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Paediatric Cushing Disease: one patient's path to cure

The authors have nothing to disclose

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Objectives

History:

- 15 years old boy, diagnosed with Cushing's syndrome elsewhere
  - Initial signs and symptoms ≥2 yrs
  - Weight gain, growth arrest, skin changes, emotional lability, poor memory for recent events, eye problems
- Numerous inconclusive investigations for 6 mo – Metformin therapy
- TSS – unsuccessful (*no further treatment*)
- Presented 2 mo after TSS with escalating deterioration

Physical examination:

- Weight 71.0 kg (SDS 1.25), height 148.1 cm, (H SDS -2.67, TH SDS -1.16), BMI 32.37 kg/m2 (SDS 2.96)
- Central obesity, "moon" face, buffalo hump
- Skin changes: acne, striae, hypertrichosis, bruises, flush, acanthosis
- Eye changes: discrete exophthalmos
- Pubertal: Tanner stage IV, TV 15 ml
- BP 115/89 mmHg, HR 84/min

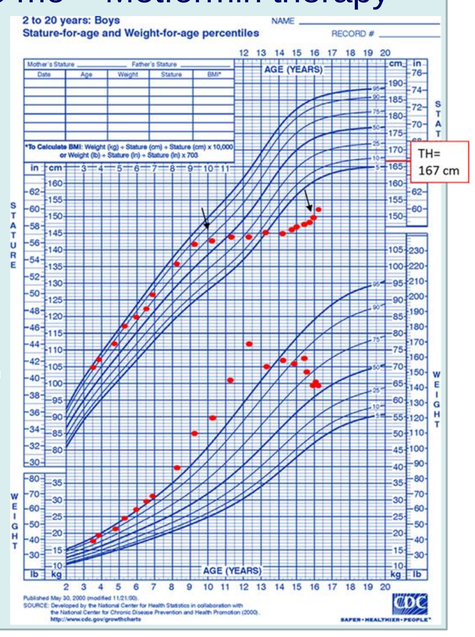


Table 1. Hormonal investigations - presentation and follow-up (FU) - 6/9 months

Name	Presentation	FU 6 mo	FU 9 mo	Ref. range	Unit
Cortisol 00:00	601.94 (awake)	*on HC	*on HC	<50	nmol/l
Cortisol 08:00	977.5	255.9	48.04	50-550	nmol/l
ACTH	117.0	228	572	<46	pg/ml
UFC	1012.0	233.8	320.5	55.5-286	mkg/24h
IGF	159.0	193	595	237-996	ng/ml
LH	0.52	3.0	2.73	0.5-5.3	mIU/ml
FSH	4.0	4.0	4.34	0.3-8.2	mIU/ml
Testosteron	4.3	10.1	11.9	2.95-41.66	nmol/l
TSH	1.6	1.3	2.65	0.4-4	uIU/ml
FT4	14.4	13.8	13	10.3-24	pmol/l
Prolactin	72.7	89.3	92.4	53-360	uIU/ml

Methods

Investigations: proved CD and localised hypophyseal corticotroph adenoma (Tables 1 & 2)

- Cortisol –↑ morning and midnight values, disturbed circadian rhythm
- Coupled plasma ACTH/cortisol – inappropriately elevated
- UFC – increased
- Overnight Dexamethasone suppression test (8 mg)
  - Cortisol (88.2%) and ACTH (90.5%) suppression >85%
- IPSS– basal ACTH ratio central/periphery >2/1 and left/right >1.5
  - *First time in the country*

- MRI of the pituitary region – no adenoma found
- Pituitary function tests: partial gonadotrophin deficiency, low IGF-1
- Other: ↑ total and LDL cholesterol, no bone loss on DEXA

Management:

- Oral Ketoconazole (2x200mg) + planned for a second TSS
- Liver toxicity after 3 weeks on Ketoconazole and deterioration, related to the hypercortisolaemia
  - increased BP, hypokalemia and tendency towards hypernatremia, incipient heart decompensation

- **Decision for bilateral adrenalectomy (BA), due to the rapid health decline -** *lack of other oral adrenolytics in the country*

