Congenital Adrenal Hypoplasia—An X-linked Disease

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Dacou and DiGeorge (1968) reported in abstract form their findings from a study of three male infants with adrenal hypoplasia. These infants by history had a common mother and two different fathers. At about the same time Bickham, Silvestre, and Mellinger (1968) reported on two affected male sibs who had a common mother and different fathers. Both authors suggested X-linked inheritance in this disorder, but genetic data documenting the paternity of these individuals were not presented in either instance.

The present report describes an additional affected male born to the mother of the patients studied by Bickham, and includes genetic data documenting differing paternity and pathological confirmation of adrenal hypoplasia.

Case Report

The patient was first seen at the Henry Ford Hospital at 8 days of age. His mother became concerned when he began persistent vomiting two days before admission, because two of three older children, who were known to have adrenal hypofunction, had experienced similar symptoms.

The patient was a male infant born after an uncomplicated 40-week pregnancy. The only medications taken during pregnancy were iron and vitamins. His birthweight was 4082 g. He had lost weight continuously since birth and there was gradually increasing lethargy.

The family pedigree obtained from the mother is indicated in Fig. 1. In two marriages she had borne four children, all male. The first child (II.1) has adrenal hypofunction and is under treatment. The second child (II.2), who was born in a second marriage, is normal. The next child (II.3) had adrenal hypoplasia and is under treatment, and the proband is shown as II.4. There were no miscarriages. The first child was diagnosed as having adrenal hypoplasia at the age of 3 years 4 months. However, he had not gained weight during the previous two years and weighed only 11·8 kg. Growth and development have been normal since beginning corticosteroid therapy. The diagnosis in the

second affected child (II.3) was made at 14 days of age when he was admitted to hospital because of weight loss, dehydration, and lethargy. His growth and development have also been normal since the institution of specific therapy.

The initial physical examination when the patient was 8 days old revealed a thin, dehydrated, lethargic white male infant. His pulse was 160 a minute and his blood pressure was 64 mm. Hg systolic. He weighed 3515 g. and was 53 cm. long. The anterior fontanelle was sunken and the oral mucous membranes were dry. The lungs were clear and the heart had no murmurs. No intra-abdominal masses were palpable. A reducible right inguinal hernia was present. The genitalia were those of a normal male. There were no abnormalities of the extremities and no apparent abnormality of skin pigmentation.

Laboratory studies. The haemoglobin was 9·0 g./ 100 ml., WBC 16,000/cu. mm.; the differential count, urinalysis, blood urea nitrogen, and creatinine were normal. The serum sodium was 125, potassium 8·6, chloride 100 and CO_2 13 mEq/l. Calcium was 9·7 and phosphorus 4·2 mg./100 ml. Radiological examination of the chest was normal.

The patient was treated with intravenous fluids and electrolytes, desoxycorticosterone acetate, and cortisone. After his condition was stabilized he was given hydrocortisone and fluorhydrocortisone orally and additional sodium chloride in his formula. He was discharged at 6 weeks of age weighing 4450 g. and was well until 3 months of age when he was readmitted for the repair of a right inguinal hernia. Local anaesthesia was used for the operation, and 50 mg. of cortisone acetate was given intramuscularly the evening before and the morning and evening of the operation. During operation unexpected difficulty was encountered in reducing the hernia.
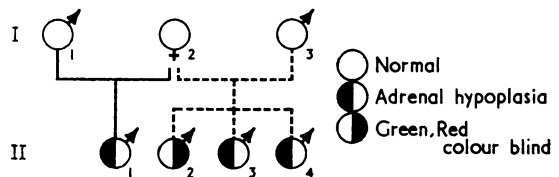
FIG. 1. The family pedigree, obtained by history.

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TABLE I

ACTH STIMULATION TEST

Patient	Age (yr.)	Test Day	Creatinine (mg./24 hr.)	17-OHCS (mg./24 hr.)	17-KS (mg./24 hr.)	17-KGS (mg./24 hr.)	Pregnanetriol (mg./24 hr.)
1.2	Adult	Control ACTH (50 U × 3-day)		10·3 41·6	7·1 18·7		
II.1	34/12	Control ACTH (40 U b.i.d.)	118 148		0·3 0·8	2·4 3·5	
II.2	5	Control Control ACTH (20 U b.i.d.)	157 138 173	2·3 2·7 6·1	1·8 2·7 1·7	4·5 3·2 11·6	
II.3	2 wk.	Control Control ACTH (20 U b.i.d.) ACTH (20 U b.i.d.)	63 40 54 69	0·5 0·6 0·5 1·1	0·4 0·6 0·4 0·3	0·8 0·4 1·0 2·3	0·1 0·1 0·15
II.4*	< 2 wk.	Control Control ACTH (40 U b.i.d.) ACTH (40 U b.i.d.)	24 34 43 48	1·4 1·9 2·2 2·7	0·2	2·4 3·1 4·1 4·0	0·01

* Patient was receiving fluorhydrocortisone 0·1 mg. b.i.d.

