The prevalence of testicular adrenal rest tumors and associated factors in postpubertal patients with congenital adrenal hyperplasia caused by 21-hydroxylase deficiency

Min Jae Kang\(^1\), Jae Hyun Kim\(^2\), Sun Hee Lee\(^3\), Young Ah Lee\(^1\), Choong Ho Shin\(^1\) and Sei Won Yang\(^1\)

\(^1\) Department of Pediatrics, Seoul National University College of Medicine, Seoul, 110-769, Korea
\(^2\) Department of Pediatrics, Inje University Ilsan Paik Hospital, Goyang, 411-706, Korea
\(^3\) Department of Pediatrics, Inje University Pusan Paik Hospital, Pusan, 614-735, Korea

Abstract. Development of a testicular adrenal rest tumor (TART) is common in males with congenital adrenal hyperplasia, and it can be an important cause of infertility. In the present study, we observed the prevalence of TARTs, and analyzed its associated factors in patients with 21-hydroxylase deficiency. Testicular ultrasonography was performed in 48 postpubertal male patients aged 10.6 to 27.1 years. To determine whether patients were undertreated, we analyzed the serum 17-hydroxyprogesterone (17-OHP) levels to the time of ultrasonographic measurement and calculated the percentage of measurements when serum 17-OHP level was \(>10\) ng/mL relative to the total number of measurements during the follow-up period. We divided the 6-year period before ultrasonographic measurement (time 0) into three 2-year intervals and calculated the average concentration of serum 17-OHP in each interval to give a \(-2\) to \(0\) year-average concentration (\(-2\text{-}0\text{YAC}\)), \(-4\text{-}2\text{YAC}\) and \(-6\text{-}4\text{YAC}\). A TART was detected by ultrasonography in 31 of 48 patients (64.6\%) and the median maximal cross-sectional area of the TARTs was 0.71 (0.03, 4.95) cm\(^2\). The corrected final adult height was lower, and \(-4\text{-}2\text{YAC}\) and body mass index were higher in patients with TART than in those without. After controlling for the type of 21-hydroxylase deficiency, hydrocortisone-equivalent dose, age, and \(-6\text{-}4\text{YAC}\), the size of TART was associated with a high undertreatment percentage with a marginal statistical significance. These results suggest that strict disease control is mandatory and regular examination with testicular ultrasonography is recommended in male patients, regardless of the type of 21-hydroxylase deficiency.

Key words: Testicular adrenal rest tumor, Congenital adrenal hyperplasia

CONGENITAL adrenal hyperplasia (CAH), caused by 21-hydroxylase deficiency, is a lifelong disorder. Issues such as quality of life, sexual function, and reproductive capacity should be considered in early adulthood in such patients [1]. Development of a testicular adrenal rest tumor (TART) is a common and important cause of infertility [1-4].

First described by Wilkins et al. in 1940 [5], a TART originates from the ectopic adrenal cortical tissue in the testis. Because both the adrenal glands and gonads arise from the common urogenital ridge, the adrenal cortical tissue can fuse into the testis when gonads migrate caudally in the early embryonic period [6-7]. In some cases, a TART presents on only one side [8] but usually exists bilaterally [9], which can be explained by the embryology described above.

Adrenal tissue remnants in the testis are observed in 7.5%-15\% of normal neonates but regress during infancy in most cases [6-10]. In the presence of chronically high adrenocorticotrophic hormone (ACTH) lev-
els, the adrenal tissue remnants become hyperplastic and eventually develop tumors. Thus, TARTs are also found in other diseases with high ACTH levels, such as Nelson’s syndrome and Cushing’s disease [11], and the size of a TART is reduced by adequate suppression of ACTH secretion by treatment [12]. TARTs do not occur in patients with nonclassic or late-onset CAH, because ACTH level is not elevated enough [3].

The reported prevalence of TARTs in patients with CAH varies between 0% and 94% [3, 6, 12], depending on the age of the patients, type of CAH, method of detection, and target range of disease control [13-14]. We performed this study to observe the prevalence of TARTs, measured by testicular ultrasonography, and to analyze its contributing factors, such as the degree of disease control, in postpubertal patients with CAH caused by 21-hydroxylase deficiency.

