The following full text is a publisher's version.

For additional information about this publication click this link.
http://hdl.handle.net/2066/53524

Please be advised that this information was generated on 2019-05-14 and may be subject to change.
BRIEF REPORT

Testicular Adrenal Rest Tumors in Adult Males with Congenital Adrenal Hyperplasia: Evaluation of Pituitary-Gonadal Function before and after Successful Testis-Sparing Surgery in Eight Patients

Hedi L. Claahsen-van der Grinten, Barto J. Otten, Satoru Takahashi, Eric J. H. Meuleman, Christina Hulsbergen-van de Kaa, Fred C. G. J. Sweep, and Ad R. M. M. Hermus

Departments of Paediatric Endocrinology (H.L.C.-v.d.G., B.J.O.), Radiology (S.T.), Urology (E.J.H.M.), Pathology (C.H.-v.d.K.), Chemical Endocrinology (F.C.G.J.S.), 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 (TART) are frequently present. These tumors can interfere with testicular function. Intensifying glucocorticoid therapy does not always lead to tumor regression and improvement of testicular function. Recently, testis-sparing surgery was introduced for treatment of TART.

Objective: The aim of this study was to evaluate tumor volume, symptoms, and pituitary-gonadal function in male patients with CAH caused by 21-hydroxylase deficiency and bilateral TART before and after testis-sparing surgery.

Setting: This study was conducted at Radboud University Nijmegen Medical Centre in The Netherlands.

Patients: Eight adult male CAH patients with bilateral TART and infertility were included.

Interventions: Evaluation of testicular magnetic resonance imaging, symptoms, fasting serum concentrations of ACTH, LH, FSH, inhibin B, 17-OH progesterone, androstenedione, testosterone, and estrone, and semen analysis (six of eight patients) was performed before and 6 and 22 months after testis-sparing surgery.

Main Outcome Measures: The main outcome measures were absence of residual tumor and improvement of symptoms and pituitary-gonadal function.

Results: Residual tumors were not found on any of the patients’ magnetic resonance imaging after surgery. Two patients reported testicular pain and discomfort that disappeared after surgery. Parameters of pituitary-gonadal function did not improve after surgery: semen analysis showed azoospermia (five patients) or oligospermia (one patient) without improvement, and all patients had persistently low inhibin B concentrations.

Conclusion: Testis-sparing surgery did not improve pituitary-gonadal function despite successful removal of the tumors. Further studies are needed to investigate whether surgery at an earlier stage in the natural history of TART can prevent permanent testicular damage.

First Published Online November 7, 2006

Abbreviations: A, Androstenedione; BMI, body mass index; CAH, congenital adrenal hyperplasia; MRI, magnetic resonance imaging; 17OHP, 17-OH progesterone; TART, testicular adrenal rest tumor.

JCEM is published monthly by The Endocrine Society (http://www.endo-society.org), the foremost professional society serving the endocrine community.

In adult male patients with congenital adrenal hyperplasia (CAH), testicular adrenal rest tumors (TART) are frequently present with a reported incidence of 50–95% (1, 2). Because of their location in the mediastinum testis, these tumors can lead to obstruction of seminiferous tubules. In addition to these mechanical effects of the tumor, steroids produced by the tumor may reach the circulation interfering with the secretion of FSH and LH by the pituitary and they may also be toxic to testicular tissue in a paracrine manner, thereby contributing to testicular dysfunction (3–5).

Treatment with high doses of glucocorticoids may lead to suppression of ACTH secretion and reduction of tumor size (6–9). However, high doses of glucocorticoids do not always restore testicular function and may have several side effects (10).

Because of the benign character of the tumors, testis-sparing surgery has been proposed for the treatment of TART. Walker et al. (11) performed testis-sparing surgery in three CAH patients. Postoperatively, there was good vascular flow and no recurrence of the tumor. Tiryaki et al. (12) reported two CAH patients with steroid-unresponsive testicular tumors who were also treated by testis-sparing surgery. In both studies no information about pituitary-gonadal function before and after surgery was reported.

