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REVIEW

GENETICALLY DETERMINED STUNTING: MODERN POSSIBILITIES OF DIAGNOSIS AND TREATMENT

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

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

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ABSTRACT

In many inherited genetic diseases short stature very frequently represents a serious psychological problem and the cause of social adaptation failure or dysadaptation. Small stature is the most common feature of Shereshevsky-Turner syndrome. The occurrence rate of this syndrome is 1 case per 2,000-2,500 of live-born girls. The disease is of sporadic character. The triad of signs is typical of the mentioned pathology: short height, gonad dysgenesia and various organ congenital anomalies. The cases of stunting are Prader-Willi syndrome, Noonan syndrome, Silver-Russell syndrome, Cornelia de Lange syndrome. Development of genetically engineered method for obtaining recombinant growth hormone has triggered a real revolution in treatment of children with various forms of stunting. Particularly, an opportunity to increase growth rate in children has appeared, thereby improving growth prognosis. The patients with genetically determined stunting have a high incidence of congenital malformations and presence of various comorbidities, which require life-long monitoring by various health professionals. Observation of patients with the above syndromes must be comprehensive and should take into account different age-related needs. Timely medical intervention in the precise group of patients significantly reduces the risk of early morbidity and mortality and improves the quality of life. The challenges of early diagnosis with the use of modern methods of investigation remain unresolved and determine the relevance of the problem.

Keywords: *short height, genetic diseases, syndromes, growth hormone.*

In many inherited genetic diseases short height very often represents a serious psychological problem and the cause of social adaptation failure or dysadaptation. Development of genetically engineered method for obtaining recombinant growth hormone (rGH) has triggered a real revolution in treatment of children with various forms of stunting. Particularly, an opportunity to increase growth rate in children has appeared, thereby improving growth prognosis. The present review presents modern opportunities for diagnosis and treatment of some syndromal forms of stunting.

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

Shereshevsky-Turner syndrome: Shereshevsky-Turner syndrome is of sporadic character and its occurrence rate is 1 case per 2,000-2,500 of live-born girls [*Saenger P., 1999; Sybert V., McCauley E., 2004*]. The triad of signs is typical for the mentioned pathology: short height, gonad dysgenesia and various organ congenital anomalies [*The Turner Syndrome Study Group, 2006*]. Shereshevsky-Turner syndrome is the most common chromosome anomaly, which causes stunting in girls [*Gravholt C., 2004*]. The syndrome is either caused by a complete absence of one of the two X-chromosomes or its structural anomalies (deletions of the short or long arms, translocations) or various mosaic karyotypes. Only 1% of the embryos with 45XO karyotype get the fetal state, others do not attain 28 weeks of gestation and about 10% of spontaneous abor-

tions is due to X monosomy [*Saenger P., 1999*]. The presence of Y chromosome (either complete or partial) in a number of cells (45X/46XY variant is clinically manifested by virilisation, gonade mixed dysgenesia is observed which is the risk factor in gonadoblastoma development) is possible in some patients [*Dedov I. et al., 2002 a*].

