

THE ANSWER TO THE TREATMENT OF THE CHILDREN WITH GH DEFICIENCY

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Abstract

The aim: the evaluation of the results of the treatment with growth hormone, obtained by genetic recombination (rhGH) to a group of 47 children with pituitary dwarfism. The method: the patients have used for a year a treatment of growing advance with 0,2mg/kg/a week rhGH, (Zomacton) taken every day. We have followed: the change of the anthropometric parameters under therapy; the relation between the different parameters and the answer to the treatment. The results: during the treatment we noticed a significant improvement of the growing speed, from 1,73 cm/year to 9,50 cm/year. As well as, the growing deficit has improved from -3,07 SD to -2,33 SD. To the studied group we found relations between the growing speed under treatment and the following parameters: the chronological age and the bone age at the beginning of the treatment; the delay of the bone age with more than 3 years. Conclusions: the obtained results show the fact that the treatment with rhGH to the children with pituitary dwarfism is an important ally regarding the improvement of the consequences caused by the hormone deficiency, its main purpose being the improvement of the height during the childhood and the obtaining of a final, normal height.

Key words: GH, GH deficiency, rhGH

Introduction

The pituitary dwarfism is a debilitating disease, regarding not only the social status of the short person, but also because of the effects of the hormone deficiency in the body, during the childhood and the adult period. This aspect motivates the early diagnostic of GHD deficiency, using very clear criteria in order to begin the replacement therapy.

The patients with such problems can be treated with GH obtained through genetic recombination (rhGH) as soon as possible after the diagnosis. The main objective of the therapy is represented by the obtaining the normal height during the childhood and also as an adult.

The growing as an answer to the exogenous GH varies on many parameters: the frequency of the treatment, the dosage, the age of the patient at the beginning of the treatment, the weight, genetic factors, the serum level of GHBP and, if possible, the season (1-4). This thing motivates the study of the relations between different

parameters and the answer to the treatment in order to obtain the best results

Generally speaking, a daily treatment of rhGH with the prescribed dosages, the children with GHD have a growing speed from 3-4 cm/year in pretreatment to 10-12 cm/year in the first year of therapy and to 7-9 cm/year in the second and the third year of therapy.

The age at the beginning of the treatment inversely correlates with the answer on growing and it is very important that the rhGH substitution therapy should be installed before the puberty start, because it is a fact that the estrogens fasten the maturity of the bones (5, 6).

The genetic factors which influence the growing as an answer to the rhGH therapy, remain mostly unknown. Up to now there were information only about the gene of the GH (GHRP) receiver. Polymorphisms of this gene have been reported to the general population and they were described in the exons 3, 6 and 10. Two of the most-known isoforms of human GHR gene are generated by the presence or the absence of the exon 3: GHR-fl (full-length GHR) and GHRd3 (exon 3 deleted GHR). In the last years there have been studies on children with growth hormone deficiency and on children with a short stature, but without GH deficiency. The problem of the dependence of the answer of the rhGH substitution therapy to the genotype of the gene receiver of the growing hormone still remains a controversial subject, due to the fact there are pro and against data (4, 7-9).

The possible role of the composition of the body in the answer to rhGH therapy at the children with GHD require more investigations (2).

The Aim

The study has as a goal the evaluation of the results of the treatment of the growing promotion in the case of weakness stature due to the growth hormone deficiency.

The material and the method

We included in our group 47 of children with growing hormone deficiency, who were selected from the children that came to the Endocrinology Clinic and Ambulatory of the Emergency County Hospital from Craiova, between 2005-2010.

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In order to establish the diagnostic of GH deficiency we used the clinical criteria (history, objective examination) and paraclinical criteria.

Clinic criteria of including the patients in the study:

- The delay in the height of two or more standard deviations (SD) related to the average of age and sex.
- The growing speed is slow in the last year.
- The normal stature of the parents.
- Suggestive clinic features for the GH deficiency (acromicrie, pigmentation “in butterfly” of the facial skin, facies infanto-senescent, extreme body build, thin voice, upholstered adiposity, micropenis).
- Morfotip harmonic (the pituitary dwarfism is a harmonic one).
- Anamnesis for the exclusion of a psycho-social dwarfism.
- Late bone age < than the chronological age (a delay of, at least, two years).
- At two stimulation tests the value of GH < 10 mUI/1.
- A small basic value of GH (or in the normal range, but correlated with post-stimulated values < 10 mUI/1).

