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# CLINICAL FEATURES OF GROWTH HORMONE DEFICIENCY IN CHILDREN

**VOLEVODZ N.N.[1,2], MARKOSYAN R.L.[3,4]**

[1] Department of Endocrinology and Diabetology of Pediatric Faculty, Moscow, Russia
[2] First Moscow State Medical University after I.M.Sechenov, Russian State Scientific Center for Studying Endocrinology, Moscow, Russia
[3] Yerevan State Medical University, Department of Endocrinology, Yerevan, Armenia
[4] "Muratsan" Yerevan State Medical University Hospital, Yerevan, Armenia

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***ABSTRACT***

*The pathological growth takes one of the leading places in the structure of endocrine pathologies. In contemporary literature the clinical and hormonal-metabolic features of the most studied causes of growth retardation such as growth hormone deficiency, hypothyroidism, skeletal dysplasia, psychosocial disorders and chromosomal anomalies are widely discussed. The incidence of growth retardation due to growth hormone deficiency varies from 1:4000 to 1:10000 newborns. Growth retardation is more typical for men. Children with growth hormone deficiency have combined clinical, anthropometric, radiologic, hormonal, genetic and metabolic changes. Causes of growth hormone deficiency syndrome are either total or partial deficiency of growth hormone or secretion of pathological growth hormone and decreased levels of growth factors. The gene engineering method of creating recombinant growth hormone (somatotropine) made a real revolution in the treatment of children with different forms of short stature and gave the opportunity to the patients to receive permanent replacement therapy for reaching normal height.*

***Keywords:*** short stature, growth hormone, hypopituitarism.

## INTRODUCTION

During recent years a huge progress in science, especially in endocrinology, has been reported due to the development of molecular genetics. The pathological growth takes one of the leading places in the structure of endocrine pathologies. In contemporary literature the clinical and hormonal-metabolic features of the most studied causes of growth retardation such as growth hormone deficiency, hypothyroidism, skeletal dysplasia, psychosocial disorders and chromosomal anomalies are widely discussed [*Zagar A.H. et al., 1998*].

The most important clinical problem in children with growth retardation is differential diagnosis of different causes of nanism for determining the accurate type of nanism, prognosing and prescribing corresponding therapy. The most severe growth retardation is seen in growth hormone deficiency (somatotropin deficiency) [*Markosyan R., Volevodz N., 2012*]. The incidence of growth retardation due to growth hormone deficiency varies from 1:4000 to 1:10000 newborns [*Dedov I., Peterkova V.A., 2006*]. Growth retardation is more typical for men. Recent studies showed significant heterogeneity in clinical signs of the disease depending on etiology and type of growth hormone deficiency. Molecular defects in number of genes are determined, which have resulted in defects of synthesis and secretion of growth hormone or peripheral action of growth hormone and growth factors.

Children with growth hormone deficiency have combined clinical, anthropometric, radiologic, hormonal, genetic and metabolic changes. Causes of growth hormone deficiency syndrome are either total or partial deficiency of growth hormone or secretion of pathological growth hormone and decreased levels of growth factors.

Growth hormone deficiency is classified into two groups: total and partial deficiency of growth hormone. Besides, the deficiency can be isolated or combined with deficiency of other tropic hormones of anterior pituitary." Panhypopituitarism"

***ADDRESS FOR CORRESPONDENCE:***
Yerevan State Medical University after M. Heratsi
2 Koryun Street, Yerevan, 0025, Armenia
Tel.: (+374 94) 450 469
E-mail: renatamarkosyan@mail.ru

is defined as a state in which all hormones, produced by anterior pituitary gland are deficient.

The deficiency of growth hormone can be congenital or acquired and manifest at any time after birth. Most often causes of growth hormone deficiency are the pathologies of hypothalamus and the hypophyseal stalk which have resulted in deficiency of hypothalamic signals to hypothesis. It's noted that often mothers of patients with GH deficiency had different pathologies of pregnancy and placenta in the late stages of pregnancy or delivery trauma. Congenital hypopituitarism can be either the result of midbrain defects or the result of gene pathologies which control GH production or pathology of genes involved in pituitary formation (POU1F1, PROP-1, HESK-1, LHX-3, LHX-4, PITX-2) and GHRH signal formation (GHRH-R) [*Stelling M. et al., 1980*].

