Синдром Кушинга у ребенка первого года жизни

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Эндогенный гиперкортицизм у детей первого года жизни встречается крайне редко. Среди причин синдрома Кушинга в раннем детстве — объемные образования надпочечников и двусторонняя гиперплазия надпочечников. АКТГ-независимый гиперкортицизм за счет двусторонней узелковой гиперплазии надпочечников у детей первых месяцев жизни чаще всего обусловлен синдромом МакКьюна—Олбрайта—Брайцева. Этот синдром — редкое заболевание, в основе которого лежит гиперфункция стимулирующей альфа-субъединицы G-белка вследствие соматических мутаций в гене *GNAS*. Синдром МакКьюна—Олбрайта—Брайцева — мультикомпонентное заболевание, клиническими проявлениями которого являются пятна цвета «кофе с молоком», фиброзная дисплазия и различные варианты эндокринной гиперфункции, среди которых одним из редко встречающихся является гиперкортицизм. Клиническая картина синдрома Кушинга, манифестировавшего в раннем детстве, имеет свои особенности, которые могут отсрочить время постановки правильного диагноза: первыми проявлениями могут быть низкий вес и рост при рождении, задержка физического развития при отсутствии характерного для синдрома Кушинга перераспределения подкожно-жировой клетчатки, задержка психомоторного развития и осложнения, обусловленные иммунодефицитом и артериальной гипертензией. Описан случай АКТГ-независимого гиперкортицизма у ребенка первого года жизни.

Ключевые слова: *синдром МакКьюна—Олбрайта—Брайцева, синдром Кушинга, пятна цвета «кофе с молоком», двусторонняя гиперплазия надпочечников*

Cushing's syndrome in an infant

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Endogenous hypercorticism in infants occurs extremely rare. The causes of Cushing's syndrome in early childhood include space-occupying lesions and bilateral hyperplasia of the adrenal glands. ACTH-independent hypercorticism due to bilateral nodular hyperplasia of the adrenal glands in children in the first months of life is most often associated with McCune-Albright-Braitsev syndrome. This syndrome is a rare disease caused by hyperfunction of the stimulatory G-protein alpha-subunit due to somatic mutations in the *GNAS* gene. The McCune-Albright-Braitsev syndrome is a multicomponent disease, the clinical manifestations of which include café-au-lait spots, fibrous dysplasia, and different types of endocrine hyperfunction, among which hypercorticism is one of the rare cases. The clinical picture of Cushing's syndrome manifested in early childhood is characterized by some peculiarities that can delay the correct diagnosis: the first manifestations include low weight and height at birth, physical retarfation in the absence of a redistribution of subcutaneous fat typical of Cushing's syndrome, psychomotor retardation, and complications caused by immunodeficiency and hypertension. We present a case of ACTH-independent hypercorticism in an infant.

Keywords: *McCune—Albright—Braitsev syndrome, Cushing's syndrome, café-au-lait spots, bilateral adrenal hyperplasia.*

Endogenous hypercorticism caused by dysregulation of the hypothalamic-pituitary-adrenal axis, hyperfunction of the adrenal cortex, or ectopic ACTH secretion is rare in childhood. Adrenal adenoma is the most common cause of Cushing's syndrome (CS) in children, with the manifestation peak at the age of 1—4 years [1, 2]. Manifestations of CS are extremely rare during infancy. Despite the fact that single cases of congenital hypercorticism due to ACTH-secreting adenomas of the pituitary gland, unilateral hyperplasia, or adenoma of the adrenal cortex and ectopic secretion of ACTH by pheochromocytoma have been described, the cause of ACTH-independent hypercorticism in infants typically is bilateral hyperplasia of the adrenal glands associated with the McCune—Albright syndrome (MAS) [1, 3—9].

MAS is a rare disease associated with hyperfunction of the stimulating G protein alpha subunit (Gas) due to somatic mutations in the *GNAS* gene arising during early embryogenesis [10, 11]. Clinical manifestations of the disease include fibrous dysplasia (FD), endocrine hyperfunction of various glands (gonadotropin-independent precocious puberty, thyrotoxicosis, STH hypersecretion, hypophosphatemic rickets associated with the increased FGF-23 levels, and hypercortisolism), café-au-lait spots, and possible pathology of non-endocrine organs (tachycardia, pathology of the hepatobiliary tract, etc.) [12—14]. CS is one of rare manifestations of MAS that on average occur in 7% of cases [6]. CS can be the earliest manifestation of the disease, since ACTH-hypersecretion is congenital and the symptoms of hypercorticism appear by the time when the child is born [6, 14].

