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CORTICOSTEROID-INDUCED DWARFISM IN STILL'S DISEASE TREATED WITH HUMAN GROWTH HORMONE

CLINICAL AND METABOLIC EFFECTS INCLUDING HYDROXYPROLINE EXCRETION IN TWO CASES

BY

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Children suffering from chronic diseases of many types often show a failure to grow in height (Ansell and Bywaters, 1956; Falliers, Szentivanyi, McBride, and Bukantz, 1961). This problem may be aggravated when such illnesses are treated for long periods with corticosteroids (Blodgett, Burgin, Iezzoni, Gribetz, and Talbot, 1956; Fleisher, McCrory, and Rapoport, 1960; Falliers, Tan, Szentivanyi, Jorgensen, and Bukantz, 1963), as in juvenile rheumatoid arthritis (Still's disease) when the decreased rate of growth can become a factor of major concern to both patients and their relatives.

Following observations that growth rate can be increased in some cases of dwarfism by means of parenteral human growth hormone (HGH) administration (Jasin, Fink, Wise, and Ziff, 1962), the present study was undertaken to see if it was possible to overcome this stunting in two children with Still's disease on maintenance corticosteroid therapy, by giving HGH for 12 months. A striking relationship between human growth and urinary hydroxyproline excretion has been demonstrated by Jasin and others (1962), and this correlation was investigated during the present study with particular reference to the value of urinary hydroxyproline estimations in predicting the long-term response to HGH therapy.

Patients

Two girls with Still's disease were selected. They had been maintained on corticosteroids for periods of 7 and 9 years respectively, and were stunted in height; both were below the age of puberty, and although epiphyseal development was retarded for their chronological age, neither had sufficient damage to the epiphyses to indicate that this would interfere with growth.

Case 1 (Fig. 1) was aged 9 years 8 months. The onset of Still's disease occurred at 18 months of age; oral corticosteroid therapy was introduced after 1 year and had been continued. The dosage had been constant at 3 mg. prednisone per day for 2 years preceding this study and was maintained at this level throughout, as the arthritis remained moderately active and further reduction was considered undesirable. HGH therapy was begun on April 14, 1964, and was continued in a dose of 10 mg. intra-muscularly twice weekly for one year.

Case 2 (Fig. 2) was aged 10 years 8 months. The onset of Still's disease occurred at 18 months of age; she has had chronic iridocyclitis for which corticosteroid therapy has been maintained, the arthritis showing only minimal activity. The dose of corticosteroid had varied between 5 and 6 mg. prednisone daily for 3 years preceding this study and was continued at 5 mg. per day throughout. HGH therapy was begun on April 14, 1964, and was continued in a dose of 10 mg. intra-muscularly twice weekly for one year; in addition, on two occasions during this year, doses of 50 mg. were given to assess the effect on urinary hydroxyproline excretion.

Methods

Before HGH therapy was started, as well as a full clinical assessment and repeated measurements of height, an intravenous insulin tolerance test, balance studies, and urinary hydroxyproline estimations were carried out. During treatment the patients attended regularly for clinical assessment, including measurement of standing height. Serum calcium, phosphorus, alkaline phosphatase, blood urea, and blood sugar determinations were performed at intervals. In Case 2 antibodies to HGH were looked for 6 months after starting treatment.

Serum Growth Hormone Levels.—These were estimated by the radio-immunoassay described by Hartog, Gaafar,

