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CUSHING'S SYNDROME IN CHILDHOOD, ADOLESCENCE, AND YOUNG ADULTHOOD: A RETROSPECTIVE ANALYSIS

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Abstract
In this article, the authors present literature data on the frequency and structure of causes of hypercorticism in children and adolescents. Based on the analysis of retrospective clinical data for 10 years, it was found that among patients with various forms of hypercorticism in this age period, patients with Itsenko-Cushing's disease predominated - 26 patients (66.6%), that is, with pituitary microadenomas, compared with patients with Itsenko-Cushing's syndrome - 4 (10.2%) and other forms of hypercorticism: juvenile dyspituitarism (JD) - 7 (17.9%), obesity with ACTH/cortisol secretion rhythm disorder - 1 (2.5%) and iatrogenic hypercorticism - 1 (2.5%).

Keywords: Cushing's syndrome and disease, hypercorticism, adolescents, course characteristics.

Introduction

In 1932, Harvey W. Cushing reported on 12 patients with a severe metabolic disorder that he attributed to basophilic tumors of the pituitary gland [1]. Currently, the term Cushing's syndrome (CS) refers to the clinical symptoms and signs of inappropriately elevated plasma glucocorticoid levels. Exogenous (iatrogenic) CS is common, while endogenous causes of CS are rare and can be broadly divided into adrenocorticotropic hormone (ACTH)-dependent (approximately 80%; Cushing's disease (CD), ACTH-secreting ectopic tumors, corticoliberin-secreting tumors (CRH)) and ACTH-independent (20%; adrenal tumor, carcinoma, and macronodular hyperplasia (MAH)) Cushing's syndrome (CS) is a multisystem disorder resulting from long-term exposure to excess glucocorticoids. In children, CS most often results from exogenous steroid administration, and the typical manifestation is growth retardation combined with weight gain. Endogenous and ectopic causes are rare [1-3].

In most children, the onset of CS is insidious. [2-4] The most common symptom is weight gain. In childhood, the most common manifestation of CS is failure to thrive despite weight gain.

In 2015, the Endocrine Society published clinical practice guidelines for the treatment of Cushing's syndrome; however, they are not specific to children. Transsphenoidal surgical resection (TSR) of a corticotropin-secreting pituitary tumor remains the first-line therapeutic intervention for DS. In specialized centers with experienced neurosurgeons, the success rate of first TSR is close to or even exceeds 90%. [5, 6] Pituitary surgery may be unsuccessful, and the disease may recur years after the initial surgery.

Childhood CC may have long-term adverse health consequences due to prolonged exposure to high levels of glucocorticoids and morbidity associated with surgery or radiation treatment [7-9].

Manifestation of symptoms

The first signs can appear as early as the neonatal period, and by the age of one year, they occur in 40% of patients. Among young children, girls are three times more likely to be affected than boys, and the cause is usually adrenal cortex tumors (carcinomas and adenomas). In young children, the disease manifests itself in a more severe form and is more pronounced than in adults.

In most children, the onset of CK syndrome is insidious [10]. The most common symptom is weight gain; in childhood, failure to thrive accompanied by weight gain is the most common manifestation of CK syndrome. Other common problems reported in children include facial plethora, headaches, hypertension, hirsutism, glucose intolerance, kidney stones, fractures, amenorrhea, and delayed puberty.

Specific symptoms of BIC in children:
A decrease in linear growth along with increasing obesity [10]. Growth slows down due to a number of reasons: 1) excess glucocorticoids suppress the secretion of GH (growth hormone), 2) obesity in turn also reduces the secretion of GH, 3) the effect of compression of the tumor mass by GH-secreting cells.

Features of the flow
In older children, the disease occurs equally in both boys and girls. Increased susceptibility to infections is noted. Children with Cushing's disease are usually very frail. Sometimes, this disease in children is associated with congenital malformations.

Clinical symptoms in children and adolescents
The most important and early symptoms of ICD in children are progressive obesity, decreased growth rate, elevated blood pressure, and (often) premature hair growth in the genital area. Other symptoms include a moon-shaped face, headaches, irritability, thinning skin, purplish changes on the skin resembling bruises, fatigue, hyperglycemia, and thinning of the arms and legs.
In children before puberty, there was a developmental delay, while with the onset of BIC in the post-pubertal period, there was a developmental delay.
Chronic Excess glucocorticoids also have a detrimental effect on the sexual development of adolescents. ACTH is known to primarily stimulate the synthesis of cortisol, aldosterone, and androgens in the adrenal glands. Excess androgens and cortisol lead to suppression of the gonadotropic function of the pituitary gland, which is accompanied by a violation of sexual function – delayed puberty. On the other hand, hypogonadism in Itsenko-Cushing's disease is caused by a decrease in the secretion of LH and FSH, which is also due to the effect of compression of the tumor mass of gonadotroph cells [10]. In girls, after the onset of menstruation, they sometimes completely cease. Excessive production of androgens causes acne, hirsutism, and sometimes virilization.
Skeletal maturation is usually delayed, but may also be normal. In children with features of Cushing's disease, bone age typically lags behind chronological age by an average of 2 years. Osteoporosis, characterized by decreased bone density, is often observed, most evident on spinal X-rays. Pathological fractures are possible [2].
Slight hair growth, which is more characteristic of Itsenko-Cushing's disease, is caused by a moderate increase in the production of androgens by the perplastic adrenal cortex.

