Testicular Tumors in Patients with Congenital Adrenal Hyperplasia due to 21-Hydroxylase Deficiency Show Functional Features of Adrenocortical Tissue


Departments of Paediatric Endocrinology (H.L.C.-v.d.G., B.J.O.), Chemical Endocrinology (F.C.G.J.S., P.N.S., H.A.R.), Urology (E.J.H.M.), and Endocrinology (A.R.M.M.H.), Radboud University Nijmegen Medical Centre, 6500 HB Nijmegen, The Netherlands

Context: In male patients with congenital adrenal hyperplasia (CAH), testicular adrenal rest tumors are frequently found that may interfere with gonadal function.

Objective: Our objective was to determine steroid-producing features of testicular adrenal rest tumors.

Design and Setting: The study is descriptive and took place at a university medical center.

Patients: Eight adult CAH patients with bilateral testicular adrenal rest tumors were treated with testis-sparing surgery.

Interventions: In all but one patient, spermatic veins were cannulated during surgery and blood samples collected to measure the adrenal-specific steroid 21-deoxycortisol (21DF) and 17-hydroxyprogesterone (17OHP), and androstenedione (A). The same parameters assessed that AII may be an additional factor responsible for testicular adrenal rest tumor growth.

Main Outcome Measures: Adrenal-specific steroids/enzymes were measured in all spermatic vein samples. The ratio (mean ± SD) between spermatic vein and simultaneously taken peripheral blood samples was 37.8 ± 56.3 (21DF), 132.0 ± 249 (17OHP), and 57.0 ± 68.2 (A). CYP11B1, CYP11B2, and ACTH and AII receptor mRNAs were detected in all tumors with a strong correlation between ACTH receptor mRNA in tumors and 21DF (r = 0.85; P = 0.015), 17OHP (r = 1; P = 0.01) and A (r = 0.89; P = 0.007) concentrations in peripheral blood.

Conclusion: Testicular adrenal rest tumors produce adrenal-specific steroids and express adrenal-specific enzymes and ACTH and AII receptors, confirming the strong resemblance with adrenal tissue. Because AII receptors are present in tumor tissue, it can be hypothesized that AII may be an additional factor responsible for testicular adrenal rest tumor growth. (J Clin Endocrinol Metab 92: 3674–3680, 2007)

In 1940, WILKINS et al. (1) first reported the presence of a testicular tumor in a male patient with congenital adrenal hyperplasia (CAH). Two recent studies found that the prevalence of testicular tumors in these patients is remarkably high (2, 3). The tumors are almost always bilaterally present and have benign features, but because of their location in the mediastinum testis, they can lead to obstruction of the seminiferous tubules leading to gonadal dysfunction and infertility. The testicular tumors are thought to arise from aberrant adrenal cells in the testes that are stimulated by ACTH. Therefore, they are called testicular adrenal rest tumors. However, until now, the etiology and functional features of the tumors were not completely known. Microscopically, the tumors show features of steroid-producing tissue, but the histological differentiation between tumors derived from Leydig cells and from adrenocortical cells is difficult (4–6).

The clinical observations that high doses of glucocorticoids can reduce tumor size, most probably due to suppression of ACTH secretion, and that tumor growth may be promoted in conditions where ACTH concentration is high, such as in poorly controlled CAH patients or in patients with Nelson’s syndrome or Addison’s disease, suggests the presence of ACTH receptors on tumor cells (7–11). However, intensifying of glucocorticoid treatment with suppression of ACTH secretion is not always successful in reducing tumor size and even in well-controlled CAH patients, with normal or suppressed plasma ACTH levels, testicular adrenal rest tumors are found (2, 3, 12). Therefore, most probably other unknown factors contribute to tumor growth.

In the past, a limited number of in vivo and in vitro studies, mainly in single patients, were performed to investigate the etiology and the functional features of testicular adrenal rest tumors in CAH patients. Clark et al. (13) described the presence of the adrenal-specific enzyme CYP11B1 (11β-hydroxylase) in tumor tissue of a single CAH patient with testicular adrenal rest tumors. Bercovici et al. (14) demonstrated the
presence of adrenal-specific steroids in one testicular adrenal rest tumor. The presence of adrenal-specific 11β-hydroxylated steroids such as 21-deoxycorticosterone (21DB) and 21-deoxycorticisol (21DF) in blood taken from the gonadal veins is reported in three single cases (14–16). This indicates the presence of adrenal-like tissue in the testes of these CAH patients with 21-hydroxylase deficiency, because these steroids can only be synthesized by adrenal-specific 11-hydroxylation, without the need of the deficient 21-hydroxyla-
tion step.

