Adrenocortical tumours in children: our experience with nine cases

CACCIARI E., CICOGNANI A., PIRAZZOLI P., PAOLUCCI G.*, MANCINI A.*, TASSINARI D., PASCUCCI M.G., TACCONI M.

Clinica Pediatrica II and Clinica Pediatrica III*, University of Bologna, Italy.

Abstract

Nine cases of adrenocortical tumor are presented, six were males. Four were less than three years and five were between 5 and 10 years of age. Clinical virilization was found in 8 children, one had only signs of hypercortisolism and another showed signs of virilization and hypercortisolism simultaneously. Urinary 17-KS and 17-OHCS were high in all patients. Plasma levels of testosterone and of the other adrenal androgens were high in all the cases tested. Plasma level of cortisol was elevated only in few cases. In two out of five cases steroids were only partially suppressed by dexamethasone. Computed tomography and abdominal sonography have been useful tods for the localization of the tumour. The resection of the tumour, independent of hystopathological diagnosis, led to a complete normalization of the clinical and hormonal picture in eight cases evaluated at a distance of 2 months 10 years after surgery. In one case a hepatic metastasis was observed and removed three years after surgery.

Adrenocortical tumours are rare (Javadpour et al., 1980) and the vast majority of them are hormone secreting. Although cases have been described which showed feminilization and hyperaldosteronism (Bacon & Lowrey, 1965; Bhettay & Bormici, 1977; Crane et al., 1961; Gauguly et al., 1980), virilization and hypercortisolism are most commonly found (Hayles et al., 1966).

This paper illustrates our experience with nine cases of adrenocortical tumour, eight of whom showed inappropriate virilization with or without hypercortisolism and one of whom was a classic case of Cushing's syndrome.

Methods and Case Reports

Plasma testosterone, estradiol, Δ4-androstenedione, dehydroepiandrosterone (DHA) and Dehydroepiandrosterone sulphate (DHA-S) were assayed with a RIA method (Cacciari et al., 1974; Cacciari et al., 1980).
Plasma cortisol was assayed using a commercial RIA kit (Corning). Urinary 17-OHCS were assayed according to Porter and Silber reaction (Silber & Porter, 1954). Urinary 17-KS were evaluated according to the modified method of Zimmerman (Medical Research Council, 1963). The corticotropin suppression test was performed by dexamethasone administration (0.5 mg every 6 hours for 4 days). Bone age was evaluated according to Greulich and Pyle (1950). The pituitary reserve of gonadotropins was evaluated by means of an LHRH test. Gonad volume in males was measured using Prader's orchimeter (Prader, 1966).

Case no. 1: C.F. was a four month old infant seen by us in 1975. This child had rapidly increased in weight and height over the last three months and was of a decidedly Cushing-like appearance. Urinary 17-KS and 17-OHCS in particular were high (Tab. I). Routine laboratory data, including electrolytes, were normal. Urography revealed that the upper pole of the right kidney was compressed and displaced downwards by a mass originating in the suprarenal region. During surgery, the right kidney and adrenal were removed. The adrenal gland appeared as a mass 7 cms long and 5 cms wide affecting both the upper renal pole and the hilar region. The pathological diagnosis was carcinoma of the adrenal gland. After surgery, the patient returned to normal, clinically and endocrinologically. This child underwent no course of therapy and is now 10 years old and in good health.

Case no. 2: B.A. was seven months old when seen in 1977. For the previous month she had shown development of pubic hair and clitoromegaly. Bone age was 10 months and height and weight were at the 50th and 97th centile respectively according to Tanner's tables (Tanner et al., 1966). Urinary 17-KS and 17-OHCS were high, as was plasmatic testosterone (Tab. I). Plasmatic estradiol and cortisol were normal as were routine laboratory tests including electrolytes. Blood pressure was normal. An LHRH test showed gonadotropin values below normal. Urography showed that the left kidney had shifted in a lateral and downwards direction due to a roundish mass, the size of a large mandarin orange. During surgery, a roundish mass, 6 cms in diameter and well-encapsulated, was removed from the left adrenal region. Hystological tests led to a diagnosis of adrenal adenoma. After surgery, urinary 17-KS and 17-OHCS, and plasma testosterone values reverted to normal while LHRH indicated a normal pituitary reserve of gonadotropins. Six years later, the endocrinological picture was normal while clitoromegaly and small hairs on the labia majora were still present. Bone age had increased by one year, while height and weight were at the 50th centile.

