Familial Congenital Adrenal Hypoplasia

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Congenital adrenal hypoplasia was first described by Sikl (1948). Other reports appeared, and Mitchell and Rhaney (1959) recorded the first occurrence in a male sibling and suggested a familial basis. Boyd and MacDonald (1960) reported the necropsy findings in another pair of brothers who died in the neonatal period.

The following report presents two further pairs of brothers born in Scotland who are thought to have familial congenital adrenal hypoplasia. All four cases developed symptoms of adrenal insufficiency in the neonatal period. One of each pair died and necropsy was performed. Both surviving children received steroids for a period, fare reasonably well for some time after withdrawal of steroids, but presented with Addisonian findings in later childhood.

Case Reports

Case 1. This boy was referred at the age of 5 years and 5 months to Stobhill Hospital, Glasgow, in 1965, with a two-month history of loss of energy.

Past history. The child had been admitted to Stobhill Hospital in 1959 at the age of 3 weeks. After a normal pregnancy and home delivery, his birthweight was 4-8 kg. He subsequently refused his feeds and lost weight, but vomiting was not an initial feature and he was not dehydrated. 10 days later, however, vomiting and dehydration appeared. The plasma urea was 80 mg./100 ml., chloride 104 mEq/l., sodium 139 mEq/l., and potassium 7-8 mEq/l.

He was treated with intravenous N/4 saline dextrose and hydrocortisone, followed by cortisone acetate orally. The urinary 17-ketosteroids were excreted at a level of 0-2 mg./24 hr., and a tentative diagnosis of congenital adrenal hyperplasia was, therefore, abandoned. Cortisone treatment was stopped after 12 days and the child's subsequent progress was entirely satisfactory. Plasma chemistry when last seen aged 1 month: urea 50 mg./100 ml., chloride 104 mEq/l., sodium 137 mEq/l., potassium 5-0 mEq/l.

Family history. He had 3 live sisters and 5 live brothers. His parents were unrelated. There had also been 2 stillbirths before the birth of the patient, and a younger brother (Case 2) had died in infancy. Of the living members of the family, father had been successfully treated for a patent ductus arteriosus and one child suffered from asthma. All others were well and there was no history of similar disorders. Serum electrolytes on all other members of the family were normal.

Examination. The striking feature was bronze pigmentation around, but not inside, the mouth, and in the flexural areas of the elbows and knees. His blood pressure was 100/60 mm. Hg, and systematic examination was negative. He weighed 17-2 kg. and was 100 cm. in height, both being less than the expected, particularly the latter.

Investigation. Urinalysis, chest x-ray, blood picture, electrocardiography were all normal. Serum urea 55 mg./100 ml.; sodium 113 mEq/l.; potassium 5-2 mEq/l.; chloride 93 mEq/l.; calcium 10-6 mg./100 ml.; protein 7-6 g./100 ml.; inorganic phosphate 4-5 mg./100 ml.; alkaline phosphatase 16 KA units. Bone age normal (wrists); fasting blood sugar 138 mg./100 ml.; urine urea 1 g./100 ml.; urine amino acid chromatogram normal. X-ray of abdomen showed no adrenal calcification.

Protein-bound iodine 5-5 µg./100 ml. Thyroid precipitin test negative. Tanned red cell agglutination test negative. Adrenal antibodies negative (Dr. John Anderson, Western Infirmary, Glasgow).

Other investigations of adenocortical function are shown in Tables I and II.

Progress and treatment. Cortisone acetate 12-5 mg. b.d., and fluocortisone 0-05 mg. daily were given. His serum electrolytes rapidly returned to normal, there was a marked improvement in general wellbeing, and subsequent progress was entirely satisfactory.

Case 2. (Brother of Case 1.) Born in 1963; birthweight 3-6 kg. (details kindly supplied by Professor J. H. Hutchison).

The baby was slow to establish respiration but thereafter progressed normally until the 4th day when he became reluctant to feed. Moderate dehydration developed and was accompanied by a rise in serum potassium and chloride. High urinary chlorides suggested adrenal insufficiency, but he died suddenly and unexpectedly at the age of 11 days before investigation was undertaken or treatment was begun.

