Clinical, Hormonal and Metabolic Aspects of Some Forms of Stunting in Children

Renata Markosyan[1,*] and Natalya Volevodz[2]

[1]*Yerevan State Medical University, Department of Endocrinology, "Muratzan" Yerevan State Medical University Hospital, Yerevan, Armenia*

[2]*Department of Endocrinology and Diabetology of Pediatric Faculty, First Moscow State Medical University after I. M. Sechenov, Russian State Scientific Center for Studying Endocrinology, Moscow, Russia*

Abstract: The goal of the present research was to study the structure and clinical features of various clinical-pathogenetic forms of growth retardation in children, determine the variant of hormonal and metabolic changes in different forms of stunting. The present paper demonstrates heterogenicity of anthropometric, hormonal, radiological manifestations in various forms of stunting, which proves the necessity of differenciated approach to the problem of stunting.

Keywords: Stunting, growth hormone, constitutional growth retardation.

1. INTRODUCTION

Children's height is regulated by the interaction of genetic, hormonal, metabolic and cellular and many other most complicated systems and is one of the main health indices of the growing organism. The etiology of stunting is various. According to the data of various authors the stunting occurrence makes from 3 up to 7% [1]. Growth retardation is most often caused by the child's development and growth constitutional peculiarities, and the most expressed clinical manifestations and the most severe prognosis of the disease have the patients with growth hormone (GH) deficiency who make about 8-9% of the whole number of dwarfish children [2].

The goal of the present research was to study the structure and clinical features of various clinical-pathogenetic forms of growth retardation in children, determine the variant of hormonal and metabolic changes in different forms of stunting.

2. MATERIAL AND METHODS

Data analysis of the examination of 1500 schoolchildren of Yerevan (780 girls and 720 boys) has been carried out with the aim to study the stunting rate in children. Stunting structure was analysed considering the examination data of 189 patients, previously not examined, with growth retardation more than 2 SDS (standart deviation score). 15 patients with somatotropic deficiency were treated by r-GH during 1 year.

All the patients underwent anthropometry. Measurements were carried out according to the standart technique [3]. Physical development parameters (growth, growth speed) expressed in SDS were evaluated by the standarts of Tanner 1976 [4]. Sexual development evaluation was carried out by Tanner's classification (1968). The testicles volume was measured by means of Prader's orchidometer.

Bone age was carried out basing on Greulich-Pyle hand and wrist X-ray atlas. The dynamics of bone maturity was evaluated as bone age measuring for a certain period of time.

Calculation of the prognosed growth was done by Bayey-Pinneau method. Target growth was calculated by the formula–father's growth + mother's growth/2 ± 6.5.

To evaluate the thyroid status the TSH and free T4 level was determined, as well as prolactin and cortisol levels. Hormonal study was done by electro-chemiluminiscent analysis on Eleccsis (Hoffman La Roche, 2010) analysator.

The hypophyseal somatotropic function was based on the study of the stimulated secretion of growth hormone in the blood serum.

The stimulated secretion was studied against the background of the standart pharmacological tests with arginine and clofeline [5]. The level of serum GH, IGF-1 (SDS), IGFBP-3 was measured by IFA method. The patients underwent blood biochemical analysis. The patients with GH deficiency and idiopathic short stature

*Address correspondence to this author at the Yerevan State Medical University, Endocrinology Clinic, "Muratzan" University Hospital; Tel: +374 60621530, 094450469; E-mail: renatamarkosyan@mail.ru

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underwent brain MRI. Kariotype was determined in all the girls. The safety and efficiency of r-GH treatment was studied in 25 children during one year. Monotherapy by r-GH was administered in isolated GH deficiency. In combined deficiency of other tropic hormones of the hypophysis the substitutional therapy corresponding to the deficiency type was carried out. Therapy efficiency was evaluated by the growth speed change (cm /year and in SDS), growth SDS dymanics (ΔSDS growth) as well as bone maturity dynamics. Statistical analysis was done by means of statistical parametric and non-parametric programs (SPSS). The reliable value was $p < 0.05$.

3. RESULTS

The stunting structure of the patients examined in the Endocrinology department of "Muratzan" hospital. 189 patients, referred by pediatricians and pediatric endocrinologists due to growth retardation more than -2SDS, were studied.