**Materials and Methods**

**Patients**

Forty-eight male patients, older than 10 years and followed up regularly through the outpatient clinic for the treatment of congenital adrenal hyperplasia caused by 21-hydroxylase deficiency, were included. Prepubertal patients were excluded. Of the 48 patients, 36 (75.0%) had the salt-wasting (SW) type and 12 (25.0%) had the simple-virilizing (SV) type. They had a median age of 16.3 years (range 10.6-27.1). The study protocol was approved by the institutional ethics committee, and informed consent was obtained from patients and their parents.

**Methods**

We retrospectively reviewed the medical records and measured or calculated the height, weight, body mass index (BMI), and frequency, dose and type of medications at the time of ultrasonographic measurement. In general, most patients with CAH achieve a final adult height below their target height [15]. Therefore, the final adult height, expressed as a standard deviation score (SDS), was corrected for genetic potential (final adult height SDS minus mid-parental height SDS) in patients who reached their final height. Disease duration was calculated as time of diagnosis to the time of ultrasonographic measurement.

We defined the adequate control of CAH as a serum level of 17-hydroxyprogesterone (17-OHP) ≤10 ng/mL [16]. We recorded the past random levels of serum 17-OHP to the time of ultrasonographic measurement. To determine whether the patients were undertreated, we calculated the percentage of serum 17-OHP measurements >10 ng/mL relative to the total number of measurements during the follow-up period. To adjust the different number of measurements of each subject, we used the percentage in the analysis (number of measurements; mean±SD (min., max.), 23.6±6.4 (10, 32)). We arbitrarily divided the 6-year follow-up period just before ultrasonographic measurement (time 0) into three 2-year intervals and calculated the average concentration of serum 17-OHP in each interval, -2nd to -0 year-average concentration (-2-0YAC), -4th to -2nd year-average concentration (-4-2YAC) and -6th to -4th year-average concentration (-6-4YAC).

Color Doppler ultrasonography of the testis was performed by experienced pediatric radiologists. The high resolution ultrasound (LOGIQ 9, General Electric Company, Milwaukee, WS, USA or Acuson Sequoia 512, Siemens Medical Solutions USA, Mountain View, CA, USA) with 12-15 MHz linear probe was used in the examination. Low-echoic and hypervascular masses were identified as TARTs, which were larger than 0.1 cm. The maximal cross-sectional area and the volume of the TARTs were calculated using the formula for a prolate ellipse as follows:

Maximal cross-sectional area of TART (cm$^2$) = $\pi \times \frac{d1(cm) \times d2(cm)}{4}$ ($\pi = 3.14$)

Volume of TART (cm$^3$) = $\pi \times \frac{d1(cm) \times d2(cm)}{3} \times \frac{d3(cm)}{6}$ ($\pi = 3.14$)

where $d1$ is the largest diameter, $d2$ is the medium-sized diameter, and $d3$ is the smallest diameter.

When there were multiple masses, the largest one was selected for calculation.

**Statistics**

The data are presented as median and range (minimum, maximum). Statistical analyses were performed using SPSS 17.0 for Windows (SPSS Inc., Chicago, IL, USA). Differences between two subgroups classified according to the type of CAH and the existence of a TART were assessed by Mann-Whitney test and Fisher’s exact test. Comparison among three 2-year interval average concentrations was analyzed by Friedman test. Spearman’s rho was used to identify the associations between the maximal cross-sectional area of each TART and the continuous variables. In multiple regression analysis, the maximal cross-sectional area of a TART was transformed to the loga-
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rithmic value to make it parametric. Several factors, which were identified to be correlated with the size of a TART by the simple correlation analysis, were used as independent variables. *P*-values <0.05 were considered significant.

Results

Clinical characteristics of the patients

The median age of the patients at the time of ultrasonographic measurement was 16.7 years for those with the SW type and 12.7 years for those with the SV type. The median duration of disease was 15.6 and 6.2 years, respectively. The median age and disease duration showed differences between the SW and SV type (age, *P*=0.038; disease duration, *P*=0.001).

Of the 48 patients, 21 (42.9%) were treated with hydrocortisone, and 28 (57.1%) were treated with prednisolone. The median hydrocortisone-equivalent dose at the time of ultrasonographic measurement was 16.2 mg/m²/day, assuming that prednisolone is four times more potent than hydrocortisone. The BMI of total patients was 24.0 (17.8, 34.0) kg/m². The corrected final adult height SDS of 40 patients was -1.8 (-4.9, 0.7).