Case no. 3: M.M. was a male, aged 2.5 years who, since the very first months of life, had shown development of pubic hair and an increase in penis volume. When seen by us in 1977, the subject showed PH3, a penis 5 cms in length, testicles with a volume of 1.5 ml and pigmentation of the genitals. Bone age was 3.5 years, height and weight were at the 75th and 50th centile respectively. Urinary
17-KS and 17-OHCS and plasma testosterone were high. Plasma cortisol and routine tests were normal.

Blood pressure was normal. A dexamethasone suppression test led to an unsatisfactory decrease in 17-KS, 17-OHCS and testosterone. An LHRF test showed a low pituitary reserve of gonadotropins. Urography showed a small mass the size of a large chestnut at the level of the left adrenal gland. During surgery, an encapsulated mass 5 cms in diameter was removed. Hystological examination led to a diagnosis of adrenal adenoma. After surgery, 17-KS, 17-OHCS and testosterone reverted to normal. Over the next few months, the large pubic hairs disappeared while this area retained residual pubic hair and the pigmentation disappeared from the genitals. Seven years later, bone age had advanced by 2.5 years and height and weight were at the 75th and 50th centile respectively. The endocrine picture was normal.

Case no. 4: U.M. was a 7 year-old male seen by the family doctor since for several months this subject had had an increase in penis volume, development of pubic hair and acne located generally on the face. The subject showed PH3, a penis 9 cms in length, acne of the face and stature and weight at the 90th and 75th centile respectively. Bone age was 10 years. Testicular volume was prepubertal (1 ml). Urinary 17-KS and 17-OHCS were high and did not decrease after dexamethasone administration. Blood pressure was 140/90. Routine tests were normal. Abdominal sonography showed a mass in the area of left adrenal gland. Surgery led to the removal of a roundish encapsulated mass with a stalk which did not affect the kidney. Hystopathologic diagnosis was adrenal carcinoma. Radiotherapy was performed to a total of 2500 rad. After surgery, 17-KS, 17-OHCS, testosterone and blood pressure reverted to normal. Eight months later, the patient still showed residual pubic hair and no change in penile size. The endocrine picture was normal and bone age and the auxological picture had undergone only slight modification. The patient has not returned.

Case no. 5: I.R. was a female aged 5.16 years when seen by us. For some time her weight had increased considerably and hair had developed on the pubis, armpits, face and back. The subject had slight clitoromegaly. Bone age was 10 years and height and weight were at the 25th and 97th centile respectively. Urinary 17-KS and 17-OHCS, plasma testosterone and cortisol were high and did not decrease after dexamethasone.

Blood pressure was 125/90 and routine tests were normal. Urography showed that the right kidney was lower than normal and that in the adrenal region on the same side there was a roundish mass the size of a table tennis ball. Abdominal aorthography confirmed that in the right adrenal region there was a mass vascularized by branches of the adrenal artery. Surgery was performed and the right adrenal and an encapsulated mass 3.5 cms in diameter, weighing 14 g, were removed. Hystopathology led to a diagnosis, albeit with some doubt, of adrenal carcinoma. After surgery, 17-KS, 17-OHCS, testosterone and cortisol values reverted
to normal. Six months after surgery there was a clearly-marked decrease in hirsutism and weight, bone age was 10.5 years, height and weight were at the 45th and 25th centile respectively and the endocrinological picture was normal. At the age of 6.6 years hairs remained only on the pubis while initial breast development was evident and pelvic ecography showed an increase in uterine and ovarian volume. An LHRH test showed a pituitary reserve of gonadotropins of pubertal type. Bone age was 11 years. Height and weight were at the 50th and 30th centile respectively. Treatment with cyproterone acetate was started.

