Clinical and laboratory parameters predicting a requirement for reevaluation of growth hormone status during growth hormone treatment

Dogus Vuralli, Nazlı Gonc, Alev Ozon, Ayfer Alikasifoglu, Nurgun Kandemir

Hacettepe University Faculty of Medicine, Department of Pediatric Endocrinology, Ankara, Turkey

*Authors have nothing to disclose

BACKGROUND

The clinical and the laboratory criterias used in the diagnosis of growth hormone deficiency (GHD) have low sensitivity and specificity. The inadequancy of auxological and biochemical parameters, low reproducibility and high intra-individual variability of the stimulation tests are important problems in diagnosis. When evaluated at the end of their growth, 25-75% of the children who are treated for GHD have normal growth hormone (GH) levels. Repeat evaluation early in childhood during treatment may help detect cases with normal GH status earlier.

OBJECTIVE AND HYPOTHESES

We repeated stimulation tests in patients who were diagnosed as GHD and were receiving GH replacement therapy to detect patients with normal responses, and analyzed clinical and laboratory features in order to define the characteristic findings that may point to patients who require reassessment of GH status.

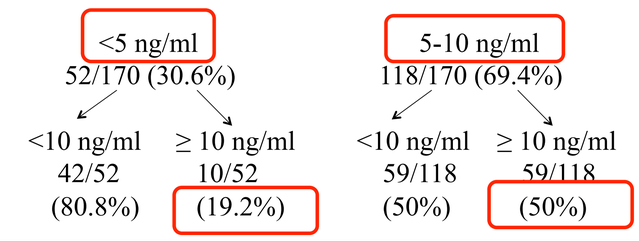
METHODS

One year after the onset of therapy, GH tests were repeated in 265 patients (104M/61 F). Multiple pituitary hormone deficiency (MPHD) was present in 35.8%, isolated growth hormone deficiency (IGHD) was present in 64.2%. Auxological data, pubertal stage, IGF-1, IGFBP-3 levels, and imaging of the pituitary gland were analyzed. After retest, patients with GH <10 ng/ml continued to receive treatment, whereas treatment was discontinued for patients with GH ≥10 ng/ml. For those who reached the final height, final heights of the cases were recorded.

RESULTS

The mean age, bone age, height SDS at diagnosis were 10.4±4.1, 7.4±3.9 and -2.8±1.1 respectively. **At retest GH ≥ 10 ng/ml was observed in 69/265 (26%) patients. None of the patients with MPHD had GH ≥ 10 ng/ml. GH response was ≥10 ng/ml in 69/179 (40.6%) cases with IGHD.**

Figure 1. The distribution of the patients with respect to peak GH levels at diagnosis and retest



The height SDS, height velocity, IGF1 and IGFBP3 did not differ between the cases with IGHD <10 ng/ml and IGHD ≥ 10 ng/ml but peak GH levels and age at diagnosis were lower in the IGHD <10 ng/ml group.

Table 1. Clinical and laboratory features of the cases according to the type of hormone deficiency and peak GH levels at retest

	IGHD <10 ng/ml (n=101)	IGHD≥ 10 ng/ml (n=69)	MPHD <10 ng/ml (n=95)	P value[a]
Age at admission	8.0±4.2[b]	10.3±3.2[b,c]	7.3±4.7[c]	≤ 0.001
Age at diagnosis	9.7±3.8[b]	11.8±2.7[b,c]	8.9±4.8[c]	≤ 0.001
Bone age at diagnosis	7.1±3.8[b]	9.1±2.8[b,c]	6.0±4.2[c]	≤ 0.001
Δ Height SDS at diagnosis	-0.9±0.4[d]	-0.8±0.2[c]	-1.5±1.9[c,d]	0.002
Height SDS at diagnosis	-2.7±1.0[d]	-2.6±0.7[c]	-2.9±1.3[c,d]	0.025
IGF-1 SDS at diagnosis	-1.0±0.6	-1.1±0.5	-1.2±0.9	0.241
IGFBP3 SDS at diagnosis	-1.7±1.5[d]	-1.6±1.5[c]	-2.8±1.4[c,d]	≤ 0.001
Peak GH level at diagnosis	5.4±2.6[b,d]	7.2±2.0[b,c]	1.7±2.1[c,d]	≤ 0.001

a: One side variance analysis, b: The difference between the groups IGHD < 10 ng/ml and IGHD ≥ 10 ng/ml is statistically significant (p < 0.05), c: The difference between the groups IGHD ≥ 10 ng/ml and MPHD <10 ng/ml is statistically significant (p < 0.05) d: The difference between the groups IGHD < 10 ng/ml and MPHD < 10 ng/ml is statistically significant (p < 0.05)