In the present study, we measured the concentrations of the adrenal-specific steroid 21DF and of 17-hydroxyproges-
terone (17OHP) and androstenedione (A) in blood taken from the spermatic veins during testis-sparing surgery in seven male CAH patients with bilateral testicular adrenal rest tumors. Furthermore, we measured the mRNA expression of the adrenal-specific enzymes CYP11B1 and CYP11B2 as well as of ACTH and angiotensin II (AII) receptors in 16 testicular tumors of eight patients by quantitative PCR. We demonstrate that the testicular tumors in CAH patients show functional features of adrenocortical tissue, which is in line with the hypothesis that they are derived from aberrant adrenal cells.

Patients and Methods

Patients

Eight male CAH patients (mean age 31 yr; range 23–51 yr) with bilateral testicular adrenal rest tumors were selected for testis-sparing surgery because of infertility (n = 5), poor hormonal control despite rigorous treatment (n = 2), pain or discomfort (n = 2), or hypogonadism (n = 2). Five patients (1, 2, and 4–6) had been treated by intensifying the glucocorticoid treatment, which was mostly with dexamethasone (DXM), in the past to reduce tumor size and improve testicular function without success, suggesting the development of fibrotic or autonomous tissue within the tumor. Three patients refused intensifying the glucocorticoid treatment. Written informed consent was obtained from all patients. The study was approved by the local ethics committee. The patients’ character-
istics are listed in Table 1. The diagnosis of CAH due to 21-hy-
droxylation deficiency was confirmed by mutation analysis in all patients. Sample preparation and the method used for mutation analysis were performed as described earlier (17). All but one patient had the classic salt-wasting (SW) form of CAH and were treated with glucocorticoids and mineralocorticoids since the neonatal period. One patient had the simple virilizing (SV) form of CAH diagnosed at the age of 5 yr.

In all patients, biochemical and semen analyses were performed before and after operation to evaluate pituitary-gonadal function. All patients were azoosperm or oligosperm with low blood inhibin B levels before operation. In three patients (1, 2, and 5), hypogonadotropic hypo-
gonadism was present due to elevated serum A/estrone levels in these patients (Table 2). The results of the biochemical analyses have been described in detail elsewhere (18). For comparison, the same patient numbers are used in the current paper.

Spermatic vein sampling

Testicular tumor enucleation took place under general (n = 1) or loco-regional (n = 7) anesthesia. Just before operation, all patients re-
ceived 2.5 mg DXM iv as stress medication. In patients 1–4, the operation started on the left side; in patients 5–8, the operation started on the right side. Via an inguinal incision and after opening of the inguinal canal, the spermatic cord was exposed. During this procedure, special care was taken not to manipulate the testis, to prevent unwanted secretion of hormones into the circulation. The spermatic vein was cannulated, and blood samples were collected to measure 21DF, 17OHP, and A concen-
trations. Simultaneously, peripheral blood was collected from a cubital vein to measure the same hormones. The same procedure was per-
formed at the other side after finishing the operation on the first side. A second simultaneous peripheral blood sample was not taken. ACTH stimulation tests or DXM suppression tests were not performed during spermatic vein cannulation to avoid prolonged anesthesia in the pa-
ients. Patient 1 was operated without spermatic vein sampling. In patient 7, the spermatic veins at the right side were atrophic, and the volume of collected blood was not sufficient for biochemical analyses. All sera were stored at −20 C until measurements.

Tumor tissue preparation

All removed tumor tissue was investigated macroscopically and micro-
scopically. A portion of the tumor was fixed in 10% buffered formalin. Tissue sections of 5 μm were cut and stained with hematoxylin and eosin and with Von Giesons elastin stain. Another portion of the tumor was frozen immediately in liquid nitrogen and stored at −80 C until processing.

