

ONLINE FIRST

This is a provisional PDF only. Copyedited and fully formatted version will be made available soon.



ISSN: 0423-104X

e-ISSN: 2299-8306

## Distinct clinical picture of Cushing's syndrome in a patient with Morris' syndrome - first literature report

**Authors:** Ewa Cyrańska-Chyrek, Ewelina Szczepanek-Parulska, Piotr Stajgis, Aleksandra Czarnecka, Katarzyna Karmelita-Katulska, Marek Ruchała

**DOI:** 10.5603/EP.a2019.0042

**Article type:** Case report

**Submitted:** 2019-07-22

**Accepted:** 2019-07-29

**Published online:** 2019-09-26

This article has been peer reviewed and published immediately upon acceptance. It is an open access article, which means that it can be downloaded, printed, and distributed freely, provided the work is properly cited.

Articles in "Endokrynologia Polska" are listed in PubMed.  
The final version may contain major or minor changes.

Clinical Vignette

**Distinct clinical picture of Cushing's syndrome in a patient with Morris' syndrome — first literature report**

**Running title:** Coexistence of Morris' syndrome and Cushing's syndrome

**10.5603/EP.a2019.0042**

Ewa Cyranska-Chyrek<sup>1</sup>, Ewelina Szczepanek-Parulska<sup>1</sup>, Piotr Stajgis<sup>2</sup>, Aleksandra Czarnecka<sup>1</sup>, Katarzyna Karmelita-Katulska<sup>2</sup>, Marek Ruchała<sup>1</sup>

<sup>1</sup>*Department of Endocrinology, Metabolism, and Internal Medicine, Poznan University of Medical Sciences, Poznan, Poland*

<sup>2</sup>*Department of General Radiology and Neuroradiology, Poznan University of Medical Sciences, Poznan, Poland*

**Corresponding author:**

Ewa Cyranska-Chyrek, MD, PhD, Department of Endocrinology, Metabolism, and Internal Medicine, Poznan University of Medical Sciences, Poland, 49 Przybyszewskiego St, 60–355 Poznan, tel: (+48) 61 869 13 30, fax: (+48) 869 16 82; e-mail: ewacyranska@gmail.com

**Key words:** Morris' syndrome; Cushing's syndrome; ACTH-dependent hypercortisolaemia; hypoestrogenism; osteopaenia

**Introduction**

Complete androgen insensitivity syndrome (CAIS), or Morris' syndrome, is an X-linked recessive disorder of sex development, in which affected individuals are phenotypically female but have an XY karyotype and testes, with an estimated prevalence between 1:20400 and 1:99100

among genetic males [1]. Patients present with female external genitalia, short blind ended vagina, absent uterus, normal breast development, but scant pubic and axillary hair.

Cushing's Syndrome (CS) is a clinical state related to hypercortisolaemia. In women, it may present with menstrual cycle disturbances, mainly oligo- or amenorrhoea. Additionally, overproduction of adrenal androgens leads to hirsutism, acne, and infertility [2], which will not be noticed in CAIS patients, leading to diagnostic difficulties.

The aim of this report is to present the specificity of the clinical picture of CS, developed in a patient with CAIS.

### **Case report**

Our patient, at three months of age, was diagnosed due to bilateral inguinal tumours (right 26 × 13 mm, left 25 × 15 mm, on MRI), which, following removal, were confirmed to be testes. A hypoplastic vagina, together with lack of uterus and ovaries, were demonstrated. Hormonal evaluation revealed markedly elevated testosterone, follitropin (FSH), and luteinising hormone (LH) serum concentrations. Genetic test revealed a 46 XY karyotype. The patient was brought up as a girl. During pubertal period, oestrogen therapy was introduced, resulting in the development of a full female phenotype.

At the age of 27 years the patient presented with central fat tissue accumulation, supraclavicular pads, and slimming of limbs. She also reported muscle weakness and a weight increase of 8 kg in three years. The results of laboratory tests were suggestive of ACTH-dependent hypercortisolaemia (Tab. I). In addition, very high gonadotropin concentrations were detected, accompanied by low oestradiol and normal testosterone levels. Other biochemical tests revealed a slight TSH suppression combined with low free triiodothyronine (fT3) concentration, which might also reflect hypercortisolaemia. On densitometry osteoporosis of the lumbar spine (T-score minus 2.8), osteopaenia in the femur neck (T-score minus 1.8) was detected. MRI demonstrated a pituitary microadenoma (Fig. 1). She underwent transsphenoidal surgery. Histopathological examination confirmed the diagnosis of an ACTH-secreting pituitary adenoma. The patient achieved complete biochemical remission, with no evidence of hypopituitarism. Postoperative MRI demonstrated no signs of recurrence (Fig. 2). A sustained remission of the disease was observed on 12-month follow-up visit.