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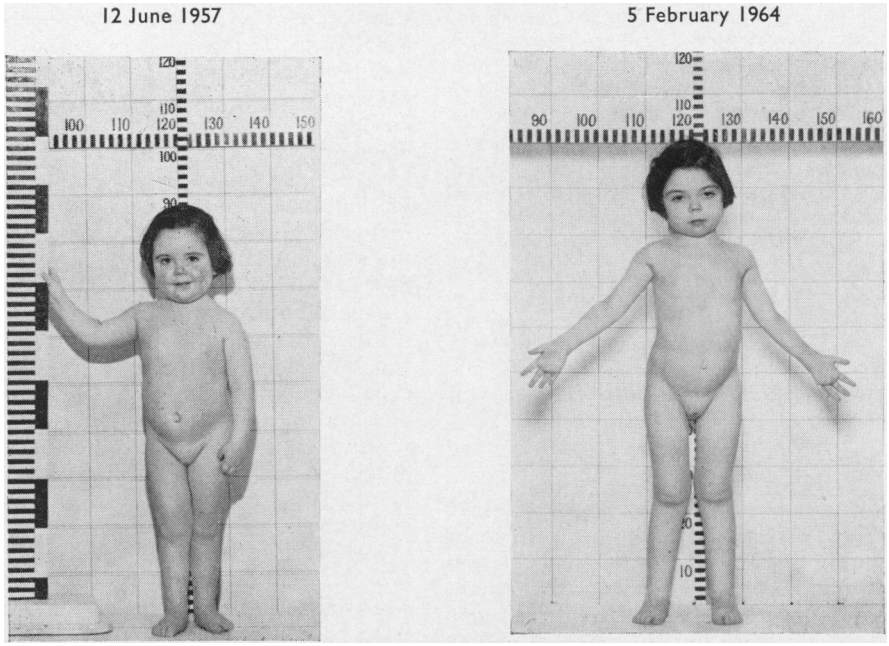

Fig. 1.—Case 1. Onset of Still's disease in 1956 at 18 months. Corticosteroid therapy started at age 2½ years in 1957.

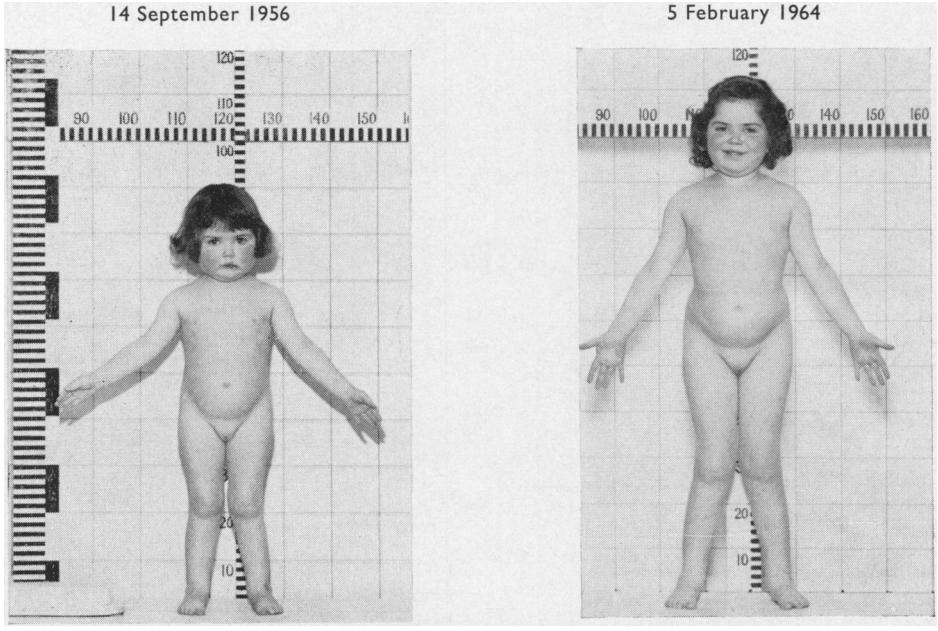

Fig. 2.—Case 2. Onset of Still's disease in 1956 at 18 months. Maintained on corticosteroid therapy from the onset because of severe iridocyclitis.

and Fraser (1964). After an overnight fast, having previously been on a normal ward diet for several days, both patients were given 0·2 units/kg. soluble insulin intravenously. Blood sugars and serum growth hormone levels were estimated on venous blood samples taken fasting and at 30, 60, 90, and 120 minutes after the insulin was given.

