Familial Congenital Adrenal Hypoplasia

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Adrenal hypoplasia is an invariable finding in infants with anencephaly. Hypoplastic adrenal glands have been described in infancy associated with congenital hypoplasia of the pituitary gland (Mosier, 1956). Sikl (1948) was probably the first author to describe congenital adrenal hypoplasia unassociated with other congenital abnormalities, though he mentions some similar cases described by earlier authors. Mitchell and Rhaney (1959) were the first authors to describe adrenal cortical hypoplasia in sibs, and all the reported cases were reviewed recently by Roselli and Barbosa (1965) who added a family with 2 affected sibs.

Adrenal failure in early infancy due to congenital defect of the adrenal glands is most commonly due to adrenal hyperplasia, where a variety of enzymatic abnormalities have been described (Prader, 1967). The rare condition of lipid adrenal hyperplasia, reviewed by O’Doherty (1964), is associated with adrenal insufficiency in infancy and with male pseudohermaphroditism. Congenital adrenal hypoplasia unassociated with other congenital anomalies produces an uncomplicated deficiency of adrenocortical hormones which can be replaced to restore normal metabolic function. A family with this condition is here described.

Both parents are healthy and unrelated. The mother was an only child and her mother had no other pregnancies. The father was one of five children; his mother had one miscarriage.

Case Reports

Case 1. The first child, a female, was born in May 1959, after delivery 2 weeks over term; birthweight 4260 g. Labour was prolonged and delivery was by forceps. The infant was described as shocked at birth and was nursed in an incubator for 5 days. Some respiratory difficulty occurred and was thought to be due to atelectasis. Vomiting after feeds was a problem in the first 2-3 months but then ceased and the baby thrived normally. During the exceptionally fine summer of 1959, the child, who had fair hair, became deeply pigmented, and the mother claimed that she had noticed this in the first month of life. Eventually she became 'almost black' and retained much of this pigmentation throughout the following winter. She appeared healthy and had no illnesses of note except for acute febrile reactions after triple immunization injections.

Her final illness began in September 1960, when she became suddenly febrile. She was given aspirin, and 24 hours later her temperature had fallen to below normal and she was listless and apathetic. After 36 hours she began to vomit and became hyperpyrexial. She was given penicillin and cortisone and was admitted to hospital. Convulsions then occurred and she died about 44 hours from the onset of her illness.

At necropsy the macroscopical appearances were as follows. The body was that of a well-formed, flaxen-haired female child, the size corresponding to the stated age. The skin showed a striking degree of pigmentation involving the entire body, the exposed parts being more deeply pigmented than those parts covered by clothing. The skin of the abdominal wall was deeper in colour than that of the remaining covered surfaces. The lungs were deeply congested and mottled in appearance and showed multiple subpleural petechial haemorrhages. The smaller bronchi contained thin mucus. Both lower lobes were firm and partly consolidated. The heart was normal in size and showed no anatomical defect. The gastro-intestinal tract was normal in appearance. The mesenteric lymph nodes were moderately enlarged and congested. The uterus, ovaries, pancreas, and kidneys appeared normal. The spleen was slightly enlarged and congested. The adrenals were located with difficulty but were normal in position. Both were remarkably small but were normal in outline (Fig. 1). No ectopic adrenal tissue was found. The brain was not examined.

Histological examination of the lungs showed them as strikingly congested and oedematous, and there were occasional areas of frank haemorrhage. The interstitial tissues contained a lymphocytic inflammatory exudate in some areas. The findings suggested a pneumonia probably of viral origin. The skin showed a marked increase in pigmentation, the pigmented area extending into the stratum granulosum.

Both adrenals (combined weight 0.8 g) had an identical histological appearance (Fig. 2). Beneath the capsule, a thin rim of adult-type cortex was present in which the three layers could be identified. The zona glomerulosa and zona reticularis were well developed,
Fig. 1.—Case 1. The adrenal glands (below) compared with adrenals from a child of the same age (above).

Fig. 2.—Case 1. Section of the adrenal gland, showing narrow rim of cortical tissue. (H. and E. × 22.)
but the zona fasciculata was relatively reduced in amount (Fig. 3). Beneath the adult-type cortex and forming the bulk of the cortical tissue was a mass of irregularly arranged large pale polygonal cells with vesicular nuclei. These cells had little resemblance to the normal fetal-type cortex. The medulla of the glands appeared histologically normal.