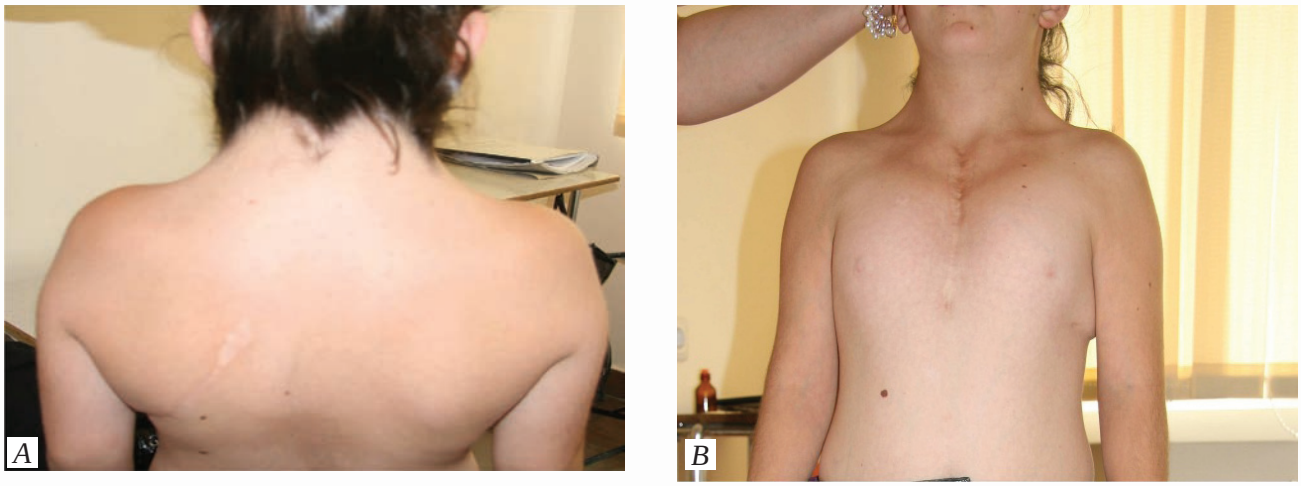
The syndrome clinical manifestations development is connected with deletion of genes SHOX (segment Xp22.33), ZFX (segment Xp22.11), USP9X (segment Xp11.4), RPS4X (segment Xq 13.1) and DIAPH2 (segment Xq22), as well as with unidentified gene deletion in Xp11.3 area [*Rappold G. et al., 2002; Mao X., Liu L., 2012*].

It is considered that ZFX and SHOX genes deletion causes stunting, RPS4X gene deletion is responsible for lymphatic edema and low survival rate during intrauteral period, USP9X and DIAPH2 genes injury is likely to explain early ovarial deficiency [*Morgan T., 2007; Melnichenko G. et al., 2013*].

The typical manifestations of Shereshevsky-Turner syndrome are as follows: short and wide neck with pterygoid skin folds stretching from the neck lateral surface to the shoulders ("the sphinx neck"), low-set hair line on the back of the head, bulge ears, wide chest with widely located nipples, epicanthus, hypoplastic convex nails (Picture 1 A; B). Micrognathia, high "gothic" palate, malocclusion are typical for 80% of patients. In female patients with Shereshevsky-Turner syndrome inner organ anomalies are frequently observed: aorta coarctation, kidney and ureter development defects; girls and women with this syndrome are most liable to develop obesity.

Growth disturbance is observed in 95% of Shereshevsky-Turner syndrome cases; it is displayed by decreased mass-growth indices at birth, growth low rate and speedy growth or growth spurt absence in adolescence. Already at the intrauterine stage girls with Shereshevsky-Turner syndrome display stunt (3 *cm* on the average) and delay in weight (500 *g* on the average). During the first 3 years of life the growth rate is relatively stable and is insignificantly distinguished from the norm. The period of osseous age of 3-11 years is characterized by a growth spurt progressive gradual decrease compared to the norm [*Lyon A. et al., 1985; Dedov I. et al., 2002 a; b*]. Growth maximum decrease is observed at the age of 14. All this causes short final height, which is by 20 *cm* lower than population average height in females and in different populations varies from 140 to 147 *cm* [*Ranke M. et al., 1988; Fonteles A., Dondoni R., 2011*].