Hormone assays

Methods of measuring serum LH, FSH, testosterone, inhibin B, and estrone concentrations were described in detail in an earlier publication (18). 17OHP and A concentrations in serum were measured by RIA after extraction and paper chromatography (19, 20). For 17OHP, the within-assay coefficient of variation (CV) was 6.1%, and the between-assay CV was 8.5% at 4.9 nmol/liter. For A, the intraassay CV was 4.9% and the interassay CV was 7.6% at 4.2 nmol/liter. Serum 21DF was assayed by RIA after prepurification by means of HPLC of ether extracts of the samples, including correction for procedural losses. To summarize briefly, [3H]21DF was added before extraction to correct for procedural losses. A Hypersil Gold column with a mobile phase consisting of methanol/ water (47/53) gave full separation between 21DF and the potentially cross-reacting steroids cortisol, corticosterone, and 11-deoxycorticisol. The [3H]21DF-containing fractions were evaporated to dryness and dis-
solved in ethylene glycol-water. The recovered radioactivity was mea-
sured by liquid scintillation counting of an aliquot from the eluate. Subsequently, [3H]21DF tracer and antiserum (raised against cortisol 21-hemisuccinate-BSA) were added, and after incubation, free and bound tracer were separated by means of dextran-coated charcoal. The antibody-bound radioactivity was assessed by liquid scintillation count-
ing of the supernatant. The calculations were performed by software specially designed to correct for the contribution of mass and radioac-
tivity of the recovery tracer in the RIA. Increasing cortisol levels up to 5 μmol/liter revealed an overall contribution of cortisol in the measured 21DF of less than 0.1%. Additions to serum of 21DF up to 35 nmol/liter were fully recovered (102 ± 1.8%). The detection limit was 0.16 nmol/liter, when using a sample volume of 0.5 ml. Between-run CV was 7.8% at a level of 10.6 nmol/liter. In 32 healthy volunteers (16 male, 16 female), values up to 1.8 nmol/liter were found. In three of these healthy indi-
viduals, 21DF levels were below the detection limit of the assay. ACTH was measured by a two-step immunoradiometric assay (Dynotest BRAHMS, Berlin, Germany) based on two monoclonal antibodies di-
rected against different antigenic determinants on the ACTH 1–39 mol-
ecule. Plasma renin was measured by immunoradiometric assay pro-
vided by CIS Bio International (Gif-sur-Yvette, France). Within- and between-run CVs were 7.4 and 7.2% at 6.8 mU/liter, 6.2 and 2.0% at 37.4 mU/liter, and 1.3 and 4.7% at 216.8 mU/liter. Reference values are 7–75 mU/liter.

Molecular analysis

RNA extraction. Tissues stored at −80 C were pulverized using a mi-
crodismembrator (Braun, Melsungen, Germany) and kept in liquid ni-
trogen until RNA isolation. Total RNA was isolated from 20 mg tissue powder using the RNeasy mini kit (QIAGEN, Hilden, Germany) with on-column DNase I treatment. Quality of the RNA was checked by examining rRNA bands after agarose gel electrophoresis and by am-
plifying three housekeeping genes as a control (see below) (21). RNA concentrations were determined from the spectrophotometric absorp-
TABLE 1. Age, height SD score-target height SD score, body mass index, and medication at the time of testicular surgery, phenotype, mutation analysis, and operation indication in eight male CAH patients with bilateral testicular adrenal rest tumors before testis-sparing surgery