**Case 2.** The second child, a female, was born in March 1960, after a spontaneous delivery 5 days before term; birthweight 3990 g. She was normal at birth and developed normally in the first two years of life. After the death of the third child (Case 3) it was decided to investigate her adrenal cortical function. She was admitted to hospital in May 1962, and remained for 24 hours. A 24-hour urinary collection was obtained with difficulty (vol. 210 ml.), and contained 0·5 mg. 17-ketosteroids. On the admission day, blood obtained by heel-stab contained sodium 136·9 mEq/l. and potassium 7·6 mEq/l. On the following day, potassium was 7·8 mEq/l. On that day her ECG was normal. During the following month, three further electrolyte estimations were done with the following results: on the capillary blood, sodium was 139 and 136·9 mEq/l. and potassium was 7·8 and 7·0 mEq/l., and on a venous sample, potassium was 6·0 mEq/l. No haemolysis was reported in any specimen. She was then admitted for an ACTH stimulation test (Clayton, 1961). After an initial control day, ACTH 20 units 12-hourly was given intramuscularly for a total of six doses and 24-hour urine collections were obtained. The results obtained were within normal limits for her age.

Since 1962 this child has remained perfectly well and has overcome the usual childhood infections without any unusual complications occurring. The curious electrolyte abnormality remains unexplained, and the parents are not anxious for further investigation of this child.

**Case 3.** The third child, a male, was born in April 1962 after labour was induced 2 weeks over term; birthweight 3900 g. Delivery was spontaneous and easy. Oxygen was administered immediately after birth, but his colour quickly became normal and he was transferred to a cot. No abnormal pigmentation was noticed. He fed normally after about 12 hours. After 24 hours he became cyanosed and grey in appearance. He was limp and appeared unconscious. It was considered that he might have had a cerebral haemorrhage but, because of the history of the firstborn, hydrocortisone, 50 mg., was given intramuscularly but without benefit. He died 28 hours after birth.

At necropsy, the lungs were congested, and alternating areas of atelectasis and compensatory emphysema were present. The liver was congested. The kidneys, spleen, thyroid, testes, and pancreas were normal. The pituitary was examined and was normal and the brain was also normal.

Both adrenals were tiny (7 × 2 × 20 mm. approx.) but, unfortunately, were not weighed. Histologically they were abnormal and resembled closely the adrenals
of the other sib, i.e. there was a thin rim of adult-type cortex in which the three zones of cells could be distinguished, the zona fasciculata being relatively reduced. Beneath the adult-type rim of cortex, there was a zone of degenerated fetal-type cortex, the cells of which were not eosinophilic but were vacuolated (Fig. 4). The adult and fetal type cortices were roughly equal in volume.

**Case 4.** The fourth child, a male, was born in October 1963, after labour was induced two weeks after term; delivery spontaneous; birthweight 4320 g. He cried immediately but was cyanosed and limp. After aspiration of the upper respiratory tract, transfer to an incubator and the administration of oxygen, he remained limp and no improvement in colour occurred. His breathing was shallow and bradycardia was present. After 30 minutes, intravenous hydrocortisone hemisuccinate, 20 mg., was given intravenously via an umbilical vein catheter. General improvement followed rapidly on this injection. During the next 5 hours, he became vigorous and his cry was strong. However, his skin colour remained ashen. He had no abnormal pigmentation of the scrotum or elsewhere. Cord blood electrolyte estimations were as follows: serum sodium 139 mEq/l. and serum potassium 5 mEq/l. The plasma cortisol estimation in cord blood was 4·1 μg./100 ml. (mean of triplicate estimations ranging from 3·4 to 4·5 μg./100 ml.). The cortisol was measured fluorimetrically. Plasma corticosterone was not detected. Plasma 17-hydroxy-corticosteroids in a specimen of blood taken from the mother immediately after delivery measured 549 μg./100 ml. These were estimated as Silber-Porter chromogens, predominantly cortisol. The normal non-pregnant adult range by this method is 5 to 25 μg./100 ml. Two months after delivery, the mother's serum cortisol level was 36·9 μg./100 ml and corticosterone was 6·5 μg./100 ml. (B. T. Rudd, Institute of Child Health, University of Birmingham).

After 6 hours, serum sodium was 128 mEq/l. and serum potassium 6·6 mEq/l., and after 10 hours, sodium was 132 mEq/l. and potassium 7·2 mEq/l. (capillary blood). Cortisone 10 mg. was given by intragastric tube 6 hours after birth and fludrocortisone, 0·025 mg., was given in the same way 7 hours after birth. A dextrose-saline (NaCl 0·45%) intravenous infusion was started at that stage and subsequent administration of hydrocortisone on the first day was by the intravenous route. During the first 24 hours he received hydrocortisone 60 mg. and fludrocortisone 0·075 mg. and, over the next 6 days, the daily doses were gradually reduced to 20 mg. and 0·05 mg., respectively. After 48 hours, he developed generalized oedema. This was interpreted as an inability to excrete a water load as in the Robinson-Power-Kepler test, and the intravenous infusion was stopped. The oedema gradually disappeared during the next 3 days.
After the first week, oral cortisone was substituted and up to 25 mg. daily was given over the next 4 weeks. Fludrocortisone dosage was increased to 0.2 mg. daily because of serum potassium estimations of up to 7.4 mEq/l. at times. Beginning 5 weeks after birth, dexamethasone was gradually substituted for cortisone, increasing to a dose of 0.25 mg. twice daily. An ACTH stimulation test was carried out, beginning three days after stopping cortisone therapy and while the patient was on dexamethasone and fludrocortisone. ACTH gel, 20 units, 12-hourly, intramuscularly, was given for a total of 6 doses. Blood was collected before the test and daily at the same time during the test. The hormone assays were performed by Mr. B. T. Rudd, and he reported that neither cortisol nor corticosterone could be detected in any of the 4 samples.

