Effect of Administered Human Growth Hormone on Growth Retardation in Inflammatory Bowel Disease

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In a previous study of 22 severely growth-retarded children with inflammatory bowel disease (IBD), endocrinologic evaluation revealed hypogonadism and low growth hormone (HGH) levels. This was attributed to a secondary hypopituitarism. In order to assess this hypothesis, two individuals from this group and another similar child who was not so severely growth-retarded as to be included in the initial study were given HGH replacement in an acute trial and for a 6-month interval. No significant height increment could be attributed to the HGH administration, although a definite anabolic response was present in each patient during the acute trial. It appears that the youngsters with IBD may have a relative end-organ resistance to the metabolic and growth-promoting effects of HGH and that their growth problems are not related to hypopituitarism.

Growth retardation secondary to hypopituitarism responds to long-term human growth hormone (HGH) replacement, whereas in so-called idiopathic growth retardation the response has generally been disappointing in terms of linear height acceleration (1–6). Nevertheless, under the conditions of an acute metabolic trial, there is an anabolic response to HGH in patients with retarded growth attributed to either of these entities (7–9)

In a previous study of 22 severly growth-retarded children with inflammatory bowel disease (IBD), depressed growth hormone responsiveness to insulin-induced hyploglycemia was identified in 11 of 13 children tested and was associated with decreased urinary bioassayable gonadotropin in five patients above age 16 judged clinically to be hypogonadal. The growth problem was suspected to be secondary to partial hypopituitarism (10). In order to assess the effectiveness of HGH replacement in these youngsters, three individuals with quiescent IBD underwent both a metabolic balance study to assess the anabolic effectiveness of HGH and a 6-month trial of HGH therapy to assess the long-term effectiveness of HGH upon growth.

PATIENTS AND METHODS

Three IBD subjects with deficient plasma growth hormone response to insulin-induced hypoglycemia and growth retardation were ad-

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mitted to this study. Two subjects (W.S. and D.R.) had been included in the initial evaluation (10); the third (C.M.) had growth retardation not so severe (below the 5th percentile) as to be included in the initial study. All three individuals were judged clinically well without evidence of active IBD for at least 6 months before and during the course of this investigation. Two individuals (D.R., C.M.) had never received adrenal steroids. The third (W.S.) discontinued steroid therapy at least 6 months prior to study. The subjects were admitted to the University of Chicago Clinical Research Center and placed on a constant-weight-maintenance diet of their choice. Anthropomorphic data (height, weight, trunk:limb ratio) were obtained on admission and on alternate days throughout the hospitalization (11). Skeletal age was determined on admission. Hemoglobin, hematocrit, and leukocyte counts were collected on a weekly basis. Daily blood studies included serum calcium, sodium, potassium, chloride, urea nitrogen, glucose, and alkaline phosphatase. Twenty-four-hour urines were collected for urinary nitrogen determinations. Plasma immunoassayable growth hormone in response to insulin-induced hypoglycemia and to arginine infusion were performed on admission to verify the depressed growth hormone responsiveness (12–14). A modification of Catt's solid phase method was used to measure serum HGH (15). An aliquot of blood was collected before and after the acute trial of HGH and at monthly intervals during the long-term administration of hormone for the detection of HGH antibodies. After establishing a base-line nitrogen balance, an acute trial of 10 mg HGH daily was instituted for 5 days.

Long-term HGH replacement was continued at a dosage of 3 mg three times a week for 6 months. Monthly follow-up was obtained in the outpatient department where anthropomorphic data and blood samples were gathered for continued assessment. The criteria for growth response to the long-term administration of HGH were those of Soyka et al (16).