During the period from 2010 to 2012, based on the "Muratsan" Hospital Complex 15 girls were observed due to complaints of stunting; later on they were diagnosed with Shereshevsky-Turner syndrome. Karyotype analysis showed that 53% of the surveyed girls had pure gonadal agenesis (karyotype 45XO), and the remaining 47% of



Picture 1. A. *Shereshevsky-Turner syndrome. Patient A.B. 14-year-old. Karyotype 45XO. Pterygoid skin folds stretching from the neck, low-set hair line on the back of the head.*
B. *Shereshevsky-Turner syndrome. Patient B.N. 15-year-old. Karyotype 45XO. Wide chest with widely located nipples, pterygoid skin folds stretching from the neck.*

patients had a mosaic form (mosaicism). In one patient we found partial presence of Y-chromosome (SRY sex-determining region Y) [*Volevodz N., Markosyan R., 2013*]. The average chronological age of the patients at diagnosis setting was 12.4 years (4.3÷15.4), the average height of girls at the time of admission was 122.2 *cm* (87.5÷143.0), standard deviation score (SDS) of growth made -3.3 (-2.8÷-4.4). In carrying out the hand rentgengraphy average bone age indices in girls made 9.8 years (3.5÷15.0).

According to numerous data the growth hormone (GH) deficiency does not play a significant role in growth retardation in Shereshevsky-Turner syndrome [*Ranke M. et al., 1988; Sybert V., McCauley E., 2004; The Turner Syndrome Study Group, 2006*]. Spontaneous and stimulated GH secretion in Shereshevsky-Turner syndrome female patients is on the normal or subnormal level till pubertate age. The GH secretion decrease in girls with Shereshevsky-Turner syndrome at the age of proper, but not begun pubertate is due to hypoestrogeny and is compensated by estrogen low doses used in substitutive therapy [*Ranke M. et al., 1988*]. In the recent decades it has been proved that direct genetic defects play a leading role in stunting pathogenesis at Shereshevsky-Turner syndrome due to SHOX gene deletion causing disorders of GH spontaneous secretion, insusceptibility to GH and disfunction of a system GH – insulin-like growth factor 1(IGF-1) [*Turtle E. et al., 2013*].

The main tasks in treatment of children and teenagers with Shereshevsky-Turner syndrome are increase of the final height, formation of the secondary sexual characteristics and regular menstrual cycle, correction of developmental defects, accompanying diseases treatment, osteoporosis prophylaxis. At present the correction of growth defects, sexual development and accompanying disseases is carried out according to the recommendations on Shereshevsky-Turner syndrome diagnosis and treatment adopted in 2006 [*The Turner Syndrome Study Group, 2006*].

Now stunting treatment in Shereshevsky-Turner syndrome includes application of rGH obtained by recombinant DNA technology use. The experience of rGH application in international practice for the last 15 years has allowed to consider this therapy to be a choice method for stunting treatment in Shereshevsky-Turner syndrome [*Blum W. et al., 2013*]. The contemporary method of human rGH application for stunting treatment in female patients with Shereshevsky-Turner syndrome recommends the following therapeutic scheme: daily subcutaneous administration of 0.05 *mg/kg* of the mentioned substance in the evening (at 8:00–10:00 p.m.). The specified dose by 50% exceeds the standard dose used in children with somatotrophic deficiency (hypophysial nanism) [*Dedov I. et al., 2002 a; The Turner Syndrome Study Group, 2006*]. The rGH therapy is discontinued, when the osseous age of the patient is equal to 15 years and growth speed falls up to 2 *cm* a year [*Dacou-Voutetakis C. et al., 1998; American Association of Clinical Endocrinologists, 2003; The Turner Syndrome Study Group, 2006*]. The osseous age is evaluated according to the results of the left hand X-ray study. The aim of rGH-based treatment in Shereshevsky-Turner syndrome is to stimulate the growth over the genetic potential. The longer growth stimulating treatment in prepubertal period, the higher is the final height. Individual differences in susceptibility to the growth stimulating therapy are noted depending on such factors as stunt degree at the moment of therapy start, targeted height (based on the parents' height indices), the age at the moment of therapy start, therapy duration [*Donaldson M. et al., 2006*].