The median percentage of undertreatment of the 48 patients was 82.4 %. The mean serum 17-OHP concentration was 74.2 ng/mL at -2-0YAC (n=48), 53.0 ng/mL at -4-2YAC (n=47), and 58.0 ng/mL at -6-4YAC (n=45) (Table 1). The -2-0 YAC value was significantly higher than the others (*P*=0.010).

Table 1

<table>
<thead>
<tr>
<th>Description</th>
<th>Total (n=48)</th>
<th>SW (n=36)</th>
<th>SV (n=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age* (years)</td>
<td>16.3 (10.6, 27.1)</td>
<td>16.7 (10.6, 26.7)</td>
<td>12.7 (10.9, 27.1)</td>
</tr>
<tr>
<td>Disease duration (years)</td>
<td>15.0 (2.3, 26.6)</td>
<td>15.6 (6.1, 26.6)</td>
<td>6.2 (2.3, 21.8)</td>
</tr>
<tr>
<td>BMI* (kg/m²)</td>
<td>24.0 (17.8, 34.0)</td>
<td>24.0 (17.8, 34.0)</td>
<td>23.8 (18.6, 32.3)</td>
</tr>
<tr>
<td>Corrected final adult height SDS</td>
<td>-1.8 (-4.9, 0.7) (n=40)</td>
<td>-2.0 (-4.9, 0.7) (n=31)</td>
<td>-1.1 (-3.2, 0.1) (n=9)</td>
</tr>
<tr>
<td>Type of medication* (HCS:PD)</td>
<td>20:28</td>
<td>13:23</td>
<td>7:5</td>
</tr>
<tr>
<td>Hydrocortisone-equivalent dose* (mg/m²/day)</td>
<td>16.3 (11.8, 20.8)</td>
<td>17.1 (11.8, 20.8)</td>
<td>15.2 (12.9, 18.5)</td>
</tr>
<tr>
<td>Under treatment percentage (%)</td>
<td>82.4 (0.0, 100.0)</td>
<td>82.4 (0.0, 100.0)</td>
<td>73.5 (7.7, 100.0)</td>
</tr>
<tr>
<td>-2-0YAC (ng/mL)</td>
<td>74.2 (0.3, 125.0)</td>
<td>81.6 (0.3, 125.0)</td>
<td>64.3 (7.0, 119.0)</td>
</tr>
<tr>
<td>-4-2YAC (ng/mL)</td>
<td>53.0 (0.1, 125.0) (n=47)</td>
<td>60.5 (0.1, 125.0) (n=35)</td>
<td>40.8 (0.6, 83.4) (n=12)</td>
</tr>
<tr>
<td>-6-4YAC (ng/mL)</td>
<td>58.0 (0.1, 125.0) (n=45)</td>
<td>59.8 (0.1, 125.0) (n=35)</td>
<td>36.4 (2.7, 96.0) (n=10)</td>
</tr>
</tbody>
</table>

Data are expressed as the median (range). *At the time of ultrasonographic measurement. Abbreviations: SW, salt-wasting CAH; SV, simple-virilizing CAH; BMI, body mass index; SDS, standard deviation score; HCS, hydrocortisone; PD, prednisolone; -2-0YAC, -2nd to 0 year-average concentration; -4-2YAC, -4th to -2nd year-average concentration; -6-4YAC, -6th to -4th year-average concentration.

Conversion factor: 17OHP, ng/mL x 3.02 → nmol/L

Fig. 1 Longitudinal ultrasound (A) and color Doppler (B) images of the left testis in one patient are shown. The low-echoic and hypervascular mass adjacent to the mediastinum testis is identified as testicular adrenal rest tumor, as indicated by the arrows.
The age at the time of ultrasonographic measurement, disease duration, hydrocortisone-equivalent dose, undertreatment percentage, -2-0YAC, and -6-4YAC did not significantly correlate with the presence of a TART. However, the patients with a TART had a significantly lower corrected final adult height and higher BMI and -4-2YAC to compare with those without a TART (Table 3).

There were no significant differences among three 2-year interval average concentrations in patients with a TART ($P=0.111$).

