Androgen secreting adrenocortical tumours

O D Wolthers, F J Cameron, I Scheimberg, J W Honour, P C Hindmarsh, M O Savage, R G Stanhope, C G D Brook

Abstract

Background—Androgen secreting adrenocortical tumours are rare in children and the determination of their malignant potential can be difficult.

Objectives—To assess the presentation, histology, and clinical behaviour of these tumours.

Setting—Two tertiary referral centres.

Study design—Retrospective analysis of children diagnosed with an androgen secreting adrenocortical tumour between 1976 and 1996.

Patients—Twenty three girls and seven boys aged 0–14 years.

Results—Pubic hair was observed in all children, clitoromegaly or growth of the phallus in 23 children, acceleration of linear growth in 22 children, and advanced bone age (> 1.5 years) in 18 children. Hypersecretion of androgens was detected by assessment of serum androgen concentrations alone in four patients and by 24 hour urine steroid excretion profiles in 22 patients. All 16 tumours measuring < 5 cm in diameter were benign. Of the tumours measuring 5–9 cm, three were malignant and seven were benign, whereas all four tumours > 10 cm were malignant. Histological slides were available for reassessment in 25 children. Although mitoses and necrosis were more characteristic of tumours with malignant behaviour, no exclusive histological features of malignancy were seen.

Conclusion—Histological criteria for malignancy are not reliable, whereas tumour size is important in assessing malignant potential.

Keywords: androgen secreting adrenocortical tumours; malignancy

Diagnosis and management of adrenocortical tumours in children is often problematical. Experience with these uncommon tumours is limited and most published observations are based on individual cases. They may secrete various steroid hormones including androgens, oestrogens, cortisol, and aldosterone. Accordingly, patients may present with virilisation, feminisation, hypercortisolism, or hyperaldosteronism, alone or in combination. The majority of these tumours secrete androgens, and it has been suggested that most of them are carcinomas, and that pure virilising adenomas are rare. Criteria for assessment of the malignant potential of purely virilising adenomas in children have not been established. Our aim was to review our population of children with androgen secreting adrenocortical tumours diagnosed during the last two decades with respect to clinical presentation, markers of androgen hypersecretion, histology, and outcome.

Patients and methods

We studied, retrospectively, records from two tertiary centres of children aged 0–14 years with a diagnosis of an androgen secreting adrenocortical tumour made between 1976 and 1996. We collected data on sex, age at presentation, duration of symptoms before diagnosis, clinical features of virilisation, pubertal stages according to Tanner ratings, height, and bone age performed by the TW2 method. Acceleration of growth was defined as crossing two or more height centiles. Data on metastases, chemotherapy, and follow up were also collected.

Serum concentrations of dehydroxyepiandrosterone-sulphate (DHEA-S), androstenedione, testosterone, cortisol, 17-hydroxyprogesterone, aldosterone, and oestradiol, and 24 hour urine steroid data were recorded. Furthermore, imaging (computed tomography and magnetic resonance imaging), and histological descriptions were noted. Based on imaging and/or the histopathology description we rated tumour size as small (< 5 cm in diameter), moderate (5–9 cm), or large (> 10 cm). The weight of the tumours was also recorded. Slides were provided from the archives of the histopathology departments involved and were reviewed (by IS) for the following features: pleomorphism, mitoses, necrosis, venous and capsular invasion, and fibrous bands.

Results

We identified 32 cases but excluded two with benign tumours because of missing data. Twenty three of the children were girls, seven were boys. At the time of diagnosis, 18 children were 0–4 years old, 10 were 5–9 years old, and two were 10–14 years old. The overall age range was 0.4–12.3 years with a mean of 4.9.

SYMPTOMS

The time from the first observation of virilising symptoms to the time of diagnosis was 0.1–2 (mean 0.6) years. The most frequent sign was pubic hair. Twenty eight children presented with stage III pubic hair, one with stage II, and one with stage V. Clitoromegaly or growth of the phallus was recorded in 23, acne in 12, and hirsutism in 10. Cushingoid facies were observed in four children, deepening of the voice in two girls, and gynaecomastia in one boy.
GROWTH AND BONE AGE

Acceleration of linear growth was noted in 22 children; growth was normal in three. Bone age assessments were reported in 25 children, showing advances > 1.5 years in 18 of these children.

BIOCHEMICAL ASSESSMENTS

Serum concentrations of testosterone, androstenedione, and DHEA-S were available in 22, 10, and 11 patients, respectively, and were high in 18, six, and 11 of the investigated cases. Serum oestradiol, cortisol, and 17-hydroxyprogesterone were assessed in seven, nine, and 13 patients, respectively. Cortisol was high in three patients, otherwise the data were within normal ranges.

Twenty four hour urine steroid excretion rates were assessed in 22 patients. 11β-Hydroxyandrosterone was the major steroid in nine children, DHEA-S in seven, and androsterone, aetiocholanolone, and 16α-hydroxy-DHEA-S in two children, respectively. The androgen metabolites, androstenetriol (n = 6) and pregnanetriol (n = 2) were also detected.