Case description

A 4-month-old boy was admitted to the Endocrinology Research Center with suspected ACTH-secreting adenoma of the adrenal cortex.

The child was born to an unrelated couple (second pregnancy, second labor, timely delivery). Height and weight at birth were normal (height 50 cm, weight 3,860 g). Café-au-lait spots were detected at the age of 1 month,

doi: 10.14341/probl201763292-97

while no spots had been observed at birth. The boy suffered right upper lobe pneumonia at the age of 2 months. According to the medical records, increased level of 17-OH progesterone (34.4 nmol/l), cortisol level of 550 nmol/l and ECHO signs of bilateral adrenal hyperplasia were noted during that period. However, the child was discharged after his condition improved without any additional examination. Second hospitalization took place two weeks after the discharge in connection with febrile fever, enterocolitis (frequent mucousy stool) and signs of urinary tract infection (microhematuria or leukocyturia). Several courses of antibiotic therapy (cefepime, amikacin, vancomycin, meronem, and ampicillin) were administered. Subfebrile fever and inflammatory changes in blood parameters persisted (neutrophilic leukocytosis, increase in C reactive protein ++++, increased level of procalcitonin up to 10 ng/ml, while the normal level is <2 ng/ml). Recurrent episodes of tachycardia up to 190 bpm and tachypnea of up to 60 breaths per min, along with the signs of respiratory failure (cyanosis of the nasolabial triangle) were noted during the 2.5-month hospital stay.

MSCT revealed signs of diffuse enlargement of the adrenal glands as well as foci of rarefaction of pelvic and vertebral bone tissue. MRI showed signs of a massive structure in the left adrenal gland and hyperplasia of the right adrenal gland. The MRI data combined with bone tissue pathology indicated suspected adenocarcinoma of the adrenal gland. Laparoscopic puncture of the left adrenal gland was performed, and the patient was diagnosed with clear-cell adenoma of the adrenal cortex by histological examination. Laboratory analysis showed ACTH-independent hypercorticism **(Table 1)**. The boy was diagnosed with ACTH-independent hypercorticism associated with adrenal adenoma and transferred to the Endocrinology Research Center.

During the examination at the Endocrinology Research Center when the boy was aged 4 months, attention was drawn to the pronounced delay in his physical development (height 54.5 cm, height SDS –4.666, weight 4.44 kg, weight SDS –3.624), matronism, café-au-lait spots, rapid fatigability during feeding, signs of respiratory failure (tachypnea and pale nasolabial triangle), psychomotor developmental delay (the boy was unable to hold head upright and to roll over). Changes in the clinical and biochemical blood parameters persisted: neutrophilic leukocytosis with ESR increased to 38 mm/h (no data on the presence of inflammation focus were available; procalcitonin and C-reactive protein levels were normal), thrombocytosis (1086 $\cdot 10^9$ cells/l, with the normal value being <339), grade 1 iron deficiency anemia, increased ALT and AST levels (177 and 136 mmol/l, with the normal level being 56 and 36, respectively), ALP 844 U/l with the normal level being <518 U/l. Tachycardia up to 140 bpm was observed; no ECG data confirming hypertrophy of the left ventricle were available. Consecutive analysis of histological specimens (according to the results of the left adrenal gland biopsy performed at the place of residence) revealed no data on massive adrenal neoplasms: three small fragments of adrenal tissue with morphological features of nodular hyperplasia of the cortical layer were detected in two specimens.

Café-au-lait spots in combination with bilateral hyperplasia of the adrenal glands and MSCT signs of fibrous dysplasia allowed us to diagnose the boy with the McCune—Albright syndrome. Trial treatment with steroidogenesis inhibitors was rejected due to the elevated level of transaminases and the lack of confidence about therapy efficiency. Taking into account the bilateral nature of the adrenal gland lesion and the high risk of recurrence in the case of unilateral adrenalectomy, bilateral resection of adrenal glands was conducted. Substitution therapy with gluco- and mineralocorticoids was prescribed. Patient's condition improved after surgical treatment (normalized clinical and biochemical parameters and increased rates of physical and psychomotor development) **(Figs. 1—4)**. Parameters recorded during examination at the age of 1 year were as follows: height, 63.7 cm; height SDS, –3.62; weight, 6.8 kg; SDS BMI, –2.14. The child started walking and pronouncing individual words. Screening for possible components of the disease revealed no manifestations of MAS except for the signs of FD (rarefaction foci of bone tissue of the upper one-third of the femur).

