Metabolism
Clinical and Experimental

VOL 46, NO 8 AUGUST 1997

Response to Nutritional and Growth Hormone Treatment in Progeria

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Hutchinson-Gilford progeria syndrome (HGPS) is a rare condition with an unknown molecular defect. Patients with HGP progressively develop failure to thrive (FTT), alopecia, loss of subcutaneous fat, scleroderma, stiffening of various joints, and severe atherosclerosis. The median life span is 13 years, and the main cause of death is cardiovascular complications. There are few reports of endocrine and metabolic studies because of the rarity of this condition, and the response to long-term growth hormone (GH) treatment has not been described. We report the results of endocrine and metabolic studies performed to investigate the etiology of growth failure in five patients with HGP. Additionally, the response to nutritional therapy (NT) and GH treatment in three of these patients is presented. Our results suggest that elevated GH levels are characteristic of this disease and that an elevated basal metabolic rate (BMR) could be the cause of the FTT seen in HGP. Nonaggressive NT slightly improved weight gain and growth velocity (GV). Combined NT and GH treatment in three patients improved the GV, increased the levels of growth factors, and paradoxically resulted in decreased BMRs. However, the response to these therapies decreased over time and did not seem to prevent the progression of atherosclerotic disease.

HUTCHINSON-GILFORD PROGERIA syndrome (HGPS) is a rare condition with a reported incidence of 1 in 8 million births.[1,2] The diagnosis is based on clinical features, which become typical by 2 to 4 years of age. They include failure to thrive (FTT), alopecia, loss of subcutaneous fat, scleroderma, stiffening of various joints, atherosclerosis, characteristic facies, and normal intelligence.[1-3] The median life span is 13 years, and death is mostly due to cardiovascular complications.[4-6]

There is no biochemical test to diagnose HGPS. These patients may excrete increased amounts of hyaluronic acid,[7] but the underlying molecular defect is unknown. The inheritance pattern argues that it is due to an isolated sporadic dominant mutation, although a few cases may be due to a germ line mutation.[2,8] Endocrine and metabolic studies have been reported for individual patients.[9-15] However, it is uncertain whether abnormal findings such as insulin resistance[11] or an increased basal metabolic rate (BMR)[15] occur in all individuals with HGPS. We report the results of endocrine and metabolic studies performed to investigate the etiology of growth failure in five patients with HGP. Additionally, the response to nutritional therapy (NT) and growth hormone (GH) treatment in three of these patients is presented.

Our results suggest that elevated GH levels are characteristic of this disease and that an elevated BMR could contribute to the FTT seen in HGPS. NT resulted in a slight increase in weight gain and growth velocity (GV). Combined NT and GH treatment improved growth, increased the levels of growth factors, and paradoxically resulted in a decreased BMR. The response to these therapies decreased over time and did not seem to prevent the progression of atherosclerotic disease. Additionally, resistance to insulin and other hormones seems to develop in older patients with HGPS.

SUBJECTS AND METHODS

Patients

Five patients with HGPS were studied over a 2-year period. The diagnosis was confirmed by W.T. Brown, Director of the International Progeria Registry.[2] In all cases, the family history was negative for birth defects or consanguinity. The patients' clinical information at the time of our initial evaluation is presented in Table 1. Patient no. 3 was the subject of a previous report dealing with dental problems.[16] The studies were approved by the Hospital's Institutional Review Board. An informed-consent form was signed by the parents and/or patients according to their age.

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Submitted July 27, 1995; accepted January 28, 1997.

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Supported in part by a grant from the Bedminister Foundation and the Maimonides Research and Development Foundation.