Balance Studies. Before beginning therapy, calcium and nitrogen balance studies were performed in February, 1964. During the balance period, both patients were given 10 mg. HGH intra-muscularly on 3 successive days.

Urinary Hydroxyproline Estimations.—These were performed frequently throughout the year on aliquots of 24-hr urine samples, by the method of Prockop and Udenfriend (1960) as modified by Jasin and others (1962). Extra estimations were performed in Case 2 after the 50-mg. injections of HGH. Before urine collections were made, the patients were on a gelatin-free diet for at least 48 hours.

Results

Both patients showed a satisfactory fall in blood sugar after intravenous insulin. In Case 1 the blood sugar fell from 60 to 35 mg./100 ml. and this was associated with a rise in the serum growth hormone level from 10 to 42 mμg./ml. In Case 2 the blood sugar fell from 45 to 20 mg./ml. and the serum growth hormone level rose from less than 4 to 23 mμg./ml. (Fig. 3). Case 2 had mild symptoms of hypoglycaemia.

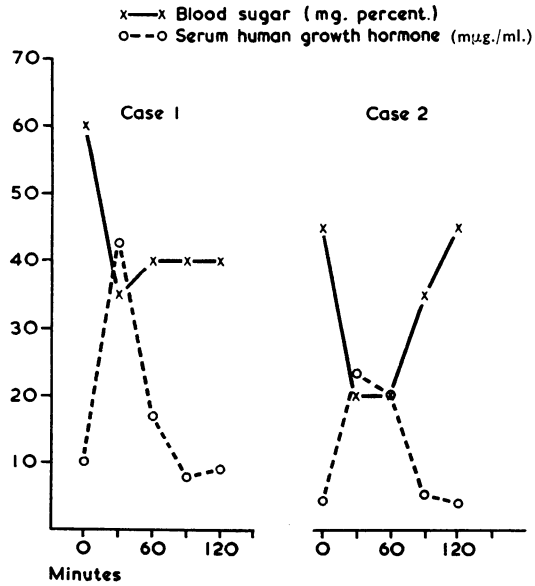

Fig. 3.—Fall in blood sugar level and rise in serum growth hormone level following intravenous insulin in Cases 1 and 2.

Balance studies demonstrated that 10 mg. HGH given on three successive days caused a reduction in urinary nitrogen excretion in both patients. In Case 1 the mean daily nitrogen excretion dropped from 260 to 180 mg./kg. during the days when HGH was being administered. This represents a mean daily nitrogen retention of 80 mg./kg., since faecal nitrogen is hardly affected. In Case 2 the corresponding figures were 216 and 171 mg./kg., representing a mean daily nitrogen retention of only 45 mg./kg. The fall in urinary nitrogen was associated with a slight fall in blood urea in both cases. Additional studies showed a slight rise in urinary calcium after HGH administration in Case 2 but not in Case 1.

Control urinary hydroxyproline values as delineated by Jasin and others (1962) range between 41·9 and 145 mg./m.² surface area per day for growing children and between 9·3 and 30·6 mg./m.² surface area per day for non-growing adults. The initial values of 24 to 28 mg./m.² and 22·5 to 29·5 mg./m.² in our patients were in the non-growing range. During HGH therapy the values for Case 1 were all above those found in non-growing adults, whereas those for Case 2 continued in the non-growing range (Fig. 4). To investigate this further, 50 mg. HGH was given to Case 2 on two occasions, but even with these high doses there was still no rise in urinary hydroxyproline levels. Antibodies to HGH were therefore looked for in Case 2 but were not demonstrated.