CASE REPORTS

W.S.,* U.C. 88-47-12. This youngster (age 16) was in excellent health and known to have been of average height and weight until the fall of 1963, when growth appeared to stop with the onset of frequent semisolid, nonbloody, loose stools. He was treated initially with various symptomatic measures unsuccessfully and was hospitalized in February 1964. A diagnostic and therapeutic stay was not illustrative of a diagnosis. His symptoms continued. In January 1965 recurrent perianal abscesses appeared, and he was referred to the University of Chicago for evaluation. His physical examination revealed a markedly undernourished, thin, pallid youngster appearing quite younger than his stated age. Positive findings consisted of a soft, nontender abdomen without any palpable organs and with slightly increased bowel sounds, absent secondary sex characteristics, and height below the 3rd percentile. Barium x-ray evaluation revealed ulcerations in the ascending colon and cecum. Proctoscopic examination exhibited some minimal friability at 13–16 cm. A diagnosis of granulomatous colitis was made and Lomotil, Furoxone, and phenobarbital were instituted. During the subsequent hospital course, he developed fever and abdominal pain interpreted as evidence of severely active IBD, and prednisone was prescribed. Defervescence occurred along with improvement in appetite and general well-being. He was discharged on gradually tapering doses of prednisone and did quite well, even after discontinuing the prednisone in April 1966. However, in August 1966, an insidious weight loss and anemia developed, and in the ensuing months, became associated with abdominal pain and diarrhea 1 month prior to admission in March 1967. He still exhibited a prepubescent physical appearance along with a severely depressed bone age. X-ray evaluation was essentially unchanged. Prednisone was reinstituted. During the course of hospitalization, localized RLQ pain with dysuria developed. Because of suspected appendicitis and abscess formation, an exploratory laparotomy was performed and revealed Crohn's disease of the cecum and ascending colon and a gangrenous appendicitis. An ileosigmoidostomy was performed, and the patient did well with discontinuation of all drugs in May 1968. In the later weeks of February 1970 he exhibited weight loss, morning diarrhea, nocturnal spiking temperatures, and mild anemia. Except for retarded growth and sexual immaturity, physical examination was unremarkable. Because of the historical precedent set by the indolent nature of active Crohn's disease in this youngster, prednisone was begun in March 1970, with complete reversal of his symptoms. However, in April he complained of low back pain and dysuria. Pyuria without protein was present. An impending fistula and/or abscess adjacent to the ureter and bladder was suspected and he was readmitted to the hospital. Surgical removal of an abscess in

*Growth and endocrinologic data previously reported (10).

the right pelvis involving the right ureter was performed. Subsequently, he did well on tapering doses of hydrocortisone. All steroids were discontinued 6 months before initiating the HGH study, and in that interval, he remained well without evidence of active bowel disease. For 3 years prior to resection of the diseased bowel in 1967, this patient had grown less than 2.5 cm yearly. In the year following resection, he grew almost 8 cm. This growth rate tapered to 3 cm in the 6 months prior to the HGH trial.

C.M., U.C. 94-17-18. This young man (age 16) was in good health until mid-1963, when he developed intermittent episodes of periumbilical cramping, abdominal pain, and nonbloody diarrhea. This persisted until December 1966, when fever and a right lower quadrant mass was associated with his previously described symptom complex. A small-bowel x-ray evaluation revealed regional enteritis, and he was referred to the University of Chicago for continued follow-up. Physical examination revealed a prepubescent youngster with absent secondary sex characteristics and appearing younger than his stated age. His height was below the 5th percentile. Bone age was 13 for a chronological age of 16. Prior to HGH therapy, his growth rate for 6 months was 3.5 cm. The sella turcica was normal in size. Thyroid studies (PBI, T_3) were normal. Urinary gonadotropins and steroids (17-hydroxy- and 17-ketosteroids) were not measured. A nontender mass was palpable in the RLQ. Subsequent follow-up examination exhibited no change in the characteristics of the mass. However, radiological evaluation revealed fistula formation within the mass. Because of these findings and family concern for the lesion, he underwent resection of the mass, the involved terminal ileum, and the right colon in August 1968. The pathological interpretation was Crohn's disease localized to the resected area. Subsequently he has been asymptomatic. Steroids had never been used in his treatment program.

D.R.,* U.C. 97-00-51. This young man (age 20) had exhibited depressed growth rate and short stature (height < 10th percentile) from age 2 years but was in good health until the onset of lower abdominal pain, weight loss, and fever in January 1967, when he was 16 years old. Proctoscopic examination by his family physician revealed a picture consistent with ulcerative proctitis. He was referred to the University of Chicago for follow-up. During the subsequent year his symptoms continued intermittently. In January 1968, because of marginal response to drug therapy, he was hospitalized. Physical examination revealed a very young-appearing 20-year-old with no evidence of developing secondary sex characteristics. His height was below the 3rd percentile. Few epiphyses were still open and bone age was estimated at 18–20 years. No additional positive findings were notable. X-ray examination revealed regional enteritis involving the terminal ileum. Proctoscopic evaluation was normal.