Since 1958 only growth hormone extracted from human cadaver pituitary gland was used for the treatment of growth hormone deficiency (cadaverik material). It turned out that this kind of treatment is associated with high risk of fatal Creutzfeldt-Jakob disease affecting central nervous system. Since 1985 using the extracted growth hormone has been officially prohibited.

The gene engineering method of creating recombinant growth hormone GH made a real revolution in the treatment of children with different forms of short stature and gave the opportunity to the patients receiving permanent replacement therapy to reach normal height.

Meanwhile till now the detailed evaluation of this problem hasn't been done in Armenia.

Thus, the aims of this study are studying the features and evaluation of anthropometric, clinical-hormonal and metabolic changes in children with short stature in Armenia.

## Material and methods

General examination of all patients with growth retardation (history taking, examination, anthropometry and evaluation of physical and sexual maturity) were held in the Department of Endocrinology of "Muratsan" University Hospital. In pediatric practice for the growth estimation the indicator SDS (standard deviation score - coefficient of the standard deviation) of growth rate showed how many standard d-deviations (sigma deviations) the indicators of individual growth differ from average values [*Physical status, 1995*]. Calculation was carried out according to the following formula:

$$\text{SDS of growth} = \frac{x - X}{SD},$$

where: x - growth of the child; X - average growth for the given sex and chronological age; SD- standard deviation of growth for the given sex and chronological age. Advantage of the method is in possibility to estimate and describe sharply expressed deviations which characterize endocrine pathology more often. Deviations of the studied parameter more than 2 SD (SD> +2 and SD <-2) are regarded as pathological, and children are subjected to the further deepen examination [*Markosyan R. et al., 2012*]. Proceeding from it, the criteria of including the patients were: age at the moment of diagnose statement - ≤18 years, growth - SD <-2, normal indicators of length and weight at the birth->-2 SD according to the term of gestational age, absence of body disproportionally, chronic systemic diseases and developmental abnormalities.

All children were examined by common plan which included the following points:

1. Height measurement in the morning by standard technique (heels brought together, buttocks and scapulas pressed against the vertical plate of stadiometer, the head in the plane of Frankfurt, height fixed on the exhale) accurately up to centimeters. The mean height from three consequent measurements was used [*Flugel B.et al., 1986; Hall J. et al., 2008*]. The percentile tables of normal height and weight based on the measurements of national representative group for girls and boys were used to evaluate height and physical development of children [*Tanner J.M., Whitehouse R.H., 1976*].

2. The weight was measured fasting, in the morning. BMI was calculated according to the following formula: body, max, index (BMI) = weight (kg)/height$^2$ (m$^2$). The scores were evaluated according to the normative tables of body mass index (kg/m$^2$) for children and adolescents depending on sex and age [*Hammer L.D. et al., 2009*].

3. Evaluation of sexual maturity was done according to classification of Tanner (1976).The volumes of testes were measured by Prader's orchidometer.

4. The results of wrist X-rays (hand bone age) were evaluated by radiological atlas of W.W.Greulich and S.I.Pyle [*Greulich W.W., Pyle S.I., 1979*].

The genetically expected growth (GEG) was calculated by these formulas:

For boys:

$$GEG = \frac{\text{father's height + mother's height +12,5}}{2}$$

for girls

$$GEG = \frac{\text{father's height + mother's height -12,5}}{2}$$

5. Besides absolute indicators of growth the most important indicator in process of growth is growth of rate. Growth rate presents the cumulative indicator reflecting dynamics of growth in time. Growth rate is measured in cm/year. Definition of growth rate (cm/year) was carried according to the following formula:

$$\text{growth rate} = \frac{H_2 - H_1}{CA_2 - CA_1},$$

where: $H_1$- height of a child at the moment of the previous study (at least 6 months); $H_2$ - height of a child at the moment of current study; $CA_1$- chronological age at the moment of previous study (at least 6 months), $CA_2$ - chronological age at the moment of current study.