Data of numerous studies show that rGH therapy administration causes growth rate increase and significantly improves growth prognosis [*Carel J. et al., 1998; Dacou-Voutetakis C. et al., 1998; Betts P. et al., 1999; Hochberg Z., Zadik Z., 1999*]. On average, in long-term therapy the growth rate increase up to 7 *cm/year* was observed during the first year, during the 2nd year its increase was almost 6 *cm/year* and during the 3rd year – 5 *cm/year*, which was still more than in non-treated patients [*Nilsson K. et al., 1996; Rosenfeld R. et al., 1998; Dedov I. et al., 2010*]. The studies conducted at the Research Center of Endocrinology (Russia) showed that treatment of Shereshevsky-Turner syndrome female patients with rGH brought to growth increase by 8.7 *cm* (before treatment girls

grew about 4 *cm* a year on average) and by 6 *cm* during the 2nd year of therapy [*Pareren Y. et al., 2003; Dedov I. et al., 2010*].

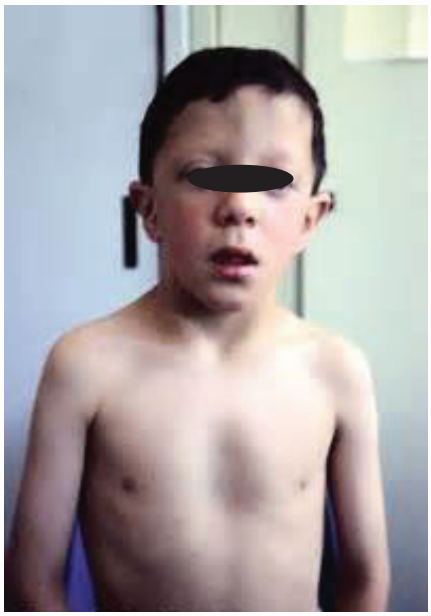
According to data of different researchers, the growth final increase determined as the difference between the final growth and predicted growth before the treatment start made from 3.5 *cm* up to 9.0 *cm*, and individual indices made from 4.7 up to 21.0 *cm* [*Dacou-Voutetakis C. et al., 1998; Rosenfeld R. et al., 1998; Hochberg Z., Zadik Z., 1999; Quigley C. et al., 2002*]. If the treatment begins in due time and adequate dose administration regimen of rGH preparations, optimized estrogen therapy are used, the final growth could be reliably increased up to the 5th percentile of healthy female population [*Quigley C. et al., 2002; The Turner Syndrome Study Group, 2006*]. Monitoring of a pediatrician-endocrinologist is necessary every 3-6 months, while growth-stimulating therapy is carried out [*Davenport M. et al., 2007*].

What concerns pubertate induction in girls with Shereshevsky-Turner syndrome, it is necessary to begin estadiol substitutive therapy starting from the age of 12 according to the last Consensus [*Dedov I. et al., 2002 a; Quigley C. et al., 2002*]. Besides the oral intake of medicine, transdermal estrogens could be used, as well as depo-forms as a more physiological alternative. The initial dose is 1/10 (0.2 *mg*) or 1/8 (0.25 *mg*) of the estradiol adult dose (2 *mg*) with the dose gradual increase during 2 years. Later on, doses equivalent to the doses of young women are administered: 2 *mg* of estradiol daily, 0.1 *mg* transdermal estadiol daily, or 2.5 *mg/month* estradiol dipropionate intramuscularly [*Hanton L. et al., 2003; Bondy C., 2009; Torres-Santiago L. et al., 2013*].

For normal formation of the uterus and mammary glands, it is considered appropriate to begin progesterone administration not earlier than in 2 years after the estrogen therapy start or before the first occurrence of menstruation. Synthetic oral contraceptives are not recommended, as they contain high doses of synthetic estrogen, and synthetic progestins prevent normal formation of the genital organs [*The Turner Syndrome Study Group, 2006*].