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0026-0495/97/4608-0001$03.00/0

Table 1. Clinical Characteristics of the Patients

Characteristic	Patient No. 1	2	3	4	5
Sex	Male	Female	Male	Female	Male
Ethnicity	White	White	Black	White	White
Birth weight (kg)/percentile	3.24/50	2.75/25	2.55/90	3.02/25-50	2.75/50-75
Birth length (cm)/percentile	50.5/75	49.5/50	NA	53/90	50/75-90
Gestational age	Term	Term	33 wk	Term	36 wk
Mother's age at birth (yr)	29	21	24	30	25
Father's age at birth (yr)	30	25	23	31	30
Age at diagnosis (yr)	3.6	2.8	2	1.2	1
Clinical presentation					
Age (yr, initial evaluation)	4.2	5.8	13.5	8.3	6.9
History of diarrhea	No	No	Yes	No	Yes
Alopecia	Partial	Total	Total	Almost total	Almost total
Decreased subcutaneous tissue	Mild	Moderate	Severe	Moderate	Mild
Xanthomas	No	Yes	No	No	No
Hip dislocation	No	No	Yes/bilateral	No	No
Joint contractures	Severe	Severe	Mild	Mild	Mild
Pectus excavatum	Mild	Mild	No	No	Mild
Cardiac abnormalities	No	Mitral Regurgitation	Angina	No	No
Headaches	No	Yes	Yes	Yes	Yes
Strokes/age at 1st episode	No	Yes/5.6 yr	No	Yes/8.2 yr	No

Abbreviation: NA, not available.

*All patients had a high forehead, prominent veins, micrognathia, scleroderma, and FTT. Other findings, which varied from patient to patient, are listed.

Initial Evaluation

All five patients underwent a physical examination, anthropometry, determination of BMR, biochemical nutritional evaluation, and endocrine testing (described later), which included measurement of spontaneous GH secretion, the GH response to GH-releasing hormone (GHRH), and the endocrine response to a combined hormonal stimulation test.

NT

After the initial evaluation, patients no. 2, 3, and 5 were placed on NT for periods of 4 to 10 months. NT was aimed to achieve the maximum tolerated caloric intake without using tube feedings. The caloric composition of the diet was maintained at 50% to 60% for carbohydrate, 25% to 30% for fat, and 15% to 20% for protein. Different high-calorie supplements were used according to tolerance. Nutrient intake was assessed through 24-hour dietary recalls obtained by a nutritionist on semistructured interviews using food models and measuring devices as a guide. The diet was analyzed with a nutrient analysis system (NutriQuest II; Capital Systems, Kensington, MD).

Nutritional and GH Therapy

Patient no. 1 was readmitted a few weeks after the initial evaluation. Patients no. 2, 3, and 5 were readmitted after NT. All of them underwent an intravenous (IV) glucose tolerance test (IVGTT) followed by an insulin-like growth factor-I (IGF-I) generation test. After that, patients no. 1, 2, 3, and 5 were discharged on NT and GH treatment with recombinant human GH at a dose of 0.06 mg/kg three times per week (0.18 mg/kg/wk). Patients no. 1, 2, and 5 were evaluated for 6 to 18 months and readmitted every 3 to 6 months. Patient no. 3 could not be reevaluated, and GH treatment was discontinued after 4 months. Patient no. 4 underwent only the initial evaluation.

Tests

For spontaneous GH secretion, blood was obtained through a heparin lock every 20 minutes for 12 hours starting at 8:00 PM. The combined hormonal stimulation test was performed at 9:00 AM as previously described.[17] For the GHRH stimulation test, after a 12-hour fast, 1 μg/kg (1-44) hpGHRH-NH_2 (Peninsula Laboratories, Belmont, CA) was infused IV over 90 seconds. Blood for GH assay was obtained at 0, 15, 30, 45, 60, 90, and 120 minutes. The IVGTT was performed at 9:00 AM after an overnight fast. Glucose was administered at 0.5 g/kg IV over 3 minutes. Blood for glucose and insulin assay was obtained at −10, 0, 1, 3, 5, 7, 10, 15, 20, 30, 45, 60, and 90 minutes. For the IGF-I generation test, IGF-I and IGF binding protein-3 (IGFBP-3) were determined at 9:00 AM before and after 4 consecutive days of rhGH (0.06 mg/kg per dose) administered at 7:00 PM.

