Challenges in diagnosis and treatment of cushing disease in a 12-year-old boy. Case report

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Abstract

Cushing's Disease (CD), defined as hypercortisolism caused by excess Adrenocorticotropic Hormone (ACTH) secretion by a pituitary corticotroph adenoma, rarely presents in the pediatric age range. The aim is to describe a 12-year-old Albanian boy with a challenging pathway to diagnosis and treatment process for Cushing's disease. He presented with headaches, rapid weight gain during the last three years, stunting, increased body hair growth, and a typical Cushingoid appearance. After a consultation in the Pediatric Endocrinology Unit at the University Hospital Center, "Mother Teresa," in Tirana, the boy was pre-diagnosed with Cushing Syndrome, and hypophyseal adenoma was suspected due to suggestive laboratory tests, although non-consistent imaging results. An ectopic ACTH-dependent Cushing syndrome was suspected together with neuroendocrine neoplasia (carcinoid tumor) as a thoracic CT showed a nodular lesion with regular-lobulated sharp contours in the lower lobe of the right lobe resulted in pulmonary tuberculosis granuloma. Even imaging failed to identify the ACTH-secreting microadenoma; the decisive examination was an intervention to collect samples from the inferior petrosal sinus during the CRH test, which found a left-side ACTH-secreting focus. Left hemi-hypophysectomy was performed using gamma knife therapy, resulting in effective normalization of hypercortisolism, but with the side effect of growth hormone deficiency.

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Introduction

Cushing's Disease (CD) is rare in pediatric practice after the age of 5 years[1,2] and requires prompt investigation, diagnosis, and therapy to prevent long-term complications. Its incidence is approximately 5% of that seen in adults,[3] resulting in pediatric endocrinologists having limited experience diagnosing or treating this essentially adult disorder. The principles of investigation and treatment should be conducted in pediatric facilities based on adult experience. Defined as hypercortisolemia caused by an ACTH-secreting corticotroph adenoma, pediatric CD accounts for approximately 75–80% of all pediatric CS cases,[3,6,7] and most of them are microadenomas with diameters <5 mm.[7] These microadenomas have a hypointense signal, which fails to enhance with gadolinium.[9] Approximately 50% of them were visible on pituitary MRI,[6] making pituitary imaging relatively unhelpful, showing a regular appearance in over half of the patients, with a low predictive value of the position of the adenoma, as identified at surgery.[10] The median age of CD presentation is 14.1 years, with the youngest reported case being 6.2 years.[11]

Case Report

The patient, a 12-year-old boy, presented with headaches and rapid and marked weight gain, mainly during the last three years, together with stunting, increased body hair growth (hypertrichosis), chest pain, dry cough, and a typical Cushingoid appearance. For these reasons, it is referred to the pediatric endocrinology unit at the University Hospital Center, "Mother Teresa," in Tirana, Albania, when he was 11 years and 11 months old. The patient was conscious, cooperative, and well-oriented with a "moon face" appearance, plethora, and exophthalmos. The cardiovascular system was regular without any murmur. No

hepatomegaly. There were extensive striae rubra (red stretch marks) on the abdomen and lower extremities, buffalo hump, and acanthosis on the neck. Hyperthricosis and an increased number of nevi were visible (Figure 1).

The growth indicators at the first visit were as follows: weight: 70 kg (+2.11 z-score); height: 137.6 cm (-1.59 z-score); BMI: 36 (+4.11 z-score) (Figure 2).

He had virilization expressed by premature adrenarche and pubarche (A2; P3-4), but he was considered in the prepubertal stage on the Tanner stage method refers to based testicular volume (G1- testicular volume less than two cc) and penile length: 2.5 cm (micropenis evident).

The pregnancy was expected, and there were no problems. He was born naturally during the entire term. His birth weight was 5000