We treated eight adult infertile CAH patients with bilateral TART with testis-sparing surgery. The aim of our study was to evaluate whether testis-sparing enucleation of the tumor can improve pituitary-gonadal function. Here we describe the results of the clinical, biochemical, radiological, and histological evaluation of the patients before and 6 and 22 months after the operation.
**Patients and Methods**

**Patients and surgical procedure**

Eight male patients with CAH caused by 21-hydroxylase deficiency were selected for operation. Written informed consent was obtained from all patients. All patients had bilateral TART. Five patients had palpable masses (patients 1–4 and 6). Two patients reported pain and discomfort. Five patients (patients 1, 2, and 4–6) had been treated with high doses of glucocorticoids in the past to reduce tumor size without success. The indications for operation are listed in Table 1. The age of the patients was $30 \pm 8.9$ yr (mean $\pm$ sd; range, 23–51 yr). Height sd score was $-2.0 \pm 1.0$ (range, $-3.5$–0.2) and body mass index (BMI) was $28.1 \pm 4.4$ kg/m$^2$ (range, 23.7–38.2). Seven patients were white and one patient (patient 8) was of West Indian ethnicity.

Testicular tumor enucleation took place after general or locoregional anesthesia. The testis, including its tunica vaginalis, was luxated through an inguinal incision and the testicular tissue until the margin of the tumor was reached. Then, a careful blunt dissection of the tumor was undertaken. Finally, the tunica albuginea and the tunica vaginalis were closed and the testis was repositioned in the scrotum.

**Biochemical analysis**

Biochemical analysis was performed in all patients before and after operation. Patient 1 underwent operation without complete preoperative hormonal and radiological evaluation. Venous blood was collected from an antecubal vein at 0900 h after overnight fasting and before taking the morning medication to measure serum levels of $17$-OH progesterone ($17OHP$), androstenedione ($A$), testosterone, estrone, ACTH, LH, FSH, and inhibin B. The next day at 0900 h, after overnight fasting, blood was taken in one to three doses.

**Hormone assays**

Serum testosterone and $17OHP$ were assessed by $^3$H-RIA after pre-purification by means of paper chromatography of ether extracts of the samples, as described previously (13, 14). Serum A concentrations in serum and saliva were measured as described earlier (14). Serum estrone was measured by RIA after extraction and Sephadex LH-20 chromatography. The within- and between-assay coefficients of variation were 4.8% and 7.5%, respectively. ACTH was measured by a two-step immunoradiometric assay (Dytnost brahms, berlin, Germany). Serum FSH and LH were determined with a Fluorescence Immuno Enzymatic Assay (Abbott diagnostics, hoofddorp, the netherlands) using a random access analyser (type axsym; Abbott). Dimeric inhibin B was quantified using an ELISA (oxford bio-innovation ltd., Oxford, uk).

**Semen analysis**

In six of the eight patients, semen analysis was performed after more than 2 d of sexual abstinence before and 6 and 22 months after operation (15). One patient (patient 5) refused semen analysis. Another patient (patient 6) was sterilized in the past.

**Radiological evaluation**

All patients underwent testicular magnetic resonance imaging (MRI) before and 6 and 22 months after surgery. All MR studies were performed on a 1.5-T scanner (magnetom Sonata, Symphony or Avanto; siemens, Erlangen, Germany), using a body phased-array coil.

**Histopathology**

All removed tumor tissue was investigated macroscopically and microscopically. Tumors and testis biopsies were fixed in 10% buffered formalin. Tissue sections of 5 mm were cut and stained with hematoxylin and eosin and with von gieson elastin stain. Testis biopsy specimens were scored according to Johnsen with a score varying from 0 to 10. A johnsen score of more than 8 is associated with fertility (16).

**Results**

Radiological evaluation

No apparent residual tumor was seen in any patient on postoperative images. The measured volume of the testicular tumor (mean, 9.6 ml; range, 0.5–29.6) showed a good correlation with the tumor weight ($R^2 = 0.98$). Testicular volumes decreased after surgery in all patients (range, $-8$ to $-87$%).