6. Expected final height was calculated according to the tables of Bayley-Pinneau [*Baley N., Pinneau S.R., 1987*].

7. Definition of levels of hormones in serum of children - somatothropic hormone (STH), thyritropic hormone (TTH), free thyroxine (free $T_4$), prolactin (PRL), cortisol (CORT) was carried out according to electrochemiluminescence method on the device «Elecsis 2010" ("Hofman La Rosh", Switzerland). The diagnostics of growth hormone deficiency was carried out according to the common standards. Stimulating tests with arginine and/or clonidine were used to diagnose GH deficiency in the hospital, fasting at 9:00 a.m. in the presence of the doctor [*Gallussi F. et al., 2006; 2009*].The results of stimulating test were evaluated according to the following way: the concentration of growth hormone above than 10ng/ml (in both tests) was considered to be normal; the concentration of growth hormone less than 7ng/ml was considered as total growth hormone deficiency. Values between 7-10ng/ml were considered to be partial deficiency of growth hormone.

8. Level definition of insulin-like growth factor-1 (IGF-1) in serum was carried out according to immunoenzymatic method (ELISA) («DRG-International Inc.», Germany) on the device "StatFax 2600" (USA). The biochemical analysis of blood was carried out in the stidied group of children.

9. All children with growth hormone deficiency underwent brain MRI.

10. Treatment of patients was carried out by gene engineered drug of the growth hormone registered in Armenia «Nordilet» ("Novo Nordisk", Denmark) in the dose of 0.033 *mg/kg* (0.1 I *U/kg*) a day, daily at 21:00-22:00. The growth hormone was injected in anterior surface of the thigh and lateral surface of the arm subcutaneous and rotating.

Monotherapy with recombinant GH was prescribed to the patients with isolated growth hormone deficiency. The corresponding replacement therapy with levothyroxine, sex steroids, hormones of adrenal cortex or antidiuretic hormone. was prescribed to the patients with combined deficiency of several tropic hormones.

## Results and discussion

Structural analysis of short stature was carried out according to data of patients' referring in Department of Endocrinology of University hospital "Muratsan" from May 2008 to May 2013 . According to our data the incidence of different forms of nanism was:

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|---|---|
| Growth hormone deficiency | 16% |
| Primary hypothyroidism | 9% |
| Systemic skeletal diseases | 5% |
| Idiopathic nanism | 28% |
| Constitutional delay of growth and puberty | 32% |
| Nanism due to a genetic syndrome | 10% |

Of the total number of patients who referred for studying the anthropometric and clinical-metabolic features in children with growth hormone deficiency 33 children at age of 1.8-17.5 were examined. Average chronological age was 9.4 years. Average age of referring to the doctor was 8.4 years for boys and 6.7 years for girls.

In the studied groups of patients with growth hormone deficiency predominated 25 boys (7.6%) and 8 girls (24%). Girls to boys average ratio was 3:1. All children at the moment of examination and stimulation tests had no signs of puberty (Tanner stage 1). Nobody received growth hormone or anabolic steroids during minimum one year before the study began.

The average SDS in growth hormone deficiency accounted (-4).

Based on the form of deficiency the patients were divided in the following way: isolated deficiency of growth hormone in 22 children (67%), combined deficiency of hormones of adenohypophysis or neurohypophysis in 11 children (33%). From 22 patients with isolated growth hormone deficiency 14 (64%) the total deficiency was diagnosed (stimulated GH less than 7 ng/ml) and in 8 patients (36%) partial deficiency was diagnosed (stimulated GH above than 7ng/ml but less than 10 ng/ml).

All 33 patients with growth hormone deficiency GH levels after stimulating tests with arginine and clofeline less than 10ng/ml) underwent MRI of hypothalamic-pituitary region. The morphological and structural characteristics of hypothalamic-pituitary region were evaluated.

The results of MRI revealed no pathology of hypothalamus-pituitary region in 11 children (33.5%), high prevalence of hyperplasia of adenohypophysis in 13 children (39.5%), brain neoplasia in 4 children (12%). Combined hyperplasia of adenohypophysis and ectopy of neurohypophysis were revealed in 3 children (9%) and empty sella turcica in 2 patients (6%).

### Conclusion

Thus, summarizing the above mentioned, it is possible to conclude, that in Armenia there is also the problem of short stature which is very actual in children endocrinology in our days. Priority problems to make decision, in our opinion, are the following - revealing the incidence of GH deficiency, structural analysis of nanism in children, creation of national register of the patients with somatotropic deficiency, and working-out guidelines for early diagnostics and optimal treatment.

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