Diagnosis of the disease
1) The attending physician should first compare the child's photo dynamics over several years. 2) It is necessary to perform anthropometric measurements (height, weight, growth velocity, height SDS, weight SDS, etc.) based on the Tanner-Whitehouse height-weight chart. 3) Determine the level of free cortisol in daily urine and blood. An increase in plasma

cortisol at midnight is an early sensitive marker of NIC! 4) Study the rhythm of blood cortisol secretion during the day. 5) Determine the level of ACTH in the blood. 6) Perform MRI (CT) of the pituitary gland and adrenal glands, chest. 7) Perform a dexamethasone test.

The aim of the study is To study the structure of the causes of hypercorticism in childhood, adolescence and youth based on retrospective analysis data.

Material and methods of research

We performed a retrospective analysis of archival data from case histories of patients with various forms of hypercorticism aged 9 to 21 years from 3 departments (children's department, endocrine surgery department and neuroendocrinology department)The Republican Scientific and Practical Medical Center of Endocrinology of the Ministry of Health of the Republic of Uzbekistan conducted a comprehensive study from 1999 to 2024. During this period, 78 patients with various forms of hypercorticism were hospitalized, including 25 boys (32%) and 53 girls (68%). The average age of boys was 13.05 years, and that of girls was 14.15 years.

All patients underwent a range of studies, including endocrine status, general clinical, biochemical, hormonal (ACTH, STH, cortisol, cortisol secretion rhythm, prolactin, small and large dexamethasone tests, free urine cortisol, etc.), radiological (CT/MRI of the sella turcica and adrenal glands, chest X-ray) and other studies.

Research Results

Among the causes of hypercorticism, we identified 5 groups of patients: Group 1 – ACTH-dependent SC (ACTH-DSC) – 55 (70.6%), Group 2 – ACTH-independent SC (ACTH-NSC) – 13 (16.6%), Group 3 – hypothalamic syndrome with a disturbance in the rhythm of ACTH/cortisol secretion – 7 (8.9%) and Group 4 – iatrogenic hypercorticism – 3 (3.8%).

All patients received conservative therapy, including adrenalectomy in 13 patients in Group 2, pituitary radiation therapy in 2 patients in Group 1, and transnasal selective hypophysectomy in 12 patients in Group 1. Postoperatively, pituitary tumor recurrence was observed in 1 patient in Group 1. The distribution of patients by gender and age is presented in Table 3.

Table 1. Distribution of patients by gender and age (according to WHO classification)

Age, years	Boys	Girls
1-3 years early childhood	-	-
4-7 years old: early childhood	-	-
8-12 years old boys 8-11 years old girls	13	13
Boys aged 13-16 12-15 year old girls Adolescence	6	18
17-21 years old Adolescence	8	22
Total (n=78)	25	53

The study of the hormonal status revealed that in patients of all groups the average basal cortisol level was elevated: on average 953 nmol/ml, while basal ACTH levels did not increase significantly (43 pg/ml) in any of the groups. In patients of group 1, total hypercorticism was detected: the daily rhythm of its secretion was disturbed and on average it reached levels of 1200 nmol/ml (8 h) - 1005 nmol/ml (18 h) - 971 nmol/ml (24 h). Conducting a large test with dexamethasone in patients of groups 1 and 2 revealed the corresponding changes, namely, in group 1 there was a reliable decrease in the cortisol level (on average to 234 nmol/l), while in patients of groups 2, 3, 4 and 5 no reliable decrease of more than 50% was observed. Table 4 shows the average values of cortisol and ACTH by group.