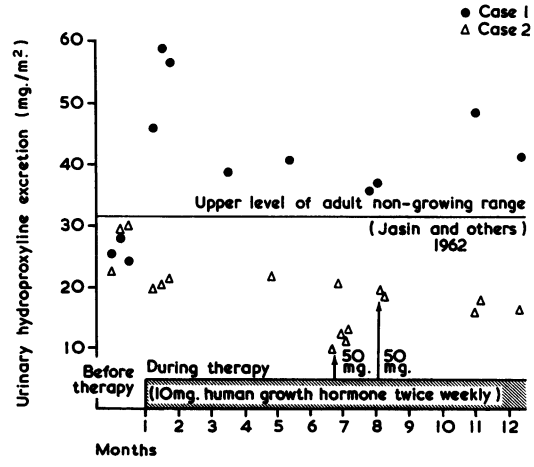

Fig. 4.—Urinary hydroxyproline excretion before and during HGH therapy. Case 1 showed a satisfactory rise in hydroxyproline excretion into the growing range and this child did grow. Case 2 showed no such rise even after 50 mg. HGH on two occasions and did not grow.

In response to HGH therapy, Case 1 showed an increase in rate of growth which paralleled the normal rate (Fig. 5) and this resulted in an increase of 6 cm. in height during the treatment year, compared with an expected increase of 5 cm. for children of the same age in the 10th percentile group. In Case 2 there

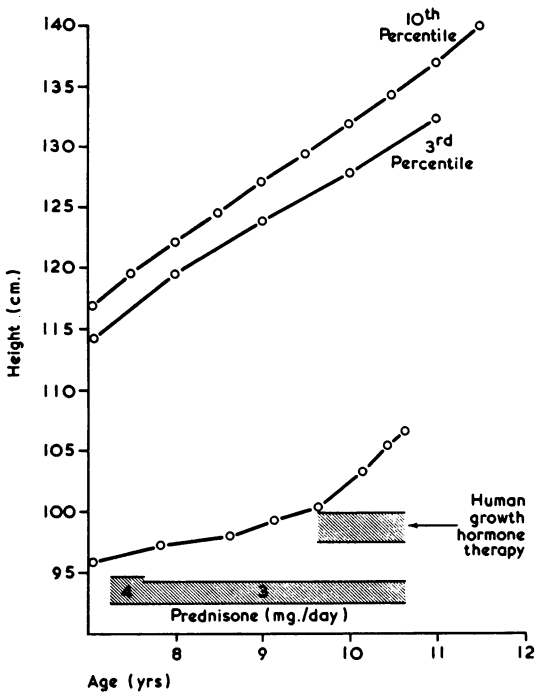

Fig. 5.—Effect of 12 months' treatment with HGH on standing height compared with normal growth in Case 1. (3rd and 10th Percentiles taken from Nelson's "Textbook of Paediatrics", 8th ed., 1964).

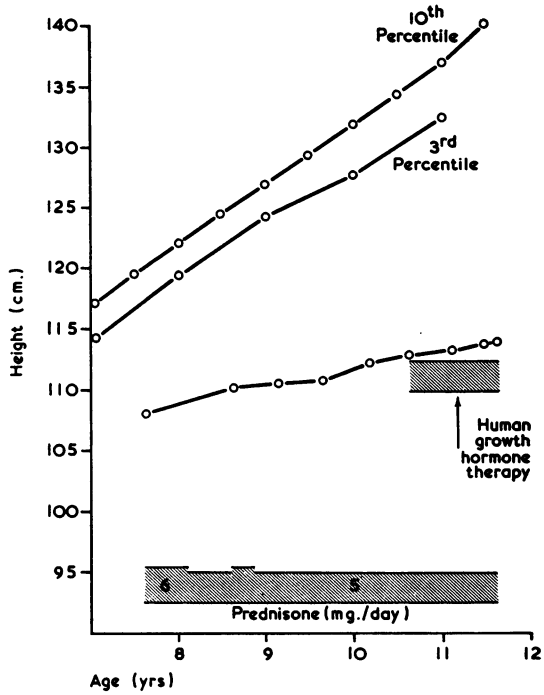

Fig. 6.—Effect of 12 months' treatment with HGH on standing height compared with normal growth in Case 2. (3rd and 10th Percentiles taken from Nelson's "Textbook of Paediatrics", 8th ed., 1964.)

was no noticeable increase in growth rate (Fig. 6), and height increased by only 1·6 cm. compared with an expected increase of 6 cm. for children of the same age in the 10th percentile group.