Noonan syndrome: The syndrome resembling Shereshevsky-Turner syndrome, but differing from it in the normal chromosome set has the occurrence rate 1:1,000 or 1:2,500 newborns of both genders [*Chacko E. et al., 2012; Roberts A. et al., 2013*]. The following is typical: stunting, low-set or abnormal ears, ptosis, antimongoloid form of the eyes, arched eyebrows, shortened neck, pterygoid neck folds, slight mental retardation (25-50% of patients), retarded pubertal development, smaller-size penis in boys, cryptorchidism; hypergonadotropic hypogonadism is observed in boys of puberty age [*Romano A. et al., 2010*].

Patients with Noonan syndrome often display defects of the heart right chambers (pulmonary artery valve stenosis). What concerns stunting, the final height of the non-treated boys with Noonan syndrome makes162 *cm* and that of girls – 152 *cm* (Picture 2) [*Dahlgren J., 2009; Westphal O., 2009*].



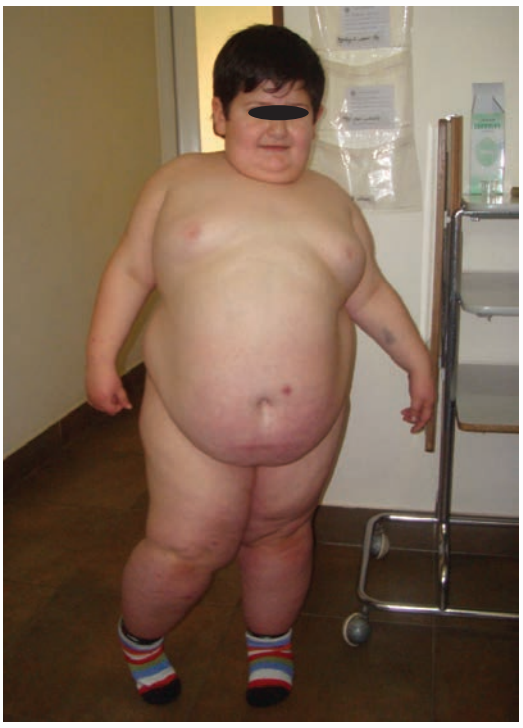
Picture 2. *Noonan syndrome. Patient A.F. 13-year-old. Low-set ears, shortened neck, pterygoid neck folds.*

The issue of rGH treatment efficacy still remains disputable, but in many countries the treatment of children with the specified syndrome is carried out at the dose of 0.05 *mg/kg/day*, i.e. dose similar to that used for treatment of girls with Shereshevsky-Turner syndrome [*Kappelgaard A., Laursen T., 2011; Tartaglia M. et al., 2011*]. In hypergonadotropic hypogonadism a substitutive therapy with androgens is indicated; in cryptorchism the orchidopexy is possible.

Prader-Willi syndrome: Prader-Willi syndrome (PWS) is a multisystemic genetic disease occurring in the result of deficient expression of the inherited paternal imprinting gens of the 15th chromosome (loci 11-13) [*McCandless S., 2011; Falaleeva M. et al., 2013; Liu A. et al., 2013*].

The syndrome occurrence rate is 1:15,000-1:25,000 of the newborns [*Butler M., Thompson T., 2000; Whittington J. et al., 2001; Vogels A. et al., 2004*]. PWS is characterized by neonatal muscular hypotension, poor weight increase during the first year of life with subsequent hyperphagia development, obesity progressing up to the morbid one, growth delay, psychomotoric development retardation, hypogonadism [*Butler M., Thompson T., 2000; Whittington J. et al., 2001; Vogels A. et al., 2004*].

The following specific phenotypic peculiarities are typical for PWS patients: narrow temporal area of the skull, dolichocephalism, acromicria (small size of hands and feet), almond-like eyes, strabismus, thin upper lip (Picture 3). The decrease in muscular mass, energy exchange, mineral density of the osseous tissue is also observed in such patients. Respiratory dysfunctions, including sleep apnea, hypoventilation, respiratory infectious diseases occur no less than in 50% of cases and are the main causes of lethal outcomes in PWS [*Nixon G., Brouillette R., 2002; Tauber M. et al., 2008; Williams K. et al., 2008; Gallego J., 2012*].