Discussion

Differential diagnosis of CS in infants includes decision on several matters: confirming the endogenous nature of hypercorticism, determining the level of disturbance of the hypothalamic—pituitary—adrenal axis, and, in the case of ACTH-independent hypercorticism, adrenal examination to assess the lesion nature: either it is an adenoma or bilateral hyperplasia. Massive neoplasm in the adrenal gland in infant can be either benign or malignant or even reflect ectopic ACTH secretion by pheochromocytoma rather than adenoma [1, 5]. CS associated with bilateral adrenal hyperplasia in infancy is usually caused by MAS. [3, 4, 6, 9, 15—17]. In addition to MAS, adrenal hyperplasia can be triggered by activation of the regulatory α-subunit of protein kinase due to heterozygous mutation in the *PRKAR1A* gene (OMIM 610489), while combination with other manifestations of the Carney complex is often observed [18, 19]. Other cases of bilateral adrenal hyperplasia in infants are very rare: the Beckwith—Wiedemann syndrome, cyclical CS associated with bilateral adrenal hyperplasia of unknown genesis (*GNAS* and *PRKAR1A* pathologies were excluded) [20, 21]. In our case, malignant neoplasm in the adrenal gland was initially suspected due to the fact that hyperplasia was more developed on one side, and the MSCT signs of bone pathology were regarded as metastases. The initial pathomorphological conclusion corresponded to the diagnosis of adrenal adenoma. However, the MSCT data and repeated examination by a pathomorphologist ruled

 DOI: http://dx.doi.org/10.14341/probl201763292-97

***Table 1*. Results of laboratory examination of the boy with Cushing's syndrome**

Examination at the age of 2 months		
Hormonal profile		
Parameter	Result	Reference value
ACTH, pg/ml	<5	7—80
Testosterone, nmol/l	3.81	0.2—0.6
DHEA-S, μmol/l	44.4	0.1—5.0
17-OH progesterone, nmol/l	34.6	0.09—2.7
TTH, mU/ml	0.51	0.64—5.76
FT4, pmol/l	18.9	11.5—20.4
TPOAb	0	
	Circadian rhythm of cortisol secretion	
	morning	evening
Cortisol, nmol/l	752.7	878.6
	High-dose dexamethasone test	
	0'	After administration of dexamethasone (8 mg)
Cortisol	752.7	1063
Examination at the age of 4 months		
Hormonal profile		
Parameter	Result	Reference value
ACTH, pg/ml	1.9	7—66
Testosterone, nmol/l	2.1	0.2—0.6
Cortisol, nmol/l	1240	77—630
STH, ng/ml	3.2	0—5
IGF1, ng/ml	70	8—290
TTH, mU/ml	1.2	0.64—5.76
FT4, pmol/l	13.2	11.5—20.4
TPOAb	0	

this diagnosis out. There were also spots typical of MOS, which facilitated the diagnosis. Bone rarefaction foci are typical of MOS, being a manifestation of fibrous dysplasia. However, MOS should have been suspected even if primary examination revealed no spots. They may not appear immediately or even be absent, whereas other components of the syndrome may appear at any age, typically during the first decade of life [14]. Analysis of the reported cases of CS in infants revealed no episodes related to the proven pigmentary nodular hyperplasia of the adrenal glands. Other causes are casuistically rare. Therefore, MOS should be first suspected in an infant with CS associated with bilateral adrenal hyperplasia.

An important feature of CS in MOS is the possibility of spontaneous regression, which requires choosing the treatment strategy between adrenalectomy and prescribing steroidogenesis inhibitors [6]. Unilateral adrenalectomy in infants with MOS was first believed to make no sense, since both adrenal glands are always affected. However, cases of hypercorticism regression after resection of a larger adrenal gland have been reported [17]. Decision on treatment strategy is made individually in each case based on severity of the disease and either presence or absence of hypercorticism complications.