Table 2. MRI findings according to peak GH level at retest

	IGHD <10 ng/ml n=101	IGHD ≥ 10 ng/ml (n=69)	MPHD <10 ng/ml n=95	P value[a]
Normal or anterior pituitary hypoplasia	81 (80.2%)	68 (98.6%)	27 (28.4%)	<0.001[a]
Organic lesions or posterior pituitary localization defects	20 (19.8%)	1 (1.4%)*	68 (71.6%)	
	101 (100%)	69 (100%)	95 (100%)	

a: Pearson's chi square test *Ectopic posterior pituitary with no pituitary stalk interruption

Table 3. Factors affecting peak GH levels at retest

Factors	IGHD <10 ng/ml	IGHD ≥ 10 ng/ml	p value	OR (95% CI)
Age at diagnosis	9.75±3.80	11.89±2.72	<0.001[a]	1.192 (1.094-1.299)
Pubertal status at diagnosis				
Prepubertal	79 (%78.2)	36 (%52.2)	-	1.000
Pubertal	22 (%21.8	33 (%47.8)	<0.001[b]	3.436 (1.834-6.440)
IGF-1 SDS at diagnosis	-1.02±0.63	-1.15±0.50	0.241[a]	0.732 (0.522-1.027)
IGFBP-3 SDS at diagnosis	-1.78±1.59	-1.64±1.53	0.575[a]	1.321 (1.089-1.601)
Peak GH level at diagnosis				
0-5 ng/ml	42 (%41.6)	10 (%14.5)	-	1.000
5-10 ng/ml	59 (%58.4)	59 (%85.5)	<0.001[b]	11.721 (5.250-26.170)
MRI Findings				
Organic Lesion/ Localization defects	20 (%19.8)	1 (%1.4)	-	1.000
Normal/ Hipoplasia	81 (%80.2)	68 (%98.6)	<0.001[b]	52.826 (7.159-389.814)
Pubertal status at retest				
Prepubertal	49 (48.5%)	20 (29%)	-	1.000
Pubertal	52 (51.5%)	49 (71.0%)	0.010[b]	2.235 (1.199-4.167)
Δ Height SDS 1st Year	0.84±0.62	0.44±0.28	0.008[a]	0.097 (0.037-0.254)

Results of one variant analysis a: Student's t test, b: Pearson's chi-square test

Table 4. Analysis of the effects of factors that are mostly determinant to distinguish patients with IGHD < 10 ng/ml and IGHD ≥ 10 ng/ml, results of multivariate logistic regression analysis

	Odds Ratio	95% Confidence Interval Lower limit	Upper limit	Wald	P-value
Age at diagnosis	1.309	0.958	1.790	2.850	0.091
Δ Height SDS at diagnosis	1.098	0.151	7.994	0.008	0.927
Being pubertal at diagnosis	0.760	0.246	2.346	0.227	0.633
IGF1 SDS at diagnosis	2.465	0.867	7.011	2.862	0.091
IGFBP3 SDS at diagnosis	0.723	0.575	0.908	7.748	0.055
Peak GH level 5-10 ng/ml at diagnosis	13.179	5.966	29.114	40.665	< 0.001
Δ Height SDS 1st year	0.122	0.031	0.485	8.918	0.003
Being pubertal at retest	0.521	0.168	1.618	1.271	0.260

The odds of having GH ≥ 10 ng/ml at retest was higher for patients who had GH levels between 5-10 ng/ml at diagnosis, and for patients who had height gain <0.61 SDS in the first year of treatment.

