

Testicular Adrenal Rest Tumors in Patients With Congenital Adrenal Hyperplasia

Prevalence and Sonographic, Hormonal, and Seminal Characteristics

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Objective—Testicular adrenal rest tumors have been described in patients with congenital adrenal hyperplasia (CAH). The aim of this work was to (1) evaluate the prevalence of testicular adrenal rest tumors in patients with CAH; (2) study the hormonal profile; (3) define the sonographic features; (4) assess the seminal profile; and (5) initiate a longitudinal study on the possible role of corticotropin (ACTH) plasma levels in the induction and persistence of testicular adrenal rest tumors.

Methods—Eighteen patients affected by CAH, aged 21 to 41 years, were studied. These were all patients referred to our endocrinology unit for the first time to undergo a clinical evaluation. All of the patients were taking long-term cortisone acetate and fludrocortisone replacement therapy. The study included (1) a physical examination, (2) testis sonography, (3) a hormonal profile, (4) semen analysis.

Results—Sonography showed testicular adrenal rest tumors in 11 patients (61.1%); of these, 9 cases (50.0%) were bilateral, and 2 (11.1%) were unilateral. The diameter ranged from 4 to 38 mm. In 9 patients, the lesions were hypoechoic, whereas in 2, they were hyperechoic. High plasma ACTH levels were detected in all of the patients with tumors despite long-term therapy. Semen analysis found 2 cases of azoospermia and 6 cases of oligoasthenoteratozoospermia; the 3 remaining patients were normospermic. The preliminary longitudinal study has shown 3 patients with a disappearance or reduction of the tumors after 6 months of modified treatment.

Conclusions—This study confirms the high prevalence of testicular adrenal rest tumors in patients with CAH and the major role played in its pathogenesis by high plasma ACTH levels.

Key Words—congenital adrenal hyperplasia; semen analysis; testicular adrenal rest tumors; testicular sonography

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Abbreviations

ACTH, corticotropin; CAH, congenital adrenal hyperplasia

Congenital adrenal hyperplasia (CAH) describes a group of genetic disorders with autosomal recessive transmission (the most frequent is caused by a deficit of 21- α -hydroxylase) characterized by enzymatic defects in cortisol and, in a few cases, aldosterone synthesis. The negative feedback due to the cortisol defect produces an increase in plasma corticotropin (ACTH) levels. The consequences are hypertrophy of the adrenal glands and the accumulation of precursor hormones with overproduction of adrenal androgens.^{1–4} In these patients, testicular adrenal rest tumors have often been found, which originate from aberrant adrenal cells in the testes.

The presence of these tumors was first described in 1940 by Wilkins et al.⁵ Many hypotheses regarding the origin of these lesions have been proposed. Avila et al^{1,2} and Martinez-Aguayo et al⁶ suggested that these masses could derive from testicular hylar pluripotent cells, which proliferate as a result of high plasma ACTH levels. Another hypothesis put forward an embryologic origin: during fetal development, the adrenal glands are in close proximity to the undifferentiated gonad, and part of the adrenal cells may be included in the gonad. The result is aberrant adrenal tissue that descends with the testes.^{3,7,8} In the literature, there are reports of different prevalence rates of these tumors in patients with CAH, even reaching 94%.^{3,9–11}

The aim of this work was to (1) evaluate the prevalence of testicular adrenal rest tumors in patients with CAH; (2) consider the relationship between these tumors and the hormonal profile; (3) define the sonographic features; (4) assess the seminal profile; and (5) initiate a longitudinal study to evaluate the possible role of plasma ACTH levels in the induction and persistence of these tumors.

Materials and Methods

Patients

Patients with CAH ($n = 18$; aged 21–41 years; mean age $\pm$ SD, 26.6 ± 5.8 years; median, 24.5 years) were selected. These patients had been referred to our endocrinology unit for the first time to undergo a clinical evaluation between January 2006 and December 2010. All of the patients were taking long-term cortisone acetate and, when indicated, fludrocortisone replacement therapy but had not undergone hormone evaluation for more than 2 years.