Average chronological age of the examined patients was 8.87 ± 4.6 (2.8 ÷ 17.0). The patients' average growth expressed in growth SDS made -3.37 ± 1.06 (-2.1 ÷ - 8.0). Based on the complex clinical hormonal study, the mentioned cohort of stunting children was divided as follows: growth retardation in 2.1% of children was due to a chronic disease, bone system pathology was revealed in 9% and intrauteral growth retardation was diagnosed in 5.3% of patients. Shereshevsky-Turner syndrome was diagnosed in 9% of the female patients according to the karyotype data. According to the stimulation test data a normal secretion of GH in stimulation (> 10 ng/ml) was observed in 81 patients. Later, in that cohort of the patients, constitutional growth delay with puberty retardation (sexual growth retardation- mammal glands growth absence in 13-years old girls, testicles volume less than 4 mm in boys) was diagnosed in 14.3% of children. The rest 28.6% of the patients made the pre-pubertal children group with idiopathic stunting. According to the results of stimulation tests with arginine and clofeline the somatotropic deficiency was revealed in 16.4% of the patients. In the rest of 15.3% stunting was due to the primary hypothyroidism.

Analysing growth SDS of the patients with different forms of stunting it can be suggested that the most expressed growth retardation is noted in stunting due to GH deficiency. The least retardation in stunting was observed due to various chronic diseases.

3.1. Anthropometric Study Data of Yerevan School Children

To reveal the stunting occurance rate in children growth measurement of 1500 schoolchildren living in Yerevan was carried out. Average chronological age of the examined children made 10.08 ± 3.28 (5.8 ÷ 18.0) years. The number of boys was 53.5% (n = 802) and girls–46.5% (n = 698) among all the examined children. SDS growth analysis showed that the growth of 93% of children (n = 1394) corresponded to the age norms (-2 SDS ÷ + 2 SDS). Among the examined ones 3.7% (n = 56) of children had the growth higher + 2 SDS, in which boys made 46.4%, and girls – 53.6%. Stunting (growth below -2 SDS) was revealed in 3.3% (n = 50). According to the gender the number of the dwarfish children was as follows: boys – 52% (n = 26), girls – 48% (n = 24). The number of the dwarfish boys prevailed a little over the number of the dwarfish girls, but the obtained difference is not statistically reliable ($p > 0.05$).

In the result of stimulation tests of the children referred due to stunting, the GH deficiency was diagnosed in 31 patients. The analysis of the patient's distribution according to gender showed that GH deficiency was diagnosed in 74.2% boys (n = 23) and 25.8% girls (n = 8) and their ratio was 3:1 on average. Comparing the mean age by gender no statistically reliable age difference among boys and girls was revealed ($p > 0.05$).

Analysing BMI SDS of the patients in the mentioned group it was revealed that BMI SDS was within norm for that age and gender in 18 patients (58%) with GH deficiency, elevated – in 10 patients (32.3%) and lowered – in 3 (9.7%) patients correspondingly. In correlation analysis of growth SDS and BMI SDS a positive correlation ($r = 0.625$; $p = 0.002$) is revealed in that patient group. Analysing growth (SDS growth) and bone age retargation in the patients with somatotropic deficiency, the expressed both growth and skeletal differentiation were revaled. SDS growth in those children made - 4.2 ± 1.4 on average and its values varied from -8.0 to -2.2. Bone age retardation from the chronological one was 3.8 ± 1.9 (2.1 ÷ 6.5) years on average. In correlation analysis negative correlation between the patient's age and SDS growth at the moment of study was revealed, i.e. the elder the child the more was growth retardation presented in SDS ($r = -0.38$; $p = 0.036$). Negative correlation of SDS growth and bone age retardation was also revealed ($r = -0.53$: $p = 0.002$).

