient. Roentgenographs show thoracic and lumbar vertebral bodies that illustrate a flat irregular wedged-shaped anterior portion. The proximal femoral epiphyses are deformed.

A.A., a 12 7/12-year-old boy, was referred to us because of short stature. His height was 117 cm (below the third percentile) and the trunk/lower extremity ratio was 57/60 cm. His arm span was 120 cm and the bone age was determined at ten years. His testicular volume was 2 × 2 ml and he was classed as being in Tanner's Pubic Hair Stage 1. He was the third born male child of parents who were first-degree relatives (Fig. 2a). Radiographic studies revealed hypochondroplasia (Figs. 2b, c).



2a



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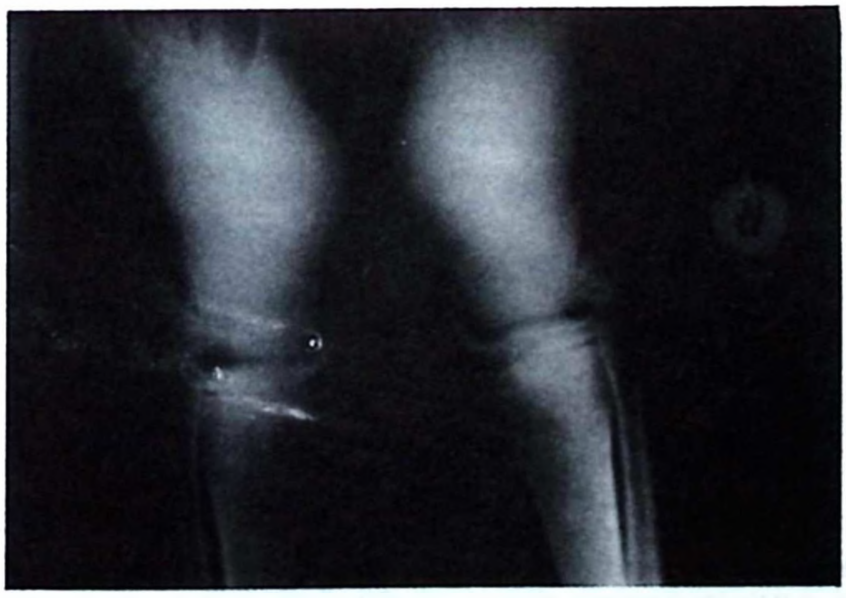
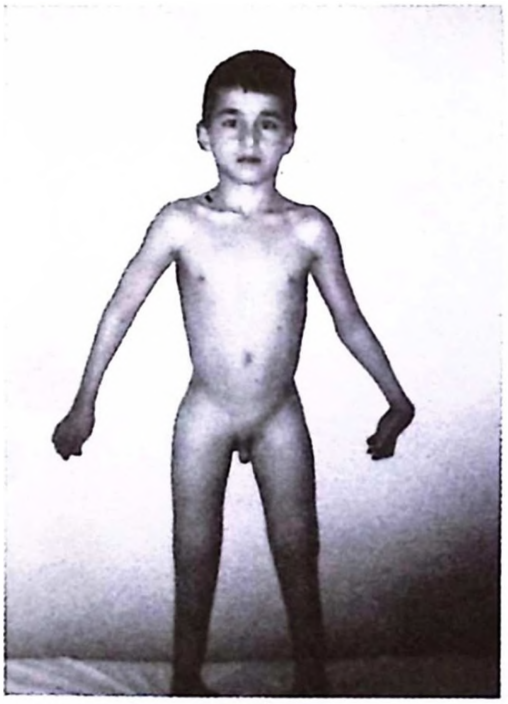