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<table>
<thead>
<tr>
<th>TABLE I</th>
<th>Urinary Excretion of Steroid Metabolites (mg./24 hr.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>17-KS</td>
</tr>
<tr>
<td>Basal 1</td>
<td>1·7</td>
</tr>
<tr>
<td>Basal 2</td>
<td>0·7</td>
</tr>
<tr>
<td>Basal 3</td>
<td>1·1</td>
</tr>
<tr>
<td>ACTH I.M. 20 units b.d. x 4 days</td>
<td>1·5</td>
</tr>
</tbody>
</table>

Necropsy. This showed abnormally small adrenal glands, each measuring approximately 1 x 0·4 cm. Histologically both glands consisted entirely of large cells, with abundant eosinophilic cytoplasm and nuclei of variable size. There was no suggestion of zonal differentiation. The appearances were those of bilateral agenesis of the adrenal cortex.

Case 3. This child, born in 1960, birthweight 4·1 kg., was the product of a normal pregnancy and delivery. His condition was satisfactory at birth, but he subsequently began to lose weight and to vomit, and at 2 weeks was transferred to the Royal Hospital for Sick Children, Edinburgh.

Family history. Both parents were well. Their first child had been born with spina bifida and lived 18 days, the second was born prematurely and died on the third day. The third, a boy, remained well, and the child immediately preceding the patient (Case 4) died in the neonatal period.

Examination. Moderate dehydration was present, and peristalsis was easily seen over the abdomen. No pyloric tumour could be felt. The external genitalia were normal.

Investigation. Urinalysis, blood picture, chest x-ray, and x-ray of abdomen were normal. Blood urea nitrogen 39 mg./100 ml., serum sodium 143 mEq./l., chloride 86 mEq./l.; successive estimations of serum potassium were 8·8, 10·4, and 10·5 mEq./l.

Progress and treatment. These findings, together with the brother's earlier death from adrenal hypoplasia, prompted immediate treatment with intravenous saline and cortisone acetate. His condition improved rapidly and 3 days later he was feeding well, was no longer dehydrated, and was gaining weight. At age 7 weeks the 24-hour urinary 17-KS output was 0·14 mg./day. When 11 weeks old he was discharged on cortisone acetate 10 mg. b.d. with 1 g. NaCl b.d.

During the subsequent 2 years there were four readmissions to hospital precipitated by various upper respiratory tract infections and each covered by an increased dose of steroid. At 2 years steroids were withdrawn altogether. When assessed 2 months later a Thorne test showed a 50% fall in eosinophils after 20 units of intravenous ACTH, which was taken to signify a satisfactory adrenal response.

Adrenal function was reassessed further when he was aged 5. A single I.M. dose of ACTH—10 mg./kg. raised the 24-hour urinary output of 17-OHCS metabolites from 3·9 to 8·5 mg. This response was considered adequate and he was left without treatment. Height, weight, and bone age were normal, as was the urinary pregnanetriol of 85 μg./24 hours.

Aged 7 years, he was readmitted to the Royal Hospital for Sick Children in typical Addisonian crisis, with vomiting, lethargy, Addisonian pigmentation, and blood pressure 75/50 mm. Hg. No precipitating cause could be found. The blood urea nitrogen was 40 mg./100 ml.; serum sodium 124 mEq./l.; potassium 6·2 mEq./l.; chloride 88 mEq./l.; CO₂ combining power 22·5 mEq/l. He was treated with intravenous saline and hydrocortisone, with rapid improvement, and was discharged taking cortisone acetate 10 mg. b.d., and added salt 4 g./day.

Case 4. (Brother of Case 3.) This baby born in 1958 at 42 weeks' gestation at the Eastern General Hospital, Edinburgh, after a normal pregnancy and delivery, weighed 3·05 kg., and thrived successfully for the first 16 days of life. On the 17th day he was admitted to the Royal Hospital for Sick Children, Edinburgh, with a one-day history of vomiting. He was cyanosed, collapsed, and dehydrated; visible peristalsis was present, but no pyloric tumour or other abdominal masses were felt. Intestinal obstruction was suspected on plain x-ray examination of the abdomen. He was rehydrated with intravenous saline, and his condition rapidly improved. No further measures were undertaken, but he died suddenly and unexpectedly on the 23rd day of life.

Necropsy (Dr. A. D. Bain). The body was that of a male infant weighing 3·1 kg., poorly nourished but with no external abnormalities.

Both adrenals were exceedingly small, their combined weight being 0·68 g. The testes and thyroid showed no naked eye abnormality, nor did the pituitary.