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age (yr)</th>
<th>Phenotype</th>
<th>Allele 1&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Allele 2&lt;sup&gt;a&lt;/sup&gt;</th>
<th>HSDS-THSDS&lt;sup&gt;b&lt;/sup&gt;</th>
<th>BMI (kg/m&lt;sup&gt;2&lt;/sup&gt;)</th>
<th>Daily glucocorticoid therapy (mg/m&lt;sup&gt;2&lt;/sup&gt;)&lt;sup&gt;f&lt;/sup&gt;</th>
<th>Daily mineralocorticoid therapy (μg&lt;sup&gt;2&lt;/sup&gt;)&lt;sup&gt;d&lt;/sup&gt;</th>
<th>Operation indication&lt;sup&gt;e&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>24</td>
<td>SW CAH</td>
<td>Large deletion or conversion</td>
<td>Large deletion or conversion</td>
<td>–2.8</td>
<td>27.4</td>
<td>32.2 (HC 20–20–20 mg)</td>
<td>400</td>
<td>1, 2</td>
</tr>
<tr>
<td>2</td>
<td>29</td>
<td>SW CAH</td>
<td>Large deletion or conversion</td>
<td>Large deletion or conversion</td>
<td>–0.7</td>
<td>25.7</td>
<td>16.0 (HC 20–10 mg)</td>
<td>125</td>
<td>1, 2</td>
</tr>
<tr>
<td>3</td>
<td>23</td>
<td>SW CAH</td>
<td>IVS2–13A/C→G</td>
<td>IVS2–13A/C→G</td>
<td>–0.7</td>
<td>25.6</td>
<td>8.2 (HC 8–4 mg, DXM 0.1 mg)</td>
<td>62.5</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>32</td>
<td>SW CAH</td>
<td>IVS2–13A/C→G</td>
<td>IVS2–13A/C→G</td>
<td>NA</td>
<td>28.3</td>
<td>16.9 (HC 25–10 mg)</td>
<td>100</td>
<td>2, 3</td>
</tr>
<tr>
<td>5</td>
<td>26</td>
<td>SW CAH</td>
<td>IVS2–13A/C→G</td>
<td>IVS2–13A/C→G</td>
<td>–1.0</td>
<td>38.2</td>
<td>10.8 (HC 10–5–10 mg)</td>
<td>62.5</td>
<td>1, 4</td>
</tr>
<tr>
<td>6</td>
<td>51</td>
<td>SV CAH</td>
<td>I172N</td>
<td>Large deletion or conversion</td>
<td>–2.95</td>
<td>29.0</td>
<td>16.2 (HC 20–10 mg)</td>
<td>62.5</td>
<td>5</td>
</tr>
<tr>
<td>7</td>
<td>31</td>
<td>SW CAH</td>
<td>Large deletion or conversion</td>
<td>Large deletion or conversion</td>
<td>–1.3</td>
<td>27.0</td>
<td>30.1 (HC 25–40 mg)</td>
<td>125</td>
<td>2</td>
</tr>
<tr>
<td>8</td>
<td>26</td>
<td>SW CAH</td>
<td>IVS2–13A/C→G</td>
<td>IVS2–13A/C→G</td>
<td>–2.9</td>
<td>23.7</td>
<td>12.1 (DXM 0.5 mg)</td>
<td>62.5</td>
<td>2, 3</td>
</tr>
</tbody>
</table>

BMI, Body mass index.
<sup>a</sup> Nucleotides are numbered according to Higashi's functional CYP21 sequence (35). To detect a large deletion or conversion, Southern blotting was used (17).
<sup>b</sup> Height is expressed as SD score and corrected for target height SD score (HSDS-THSDS).
<sup>c</sup> Doses of DXM were converted to hydrocortisone (HC) equivalents (1 mg DXM = 40 mg hydrocortisone).
<sup>d</sup> Mineralocorticoid medication (9α-fluorohydrocortisone acetate) was taken in one to three doses.
<sup>e</sup> 1, Poor hormonal control; 2, infertility; 3, pain/discomfort; 4, hypogonadotropic hypogonadism; 5, hypergonadotropic hypogonadism.
RT-PCR. Purified total RNA (1.0 μg) was denatured for 10 min at 70°C and immediately cooled on ice. RT was performed using the Reverse Transcription System (Promega Benelux B.V., Leiden, The Netherlands) according to the manufacturer's protocol. After annealing of random hexamers for 10 min at 20°C, cDNA synthesis was performed for 60 min at 42°C followed by an enzyme inactivation step for 5 min at 95°C. Quantitative PCRs for CYPI1B1, CYPI1B2, ACTH receptor, All receptor, and PBGD were performed using Sybr Green Master Mix (PE Applied Biosystems, Nieuwerkerk a/d IJssel, The Netherlands) in a volume of 25 μl. The primers used were CYPI1B1 forward, ggc aga gga gag gat gct g; CYPI1B1 reverse, tct tgg tgt gat gcc acc acct gc; CYPI1B2 forward, ggc aga gga gag gat gct g; CYPI1B2 reverse, ctt gga gtt tca cca cca gga g; ACTH receptor forward, cga tcc cac acc agg aag at; ACTH receptor reverse, tca gtt taa cgg ccc tct tc; AII receptor forward, cct cgc tgt ggc tga ttt act c; AII receptor reverse, ttc tgc tca cag gtc cca g; PBGD forward, cat tgc tgg taa cgg cca tgg t; and PBGD reverse, gta cga ggc ttt cca tgt tg.