This study was conducted according to the guidelines of our Hospital Ethics Committee. Informed consent was obtained from all patients.

Andrologic Clinical Examination

The andrologic clinical examination was performed according to World Health Organization guidelines¹² and comprised body proportions; body hair distribution; testicular site, volume, and consistency; epididymis; penis; possible presence of varicocele or hydrocele; and evaluation of possible gynecomastia.

Testicular Sonography

Testicular sonographic examinations were performed with an HDI 4000 system (Philips Healthcare, Tokyo, Japan) and a linear transducer probe from 7 to 12 MHz. Sonography was used to evaluate testicular size using the ellipsoid formula [(maximum testicular length) $\times$ (maximum width)

$\times$ (maximum depth) $\times 0.52$] and to detect any intratesticular abnormalities. The sonograms were obtained in transversal and longitudinal planes. Color Doppler sonography was performed to evaluate vascular patterns.^{13,14}

Hormonal Profile

Corticotropin, 17- α -hydroxyprogesterone, follicle-stimulating hormone, luteinizing hormone, and testosterone assays were performed.

Standard Semen Analysis

The analysis was performed according to World Health Organization guidelines.¹⁵ Samples of sperm were collected by masturbation after 3 to 5 days of sexual abstinence. Sperm concentration and motility were assessed by a superimposed image analysis system.^{16,17}

Statistical Analysis

The Student t test was used for statistical analysis, performed with the SPSS statistical package (SPSS Inc, Chicago, IL). $P < .05$ was considered statistically significant.

Results

Physical Examination of the Testis

Physical examination showed a palpable mass in only 1 patient (5.6%), in disagreement with Stikkelbroeck et al,³ who found a palpable tumor in 35.3% of cases.

Prevalence of Testicular Adrenal Rest Tumors

Tumors were observed in 11 patients (61.1%) with CAH; 9 cases were bilateral, whereas 2 were unilateral (Table 1).

Table 1. Sonographic Features of Congenital Adrenal Hyperplasia Patients With Testicular Adrenal Rest Tumors

Patient	Side	Maximum Diameter, mm	Echoic Pattern	Color Doppler Sonographic Pattern
1	Unilateral	11.2	Hypo	1
2	Unilateral	7.4	Hypo	2
3	Bilateral	8.3	Hypo	2
4	Bilateral	6.8	Hypo	1
5	Bilateral	9.2	Hypo	1
6	Bilateral	8.2	Hypo	1
7	Bilateral	10.7	Hyper	1
8	Bilateral	23.9	Hyper	1
9	Bilateral	11.4	Hypo	1
10	Bilateral	6.8	Hypo	3
11	Bilateral	9.1	Hypo	1

Pattern 1, no flow signal; pattern 2, perilesional flow; pattern 3, perilesional and intralesional flow.

Sonographic Features

The lesions had maximum diameters ranging between 4 and 38 mm. The sonographic features were hypoechoic in 9 patients and hyperechoic in the remaining 2 (Table 1). The hypoechoic lesions were usually roundish (Figures 1 and 2), whereas the hyperechoic lesions appeared elongated or tubular (Figures 3 and 4). Color Doppler sonography (Table 1) showed perilesional flow (pattern 2) in 2 patients, perilesional and intralesional flow (pattern 3) in 1, and no flow (pattern 1) in the remaining patients (Figures 5 and 6).

Hormonal Profile

The hormonal evaluation showed elevated plasma ACTH levels in all 11 patients with tumors despite long-term cortisone acetate therapy. The 7 patients without tumors had hormonal parameters in the normal range (Table 2).

Seminal Profile

Of the 11 patients with CAH, 2 had azoospermia; 6 had oligoasthenoteratozoospermia; and 3 were normospermic. In the patients without tumors, only 1 had oligoasthenoteratozoospermia; the others were normospermic (Table 3).