Microscopic examination of the adrenal cortices showed that they were composed of cells larger than normal and not infrequently vacuolated. The cell nuclei were large and irregular in shape (Fig. 1). The pituitary was normal.

Discussion

The precise diagnosis of congenital adrenal hypoplasia ultimately depends on necropsy. The
association of adrenal hypoplasia and anencephaly has been known for a long time. Angevine (1938), in reviewing a series of anencephalics, described adrenal changes and pointed out that the association was recognized by Mechel as long ago as 1812. Similar changes are described in congenital absence of the pituitary gland, with involvement of the testes and thyroid (Blizzard and Alberts, 1956; Brewer, 1957; Reid, 1960), and Mosier (1956) reported the occurrence in a pair of sibs. The adrenal histology in these cases shows good development of the adult cortex with zonal differentiations, but conspicuous reduction or absence of the fetal cortex.

By contrast, the histological findings in the adrenal cortices of Cases 2 and 4 presented here, showed the glands to be composed of large cells, irregularly arranged, with eosinophilic cytoplasm, vacuolation, and variable size of nuclei. These findings resemble those cases previously described, both familial (Mitchell and Rhaney, 1959; Boyd and MacDonald, 1960) and sporadic (Sikl, 1948; McMahon, Wagner, and Weiner, 1957; Harlem and Myhre, 1957), in which no pituitary abnormality was noted. Macgregor (1960) also made this histological distinction while recognizing a grossly macroscopical similarity in the adrenals.

A description of congenital adrenal hypoplasia occurring in 2 sisters with associated pituitary abnormalities appeared in 1965, but the subsequent review of the literature did not differentiate between the two types of adrenocortical histology (Roselli and Barbosa, 1965).

Two reports have also been published on familial glucocorticoid deficiency without hypoaldosteronism. Shepard, Landing, and Mason (1959) found two sisters, the first of whom died at 30 months, showing pigmentation, weakness, and convulsions. Necropsy revealed small adrenals, and cells of the zona fasciculata and reticularis were absent, but clumps of cells remained in the zona glomerulosa. Because both acidophilic and basophilic cells in the pituitary were scanty, the authors suspected a primary fault at that level. Her sister was shown to have a selective glucocorticoid deficiency with retention of normal electrolyte balance and normal aldosterone production. Two brothers were described by Stempfel and Engel (1960). The first died in the neonatal period and the adrenals were completely absent. The surviving brother showed signs of adrenal insufficiency shortly after birth and he was given cortisone. Subsequent investigation at the age of 3½ years again suggested impaired cortisol but normal aldosterone production. He had, however, received cortisone throughout the interim period.

The diagnosis of familial congenital adrenal hypoplasia in life, therefore, depends on the demonstration of adrenal insufficiency in a child who is known to have, or subsequently has, a sib in whom the typical histological pattern of adrenal hypoplasia is found.
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Associated familial syndromes in children with Addison's disease include spastic paraplegia (Harris-Jones and Nixon, 1955) and cerebral sclerosis (Fanconi et al., 1963).

None of the above associations was found in either of the surviving children, and it is suggested that congenital hypoplasia should also be considered in the differential diagnosis of Addison's disease occurring in children after the newborn period.

With regard to aetiology, little can be added to the knowledge of the cause of congenital adrenal hypoplasia, but it does seem useful to recognize two groups, as emphasized by Kerenyi (1961), i.e. primary and secondary. The primary group have no pituitary abnormality apart occasionally from a secondary basophilism, such as was noted by Boyd and MacDonald (1960), and the adrenal histology (Fig. 1) shows persistence of the fetal pattern in the cortex, with cytomegaly, pleomorphism, and irregular arrangement of cells, with eosinophilic and often vacuolated cytoplasm.

It has been tacitly assumed that this group is an instance of primary failure of organogenesis in relation to the differentiation of the adult cortex (Harlem and Myhre, 1957), and there are no associated abnormalities. The secondary group usually show abnormalities of the pituitary involving reduction in number or absence of the eosinophil cells of the anterior lobe, and there are often changes in the thyroid and gonads. Here the cortex, though small, shows good differentiation along the adult pattern (Fig. 2). Mosier (1956) and Angevine (1938) thought that this was the absence of a corticotrophic factor from the eosinophil cells of the pituitary which was the primary defect. However, Winquist (1961) found a case with cortical hypoplasia of the secondary type in which the pituitary seemed normal, and cast some doubt on its role. The proportion of eosinophils in the anterior lobe was 20%, as opposed to the 30% from the figures of Rasmussen (1950) for the newborn.