Estimations of serum calcium, phosphorus, and alkaline phosphatase, blood sugar, and blood urea were all within normal limits throughout the study.

Discussion

The mechanism whereby corticosteroids interfere with growth is not known; it may be the result of central or peripheral effects or a combination of the two. Frantz and Rabkin (1964) demonstrated the central effect of cortisone as shown by its ability to suppress the normal rise in the serum level of growth hormone secondary to insulin-induced hypoglycaemia. That peripheral antagonism between growth hormone and cortisone exists has been shown by Soyka and Crawford (1964) in both patients and laboratory animals.

In Case 1 the fasting level of HGH was 10 mμg./ml. while in Case 2 it was too low for accurate measurement. The method used for estimating HGH was not sensitive enough to measure either subnormal values or those at the lower level of normality (Hartog and others, 1964), but showed that both subjects were capable of secreting growth hormone in response to the stimulus of hypoglycaemia. This suggests a peripheral rather than a central antagonism to endogenous growth hormone in our two cases. In an attempt to overcome this antagonism, both patients were treated with exogenous HGH for 12 months. In Case 1 there followed an increase in the rate of growth equivalent to that for normal children of her age but this was not observed in Case 2. The possibility that circulating antibodies to HGH might be responsible for this failure to respond was considered, but no such antibodies were demonstrated. It seems therefore, that whereas HGH 10 mg. twice weekly is sufficient to overcome the effect on growth of 3 mg. prednisone daily, much larger quantities may be necessary to overcome even small increments in the dose of prednisone above this level.

Because of the scarcity of HGH it is important to try to find a reliable method of predicting its growth-promoting effect in any one individual without having to rely on clinical measurements made over a long period. Two possible ways of making such an assessment were considered: nitrogen balance studies and urinary hydroxyproline estimations.

(1) Exogenous HGH causes a greater degree of nitrogen retention in subjects deficient in growth hormone (*e.g.* hypopituitary dwarfs) than in those normal subjects (Prader, Illig, Szeky, and Wagner, 1964). These authors suggest that the effectiveness of long-term treatment with HGH can be assessed by estimating the degree of nitrogen retention following short-term administration. Case 1, despite some vomiting during the balance studies, showed a retention of nitrogen similar to that seen in hypopituitary dwarfs, whereas Case 2 had comparatively slight nitrogen retention. Thus, although neither of our cases behaved like hypopituitary dwarfs in their response to hypoglycaemia, the balance studies indicated that growth hormone might be effective in Case 1 but not in Case 2. This prediction proved accurate.

(2) In Case 1 the urinary hydroxyproline level increased within 5 days of therapy and there was a subsequent increase in growth rate. In Case 2 no change was observed and there was no subsequent increase in growth rate. This may thus be a useful tool in predicting the outcome of HGH therapy. If its value in this respect is confirmed by further studies now being undertaken, it will obviously be a more convenient method than admitting patients for balance studies.

That this relationship is worth exploring further is suggested by observations on thirteen other cases of Still's disease which showed a good correlation between growth, urinary hydroxyproline excretion, and the dose of prednisone (Fig. 7). There were, however, two exceptions in which poor growth was associated with high urinary hydroxyproline levels; these two patients differed from the others in that they had severe osteoporosis with collapse of several vertebrae. Further work is obviously necessary to determine the relationship between hydroxyproline excretion and growth in the presence of osteoporosis and microfractures.