Cortisone therapy was resumed. BCG vaccination and immunization against diphtheria, pertussis, tetanus, and poliomyelitis (Salk) were completed while he was in hospital. He was discharged home 4 months after birth and was having cortisone 10 mg. daily and fludrocortisone 0.25 mg. daily. Serum sodium and potassium estimations were normal. Other investigations included a normal urinary amino acid chromatogram, a normal serum protein electrophoretic pattern, and a buccal mucosal smear which showed a normal male pattern.

Since that time, the dosage of fludrocortisone has been progressively reduced to 0.05 mg. daily and cortisone has been increased to 15 mg. daily. Fludrocortisone was reduced because of systolic blood pressures of up to 170 mm. Hg. Recent blood pressure estimations have been normal.

Now aged 4 years, he weighs 15·5 kg. and his height is 95 cm. He is a healthy intelligent child. He has overcome several acute respiratory infections without incident, the dosage of cortisone having been increased to 25 mg. daily during these illnesses. He has not had any acute infectious fevers so far. Immunization against measles was completed without incident.

Case 5. The fifth child, a male, was born by spontaneous delivery 2 weeks before term in May 1965; birthweight 3540 g. He was cyanosed at birth but quickly recovered. He remained completely well during the first 48 hours of life and subsequently. Repeated serum electrolyte estimations were normal. His progress since birth has been normal. A specimen of the mother’s blood, taken at the time of delivery, contained less than 25 μg. cortisol/100 ml., and the serum cortisol level in the cord blood was described as being slightly lower than the level in the mother’s blood, but accurate analysis was not possible because the amount of serum available was insufficient. At the age of 24 years, a 30-minute Synacthen test was done after the method of Wood et al. (1965). 0.25 mg. of Synacthen was given intramuscularly. Plasma cortisol before the test was 6·4 μg./100 ml. and, after 30 minutes, the level was 34·7 μg./100 ml. This is a normal result.

Case 6. The sixth child, a female, was born spon-

taneously at term in May 1967; birthweight 2940 g. She was cyanosed after birth but improved after suction of the upper respiratory passages. She remained well during the first 48 hours of life and maintained normal serum levels for sodium and potassium. A specimen of cord blood contained cortisol 21 μg./100 ml. plasma A specimen of mother’s blood, taken at the time of delivery, contained 135 μg/100 ml. A Synacthen 30-minute test was performed at the age of 2 months. The results for plasma cortisol were as follows: 6·4 μg./100 ml before the intramuscular injection of 0·25 mg. Synacthen and 20·6 μg./100 ml. after 30 minutes. This is a normal result.

Discussion

A study of the literature on congenital adrenal hypoplasia indicates striking differences with respect to the time of onset of symptoms, the nature of the symptoms, and the microscopical appearance of the adrenals in the cases examined at necropsy. In the reported cases, symptoms have appeared either at birth or at about the third week of life. The later development of symptoms has been explained as a consequence of the protection provided by maternal adrenal cortical hormones. The ratio of maternal-blood to cord-blood levels of 17-hydroxycorticosteroids is usually taken to lie between 5·1 and 2·1 (Aarskog, 1965). Yet, in the fourth member of this family, with symptoms present immediately after birth, the ratio was 133·1. The mother’s level of 17-hydroxycorticosteroids was remarkably high, though 2 months after delivery it had fallen to nearly normal levels, and the estimation was not abnormal in the fifth pregnancy where the child was unaffected by adrenal hypoplasia. However, the level was again high at term in the sixth pregnancy, though the infant was normal. The high maternal levels in the fourth pregnancy may have represented an effort on the part of the maternal adrenals to compensate for severe hypoplasia of the fetal adrenals. Despite this, however, little cortisol was demonstrable in cord blood and symptoms began immediately after birth. Actual weight of the adrenals cannot be correlated with length of survival. In the firstborn child of this family, dying at 18 months, the combined weight of the adrenals (0·8 g.) was considerably less than the combined weights in many cases dying at birth.