Longitudinal Study

To date, the preliminary longitudinal study has highlighted 3 patients who, after 6 months of modified cortisone acetate therapy (from the initial cortisone acetate dosage of 25–37.5 mg/d on arrival to 50 mg/d, leaving the fludrocortisone treatment unchanged), returned to normal ACTH levels with a subsequent disappearance in 2 cases and a reduction of the tumor diameter in 1.

Figure 1. Testicular adrenal rest tumor with a hypoechoic pattern.

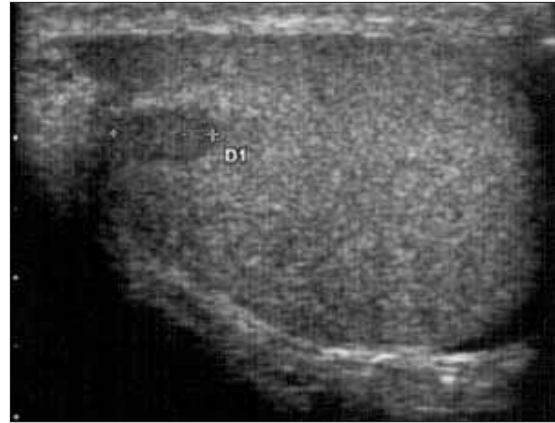


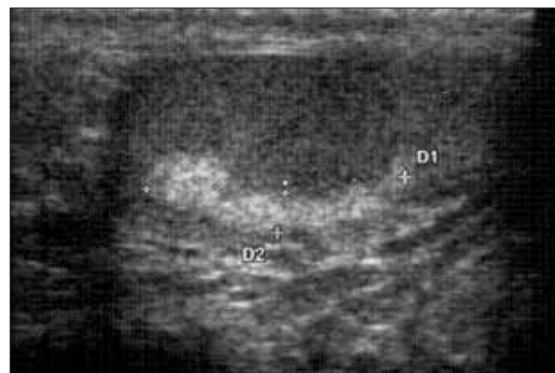
Figure 2. Testicular adrenal rest tumor with a hypoechoic pattern.

Discussion

Ectopic adrenal rest tissue can be found in up to 50% of neonates^{18–19}; the site of the tissue can be the retroperitoneum, broad ligament, ovaries, inguinal region, and, in 7.5% to 15% of cases, testes.^{3,20,21} Ectopic tissue becomes atrophic during normal development, persisting in only 1% of adults.^{22,23} However, in patients with CAH, testicular adrenal rest tumors are more frequent, with prevalence rates of up to 94%.^{3,9–11}

In this work, we considered some of the pathologic characteristics: the prevalence of the tumors, the hormonal profile, the sonographic features, the seminal profile, and a longitudinal study of these patients. Regarding the first aspect, the prevalence of the tumors in patients affected by CAH was 61.1%. All of the patients in this study were taking cortisone acetate and fludrocortisone acetate as sub-

Figure 3. Testicular adrenal rest tumor with a hyperechoic pattern.



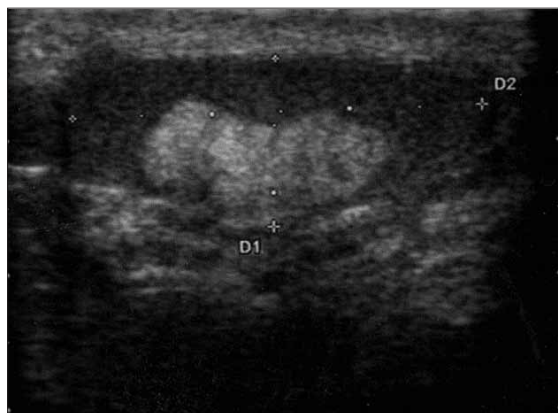


Figure 4. Testicular adrenal rest tumor with a hyperechoic pattern.

stitutive therapy, but in those with tumors, the therapy was inadequate, as shown by the higher ACTH levels compared with normal values. In confirmation of this finding, testicular adrenal rest tumors were not found in patients with normal ACTH levels. The great difference reported in the literature on the prevalence of testicular adrenal rest tumors (up to 94% in patients with CAH)⁴ is probably due to the selection of patients and to the substitutive therapy given. In addition to the elevated ACTH levels, we found higher testosterone levels in only 2 cases. The remaining patients were within the upper end of the normal range.