Adrenal gland hyperplasia in MOS is congenital; the manifestation time varies between the antenatal period and the first months of life. A retrospective analysis of a large group of patients (n=30) with CS among patients with MOS conducted by R. Brown et al. [6] in 2010 made it possible to assess the range of clinical signs of hypercorticism in this syndrome. The median age of diagnosis was 3 months; the most common signs were matronism, delayed physical development, low birth weight (66.7%, 60%, and 50%, respectively), and psychomotor development delay (44.4%). Liver (36.7%) and cardiovascular system pathologies (26.7%) are less common. The severity of CS with MOS ranges from hypercortisolemia without pronounced clinical manifestations to congenital hypercortisolism with complications presenting as immunodeficiency and heart failure [6, 8, 22, 23]. The severity is typically maximal in the case of intrauterine manifestation: a baby is born small and underweight, is prone to frequent pneumonia; complications of the cardiovascular system develop rapidly. In other cases, his/her growth rate can be reduced in the absence of immunodeficient conditions, when the diagnosis can be suspected only on the basis of the typical distribution of subcutaneous fat [23]. In our case, the earliest manifestations could be detected starting from the age of two months: reduced height and weight, matronism, infectious diseases that were difficult to cure and were indicative of possible immunodeficiency.

The possibility of spontaneous regression of hypercortisolism is caused by the fact that the fetal cortex of the adrenal gland is a source of ACTH hyperproduction; its involution can be accompanied by elimination of CS [6].

This gives a chance for regression after steroidogenesis inhibitors are presecribed during the hypercortisolism phase. However, this treatment is not suitable for everyone. First, it may be ineffective and still require adrenalectomy, since anticipation of the effect of drug therapy can be accompanied by complications. Second, CS is often accompanied by complications with respect to the hepatobiliary system, being a contraindication for the use of ketoconazole. In this case, another inhibitor of corticosteroid synthesis, metyrapone, can be used, which can help to prepare patients in serious condition for surgical treatment [8]. In our case, the decision was made to refuse such treatment, taking into account the difficulties associated with procuring metyrapone in Russia and no need to postpone surgery. Cases of regression after unilateral adrenalectomy have been reported, but there was no way to predict the successful outcome of this strategy in our patient. In this case, the course of CS was severe: a pronounced delay in physical and psychomotor development, frequent infectious diseases, episodes of respiratory failure, and increased level of hepatic transaminases. Taking into account the age and severe general condition, urgent radical treatment was required, while unilateral adrenalectomy could fail to ensure hypercorticism remission, which was associated with a hazard to life. These features of the course of the disease and the risk of developing life-threatening complications of hypercorticism led us to the decision to perform bilateral adrenalectomy. Laparoscopic bilateral adrenalectomy without complications was performed, followed by administration of permanent substitutive therapy with gluco- and mineralocorticoids. To date, the follow-up period has been 1.5 years after adrenalectomy; no adrenal insufficiency crisis has been observed. The patient undergoes annual examination involving screening for possible components of the disease. At the time of examination, the one-year-old boy had widespread café-au-lait spots and radiographic signs of polyostotic fibrous dysplasia.

Conclusion

Cushing's syndrome associated with bilateral hyperplasia of the adrenal glands manifesting during the first year of life is most frequently caused by MOS. Adequate diagnosis is possible in the presence of café-au-lait spots. However, their absence does not exclude the diagnosis. Examination should be carried out on a regular basis, since the spots can appear any time after birth during the first several years of the patient's life. The course of the Cushing's syndrome in infants has its own features. The most common clinical manifestations include delay in physical and psychomotor development, matronism in the absence of obesity, complications presenting as immunodeficiency and pathology of the cardiovascular system. The presence of fibrous bone dysplasia can be mistaken for a metastatic lesion and lead to a misdiagnosis of adrenal cancer.

A radical method to treat Cushing's syndrome is bilateral adrenalectomy due to the bilateral nature of hyperplasia. Single cases in the world practice argue in favor of the possible successful outcome of unilateral adrenalectomy of the larger adrenal gland. However, there is a risk that reoperation may be needed in these cases. The possibility of spontaneous regression of the Cushing's syndrome associated with MOS allows one to use trial therapy with steroidogenesis inhibitors. The severity of the course of Cushing's syndrome and the presence of life-threatening conditions should be taken into account when selecting the treatment strategy. Follow-up examination of patients after treatment includes, in addition to assessing compensation for hypocorticism, regular screening for all the components of MOS.

ADDITIONAL INFORMATION

Patient's informed consent. The informed consent to publish the medical data in anonymous form was obtained from the patient's legal representatives.

Conflict of interests. The authors declare no obvious or potential conflict of interests regarding publication of this article.

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ИНФОРМАЦИЯ ОБ АВТОРАХ

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ИНФОРМАЦИЯ

Рукопись получена: 15.03.2017. Одобрена к публикации: 22.03.2017.