Manipulation resulted in haemorrhage into the wall of the intestine, and a suture was required to control this bleeding. On the following day the patient developed fever, tachycardia, and vomiting. Coffee-ground material was noted in the vomitus. In spite of cortisone, desoxycorticosterone acetate, and intravenous fluids and electrolytes the infant died the next day.

Endocrine studies. Urinary 17-hydroxycorticosteroids were determined by a modification of the method of Porter and Silber (1950), the urinary 17-ketosteroids by the procedure of Sobel *et al.* (1958), 17-ketogenic steroids by the method of Metcalf (1963), and pregnanetriol by a modification of the procedure of Bongiovanni and Clayton (1954), using gas chromatography for final identification and quantitation. The results of these determinations on control days and after administration of ACTH are shown in Table I. Data were obtained from the mother and all four of her children. In the mother (I.2) and the unaffected child (II.2) urinary adrenal steroid levels were normal and rose more than twofold after ACTH administration. In the other three children, levels of corticoid metabolites were low and failed to increase after ACTH. In patient II.4 the apparent increase in 17-hydroxycorticosteroid excretion after ACTH represents only a more complete collection

of urine, as indicated by a proportional increase in creatinine level (24 mg. vs. 48 mg.). These corticoid data in conjunction with the low 17-ketosteroid and pregnanetriol values established the diagnosis of primary adrenal hypofunction.

Genetic studies. The results of blood group, colour vision, and glucose-6-phosphate dehydrogenase determinations in this family are shown in Table II. The data indicate different paternity for each of the three adrenal deficient children. The blood groups of the affected individual II.1 are compatible with those of the mother I.2 and the putative father I.1. The blood groups of affected individual II.3 and the unaffected child II.2 are compatible with the putative parents I.2 and I.3. The blood groups of the 4th child (II.4) born to the mother are considered incompatible with paternity of either I.1 or I.3. The paternity of I.1 is ruled out by the Fy^a findings. The paternity of I.3 is ruled out by C and Fy^a. These findings were confirmed by repeated specimens in two different laboratories.

All 7 subjects had normal glucose-6-phosphate dehydrogenase and all those tested except the child with normal adrenal function had normal colour vision. This child had mild red-green colour blindness of an unclassified type as determined by the Hardy–Rand–Rittler

TABLE II

	Blood Groups													G6PD	Colour Vision
	ABO	C	D	E	MN	Ss	P	Kp	Kk	C^w	Le	Jk^a	Fy^a	Xg^a		
I.1	A$_1$	Cc	D	ee	MN	Ss	−	a$^-$b$^+$	kk	−	a$^-$b$^+$	+	−	−	N	N
I.2	O	cc	D	Ee	MN	Ss	−	a$^-$b$^+$	kk	−	a$^+$b$^-$	+	−	−	N	N
I.3	B	cc	D	EE	NN	Ss	−	a$^-$b$^+$	kk	−	a$^+$b$^+$	+	−	−	N	N
II.1	A$_1$	cc	D	ee	MM	SS	−	a$^-$b$^+$	kk	−	a$^-$b$^+$	+	−	−	N	N
II.2	B	cc	D	EE	MN	Ss	−	a$^-$b$^+$	kk	−	a$^+$b$^+$	+	−	−	N	D
II.3	O	cc	D	EE	MN	Ss	−	a$^-$b$^+$	kk	−	a$^+$b$^-$	+	−	−	N	N
II.4	O	Cc	D	Ee	NN	Ss	−	a$^-$b$^+$	kk	−	a$^+$b$^+$	−	+	−	N	ND

N = Normal ND = No data D = Red-green colour blind.

pseudo-isochromatic plates. The infant II.4 was not tested for colour vision.

The Xgᵃ blood group was negative in all family members. No grandparents were available for study; the maternal grandfather was not available for colour vision testing.