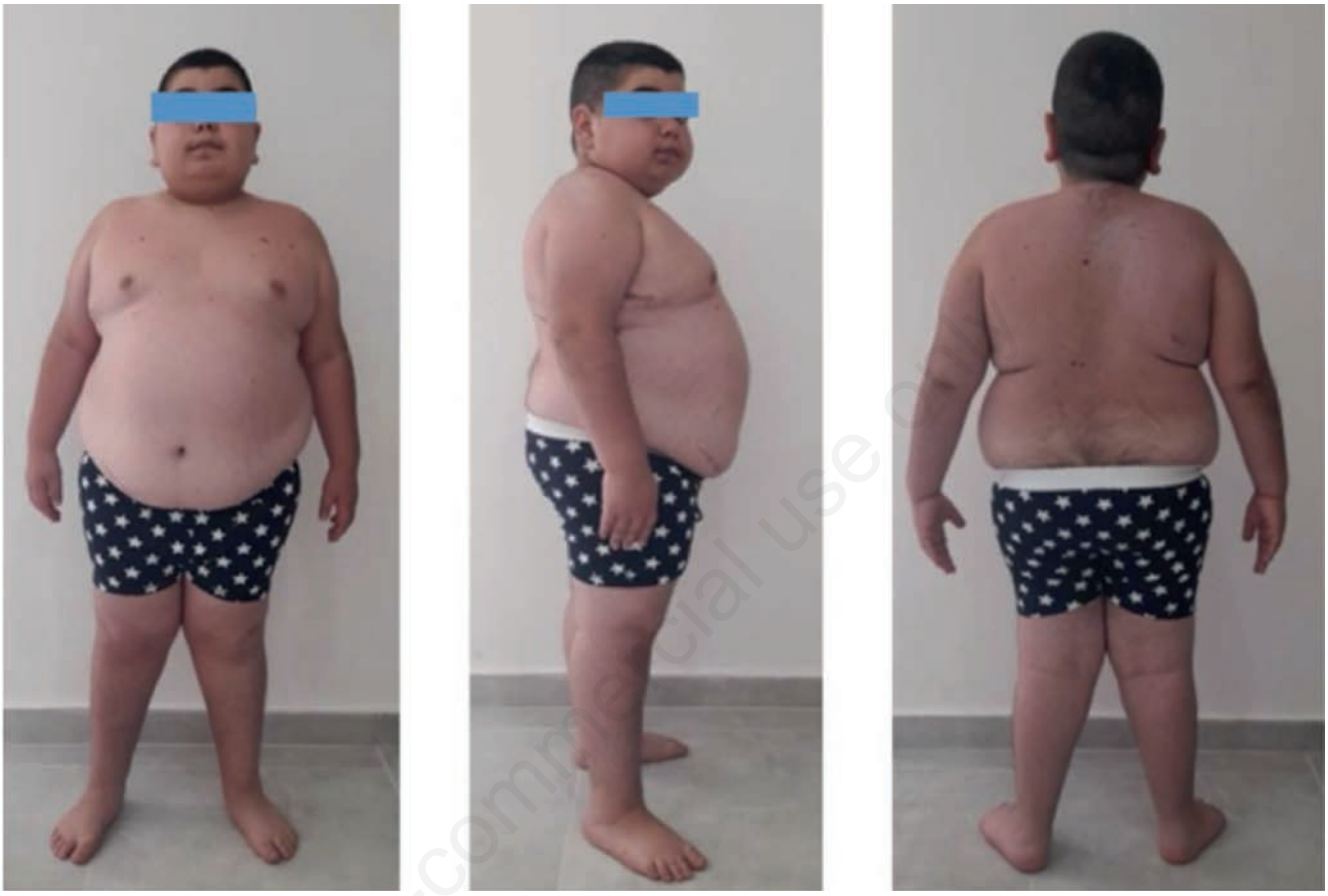

Figure 1. Physical appearance on first examination.