## **Discussion**

Our report summarises distinct clinical manifestation of hypercortisolaemia in the first patient with CAIS to suffer from CS reported in the world literature. One of the presentations of CAIS is either inguinal swellings or hernias being male testes during infancy, similarly to our patient. However, CAIS patients may remain undiagnosed until primary amenorrhoea occurs [3]. Female adolescents with CAIS develop breasts and have a pubertal growth spurt at an appropriate age, but no menses. Development of oestrogen-dependent secondary sexual characteristics occurs as a result of excessive aromatisation of androgens. Pubic and axillary hair is usually absent or scarce [4].

Patients with CAIS require careful oncological vigilance because the risk of gonadal tumour is 0.8–22%. Our patient underwent gonadectomy at infancy, but currently more authors recommend deferring removal of the gonads until after the completion of puberty. Patients require oestrogen replacement therapy from puberty to develop and preserve secondary sexual characteristics as well as maintain bone mass. Monitoring of bone mineral density in these patients is advised. Our patient presented with decreased bone mass, more pronounced in the lumbar spine than in the femur neck, which might be suggestive of the additional influence of hypercortisolaemia.

In patients with CAIS the diagnosis of CS can be difficult. Menstrual disturbances or infertility might be one of the first clinical manifestations of CS but could be not suggestive in patients with CAIS. Additionally, oestrogen therapy may lead to an increase of cortisol-binding globulin (CBG) and cause an increase in total cortisol concentration. Elevated cortisol due to CS might be erroneously interpreted as a result of oestrogen therapy and thus neglected. Therefore, the CS diagnosis should be primarily based on disturbed diurnal rhythm of cortisol secretion, accompanied by normal or increased ACTH and lack of cortisol suppression during dexamethasone test. In these patients, assessment of free serum cortisol, cortisol in saliva or 24-h urinary cortisol excretion might be more useful.

In conclusion, the complexity of the diagnostics of CS in the presence of CAIS rest upon the fact that some classic presentations of hypercortisolaemia (menstrual irregularities, virilisation, infertility) present lower diagnostic value. Moreover, biochemical diagnostics might also be

challenging. Inadequate hormonal replacement therapy and lack of the positive influence of androgens may further exacerbate the adverse effect of hypercortisolaemia on bone mineral density.

### ***Conflict of interest***

No financial, personal, or professional competing interests exist.

### ***Funding***

None.

### **References**

1. Boehmer AL, Brinkmann O, Brüggewirth H, et al. Genotype versus phenotype in families with androgen insensitivity syndrome. *J Clin Endocrinol Metab.* 2001; 86(9): 4151–4160, doi: [10.1210/jcem.86.9.7825](https://doi.org/10.1210/jcem.86.9.7825), indexed in Pubmed: [11549642](https://pubmed.ncbi.nlm.nih.gov/11549642/).
2. Cyranska-Chyrek E, Filipowicz D, Szczepanek-Parulska E, et al. Primary pigmented nodular adrenocortical disease (PPNAD) as an underlying cause of symptoms in a patient presenting with hirsutism and secondary amenorrhea: case report and literature review. *Gynecol Endocrinol.* 2018; 34(12): 1022–1026, doi: [10.1080/09513590.2018.1493101](https://doi.org/10.1080/09513590.2018.1493101), indexed in Pubmed: [30129786](https://pubmed.ncbi.nlm.nih.gov/30129786/).
3. Souhail R, Amine S, Nadia A, et al. Complete androgen insensitivity syndrome or testicular feminization: review of literature based on a case report. *Pan Afr Med J.* 2016; 25: 199, doi: [10.11604/pamj.2016.25.199.10758](https://doi.org/10.11604/pamj.2016.25.199.10758), indexed in Pubmed: [28270903](https://pubmed.ncbi.nlm.nih.gov/28270903/).
4. Hughes I, Davies J, Bunch T, et al. Androgen insensitivity syndrome. *The Lancet.* 2012; 380(9851): 1419–1428, doi: [10.1016/s0140-6736\(12\)60071-3](https://doi.org/10.1016/s0140-6736(12)60071-3).
5. Michala L, Creighton SM. The XY female. *Best Pract Res Clin Obstet Gynaecol.* 2010; 24(2): 139–148, doi: [10.1016/j.bpobgyn.2009.09.009](https://doi.org/10.1016/j.bpobgyn.2009.09.009), indexed in Pubmed: [19896906](https://pubmed.ncbi.nlm.nih.gov/19896906/).