Picture 3. *Prader-Willi syndrome. Patient S.G. 12-year-old with obesity and stunting.*

Growth retardation is one of the main signs of PWS and was included in the list of clinical criteria of the syndrome first description already in 1956. The growth disturbance is observed in 60-90% of PWS cases [*Butler M., Meaney F., 1991; McCandless S., 2011*]. In these patients height indices at birth correspond to the norm or are a little below the average values (-0.23 SDS in boys and -0.53 SDS in girls) [*Wollmann H. et al., 1998; Hauffa B. et al., 2000*]. Later on, growth speed decrease could be noted which is especially expressed in prepubertal or pubertal age due to low growth spurt.

Some PWS patients could display acceleration of growth speed and normal growth indices in childhood (mainly due to preterm adrenarche); nevertheless, the final height prognosis remains unfavourable due to accelerated closure of the growth zones. The average final height of adult PWS patients is lower than the average population values by 2 standard deviations [*Butler M., Meaney F., 1991; Wollmann H. et al., 1998; Hauffa B. et al. 2000*] and makes 159.0±5.3 *cm* for males and 148.0±5.5 *cm* for females (Picture 3) [*Greenswag L., 1987; Butler M., Meaney F., 1991*]. Earlier research on hypophysis somatotropic function in PWS children displayed low values of GH in response to the stimulation according to data of different growth hormone-stimulation tests [*Costeff H. et al., 1990; Angulo M. et al., 1991; Lee P. et al., 1992*]. However, considering the low level of GH at "ordinary" obesity not connected with the syndrome [*Kokkoris P., Pi-Sunyer F., 2003*], the doubts in true GH deficiency in the mentioned syndrome have been present for some years. In norm GH is synthesized in the anterior lobe of the hypophysis; penetrating through the blood bed into liver, it stimulates the formation of IGF-1, due to which the tissue growth, including bones and muscles, proceeds. In true GH deficiency IGF-1 level is usually very low; it is associated with the linear growth decrease.

At present there are numerous data showing GH decreased function in PWS patients. A decreased basal secretion of GH, its weak maximum reaction to the provoking test and low concentra-

tion of IGF-1 in blood serum were observed in at least 15 studies, involving almost 300 children with the mentioned pathology [*Angulo M. et al., 1991; Grosso S. et al., 1998; Grugni G. et al., 1998; 2001; Thacker M. et al., 1998; Corrias A. et al., 2000; Burman P. et al., 2001*].

Thus, PWS patients are characterized by GH deficiency, the degree of which varies from the weak up to the severe one, and these patients display such signs typical of somatotropic hormone (STH) deficiency as obesity, belly fat excess, body content disturbance combined with muscular mass decrease and mineral density of the osseous tissue. Osseous age lag is noted in some patients [*Wollmann H. et al., 1998*].

At present, according to data of numerous studies, the following arguments witness in favor of GH true deficit in PWS:

- stunt in 60-90% of patients [*Butler M., Meaney F., 1991; Burman P. et al., 2001*],
- GH low level at stimulation tests (58-100%) [*Angulo M. et al., 1996; Burman P. et al., 2001; Diene G. et al., 2010*];
- low level of IGF-1 and IGF-binding proteins-3 in almost 100% cases [*Eiholzer U. et al., 1998; Dong-Kyu Jin, 2012*], while in "ordinary" obesity these indices are in norm or increased [*Kokkoris P., Pi-Sunyer F., 2003*];
- MRI reveals hypophysis hypoplasia in 50-60% cases [*Miller L. et al., 1996; Iughetti L. et al., 2008*];
- hypothalamic syndrome [*Swaab D., 1997*].