TUMOUR CHARACTERISTICS

Nineteen tumours were located in the left adrenal cortex, 10 in the right, and one tumour was found in ectopic adrenocortical tissue in the left iliac fossa (patient 14; table 1).

Twenty five of the 30 histological case slides were retrieved from the histopathology departments. The tumours in the five un retrievable cases were all small and all behaved in a benign way. Of the 25 tumours studied histologically (table 1) seven behaved as malignant. All four large tumours (≥ 10 cm) were malignant; two weighed more than 500 g (patients 4 and 19), one weighed 189 g (patient 20), and the weight of the other was unknown (patient 11). Three moderate sized tumours (5–9 cm) weighing 164 g and 173 g (patients 18 and 16, respectively) were malignant. Seven other moderate sized tumours were benign; one of those tumours weighed 308 g (patient 24). All 16 small tumours (< 5 cm) and all those weighing less than 150 g were benign. The largest benign tumour (patient 24; 308 g) had large areas of haemorrhage, which might have accounted for the excess weight.

Pleomorphism was present in both benign and malignant tumours (fig 1A and D); many benign tumours were extremely pleomorphic, although some lacked pleomorphism (fig 1C). Mitoses tended to be more numerous in malignant tumours, especially abnormal forms, but were not confined to these tumours, with numerous mitoses including abnormal forms being present in benign neoplasms. Large areas of necrosis were more characteristic of malignancy (fig 1E), but at least one benign tumour had extensive necrosis (patient 15) and another had large areas of haemorrhage (patient 24). Venous and capsular invasion were found in both benign and malignant tumours (fig 1F) but many had neither of these features. In general, malignant tumours had more fibrous bands, but these were also found in some benign tumours (patients 19 and 25) (fig 1E and B).

TREATMENT AND OUTCOME

All patients had an adrenalectomy, except the child with an ectopic tumour who had the tumour and the ectopic tissue excised. Two children with local tumour growth (patients 11 and 19) had an ipsilateral nephrectomy.

Treatment and outcome data in the seven children with malignant tumours are given in table 2. No signs of recurrent tumour activity were detected in 16 children with small tumours or in seven with moderate tumours during ≥ 5 years (n = 15), 4 years (n = 3), 2

<table>
<thead>
<tr>
<th>Patient</th>
<th>Pleomorphism</th>
<th>Mitoses</th>
<th>Necrosis</th>
<th>Venous invasion</th>
<th>Capsular invasion</th>
<th>Fibrous bands</th>
<th>Weight</th>
<th>Size*</th>
<th>Behaviour</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>+++</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>12 g</td>
<td>1</td>
<td>B</td>
</tr>
<tr>
<td>2</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>25 g</td>
<td>1</td>
<td>B</td>
</tr>
<tr>
<td>3</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>12 g</td>
<td>1</td>
<td>B</td>
</tr>
<tr>
<td>4</td>
<td>++</td>
<td>+</td>
<td>++</td>
<td>++</td>
<td>–</td>
<td>+</td>
<td>1200 g</td>
<td>3</td>
<td>M</td>
</tr>
<tr>
<td>5</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>21 g</td>
<td>2</td>
<td>B</td>
</tr>
<tr>
<td>6</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>7 g</td>
<td>2</td>
<td>B</td>
</tr>
<tr>
<td>7</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Not stated</td>
<td>1</td>
<td>B</td>
</tr>
<tr>
<td>8</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>Not stated</td>
<td>2</td>
<td>B</td>
</tr>
<tr>
<td>9</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>++</td>
<td>Not stated</td>
<td>1</td>
<td>B</td>
<td>B</td>
</tr>
<tr>
<td>10</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>12 g</td>
<td>1</td>
<td>B</td>
</tr>
<tr>
<td>11</td>
<td>+++</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>Not stated</td>
<td>3</td>
<td>M</td>
</tr>
<tr>
<td>12</td>
<td>++</td>
<td>+</td>
<td>++</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Not stated</td>
<td>2</td>
<td>M</td>
</tr>
<tr>
<td>13</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>39 g</td>
<td>2</td>
<td>B</td>
</tr>
<tr>
<td>14</td>
<td>++</td>
<td>+</td>
<td>++</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Not stated</td>
<td>1</td>
<td>B</td>
</tr>
<tr>
<td>15</td>
<td>+++</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>13 g</td>
<td>1</td>
<td>B</td>
</tr>
<tr>
<td>16</td>
<td>++</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>95 g</td>
<td>2</td>
<td>B</td>
</tr>
<tr>
<td>17</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>173 g</td>
<td>2</td>
<td>M</td>
</tr>
<tr>
<td>18</td>
<td>++</td>
<td>+</td>
<td>++</td>
<td>–</td>
<td>++</td>
<td>Not stated</td>
<td>164 g</td>
<td>2</td>
<td>M</td>
</tr>
<tr>
<td>19</td>
<td>++</td>
<td>+</td>
<td>++</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>1400 g</td>
<td>3</td>
<td>M</td>
</tr>
<tr>
<td>20</td>
<td>+++</td>
<td>+</td>
<td>++</td>
<td>–</td>
<td>++</td>
<td>189 g</td>
<td>3</td>
<td>M</td>
<td>M</td>
</tr>
<tr>
<td>21</td>
<td>+++</td>
<td>+</td>
<td>++</td>
<td>–</td>
<td>+</td>
<td>Not stated</td>
<td>1</td>
<td>B</td>
<td>B</td>
</tr>
<tr>
<td>22</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Not stated</td>
<td>1</td>
<td>B</td>
</tr>
<tr>
<td>23</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>55 g</td>
<td>2</td>
<td>B</td>
</tr>
<tr>
<td>24</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>308 g</td>
<td>2</td>
<td>B</td>
</tr>
<tr>
<td>25</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>13 g</td>
<td>1</td>
<td>B</td>
</tr>
</tbody>
</table>

