Skeletal changes following growth hormone treatment in a child with combined hypopituitarism and a skeletal dysplasia

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Abstract. A child with combined hypopituitarism and an undefined skeletal dysplasia is described. The hypopituitarism was manifested by post-natal growth failure, excessive sc fat, micropenis, and poor growth hormone response to provocative tests. Disproportionately short limbs, especially distally, and skeletal radiographs showing generalized brachydactyly, cone epiphyses of the phalanges and ossification defects in the proximal femoral metaphyses characterized the skeletal dysplasia. In contrast to the normal structure of the endochondral growth plate seen in hypopituitarism, the growth plate in this child was structurally abnormal; there was no differentiation of chondrocytes into hypertrophic and degenerative cells. Treatment with hGH for 8 months was associated with the appearance of chondrocyte differentiation, the restoration of growth plate structure to almost normal and a substantial increase in growth rate. There was no change in his disproportion or improvement in his radiographic abnormalities. These observations suggest that hGH may influence growth plate structure in certain instances and that this may be associated with increased linear growth.

Growth is the product of a series of interactions between the central nervous system, endocrine system, and skeleton (Rimoin & Horton 1978). Since it is sequential, a defect at any point in the scheme can produce growth failure. We have recently seen a child with two defects: hypopituitarism and a skeletal dysplasia. Treatment with human growth hormone (hGH) resulted in the partial restitution of normal growth rate and alterations in the structure of the growth plate. It provided a unique opportunity to investigate the interaction of these two defects and the effect of hGH on the dysplastic growth plate.

Patient and Methods

JK was the product of a normal pregnancy, labour and delivery. His parents and one brother were of normal stature. Table 1 lists his height and weight measurements and height, weight, and bone ages are depicted graphically in Fig. 1. Short stature was first observed at age 6 months. Micropenis was note at age 18 months and he was treated topically with 5% testosterone cream for 4 months. At age 3 7/12 years, evaluation revealed short stature, particularly affecting his extremities. His hands and feet were short and broad, but joint mobility was normal. He had a round and flat forehead with mild nasal hypoplasia. His abdomen was protuberant but without organomegaly, and his genitalia were small for age. Insulin and arginine tolerance tests as well as an exercise study failed to demonstrate a level of hGH above 2.0 ng/ml. Adrenal, thyroid and renal function studies as well as a banded karyotype, a cranial CAT scan, and an ophthalmologic evaluation were normal.

Skeletal radiographs showed a normal skull, spine and ribs. The pelvis was normal except for hypoplasia and flattening of the acetabular roofs. The long bones were

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mildly short and the proximal femurs and to a lesser extent the distal tibias exhibited irregular ossification of the metaphyses (Fig. 2A). The hand films revealed generalized brachydactyly with cone epiphyses of the proximal and middle phalanges (Fig. 2C). The carpal bones appeared normal. Generalized epiphyseal delay was noted. The initial iliac crest biopsy was obtained at this time.

At age 4 7/12 years, repeat insulin and arginine tolerance tests yielded a maximal hCG value of 2.6 ng/ml. Growth hormone therapy, 2 U im every other day, was begun and continued through age 5 5/12 years. He showed a substantial growth spurt during this period (8.5 cm/10 months). The disproportionality, short, broad hands and feet, however did not change, and the radiographic changes observed on previous films were not altered (Fig. 2B and D). In fact, the radiolucent areas in the proximal femoral metaphyses were slightly more pronounced. A second iliac crest biopsy was obtained at that time.

Following informed consent, the iliac crest biopsies containing resting and growth plate cartilage and underlying subchondral bone were obtained with a Bordier needle, under local anaesthesia with mild sedation. Three specimens were taken during each procedure, and all six were processed and stained in the same fashion (Sillence et al. 1979; Horton et al. 1980). Briefly, the cores were fixed and without decalcification embedded in glycol methacrylate. Semithin sections were cut and stained histochemically to demonstrate the major constituents of cartilage and bone. Comparisons were made to similarly prepared growth plate cartilage from 12 control patients ranging in age from 2–12 years.