Assays for HPRT and β-actin were performed using predeveloped assay reagents (PE Applied Biosystems) in Universal TaqMan Mix (PE Applied Biosystems). Comparison of the potential normalizing genes assay reagents (PE Applied Biosystems) in Universal TaqMan Mix (PE Applied Biosystems). Comparison of the potential normalizing genes

Statistical analysis

Data are expressed as mean ± SD. To compare different blood samples within patients, paired t test was used to determine statistical significance. Intergroup differences were tested using nonparametric tests and Spearman rank correlation for correlation between parameters. A P value < 0.05 was considered significant (two-sided). None of the parameters investigated showed a significant difference in the mRNA levels of tumors derived from the left and right testis of an individual patient. Therefore, for statistical analyses, the mean value of the measured parameters of an individual patient was used.

Results

Histopathology

The mean weight of the tumors enucleated from the first testes was 10.1 ± 11.2 g (mean ± SD; range 0.5–27.4 g) and from the second testes 8.1 ± 7.3 g (range 1.3–18.9 g) (Table 3). Macroscopically, all tumors were firm and multilobular with a yellow to tan color on the cut surface and narrow bands of fibrous tissue. Microscopically, the tumors were sharply demarcated but unencapsulated and consisted of sheets or confluent cords of large polygonal cells with abundant eosinophilic cytoplasm, separated by dense fibrous tissue strands. Reinke crystals were absent.

Spermatic vein sampling

The results of the spermatic vein samplings are listed in Table 4. In all patients, variable levels of 21DF, 17OHP, and A were measured. The mean 21DF concentration was 37.5 ± 49.4 nmol/liter (mean ± SD; range 8.5–150 nmol/liter) in the first cannulated spermatic vein and 34.1 ± 33.1 nmol/liter (range 1.5–87 nmol/liter) in the second cannulated spermatic vein. Although the 21DF concentrations in the second sper-
molecular were lower than in the first cannulated vein, probably because of ongoing suppression of ACTH due to DXM given just before surgery, the difference between the two measurements was not significant \((P = 0.09)\). The mean 21DF concentration in peripheral blood was 5.4 ± 8.0 nmol/liter \(\text{(range 0.3–22 nmol/liter)}\) and was significantly lower than the concentration in simultaneously taken first spermatic vein blood \((P = 0.02)\). The mean ratio \((\text{mean} \pm \text{SD})\) of 21DF concentration in blood of the first cannulated spermatic vein and the simultaneously collected peripheral blood was 37.8 ± 56.3 \((P = 0.02)\). The mean 17OHP and A levels in the first cannulated spermatic vein were also significantly higher compared with those in simultaneously taken peripheral blood \((P = 0.001\) and \(P = 0.01\), respectively). There were no significant correlations between the concentrations of the steroids measured in the spermatic veins and tumor weight.

**Expression analysis**

CYP11B1 and CYP11B2 mRNAs were clearly detectable in all tumor samples. The mean CYP11B1 level was 4.1 ± 3.1 \((\text{mean} \pm \text{SD}; \text{range} 0.7–8.5)\) and the mean CYP11B2 level was 3.4 ± 2.6 \((\text{range} 0.4–7.5)\) with a strong correlation between these two measurements \((r = 0.95; P < 0.01)\). mRNA of ACTH receptors \(0.2 \pm 0.2; \text{mean} \pm \text{SD}; \text{range} 0–0.6\) and AII receptors \(0.19 \pm 0.032; \text{range} 0.00032–0.112\) were also present in all tumor samples. Values are shown as relative numbers of molecule gene of interest over molecule of \(\beta\)-actin.

The correlations between mRNA expression of ACTH receptors, All receptors, CYP11B1, and CYP11B2 and the steroid hormones 21DF, 170HP, and A measured in the spermatic veins and peripheral blood are listed in Table 4. There was a strong positive correlation between tumor ACTH receptor levels and 21DF \((r = 0.85; P = 0.015)\), 170HP \((r = 1; P = 0.01)\), and A concentration \((r = 0.89; P = 0.007)\) measured in peripheral blood, suggesting a strong influence of hormonal control on ACTH receptor levels in the tumors. No other significant correlations were found.

**Discussion**

Testicular adrenal rest tumors in male CAH patients are of great interest because of their high prevalence and severe consequences for gonadal function. Although several studies describe functional characteristics of these tumors, mainly in case reports, our study is the first providing functional features of a series of 16 testicular tumors from eight adult CAH patients.