Other Evaluations

Height was measured with a Harpenden stadiometer (Holtain Limited, Crymych, UK). GV was assessed using the standards of Tanner and Davies.[18] Weight Z-score (WZS), height Z-score (HZS), weight for height adequacy (W/H), and W/H Z-score (W/HZS) were calculated using a computer program.[19] Pubertal status was evaluated by the method of Tanner,[20] and bone age according to the TW2 method using carpal bones.[21] All GH samples were assayed by a polyclonal radioimmunoassay (RIA) kit (Kallestad Diagnostics, Chaska, MN) with a minimum detectable value of 1.5 μg/L (values < 1.5 μg/L were considered as 1.5). Characteristics of the spontaneous GH secretion were evaluated as previously described.[22] Normal values for all endocrine tests were obtained from children with familial short stature studied by our group with the same methodology.[23] IGF-I level was measured with a kit from the Nichols Institute. IGF-II and IGFPB-3 levels were measured by RIA at Endocrine Sciences (Calabasas Hills, CA). Procollagen III was assessed by RIA kits (Behring, Marburg, Germany). Insulin level was measured with kits from Binax (South

Portland, ME). Insulin response during the IVGTT was evaluated by the sum of the values at 1 and 3 minutes and compared with published percentiles.[24] The glucose utilization rate (Kt) was calculated as previously described.[17] BMR measurements were conducted after an overnight fast, with the patient supine and awake and resting in a dark, quiet room. A face mask was used in all children. The child was allowed to become comfortable with the system until a stable baseline could be obtained. At that point, test recordings were started. Oxygen consumption and CO_2 production rates were obtained from two 15-minute gas-exchange recordings. Discomfort or physical activity led to discontinuation of the test. Oxygen consumption, carbon dioxide production, and the respiratory quotient were measured with an open-circuit indirect calorimeter (Sensormedics, Anaheim, CA). Standard computer programs were used to calculate energy expenditure (expressed as calories per kilogram body weight per day) using the equations of Conzolazio et al[25] and Weir.[26] BMR was predicted using Food and Agriculture Organization of the United Nations/World Health Organization. equations (Geneva, Switzerland, 1985), and the results were expressed as percentage measured/predicted. BMR studies performed with the same methodology in 21 age-matched children with familial short stature (mean age, 10.3 ± 0.9 years; range, 3 to 14) were normal (100.4% ± 0.04%).[27] Total urinary nitrogen, used to calculate the nonprotein respiratory quotient (NPRQ), was analyzed with the micro-Nessler technique. Protein oxidation was estimated from total nitrogen, and carbohydrate and fat utilization were calculated by the NPRQ.[28] Erythrocyte Na^+K^+ATPase activity was measured as previously described.[29] Measurements of the right midarm circumference and triceps skinfold were performed using a Lange caliper (Cambridge Scientific Industries, Cambridge, MD). Arm muscle and fat areas were calculated as previously described.[30]

RESULTS

Initial Evaluation

Results of the initial evaluation are summarized in Table 2. All patients showed anthropometric indices suggestive of malnutrition: decreased WZS, W/H adequacy, W/HZS, and overall low skinfold thickness. However, caloric intake was normal for age and sex. The BMR was markedly elevated, ranging from 182% to 215% of normal for age and sex (Fig 1). BMRs were also elevated when compared with normals for weight or height (data not shown). Evaluation of the NPRQ showed that patients no. 3 and 4 had high fat use and patient no. 2 a high protein use. Levels of triiodothyronin (T_3), reverse T_3, thyroxine (T_4), free T_4, and thyrotropin (TSH) were normal and the TSH response to TSH-releasing hormone was borderline high in all patients. Erythrocyte Na^+K^+ATPase activity, measured in patients no. 1, 2, and 3, was normal. Retinol-binding protein and prealbumin levels overall were low, whereas albumin, magnesium, zinc, vitamin E, cholesterol, triglycerides, free fatty acids, β-OH-butyrate, and amino acids were normal (data not shown).