**TABLE 1.** Age, phenotype, mutation analysis, height corrected for target height, BMI, and daily glucocorticoid and mineralocorticoid therapy at time of operation, and operation indication in 8 male CAH patients with bilateral testicular adrenal rest tumors

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr)</th>
<th>Phenotype</th>
<th>Allele 1$^a$</th>
<th>Allele 2$^b$</th>
<th>Height (SDS)$^c$</th>
<th>HSDDS-ThSDS$^d$</th>
<th>BMI (kg/m$^2$)</th>
<th>Daily glucocorticoid therapy (mg/m$^2$)$^e$</th>
<th>Daily mineralocorticoid therapy (µg)$^f$</th>
<th>Operation indication$^g$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>24</td>
<td>SW</td>
<td>Deletion/ conversion</td>
<td>Deletion/ conversion</td>
<td>$-2.6$</td>
<td>$-2.8$</td>
<td>27.4</td>
<td>32.2 (HC 20–20 to 20 mg)</td>
<td>400</td>
<td>1, 2</td>
</tr>
<tr>
<td>2</td>
<td>29</td>
<td>SW</td>
<td>Deletion/ conversion</td>
<td>Deletion/ conversion</td>
<td>$-2.1$</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</td>
<td>IVS2–13A/ C &gt; G</td>
<td>IVS2–13A/ C &gt; G</td>
<td>$-1.4$</td>
<td>$-0.7$</td>
<td>25.6</td>
<td>8.2 (HC 8–4 mg</td>
<td>62.5</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>32</td>
<td>SW</td>
<td>IVS2–13A/ C &gt; G</td>
<td>IVS2–13A/ C &gt; G</td>
<td>$-1.4$</td>
<td>n.a.</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</td>
<td>IVS2–13A/ C &gt; G</td>
<td>IVS2–13A/ C &gt; G</td>
<td>$-1.9$</td>
<td>$-1.0$</td>
<td>38.2</td>
<td>10.8 (HC 10–5 to 10 mg)</td>
<td>62.5</td>
<td>1, 4</td>
</tr>
<tr>
<td>6</td>
<td>51</td>
<td>SV</td>
<td>1172N</td>
<td>Deletion/ conversion</td>
<td>Deletion/ conversion</td>
<td>$-3.1$</td>
<td>$-2.95$</td>
<td>29.0</td>
<td>16.2 (HC 20–10 mg)</td>
<td>62.5</td>
</tr>
<tr>
<td>7</td>
<td>31</td>
<td>SW</td>
<td>Deletion/ conversion</td>
<td>Deletion/ conversion</td>
<td>$-0.2$</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</td>
<td>IVS2–13A/ C &gt; G</td>
<td>IVS2–13A/ C &gt; G</td>
<td>$-3.5$</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>

DXM, Dexamethasone; HC, hydrocortisone; n.a., not available; SDS, sd score.

$^a$ SW, Classic salt wasting CAH; SV, classic simple virilizing CAH.

$^b$ Nucleotides are numbered according to Higashi’s functional CYP21 sequence (18).

$^c$ Height is expressed as SDS and corrected for target height SDS (HS DDS-ThSDS).

$^d$ Doses of dexamethasone were converted to hydrocortisone equivalents (1 mg dexamethasone = 40 mg hydrocortisone).

$^e$ Mineralocorticoid medication (9-fluorohydrocortisone acetate) was taken in one to three doses.