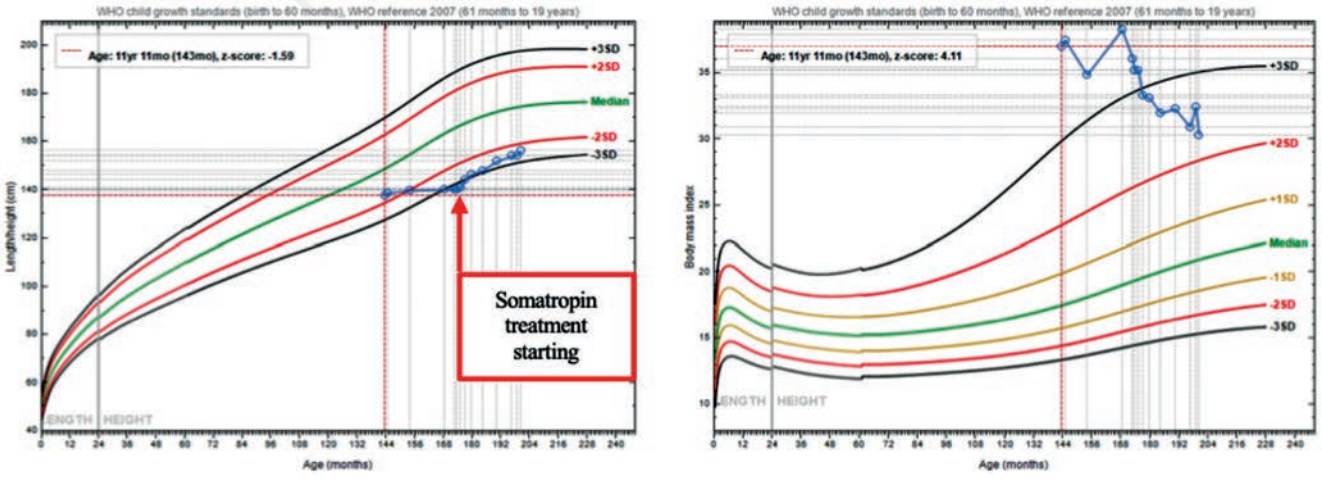

Figure 2. Height for age and BMI for age z-score based on WHO growth charts by Anthro-plus 2007.

gr, and his adaptation to extrauterine life and the neonatal period were normal. He was breastfed until 24 months (exclusively breastfeeding until 12 months old). The growth and development milestones were installed in time (his first teeth erupted at nine months, he walked around 12 months, and he talked around 12 months).

Health was generally good until nine years old, when significant weight gain was observed. He was vaccinated regularly according to the recommended Albanian vaccination schedule. There was no reaction to any medicament. At 11 years old, he underwent surgery for an anal fistula. He had two older brothers, aged 18 and 17 years, referred to as healthy without a history of any disease, and his parents were healthy without consanguinity.

His investigations at the first visit showed the following values: cortisol: 468 ng/mL, ACTH: 95.3pg/dL (08.^{00} a.m.); cortisol 306 ng/mL, ACTH: 116.2 pg/dL (04.^{00} p.m.). Salivary cortisol at 11.^{00} p.m.: 10.55 ng/dL, 25,9 ng/mL. Free cortisol in 24-hour urine: 556mcg/24 hours. High-Dose Dexamethasone Suppression Test (HDDST) was performed. However, it did not inhibit serum cortisol secretion: before the 8 mg dexamethasone suppression test, cortisol level was 136,9 ng/mL and 375 ng/mL after the test (Table 1).

The patient was pre-diagnosed with Cushing Syndrome, and hypophyseal adenoma or ectopic ACTH-secreting mass was suspected. The patient was admitted to the Neurosurgery unit with the pre-diagnosis of suspicious hypophyseal adenoma. A cranial MRI was performed, which did not reveal anything other than cortical atrophy.

Pediatric Endocrinology was reconsulted, and blood tests resulted as follows: ACTH: 65 pg/mL, cortisol: 151ng/mL, DHEAS: 853 mcg/dL, IGF1: 195,5 ng/mL, FSH<0.3UI/L, LH<0.3UI/L, total testosterone: 83ng/dL, FT4: 1.51ng/dL and TSH: 1.35 mUI/mL. Hypophyseal and cranial Magnetic Resonance Imaging (MRI) was performed again, revealing extensive cortical atrophy. However, since the patient did not have any symptoms of Posterior Reversible Encephalopathy Syndrome (PRES), such as convulsion, loss of vision, or encephalopathy, within the past three years, this cortical atrophy is thought to be secondary to the steroid effects.

On the third day of admission, the patient was evaluated at a multi-disciplinary meeting attended by neurosurgery, pediatric endocrinology, and pediatric radiology. Owing to the above test results and the absence of any evidence of adenoma in his hypophyseal MRI, ectopic ACTH-dependent Cushing syndrome was considered. An overnight 8 mg dexamethasone suppression test was performed again. His cortisol level was 185 ng/mL before and 219 ng/mL after the Dexamethasone test. In these circumstances, ectopic ACTH-dependent Cushing syndrome was strongly suspected.

A thorax and abdominal MRI was performed. The thorax RMI showed a nodular lesion with regular-lobulated sharp contours measuring 16x14x10 mm in the right lower lung lobe in the anterior-basal segment, which was primarily suggestive of a carcinoid tumor. The imaging studies also detected Genant grade 3-4 vertebral compression fractures.

On the 5th day of admission, his blood pressure was around 130/85mmHg, and amlodipine 5mg q.d. was added to the therapy. Left ventricular hypertrophy, secondary to hypertension, was detected in his echocardiogram. Furthermore, ophthalmology was also consulted, and hypertensive retinopathy first grade was detected.

