Cushing's disease - medical chameleon.

Case report of the patient with cyclic, ACTH-dependent Cushing's syndrome due to atypical pituitary macroadenoma

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Introduction. ACTH-secreting macroadenomas account for about 4-10% of Cushing's disease and are often resistant to surgical treatment and radiotherapy.

The aim of the study was to present diagnostic and therapeutic difficulties in a case of cyclic recurrent ACTH-dependent Cushing's syndrome due to atypical pituitary adenoma.

Case report. In 08.2007 50-year-old man with visceral obesity was referred to hospital because of poor control of diabetes and high blood pressure. On the basis of clinical symptoms and severe hypokaliemia hypercortisolemia was suspected and laboratory test were performed. They confirmed ACTH-dependent Cushing's syndrome (tab.1). Further investigations did not show any pathology of the pituitary. Ectopic source of ACTH excess was not found either. Between 08.2007 and 03.2008 the patient received inhibitors of steroidogenesis (ketoconazole, aminoglutetimid). The loose of weight (30kg), normalization of cortisol and ACTH levels and significant improvement of patient's well-being were observed. The treatment has been withdrawn.

Date	Weight [kg]/ BMI [kg/m^2]	Cortisol plasma 8.00 am [ug/dl] (range 4,3-22,4)	ACTH plasma [pg/ml] ([1]range 4,7-48,6, [2]range 7,2-63)	24-hour urinary free cortisol [ug/24h] (range 32-243)	Treatment	Pituitary MRI
08.2007-diagnosis	112/ 35	46,6	176[1]	15870	Ketoconazole 600-800mg	normal
11.2007	102/32	8,7	53[1]	67,6-180,0	Aminoglutetimid 750mg	normal
09.2008	79/24,6	10,5	31,3[1]	304	without treatment	
10.2009	78/24,3	13,3	57,9[1]	260	without treatment	
08.2010	77,7/24	10,6	81,7[1]	330	without treatment	normal
11.2011	82/25,5	16,7	109,9[2]	696	without treatment	normal
10.2012	82/25,5	27,2	115[2]	1285	without treatment	
05.2013	88,3/27	73,4	217,5[2]	10336	Ketoconazole 400mg	pituitary macroadenoma 15x13x15mm (fig. 1 and 2)
09.2013	83/25,9	19,6	75,6[2]	673	transsphenoidal adenomectomy	normal
06.2014	96/29,9	24,5	122,3[2]	1092	Ketoconazole 400mg	
01.2015	91/28,4	10,5	168[2]	199	Ketoconazole 600mg Stereotactic radiotherapy	recurrence of macroadenoma 10mm (fig.3)
12.2015	93/29	11,6	131[2]	356	Ketoconazole 400mg	
03.2016	100/30,9	71,9	214,6	4192	Pasireotide	
05.2016					Ketoconazole 400mg	

During further follow-up of the patient there were periodically repeated periods of moderate subclinical hypercortisolemia, observed mainly in spring and autumn. In spring 2013, significant clinical and laboratory signs of hypercortisolemia appeared and MRI revealed pituitary macroadenoma (15x13x15mm). In 09.2013 the patient underwent transsphenoidal surgery (atypical sparsely granulated coricotroph adenoma, ACTH (+), MIB1>20%). Postoperative MRI didn't show tumor remnant, but moderate hypercortisolemia was present. Because of increased levels of cortisol and ACTH, the patient restarted ketoconazole treatment (from 04.2014). A follow-up MRI (01.2015) demonstrated recurrence of the tumor. Patient was disqualified from a second surgery, in 04.2015 stereotactic radiotherapy was performed (Cyber Knife, total dose 20Gy/tumor). Since November 2015 till April 2016 he received pasireotide, but no response was observed. Currently the patient is being treated with ketoconazol (400mg/day) because of persistent hypercortisolemia. Other therapeutic options for the future are currently being considered (Themozolomide, adrenalectomy).

Conclusions.

The authors present long-term difficulties in establishing the diagnosis of Cushing's disease, mainly because of cyclic nature, long period of remission and diagnostic limitations in finding the source of ACTH excess. Delay in diagnosis of Cushing's disease leads to worse effects of treatment and the need to search for new therapeutic approaches.

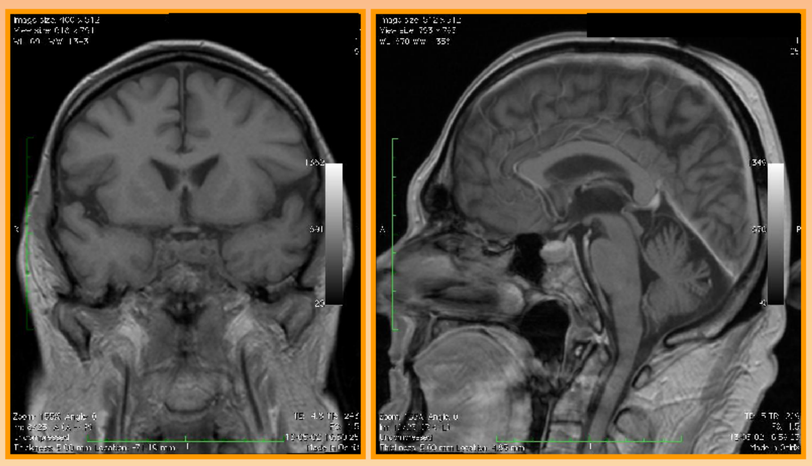

Fig. 1 and 2. MRI picture of corticotroph macroadenoma in patient with Cushing`s disease (05.2013)

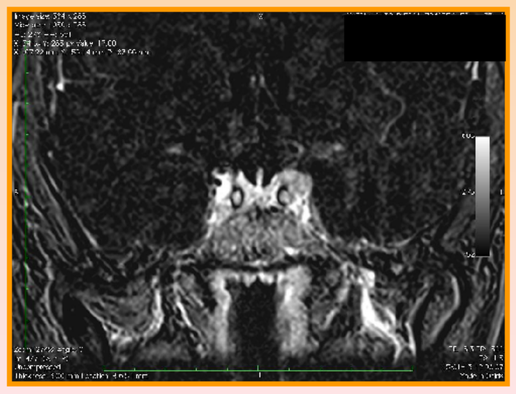

Fig. 3. MRI picture of recurrent corticotroph macroadenoma in patient with Cushing`s disease (01.2015)