**Table I.** Results of biochemical tests on diagnosis of ACTH-dependent Cushing’s syndrome and following successful neurosurgical procedure (the patient had withdrawn oestrogen supplementation two months prior to admission)

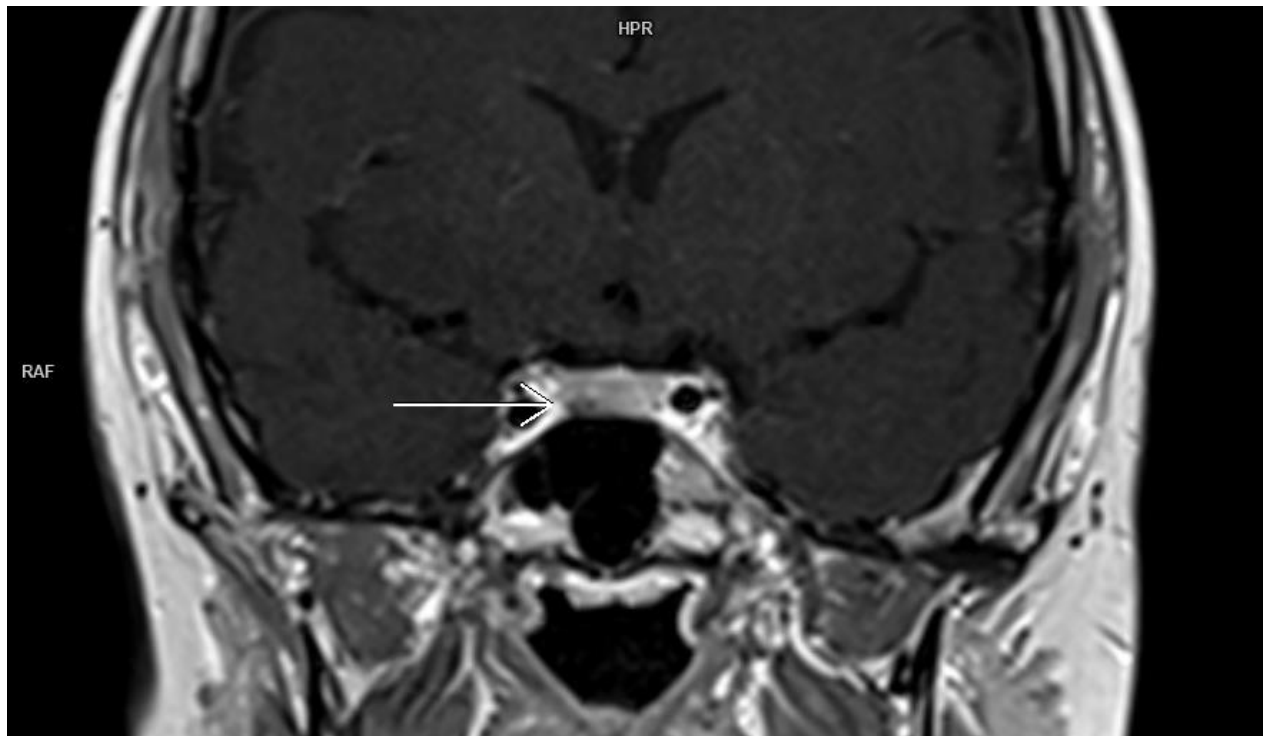
<b>Parameter</b>	<b>Before surgery</b>	<b>2 days following surgery</b>	<b>Follow-up 12 months following surgery</b>	<b>Reference range</b>
Serum cortisol [nmol/L] 8 AM	657 989	11	383	274–527