By hypophyseal hormone deficiency the patients with GH deficiency were distributed as follows: isolated somatotropic deficiency was diagnosed in 16 patients, who made 51.6% and hypophyseal hormone multiple deficiency was revealed in 15 patients, who made 48.4% correspondingly. Among the patients with hypophyseal hormone multiple deficiency the acquired GH deficiency due to craniopharingioma (according to brain MRI study) was diagnosed in 5 patients. Among the patients with adenohypophyseal hormone multiple deficiency (n = 15) secondary hypothyroidism was revealed in 12 children (80%), secondary hypocorticism – in 4 children (27%) and diabetis insipidus – in 7 patients (47%). The comparison of the case history, anthropometric and X-ray findings in the groups of isolated somatotropic deficiency and hypophyseal hormone multiple deficiencies were done. Comparing the age of the first referral in the groups of patients with isolated GH deficiency and hypophyseal hormone multiple deficiency no statistically reliable difference was revealed ($p > 0.05$). Comparing the groups by the growth retardation degree expressed in SDS, as well as by the bone age retardation degree no statistically reliable difference was noted ($p > 0.05$). Comparative analysis of BMI SDS in both groups wasn't different as well ($p > 0.05$).

GH and IGF-1 concerted effect on the growth zones is necessary for normal growth processes in children. To study the IGF-1 and IGFBP -3 secretions in children with somatotropic deficiency 31 patients (8 girls and 23 boys) were studied. In the studied group a significant decrease of IGF-1 level was observed in 77.4% of cases, in the rest 22.6% of cases the IGF-1 level corresponded to the lower border of the age norm.

In translation of the absolute values into SDS indices the IGF-1 average content was -2.65 ± 0.17 for the mentioned chronologic age, and its values varied from - 3.2 to - 0.72. Besides IGF-1 decreased level, the low level of IGFBP-3, which is the main transporting protein of IGF-1, was also revealed in children with GH deficiency. The low level of IGFBP-3 was observed in 69.9% of cases. In correlation analysis between IGF-1 and IGFBP-3 levels positive correlation was observed ($r = 0.39$; $p = 0.02$). IGF-1 and IGFBP-3 concentration comparing in the groups with isolated GH deficiency and hypophyseal hormone multiple deficiency revealed no statistically reliable defference ($p > 0.05$; $p > 0.05$).

The brain MRI study was carried out in 28 patients with somatotropic deficiency. The study revealed that 19 patients had brain pathology, among which the patients with isolated somatotropic deficiency made 36.8% (n = 7), and patients with hypophyseal hormone multiple deficiency – 63.2% (n = 12). 32.1% (n = 9) of the patients had no pathology of hypothalamic – pituitary area.

The patient group with the brain pathology fell into the following groups according to the pathology type: aplasia (hypoplasia) of the crus of the adenohypophysis – in 28.6% (n = 8), the "empty Turkish sella" syndrome – 10.7% (n = 3) of patients, atypical location of neurohypophysis combined with adenohypophysis hypoplasia and aplasia (hypoplasia) of hypothalamic- hypophyseal crus, "triade" – in 10.7% (n = 3) of children, acquired deficiency of somatotropic hormone due do craniopharingioma – in 17.9% (n = 5) of patients. Hypophyseal hypoplasia occurred in 13,3% of children with adenohypophyseal hormone multiple deficiency and in 46.2% of patients with isolated GH deficiency.

To study the lipid profile state, 31 patients with GH deficiency were examined. In the cohort with hypophyseal hormone multiple deficiencies at the moment of study all the patients were placed on the substitutional therapy (except GH) and were compensated.

Different forms of dyslipidemia were revealed in all the children according to the international criteria of blood lipid level evaluation. Hypercholesterolemia was revealed in 59.2% of children with somatotropic deficiency: bordering-high level of total cholesterol (5.2-6.2 mmol/l) – in 27% of children, and high (> 6.2 mmol/l) – in 32.2% of children. Blood serum triglyceride values were within the norm in 90% and only in 10% of the patients with somatotropic deficiency it was bordering-high.

In lipid profile analysis in children with GH deficiency a statistically reliable difference depending on isolated or hypophyseal hormone multiple deficiency was observed.

In the group with hypophyseal hormone multiple deficiency cholesterol content was statistically higher ($p = 0.01$). There was a significant difference among the subgroups in comparing LPLD ($p = 0.01$) and triglycerides ($p = 0.01$). There was no difference in LPHD amount ($p > 0.05$).