3.5 years after surgery, at the age of 8.8 years, the child was generally in good health with a bone age of 12.5 years and height and weight at the 50th and 30th centile respectively. Treatment with cyproterone acetate was suspended. Various tests were performed and excluded re-onset of tumoral activity. Five years after surgery there has been no re-appearance of the disease.

Case no. 6: V.A., a 2.5 year-old male, was brought to our department since over the previous few months he had shown an increase in penis volume, pubic hair had appeared and there had been a rapid increase in height and weight. The subject had PH₃, a testicular volume of 3 ml and penis 6 cms long. Bone age was 5.5 years while height and weight were above the 97th centile. Blood pressure and routine tests were normal. Urinary 17-KS and 17-OHCS, and plasma testosterone were high and were modified only partially after the dexamethasone suppression test. Urography revealed the left kidney deviated outwards due to a mass originating in the upper pole. Abdominal sonography of the kidney region confirmed the suspicion of a left adrenal neoplasia. During surgery, an encapsulated mass was removed from the above region. This weighed 190 grs and extended onto the anterior surface of the kidney. Two small lymph nodes were also removed. The kidney had not been infiltrated by the tumour. The hystopathological diagnosis was adrenal carcinoma. After surgery, 17-KS, 17-OHCS and testosterone reverted to normal. One year after the operation, hypertrophy of the penis was still present while pubic hair had disappeared. Bone age was 7 years and height and weight were at the 97th centile. The endocrinological picture was normal. 2.5 years after surgery there has been no sign of a re-onset of the disease.

Case no. 7: C.G., a female, was seen by us at the age of 9.8 years with rapid development over the previous few months of hair on the pubis and armpits, clitororomegaly and breast development. Bone age was 12 years, height and weight were at the 50th centile, while urinary 17-KS and 17-OHCS, plasma testosterone, 4 androstenedione, DHA, DHAS were high. Routine tests, plasma cortisol and blood pressure were normal. Abdominal sonography of the adrenals indicated a large mass in the right adrenal region which was compressing the liver. Abdominal aortography and CT confirmed the presence of a mass in the adrenal region. Hepatic scintigraphy showed a cold area in the posterior right zone. An adrenal mass on the right side, 17 x 7 cms in diameter, infiltrating the caudo-posteral sur-
face of the right lobus of the liver was removed during surgery. The hepatic tissue infiltrated by the tumour was removed. Hystopathology led to a diagnosis of adrenal carcinoma extending to hepatic tissue. After surgery, 17-KS, 17-OHCS and testosterone, Δ4 androstenedione DHA, DHAS values reverted to normal. Hepatic scintigraphy did not show the cold area apparent during the previous test. Two years after surgery, at a chronological age of 12 years, this subject had a bone age of 15 years, PH4, B4 and an adequate endocrinological picture. Height and weight were at the 50th centile. Ecography and scintigraphy indicated no signs of re-onset of the disease. Three years after surgery, testosterone level was 80 ng/dl, urinary 17-OH and 17-OHCS were 13.5 and 11.7 mgs/24 hours respectively. Hepatic scintigraphy showed a small, cold, roundish area at the posterior edge of the right lobus. This was confirmed by CT. A small mass the size of an apricot situated in the posterior zone of the right lobus was removed during surgery. Hystopathological diagnosis was metastasis of an adrenal carcinoma. Six months after the patient is apparently in good health.