Table III has been compiled after excluding cases with a definite pituitary abnormality. It can be seen that those cases showing features of primary congenital adrenal hypoplasia, both sporadic (Cases 1, 2, 4, 12, and 14) and familial (Cases 15, 17, 18, from Table II, and Cases 2 and 4 of the present series), are all male, as are the surviving members of the familial examples.

Probably, therefore, the primary type is genetically determined and sex linked.

None of the female cases recorded (Cases 6, 7, 9, 11, and 19) shows the histological pattern of the fetal or primary type, and indeed it is doubtful...
if the cases of Williams and Robinson (8, 9, 10, and 11) should be considered congenital; more probably they were acquired, due to haemorrhage and fibrosis within the gland, as suggested by the authors themselves (Williams and Robinson, 1956). The case of Welsh and Mehlin’s girl (Case 6) is also unusual in that the right adrenal gland was totally absent, and the left, while showing disruption of cortical architecture, had, in addition, extensive medullary haemorrhage (Welsh and Mehlin, 1954). The only other female children reported had histological findings of the secondary type (Weens and Golden, 1955; Winquist, 1961).

Once the diagnosis has been made, it is of the utmost importance to scrutinize subsequent children, particularly males, for the appearance of similar symptoms. The diagnosis may even be suspected from observations of the mother while the child is in utero, in that diminished oestriol output on the part of the mother in the last trimester may result from fetal adrenal abnormalities where the child is either anencephalic (Michie, 1966) or suffers from isolated adrenal hypoplasia (F. Cockburn, 1967, personal communication).

**Summary**

Two further male sibships with congenital adrenal hypoplasia are described. Histological findings from the deceased member of each pair resembled those of previously reported cases in which abnormalities of the pituitary had been excluded. They are considered to represent the primary type of familial congenital adrenal hypoplasia. This condition may be transmitted by a sex-linked genetic mechanism and should, therefore, be considered in subsequent children. Congenital hypoplasia of the adrenals should also be considered in the aetiology of Addison’s disease occurring in later childhood.

My thanks are due to Dr. E. G. Fox for permission to publish details of Case 1, and to Professor J. H. Hutchison and Dr. W. Hamilton for supplying and allowing me to publish details of Case 2. Professor J. O. Forfar and Dr. J. W. Farquhar gave much help and advice in the preparation of the manuscript and also allowed their cases to be published. Dr. A. D. Bain kindly provided the pathological material, and I am additionally grateful to Mr. D. Henry for the photomicrographs.

**References**


TABLE III
Previously Reported Cases of Congenital Adrenal Hypoplasia without Defined Pituitary Abnormality