On the 11th day of admission, the patient was preoperatively given a push steroid dose of 50mg/m2 followed by a steroid infusion at 100mg/m2/day and underwent the planned surgery. The lower lobe of the right lung was resected during the video thoracoscopic lobectomy (video thoracoscopy + lung resection + mediastinal lymph node dissection). A prophylactic dose of enoxaparin was given to him due to hypercoagulability. Twenty hours after the surgery, ACTH was 34 pg/mL and cortisol 150 ng/mL. Upon pathologic evaluation of tissue excised during the surgery, it was found that there was a necrotizing granulomatous focus (more consistent with TBC) rather than a bronchial carcinoid. Chromogranin A and ACTH staining results were negative, and Erlich-Ziehl-Neelsen (EZN) was positive. The steroid therapy was discontinued. Pediatric pulmonary medicine and pediatric infectious disease were consulted due to suspicion of tuberculosis. The tissue excise during the operation was tested for ARB (for tuberculosis).

Additionally, tuberculosis culture and M. TBC PCR test were performed. The QuantiFERON-TB Gold test (QFT-G) and sediment tests were ordered. Based on the pathological diagnosis, fasting gastric secretion samples were collected three times and were tested for

Table 1. Results of hormonal testing from the first visit to 2 years follow up. High values are indicated in bold.

Examination tests	Date of examination									
	17 Apr. 2019	27 May 2019	28 Feb. 2020	7 May 2020	8 May 2020	13 May 2020	15 May 2020	01 Feb. 2021	04 Feb. 2021	06 Feb. 2021
IGF1(ng/ml)								195		
TSH (0.4-4.0 mUI/mLl)	3.45		2.37					1.35		
FT4 (pg/mL)			1.28					1.51		
17-OH Progesterone (ng/mL)			0.13							
ACTH ora 08^{oo} (6-48pg/mL)	**95.39**	**49.74**	**102.1**			46	24			
ACTH ora 16^{oo} (3-30 pg/mL)	**116.2**							**65**		
Cortizoli 08^{oo} (72.6-322 ng/mL)	**468**	136.9	**375**			138	127		185	219
Cortizoli 16^{oo} (32.4-150 ng/mL)	**306.32**							**151**		
Free U. Cortisol (30-350 ug/24hr)	**556.1**	**821.5**								
Salivar Cortisol (ng/mL)				**10.55**	**25.9**					
FSH (1.5-11.8 UI/L)	0.62							0.3		
LH (1.1-25 UI/L)	0.21							0.3		
Testosterone (2.2-10.5 ng/mL)	1.345		0.959					0.83		
DHT (250-790 pg/dL)	**852.41**		**999.6**							
DHEA-S (16.6-242.7 ug/dL)		**580.2**	**894.2**					**853**		
Prolaktin (2.54-15.98 ng/mL)	22.69									

Antibiotic-Resistant Bacteria (ARB), TB culture, and mycobacterium tuberculosis CRP. The results confirmed the diagnosis of pulmonary TBC, and anti-tuberculosis treatment was started.

A Low-Dose Dexamethasone Suppression Test (LDDST) was performed to reevaluate the boy for hypercortisolism. No suppression of cortisol level was detected. ACTH level was measured at 65 pg/mL again. Neurosurgery and physiotherapy were consulted regarding the compression fraction detected in the imaging studies. In the absence of neuromotor deficit, conservative treatment was recommended for Genant grade 3-4 vertebral compression fractures. On the 17th day of admission, an 18 F-fluorodeoxyglucose Positron emission tomography-computed tomography (FDG PET/CT) was performed (Figure 3). No ectopic ACTH-depended focus was detected.

On the 24th day of admission, an intervention to collect samples from the inferior petrosal sinus was performed under general anesthesia. Findings were consistent with a left-side ACTH-secreting focus (ACTH: 139pg/mL in right petrosal sinus and >2000pg/mL in left petrosal sinus after CRH). The previous hypophyseal MRI images were reviewed, and suspicious focus was definitively considered. The neurosurgeons planned a left hemi-hypophysectomy, but because the intervention had to be done in a dangerous area, the decision was made to intervene with a gamma knife. On the 33rd day after admission, he was discharged with this therapy: ketoconazole 2x200mg for medical adrenalectomy; amlodipine 5mg tablet; pantoprazole 40mg vial; enoxaparin sodium 40mg/0.4ml injector; piperacillin and tazobactam 4.5gr vial; salbutamol 2.5mg/2.5ml nebulizer; iridoid (chondroitin polysulfate) cream; Calcimax-D3 (calcium carbonate and vitamin D) effervescent tablet, and a quadruple anti-TB treatment (oral INH 1x300mg; PRZ 1x1500mg; EMB 1x1500mg; rifamycin 1x600mg) for 12 months.