3.2. 25 patients with Somatotropic Deficiency were Administered r-GH During 1 Year

In the mentioned cohort 10(40%) patients had hypophyseal hormone multiple deficiencies and were compensated at the moment of study. The rest 15

(60%) patients had isolated deficit of GH. All the patients got r-GH in the dose 0.033mg/kg/24 hours (according to the international recommendations on growth hormone deficiency treatment).

Thus, growth hormone therapy in the patients with somatotropic deficiency leads to the normalization of IGF-1 content in the blood serum as well as IGFBP-3 content increase up to their normal values.

It can also be suggested that growth hormone therapy in the patients with somatotropic deficiency causes normalization of the total cholesterole content, low density lipoproteins and didn't influence other parameters of the lipid exchange (LPHD, trigycerides) (Table **1**). In r-GH therapy the changes in renal function indices (creatinine, urea), hepatic function parameters (ALT, AST, total protein), as well as in carbohydrate exchange indices (glycemia, HbA1C) weren't observed. In the thyroid gland function and adrenal gland function study there was observed free T4 concentration decrease in 3 patients during 1 month, and 2 patients showed cortosole level decrease, later the data came back to normal.

4. IDIOPATHIC STUNTING

According to the stimulation test data (stimulated growth hormone level in the test higher 10ng/ml), idiopathic stunting was diagnosed in 54 patients. At the beginning of the study all the children were in pre-pubertal state. Patients' gender analysis showed that idiopathic stunting delay was diagnosed in 79.63% (n = 43) boys and 20.37% (n = 11) girls. Boys and girls proportion in the mentioned cohort of patients made on average 4:1.

There was no statistically reliable age difference (P > 0.05) of the boys and girls referred to the clinic. BMI SDS analysis of the patients in the mentioned cohort showed that BMI SDS was within the norm for that age and gender in 38 patients (70.4%) with idiopathic stunting, it was increased in 10 patients (18.5%), and the decreased one was observed in 6(11.1%). Analysing the degree of growth retardation (SDS growth) and bone age we determined that SDS growth in the studied group was -2.9 ± 0.55 (-4.8÷-2.2) on average. At that, 16 children (29,6%) had growth expressed lagging. Bone age dropped behind the chronological one by 1.6 ± 1.2 (0 ÷ 3.6) years on average. SDS growth speed in the mentioned group was -1.54 ± 1.39(-4.92÷1.15). No correlation in the growth retardation degree with gender, body length and mass at birth (SDS) was observed.

In the studied group family stunting was observed in 35% of children with idiopathic stunting. Growth retardation over 1.5 SDS of at least one of the parents was chosen as criteria of family stunting (according ESPE classification). In the present cohort the patients age varied from 3.2 to 11.9 years and made 6.9 ± 2.7 years on average. Growth SDS for the mentioned cohort of patients made -3.0 ± 0.65(-4.8÷-2.4) on average. Studying the family stunting group (n = 19), it was revealed that both patients were dwarfish in 53%

Table 1: Clinical and Laboratory Features of Patients with GH Deficiency before and after Treatment

	Before Treatment	After 6 Month Treatment	After 12 Month Treatment	P Value (6 Month, 12 Month)
Height (cm)	108,9 ± 15,0 (87,0 ÷ 131,0)	113,2 ± 15,2 (92,0 ÷ 136,0)	117,2 ± 14,6 (95,5 ÷ 139,0)	P=0.001; P=0.001
Height SDS	- 3,8 ± 1,0 (- 6,3 ÷ - 2,6)	- 3,4 ± 1,0 (- 5,9 ÷ - 2,2)	- 2,9 ± 0.96 (- 5,2 ÷ - 1,7)	P=0.001; P=0.001
Bone age	5,5 ± 2,6 (2,0 ÷ 10.0)	6,1 ± 2,5 (4,0 ÷ 11,0)	6,9 ± 2,5 (4,0 ÷ 11,0)	P=0.001; P=0.001
BMI SDS	1,7 + 0.7 (1,3 ÷ 5,5)	I,4 ± 0.6 (1,1 ÷ 5,3)	I,4 ± 0.9 (0.9 ÷ 5,1)	P>0.05; P>0.05
IGF- 1	53,25 ± 44,7 (11,0 ÷ 175,0)	217,9 ± 66,1 (160.0 ÷ 354,0)	248,7 ± 70.7 (160 ÷ 354)	P=0.001; P=0.001
IGFBP- 3	745 ± 443 (324 ÷ 854)	1653 ± 437 (1200 ÷ 2398)	1653 ± 437 (1200 ÷ 2398)	P=0.001; P=0.001
Cholesterol	5,68 ± 1,55 (3,21- 12,39)	4,79 ± 1,05 (2,93- 9,23)	4,79 ± 1,01 (3,05- 7,3)	P=0.001; P=0.001
LPLD	3,83 ± 1,44 (1,3- 10.86)	3,14 ± 1,19 (0.76- 8,81)	3,17 ± 1,07 (0.92- 5,62)	P=0.001; P=0.001
LDHD	1,24 ± 0.24 (0.68- 2,02)	1,19 ± 0.26 (0.61- 2,0)	1,29 ± 0.29 (0.60- 2,8)	P>0.05; P>0.05
Triglyceride	0.9 ± 0.4 (0.5 ÷ 1,8)	0.9 ± 0.3 (0.6 ÷ 1,7)	0.9 ± 0.3 (0.7 ÷ 1,7)	P>0.05; P>0.05