Table 5. Follow up of growth according to retest responses in cases who reach final height

	IGHD < 10 ng/ml (n=19)	IGHD≥ 10 ng/ml (n=30)	MPHD < 10 ng/ml (n=30)	p-value
Final Height SDS	-1.3± 0.7	-1.5± 0.7	-1.3± 1.0	0.230[a]
Δ Final-Diagnosis Height SDS	1.1± 0.8	0.9± 0.7	1.3± 1.1	0.070[a]
Δ Final-Target Height SDS	0.1± 0.8	0.2± 0.7	0.1± 0.8	0.485[a]
Δ Height SDS 1st Year	0.8±0.6[c,d]	0.4±0.2[c,e]	1.1±1.0[d,e]	<0.001[b]
Δ Height SDS 2nd Year	0.4±0.3	0.4±0.2	0.5±0.4	0.050[b]
Δ Height SDS 3rd Year	0.5±0.3	0.4±0.3	0.5±0.4	0.180[b]

a. Student's t test b: One way variance analysis, c: The difference between the groups IGHD < 10 ng/ml and IGHD ≥ 10 ng/ml is statistically significant (p=0.008), d: The difference between the groups IGHD < 10 ng/ml and MPHD is statistically significant (p=0.008), e: The difference between the groups IGHD ≥ 10 ng/ml and MPHD is statistically significant (p < 0.001).

The patients who did not continue treatment and patients with ongoing treatment had similar final heights and their final heights were consistent with the target heights. The height gain in the 1st year of treatment was highest in MPHD patients, moderate in patients with IGHD < 10 ng/ml, and the lowest in patients with IGHD ≥ 10 ng/ml.

CONCLUSION

- **Patients with MPHD do not need reevaluation for GH status**
- **Patients with IGHD who have following features should be reevaluated:**
  - **Peak GH >5ng/ml at diagnosis**
  - **Normal/hypoplastic pituitary gland**
  - **Height gain <0.61SDS during the first year of therapy**
- Our results indicate that reevaluation of patients with respect to GHD in the early period is reliable, given the similarity between the final heights in patients who did not continue treatment, and patients who continued treatment.

REFERENCES

1. Nicolson, A., Toogood, A.A., Rahim, A.,Shalet, S.M. (1996) The prevalence of severe growth hormone deficiency in adults who received growth hormone replacement in childhood. Clinical endocrinology, 44 (3), 311-316.
2. Cacciari, E., Tassoni, P., Cicognani, A., Pirazzoli, P., Salardi, S., Balsamo, A., et al. (1994) Value and limits of pharmacological and physiological tests to diagnose growth hormone (GH) deficiency and predict therapy response: first and second retesting during replacement therapy of patients defined as GH deficient. The Journal of clinical endocrinology and metabolism, 79 (6), 1663-1669.
3. Wacharasindhu, S., Cotterill, A.M., Camacho-Hubner, C., Besser, G.M.,Savage, M.O. (1996) Normal growth hormone secretion in growth hormone insufficient children retested after completion of linear growth. Clinical endocrinology, 45 (5),553-556.
4. Loche, S., Bizzarri, C., Maghnie, M., Faedda, A., Tzialla, C., Autelli, M., et al. (2002) Results of early reevaluation of growth hormone secretion in short children with apparent growth hormone deficiency. The Journal of pediatrics, 140 (4), 445-449.
5. Tauber, M., Moulin, P., Pienkowski, C., Jouret, B.,Rochiccioli, P. (1997) Growth hormone (GH) retesting and auxological data in 131 GH-deficient patients after completion of treatment. The Journal of clinical endocrinology and metabolism, 82(2), 352-356.
6. Zucchini, S., Pirazzoli, P., Baronio, F., Gennari, M., Bal, M.O., Balsamo, A., et al. (2006) Effect on adult height of pubertal growth hormone retesting and withdrawal of therapy in patients with previously diagnosed growth hormone deficiency. The Journal of clinical endocrinology and metabolism, 91 (11), 4271-4276.
7. Thomas, M., Massa, G., Maes, M., Beckers, D., Craen, M., Francois, I., et al. (2003) Growth hormone (GH) secretion in patients with childhood-onset GH deficiency: retesting after one year of therapy and at final height. Hormone research, 59 (1), 7-15.