$^f$ 1, Poor hormonal control; 2, infertility; 3, pain/discomfort; 4, hypergonadotropic hypogonadism; 5, hypergonadotropic hypogonadism.
Discussion

Our study is the first to our knowledge to provide a comprehensive evaluation of pituitary-gonadal function and testosterone levels in CAH patients after bilateral testis-sparing surgery, without complications. In our study, two patients (patients 4 and 8) showed elevated LH and FSH and testosterone levels, while the rest of the patients had normal levels of LH and FSH. Two patients (patients 6 and 7) showed elevated LH and FSH, and in one patient (patient 6) showed elevated levels of LH and FSH. Two patients (patients 6 and 7) showed elevated testosterone levels. The patients showed a variable increase in FSH and LH levels, suggesting additional testicular damage caused by high-serum estrone levels induced by aromatase activity. In three of these patients (patients 1, 2, and 5), we found suppressed LH and FSH levels in testis-sparing surgery in eight male CAH patients with bilateral testicular adrenal rest tumors.

Before operation, azoospermia was found in five patients and oligozoospermia was found in one patient. After operation there was no improvement of sperm quality.

Histopathology

Before operation, azoospermia was found in five patients and oligozoospermia was found in one patient. After operation, there was no improvement of sperm quality.

TABLE 2. Testicular volumes measured by MRI and parameters of pituitary-gonadal axis function and levels of 17OHP progesterone and androstenedione before and 6 and 22 months after testis-sparing surgery in eight male CAH patients with bilateral testicular adrenal rest tumors

<table>
<thead>
<tr>
<th>Patient</th>
<th>Testicular volume (ml)</th>
<th>Serum FSH (U/liter)</th>
<th>Serum LH (U/liter)</th>
<th>Serum testosterone (nmol/liter)</th>
<th>Serum inhibin B (ng/liter)</th>
<th>Serum 17OHP (nmol/liter)</th>
<th>Serum A (pmol/liter)</th>
<th>Serum estrone (pmol/liter)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre Post 6 22</td>
<td>Pre Post 6 22</td>
<td>Pre Post 6 22</td>
<td>Pre Post 6 22</td>
<td>Pre Post 6 22</td>
<td>Pre Post 6 22</td>
<td>Pre Post 6 22</td>
<td>Pre Post 6 22</td>
</tr>
<tr>
<td>L</td>
<td>1 R 1 L nd nd 1.7</td>
<td>&lt;0.2 &lt;0.2 0.7</td>
<td>&lt;0.2 &lt;0.2 0.2</td>
<td>37.0 23.0 3.6</td>
<td>nd nd 0</td>
<td>720 160 340</td>
<td>100 74 131</td>
<td>2700 4100 790</td>
</tr>
<tr>
<td>R</td>
<td>2 R 17.6 9.9 9.5</td>
<td>0.6 12.3 0.7</td>
<td>&lt;0.2 &lt;0.2 0.2</td>
<td>14.0 10.0 13.0</td>
<td>65 25 61</td>
<td>480 410 834</td>
<td>96 60 98</td>
<td>1100 1200 1900</td>
</tr>
<tr>
<td>L</td>
<td>3 R 8.5 2.9 2.2</td>
<td>8.6 79.2 53.0</td>
<td>5.2 62.6 43.6</td>
<td>17.0 9.5 11.0</td>
<td>61 16 23</td>
<td>26 18 62</td>
<td>1.5 0.74 4.8</td>
<td>140 160 300</td>
</tr>
<tr>
<td>R</td>
<td>4 R 8.1 3.4 3.8</td>
<td>15.9 24.0 24.2</td>
<td>2.9 20.8 17.4</td>
<td>13.0 15.0 12.9</td>
<td>47 19 15</td>
<td>367 470 840</td>
<td>14 23 53.2</td>
<td>650 810 1380</td>
</tr>
<tr>
<td>R</td>
<td>5 R 10.9 5.9 8.0</td>
<td>10.9 5.9 8.0</td>
<td>&lt;0.2 4.9 30.0</td>
<td>&lt;0.2 0.6 10.0</td>
<td>9.8 12.0 11.0</td>
<td>80 17 31</td>
<td>865 630 390</td>
<td>50 52 25</td>
</tr>
<tr>
<td>L</td>
<td>6 R 11.1 3.5 5.3</td>
<td>6.9 6.3 5.5</td>
<td>55.2 63.3 17.2</td>
<td>44.9 37.2 5.2</td>
<td>7.1 1.3 9.8*</td>
<td>10 4 &lt;10</td>
<td>5.1 1.7 2.0</td>
<td>2.8 210 230</td>
</tr>
<tr>
<td>R</td>
<td>7 R 5.2 3.8 4.1</td>
<td>8.4 5.7 5.4</td>
<td>39.3 42.2 24.5</td>
<td>12.3 10.2 19.4</td>
<td>18.8 18.0 10.0</td>
<td>9 17 15</td>
<td>4.3 2.7 12.0</td>
<td>1.2 11.0 9.96</td>
</tr>
<tr>
<td>L</td>
<td>8 R 7.7 6.2 5.6</td>
<td>7.6 1.4 1.0</td>
<td>6.3 4.0 &lt;0.2</td>
<td>5.6 28.2 &lt;0.2</td>
<td>20.0 13.0 34.1*</td>
<td>5 18 25</td>
<td>10 3.0 195</td>
<td>2.2 0.68 12.6</td>
</tr>
</tbody>
</table>
| R       | 9 R 6.6 4.8 3.4       | L, Left testes; R, right testes; nd, not determined; Post, 6 and 22 months after operation; Pre, before operation.