of cases, only father – in 21.6% of cases and only mother – in 25.4% of cases. The bone age in the family stunting group made 5.5 ± 2.9(2.0 ÷ 12.0). Studying the bone age retardation from the chronologic one made 1.3 ± 0.4(0.1÷2.8).

Non-family form of idiopathic sunting included 65% (n = 35) of patients. Patients' age varied from 3.0 to 12,0 years and was 8.6 ± 2.5 years on average. Bone age in the group with family stunting was 7.1 ± 2.5 (2.0 ÷ 11.0) years. Bone age lagging analysis revealed 1.8 ± 1.4 (0.1 ÷ 3.5) years.

Growth factor study (IGF-1, IGFBP-3) was carried out in the group of idiopathic stunting. IGF-1 average amount was 136.85 ± 73.20(34.0 ÷ 321.0) ng/ml, its SDS made -0.39 ± 0.3 (-2,3 ÷ 1,5). IGF-1 level decrease was observed in the studied group in 22% of patients (n = 12), in the rest 77,8% (n = 42) of patients IGF-1 level was within the norm. In 16,7% of cases in the group of children with idiopathic stunting low level of IGFBP-3, the main transporting protein IGF-1 was revealed as well. IGFBP-3 average amount in the blood serum varied, making 1185 ± 411 (675 ÷ 2450) ng/ml. In correlation analysis no connection was revealed between the maximum concentration of the growth hormone and IGF-I level (r = -0.02: p = 0.148). In correlation analysis positive correlation (r = 0.79: p = 0.000) between IGF-1 and IGFBP-3 levels is observed. The study of growth hormone secretion effect didn't reveal any correlation between the growth hormone peak and growth retardation degree (p>0.05) (Figure **1**). No correlation was revealed in correlation analysis of growth SDS from GH maximum concentration. (r = 0.020; p = 0.886). Correlation between IGF-1 level and growth SDS was revealed in correlation analysis by Spearman (r = 0.34, p = 0.008).

22 patients with idiopathic stunting underwent hypothalamic–pituitary area MRI. The evaluation of the structural, morphological characteristics of hypothalamic -pituitary area was carried out. According to the brain MRI findings normal MRI image was observed in 77% (17 patients) of children with idiopathic stunting, and in the remaining cases the anomalies of various degree were observed: hypoplasia (aplasia) of the adenohypophysis crus in 14% (3 patients) of cases, 1 patient displayed Arnold-Chiari malformation (4.5%) and 1 patient had the "empty Turkish sella" syndrome - (4.5%).

5. SHERESHEVSKI-TURNER SYNDROME

To find out the cause of stunting all the girls underwent karyotype study, which revealed 17 patients with Shereshevsky-Turner syndrome. Case history study showed that most of the examined patients with Shereshevsky-Turner syndrome had the body length and mass decrease at birth under normal gestation terms. Weight SDS at birth varied from -1.2 to 0.6 and made -2.1÷0.3 on average. The average growth SDS of the parents made -0.7 ± 0.9(-2.0 ÷ 0.8) and didn't differ from that of healthy population.