+, mild; ++, moderate; ++++, severe.

*1, < 5 cm; 2, 5–9 cm; 3, > 10 cm.

B, benign; M, malignant.
years (n = 2), 1 year (n = 2), and < 1 year (n = 1) of follow up.

**Discussion**

Adrenocortical tumours comprise less than 0.5% of tumours in children and represent a small percentage of tumours of the adrenal gland. The incidence is reported to vary between 0.3 and 4/1 000 000 children below the age of 15 years, and these tumours are more likely to occur in girls than in boys, as is confirmed by our data. The peak incidence in the present series was under 5 years of age, in accord with previous observations.

More than 95% of adrenocortical tumours in children secrete hormones. In virilising tumours, clinical symptoms are caused by...
hypersecretion of androgens, with resultant pseudosexual precocity in boys and virilisation in girls. Typically, precocious development of pubic hair is seen, together with tall stature, and acceleration of growth rate and bone maturation. In girls enlargement of the clitoris occurs. In boys growth of the phallus contrasts to prepubertal testicular volumes. However, as indicated from our findings in one boy, pubertal testicular volumes may be seen occasionally. This might be a result of androgen stimulation of tubular growth or androgen stimulation resulting in true precocious puberty.

The diagnosis of a virilising adrenocortical tumour depends on the detection of raised markers of androgen secretion in combination with imaging. High concentrations of adrenal androgens, especially DHEA-S, are highly suggestive of a tumour. Assessment of steroid metabolites in 24 hour urine is useful for diagnosis, but principally for follow up of the androgen hypersecretory state. The most frequently detected raised androgens are 11β-hydroxyandrostenedione and DHEA-S. The urine profile analysis becomes normal after successful surgery, whereas recurrence of abnormal urine steroid profiles suggests recurrent tumour activity. However, adrenocortical tumours might show considerable biochemical heterogeneity, and the steroid excretion pattern may change spontaneously.

Certain morphological criteria of malignancy have been proposed in adrenal tumours in adults. These include broad fibrous bands, diffuse growth pattern, vascular invasion, widespread tumour necrosis, > 10 mitoses per high power field, cellular pleomorphism, and capsular invasion. These criteria have been suggested as less reliable in predicting malignant behaviour in children. Furthermore, in the paediatric population, adrenocortical tumours have been considered as predominantly malignant. However, most of the previous reports included tumours with a heterogeneity of hormonal secretion patterns. Our series is the largest population of purely androgen secreting tumours published and the histopathology was uniformly re-evaluated. This might explain why only about a quarter of the patients were diagnosed as having a malignant tumour. Although certain histological features suggest malignancy, such as the presence of numerous mitoses with abnormal forms, widespread necrosis, and broad fibrous bands, these features can also be found in some benign tumours. Paediatric benign tumours, both in our experience and in that of others, have been considered as less reliable in predicting malignant potential. In the future, studies targeting cellular oncogenes and tumour suppressor genes may provide tumour markers useful in the clinical assessment of the malignant potential of androgen secreting tumours in children. It has been reported that malignant adrenal tumours do not express major histocompatibility complex class II antigens, whereas most benign tumours do; but it is not yet clear whether this observation is clinically relevant.


Androgen secreting adrenocortical tumours

O D Wolthers, F J Cameron, I Scheimberg, J W Honour, P C Hindmarsh, M O Savage, R G Stanhope and C G D Brook

Arch Dis Child 1999 80: 46-50
doi: 10.1136/adc.80.1.46

Updated information and services can be found at:
http://adc.bmj.com/content/80/1/46

These include:

References
This article cites 21 articles, 3 of which you can access for free at:
http://adc.bmj.com/content/80/1/46#BIBL

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Topic Collections
Articles on similar topics can be found in the following collections

Reproductive medicine (945)
Sexual health (352)
Oncology (777)

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/