Case no. 8: L.D. was an 8.8 year-old male who over the previous three years had shown a development of hair on the pubis and armpits and an increase in penis volume. When seen by us, this subject had PH4, gynecomastia, armpit hair, a penis 6 cm long and testicular volume of 2.5 ml. Height age was 13 years, bone age 14 years and weight age 12 years. Blood pressure was 120/70. Routine tests were normal. Pituitary reserve of gonadotropins was of prepubertal type. Urinary 17-KS and 17-OHCS, plasma testosterone and DHAS were high. Urography indicated an increase in volume of the right adrenal gland which seemed to compress the upper pole of the kidney. Abdominal sonography and CT confirmed the suspicion of a tumour of the right adrenal gland. During surgery, an adrenal weighing 30 grs with a nodule 3.5 cm in diameter was removed. Hystopathological diagnosis was adrenal adenoma. After surgery, testosterone, DHAS, 17-KS and 17-OHCS reverted to normal. Four months later, the patient showed an increase in testicular volume (4.5 ml), in plasmatic testosterone (420 ng/dl) and in the pituitary reserve of gonadotropins. Nine months after surgery the patient has a chronological age of 9.6 years, bone age of 14.5 years, height age of 13.5 years, PH4, testicular volume of 8 ml and weight age of 12.5 years. DHAS was normal. All other investigations confirmed that there was no re-onset of the disease. This subject underwent surgery at the age of 3 years due to pulmonar congenital stenosis.

Case no. 9: C.G. is a male, 6.4 years of age when his parents reported that over the previous few months pubic hair had appeared and penis volume had increased. When seen by us, he had a height age of 10 years, bone age of 13 years, weight age of 12 years and PH3. The pituitary reserve of gonadotropins was very low. Testicular volume was 5 ml and penis length 6 cms. Blood pressure was 120/75. Urinary 17-KS and 17-OHCS, plasma testosterone and DHAS were high and were not modified after dexamethasone suppression
Table I. Hormonal data in 9 children with adrenocortical tumours gland.

<table>
<thead>
<tr>
<th></th>
<th>CASE No.</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td><strong>URINE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17-KS (mg/dl)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative</td>
<td>4.6</td>
<td>6.8</td>
<td>6.5</td>
<td>33</td>
<td>50</td>
<td>135</td>
<td>74.2</td>
<td>24.8</td>
</tr>
<tr>
<td>Suppression</td>
<td>2.4</td>
<td>57</td>
<td>41.5</td>
<td>80</td>
<td></td>
<td>1.7</td>
<td>2</td>
<td>1.2</td>
</tr>
<tr>
<td>Postresection</td>
<td>0.8</td>
<td>1</td>
<td>0.7</td>
<td>2</td>
<td>1.1</td>
<td>1.7</td>
<td>2</td>
<td>1.2</td>
</tr>
<tr>
<td>17-OHCS (mg/dl)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative</td>
<td>15.0</td>
<td>4.7</td>
<td>7.1</td>
<td>7</td>
<td>18.5</td>
<td>7.6</td>
<td>101</td>
<td>6.10</td>
</tr>
<tr>
<td>Suppression</td>
<td>3.2</td>
<td>5.3</td>
<td>22.7</td>
<td>2.9</td>
<td></td>
<td>1.6</td>
<td>7</td>
<td>2.3</td>
</tr>
<tr>
<td>Postresection</td>
<td>0.9</td>
<td>0.8</td>
<td>1.9</td>
<td>2.6</td>
<td>0.5</td>
<td>1.6</td>
<td>7</td>
<td>2.3</td>
</tr>
<tr>
<td><strong>SERUM</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Testosterone (ng/dl)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative</td>
<td>531</td>
<td>213</td>
<td>190</td>
<td>260</td>
<td>68</td>
<td>90</td>
<td>48</td>
<td>1453</td>
</tr>
<tr>
<td>Postresection</td>
<td>19</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>14</td>
<td>30</td>
<td>15</td>
<td>33</td>
</tr>
<tr>
<td>Cortisol (ng/dl)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative</td>
<td>148</td>
<td>80</td>
<td>300</td>
<td>190</td>
<td>136</td>
<td>210</td>
<td>150</td>
<td></td>
</tr>
<tr>
<td>Postresection</td>
<td>88</td>
<td>97</td>
<td>53</td>
<td>191</td>
<td>180</td>
<td>260</td>
<td>240</td>
<td></td>
</tr>
</tbody>
</table>
test. Plasma cortisol was normal, as were routine tests. Urography indicated a lowering of the left kidney, the upper pole of which was compressed by a large mass. Abdominal sonography and CT confirmed the presence of a roundish mass in the left adrenal region. During surgery, an adrenal tumour weighing 130 gr was removed. The hystopathological diagnosis was adrenal adenoma. After the operation, 17-KS, 17-OHCS testosterone and DHAS reverted to normal. Blood pressure was 105/70. Two months later, there have been no signs of a re-onset of the disease.