Exclusion criteria: GH deficiency with an organic cause (tumor cause), head injury with hypothalamic-pituitary damage, GH deficiency secondary to the radiotherapy, weakness stature due to some chronic problems, Turner syndrome, a short stature in the family.

For analysis the delay of growing against the average of age and sex, the Z score of the stature was calculated after the formula:

The Z score = the real stature - the medium stature for age and sex/SD (standard deviations for age and sex). The medium stature and the standard deviations for age and sex were obtained using the standard anthropometric tables, made by Prader and collaborators (1988). The deviation of the stature from the average for age and sex was expressed in standard deviations (SD).

The medium height of the parents - MPH- was calculated after the formula:

MPH = (the father's height + the mother's height + 13 cm)/2, for boys

MPH = (the father's height + the mother's height - 13 cm)/2, for girls

The body mass index (BMI) = the weight/height² (kg/m²).

Paraclinic investigations:

- The usual hematological and biochemical investigations: the full blood count, the glucose, the lipidograma (the cholesterol, the lipemia, the serum triglycerides), the liver enzymes (GOT, GPT), the urea and the serum creatinine, the calcemia (total, ionic), magneziemia, fosfatemia, the total proteins.

- The hormone investigations: GH, IGF-1, TSH, FT4, FT3, ATPO, FSH, LH, PRL, estradiol, progesterone, plasma testosterone, plasma cortisol. We have used ELISA methods or immunochemical with detection through electrochemiluminiscenta, depending on the type of the

laboratory or its equipment, and the obtained hormone values were reported to the dosing kits.

- Tests of the stimulation of GH secretion: the test of the hypoglycemia caused by insulin, the test to the arginine, the test to the clonidine.

- The imaging investigations: the skull radiography profile for the Turkic saddle, the radiography of the carpal bones of the non-dominant hand, for evaluating the age of the bones, CT/RM exams of the skull for establishing the etiological diagnoses to the patients who have supposed to present changes at the skull radiography profile.

To the patients from our group who have presented modified values of TSH and ATPO, we have made ultrasound of the thyroid gland.

All the 47 children of our group have followed for a year a treatment with rhGH 0,2 mg/kg/a week, given every day. We used Zomacton, of rhGH preparations, because it has the advantage that is administered subcutaneously, through “no needle” jet injection, thus increasing patient compliance. Because of how easy administration, Zomacton not cause pain, not cause local skin irritation or lipodystrophy.

We analyzed the following issues:

A. The change of the anthropometric parameters under the therapy.

B. The relationship between different parameters and the answer to the treatment, evaluated in the number of cm gained in a year of GH administration (the growth speed).

The Results of the Study

The distribution on the sex type of the 47 patients was made in this way:

15 girls → 31.91%

32 boys → 68.09%

As regarding the age, 7 girls were in the prepuberty period (3-9 years) -14.89% and 8 were of pubertal (≥ 10 years) – 17.02%. 19 boys (40.43%) were in the prepubertal age (3-11 years) and 13 boys (27.66%) were 12 years or older than this age (fig.1).

Out of the 47 children under treatment for a year, 46 had showed isolated GH deficiency, 8 of them also having increased values of TSH, and a patient had a pituitary dwarfism pluritrop (GH, FSH, LH, ACTH) and increased TSH. At the 9 children with increased TSH, the FT4 and FT3 values are normal, so the diagnosis established was subclinical hypothyroidism. At these patients, the TSH value was normalized by substitution with Levothyroxine (Euthyrox), before introducing the rhGH treatment.

One of our patients presented an increased value of ATPO.

A. THE CHANGE OF THE ANTHROPOMETRIC PARAMETERS UNDER TREATMENT

The anthropometric marks of the 47 patients at the beginning of the therapy are presented in the table nr.1.

