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Experience with the use of growth hormones in a patient with Cushing's syndrome

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Abstract: Cushing's disease (CD), defined as hypercortisolism caused by excess adrenocorticotropic Hormone (ACTH) secretion by a pituitary corticotroph adenoma, presents rarely in the paediatric age range. However, this serious disorder requires early diagnosis and specialised management because the morbidity related to chronic hypercortisolism in paediatric patients is considerable. Growth retardation to the point of complete cessation of growth is a hallmark of Cushing's syndrome in children. The main mechanism for this is considered to be glucocorticoid-induced resistance of target tissues to insulin-like growth factor 1 (IGF-1) and other growth factors and growth hormone (GH) deficiency. This article describes a case of the use of synthetic growth hormone in a teenager with Cushing's syndrome, a feature of which is the presence of positive dynamics in the patient's growth.

Keywords: Cushing's disease, children, growth retardation, synthetic growth hormone.

Cushing's disease (CD) is a severe neuroendocrine disease caused by chronic overproduction of adrenocorticotropic hormone (ACTH) by a pituitary tumor. An increase in ACTH secretion leads, in turn, to chronic increased production of cortisol by the adrenal cortex and the development of the symptom complex of endogenous hypercortisolism [1,2,6]. Cushing's disease is the most common cause (80-85%) of organic hyperproduction of cortisol - endogenous hypercortisolism (EH). The incidence of CD varies according to various sources from 1.2–2.4 cases per million population per year according to studies in European countries [4,5], to 6.2–7.6 cases per million population according to studies from the USA [3]. Only about 10% of new cases each year occur in children. [7] Cushing's disease accounts for approximately 75% of all cases of Cushing's syndrome in children over 7 years of age. Adrenal causes of Cushing's syndrome (adenoma, carcinoma, or bilateral hyperplasia) are the most common causes of this condition in infants and young children. Ectopic ACTH production is rare in young children; it also accounts for less than 1% of cases of Cushing's syndrome in adolescents.

Growth retardation to the point of complete cessation of growth is a hallmark of Cushing's syndrome in children. The main mechanism for this is considered to be glucocorticoid-induced resistance of target tissues to insulin-like growth factor 1 (IGF-1) and other growth factors. In a study by M.A Magiakou, M.T.Gomezi, the dynamics of growth hormone (GH) secretion was studied in patients with Cushing's disease before and within 12 months after their treatment with transsphenoidal adenomectomy. Fourteen patients had blood drawn every 20 minutes for 24 hours to determine plasma GH. These patients also underwent arginine infusion and stimulation tests with L-Dopa. Fourteen healthy volunteers matched to gender and pubertal stage were used as controls. Before therapy, the patient group had an increased BMI (31.5 ± 5 kg/m2) and a noticeable decrease in the average values of 24-hour plasma GH, peak amplitude and peak area with pulse rate similar to the control group. GH values after stimulation with arginine and L-Dopa were also subnormal in many of these patients: 2 of 8 and 8 of 10 did not have a GH response above 7 ng/mL in the corresponding test. Surprisingly, the same pattern of GH suppression was observed in patients examined 10-11 days, 3 months and 6-12 months after their cure, when their BMIs were respectively relatively stable, 26.9 ± 3.8 kg/m2 and 24.8 ± 3.3 kg/m 2. These data suggest that patients with Cushing's disease experience marked suppression of

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growth hormone during the disease, which continues for at least a year during their recovery. They thus concluded that overt GH deficiency may be another important mechanism for the growth retardation observed in children with Cushing's syndrome. Due to persistent growth hormone suppression, patients should be clinically evaluated for the potential need for growth hormone replacement therapy.

CASE REPORT. Patient Sh.,14 years old. From the anamnesis, at the age of 11 years, the parents contacted a therapist with complaints about the increase in the child's body weight and, having diagnosed alimentary obesity, the doctor recommended moderate physical activity with the correct selection of a diet for the child. There was no effect from this and by the age of 14 the patient was noticeably lagging behind his peers in growth, tinnitus, headaches and episodes of increased blood pressure (BP) appeared, for which he was sent to the endocrinology center to a neuroendocrinologist to clarify the diagnosis. Life history: boy from the 1st normal pregnancy, term birth. The early postnatal period is without features. Heredity on the maternal side is burdened with type 2 diabetes mellitus - in the grandmother. On examination, the general condition is relatively satisfactory, the mental state is adequate. The skin is dry, thinned, visible mucous membranes are pale pink, redistribution of the subcutaneous fat layer according to the Cushingoid type (central obesity), matronism and striae are not noted. When examining the musculoskeletal system, atrophy of the muscles of the arms, legs, gluteal and thigh muscles is noted. Vesicular breathing in the lungs. Blood pressure 160/100 mmHg, pulse 120 beats per minute. The genitals are developed correctly. Tanner 2. Height 134 cm (height SDS -3) Weight 62 kg (body mass index SDS +2). Diagnostics was carried out according to the scheme. Ultrasound: hepatomegaly, the contours of the adrenal glands are not differentiated against the background of fatty tissue. Additional pathological formations in their projection are not determined. MRI of the pituitary gland with contrast did not reveal the presence of formations in the pituitary gland. The level of basal hormones is presented in table 1.