The five patients demonstrated severe growth retardation (Table 2), with a HZS of −4.92 to −6.50 and abnormal GV. However, high GH levels were obtained in the spontaneous and/or stimulated GH secretion tests. Levels of IGF-II and IGFBP-3 were low or borderline low in patients no. 1 and 2. Bone age was normal in all but patient no. 1, whose bone age at 4.2 years was 2.7 years. Cortisol, prolactin, luteinizing hormone (LH), and follicle-stimulating hormone levels were measured in the combined hormonal stimulation test and were normal, except for patient no. 3 with high LH and prolactin responses (120 MIU/mL and 63.5 μg/L, respectively). His total testosterone level was 173 ng/dL.

Response to Nutritional Treatment

Patients no. 2, 3, and 5 underwent NT. During treatment, their caloric intake increased 23% to 38% above basal. However, weight gain was poor and growth rate improved only slightly, remaining at less than the normal limits for age. There were no significant changes in the levels of growth factors. BMR remained markedly elevated. Retinol-binding protein and preal-

Table 2. Results of the Initial Evaluation

Parameter	Patient No. 1	2	3	4	5
Age (yr)	4.2	5.8	13.5	8.3	6.9
WZS	−4.05	−5.45	−4.36	−4.11	−4.42
W/H adequacy	78.8	64.4	73.8	71.6	78
W/HZS	−2.34	−3.83	NA	−3.23	−2.52
Arm muscle area (mm^2)	1,036*	770*	1,755*	1,015*	1,152*
Arm fat area (mm^2)	318*	163*	170*	187*	328*
Caloric intake (cal/kg/d)	108	99	87	83	144
BMR (% of normal)	195	182	214	215	NA
Substrate use, CHO/protein/fat (% of total calories)	47/10/43	52/18/30	17/10/73	26/10/64	NA
HZS	−4.92	−6.5	−5.37	−4.93	−5.28
GV (cm/yr)	2*	2.8*	3.3*	3.8*	3.3*
Mean spontaneous GH secretion (μg/L)	8.3†	6.9†	11†	8.9†	4.3
Peak [GH] combined hormonal stimulation (μg/L)	38.6†	8.4	26.6†	14.2	20.1†
Peak [GH] GHRH (μg/L)	92.2†	24.1†	3.9	9.7	82.8†
IGF-I	50	59	545	230	118
IGF-II	312*	317*	381	504	433
IGFBP-3	1.2*	1.6	3.8	3	2.3

*Below normal for age/sex.
†Above normal for age/sex.

bumin increased to normal limits, and serum levels of albumin, Mg, Zn, vitamin E, and amino acids did not change significantly.

Response to the IGF-I Generation Test

Response was positive in the four patients studied (no. 1, 2, 3, and 5), with increase in IGF-I and IGFBP-3 levels from 242% to 600% and 122% to 200%, respectively.

Response to NT and GH Therapy

Patients no. 1, 2, and 5 underwent this combined treatment for 18, 6, and 12 months, respectively. Patient no. 1 was able to maintain a caloric intake of 17% above the baseline during the first 6 months, when he had a stroke. After that, his caloric intake could not be sustained and decreased to a mean of 90 cal/kg/d. Patients no. 2 and 5 were able to maintain a mean caloric intake of 24% and 20% above the baseline, respectively, throughout GH treatment. Weight gain in the three patients was poor. GV increased to 5.0, 7.0, and 4.5 cm/yr, respectively. However, the effect on GV was more pronounced in the first 4 months. Levels of IGF-I, IGF-II, and IGFBP-3 increased, and there was also an increase in procollagen and hydroxyproline levels compared with pretreatment values (data not shown). Patients no. 1 and 2 showed a marked decrease in BMR, which was sustained throughout the treatment (Fig 1). Both patients also showed an increase in the use of protein, reaching 15.7% and 25.9%, respectively. T_3 levels increased in the three patients, whereas T_4, free T_4, and erythrocyte Na^+K^+ATPase activity remained within normal levels.

