*Acta Paediatrica Academiae Scientiarum Hungaricae, Vol. 22 (1–2), pp. 13–18 (1981)*

# Growth hormone deficiency: analysis of 49 patients

By

G. GÁCS, S. KISS, Eva PARAICZ, C. BÁNOS

Second Department of Paediatrics, Semmelweis University Medical School, and János Hospital, Budapest

(Received November 26, 1980)

In a survey of 49 children with idiopathic growth hormone deficiency, a sex ratio of 3 : 2 was found. Multiple pituitary hormone deficiency (MPHD) was seen in 31 and isolated growth hormone deficiency (IGHD) in 18 cases. The incidence of breech delivery was 32.5%; it occurred more frequently in MPHD than in IGHD. In one family there were two affected brothers whose birth weight was 4800 and 4900 g, respectively, and who were extremely retarded in growth.

Screening of 594 children 1 to 9 years of age with cleft lip and palate was carried out; 1 child with growth hormone deficiency was detected.

A study of the value of different thyroid hormones in the diagnosis of secondary and tertiary hypothyroidism showed that in spite of low free thyroxin concentrations the thyroxine and triiodothyronine levels are often normal. The discrepancy is probably due to a significantly higher plasma level of thyroxine-binding globulin demonstrated in children with hypopituitarism.

In Hungary, the number of detected cases of idiopathic growth hormone (GH) deficiency now is 110. This paper will describe some features of 49 cases diagnosed and treated at our Department since 1970. The main points we shall consider will be birth weight, type of delivery, height of the parents, occurrence of different pituitary hormone deficiencies, and the prevalence of growth hormone deficiency among children with cleft lip and palate. A study of the value of determination of thyroid hormones in the detection of secondary hypothyroidism will also be discussed.

## MATERIAL AND METHODS

Mean age of the patients at diagnosis was 8.4 years (1 month to 15 years). There were 30 boys and 19 girls (ratio, 3 : 2). The gestational age was uncertain in many cases and is not considered in this survey. A reliable perinatal history could be obtained in 43 cases. The height of both parents was measured in 23 cases and was compared to local standards. A child was regarded GH deficient if the plasma level measured in the arginine and insulin tests did not exceed 7 ng/ml and the height was at least 2.5 SD below the mean for age. The diagnosis of TSH deficiency was based on a low thyroxine ($T_4$) value ($<5.0$ $\mu$g/dl) measured either before or during GH treatment. In the last years, the TRH test was

also performed. ACTH secretion was assessed by the metyrapone test and by measurement of plasma cortisol during insulin hypoglycaemia. FSH and LH deficiency was established either on the basis of a complete lack of response to LH-RH, or in cases who failed to show signs of puberty at an appropriate bone age. Some of the patients with isolated GH deficiency will probably prove to have gonadotropin deficiency as well.

GH was measured as described previously [4], the other hormones were estimated by commercial kits: TSH-Byk Mallinckrodt, FSH and LH-Biodata, $T_4$ and $T_3$ Amersham, reverse-$T_3$-Biodata, TBG-Behring, free $T_4$-Corning. Statistical analysis was done by the $t$ test.

## Results

*Thyroid function.* In ten children with GH and TSH deficiency, the plasma concentration of $T_4$, free-$T_4$, $T_3$, $rT_3$ and TBG were measured to evaluate their reliability in the diagnosis of secondary or tertiary hypothyroidism. Figure 1 shows the level of these hormones prior to and 1 month after the initiation of GH treatment. As can be seen, only the free-$T_4$ levels were found invariably in the hypothyroid range. The $T_4$ concentration in 3 cases was low-normal and the $T_3$ levels were also often normal, particularly during GH therapy. This discrepancy between the $T_4$ and free-$T_4$ values may be explained by the high TBG concentrations: $35 \pm 5$ $\mu$g/ml *vs.* $28 \pm 4.5$ $\mu$g/ml in healthy controls ($p < 0.001$). High TBG levels ($39 \pm 4.0$ $\mu$g/ml) were found also in the patients with isolated GH deficiency. The incidence of a deficiency of some pituitary hormone is shown in Table I. The number