2c

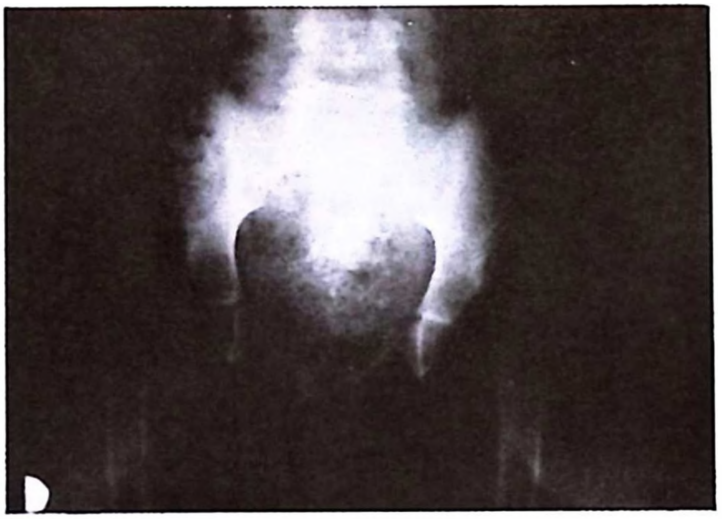
Fig. 2a, 2b, 2c: Hypochondroplasia. Roentgenographs show typical narrowing of the interpediculate distances of the L4, L5 vertebra and bilateral elongated distal ends of the fibula in respect to the tibia.

C.G., a 9 5/12-year-old-boy had a height of 110 cm (below the third percentile) the trunk/lower extremity ratio was 61/49 cm and he had an armspan of 115 cm. He had multiple skeletal deformities and a congenital hip dislocation. He had flexion contracture of both fingers and elbows and a talipes equinovarus deformity (Fig. 3a). His skeletal age was determined at eight years. The child had cryptorchidism and was classed as being in Tanner's Pubic Hair Stage 1.

There was no history of consanguinity in the family. Radiographic studies along with a physical examination led to the diagnosis of multiple epiphyseal dysplasia (Figs. 3b, c).



3a



3b

3c

Fig. 3a, 3b, 3c: Multiple epiphyseal dysplasia. An anteroposterior radiogram of the pelvis shows bilateral marked acetabular dysplasia, dislocation of the hips and hypoplasia of the proximal femoral epiphyses. On the tibia-fibula roentgenograms there are markedly irregular, deformed tarsal bones. The lateral part of the lower tibial epiphyses is thinned and deformed.

Insulin-induced hypoglycemia tests (ITT) using 0.15 units of insulin/kg body weight primed with testosterone were performed on all patients which yielded normal results (growth hormone levels above 10 ng/ml). All measurements were taken with a Harpenden stadiometer and bone ages were determined using the method devised by Greulich-Pyle[4]. The patients were followed for two years prior to initiation of therapy. The growth velocity of the patient with spondyloepiphyseal dysplasia congenita was 2.5 cm/yr, the patient with hypochondroplasia 2.0 cm/yr, and the patient with multiple epiphyseal dysplasia 1.5 cm/yr.

After obtaining patient and parental consent, oxandrolone therapy was administered to the patients with skeletal dysplasia in a dose of 1.25 mg/day. These patients were followed up for one year.

Results

A noticeable increase was observed in the growth rates of all patients during the first year of oxandrolone therapy (Tables I-III). The increase was most marked in the patient with multiple epiphyseal dysplasia whose growth rate increased from 1.5 to 8.0 cm/year, while the growth rate of the patient with spondyloepiphyseal dysplasia congenita increased from 2.5 to 6.7 cm/year, and the patient with hypochondroplasia increased from 2 to 5.3 cm/year. These patients all remained in the prepubertal stage and the bone ages did not unduly accelerate during this period of treatment, but positive correlations were found, both pretreatment and posttreatment, with respect to height standard deviation scores, and bone age and chronological age values in all patients during the said period.

