Testicular feminization syndrome as a rare cause of tumor-level serum testosterone in women

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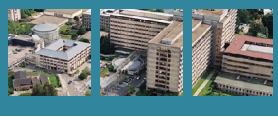


OBJECTIVE

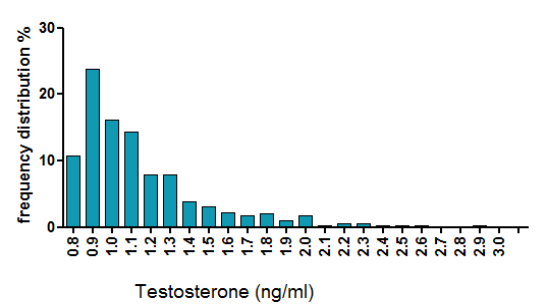
The aim of our work was to evaluate the number and the final diagnosis of women with an elevation of total testosterone levels within tumor range, i.e. ≥ 1.6 ng/ml by a direct RIA (normal range: 0.2-0.8 ng/ml).

PATIENTS AND METHOD

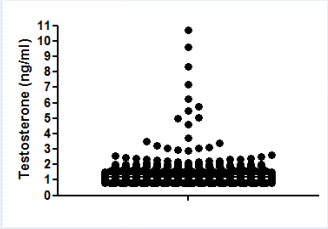
Analysis of the lab database (between 2004 and 2013) identified 132 women.

Testosterone > 0.8 ng/ml 1057 patients → Testosterone > 1.6 ng/ml 132 patients → Testosterone > 3.0 ng/ml 17 patients

The distribution showed that over half of the patients had a total testosterone serum level < 2 ng/ml and 85 % ≤ 3 ng/ml.

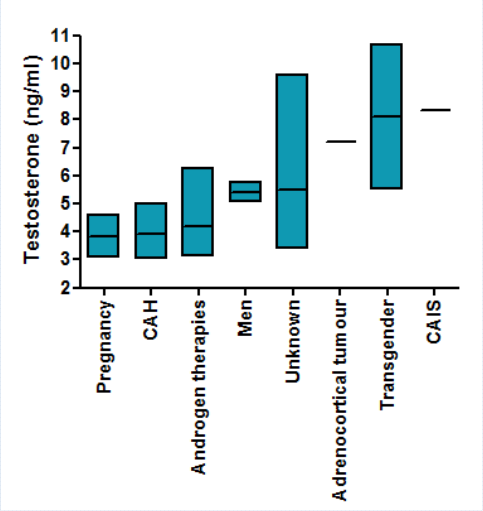


Only 17 patients had serum testosterone concentrations above 3 ng/ml.



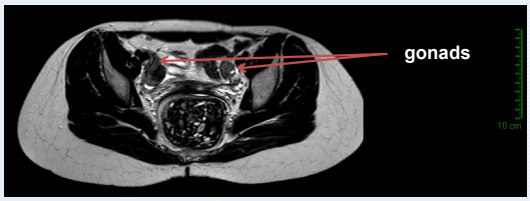
RESULTS

In the 17 patients with a total testosterone level > 3 ng/ml, diagnosis were: pregnancy with normal index of free testosterone (n = 2), congenital adrenal hyperplasia (CAH) (n = 3), androgen therapies in post-menopausal women (n = 3), men misclassified as women by data processing (n = 2), unknown for 3 patients without available clinical data, adrenocortical tumour (n = 1) transgender patients (n = 2) and complete androgen insensitivity syndrome (CAIS) (n = 1).



RESULTS

This last 24-year-old woman was initially referred by her gynaecologist for a pelvic MRI because of suspicion of Mayer-Rokitansky-Küster-Hauser syndrome on the basis of primary amenorrhea. The patient had a female phenotype with normal external genitalia and normal breast development. There were no clinical signs of hyperandrogenism or virilisation. No uterus was detected at ultrasound examination. The pelvic MRI confirmed the absence of Müllerian structures (uterus, Fallopian tubes) and the presence of two gonads in the abdominal cavity.



Biology showed elevated total testosterone (8.4 ng/ml) with normal SHBG conferring elevated index of free testosterone, low estradiol and normal LH and FSH levels.

Biological characteristics	Value	Normal value
FSH (Follicle Stimulating Hormone)	2 U/L	
LH (Luteinizing Hormone)	16 U/L	
Estradiol	<20 ng/L	
Progesterone	0.81 µg/L	
17-OH Progesterone	0.67 ng/ml	
PRL (Prolactin)	231 µU/ml	< 500
Total Testosterone	**8.4** ng/ml	0.2 - 0.8
SHBG (Sex Hormone Binding Globulin)	17 ng/ml	8.7 - 26
Index of free testosterone	**50**	0.4 - 9.1
Δ-4 androstenedione	2.9 ng/ml	0.2 - 3.1
DHEA-s (Dehydroepiandrosterone-sulfate)	**3701** ng/ml	900 - 3500

Karyotype analysis revealed a male chromosomal sex (46,XY) in the presence of a female phenotype confirming the diagnosis of complete androgen insensitivity syndrome. Finally, FISH analysis using a SRY gene probe confirmed the presence of SRY gene on Y chromosome.

DISCUSSION

Complete androgen insensitivity syndrome is an X-linked recessive disorder with an estimated incidence between 1/20000 and 1/99000 live male births. It is caused by mutation in the androgen receptor (AR) gene which is located on the long arm of the X chromosome (Xq11-12).

The syndrome was first described in 1953 by John Morris as "testicular feminization syndrome", who reviewed the clinical features of 82 patients. The patients were women and girls with bilateral testes that seemed to produce oestrogen-like hormones. The syndrome was later given the name of androgen insensitivity syndrome because of the resistance to androgens.

In its complete form, as in our case, patients have a male karyotype (46,XY) with female phenotype. Indeed, despite testicular production of testosterone, they do not develop male genitalia or male secondary sexual characters due to androgen resistance. Moreover, since the testicular Sertoli cells produce anti-Müllerian hormone (AMH), they do not develop Müllerian structures (uterus, Fallopian tubes and upper vagina). Development of oestrogen-dependent secondary characteristics occurs as result of androgen aromatization. Their serum testosterone levels are within or above the normal range for males, and their LH and serum estradiol concentrations are higher than in males but lower than in females without CAIS. FSH concentrations are usually normal.

CONCLUSION

A systematic analysis of a lab database could allow to spot unusual cases that were possibly undiagnosed.

In this case of a woman with CAIS, management is dependent on a multidisciplinary team (endocrinologist, gynaecologist, clinical psychologist) in order to address functional, sexual and psychological issues such as disclosure to the patient, gonadectomy and subsequent hormone replacement, creation of a functional vagina and genetic counseling.

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