Nowadays, PWS patients treatment should be complex and include adequate nutrition along with eating behavior control, limited physical exertion, symptomatic therapy. A certain experience in treatment of PWS patients with rGH has been gained by present times. The primary investigations were focused on rGH growth effect and showed significant growth acceleration by means of therapy [*Lee P. et al., 1987; Carrel A. et al., 1999*]. However, they were uncontrolled and included not large contingent of patients. Due to insufficient study of the issue, later a number of researchers conducted clinical assays on evaluation of growth stimulating therapy efficacy [*Jørgensen A. et al., 2013*]. Growth steady effect and improvement of the predicted final height parameters on condition of rGH prolonged use (2-5 years) were noted in most patients [*Carrel A. et al., 2002; Lindgren A., Ritzen E., 1999; Eiholzer U., L'Allemand D., 2000*]. At present there are recommendations, according to which rGH dose used for PWS patients treatment is the same as for treatment of children with STH deficiency and makes 1 *mg/m*^{2} or 0.035 *mg/kg/day*, but not more than 2.7 *mg/day* [*Goldstone A. et al., 2008; National Institute for Health, 2010; Meinhardt U. et al., 2013*].

In obese PWS patients it is recommended to calculate rGH dose according to the body surface to decrease the risk of side effects due to the therapy [*But W. et al., 2012; Koch L., 2013*].

The indications to discontinue rGH therapy in PWS patients are as follows:

- uncontrolled progressing obesity;
- respiratory function infringement at sleep independently on IGF-1 normal values, adeno- and tonsillectomy;
- final growth attainment (with subsequent rGH substitutive therapy at metabolic doses);
- rGH therapy effect absence (growth increase less than 50% or less than 2 *cm* a year during the first year of treatment) [*Goldstone A. et al., 2008; Guidelines, 2010; But W. et al., 2012*].

Silver-Russell syndrome: At present the occurrence rate of this disease varies from 1 per 30,000 up to 1 per 100,000. The cause of the disease in most cases is still unidentified [*Fuke T. et al., 2013*]. Dislocations in the area 17q23-q25 were revealed in some patients, in others – duplication in proximal part of the short arm of the 7th chromosome [*Bliek J. et al., 2006; Lamzouri A. et al., 2013*]. Anomalies of the 11th chromosome (segment 11p15) were also observed. Families with the syndrome inherited by autosome-dominant type were described. About 7-10% of patients have monoparental maternal disomy on the 7th chromosome (both homologic chromosomes are inherited from mother) [*Price S. et al., 1999; Monk D. et al., 2002; Melnichenko G. et al., 2013*]. Such patients display intrauterine development delay (less than 10 percentile for the pregnancy corresponding term), stunt after birth (less than 3 percentile for the corresponding age), asymmetry of the limbs, trunk and face [*Binder G. et al., 2011*].

Among the external signs of Silver-Russell syndrome the following is distinguished: triangular-