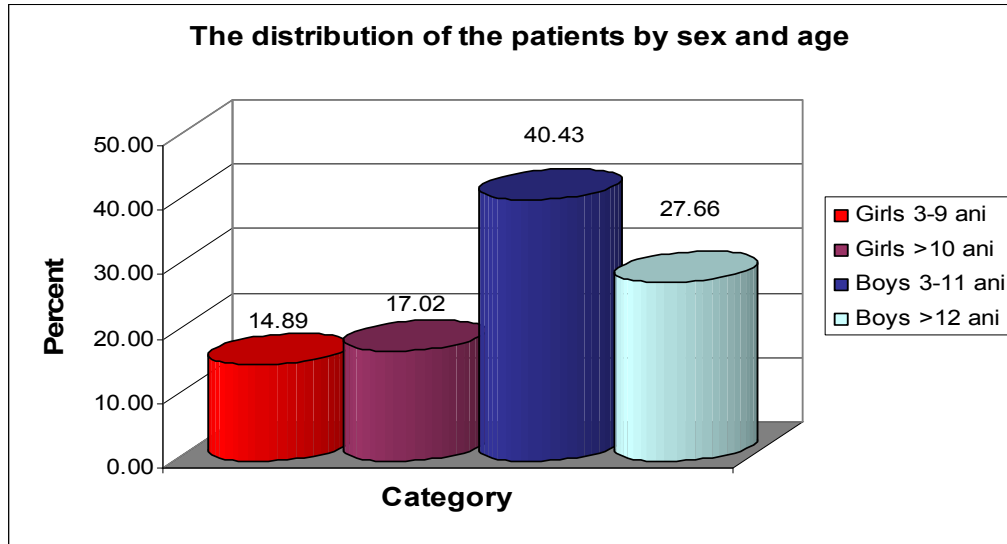


Figure nr. 1 The distribution of patients by sex and age.

Table nr.1 - Anthropometric Marks of the Patients at the Beginning of the Treatment

Parameters	Nr.	Media	Standard deviation	C.V. (% Ds/M)
The Chronological Age (years)(Chr A)	47	10.29	3.23	31.37
The Bone Age (years) (BA)	47	7.33	3.02	41.23
The Height Age (years) (HA)	47	7.11	2.67	37.54
BA - HA	47	0.21	0.95	
BA Delay (Chr A - BA)	47	2.99	0.61	20.40
The Growth speed prior to the treatment (cm/years)	47	1.73	0.62	36.04
The Z Height Score (SD)	47	-3.07	0.84	-27.23
The Index of the Body Mass (BMI)	47	16.14	2.17	13.42
The Medium Height of the Parents (MPH)	47	169.98	6.61	3.89
Peak GH Insuline Test	41	3.79	2.19	57.84
Peak GH Arginine Test	18	5.23	3.4	64.9
Peak GH Clonidine Test	10	3.5	2.17	62

The 47 children received treatment as it follows:

- 37 patients with isolated GH deficiency received recombinant growth hormone (ZOMACTON) 0,2mg/kg/week, subcutaneously given daily;
- 8 patients with GH deficiency and subclinical hypothyroidism received Euthyrox in doses (3-5 µg/kg/day)-until the normalization of the TSH value, then we added the growth hormone;
- the patient with GH deficiency and chronic autoimmune thyroiditis received Euthyrox 25 µg/day (1,44 µg/kg/day) plus Zomacton 0,2 mg/kg/week;
- the patient with plurtrop deficiency received Zomacton associated with Euthyrox 50 µg/day and Prednison 7,5mg/day.

After a year of treatment we calculated:

- the growth speed under treatment (cm/year), given by the difference between the height measured at the end of the treatment and the height measured at the beginning of the treatment;
- the Z score of the height after a year of treatment (in SD);
- the difference between the Z score of the height after a year of treatment and the Z score of the height at the beginning of the treatment.

The comparison between the values of these parameters from the beginning and from the end of the treatment are presented in the tables 2 and 3.

Table nr. 2- Anthropometric marks of the patients at the beginning and the end of the treatment.

The parameter	Nr.	Media	Standard deviation	C.V. (% Ds/M)
The growth speed prior to the treatment (cm/year)	47	1.73	0.62	36.04
The growth speed during the treatment (cm/year)	47	9.50	2.30	24.17
The Z score of the height prior to the treatment (SD)	47	-3.07	0.84	-27.23
The Z score of the height after the treatment (SD)	47	-2.33	0.91	-38.96
The difference of the Z score (SD)	47	0.74	0.54	72.49

Table nr.3 - The distribution on the sex of the anthropometric marks after a year of treatment.

The parameter	GIRL				BOYS			
	Nr. patients	Media	Std. dev.	C.V.(% Ds/M)	Nr. patients	Media	Std. Dev.	C.V.(% Ds/M)
The Z score of the height	15	-2.58	1.13	-43.88	32	-2.21	0.77	-34.92
The growth speed (cm/year)	15	9.53	2.20	23.07	32	9.48	2.37	25.03

B. THE CORELLATION BETWEEN THE DIFFERENT PARAMETERS AND THE ANSWER TO THE TREATMENT

Regarding the basic marks we have and the answer to the treatment of our group of patients, we tried to find parameters which correlate well with the growth speed under the treatment.