Results

Substantial differences were observed in the appearance of the growth plate before and after treatment. In all three samples taken before treatment, there was consistent lack of chondrocyte proliferation and maturation (Fig. 3A). Although there were occasional groups of 2–5 cells which had divided longitudinally, the columns that normally characterized the growth plate were absent. The cartilage-bone interface was irregular because of the occasional extension of small areas of unmineralized cartilage a short distance into the subchondral bone. Provisional calcification of the cartilage matrix as well as mineralization of the bone matrix was otherwise normal. There was no layer of subchondral bone which 'sealed off' the cartilage from the bone. The resting cartilage appeared normal and no abnormalities in the distribution of collagen or glycosaminoglycan were noted. Many of the resting chondrocytes appeared to have more non-specifically staining cytoplasmic debris than normal. In some cases this material resembled lipid droplets often seen in chondrocytes, but it did not stain with oil red 0.

The growth plate in the specimens taken after therapy had an almost normal appearance (Fig. 3B). Clusters of proliferative, hypertrophic and degenerative chondrocytes forming columns were
Fig 2.
Skeletal radiographs of the pelvis (A and B) and the hands (C and D), before therapy (A and C) and after therapy (B and D). Note the irregular ossification of the proximal femurs in the hip films and the generalized brachydactyly and cone epiphyses in the hand films.
seen in all three cores. The cartilage-bone interface was still uneven, and nests of hypertrophic chondrocytes were incorporated into the subchondral bone. The mineralization of cartilage and bone matrix was normal. The resting cartilage appeared normal except for an increased proportion of dividing cells, especially in the resting cartilage near the growth plate. The poorly defined cytoplasmic material appeared the same as in the pre-treatment tissue. No abnormalities in the distribution of collagen or glycosaminoglycan were observed. The iliac crest biopsies from the 12 control patients revealed an intact growth plate with proliferating, maturing and degenerating chondrocytes in all specimens.

Discussion

This child had two disease processes occurring simultaneously. The short stature, reduced growth rate, and poor response to hGH provocative tests are consistent with hGH deficiency. Although thyroid and adrenal function studies were normal, the small genitalia suggest that gonadotrophins were deficient as well, placing him in the category of multiple pituitary hormone deficiency.

He demonstrated a substantial weight gain between ages 2 and 3 years after being treated briefly with topical testosterone. The possibility of a systemic effect of this therapy must be considered, however, the lack of acceleration of skeletal maturation and the fact that most of the weight gain occurred after therapy had been discontinued make it unlikely.

The skeletal disporportion and radiographic skeletal abnormalities indicate a skeletal dysplasia. A metaphyseal chondrodysplasia is suggested, but the radiographic changes are not consistent with the recognized disorders in this category (Spranger et al. 1974; Rimoin 1975). They resemble those seen in two sibs described by Saldino & Mainzer (1971). Unlike the present case, these sibs also had renal disease, retinitis pigmentosa, and cerebellar ataxia. Thus, a specific skeletal dysplasia was not identified.

hGH therapy produced an increase in growth rate. This could be interpreted as simply the correction of that portion of his growth deficit due to hGH deficiency. However, the change from a hypoproliferative growth plate without chondrocyte differentiation to an almost normal appearing structure with therapy suggests that hGH may have affected the skeletal dysplasia itself. This contention is supported by the greater than usual acceleration in skeletal maturation that was observed during therapy.

Growth plate structure has received little atten-
Fig. 3.
Iliac crest biopsies before therapy (A) and after therapy (B). Note that the differentiation of chondrocytes into clusters of hypertrophic and degenerative cells seen in B is absent in A. The uneven mineralization (black) at the cartilage-bone interface is seen in both. Von Kossa-trichrome strain. Original magnification × 160.

dition in hypopituitarism. In the one childhood case in which it was reported, 15–20 rows of cells growing toward the diaphysis were described (Altman 1930). Provisional calcification was somewhat uneven, and an almost unbroken layer of cartilagenous bone separating the cartilage from medullary bone was noted. No photographs were published, however. Similar findings were observed by Erdheim (1916) in a 38-year-old man with hypopituitarism whose epiphyses had not ‘closed’. Photomicrographs of the costochondral junction from this case showed the sealing off phenomenon but also the proliferation and maturation of chondrocytes to form columns characteristic of the growth plate (Jaffe 1972).