Sonography showed various echoic patterns. It is essential to distinguish between testicular adrenal rest tumors and other testicular lesions (in particular, Leydig cell tumors). In fact, a testicular adrenal rest tumor is often an incidental finding, and there is a risk of unnecessarily re-

ferring patients for surgical orchiectomy for suspected Leydig cell tumors or other testicular lesions. Certain criteria^{22,24} have been suggested to make a correct clinical diagnosis: (1) testicular adrenal rest tumors are bilateral in a high percentage of cases; in our study, 6 of 7 cases (85.7%) had bilateral lesions; (2) often, patients with Leydig cell tumors had gynecomasty; in our study, none showed gynecomasty; (3) Reinke crystals, which can be found in 25% to 40% of Leydig cell tumors, are absent in testicular adrenal rest tumors.

The seminal profile, in agreement with other authors,^{23,25,26} showed oligoasthenoteratozoospermia in 6 patients and azoospermia in the remaining 2. The spermatogenesis failure could be due to the inhibitory effects of the high levels of androgens or to possible interference of ACTH/corticotropin-releasing hormone in the spermatogenesis process. Regarding the azoospermic patients, there is also a mechanical pathogenetic hypothesis²⁵ that testicular adrenal rest tumors could cause compression and consequent obstruction of the rete testis. Finally, in the longitudinal study, 3 patients who, after 6 months of modified cortisone acetate therapy (from 25–37.5 to 50 mg/d), returned to normal ACTH levels with a consequent disappearance or reduction in the tumor diameter.

This study had certain limitations, such as the small number of patients treated with the modified protocol. In addition, there was no histologically based confirmation, given that every effort was made to avoid unnecessary surgical intervention. However, on the basis of the results, we can conclude that (1) testicular adrenal rest tumors are a frequent manifestation of inadequate substitutive therapy in patients with CAH; (2) there is an alteration in the spermatogenetic process; (3) testicular adrenal rest tumors are

Figure 5. Testicular adrenal rest tumor with absence of lesional flow (pattern 1).

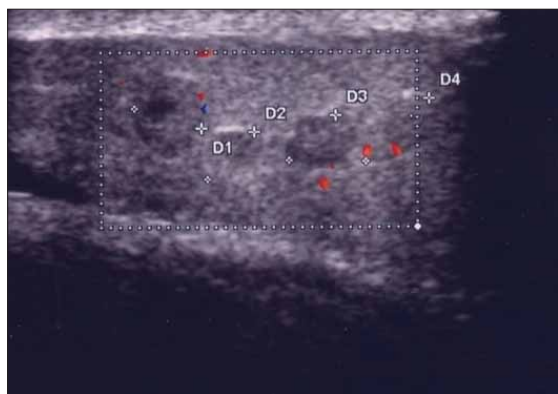


Figure 6. Testicular adrenal rest tumor with perilesional and intralesional flow (pattern 3).

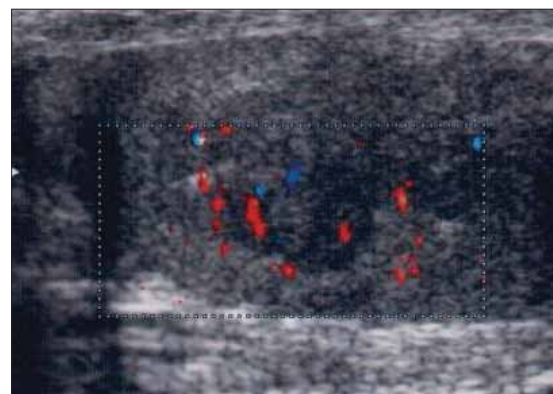


Table 2. Hormonal Profile of Congenital Adrenal Hyperplasia Patients With and Without Testicular Adrenal Rest Tumors