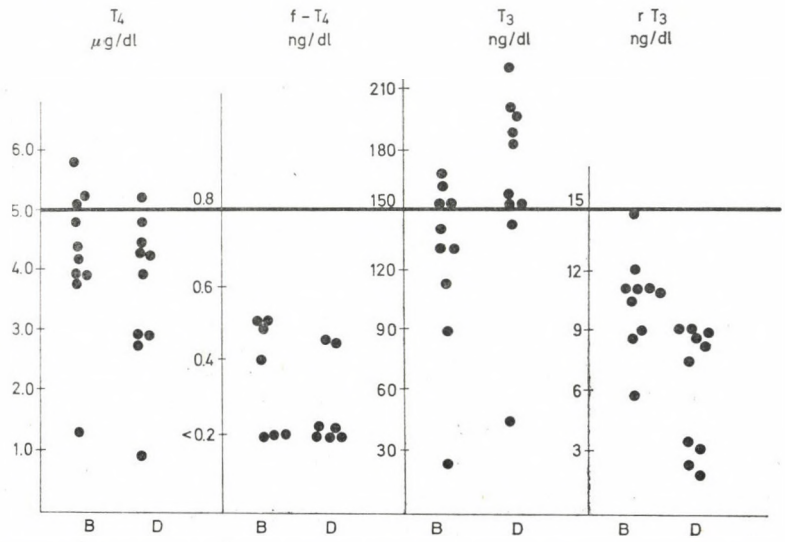


Fig. 1. Plasma level of thyroid hormones before (B) and during (D) growth hormone treatment in TSH deficient patients

TABLE I

Number of hypopituitary patients with different types of hormone deficiency

| | IGHD | GH + ACTH | GH + Gn | GH + TSH | GH + TSH + + ACTH | GH + + TSH + + Gn | GH + TSH + + ACTH + Gn |
|---|---|---|---|---|---|---|---|
| Boys | 13 | 1 | 1 | 7 | 1 | 6 | 1 |
| Girls | 5 | — | — | 11 | — | 3 | — |
| Total | 18 | 1 | 1 | 18 | 1 | 9 | 1 |

TABLE II

Type of delivery in children with growth hormone deficiency

| | Boys | | Girls | | Total | |
|---|---|---|---|---|---|---|
| | n | per cent | n | per cent | n | per cent |
| Vertex | 15 | 51.7 | 11 | 78.5 | 26 | 60.4 |
| Breech | 12 | 41.3 | 2 | 14.2 | 14 | 32.5 |
| Caesarean section | 2 | 7.8 | 1 | 7.3 | 3 | 7.0 |

of cases with multiple pituitary hormone deficiency (MPHD) exceeds those with isolated GH deficiency (IGHD) (17 *vs.* 13 in boys, and 14 *vs.* 5 in girls).

*Birth weight.* In the years between 1960 and 1980, the mean birth weight of boys ranged from 3170 g to 3246 g and that of girls from 3039 to 3115 g. In GH deficiency the mean birth weight of boys was 3210 g and that of the girls 3870 g; 17.2% of boys and 14.3% of girls had a birth weight less than 2500 g. In Hungary the incidence of low birth weight has been 10.5 to 11.5% in the last 20 years.

*Perinatal history.* Table II shows the type of delivery in boys and girls separately. The incidence of breech delivery was very high, particularly among boys, the difference between boys and girls was, however, not significant. The incidence of breech delivery of children with MPHD was 46.1% and in those with IGHD 17.6%. The general incidence of breech delivery in Hungary is 4.3%.

*Height of the parents.* Mean height of the fathers was 172.4 cm (−0.54 SDS) and that of mothers, 156.2 cm (−0.75 SDS).

*Familial occurrence of GH deficiency.* Isolated GH deficiency was found in two brothers with growth retardation of extreme degree. The older was first seen at the age of 14 years when his height was 90 cm and bone age 8 years, the younger at the age of 8 years was 82 cm high with a bone age of 3.5 years. They had a large head and a small nose with retracted

bridge. Their birth weights were 4900 and 4800 g and the perinatal period was uneventful. Their two brothers with normal stature had normal birth weights. The mother has no diabetes mellitus. Both these patients responded well to GH treatment without formation of antibodies.