Table 2. Average ACTH and cortisol values by groups.

hormones	**1 g, n = 55**	**2 grams n = 13**	**3 grams n = 7**	**4 grams n = 3**	**control n = 12**
ACTH	57.3 pg/ml*	34.4 pg/ml	23.8 pg/ml	22.5 pg/ml	21.6 pg/ml
cortisol	1200 nmol/ml	1156 nmol/ml	879 nmol/ml	964 nmol/ml	499 nmol/ml
p*	> 0.05	> 0.05	> 0.05	> 0.05	> 0.05
p**	< 0.005	< 0.005	< 0.005	< 0.005	< 0.005

Note:P* - reliability of differences compared to the norm for ACTH

P** - reliability of differences compared to the norm for cortisol

CT/MRI of the pituitary gland revealed the following changes: 55 patients with pituitary tumors had intrasellar pituitary microadenomas, with all patients in Group 1 having bilateral adrenal hyperplasia. Patients in Group 2 had unilateral adrenal tumors in 10 patients and adrenal hyperplasia in three.

Visual fields and visual acuity were normal in all patients.

Table 3 presents the frequency of complications of hypercorticism in general in 5 groups of patients.

Table 3. Frequency of complications of hypercorticism in the studied groups of patients.

No.	Nature of the complication	Number of patients	% of the total number of patients
1	Cushingoid obesity	78	100%
2	diffuse osteoporosis	71	61.5%
3	short stature	62	91.0%
4	delayed puberty	38	48.7%
5	arterial hypertension	65	83.3%
6	urolithiasis	15	6.4%
7	primary amenorrhea	6	7.7%
8	pathological fracture of the vertebrae in the thoracic-lumbar region	4	5.1%
9	viril syndrome	53	67.9%
10	hirsutism	25	32.1%
11	hydronephrosis	2	2.5%
12	impaired glucose tolerance	4	5.1%
13	coxarthrosis	2	2.5%
14	femoral neck necrosis	2	2.5%
15	acute coronary syndrome	1	1.2%

It should be noted that we did not observe striae in any child in the prepubertal period. Among the concomitant diseases were observed: chronic pyelonephritis - 8 (10.2%), chronic hepatitis -12 (15.4%), diffuse goiter 1-2 st -10 (12.8%), astheno-neurotic syndrome -7 (8.9%), hypothyroidism - 6 (7.7%), chronic glomerulonephritis - 4 (5.1%), chronic cholecystitis -4 (5.1%), chronic colitis -2 (2.5%), chronic pancreatitis - 2 (2.5%), anemia -2 (2.5%), intracranial hypertension -2 (2.5%).

Discussion of literature data and obtained results:

1) There is no information in the literature on the frequency of precocious puberty (PP) and delayed sexual development (DSD) in children and adolescents with CP, on the characteristics of disorders of sexual development, the time of onset of puberty, etc. 2) There are reports of both acceleration of skeletal development and its delay by more than 2 years [4,5].

There is a report (USA) that included 33 children with ICD (17 girls and 16 boys). The average age was 13 years. Typical symptoms were: obesity (91%), growth retardation (83%), moon facies (61%), hirsutism (58%), headaches (45%), abdominal striae (42%), acne (3%), amenorrhea (24%), and hypertension (24%). In 67% of cases, MRI revealed a pituitary tumor. 55% underwent adrenalectomy and 45% hypophysectomy. 44 months after treatment, signs of remission persisted in 91% of children [8].

There is another report (India), according to which the authors present their 20-year experience of observing 48 (29 boys and 19 girls) children and adolescents with ICD, who were included between 1988 and 2008. The average age was 14.5 years. 27 (56%) patients achieved remission thanks to TAG, especially in the case of microadenoma (75%). Eight

patients underwent radiotherapy after TAG, of which four achieved remission. It is noted that remission is more difficult to achieve in the case of macroadenoma and after the first operation, which is a reason for repeated TAG [4].

According to other authors, primary pigmented nodular adrenal disease may also be a cause of Cushing's syndrome. This is a rare disease of the adrenal glands. It is characterized by hypersecretion of cortisol. The authors (Greece) report a case of the disease in a 7-year-old girl. It is a rare cause of Cushing's syndrome. The clinical picture is typical of PID in children. The patient underwent adrenalectomy. In the 2nd year after surgery, urinary cortisol was elevated. Osteopenia. After surgery, there was a growth spurt, but growth remained low for the next 2 years. Upon reaching puberty, gonadotropin-releasing hormone agonists were included, which initiated a growth spurt. Left adrenalectomy was performed 5 years later. Overall, remission occurred [6].

ACTH-ectopic Cushing's syndrome in children is rare. This is reported by authors from France. This multicentric study included 18 clinics. According to their data, they observed 10 adolescents aged 14 to 20 years with1985to2008. Eight patients had highly differentiated neuroendocrine tumors: 5 bronchial carcinoids, 1 mediastinal lymph node, 1 thymus. One patient suffered from poorly differentiated carcinoma of the thymus, and 1 – stromal tumor of the liver. Nine patients achieved remission after tumor removal. One patient died. The authors recommend that the full range of diagnostic tests be performed in children as in adults [7].

