CLINICAL CASE

MANAGEMENT OF RECURRENT POSTOPERATIVE CUSHING'S DISEASE

Ana Valea[1,2], Roxana. Turturea[2], Oana Botezan[2], Mara Carsote[3], Adina Ghemigian[3], Carmen Emanuela Georgescu[1,2]

[1]I. Hatieganu University of Medicine and Pharmacy
[2]Clinical County Hospital, Cluj-Napoca, Romania
[3]C.I. Parhon National Institute of Endocrinology, Bucharest, Romania Romania

Corresponding author: Mara Carsote
Phone no.: 0040213172041
E-mail: carsote_m@hotmail.com

Abstract

Although adenomectomy remains the first-line treatment in Cushing's disease, it is not always curative for most patients. Sooner or later persistent or recurrent disease can be found in some cases.Case report: A 13-year-old girl was admitted for weight gain, menstrual disturbances, and transient headache. Hormonal profile confirmed the clinical suspicion of Cushing's disease. Pituitary MRI highlighted a microadenoma of 5.2 mm resected through transsphenoidal adenomectomy. No complications were registered during the procedure. After a 7 days hospitalization, the patient was discharged without any medications. Periodic evaluations confirmed the disease's remission that was maintained for a period of 2 years. During this period, the patient received only thyroxine and progesterone treatment. Two years after surgery, the adrenal hormone profile confirmed the recurrence of the disease. According to the patient's age, ketoconazole and carbergoline treatment was instituted without any significant improvement. Because no obvious tumor mass has been revealed on the pituitary MRI, pasireotide treatment was introduced at the age of 18. An obvious improvement in the hormonal profile was achieved after three months of treatment. Cushing's disease control requires therapeutic alternatives consistent with the patient's age and the complications of the disease. Pasireotide treatment may be a good choice for adult patients with recurrent disease after transsphenoidal adenomectomy.

Keywords*: Cushing's disease, adenomectomy, dexamethasone, hypercortisolism*

Introduction

Cushing's disease in children and adolescence is a rare condition estimated at 10 % of total hypercortisolism [1,2] . Establishing diagnosis and appropriate therapy often remains a challenge. The clinical picture is sometimes different from the adult, as there are particularities related to the response to the inhibitory tests [3,4]. The main cause of hypercortisolism in children and adolescents is an ACTH (Adrenocorticotropic hormone)-secreting pituitary adenoma [5,6]. As a form of endogenous hypercortisolism, Cushing's disease has several therapeutic approaches. Transsphenoidal adenomectomy is the first therapeutic line regardless of the patient age. Initial postoperative remission is estimated at 70-98% and long-term remission at 50-98% [7,8]. Postoperative relapse, estimated at 15%

after 2 years of surgery, requires alternative therapeutic methods. Medical treatment is a good choice due to reduced side effects, often reversible after the cessation of treatment [9]. Pasireotide, by binding to somatostatin receptors, especially SSTR5 (Somatostatin Receptor Type 5), can provide optimal disease control in patients aged over 18 [10].

Case presentation

A 13-year old girl with no prior medical history, was admitted for weight gain with central distribution, transient headache, moderate asthenia and oligomenorrhoea. On admission, the physical examination reveals: height of 160 cm, weight of 70 kg, over the percentile of 95%, normal blood pressure, purple striae with periumbilical distribution and at the root of the limbs, moon face, moderate buffalo hump, enlarged supra-clavicular fat pads, acne on the face, anterior and posterior thoracic walls (Figure 1 and 2). Evaluation of the corticotropic axis revealed the reversal of cortisol secretion rhythm (8 a.m plasma cortisol of 19.7µg/dL, normal:6-23µg/dL, 11p.m plasma cortisol of 22.6µg/dL, normal:2.5-13µg/dL), elevated 24- hour urine free cortisol (UFC) of 349.5µg/24h (normal:50-190µg/24h), non-suppression at low dose DXM (dexametasone) 1 mg (milligram), (of 14.6µg/dL, normal 1.8µg/dL), adequate suppression at 2 days of 8 mg DXM test, ACTH in the upper reference range, height levels of DHEAS (Dehydroepiandrosterone sulfate) (Table 1). Hormonal profile performed to evaluate the pituitary function showed normal plasma gonadotropin levels, normal prolactin (PRL) and testosterone levels (Table 1).