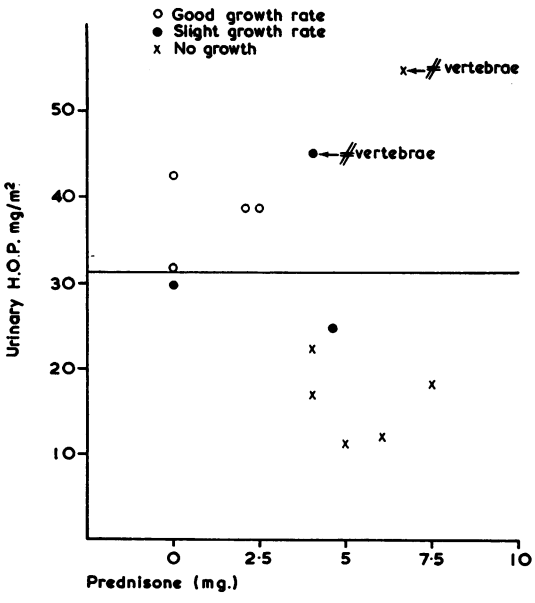

Fig. 7.—Urinary hydroxyproline levels in thirteen cases of Still's disease related to the dosage of prednisone and growth.

Summary

(1) Two patients with Still's disease maintained on small doses of prednisone who failed to grow in height were treated with human growth hormone (HGH) for 12 months.

(2) One patient, who was receiving 3 mg. prednisone daily, showed some increase in growth rate, but the other, receiving 5 mg. prednisone daily, showed none at all.

It is suggested that lack of response is due chiefly to a peripheral antagonism between corticosteroid and growth hormone: very large doses of HGH may be necessary to overcome a dose of prednisone as low as 5 mg. daily.

(3) In the absence of severe osteoporosis, there is a good relationship between growth rate and urinary hydroxyproline excretion, and this estimation promises to be of value in predicting the response of any given patient to HGH therapy.

This study was undertaken in conjunction with the M.R.C. trial on the value of human growth hormone therapy. We should like to thank Prof. Russell Frazer, Dr. Stuart Mason, and Dr. J. Tanner for allowing us to publish these results separately.

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Nanisme d'origine corticostéroïde dans la maladie de Still traité par l'hormone humaine de croissance. Effets cliniques et métaboliques, y compris l'excrétion de l'hydroxyproline en deux cas

RÉSUMÉ

(1) Deux patients atteints de maladie de Still, recevant de petities doses de maintien de prednisolone et souffrant d'arrêt de croissance, furent traités par l'hormone humaine de croissance (STH) pendant 12 mois.

(2) Le taux de croissance chez un malade, recevant 3 mg. de prednisolone par jour, augmenta un peu, mais l'autre malade, au régime de 5 mg. de prednisolone par jour, n'accusa aucune augmentation de taille.

On suggère que l'absence de résultat est due surtout à l'antagonisme périphérique entre le corticostéroïde et l'hormone de croissance; de très fortes doses de STH seraient nécessaires pour parer à l'effet d'une dose aussi faible que 5 mg. de prednisolone par jour.

(3) En l'absence d'ostéoporose sévère, il existe un bon rapport entre le taux de croissance et l'excrétion urinaire de l'hydroxyproline; la détermination de celle-ci peut aider à prédire la réponse du malade à la thérapie par la STH.

El enanismo corticosteroide en la enfermedad de Still tratado con la hormona humana de crecimiento. Efectos clínicos y metabólicos, incluyendo la excreción de hidroxiprolina en dos casos

SUMARIO

(1) Dos enfermos con la enfermedad de Still, mantenidos con pequeñas dosis de prednisolona y sufriendo de parada del crecimiento fueron tratados con la hormona humana de crecimiento (HHC) durante 12 meses.

(2) Un enfermo, recibiendo 3 mg. de prednisolona al día acusó un cierto aumento de la tasa de crecimiento, pero el otro, recibiendo 5 mg. de prednisolona al día, faltó a crecer.

Se sugiere que la ausencia del resultado deseado se debe principalmente al antagonismo periférico entre el corticosteroide y la hormona de crecimiento; se pueden necesitar muy fuertes dosis de HHC para reprimir el efecto de una dosis diaria tan pequeña como 5 mg. de prednisolona.

(3) En la ausencia de osteoporosis grave, existe una buena relación entre la tasa de crecimiento y la excreción urinaria de hidroxiprolina; la determinación de esta puede ayudar en la predicción de la respuesta del enfermo a la terapia con la HHC.