КАК ЦИТИРОВАТЬ:

Маказан Н.В., Орлова Е.М., Поддубный И.В., Карева М.А., Петеркова В.А. Синдром Кушинга у ребенка первого года жизни // Проблемы эндокринологии. — 2017. — Т. 63. — №2. — С. 92—97. doi: 10.14341/probl201763192-97

TO CITE THIS ARTICLE:

Makazan NV, Orlova EM, Poddubnyi IV, Kareva MA, Peterkova VA. Cushing's syndrome in an infant. *Problems of Endocrinology*. 2017;63(2):92-97. doi: 10.14341/probl201763292-97

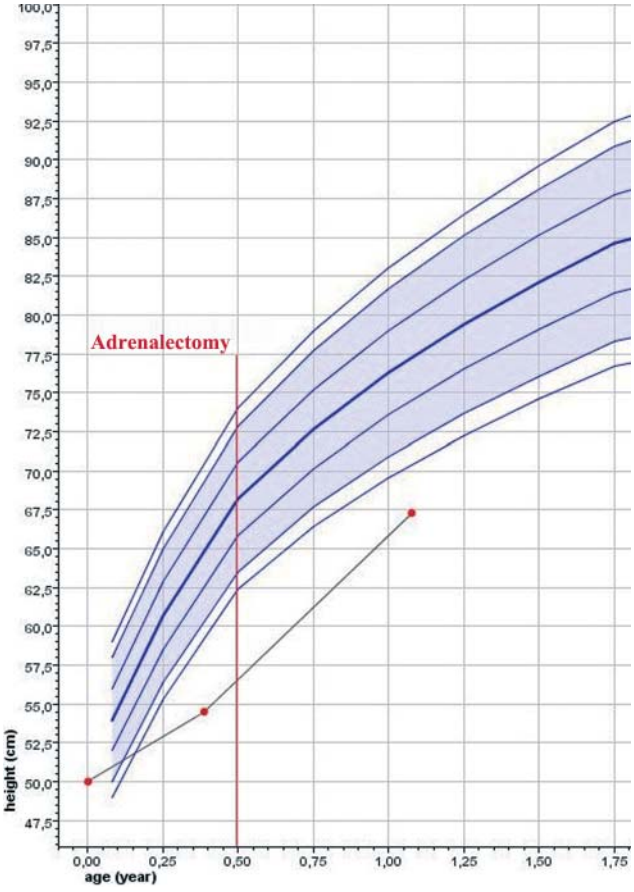

***Figure 1*. The diagram showing patient's height.**

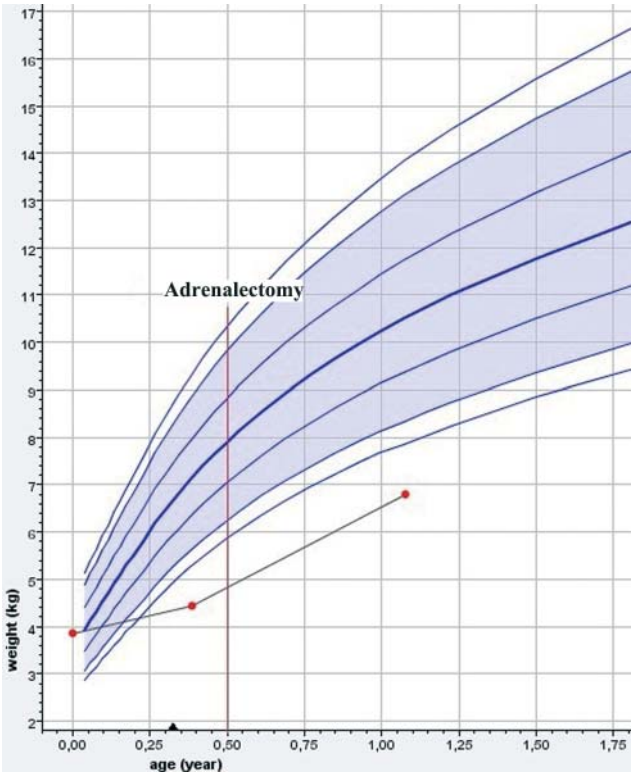