**Relationships between the maximal cross-sectional area of TARTs and indices of disease control**

The maximal cross-sectional area of the TARTs was positively correlated to the age at the time of ultrasonographic measurement, disease duration, hydrocortisone-equivalent dose, undertreatment percentage, -2-0YAC, and -6-4YAC did not correlate significantly with the presence of a TART. However, the patients with a TART had a significantly lower corrected final adult height and higher BMI and -4-2YAC to compare with those without a TART (Table 3). There were no significant differences among three 2-year interval average concentrations in patient with a TART ($P=0.111$).

### Table 2  Characteristics of Testicular Adrenal Rest Tumors

| Prevalence | 64.6% (31/48) |
| Bilaterality | Bilateral 87.1% (27/31) | Unilateral (Rt) 3.2% (1/31) | Unilateral (Lt) 9.7% (3/31) |
| Number of mass in one testis | Single 83.9% (26/31) | Multiple 16.1% (5/31) |
| Maximal cross-sectional area of TART | 0.71 (0.03, 4.95) cm$^2$ (n=31) |
| Maximal cross-sectional area of TART of the right testis | 0.81 (0.03, 4.95) cm$^2$ (n=28) |
| Maximal cross-sectional area of TART of the left testis | 0.44 (0.03, 4.38) cm$^2$ (n=30) |
| Maximal volume of TART | 0.423 (0.004, 5.935) cm$^3$ (n=31) |

Data shown are medians with range in parenthesis. Abbreviations: TART, testicular adrenal rest tumor; Rt, right; Lt, left.

### Table 3  Comparison of Characteristics between the Two Subgroups Classified by the Existence of a Testicular Adrenal Rest Tumor

<table>
<thead>
<tr>
<th>TART</th>
<th>Presence (n=31)</th>
<th>Absence (n=17)</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients (SW:SV)</td>
<td>25:6</td>
<td>11:6</td>
<td>0.300†</td>
</tr>
<tr>
<td>Age* (years)</td>
<td>16.9 (10.9, 27.1)</td>
<td>14.1 (10.6, 26.5)</td>
<td>0.140</td>
</tr>
<tr>
<td>Disease duration (years)</td>
<td>15.5 (2.3, 26.6)</td>
<td>13.4 (2.4, 26.4)</td>
<td>0.123</td>
</tr>
<tr>
<td>BMI* (kg/m$^2$)</td>
<td>25.5 (17.8, 34.0)</td>
<td>21.6 (18.6, 32.3)</td>
<td>0.029</td>
</tr>
<tr>
<td>Corrected final adult height SDS</td>
<td>-2.2 (-4.9, -0.5) (n=27)</td>
<td>-1.3 (-3.9, 0.7) (n=13)</td>
<td>0.011</td>
</tr>
<tr>
<td>Type of medication* (HCS:PD)</td>
<td>10:21</td>
<td>10:7</td>
<td>0.125†</td>
</tr>
<tr>
<td>Hydrocortisone-equivalent dose* (mg/m$^2$/day)</td>
<td>17.2 (12.9, 20.6)</td>
<td>15.2 (11.8, 20.8)</td>
<td>0.113</td>
</tr>
<tr>
<td>Undertreatment percentage (%)</td>
<td>82.6 (7.7, 100.0)</td>
<td>80.6 (0.0, 100.0)</td>
<td>0.796</td>
</tr>
<tr>
<td>-2-0YAC (ng/mL)</td>
<td>73.8 (2.4, 125.0)</td>
<td>79.5 (0.3, 115.4)</td>
<td>0.382</td>
</tr>
<tr>
<td>-4-2YAC (ng/mL)</td>
<td>60.5 (0.6, 125.0) (n=31)</td>
<td>35.3 (0.1, 97.5) (n=16)</td>
<td>0.006</td>
</tr>
<tr>
<td>-6-4YAC (ng/mL)</td>
<td>58.5 (2.7, 125.0) (n=30)</td>
<td>40.2 (0.1, 119.8) (n=15)</td>
<td>0.312</td>
</tr>
</tbody>
</table>

Data are expressed as the median (range). * At the time of ultrasonographic measurement † by Fisher’s exact test. Abbreviations: TART, testicular adrenal rest tumor; SW, salt-wasting CAH; SV, simple-virilizing CAH; BMI, body mass index; SDS, standard deviation score; HCS, hydrocortisone; PD, prednisolone; -2-0YAC, -2$^{nd}$ to 0 year-average concentration; -4-2YAC, -4$^{th}$ to -2$^{nd}$ year-average concentration; -6-4YAC, -6$^{th}$ to -4$^{th}$ year-average concentration. Conversion factor: 17OHP, ng/mL x 3.02 = nmol/L.