Carbohydrate Metabolism

Results are summarized in Table 3. Before GH treatment, patients had normal serum levels of hemoglobin A_{1C} (HbA_{1C}) and glucose. Islet cell antibodies and insulin autoantibodies were not detected. Insulin levels were normal in all but patient no. 3, who had extremely high levels during both fasting and the IVGTT. During GH therapy, patients no. 2 and 5 maintained normal glucose and HbA_{1C} with increased insulin levels. In patient no. 1, HbA_{1C} increased to slightly above the upper normal limits while fasting glucose and insulin levels remained within normal limits. However, results of the IVGTT showed a borderline low insulin response and glucose Kt.

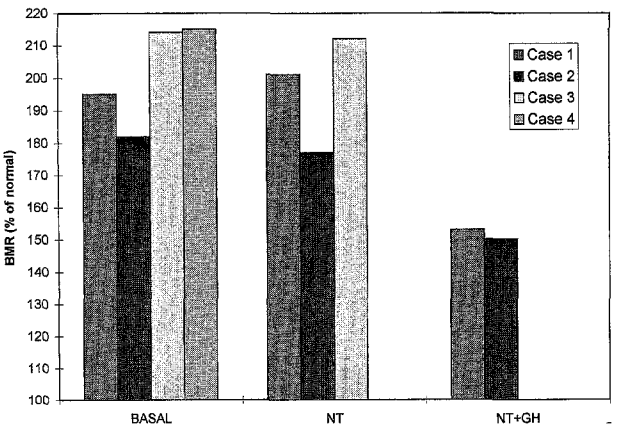

Fig 1. BMR response to treatment.

Long-Term Follow-up

Patient no. 1 died at the age of 7.5 years of a new stroke. Patients no. 2, 3, and 4 died of myocardial infarction at ages 6.9, 14.5, and 9.3 years, respectively. Autopsy was not performed in any of the patients. Patient no. 5 is in good clinical condition without signs of cardiovascular disease at age 11 years.

DISCUSSION

This study reports the clinical, nutritional, and endocrine characteristics of five patients with HGPS and the response in three of them to NT and GH therapy.

All of the patients had markedly decreased WZS, W/H adequacy, W/HZS, and skinfold thickness, a pattern resembling that of severe malnutrition. However, none of them had clinical or biochemical features suggestive of chronic protein deficiency (kwashiorkor)[31] or the intellectual deficits expected in a child with chronic calorie deprivation (marasmus).[32-34] Moreover, while receiving NT, our patients showed only a modest increase in weight gain, GV, and growth factors. Previous studies failed to demonstrate malabsorption in HGPS[15]; therefore, it is possible that their FTT is associated with an increased energy expenditure due to an elevated BMR. This possibility is sustained by our findings and those of a previous report.[15] The cause of the elevated BMR is not clear. Thyroid function, Na^+K^+ATPase activity, and protein turnover, which are known to affect the BMR, were normal in our patients. It is therefore possible that the high BMR seen in HGPS reflects alterations in mitochondrial oxidative phosphorylation and/or respiration.[9]

It is known that substrate use varies with the nutritional status of the patient, changing from normal to high fat use and subsequently to high protein use as a source of energy.[35] Accordingly, patient no. 1, whose W/H adequacy was close to normal, had a normal substrate use, patients no. 3 and 4 (W/H adequacy, 73.8% and 71.6%) showed an increased fat use, and patient no. 2 (W/H adequacy, 64.4%) had a high protein use.