Biochemical evaluation pointed slightly elevated liver samples (Table 1). Pituitary MRI (Magnetic Resonance Imagery) with IV contrast showed the presence of a 5.2 microadenoma (Figure 3). Based on these, Cushing's disease was confirmed and the patient was guided towards the neurosurgery service. Due to personal reasons, transsphenoidal adenomectomy was performed 2 years after the diagnosis was established. No any intra or post-operative complications were reported. Seven days later, the patient was discharged without any specific medication. The hormonal test performed 3 months after the surgery revealed a normal adrenal axis, low FT4 (Free Thyroxine) and progesterone levels. FT4 therapy in a daily dose of 25µg and 10 days on 10mg progesterone was introduced. After 2 years of remission, confirmed by annual evaluation, a progressive increase in plasma cortisol, ACTH and UFC levels was recorded (Table 1). Initially, treatment with ketoconazole was completed with cabergoline without any obvious improvement. Because no tumor mass was highlighted on the pituitary MRI, at the age of 18 pasireotide treatment in daily doses of 2x 600µg was introduced. Three months later, adequate disease control was obtained.

Close endocrine, biochemical, and imagery check-up is recommended.

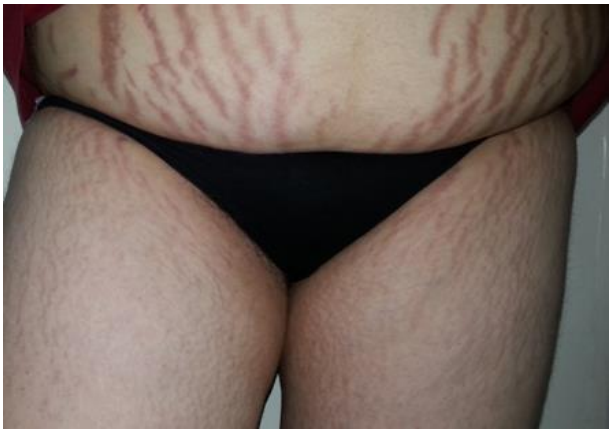

Figure 1 - Abdominal and thighs purple striae on a girls with Cushing's disease

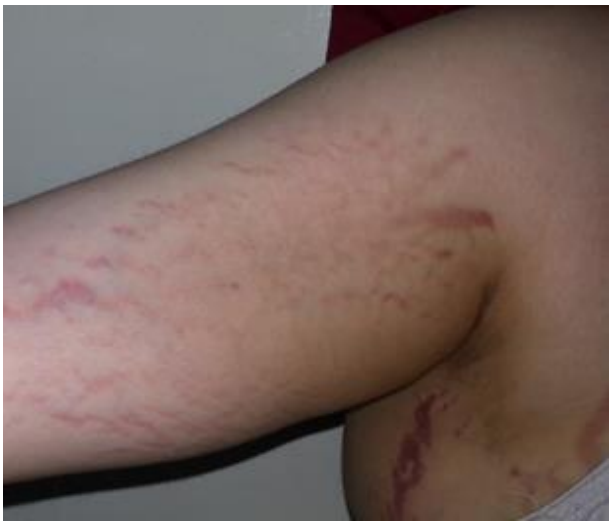

Figure 2 - Arms and breast red-purple striae, atrophic appearance of proximal arm muscle.

Parameter	Before surgey	3 months after surgery***	12 months after surgery ****	24 months after surgery *****	36 months after surgery *****	3 months after pasireotide	Normal limits	Units
Morning plasma cortisol	19.7	6.10	10.8	13.5	8.85	8.32	6-23	μg/dL
Plasma cortisol 11p.m	22.6	1.8	9.43	14.2	10.7	3.89	2.5-13	μg/dL
Morning Plasma Cortisol*	14.6	0.85	0.50	0.9	4.16	0.92	< 1.8	μg/dL
Morning plasma cortisol**	11.1	0.3			2.78	2.98	< 50***	μg/dL
24-h free urinary cortisol	349.5	6.3	10.2	153.3	441.6	109.8	50-190	μg/24h
ACTH	59.99	12.14	22.41	51.33	39.8	19.23	7.2-63.3	pg/mL
DHEA-S	523	274	312	298	301	289	44.3-331	mg/dL
Testosterone	0.75	0.15	0.19	0.29	0.10		<0.75	ng/mL
Prolactine	8.31	9,17	19.4	20.3	0.50	0.44	1.9-25	ng/mL
FSH	4.70	1.17	3.23	3.65	3.02	3.78	2.8-11.3	U/L
LH	2.70	0.68	1.22	1.98	0.79	2.14	1-11.5	U/L
Progesterone	0.12	0.04	0.08	0.14	0.09	0.17	0.18-2.84	nmol/L
TSH	0.74	0.88	0.65	0.64	0.39	1.12	0.4-4	μUI/mL
FT4	1.10	0.89	1.05	1.19	1.13	1.43	0.89-1.76	ng/mL
ALT	91	34	22	17	12	21	<35	U/l
AST	81	32	19	15	16	19	<35	U/l

Table 1: The endocrine and biochemical parameters of a young girl diagnosed with Cushing's disease: pre and post-transphenoidal adenomectomy profile, with and without specific medical treatment.