*87.1%* and each TART appeared mainly as a single mass. The median maximal cross-sectional area of the TARTs was 0.71 (0.03, 4.95) cm$^2$, and the median volume was 0.423 (0.004, 5.935) cm$^3$ (Table 2).

The prevalence (SW vs. SV; 69.4% vs. 50.0%; $P=0.300$) of the TART did not differ significantly between the SW type and SV type. But the maximal cross-sectional area of the TARTs [SW vs. SV; 1.06 (0.03, 4.95) vs. 0.12 (0.03, 1.61) cm$^2$; $P=0.024$] showed the difference according to the type of CAH.

### Comparison of characteristics between the two subgroups classified by the existence of a TART

The SW type was predominant among patients with a TART but this difference was not significant [SW vs. SV; 25 of 31 (80.6%) vs. 6 of 31 (19.4%); $P=0.300$].
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64.6% in 48 male patients with 21-hydroxylase deficiency older than 10 years. This percentage is higher than that in recent reports [4, 14, 17-19] except for the study of Stikkelbroeck et al. [13], who reported a prevalence rate of 94% for patients older than 17 years. Several factors may explain why our results were different from those of other reports. First, we excluded prepubertal patients in our study. ACTH, angiotensin II (AI I), and luteinizing hormone (LH) are known as trophic factors of TARTs, and LH receptors may exist in testicular adrenal rest tissue [3, 11]. Therefore, increased LH levels might promote the growth of a TART during puberty [11, 17]. In a study of 2-18-year-old patients, [17] TARTs were found in eight patients, six of whom were older than 10 years. In two of the six patients, TARTs had not been detected in testicular ultrasonography performed before the age of 10 years.

**Discussion**

Our results showed that the prevalence of TARTs was 64.6% in 48 male patients with 21-hydroxylase deficiency older than 10 years. This percentage is higher than that in recent reports [4, 14, 17-19] except for the study of Stikkelbroeck et al. [13], who reported a prevalence rate of 94% for patients older than 17 years. Several factors may explain why our results were different from those of other reports. First, we excluded prepubertal patients in our study. ACTH, angiotensin II (AI I), and luteinizing hormone (LH) are known as trophic factors of TARTs, and LH receptors may exist in testicular adrenal rest tissue [3, 11]. Therefore, increased LH levels might promote the growth of a TART during puberty [11, 17]. In a study of 2-18-year-old patients, [17] TARTs were found in eight patients, six of whom were older than 10 years. In two of the six patients, TARTs had not been detected in testicular ultrasonography performed before the age of 10 years.
Second, the median percentage of undertreatment was 82.4% in our study, which is considerably higher than that in other reports [18-19]. We considered the serum 17-OHP concentration greater than the upper target of 10 ng/mL to indicate undertreatment. The target range for serum 17-OHP level differs between review articles: 12 ng/mL [20] or 33.1 ng/mL [21]. The serum 17-OHP level also has a large diurnal variation and can change rapidly after administration of hydrocortisone [22-24]. Thus, a single measurement of serum 17-OHP concentration is not sufficient for evaluating the extent of disease control. For these reasons, it is possible that we overestimated the number of undertreated patients. And the number of examinations during follow-up period for each individual differed. But the undertreatment percentage serves as a cumulative indicator of the median follow-up of 12.9 years and reflects the chronic increase in plasma ACTH levels. Finally, the smallest cross-sectional area of a TART seen as low-echoic and hypervascular tissue on the ultrasound image was 0.03 cm² in our patients. This was smaller than the value in most other reports, which found that TARTs were detected when they were at least 2 mm [13, 17, 25]. For these reasons, the prevalence of TARTs in our study might be higher than expected.

Patients with a TART had a lower corrected final adult height, which indicates the clinical aspects of disease control, than those without a TART. The maximal cross-sectional area of a TART correlated with many factors but after controlling for these variables, the undertreatment percentage was shown to be the most contributing factor. The reason why the undertreatment percentage showed a marginal statistical significance in multiple regression analysis may be due to the multicollinearity, especially with -6-4YAC. When -6-4YAC was excluded, the undertreatment percentage was significantly correlated with the size of TART even after controlling for the type of CAH, hydrocortisone-equivalent dose and age at the time of ultrasonographic measurement, which we did not describe in the result. Therefore, long-term disease control is most important in the development of TARTs.