Results

Four of our cases were seen by us when they were under 3 years of age, and five between 5 and 10 years of age. The clearest symptom in all the patients was virilization except in case no. 1 who was decidedly cushingoid in appearance and in case no. 5 who simultaneously showed important signs of virilization and of hypercortisolism. Urinary 17-KS and 17-OHCS (Tab. I) were high in all patients. 17-KS were decidedly higher in cases 4-5- 6-8-9 while 17-OHCS were clearly higher in case no. 1. In two (no.s 3 and 6) of the 5 cases tested, steroids were seen to be partially suppressed by dexamethasone. Resection of tumour was seen to lead to a cure and the hormone picture reverted to normal in eight cases evaluated at a distance of 2 months to 10 years after surgery. In case no. 7, three years after surgery, a hepatic metastasis was observed and removed. All cases underwent cortisone therapy before and after surgery.

Discussion

Since 1865, when there was the first description of a child with a tumour of the adrenal gland (Ogle, 1865), approximately 300 cases have been reported up to the present moment in time (Lee et al., 1985). This demonstrates that this tumour is remarkably rare during childhood. Six of our nine patients were males and this contrasts with the distribution between the sexes encountered previously, whether in the case of children (Hayles et al., 1966) of adults (Didolkar et al., 1981). One of our cases (no. 8), showed a congenital stenosis of the pulmonary artery, confirming the frequent association of tumours of the adrenals with other congenital abnormalities (Fraumeni & Miller, 1967; Haicken et al., 1973; Wiedemann, 1983). The extremely early onset of the tumour in two of our patients (no.s 1 and 2) leads us to suspect that, at least in some cases, tumours of the adrenal gland may be of congenital origin. Weight is added to this hypothesis by the hystopathological picture of several tumours which showed a clear resemblance with adrenal fetal tissue (Dluhy et al., 1971; Hillman, 1972).

In evaluating the clinical picture emerging from our cases, several observations may be made. Signs of virilization are frequently of rapid onset whether hypercortisolism is present or not. The signs of virilization, which are almost always present, are rapid growth rate acne, pubic and facial hair, hypertrophy of the penis.
or clitoromegaly, while development of armpit hair is rarely encountered. In our youngest female (no. 2), as in the females described by other Authors (Lee et al., 1985) no "posterior labial fusion" was noted, which leads us to think that in the case of tumour of the adrenal gland, significant exposure to androgens during fetal life is improbable. As others have already reported (Lee et al., 1985; Drafo et al., 1979), one of our cases (no. 6) presented an increase in testicular volume, probably due to stimulation of tubular tissue by the hyperproduced adrenal androgens.

The features typical of Cushing's syndrome are moon facies, drastically-reduced growth rate and obesity. When the syndrome is due to tumour of the adrenal gland, the anabolizing effect of the androgens masks this picture and obesity and moon facies may be associated with an increase in physical growth. In our case no. 1, the anabolizing effect of the androgens was clearly prevalent with respect to hypercortisolism: the latter appeared to have the effect of stunting growth in case no. 5. Another characteristic effect of the androgens produced by the adrenal tumour is the acceleration of bone maturation present in all cases and which was particularly rapid in some of our patients. Despite hystopathology leading to a diagnosis of malignant tumour in many of our patients, none of them showed the characteristic signs of cachexia. It may be reasonably supposed that in this case also, it is the high levels of circulating androgens which mask this effect of the tumour.