***Figure 2*. The diagram showing patient's weight.**

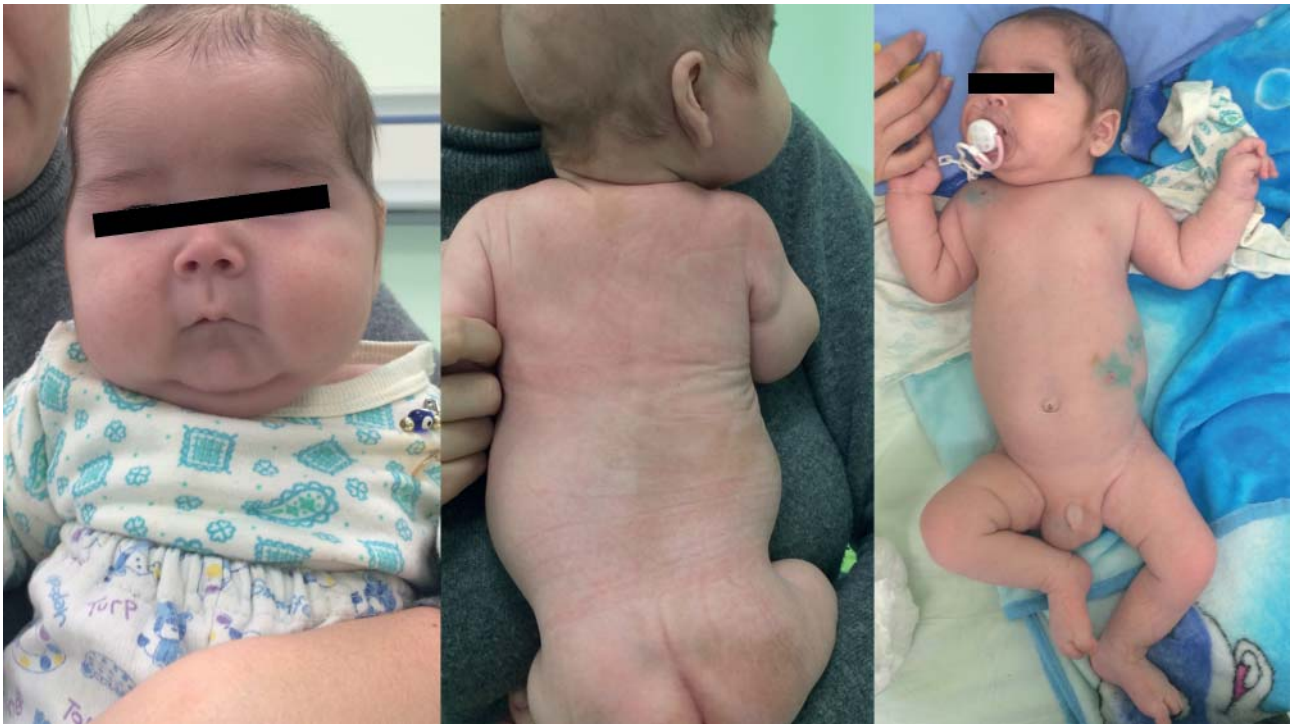

***Figure 3*. Patient at the age of 4 months.**

Height 54.5 cm, height SDS –4.6, weight 4.44 kg, weight SDS -3.6. Matronism, café-au-lait spots, no excess weight.

 DOI: http://dx.doi.org/10.14341/probl201763292-97

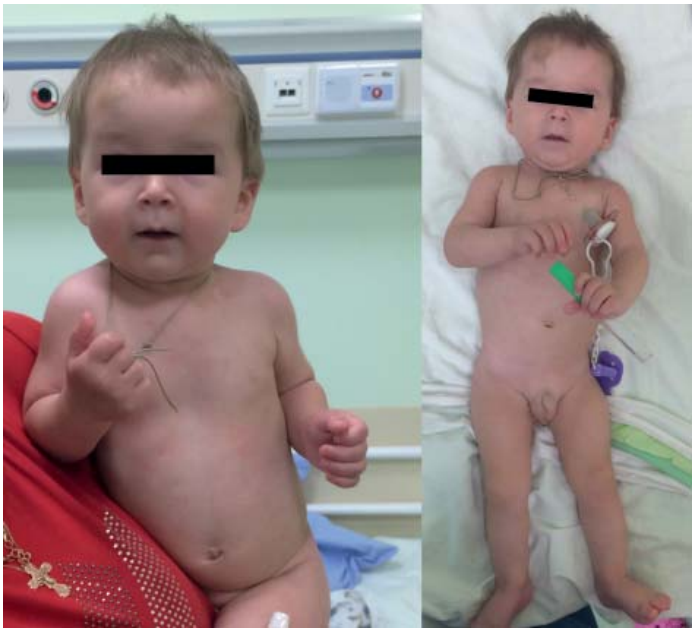

***Figure 4*. Patient at the age of 1 year, 8 months after surgery.**
Height, 63.7 cm; height SDS –3.62; weight, 6.8 kg; BMI SDS –2.14.