The correlation coefficients were not very high, indicating that other factors contribute to the growth of TARTs. Some believe that a TART can develop irrespective of disease control; [3, 11] Stikkelbroeck et al. [13] reported that TARTs were also detected in well-controlled patients. If adrenal tissue does not rest in the testis, TARTs would not develop even with high ACTH levels. However, if a large amount of adrenal tissue rests in the testis during the early embryonic period, a TART could grow under conditions of mildly elevated ACTH level or in response to other factors. Further efforts to find other trophic factors that can cause TART growth suggest a relationship between the growth of TARTs and CYP21A2 gene mutations [4, 13-14]. In most cases, the activity of 21-hydroxylase depends on the type of mutation; very low enzyme activity is associated with a high prevalence of TARTs [14]. That is, when there is no 21-hydroxylase activity, ACTH level would be very high in the early embryonic period, and the chance of the hyperplastic adrenal tissue migrating along with the testis should increase [8, 13]. In the same context, the size of a TART can differ according to the type of CAH [18]. In our study, the prevalence and maximal cross-sectional area of TARTs were not significantly associated with the type of CAH, although there might be variable genotypes within a subtype, which we cannot test because of the lack of genetic studies. Both ACTH and All have a strong trophic effect on adrenal tissue [3, 8], and clinicians should consider the effect of All in patients with the salt-wasting type of CAH.

Because testicular adrenal rest tissue also produces steroid hormones [3] and a TART is a functional tissue like the adrenal cortex, the serum levels of androstenedione and 17-OHP may be elevated in patients with a TART[2, 8]. It is difficult to identify causal relationships between the elevated serum 17-OHP level and the existence of a TART in the cross-sectional study. We calculated the average serum 17-OHP level at 2-year intervals and anticipated that the -2-0YAC in patients with a TART might be the highest of the three 2-year intervals before ultrasonographic measurement. However, the average concentration did not differ significantly among three 2-year intervals in patients with a TART, although -2-0YAC was the highest in all patients. The correlation between -2-0YAC and the maximal TART cross-sectional area was also not significant. Another limitation of our study is that we could not measure serum concentrations of 17-OHP >125 ng/mL.

The TARTs usually exist bilaterally, which is different from the other malignancies of the testis [26]. The laterality is not observed in the testicular cancer, such as seminoma, Sertoli cell tumor, and Leydig cell tumor [27, 28]. Therefore, although the median maximal cross-sectional area of TART was larger in the right testis than in left testis in our study this might have no
statistical and clinical meanings.

Generally, the prevalence of TARTs increases with age. One report [17] stated that TARTs were detected after a 1- or 2-year follow-up in patients who initially had no TART. Our result was similar in that the prevalence was >70% in patients older than 15 years and the patient’s age might affect the size of TART. Therefore, screening for the existence of a TART should be mandatory in male patients. However, because TARTs exist mainly in the rete testis and a diameter >2 cm is palpable [3], early detection by physical examination is difficult. Testicular enlargement detected by palpation can be mistaken for precocious puberty [29]. The presence of a TART is a known risk factor for infertility, which can be confirmed by blood or semen analysis [4, 13, 17-18, 30] but changes may start in childhood [4]. Thus, imaging tools such as ultrasonography and magnetic resonance imaging (MRI) are recommended for screening [10, 31]. Ultrasonographic measurement is more accessible than MRI and has equal sensitivity in detecting a mass, although MRI has better contrast resolution than ultrasound imaging for measuring the size of mass and extent of disease [12]. Thus, ultrasonography may be best for routine periodic examinations and MRI for confirming a mass, especially if a fast-growing tumor is suspected [32]. There is no consensus about the time to begin and the intervals for TART screening. Claahsen-van der Grinten [31] proposed that screening for TARTs should begin at 8 years of age and should be repeated annually; however, this is usually only recommended when patients reach puberty [1, 32-33].

In conclusion, the prevalence of TARTs was 64.6% in postpubertal male patients with CAH caused by 21-hydroxylase deficiency. The occurrence and progression of TARTs might be associated with the degree of disease control. Our results suggest that strict disease control is mandatory and that regular examination with testicular ultrasonography should be performed in male patients regardless of the type of 21-hydroxylase deficiency.

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Disclosure statements

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