	ACTH, 10.0–46.0 pg/mL		17- α -OH-Progesterone, 0.6–3.3 ng/mL		FSH, 1.0–8.0 mIU/mL		LH, 2.0–12.0 mIU/mL		Testosterone, 2.8–8.0 mIU/mL	
	With ^a (11/18 Patients)	Without (7/18 Patients)	With (11/18 Patients)	Without (7/18 Patients)	With (11/18 Patients)	Without (7/18 Patients)	With ^a (11/18 Patients)	Without (7/18 Patients)	With (11/18 Patients)	Without (7/18 Patients)
	950.0	21.0	12.5	3.3	1.5	4.3	1.2	5.1	7.2	5.5
	378.0	25.0	7.6	2.3	1.1	4.5	1.6	3.6	9.9	6.1
	362.0	38.9	6.8	2.9	3.5	6.1	3.6	3.1	4.3	4.1
	55.0	13.7	4.3	1.9	1.3	7.3	1.4	3.2	4.6	3.8
	496.0	26.5	7.5	1.8	3.6	2.7	4.3	5.3	4.5	4.8
	105.0	19.5	5.3	1.7	4.3	2.9	4.9	5.9	5.8	5.1
	71.0	11.5	4.5	2.1	4.1	3.7	3.9	4.7	4.7	5.6
	194.0		5.9		6.0		1.7		5.8	
	628.0		12.3		1.2		1.3		8.3	
	862.0		13.2		2.1		1.9		5.8	
	108.0		4.5		3.1		3.4		6.3	
Minimum	55.0	11.5	4.3	1.7	1.1	2.7	1.2	3.1	4.3	3.8
Maximum	950.0	38.9	13.2	3.3	6.0	7.3	4.9	5.9	9.9	6.1
Mean	382.0	22.3	7.7	2.3	2.9	4.5	2.7	4.4	6.1	5.0
SD	319.0	9.1	3.4	0.6	1.6	1.7	1.4	1.1	1.8	0.8

ACTH indicates corticotropin; FSH, follicle-stimulating hormone; LH, luteinizing hormone; and 17- α -OH-Progesterone, 17- α -hydroxyprogesterone.
^aP < 0.05 versus without.

reversible lesions, as shown by the reduction or disappearance after adequate replacement therapy to reduce plasma ACTH levels; and (4) a correct diagnosis is essential to

avoid surgery due to an incorrect differential diagnosis between testicular adrenal rest tumors and other neoplastic sonographic features.

Table 3. Age and Seminal Profile of Congenital Adrenal Hyperplasia Patients With and Without Testicular Adrenal Rest Tumors

	Patient Age, y		Concentration, $\geq 20 \times 10^6$ /mL		Progressive Motility, $\geq 50\%$		Atypical Forms, $< 85\%$	
	With (11/18 Patients)	Without (7/18 Patients)	Without (11/18 Patients)	Without (7/18 Patients)	With ^a (11/18 Patients)	Without (7/18 Patients)	With (11/18 Patients)	Without (7/18 Patients)
	23	41	6.0	71.0	27	38	77	55
	25	24	0.5	5.0	0	11	96	81
	26	21	0.0	34.0		37		59
	31	23	3.5	86.0	10	41	83	53
	22	24	29.0	28.0	38	26	59	64
	34	26	34.0	38.0	35	43	57	55
	21	23	36.0	76.0	33	36	57	57
	38		11.0		15		63	
	27		0.0					
	26		12.0		11		73	
	23		14.0		21		59	
Minimum	21	21	0.0	5.0	0	11	57	53
Maximum	38	41	36.0	86.0	38	43	96	81
Mean	26.9	26.0	13.3	48.3	21.1	33.1	69.3	60.6
SD	5.3	6.8	13.7	29.7	13.1	11.2	13.8	9.7

^aP < .05 versus without.

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