He was regularly based on this follow-up: i) monthly cortisol and ACTH levels evaluation for hypercortisolism with a 1mg overnight dexamethasone suppression test; ii) follow-up for potential adrenal insufficiency and electrolyte levels; iii) following testosterone levels for testicular insufficiency; iv) use of recommended corset for vertebral fractures; v) Calcimax (calcium carbonate and vitamin D) tablet, q.d.; vi) amlodipine 5mg, q.d.; vii) control hypophyseal MRI after six months and one year, respectively; viii) observation for the development of panhypopituitarism; ix) due to the anti-TBC therapy, liver function tests and hemogram levels should also be checked frequently. During the first month of his anti-TBC therapy, a follow-up at ophthalmology is recommended to assess the potential impact of EMB on the eyes. Follow-up by a pediatric infectious disease or pediatric pulmonary medicine specialist in his country of residence is advised.

The progress of growth indicators was monitored every three months. Inhibition of height growth and deterioration of the degree of obesity assessed through BMI were found (Figure 2).

For this reason, at the age of 14 years and five months, two sequential tests were performed to stimulate the secretion of growth hormone using the glucagon stimulation test. This test showed evidence of growth hormone deficiency. At this age, he weighed 69 kg (+2.33 z-score), was 140 cm (-3.36 z-score), and had a BMI of 35.2 (+3.22 z-score) (Figure 2). One month later, treatment with somatropin began at a dose of 0.25 mg/kg/day, which he is continuing with calcium and vitamin D3 supplements. He is 16 years and eight months old, weighs 74 kg, is 156 cm tall (-2.38 z-score), and has a BMI of 30.3 (+2.33 z-score) (Figure 2). DEXA bone density tests showed a significant improvement from -2.1 z-score in L1 at the beginning of treatment to -0.5 z-score currently.

Discussion

Our patient's case is characterized by several challenges: challenges in diagnosis, challenges in treatment, and challenges in follow-up.

Regarding the diagnosis, the patient left no doubt that we were dealing with Cushing's Syndrome (CS). The clinical signs and symptoms, the phenotypic manifestations, and the results of the hormonal laboratory examinations confirmed CS with more certainty. Following confirmation of CS, the priority is to determine the cause of the hypercortisolism. Cushing's Disease (CD) and Ectopic ACTH Syndrome (EAS) are the two leading causes of ACTH-dependent CS. Their clinical manifestations are similar, but their treatments are quite different, so the differential diagnosis of CD and EAS is a crucial but challenging task.[12] HDDST pointed toward Cushing's dis-