*Screening of children with cleft lip and palate (CLP) for GH deficiency.* The height of 1200 children with CLP aged 1 to 9 years was obtained from the central register for congenital malformations. The measurements were made by the parents; 135 children were found whose height was below the 3rd percentile. Their parents were requested to measure the child again; 102 responded, and in 23 children the height was at least 2.5 SD below the mean for age. These patients were requested to contact us but only 14 came. Thus, due to a lack of cooperation, 50.5% of the children were lost and the real number of the screened ones is 594. Three children were not investigated because of multiple birth defects and serious psychomotor retardation. Among the remaining 11 patients, one was found to have GH deficiency. He was born at term, delivery was normal, and he had cleft lip and palate on one side. Birth weight was 3650 g. At 6 1/2 years his height is 93.5 cm, the bone age 3.8 years, the testes measure 0.5 ml and the scrotum is ill-developed. GH was undetectable by the insulin and arginine tests. The concentrations of TSH, LH and FSH were normal during the TRH and LH—RH tests.

## Discussion

The association of GH deficiency with complications during delivery has repeatedly been noted [2, 5, 8, 15, 20] and is now considered to be the main aetiological factor. Especially breech delivery was found to be frequent, although there are considerable differences in the reported incidences. We, too, observed a high incidence of breech delivery and its higher prevalence in children with MPHD than in those with IGHD.

The occurrence of GH deficiency in siblings is well known. In most cases an autosomal recessive inheritance has been suggested [12, 13, 19, 21]. We do not know, however, of any family reported where GH deficiency was associated with high birth weight.

The two brothers described in the present paper show a striking similarity both in appearance and in the extent of growth retardation to the patients described by Illig et al [7] and called A-type isolated GH deficiency. An important difference is, however, that in their cases antibodies appeared at high concentration during GH treatment.

The association of cleft lip and palate with GH deficiency has been described previously [3, 9, 17, 22]; it is explained by the close relation of embryogenesis of the anterior pituitary and of the facial structures. Rudman et al [17] studied 200 children with CLP and found 8 cases with GH deficiency. In contrast, we detected only one case among 594 children. It is unlikely that the dif-

ference was due to an inaccuracy of the measurements made by the parents, since in all cases where we checked the data they either coincided with or were lower than our own. An important factor of the difference may be that we studied children between the ages of 1 to 9 years, whereas the patients of Rudman et al. ranged from 7 to 14 years. It is well-known that in many children with GH deficiency the reduction of height is only slight in the first years of life.

The evaluation of thyroid function in hypopituitarism is sometimes uncertain. It is only in cases of pituitary insufficiency that the TSH response to TRH administration is subnormal; it may, however, be normal or increased in hypothalamic hypopituitarism [1, 6, 11]. The low free-$T_4$ concentration often accompanied by a normal $T_4$ level in our cases indicates that the concentration of thyroxine does not reliably reflect the thyroid status. This is probably due to the high TBG level observed in the present study. Rubio et al [16] found a normal TBG affinity in GH deficiency, and this seems to contradict our observation. The discrepancy may be due to the difference between the methods used for measurement of the TBG level. After the initiation of GH treatment the plasma $T_4$ level decreases and hypothyroidism becomes apparent even in cases with previously normal $T_4$ values [10, 14, 18]. Also, in patients with normal TSH secretion there is a temporary reduction of $T_4$ values during GH treatment, but these values never decrease to the hypothyroid range. The $T_3$ levels tend to increase during GH treatment [18] and are unreliable for the detection of hypothyroidism.