All patients showed severe growth failure with increased GH levels. Additionally, growth factor levels in patients no. 1 and 2 were marginally low. This pattern, suggestive of a relative GH resistance, has been described in protein-calorie malnutrition,[36,37] and it is considered a secondary GH insensitivity syndrome.[38] It is also possible that the patients' low body fat could have contributed to the high GH secretion.[39]

Previous studies in HGP demonstrated no receptor or postreceptor defect to IGF activity.[13] On this basis, a treatment that would increase growth factor levels should improve growth in these patients. The results of the IGF-I generation test showed a good response, and accordingly, the three patients who underwent GH treatment showed an increase in growth rate above the levels attained with NT alone. The response correlated with an increase in growth factors, procollagen III, and hydroxyproline, demonstrating an anabolic effect of GH. However, the response to GH decreased over time, probably due to the limited success in improving the patient's nutrition. However, considering the relative GH insensitivity of these patients, it is possible that a higher GH dose could have improved these results.

Table 3. Carbohydrate Metabolism Response to NT and GH Therapy

	Patient No.											
	1					2			3	5		
	Basal	4 mo	8 mo	12 mo	18 mo	Basal	4 mo	6 mo	Basal	Basal	3 mo	6 mo
HbA_{1c} (5%-8%)*	5.9	9.4	8.2	9.3	8	7.1	7.3	7.3	6.3	NA	NA	NA
Basal glucose (mg/dL)	86	95	78	77	78	86	78	NA	80	NA	NA	NA
Basal insulin (μU/mL)	13	NA	10	8	8	15	22	NA	64	4	20	12
Peak insulin (1 + 3 min)	141	99	91	56	68	118	254	NA	1,996	54	97	115
Percentile	10-50	10-50	10-50	1-5	5	10-50	>50	NA	≧50	1-5	10-50	10-50
Glucose Kt (>1.2)*	2.1	1.6	1.5	2	1.2	1.7	2	NA	1.8	4.4	3.6	4

NOTE. Peak insulin is the sum of insulin levels at 1 and 3 minutes during the IVGTT.
*Normal values.

It is known that GH treatment increases the BMR via an increase in lean body mass.[40] In contrast, these HGPS patients had a decrease in BMR during GH treatment, suggesting a more efficient energy utilization.

Four of our five patients died of cardiovascular complications. One of them was never placed on NT or GH treatment, and two had cardiovascular problems that preceded treatment. Therefore, it is unlikely that the treatment affected mortality in these patients.

Patient no. 3, the oldest of our HGP patients, showed severe hyperinsulinism resembling the levels reported by Rosenbloom et al[11] in a 15-year-old patient with HGPS who developed hyperglycemia. Further investigations in that patient suggested a postreceptor defect in insulin action.[14] According to our results and those of Rosenbloom et al, it appears that severe insulin resistance may develop in adolescence in HGPS patients, first with normal glucose tolerance and later with hyperglycemia. Additionally, patient no. 3 had exaggerated LH and prolactin responses, which suggests that a generalized hormone resistance develops in HGP patients, probably related to an accelerated process of aging.[41]

As expected in children under GH treatment,[42] patients no. 2 and 5 maintained normal glucose tolerance and developed mild hyperinsulinism. Conversely, patient no. 1 showed a decrease in the first peak insulin response during the IVGTT. This response has been considered an early predictor of insulin-dependent diabetes mellitus.[24] Although this possibility cannot be ruled out, these abnormalities seemed to be unique to this patient.

We conclude that an elevated BMR is likely to play a role in the FTT in HGPS and that elevated GH levels are characteristic of the disease. Nonaggressive NT slightly improved weight gain and GV. GH treatment further increased the levels of growth factors and paradoxically decreased the BMR. GV improved, but this effect decreased over time. Furthermore, resistance to insulin and probably to other hormones seemed to develop in older patients. The cause of the elevated BMR and hormonal abnormalities, resulting from a presumed dominant genetic mutation in HGPS, has yet to be determined.

ACKNOWLEDGMENT

Part of this study was performed while the authors were affiliated with the Department of Pediatrics of North Shore University Hospital, Manhasset, NY. We thank Drs Pierini, Lejarraga, Rivarola, and Ciaccio (Hospital de Pediatria J.P. Garrahan, Buenos Aires, Argentina) for their cooperation in the study of patient no. 5, and M. O'Connor, M. Zdanowicz, and H. Spencer for technical assistance.

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