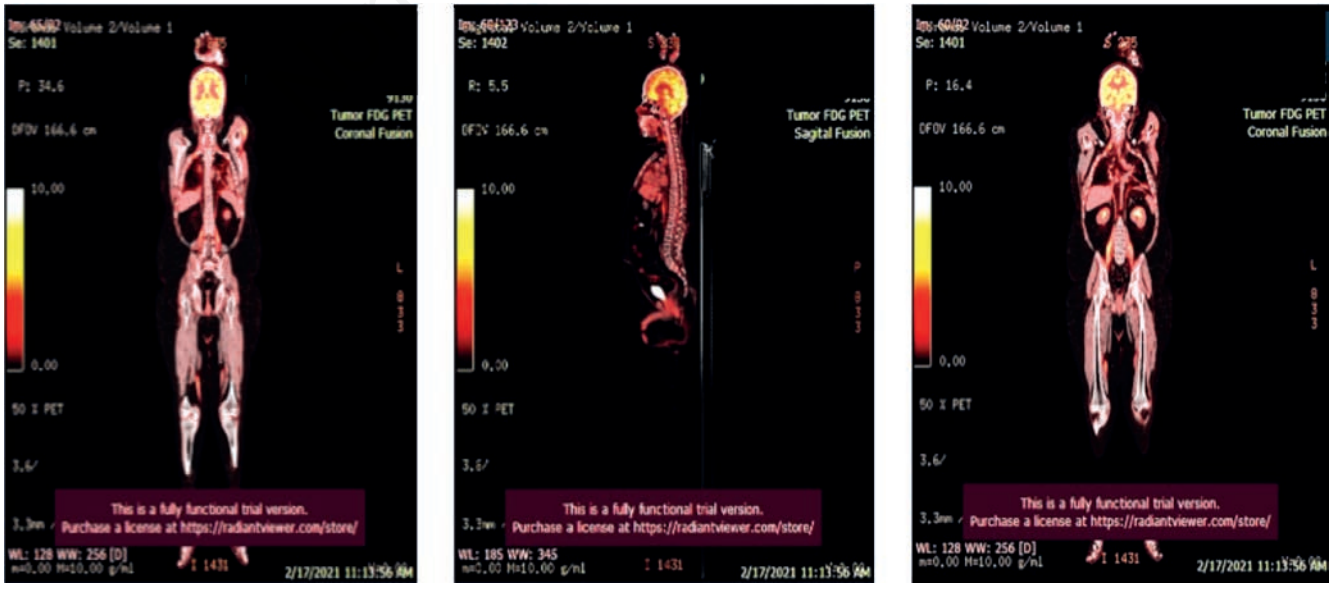

Figure 3. 18 F-fluorodeoxyglucose Positron emission tomography-computed tomography (FDG PET/CT) of the patient.

ease even though HDDST is no longer routinely performed at many centers because patients with CD show almost the same reduction of cortisol during the LDDST, which predicts the same response observed during an HDDST. A study[13] showed that two-thirds of CD patients suppressed their cortisol levels to >30% during the LDDST. Therefore, the LDDST alone can broadly discriminate between CD and other CS etiologies.

Identifying the focus of increased ACTH secretion became very difficult. Even the implementation of some contemporary imaging methods, such as CT, MRI, or PET, still needed to determine the focus definitively.

On the contrary, the presence of a focus of a tubercular lesion in the right lung is erroneously oriented towards a bronchial ACTH-secreting tumor. The decisive examination was an intervention to collect samples from the inferior petrosal sinus under general anesthesia.

Regarding treatment, Trans-Sphenoidal Pituitary Surgery (TSS), consisting of selective removal of the adenoma, is now considered the first-line therapy for pediatric CD. TSS is considered a safe and effective procedure in children.[13,14] Gamma Knife Surgery (GKS) is a second-line therapeutic option for CD with satisfactory safety and efficacy. It offers a high tumor control rate and a reasonable endocrine remission rate in patients with Cushing's disease. The cessation of cortisol-lowering medications around the time of GKS appears to result in a more rapid rate of remission. Delayed hypopituitarism and endocrine recurrence develop in a minority of patients and underscore the need for long-term multidisciplinary follow-up. However, the intervention with the gamma knife seemed to be effective in our patient. However, the accuracy and safety were only shown after about 12 months when the normalization of ACTH and cortisol levels was evident. Although a non-invasive method, it resulted in a growth hormone deficit.

The particular challenge was postoperative treatment in medical adrenalectomy with ketoconazole due to hepatotoxic effects and inhibitory effects on normal steroidogenesis by inhibiting testosterone synthesis. However, due to the lack of ketoconazole in the pharmaceutical market, it was not used for more than two months. Our patient's treatment required a multidisciplinary involvement, including a pediatric pulmonologist, a pediatric cardiologist, an ophthalmologist, an infectious disease specialist, a radiologist, a neurosurgeon, and, of course, an endocrinologist.

In hypercorticism, the patient stagnated in height growth apart from other difficulties. After normalizing cortisol levels, the patient was expected to experience height growth improvement. The absence of this growth spurt suggested evidence of a growth hormone deficit. The beginning of treatment with somatropin significantly improved the growth velocity. Together with the use of calcium supplements and vitamin D-3 and, of course, in the absence of high cortisol levels, it also improved bone density, removing the risk of fractures.

Conclusions

During the diagnosis process of a patient with CD, the dexamethasone suppression test alone was not accurate enough to distinguish between CD and EAS. A combination of dynamic tests and diagnostic imaging techniques, such as the Corticotropin-Releasing Hormone (CRH) test, HDDST, LDDST, thoracic CT scan, pituitary MRI, and Bilateral Petrosal Sinus Sampling (BIPSS), was necessary to determine the cause of ACTH-dependent CS. Even though it was not the first line of treatment, GKS succeeded in normalizing the levels of ACTH and cortisol in a gradual but stable manner, although at the cost of developing the growth hormone deficit as a treatment complication.

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