Table 1. Patient's basal hormone levels

Index	**Result**		**Reference intervals**	
TSH, mIU/ml	2,1		0,51–4,82	
free T4, pmol/l	20		11,2–18,6	
IGF-1, ng/ml	18,5		17–347	
Prolactin, honey/l	375		78–380	
Insulin, µU/ml	28,5		2,6–24,9	
ACTH, pg/ml	morning	evening	morning	evening
	54,26	57,5	5,6-56,8	2,0–25,5
Cortisol in blood, nmol/l	916	1022	77,0–630,0	64,0–327,0
cortisol in daily urine, nmol/l	1004,5		100,0–379,0	

Thus, after consultation with neuroendocrinologists, taking into account a significant decrease in growth rates (growth SDS -3.0), the appearance of phenotypic signs characteristic of hypercortisolism (redistribution of fatty tissue, the appearance of acne), disruption of the circadian rhythm of cortisol and ACTH secretion, despite the absence of obvious signs of adenoma pituitary gland, the diagnosis of ACTH-dependent endogenous hypercortisolism was not in doubt, and staged adrenalectomy with

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lifelong replacement of glucocorticoids and mineralocorticoids was recommended. The reason for choosing this treatment method was the lack of visualization of the lesion in the pituitary gland.

At the age of 15, an operation to remove the right adrenal gland was performed at the Endocrinogy center; after the operation, no changes in weight or height were observed. The patient took calcium with vitamin D3 and iodamarin. A year later, the patient is admitted to the hospital with complaints of itching in the back, headaches, weight gain, increased blood pressure, pain in the lower extremities, lethargy, and drowsiness. Objectively, the general condition is relatively satisfactory. The skin and visible mucous membranes are pale pink, matronism and striae are not observed, subcutaneous fatty tissue is developed according to the type of central obesity. Blood pressure 120/70, 130/80 genitals are developed correctly. Tanner 2. Height 134 cm (height SDS -3) Weight 62 kg (body mass index SDS +2). The level of basal hormones is presented in table 2.

Table 2. Patient's basal hormone levels

Index	**Result**		**Reference intervals**	
TSH, mIU/ml	2,1		0,51–4,82	
free T4, pmol/l	20		11,2–18,6	
IGF-1, ng/ml	1 207,1		111–402 (15-19 лет)	
STG-med/l	1,1		0,7-28 (15-19 лет)	
ACTH, pg/ml	morning	evening	morning	evening
	53,5	48,2	5,6-56,8	2,0–25,5
Cortisol in blood, nmol/l	960	933	77,0–630,0	64,0–327,0
cortisol in daily urine, nmol/l	960		100,0–379,0	
Glycated hemoglobin %	5,0 %.		3,8-7,0	
Glycemic profile mmol/l	morning	4,8	4,2-6,0	
	2 hours after eating	8,1	6,2-7,6	

Upon consultation with a neurologist, the following diagnosis was made: radicular pain syndrome. Neurasthenia. Ophthalmologist: OU retinal vascular angiopathy. The patient was admitted as planned to the Endocrinological Medical Center, where he was prepared for a left-sided adrenalectomy operation and was subsequently transferred to the intensive care unit for further correction of the condition. The postoperative period proceeded without complications; the patient experienced a decrease in ACTH levels to 10.5 pg/ml, cortisol to 14.8 pg/ml, and he was discharged home on replacement therapy with glucocorticoids and mineralocorticoids (cortef + cortineff, respectively). I would also like to note that according to the ABPM results, there was no need to continue antihypertensive therapy.

Since the patient had complexes about his short stature, the pediatrician endocrinologist recommended undergoing appropriate studies, after which it turned out that the growth zones were partially open. The endocrinologist advised to receive a synthetic analog growth hormone and the patient received growth hormone for 7 months in accordance with the regimen. In dynamics during this period, it literally grew by 21 cm. After 7 months. After re-determining the opening of growth zones, they were already closed at that time. At the moment, the patient is 22 years old. Height is 155 cm.

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Weight is 52 kg. Currently he is receiving Cortef and Cortineff in the appropriate dosage. Marital status: married, 1 child.

Thus, this clinical case is of interest due to the presence of a multifaceted clinical picture, as a result of which the diagnostic search can drag on for a long time, which contributes to the progression of the disease and severe consequences. The patient was given a clinical diagnosis in a short time, radical treatment was carried out and hormone replacement therapy was prescribed, as a result the clinic was completely leveled out. Only a clear understanding by a specialist of the etiopathogenesis of hypercortisolism, its clinical manifestations, and correct interpretation of diagnostic results make it possible to establish the correct diagnosis, subsequently prescribe adequate treatment and significantly reduce the morbidity and mortality of patients of this profile, and improve their quality of life. In addition, as evidenced by a number of studies, children and adolescents with Cushing's disease experience a noticeable suppression of growth hormone during the illness, which continues for a year or more during their recovery. In this regard, it was decided to come to an adequate decision in a short period of time regarding the use of growth hormone, thereby helping the patient from a psychological complex that could affect his subsequent life.

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