In contrast to the limited data in man, the effect of hypophysectomy on the growth plate of the rat and other laboratory animals has been studied extensively (Lebovitz & Eisenbarth 1975). Following hypophysectomy in the rat, there is a progressive decrease in the width of the growth plate due to a reduction in the number and size of chondrocytes, hypertrophic cells become less vacuolated, bone trabeculae coalesce to seal off the cartilage from the bone marrow, and cartilage uptake of $^{35}$SO$_4$ drops markedly (Simpson et al. 1950; Becks...
et al. 1945; Lebovitz & Eisenbarth 1975). In other words, there is a reduction in the width of the growth plate corresponding to a diminished metabolic activity, but the general structure is retained.

Thus both animal studies and human autopsy reports suggest that the structural changes that occur at the growth plate in hypopituitarism are primarily quantitative; the characteristic zones of proliferating, hypertrophic, and degenerative chondrocytes are never lost. The structurally abnormal growth plate seen initially in this child therefore must have been due to the skeletal dysplasia or more precisely, the combination of skeletal dysplasia and hGH deficiency since it returned to almost normal following therapy. The persistent changes seen after therapy, i.e. failure to completely resorb cartilage at the cartilage-bone interface, presumably reflect that aspect of the basic skeletal defect that did not respond to hGH. It could be argued that the discrepancy in growth plate structure observed in the two biopsies was an artifact of the sampling. This seems unlikely since the same technique was employed and, on both occasions, the three specimens exhibited the same morphology: abnormal before treatment and almost normal afterwards. Moreover, iliac crest biopsies from 12 control children displayed an intact growth plate in all instances.

The radiographic worsening of the metaphyscal ossification defects of the proximal femurs after treatment is perplexing. The explanation may lie in the anatomic origin of the radiolucent lesions. Most likely they result from the incorporation of unmineralized cartilage into the subchondral bone of the metaphyses. The phenomenon was seen both before and after therapy. However, in the former instance the trapped areas consisted of relatively quiescent resting cartilage, whereas after treatment, nests of proliferating and differentiating chondrocytes were found. Hence, as the treatment stimulated growth within the growth plate per se, it apparently produced the same effect in cartilage incorporated into the subchondral bone resulting in a worsening of the radiographic appearance.

The mechanism by which the structural changes in the growth plate were produced by hGH therapy could not be determined. They may well have been a prerequisite for the accelerated growth that occurred, and it is likely that somatomedin and/or other growth-promoting peptides, such as cartilage-derived factor, were involved, since they are thought to mediate the skeletal effects of hGH (Phillips & Vassilopoulou-Sellin 1980; Kato et al. 1981). Moreover, there is evidence that these peptides are produced locally and may function as paracrine hormones (Canalis et al. 1980; D’Ercole et al. 1980; Kato et al. 1981). If so, they may influence chondrocyte differentiation, a hypothesis that is supported by the current case. Furthermore, abnormalities in this scheme could theoretically affect growth plate structure, and conversely, certain disorders with abnormal growth plate structure might be amenable to hormonal therapy.

This child provided an opportunity to examine the effect of endocrine stimulation on endochondral ossification. Growth hormone therapy resulted in an apparent structural reorganization of the growth plate, and this was associated with increased linear skeletal growth. The observation raises two questions. First, was this child unique or can the structurally abnormal growth plate seen in many other of the skeletal dysplasias be altered by hormonal manipulation? This is generally assumed not to be the case, however, the possibility has not been carefully investigated. Second, if growth plate structure could be altered, could skeletal growth be stimulated? The answers to these questions must await further studies. In the interim, we do not suggest that children with skeletal dysplasias be treated with growth hormone or other endocrine stimulation, because, in general, they are endocrinologically intact, and because there is no evidence to date suggesting that hormonal stimulation influences growth rate in any of these disorders. Nevertheless, the possibility that the dysplastic growth plate can be therapeutically modified by hormonal intervention deserves further exploration.

Acknowledgments

This study was supported by research grants from the Human Growth Foundation and the Kansas Chapter Arthritis Foundation. We are grateful to Drs. David L. Rimoin and Ralph S. Lachman for reviewing the radiographs. The hGH used in the study was supplied by the National Pituitary Agency.

References


Received on November 4th, 1982.