*Growth and endocrinologic data previously reported (10).

An inpatient medical regimen was unsuccessful in achieving a symptomatic remission. Because of the localized area of disease, resection of the terminal ileum was performed. Crohn's disease was the pathological diagnosis. He has done well since then but advanced little in linear height. He has never been treated with steroids.

RESULTS

In two patients, C.M. and D.R., growth hormone response to insulin-induced hypoglycemia or to a 30-g arginine infusion was below the lower range obtained in 10 healthy young adult males between the ages of 16 and 22 years (Figure 1). The third patient, W.S., was nearly normal in his response to these stimuli.

A definite anabolic response to five daily injections of 10 mg HGH was seen in each patient. However, this was meager compared to that obtained in a 20-year-old normal volunteer, i.e., 6.1 g nitrogen retention contrasted to a maximum of 1.9–2.1 g in the three patients (Figure 2). These patients with growth retardation and IBD clearly did not resemble patients with true hypopituitarism, where an exaggerated anabolic response to administered HGH is seen (7).

The chronic parenteral administration of 3 mg HGH three times weekly for 6 months to these patients with IBD yielded varying results. At the termination of the 6-month treatment period, W.S. and C.M. had increased their height a total of 4.5 and 4.7 cm, respectively. D.R. essentially exhibited no growth at all, 0.2 cm for the 6 months, undoubtedly related to the absence of little if any growth potential at the outset of therapy. In true hypopituitary individuals with open epiphyses, growth approximating 11 cm/year for the initial 6 months of therapy has been reported (2, 6, 16). Such a growth acceleration, however, may represent "catch-up growth," since following this initial spurt, growth rate in such individuals gradually normalizes (2, 6).

No other anthropomorphic changes were noted nor did antibodies to HGH develop in these patients with IBD.

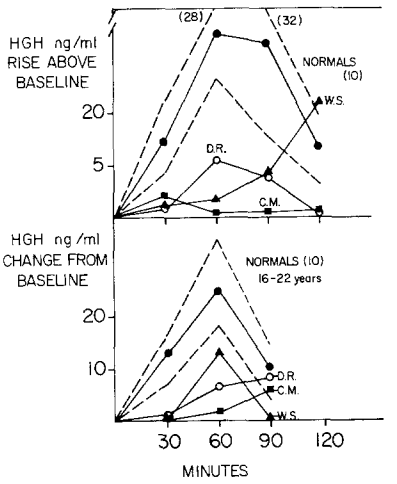

Fig 1. Human growth-hormone (HGH) response to arginine (30 g i.v. for 30 min; **top**) and to insulin-induced hypoglycemia (0.1 units/kg; **bottom**).

DISCUSSION

Although HGH administration in a metabolic balance study exerted some anabolic effect on three growth-retarded patients with quiescent IBD not requiring glucocorticoid therapy, the amount of nitrogen retention recorded was less than 40% of that observed in a normal volunteer of similar age. Clearly, the positive retention manifested in these three patients contrasts to the exaggerated response seen in true hypopituitary individuals given HGH (7). The response of these patients, however, was not entirely unlike that reported in some children with presumptive idiopathic dwarfism (7–9).

Since the anabolic outcome of an acute HGH study has not been of invariable predictive value regarding growth during long-term therapy (17), such a therapeutic trial was undertaken in these three patients with IBD. One patient (D.R.) did not grow at all. Although his bone age was only 18 years at the onset of HGH therapy, most epiphyseal closures were present, undoubtedly contributing to the apparent lack of responsiveness to administered HGH.

Although a height increment was recorded in two patients (W.S., C.M.), 4.5 and 4.7 cm in 6 months, respectively, this was not judged to represent true percentile growth advancement. Growth responsiveness to administered HGH generally is characterized by a twofold increase in growth rate or by a yearly advancement in excess of 2.5 cm over that predicted from a pretreatment observed rate of growth (16). At 16 years, C.M. had a bone age of less than 13 years and had grown 3–3.5 cm for two 6-month periods prior to HGH therapy. During the 6-month administration of HGH, only a 4.5 cm increase in height was observed. W.S., also 16 years and with a similar bone age, had manifested a significant growth spurt (8 cm) during the year prior to HGH therapy. This growth spurt followed resection of diseased intestine and contrasted to a yearly growth of less than 2.5 cm for more than 3 years before surgery. While on HGH, he grew 4.7 cm in 6 months. Whether such growth is attributable entirely to the administration of HGH or merely to the recovery of his growth rate following surgery could not be determined from this study.