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Reference</th>
<th>Author's No.</th>
<th>Sex</th>
<th>Previous Steroids</th>
<th>Familial</th>
<th>Available Histology of Adrenals</th>
<th>Pituitary</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Siki (1948)</td>
<td>1</td>
<td>M</td>
<td>No</td>
<td>No</td>
<td>Large irregularly arranged cells</td>
<td>Normal</td>
</tr>
<tr>
<td>2</td>
<td>Deamer and Silver (1950)</td>
<td>1</td>
<td>M</td>
<td>No</td>
<td>No</td>
<td>Large pale irregularly arranged eosinophilic cells</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>3</td>
<td>(Also 5 cases of hyperplasia)</td>
<td>2</td>
<td>M</td>
<td>—</td>
<td>No</td>
<td>[Patient survived]</td>
<td>—</td>
</tr>
<tr>
<td>4</td>
<td>Geppert, Spencer, and Richmond (1950)</td>
<td>1</td>
<td>M</td>
<td>Yes</td>
<td>No</td>
<td>Scattered groups of cells; eosinophilic cytoplasm</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>5</td>
<td>Provenzano (1950)</td>
<td>1</td>
<td>M</td>
<td>Yes</td>
<td>No</td>
<td>Similar to mature gland</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>6</td>
<td>Welsh and Mehin (1954)</td>
<td>1</td>
<td>F</td>
<td>No</td>
<td>No</td>
<td>Right adrenal absent; extensive medullary haemorrhage on left, cortex hypoplastic; with cells showing atrophy; fetal zone not detected</td>
<td>Normal</td>
</tr>
<tr>
<td>7</td>
<td>Weens and Golden (1955)</td>
<td>2</td>
<td>F</td>
<td>No</td>
<td>No</td>
<td>Thin but orderly zona fasciculata and zona reticulosal</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>8</td>
<td>Williams and Robinson (1956)</td>
<td>1</td>
<td>M</td>
<td>—</td>
<td>No</td>
<td>[Patient survived]</td>
<td>—</td>
</tr>
<tr>
<td>9</td>
<td>Williams and Robinson (1956)</td>
<td>2</td>
<td>F</td>
<td>No</td>
<td>No</td>
<td>Death precipitated by heat wave; hypoplastic adrenal cortices showed extensive haemosiderin and calcium deposition</td>
<td>Normal</td>
</tr>
<tr>
<td>10</td>
<td>Williams and Robinson (1956)</td>
<td>3</td>
<td>M</td>
<td>No</td>
<td>No</td>
<td>Well-differentiated hypoplastic cortex; cells not described; calcium and haemosiderin in surrounding fibrous tissue</td>
<td>Normal</td>
</tr>
<tr>
<td>11</td>
<td>Williams and Robinson (1956)</td>
<td>4</td>
<td>F</td>
<td>No</td>
<td>No</td>
<td>Whole cortex consisted of large cells without any distinct arrangement, finely vacuolated and granular cytoplasm</td>
<td>Normal</td>
</tr>
<tr>
<td>12</td>
<td>Harlem and Myhre (1957)</td>
<td>1</td>
<td>M</td>
<td>No</td>
<td>No</td>
<td>Well-formed definitive cortex; cells not described</td>
<td>Normal</td>
</tr>
<tr>
<td>13</td>
<td>Gardner (1957)</td>
<td>3</td>
<td>M</td>
<td>No</td>
<td>No</td>
<td>Not available</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>14</td>
<td>McMahon et al. (1957)</td>
<td>1</td>
<td>M</td>
<td>No</td>
<td>No</td>
<td>Irregularly arranged eosinophilic cells varying in size and shape</td>
<td>Normal</td>
</tr>
<tr>
<td>15</td>
<td>Mitchell and Rhaney (1959)</td>
<td>1</td>
<td>M</td>
<td>No</td>
<td>Yes</td>
<td>Large pleomorphin undifferentiated cells with eosinophilic cytoplasm</td>
<td>Normal</td>
</tr>
<tr>
<td>16</td>
<td>Mitchell and Rhaney (1959)</td>
<td>2</td>
<td>M</td>
<td>—</td>
<td>Yes</td>
<td>[Patient survived]</td>
<td>—</td>
</tr>
<tr>
<td>17</td>
<td>Boyd and MacDonald (1960)</td>
<td>1</td>
<td>M</td>
<td>No</td>
<td>Yes</td>
<td>Cytomegaly in zona fasciculata showing variability in size and staining properties</td>
<td>Increase in basophils</td>
</tr>
<tr>
<td>18</td>
<td>Boyd and MacDonald (1960)</td>
<td>2</td>
<td>M</td>
<td>Yes</td>
<td>No</td>
<td>Absence of fetal zona reticulosa; well-developed zona glomerulosa and fasciculata and unusually prominent \ permanent zona reticulosal</td>
<td>Probably normal</td>
</tr>
<tr>
<td>19</td>
<td>Wingquist (1961)</td>
<td>1</td>
<td>F</td>
<td>No</td>
<td>No</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


Addendum

Since this paper was submitted a further account of congenital adrenal hypoplasia has appeared (Zondek and Zondek, 1968). Two cases were presented, both male, one having a primary or cytomegalic type of cortex, the other being of the adult type. The editor was kind enough to let me see the paper of Dr. O'Donohoe and Professor Holland. Their 2 necropsied cases were felt by the authors to be of the miniature adult type histologically, yet though microscopic examinations of the pituitary are not detailed, there seems to be no gross pituitary, gonadal, or thyroidal abnormality.

These cases are thus similar to those of Winquist, Weens, and Rosselli and Barbosa. Further doubt is being cast on the role of the pituitary alone in this so-called secondary group (assuming the histological distinction is valid), and indeed Jost (1967) has shown the additional importance of the hypothalamus in the development of the adrenal, and the existence of a corticotropin release factor.

It yet remains that the primary or purely cytomegalic type of cortex has so far been described only in male infants with congenital adrenal hypoplasia.

REFERENCES