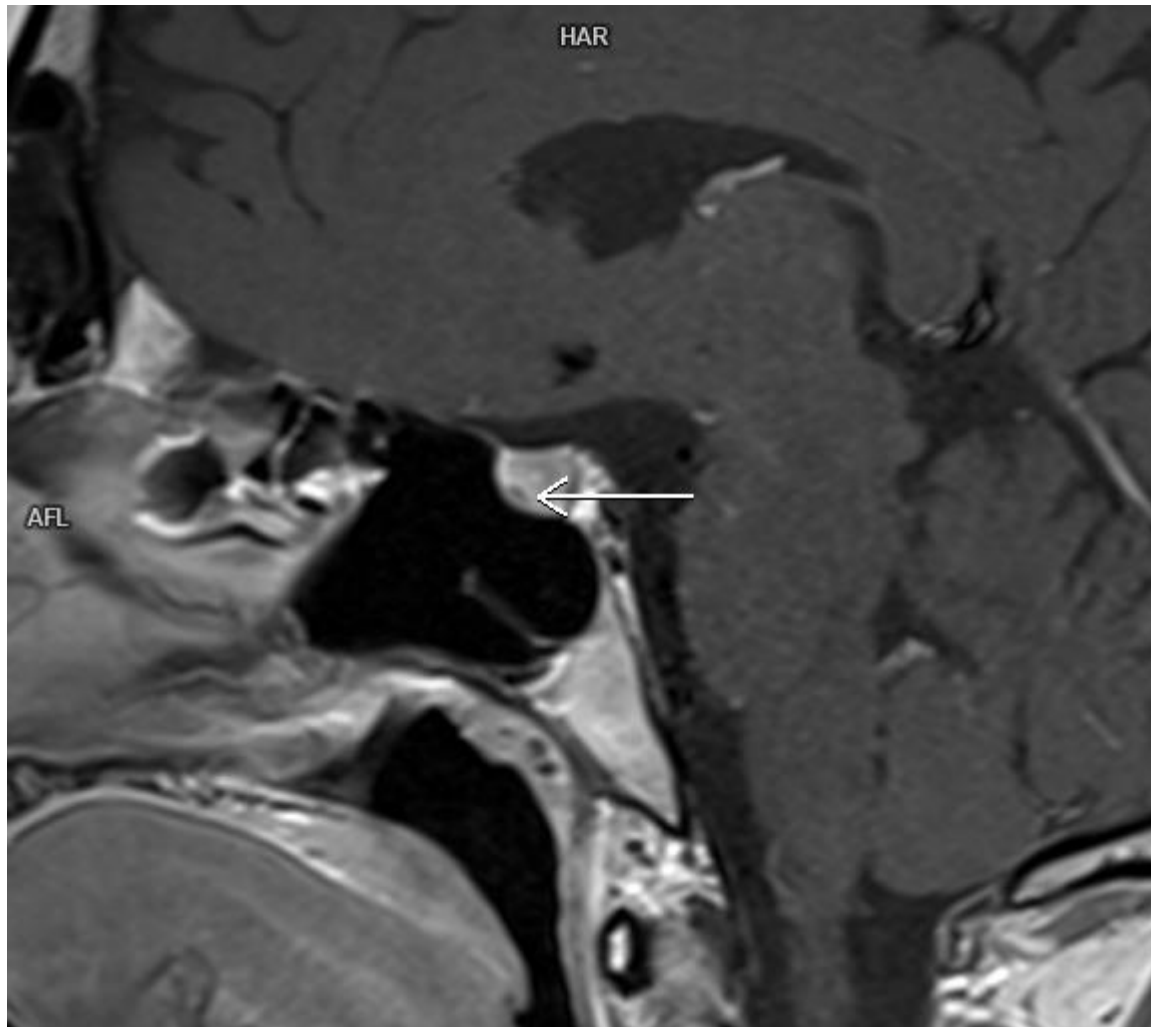
			497 (during CRH-stimulation test)	
Serum cortisol [nmol/L] 6 PM	524	–	95	
Serum cortisol [nmol/L] 11 PM	389	–	18	< 50
Serum ACTH [pg/mL]	73.61	2.63	28.77	7.20–63.30
Serum DHEA-S [ $\mu$ g/dL]	603	21	38	99–340
Urinary free cortisol [12-486] nmol/24 h	346 298	–	–	
Serum cortisol [nmol/L] 8 AM following 1 mg dexamethasone test	324	–	–	< 50
FSH [mIU/mL]	110.2	29.1	63.2	2.4–12.5
LH [mIU/ml]	79.2	7.4	48.7	3.5–12.5
Oestradiol [pg/ml]	9	–	< 5	
Testosterone [nmol/L]	2.3	–	< 0.1	0.2–2.9
Prolactin [ $\mu$ IU/ml]	406	727	364	70–510
Post-PEG prolactin	–	82%	–	
TSH [ $\mu$ IU/ml]	0.99	3.03	3.91	0.27–4.20
fT3 [pmol/l]	3.59	6.08	5.94	3.90–6.70
fT4 [pmol/l]	15.64	17.96	17.59	11.5–21.0
Fasting insulin [ $\mu$ U/ml]	16.04	–	10.81	3–17
Fasting glucose	79#	83*	87	

ACTH — adrenocorticotropin; CRH — corticotropin releasing hormone; DHEA-S — dehydroepiandrosterone sulphate; FSH — follitropin; fT3 — free triiodothyronine; fT4 — free

thyroxine; LH — luteinising hormone; PEG — polyethylene glycol; TSH — thyrotropin; #during metformin treatment 1 g/d; \*without metformin treatment

**Figure 1.** Pituitary gland before surgical treatment. Microadenoma on the right side of inferior part of anterior lobe (width 4 mm, height 2.5 mm). **A.** Coronal T1-weighted image after contrast media administration. Hypointense region represents microadenoma (arrow). **B.** Sagittal T1-weighted image after contrast media administration. Hypointense region represents microadenoma (arrow)





**Figure 2.** Pituitary gland in the same patient after surgical treatment. Complete resection of microadenoma. No visible hypointense regions corresponding to microadenoma. **A.** Coronal T1-weighted image after contrast media administration. **B.** Sagittal T1-weighted image after contrast media administration