Table I: The Results of Oxandrolone Therapy in Spondyloepiphyseal Therapy

	Pretreatment	One Year Postreatment
Chronological age* (yrs)	13 4/12	
Bone age** (yrs)	13	13 6/12
Height (cm)	128.5	135.2
Upper/Lower (cm)	61/67.5	63.7/71.5
Growth rate (cm/year)	2.5	6.7
Height SDS*** for BA	−3.18	−2.66
Height SDS for CA	−3.48	−3.32
Testicular vol (ml)	3 × 3	3 ×
Pubic Hair (Tanner)	1	1

* Chronological age: CA
** Bone age: BA
*** Standard Deviation Score: SDS

Table II: The Results of Oxandrolone Therapy in Hypochondroplasia

	Pretreatment	One Year Postreatment
Chronological age (yrs)	12 7/12	
Bone age (yrs)	10	11
Height (cm)	117	122.3
Upper/Lower (cm)	67/60	59/63.3
Growth rate (cm/year)	2.0	6.3
Height SDS for BA	−3.17	−2.60
Height SDS for CA	−4.45	−4.25
Testicular vol (ml)	2 × 2	3 ×
Pubic Hair (Tanner)	1	1

Table III: Results of Oxandrolone Therapy in Multiple Dysplasia

	Pretreatment	One Year Postreatment
Chronological age (yrs)	9 5/12	
Bone age (yrs)	7	8
Height (cm)	110	118
Upper/Lower (cm)	91/49	62/56
Growth rate (cm/year)	1.5	8.0
Height SDS for BA	−1.92	−1.43
Height SDS for CA	−3.98	−3.30
Testicular vol (ml)	undescended	undescended
Pubic Hair (Tanner)	1	1

Discussion

Skeletal dysplasias are quite a common cause of short stature and have a wide sprectrum of severity. Most individuals affected with these disorders are recognized by their disproportionate short stature[1,2].

Spondyloepiphyseal dysplasia congenita is characterized by shortness in stature. It has an autosomal dominant mode of inheritance. Afflicted individuals have a short trunk, lag in epiphyseal mineralization and flattening of the vertebral bodies (Figs. 1b, c)[1,2,5-8].

Multiple epiphyseal dysplasia is one form of skeletal dysplasia. It is transmitted in an autosomal dominant mode of inheritance and has a wide variety of expression.

Short femoral neck, acetabular dysplasia, irregular epiphyses are some roentgenographical characteristics of the disease (Figs. 3b, c)[1,2,5-8].

Hypochondroplasia is another form of skeletal dysplasia and one of the causes of disproportionate short stature. Roentgenographically, it is characterized by narrowing or constant interpedincular distances of the lumbar spine, long distal fibula and short distal ulna (Figs. 2b, c).

An autosomal dominant mutant gene etiology has been implicated in this disorder. In some cases there is a direct inheritance pattern transmitted by affected individuals, while in the majority of cases, the presumed mutation seems to have ocurred sporadically and the unaffected parents are of advanced age.

Final height attainment in adults ranges between 118.5 cm and 153 cm[1,2,5-8]. To date, there has been no known medical treatment to improve the height of these patients except for the use of biosynthetic human growth hormone which was found to be promising in acceleration of growth velocity in hypocondroplasias[9]. Oxandrolone, an anabolic steroid, administered in low doses promotes pharmacologically stimulated growth hormone release and it may be that the growth-promoting effect is by a direct effect on the tissues or via an increase in growth hormone secretion or a combination of both[10,11]. Loche et al[12], have recently demonstrated that there is an increased growth hormone response to growth hormone releasing hormone (GHRH) during oxandrolone therapy. Stanhope et al[10,13], have hypothesized that oxandrolone in 1.25 mg/day and 2.5 mg/day dose regimens induces a sustained rise in physiological growth hormone secretion and that the mode of action of this drug in producing a sustained growth acceleration is to increase endogenous physiological growth hormone secretion. Oxandrolone is especially used to treat patients with constitutional delay of growth and puberty and patients with Turner syndrome. Its growth-promoting effect has been reported by investigators[10,14-16]. Three forms of skeletal dysplasia were described in our study in which oxandrolone was the anabolic steroid used to induce growth in our patients. No deleterious side effects were observed, and at the follow-up one year later, all patients were found to still be in the prepubertal stage.

Our results suggest, but do not prove, that oxandrolone therapy may be useful in the treatment of short stature in early pubertal boys with skeletal dysplasia. However, further studies are needed to determine the optimum dosage of the drug and long-term side-effects.

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