Kariotype study detailed analysis showed that pure monosomy was revealed in 52.9 % (n = 9) of patients (XO kariotype) and the mosaic form was observed in 47.1 % (n = 8) of cases.

All the patients with this syndrome underwent thorough clinical-hormonal study. Growth and physical development disturbance was revealed in all the patients with Shereshevsky-Turner syndrome. Growth and growth speed SDS for the children with Shereshevsky-Turner syndrome was calculated twice: by percentile Tables for healthy children and for children with Shereshevsky-Turner syndrome. The growth of the examined group made 118.7 ± 14.1 (98.0 ÷ 143.0) cm on average. Growth mean SDS compared to that of the healthy population made -3.76 ± 0.8(-5.6 ÷ - 2.5), and growth mean SDS calculated for the patients with Shereshevsky-Turner syndrome made -1.1 ± 0.9(-2.4 ÷ 1.1). Bone age of the mentioned cohort of the patients made 9.1 ± 2.2(4.0 ÷ 12.0) years and dropped back of the chronological by 1.4 ± 1.1 (0 ÷ 2.0) years on average. Growth speed in that group made 4.2 ± 0.6 (3.5 ÷ 5.2) cm/year. The study, carried out by Spearman's correlation test showed negative correlation of growth SDS on the age of reference (r = -0.7; p = 0.001), i.e. the elder the patient's age at the moment of reference to the medical center, the more was growth retardation (SDS). There was no correlation between growth SDS and bone age retardation (r = -0.3; p = 0.2). Comparative analysis of growth SDS and bone age lagging in the groups with pure monosomy and the mosaic form of Shereshevsky-Turner syndrome didn't reveal statistically reliable difference (p > 0.05; p > 0.05). All the patients with Shereshevsky-Turner syndrome underwent IGF-1 level study, absolute values of which were 191.5 ± 60.8(125.0 ÷ 287.0) ng/ml on average. We observed IGF-1 low level in 7 patients (41.27%) of this patients' cohort.

6. DISCUSSION

Despite diagnostic method and stunting therapy perfection, the etiology of stunting still remains unknown in most cases. Unfortunarely, the

contemporary methods of diagnostics are not always applicable. To work out new methods of diagnostics, further study of peculiarities of anthropometric, hormonal, radiological manifestations of various forms of stunting in children is necessary. It is possible to carry out differential diagnostics of different forms of growth retardation basing on the case history data and anthropometric peculiarities. So, children with somatotropic deficiency differ from the those with idiopathic stunting by the age of reference to the endocrinologist, growth retardation intensity, bone age lagging. To make the diagnosis of idiopathic stunting it is necessary to exclude other causes of growth retardation, using modern methods of diagnostics. At that, it should be considered, that diagnosis is made by means of integrated evaluation of all the research methods.

Nowadays more than 40-years experience of r-GH preparation use for treating somatotropic deficiency has already been accumulated and the research of the effects and therapy protocol perfection is continuing [6]. The most optimal schemes and doses of r-GH preparations have been discussed so far, the criteria, which allow evaluating the efficacy of the carried out treatment, have been worked out.

A wide-scale research of various metabolic effects of r-GH long-term use in different states in children and late effect of this treatment has been started [7]. A new stage of scientific search concerning the expansion of indication to r-GH administration and its use in stunting, not connected with own GH deficiency, as well as in severe diseases and conditions, accompanied with catabolism enhancement.

In connection with this, the study of r-GH effect on metabolic processes becomes especially topical.

The present paper is the first research in Armenia, in which an attempt to evaluate clinical-metabolic peculiarities of different forms of stunting, as well as to evaluate the range of metabolic effects and the peculiarities of growth index dynamics in r-GH preparation use in children with somatotropic deficiency has been made. The results of the present research have shown that such a treatment allows not only achieving the growth index increase in patients with somatotropic deficiency, but also normalizing lipid exchange indices, to prevent cardio-vascular pathology formation at the elder age [8]. The present paper demonstrates heterogenicity of anthropometric, hormonal, radiological manifestations in various forms of stunting, which proves the necessity of diferenciated approach to the problem of stunting.

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