Variation in the clinical features of the disease has also been notable. In the first two days, collapse, cyanosis, convulsions, apnoeic attacks, and vomiting have been the main complaints, suggesting a diagnosis of cerebral haemorrhage. Vomiting, diarrhoea, and electrolyte disturbances
are more prominent features after the first 2 days, suggesting a diagnosis of congenital adrenal hyperplasia, and estimations of pregnanetriol and 17-ketosteroids may be necessary to differentiate the two conditions. Obviously a family history of the disorder is the most useful single aid to early accurate diagnosis in the newborn. Melanoderma is a clinical sign which has been observed infrequently, and may have been present at birth in the first member of this family, gradually intensifying up to the time of her death.

The curious electrolyte abnormalities in the second member of the family are not easy to explain. Electrolyte levels of sodium and potassium in the parents have been normal. A normal response to ACTH does not rule out a possible defect in the zona glomerulosa, the area where aldosterone is formed.

There has been considerable variation in the histological appearances in the cases examined at necropsy as reported by different authors. The medulla has been either normal or reduced to small islands of tissue. The cortex has varied from a well-differentiated, though hypoplastic cortex, to a complete absence of cortical tissue. Kerenyi (1961) divided the cases on the basis of adrenal morphology into a group in which the adrenals were of the type seen in association with anencephaly, and a group in which the adrenal cortex was composed mainly of large cells without any distinct arrangement. In the first group, the structure of the adrenals was of the miniature adult type, resembling the adrenals of anencephalic monsters, and the layers of the cortex and medulla were recognizable. He suggested that, in this type of hypoplasia, the lesion of the adrenal was always associated with a lesion of the pituitary, usually hypoplasia. In his second group, the cortex was composed mainly of large cells resembling the cells of the fetal zone of the cortex. These cells were often very large indeed and were either arranged haphazardly or in columns, and the characteristic layers of the cortex could not be identified. The borders of the cells were poorly defined, the nuclei stained poorly, and the cytoplasm was often eosinophilic and finely granular. The pituitary was normal, as were other endocrine organs. Our necropsied cases seem to fall into Kerenyi's first group as far as histological appearances are concerned, and yet we have no evidence of pituitary abnormality. The first child did not have histological examination of the pituitary performed, but she had grown and developed normally up to the time of death. In the second case, the histological appearances of the pituitary were normal. The boy of 4 years, who is on substitution therapy, shows no clinical evidence of pituitary hypofunction.

One of the most interesting features of the present family has been the presentation of two of the cases in the immediate neonatal period and the successful treatment of one of them as a result of the necropsy information available from his dead sibs. The diagnosis in the newborn may be extremely difficult without such prior knowledge, since the clinical manifestations of collapse, cyanosis, and apnoeic spells are non-specific and since excessive pigmentation may not be a feature. Any infant with signs of circulatory failure, lethargy, vomiting, dehydration, and failure to thrive should be suspected of adrenal insufficiency, particularly if there is a history of unexplained vascular collapse or sudden death in sibs.

Treatment of the surviving case in this family has been unexpectedly uneventful. It seems unlikely that it will be possible to withdraw his cortisone acetate in the future. Mitchell and Rhaney (1963) attempted to do this when their patient was aged 5 years, but he became listless, and pigmentation of his skin appeared. His ACTH stimulation test elicited no adrenal response, cortisol being undetectable in his plasma on days 2 and 3 of the test. However, it may be possible to withdraw fludrocortisone in our patient at a later date. There is evidence that disturbances of electrolyte balance may be present in early infancy but lessen or disappear later on. This is known to occur in some cases of congenital adrenal hyperplasia with the salt-losing syndrome. Stempfel and Engel (1960) described a family with a syndrome of adrenocortical insufficiency similar to that occurring in the family here described. One boy, who was closely studied, had a salt-losing state during the neonatal period which required treatment with cortisone and desoxy-corticosterone acetate (DOCA). DOCA was discontinued at the age of 22 months and no further disturbance of electrolyte regulation occurred, treatment being maintained with cortisone alone. Urinary aldosterone determinations were carried out at that stage and fell within the normal range.

An interesting feature of the affected children has been that, in each case, delivery has taken place past term and labour was induced in two instances. The unaffected children have been born spontaneously at or before term. The mother has commented that she knows that her child will be affected if her pregnancy goes over term. Prolonged pregnancy can occur where the fetus is anencephalic, and anencephalic monsters have hypoplastic pituitary and adrenal glands.
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One may speculate that a disturbance in the relation between pituitary and adrenal during pregnancy in cases of adrenal hypoplasia may also account for the prolongation of pregnancy.

Summary

A family of 6 children is described in which 3 members, 2 girls and 1 boy, had congenital adrenal hypoplasia.

References