Table 2. IPSS

Basal investigation	ACTH (pg/ml)			Cortisol
	right	left	peripheral	peripheral
Sinus petrosus inferior	46.7	183	39	520.7
V. jugularis int. supp.	48.5	105	44.1	513.9
V. jugularis int. inf	50.4	53	32.2	
Central/periphery ratio		4.7/1		
Lateralisation ACTH at S. petr. Inf. L/R		3.4/1		

Results

Preparation for the BA:

- Preoperatively treated with i.v. Etomidate
- 24 hours prior BA in block-replace regimen (Methylprednisolone, when desired Cortisol levels of 100-200 nmol/l reached)
- *No previous experience in the country*

Laparoscopic BA

Postoperatively

- Hydrocortisone, Fludrocortisone and antihypertensives
- Uneventful postoperative period

First weeks after the BA

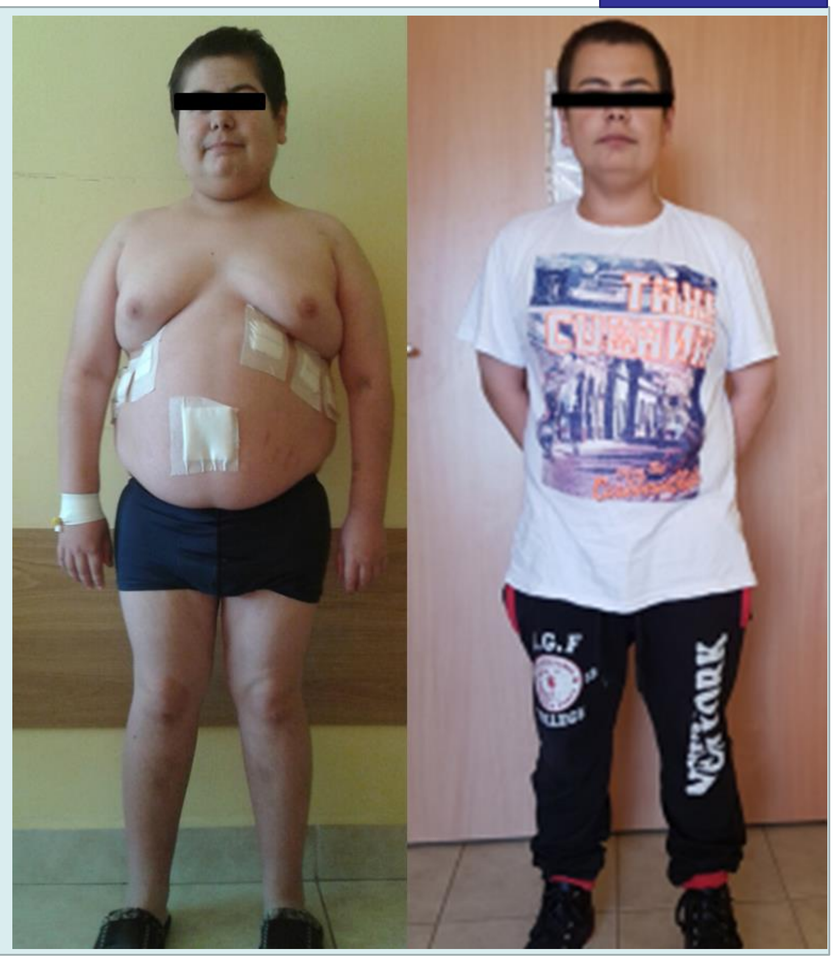
- Elevated BP
- Swelling of the legs
- Anxiety attacks

FU at 6 months

- Weight reduction -8 kg (SDS 0.17)
- No catch-up growth (1 cm/6 mo, SDS -2.79)
- Advancing pubertal development (TV 20 ml)
- BP normalised
- Overcoming depression and anxiety
- GH deficiency
  - ITT and GT GH peak <10ng/ml (5.9 and 8.44 respectively)
  - BA 14 yr 10 mo
  - Started GH therapy (1.5 mg/day)

FU at 9 months

- *Catch-up on GH (3 cm/3 mo)*
- Two more anxiety attacks, blurred vision (left)
- Further levated ACTH
  - no signs of Nelson`s syndrome (MRI – no change, no hyperpigmentation)
- Normal TSH, gonadotrophins and testosterone



Conclusions

Treatment of paediatric CD and its related complications is complex. Many factors can change the therapeutic course, including the lack of medications and experience in smaller centers. Multidisciplinary approach and collaboration with experts in the field are crucial for a successful outcome.

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