## References


1. Andler, W., Stoleck U.: Thyroid function in children with growth hormone deficiency, either idiopathic or caused by diseases of the central nervous system, Europ. J. Pediat. **128**, 273 (1978).
2. Bierich, J. R.: On the aetiology of hypopituitary dwarfism. In: Growth and Growth Hormone. Proc. Second Int. Symposium on Growth Hormone (ed. by A. Pecile and E. E. Müller), p. 408 Excerpta Medica, Amsterdam 1972.
3. Frances, J. M., Knarr, D., Martinez, R., Neuhauser, G.: Hypophysärer Zwergwuchs bei Lippen-Kiefer-Spalte. Helv. paediat. Acta **21**, 315 (1966).
4. Gács, G., Kun, E., Czirbesz, Zs.: Growth hormone secretion in children during corticosteroid treatment. Responses to arginine, Horm. Metab. Res. **5**, 106 (1973).
5. Goodman, H. G., Grumbach, M. M., Kaplan, S. C.: Growth and growth hormone. II. A comparison of isolated growth hormone deficiency and multiple pituitary hormone deficiencies in 35 patients with idiopathic hypopituitary dwarfism. New Engl. J. Med. **278**, 57 (1968).
6. Illig, R., Krawczinska, H., Torresani, T., Prader, A.: Elevated plasma TSH and hypothyroidism in children with hypothalamic hypopituitarism. J. clin. Endocr. **41**, 722 (1975).
7. Illig, R., Prader, A., Fernandez, A., Zachmann, M.: Familiärer pränataler Wachstumshormon-Mangel mit erhöhter Bereitschaft zur Bildung von Wachstumshormon-Antikörpern. Symp. dtsch. Ges. Endokr. **16**, 246 (1970).
8. Joss, E. E.: Growth Hormone Deficiency in Childhood; Evaluation of diagnostic Procedures. Karger, Basel 1975.
9. Laron, Z., Taube, E., Kaplan, I.: Pituitary growth hormone insufficiency associated with cleft lip and palate. An embryonal developmental defect. Helv. paediat. Acta **24**, 576 (1969).

10. Lippe, B. M., VanHerle, A. J., Lafranchi, S. H., Uller, R. P., Lavin, N., Kaplan, S. A.: Reversible hypothyroidism in growth hormone deficient children treated with human growth hormone. J. clin. Endocr. **40**, 612 (1975).
11. Otsuki, M., Mori, H., Baba, Sh., Hiroshige, N.: Effect of synthetic TRF on pituitary TSH secretion in normal subjects and patients with hypothalamic-pituitary disorders. Acta endocr. (Kbh.) **73**, 233 (1973).
12. Rimoin, D. L., Merimée, T. M., McKusick, V. A.: Growth hormone deficiency in man; isolated, recessively inherited defect. Science **152**, 1635—1637, (1966)
13. Rimoin, D. L., Merimée, T. J., Rabinowitz, D., Cavalli-Sforza, L. L., McKusick, V. A.: Genetic aspects of isolated growth hormone deficiency. In: Growth and Growth Hormone. Proc. First Int. Symp. (ed. by A. Pecile and A. A. Müller), pp. 418—432. Excerpta Medica, Amsterdam 1968.
14. Root, A. W., Bongiovanni, A. M., Eberlein, W. R.: Inhibition of thyroidal radioiodine uptake by human growth hormone, J. Pediat. **76**, 422 (1970).
15. Rona, R. J., Tanner, J. M.: Aetiology of idiopathic growth hormone deficiency in England and Wales. Arch. Dis. Childh. **52**, 197 (1977).
16. Rubio, G. R., Mellinger, R. C., Saeed Zafar, M., Wolf, C. B.: Evaluation of thyroid function during growth hormone therapy. Metabolism **25**, 15 (1976).
17. Rudman, D., Davis, G. Z., Priest, J. H., Patterson, J. H., Kutner, M. H., Heymsfield, S. B., Bethel, R. A.: Prevalence of growth hormone deficiency in children with cleft lip or palate. J. Pediat. **93**, 378 (1978).
18. Sato, T., Suzuki, Y., Taketani, T., Ishiguro, K., Masuyama, T., Takata, I., Sano, M., Kawashima, H., Koizumi, S., Nakajima, H.: Enhanced peripheral conversion of thyroxine to triiodothyronine during hGH therapy in GH deficient children, J. clin. Endocr. **45**, 324 (1977).
19. Sheikholislam, B. M., Stempel, R. S. jr.: Hereditary isolated somatotropin deficiency; effect of human growth hormone administration. Pediatrics **49**, 362 (1972).
20. Steendijk, R.: Diagnostic and aetiologic features of idiopathic and symptomatic growth hormone deficiency in the Netherlands. Helv. paediat. Acta **35**, 129 (1980).
21. Trygstad, O., Seip, M.: Hereditary pituitary dwarfism treated with human growth hormone. Acta paediat. scand. **53**, 527 (1964).
22. Zuppinger, K. A., Sutter, M., Zurbrugg, R. P.: Cleft lip and choroideal coloboma associated with multiple hypothalamo-pituitary dysfunctions. Endocrinology **33**, 934 (1971).

G. Gács, M. D.
Tűzoltó u. 7.
1094 Budapest, Hungary