*Testicular volume determined by MRI (* testis showing irregular-shaped hypointense area adjacent to the mediastinum testis after surgery).

Normal values of our laboratory: FSH, 0.5–11 U/liter; LH, 1.4–8.5 U/liter; testosterone, 11–45 nmol/liter; inhibin B, 100–500 ng/liter; 17OHP, 2.0–10.8 nmol/liter (morning); A, 1.4–9.7 nmol/liter (morning); estrone, 65–220 pmol/liter; with suppletion of testosterone.
toms of testicular pain and discomfort as reported in two patients disappeared after surgery.

Semen analysis did not improve after surgery with persistently low inhibin B levels in all patients reflecting persistent Sertoli cell dysfunction. As seen in patients 1, 2, and 5, Sertoli cell dysfunction can be masked by simultaneous suppression of FSH secretion caused by high-serum estrone levels induced by aromatization of adrenal A in these patients. Therefore, inhibin B is a more accurate marker for Sertoli cell function than FSH in CAH patients.

The absence of positive effects on testicular function after operation despite complete removal of the tumors strongly suggests preexisting irreversible testicular damage in our patients. Indeed, peritubular fibrosis and tubular hyalinization was seen in testes biopsy specimen taken during surgery, which confirms irreversible damage of the testes probably caused by longstanding mechanical obstruction in all patients. It is clear that at this stage surgery can no longer help to restore testicular function.

TART may produce steroids that can contribute to elevated levels of A and 17OHP. Therefore, removal of the testicular tumors may lead to a decrease in the levels of A and 17OHP. However, in our group 17OHP and A levels did not change significantly after surgery. These observations suggest that surgical treatment is not helpful in improving hormonal control.

Interestingly, all but one of our patients had a homozygous deletion/conversion genotype or a homozygous IVS2–13A/C>G genotype. In an earlier study we showed that in patients who were homozygous or heterozygous for the deletion/conversion mutation tumor size was significantly larger than in patients with other mutations (17). The present study suggests that the IVS2–13A/C>G mutation may also be a risk factor for the development of testicular tumors.

In summary, testis-sparing surgery in CAH patients is a feasible treatment for TART in CAH patients. Symptoms of testicular pain and discomfort disappeared after surgery. However, 22 months after surgery no improvement in testicular function was seen. Further studies should investigate whether, at an earlier stage in the natural history of the TART, testis-sparing surgery might be advantageous.

Acknowledgments

We acknowledge Dr. H. P. F. Koppeschaar, Dr. J. W. F. Elte, and Dr. A. A. M. Franken for kindly referring patients to our hospital for participation in this study. R. Daams, J. Hulten-van der Bruggen, and J. Rijken are acknowledged for hormone analysis.

Received June 19, 2006. Accepted November 1, 2006.

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

References