* after 1mg Dexametasone overnight test; ** after 2 days of 8 mg Dexametasone suppression test;***the lack of reduction of <50%; 24-h= 24-hours; ACTH= Adrenocorticotropic Hormone; DHEA-S= dehydroepiandrosterone; FSH=Follicle-Stimulating Hormone; LH=Luteinizing Hormone; TSH=Thyroid Stimulating Hormone; FT4=Free Thyroxine; ALT= alanine transaminaze, AST= aspartate aminotransferaze

****25 μg/day Thyroxine therapy, 10mg progesterone, 10 day/month; *****25 μg/day Thyroxine, 10mg progesterone, 10 day/month, 1 mg/week Cabergoline, 400 mg/day Ketoconazole

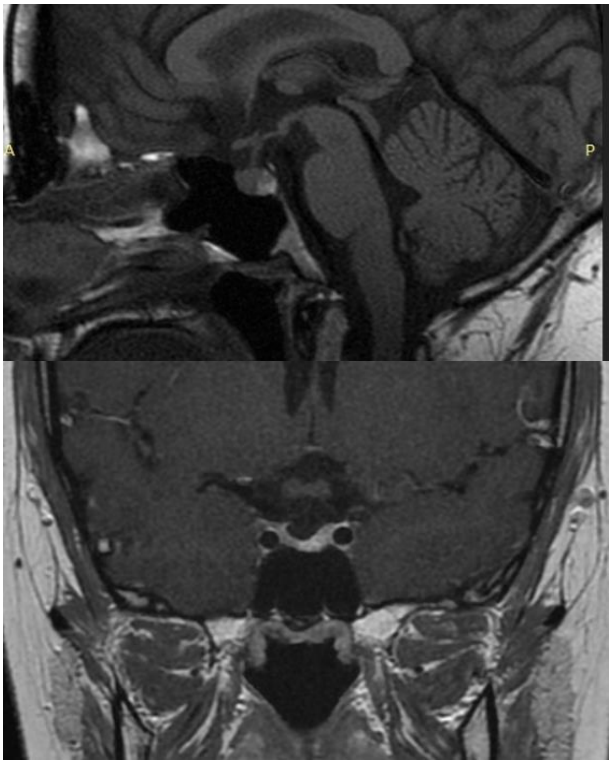

Figure 3 - Preoperative IV Contrast MRI performed on a 13-years girl: microadenoma of 5.2mm without suprasellar extension and no mass effect on the pituitary stalk. A: Sagital plane, B: Coronal plane

Discussions

Postoperative relapse of Cushing's disease in children is a challenge for the clinical practice. Although a second surgical procedure is recommended as a priority, it is often difficult for the patient to accept [11]. The main objective of the surgical treatment is to preserve healthy pituitary tissue. The tumor size, location, intraoperative visualization and the patient's age are the main factors involved in the final success rate [12]. In our case, thyroid insufficiency was the only postoperative complication mentioned and adequately controlled by a daily dose of thyroxine. Progesterone deficiency has been reported prior to surgery and replacement treatment continued for 10 days per month following adenomectomy. Pituitary radiotherapy is another therapeutic option for children and adolescents with Cushing's disease with a 40-70% remission rate. The main limitations are the risk of pituitary insufficiency and the delayed effect [13,14]. Considering the moderate hypercortisolism and the patient's age we opted for the medical treatment. Because a daily dose of 400 mg/day ketoconazole associated with 2 mg/week cabergoline did not provide any disease control, it was necessary to find a therapeutic alternative. Pasireotide treatment in a daily dose of 2x600 μg/day was the patient's choice instead of surgical reintervention.

Conclusions

Optimal control for children and adolescents with Cushing's disease remains a challenge. Post-surgery recurrence requires finding the therapeutic variants in accordance with the patient's age, the disease's aggressiveness and potential complications. For patients over 18 years, inhibition of ACTH synthesis by pasireotide may be a suitable therapeutic option.

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