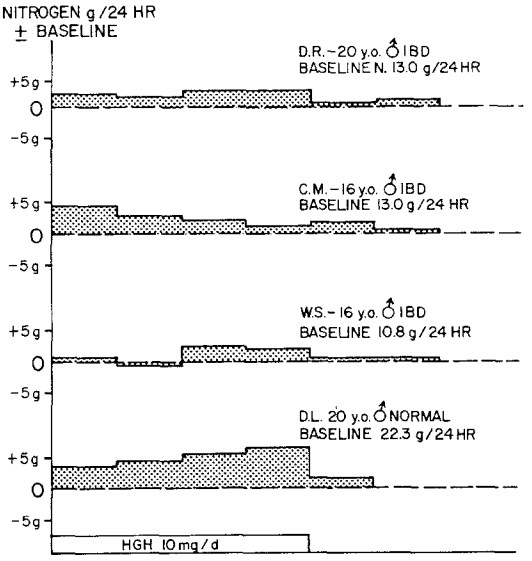

Fig 2. Nitrogen balance studies during the acute trial of HGH replacement.

Thus, one patient with almost no remaining growth potential did not grow at all and the two remaining patients did not adequately exceed their previous 6–12 month predicted growth rate. In patient W.S., who demonstrated a year of accelerated growth following intestinal resection, it may be *apropos* to state that the full effect of HGH on catch-up growth may have been lost. Nevertheless, it is pertinent to emphasize that even here, HGH-associated growth was not of a sufficient degree to advance percentile growth during the 6-month trial. Patient C.M., with a bone age of 13, clearly did not exhibit any height increment characteristic of growth-hormone-induced growth in hypopituitary individuals (2–6, 16–17).

In the six months following cessation of HGH therapy in C.M. and W.S., growth has continued at a rate nearly identical to that observed during therapy, further emphasizing the apparent lack of growth response to administered HGH. Hypopituitary dwarfs treated with HGH demonstrate a dramatic drop-off in growth rate coinciding with cessation of hormonal therapy (2, 6, 16).

In considering growth responsiveness to HGH, it can always be argued that the "long-termness" of this study may not have been of sufficient duration. Nevertheless, even though most reported series of long-term HGH replacement in hypopituitary children describe a treatment period of 1–2 years or longer, these series also emphasize that a responsive patient will manifest a growth characterized by height increments averaging 6–9 cm and percentile growth advancement within 3–6 months (2–6).

A cause-and-effect relationship for growth is often very difficult to ascertain. Normal growth has been described in individuals with absent or subnormal growth-hormone levels in the serum, indicating that the *sine qua non* for growth is not necessarily growth hormone alone (18–20). Even though depressed GH may be present in individuals with IBD, replacement does not appear to be the answer to their growth retardation. Active IBD, as reported previously, malnutrition, and the continuous employment of steroid therapy do obviously contribute to a continued plateauing of growth (10). However, only one individual (W.S.) underwent an exacerbation of his IBD, requiring steroid therapy for control, but this occurred only during the latter weeks of the investigation. Hence, it seems that the problem of growth is much more complex than secondary hypopituitarism postulated originally in these individuals with IBD.

Somatomedin (sulfation factor) has been postulated as the growth factor to explain normal growth rate and height in subjects with depressed or absent GH (21). Whether depressed concentrations of this second growth factor contribute to the growth retardation in the children with IBD is only speculative.

From these preliminary studies, it must be concluded that in individuals with IBD there appears to be relative end-organ resistance to the metabolic and growth-promoting effects of HGH. This phenomenon coupled to a suboptimal synthetic and secretory responsiveness of pituitary somatotrophs must be considered as significantly contributing to retarded growth in these children. Whether associated conditions such as trace metal, zinc, calcium, magnesium, or protein deficiency could be primarily responsible for the poor response to administered HGH or could account for poor release of endogenous hormone remains to be more thoroughly investigated.

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