Analyzing the nature of the relationship between the growth speed of the 47 patients, treated for a year, and different parameters, using Pearson's correlation coefficient, we have found the following results, presented in the table nr. 4.

The coefficients of Pearson's r correlation between the growth speed under the treatment and the chronological age, namely the bone age has the values -0,271 and -0.288, that indicates a statistic significant inverse correlation ($p < 0.05$),

that means the bigger the BA delay, the smaller is the growth.

The coefficient of the Pearson's r correlation between the growth speed under the treatment and the delay of the bone age bigger than 3 years had a value of -0.355, that means a significant statistic inverse correlation ($p < 0.05$), that signifies the bigger the delay, the smaller is the growth (fig.2). The analysis of the relationship between the growth speed under the treatment and the other parameters from table nr.4 does not show any correlation between these parameters.

The coefficient of Pearson's r correlation between the growth speed under treatment and the maximum peak of GH at the stimulation test with arginine is -0.161, that shows a weak inverse correlation, statistic insignificant because of the small number of the tested patients, that means the bigger the peak, the smaller is the growth.

Table nr. 4 - The Correlation between the growth speed and different parameters.

The parametre	The correlation coefficiency
The chronological age	-0.271
The bone age (BA)	-0.288
The BA delay (>3 years)	-0.355
The Z score prior to the treatment	-0.091
The Z score after the treatment	0.419
The difference of the Z score	0.846
The growth speed before the treatment	0.024
BMI	-0.265
MPH	0.11
Maximum peak GH insuline test	-0.056
Maximum peak GH arginine test	-0.161
Maximum peak GH clonidine test	0.166

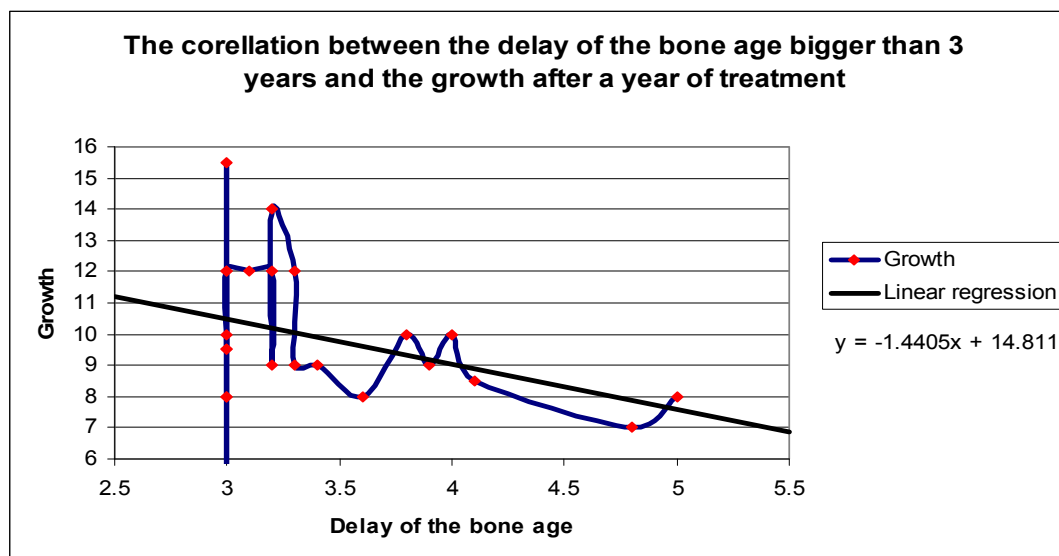


Figure nr. 2 The correlation between the delay of the bone age bigger than 3 years and the growth after a year of treatment.

Discussions

The treatment to promote of the growth with genetic recombinant hormone was given for a year to all the 47 patients with pituitary dwarfism. 26 children were at the prepubertal age and 21 were at the pubertal age.

The growth speed under treatment is the mean indicator of the therapeutic effect. After a year of treatment we noticed, at our patients, a significant improvement of the growth speed, comparatively to the year prior to the introduction of the therapy, and we also noticed an amelioration of the stature deficiency with 0.74 SD (Table 2). The growth speed under treatment and the Z score of the height had comparable values at boys and also at girls (9.48 cm/year vs. 9.53 cm/year; -2.21 SD vs. -2.58 SD) (Table 3).