Histologically, all tumors showed a similar appearance with microscopically specific features of steroid-producing cells in agreement with previous studies \((4–6)\). In all but one patient, in whom cannulation of the spermatic vein was not completely successful, the concentration of the adrenal-specific steroid 21DF in the spermatic veins was significantly higher than the concentration in peripheral blood samples, which suggests local production of these steroids in the testes. Additionally, our study clearly shows the presence at the mRNA level of the adrenal-specific enzymes CYP11B1 and CYP11B2 and of ACTH and All receptors in all testicular tumors, strongly suggesting that the tumors consists of adrenal-like tissue.

Ectopic adrenocortical tissue is found in up to 50% of neonates and usually atrophies during childhood \((22)\). Most ectopic adrenal tissue is found in the vicinity of the adrenals around the celiac axis and in the testes (surgery or autopsy findings). In the embryological period, steroidogenic cells destined to become adrenal and gonadal cells derive from neighboring areas of the coelomic epithelium and are morphologically identical. Separation of the cells takes place at approximately wk 8 of gestation, and further development of the cells depends on the expression of specific transcription factors \((23, 24)\). During further development, adrenal cells can migrate together with the descending testis. Adrenal rests within the testis occur in 7.5–15% of neonates and normally regress in early infancy \((25, 26)\). However, in CAH patients, it is believed that these cells can persist and proliferate with preservation of adrenal-like hormone-producing properties.

Functional adrenal zonation of testicular adrenal rests due to zona-specific expression of enzymes involved in steroid biosynthesis has never been described. It is known that in the human adrenal gland CYP11B1 is expressed in high levels in the zona fasciculata/reticularis where it catalyzes the 11\(\beta\)-hydroxylatation of 11-deoxy cortisol to cortisol \((27)\). CYP11B2 is exclusively expressed in the zona glomerulosa where it is responsible for the final step of the aldosterone synthesis pathway \((28, 29)\). The presence of CYP11B1 in the zona glomerulosa...
merula is controversial (30). So, the presence of CYP11B1 and CYP11B2 in tumor tissue of all patients in our study group suggests that the tumors may have functional features of both adrenal zona fasciculata and glomerulosa cells. Furthermore, our study shows that these tumors are very heterogeneous with respect to steroid hormone production and that at least the mRNA level, they contain varying amounts of steroid-producing enzymes and ACTH and AII receptors.

The factors that are responsible for growth of adrenal rest tissue in CAH patients are not fully understood. Testicular adrenal rest tumors are often found in patients with poor hormonal control and high ACTH levels, suggesting that ACTH is a dominant factor in tumor growth (2, 3). In the complete absence of 21-hydroxylase activity, plasma levels of ACTH are extremely high from early prenatal life, probably explaining the higher incidence of testicular tumors in SW CAH patients compared with SV CAH patients (12). However, in several studies, no correlation was found between ACTH levels and tumor growth (2, 3, 12). Therefore, most probably other factors contribute to tumor growth.

In our study, we found mRNA expression of AII receptors in all testicular tumors. These findings are in agreement with the study of Clark et al. (13) who described AII receptor concentrations in a testicular adrenal rest tumor of a CAH patient similar to that in normal adrenal tissue. It is known that AII has a strong trophic effect on the adrenal gland, whereas ACTH causes an acute increase of CYP11B1 mRNA levels without an effect on CYP11B2 transcription (31). We hypothesize that tumor growth in CAH patients may be stimulated not only by elevated ACTH concentrations but also by elevated AII levels, which are present in SW patients with poor hormonal control. Interestingly, in late-onset CAH patients, without clearly elevated ACTH or AII levels, testicular tumors are never described. Additional studies are necessary to study the effect of AII on growth of testicular tumors in CAH patients.

In summary, testicular adrenal rest tumors in CAH patients produce adrenal-specific steroids and contain adrenal-specific enzymes confirming the adrenal-like properties of the tumors. Based on the presence of all receptors, we hypothesize that AII may be an additional factor responsible for tumor growth in patients with poor hormonal control. Additional investigations will be necessary to determine the role of AII in testicular tumor growth.

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Address all correspondence and requests for reprints to: H. L. Claahsen-van der Grinten, M.D., Radboud University Nijmegen Medical Centre, Department of Paediatric Endocrinology (833), P.O. Box 9101, 6500 HB Nijmegen, The Netherlands. E-mail: H.Claahsen@culz.umcn.nl.

Present address for E.J.H.M.: Department of Urology, VU University Medical Centre, Amsterdam, The Netherlands.

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References


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