Our results confirm the literature on the prevalence of ACTH-dependent Cushing's syndrome in adolescence: the number of boys and girls with corticotropinomas, with an average age of 16 years, reached 26 (66.6%) of 39, while ACTH-independent Cushing's syndrome occurred in only 4 cases (10.2%). However, we did not observe any patients with precocious puberty.

Conclusions:

1) Among patients with various forms of hypercorticism in this age period, patients with ACTH-ZSK predominated - 55 patients (70.6%), group 2 - ACTH-independent SK (ACTH-NSK) - 13 (16.6%), group 3 - hypothalamic syndrome with a violation of the rhythm of ACTH/cortisol secretion - 7 (8.9%) and group 4 - iatrogenic hypercorticism - 3 (3.8%).

2) In children in the post-pubertal period of manifestation of BIC, mental retardation was most often observed – 38 patients (48.7%).

References

1. Lodish MB, Keil MF, Stratakis CA. Cushing's Syndrome in Pediatrics: An Update. //Endocrinol Metab Clin North Am. 2018 Jun;47(2):451-462. doi: 10.1016/j.ecl.2018.02.008.

2. Jarod P. McAteer, Jorge A. Huaco, Kenneth W. Gow,

Predictors of survival in pediatric adrenocortical carcinoma: A Surveillance, Epidemiology, and End Results (SEER) program study, //Journal of Pediatric Surgery, Volume 48, Issue 5, 2013, Pages 1025-1031,

3. Maya B. Lodish, Hui-Pin Hsiao, Anastasios Serbis, Ninet Sinaii, Anya Rothenbuhler, Margaret F. Keil, Sosipatros A. Boikos, James C. Reynolds, Constantine A. Stratakis, Effects of Cushing Disease on Bone Mineral Density in a Pediatric Population, // The Journal of Pediatrics,
Volume 156, Issue 6,2010,Pages 1001-1005

4. Rachel I. Gafni, Dimitris A. Papanicolaou, Lynnette K. Nieman, Nighttime salivary cortisol measurement as a simple, noninvasive, outpatient screening test for Cushing's syndrome in children and adolescents, //The Journal of Pediatrics, Volume 137, Issue 1, 2000, Pages 30-35,

5. Leah Birdwell, Maya Lodish, Amit Tirosh, Prashant Chittiboina, Meg Keil, Charlampos Lyssikatos, Elena Belyavskaya, Richard A. Feelders, Constantine A. Stratakis, Coagulation Profile Dynamics in Pediatric Patients with Cushing Syndrome: A Prospective, Observational Comparative Study, // The Journal of Pediatrics, Volume 177, 2016, Pages 227-231, https://doi.org/10.1016/j.jpeds.2016.06.087.

6. Maya B. Lodish, Evgenia Gourgari, Ninet Sinaii, Suvimol Hill, Laura Libuit, Spyridon Mastroyannis, Margaret Keil, Dalia L. Batista, Constantine A. Stratakis, Skeletal Maturation in Children with Cushing Syndrome Is Not Consistently Delayed: The Role of Corticotropin, Obesity, and Steroid Hormones, and the Effect of Surgical Cure, //The Journal of Pediatrics, Volume 164, Issue 4, 2014, Pages 801-806, https://doi.org/10.1016/j.jpeds.2013.11.065.

7. Webb SM, Santos A, Resmini E, Martínez-Momblán MA, Martel L, Valassi E. Quality of Life in Cushing's disease: A long term issue? // Ann Endocrinol (Paris). 2018 Jun;79(3):132-137. doi: 10.1016/j.ando.2018.03.007

8. Wengander S, Trimpou P, Papakokkinou E, Ragnarsson O. The incidence of endogenous Cushing's syndrome in the modern era. //Clin Endocrinol (Oxf). 2019 Aug;91(2):263-270. doi: 10.1111/cen.14014.

9. Hirsch D, Shimon I, Manisterski Y, Aviran-Barak N, Amitai O, Nadler V, Alboim S, Kopel V, Tsvetov G. Cushing's syndrome: comparison between Cushing's disease and adrenal Cushing's. Endocrine. 2018 Dec;62(3):712-720. doi: 10.1007/s12020-018-1709-y.

10. Grossman AB. The Molecular Pathology of Cushing Disease: Are We Nearly There? //J Endocr Soc. 2017 Feb 1;1(2):144-148. doi: 10.1210/js.2017-00036.

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