At our patients we tried to find correlations between the growth speed under treatment and different parameters: the chronological age, the bone age, the delay of the bone age more than 3 years, the Z score of the height before and after the treatment, the difference of Z score, IMC, MPH, the maximum peak of the GH at the stimulation tests.

In our analyze we showed that the growth speed under treatment is correlated with the chronological age at the beginning of the treatment (Table 4): the older the chronological age at the beginning of the treatment, the smaller is the growth increase. It seems that the sensitivity of the growth cartilage for the growth factors decreases as the children get older. So the delay of the beginning of the therapy specific to promote the growth could overcome the moment of maximum bone reception to the growth factors.

The fact that the age at the beginning of the treatment is inverse correlated to the answer on growth was confirmed by the studies made on groups of children with rhGH, treated at young ages, even before they are 12 months old.

At these baby patients the benefit was bigger even if the doses were small and less frequent. Although, at these children we noticed a decreased sensitivity to the endogen GH, which adds complexity at the interpretation of the information (10, 11).

In our group we found inverse correlations between the growth speed under treatment with rhGH and the following parameters: the bone age at the beginning of the treatment, the delay of the bone age with more than 3 years. An inverse correlation was established between the growth speed and the maximum peak of the GH at the anginine test, but statistic insignificant because of the small number of the patients that made this test

At our group we did not find correlations between the growth speed and the maximum peak of GH at the insuline and clonidine tests.

Many studies appreciated different variables that can influence the final height, obtained after treatment with rhGH at children with GHD: the duration of the treatment, the delay of the height appreciated in SD (standard deviations) at the beginning of the treatment, the delay of the bone age (BA), the height at the beginning of puberty, the medium height of the parents (MPH) and the growth speed in the first year of treatment (GV - growth velocity). All these variables positively correlate with the obtained height, while the age at the beginning of the treatment and the maximum peak of the GH at the stimulation tests are correlated negatively (4, 12). These factors explain only partial the individual variability to the answer at the treatment of rhGH substitution at children with pituitary dwarfism.

It seems that only the patients with severe GH deficiency (GH peak <5ng/ml post-stimulation) or those

GHD due to the congenital abnormalities of hypothalamic – pituitary (eg. interrupted pituitary stem syndrome - PSIS), the maximum peak of the GH is correlated negatively with the answer to the treatment with rhGH in the first year of therapy (13-15). There are some authors who deny this thing, who have demonstrated that the small values of GH at the stimulation tests are weak predictors of the growth (16).

Out of our group of 47 children with pituitary dwarfism, 9 of them associated subclinical hypothyroidism, and one of them was diagnosed with chronic autoimmune thyroiditis. In the case of these patients, the treatment with thyroid hormones in moderate doses should be associated with growth hormone, known being the fact that T4 multiplies the receivers for GH.

The natural course of the chronic autoimmune thyroiditis at children and teenagers presents a high variability regarding the dimensions of the thyroid and the hormonal status (17-20). The treatment with Euthyrox at these patients is controversial and, up to now, it was recommended only to the patients with goiter and hypothyroidism (21).

There are a few studies about the children with Hashimoto thyroiditis for evaluating the dimension of the thyroid under treatment with Euthyrox and most of them did not use the ultrasound as a means for measurement (17, 22, 23). In the last years it was shown that using Euthyrox is efficient in decreasing the thyroid volume (ultrasound evaluated) not only at the children with goiter and

hypothyroidism, but also at those with or without goiter and normal thyroid function (22,23).

Conclusions

1. The treatment with the growth hormone at the children with GHD is an important ally regarding the amelioration of the consequences due to the hormone deficiency, its main aim being the improvement of the height during the childhood and the obtaining of a final normal height.

2. After a year of treatment with rhGH (Zomacton), at our patients, we noticed a significant improvement of the growing speed, comparatively with the year prior to the beginning of the therapy, and we also saw an amelioration of the deficiency of the stature with 0,74 SD. The growth speed under treatment the Z score of the height had comparable values at the boys and at the girls.

3. It was shown there are different variables that correlate, in a negative or in a positive way, with the answer to the therapy with rhGH at the children with GHD. These factors only partially explain the individual variability in the case of the substitution therapy at the children with pituitary dwarfism.

4. Our results show inverse correlation between the growth speed during the treatment and the following parameters: the chronological age at the beginning of the treatment, the bone age, the delay of the bone age more than 3 years.

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