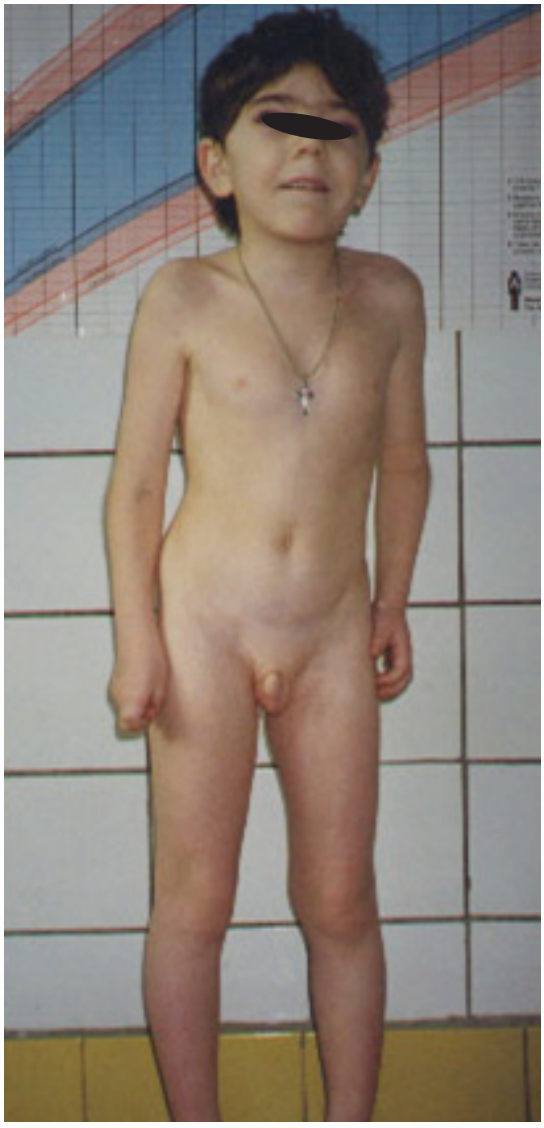
shaped face, high convex forehead, clinodactylia of the little finger, "coffee-milk" type spots on the skin (Picture 4) [*Martínez Nogueiras A. et al., 2001*]. Preterm puberty is developed in 1/3 of the patients. Renal anomalies and hypospadias are typical. As to height, the growth diagram either corresponds to the 3rd percentile or is a little lower. Pubertal growth spurt is maintained. The rGH dose used for treatment of patients with Silver-Russell syndrome makes 0.05 *mg/kg/day* [*Eggermann T., 2010; Mascarenhas J., Ayyar V., 2012*]. Some researchers showed positive growth effect and final height indices upon treatment of such patients [*Diagnosis and treatment, 2003; Ranke M., Lindberg A., 2010; Toumba M. et al., 2010*].

Picture 4. *Silver-Russell syndrome. The 5-year-old girl. Triangle-shaped face, high convex forehead.*

Cornelia de Lange syndrome: The occurrence rate of this pathology is 1 per 10,000-30,000 of newborns. The inheritance type is not clear, possibly, autosome-recessive one. The present metabolic exchange disturbances are supposed to be associated with the 9th chromosome, 5th chromosome trisomy or 3rd chromosome ring [*Gervasini C. et al., 2013; Huisman S. et al., 2013; Mariani M. et al., 2013*]. It could be a heterogenic disease, in which hereditary predisposition is combined with the environmental exposure [*Mathlouthi N. et al., 2012*].

The following is typical of this symptom: stunting, with the growth lagging noted since birth, mental retardation, peculiar face with continuous eyebrows (synophrys), curved long thick eyelashes, thin lips, low-set ears, ptosis, hypertrichosis (hirsutism), low-set hair line on the forehead and the neck, cryptorchism, restricted movement in elbow joints (Picture 5) [*Akahori Y. et al., 2012; Chatfield K. et al., 2012; Hei M. et al., 2012*]. Inner organ (kidney) defects are frequent [*Meghwal J. et al., 2013*]. Some patients have self-injuries, running in circle, rotations, stereotype movements of the hands [*Park K. et al., 2010; Barboni C. et al., 2012*].

The patients with genetically determined stunting have a high incidence of congenital malformations and various comorbidities, which require monitoring



Picture 5. *Cornelia de Lange syndrome. Patient S.T. 12-year-old. Face with continuous eyebrows, curved long thick eyelashes, thin lips, low-set ears, ptosis, low-set hair line on the forehead.*

taken by different type health professionals over the life-span. Observation of patients with the above syndromes must be comprehensive; it should take into account the age-related needs. Timely medical intervention in this group of patients significantly reduces the risk of early morbidity and mortality and improves the quality of life.

The problem of early diagnosis of genetically determined stunting with the use of modern methods of investigation remains unresolved and determines the relevance of the problem. Unfortunately, currently existing diagnostic methods are not always applicable. Until now, there are discussions on the best schemes, practiced criteria to evaluate the effectiveness of currently available diagnostic possibilities. A new stage of scientific research related to the expansion of indications for the use of rGH with genetically determined short stature not associated with the growth hormone deficiency is currently observed.

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