As regards diagnosis, our experience allows us to observe that every inappropriate and progressive sign of virilization in a child must lead us to suspect the presence of a tumour of the adrenal gland, particularly if signs of hypercortisolism are also evident. An evaluation of the auxological picture, bone age, blood pressure, hormonal state, x-ray, C.T., ultrasound and, if necessary, scintigraphic examination will allow the case to be put into the proper perspective. Whenever virilization is present, with or without hypercortisolism, testosterone level is always high and hence the assay of this hormone is fundamental. This has also been indicated by the experience of Others (Lee et al., 1985; Bauman & Beumian, 1982; Gabrilove et al., 1982).

The high levels of this androgen are probably due as much to the peripheral transformation of adrenal androgens as to direct production by the tumour (Saez et al., 1967; Saez et al., 1971). Furthermore, it is necessary to emphasize that in literature there are numerous cases of tumour of the adrenals characterized by feminilization (Halmi & Lascari, 1971; Comite et al., 1984).

In two of our cases (no.s 3 and 6) adrenal secretion appears partially suppressed after administration of dexamethasone. This confirms the results achieved by Others (Martin, 1962) and is a warning that careful interpretation is required in this test which, furthermore, allows us to differentiate between tumour and adrenal hyperplasia in the great majority of cases. We also find it interesting that in our case no. 7 hepatic scintigraphy appeared useful before surgery in order to identify the tissue affected.
Therapy is essentially based on surgery, involving the kidney (no. 1) the liver (no. 7) and the lymph nodes (no. 6). The macro and microscopic features of a tumour do not always allow a malignant tumour to be distinguished from a benign one. Indeed, it can happen that a benign tumour becomes manifest with an infiltration of the capsule and shows considerable pleomorphism upon histology (no.s 3 and 8) (Lee et al., 1985; Hough et al., 1979). The cortisol secretion may lead to the suppression of the function of the other adrenal gland. This makes replacement therapy with cortisone during the perioperative phase necessary. A few days' treatment has always appeared to be sufficient. A careful check of blood pressure and electrolytes allowed us to exclude the usefulness of treatment with mineralocorticoids, which, indeed, was considered necessary in a few cases described by other Authors (Lee et al., 1985). Radiotherapy was performed only on one of our cases (no. 4). It is a fact that there are no clear indications in literature (Lee et al., 1985) for this treatment and therefore, it cannot be used freely. Chemotherapy has been used mainly with adults and has not produced satisfactory results (Sullivan et al., 1978; Hag et al., 1980; Hoffman & Mattox, 1972). We have never been in a situation in which we found it necessary (metastases which could not be chirurgically removed or hormonal hyperproduction following resection of a tumour).

Finally, as regards prognosis, there is clear disagreement between recent data and that of over 10 years ago. Very many of the patients described recently have in fact had a good prognosis, unlike subjects described in the past, most of whom did not survive for more than two years. It may be that older patients died due to complications following surgery or to inadequate replacement therapy. The one case we saw (no. 7) who had a hepatic metastasis, which was easy to remove, three years after surgery, is now, 6 months later, in good health. The other eight patients have shown no sign of re-onset of the disease at 2 months to 10 years of follow-up. This leads us to believe that tumours of the adrenals in children may have a benign evolution despite their frequently appearing malignant from a hystopathological point of view.

References


Medical Research Council (Great Britain) (1963): Lancet I:1415.


Ogle JW (1865): Unusually large mass of carcinomatous deposit in one of the suprarenal capsules of a child. Trans Pathol Soc Lond 16: 250.