Necropsy findings. The necropsy was conducted under the direction of Dr. R. P. Patton, Department of Laboratories. There was a recent surgical incision in the right inguinal area, 5 cm. in length. Haematomas were found in the subcutaneous tissues in the area of operation and in the underlying peritoneum. There were several haematomas in the mesentery of the distal 15 cm. of the ileum. The thymus weighed 6 g. The thyroid weighed 1·5 g. and revealed no abnormalities. The heart was normal but both lungs were very congested and there were multiple subpleural haemorrhages. The bronchi contained a small amount of bloody mucoid material. Frothy, bloody material exuded from the cut surface of the parenchyma of the lungs. The spleen weighed 14·5 g. and was otherwise unremarkable. The liver, which weighed 200 g., the gall-bladder, and biliary system were all normal. The oesophagus was normal but the stomach contained blood-tinged mucoid material and there were several areas of superficial ulceration of the mucosa. Mucosal petechiae were noted in the duodenum and jejunum. Haemorrhage was present in the wall of the distal 15 cm. of the ileum, in addition to the peritoneal and mesentery haematomata. The colon and rectum were normal. The pancreas weighed 7 g. the right kidney 30 g., and the left 25 g., and the testicles weighed 2·5 g. each. All were normal. Careful examination of the suprarenal region and the para-aortic regions disclosed no evidence of adrenal glands. The brain was moderately oedematous with congestion of the leptomeninges. The pituitary gland appeared normal.

Microscopical examination revealed abnormalities only in the following organs: the right and left lung had interstitial infiltration of polymorphonuclear leucocytes and mononuclear cells, chiefly leucocytes and histiocytes. The alveolar spaces were lined with hyaline membrane and contained patchy haemorrhages. In the distal part of the ileum, diffuse congestion and haemorrhage were seen in the mucosa, submucosa, between the muscle layers, and in focal areas of the subserosa area layer. The mucosal epithelium was almost completely autolysed. A small area of interstitial haemorrhage was present in the right testicle. No ectopic adrenal cortical tissue could be seen in the sections of either epididymis. The thyroid gland, thymus, and parathyroid glands were normal on microscopical examination. Serial sections were made of perirenal fat and tissue from both paralumbar areas. Minute adrenal glands were found in the perirenal fat in the normal location. They measured 0·7 × 0·2 mm. in size, and the estimated combined weight was less than 0·5 g. There was complete disarray of the normal architecture of the adrenal cortex, with the cells arranged in a compact mass without normal zone or cord formation. Two types of cells were present. The predominant cells had eosinophilic granular cytoplasm without vacuoles and small round hypochromatic nuclei, some of which were pycnotic. Cellular limits were ill defined. The other cells were small groups of large eosinophilic cells which have been described as characteristic of congenital adrenal hypoplasia (Fig. 2 and 3). Autonomic ganglia were identified. The pituitary gland showed no remarkable changes. Staining with Pierce PAS stain demonstrated normal distribution of the cellular components of the hypophysis. Sections of the cerebrum, brain-stem, and cerebellum showed diffuse congestion and oedema without any focal lesions.

Discussion

This report documents adrenal cortical insufficiency in the newborn son of a mother who had borne three other male children, two with adrenal hypofunction. Blood group determinations established a different father for each of the affected children. The occurrence of adrenal hypoplasia in three males with the same mother and different fathers is strong evidence indicating that this congenital anomaly is due to an X-linked gene. McKusick's (1966) extensive catalogue of Mendelian inheritance in man lists hypoadrenal corticalism in the group of recessive disorders. An erroneous conclusion in this reference work could result in significant errors in genetic counselling. The possibility that this condition is due to a maternal non-genetic cause is not absolutely excluded but is considered extremely unlikely.

Unfortunately, we obtained no information regarding linkage to Xgᵃ or glucose-6-phosphate dehydrogenase, because all family members were Xgᵃ negative and had normal G6PD. Colour vision was normal in all the family members with the exception of the single unaffected child. The proband was too young to be tested. Therefore, colour vision cannot be used in this family to show crossing-over between the locus for adrenal hypoplasia and that for colour vision.

In order to substantiate further congenital adrenal hypoplasia as an X-linked disease we reviewed the reported cases of congenital hypoadrenalism. We did not exclude cases in which the pituitary was not mentioned nor those in which the patient was alive when reported. We did exclude three male sibs reported by Roberts initially in 1949 and subsequently in detail in July 1952 (Roberts and Baehren), because in the latter report it is apparent that these children had congenital adrenal hyperplasia. The results of this review support our contention that congenital adrenal hypoplasia is X-linked, and that, as suggested by Dacou and DiGeorge (1968), the pathological anatomy in affected female infants differs from that found in male infants. We found 28 cases of congenital hypoadrenalism (including

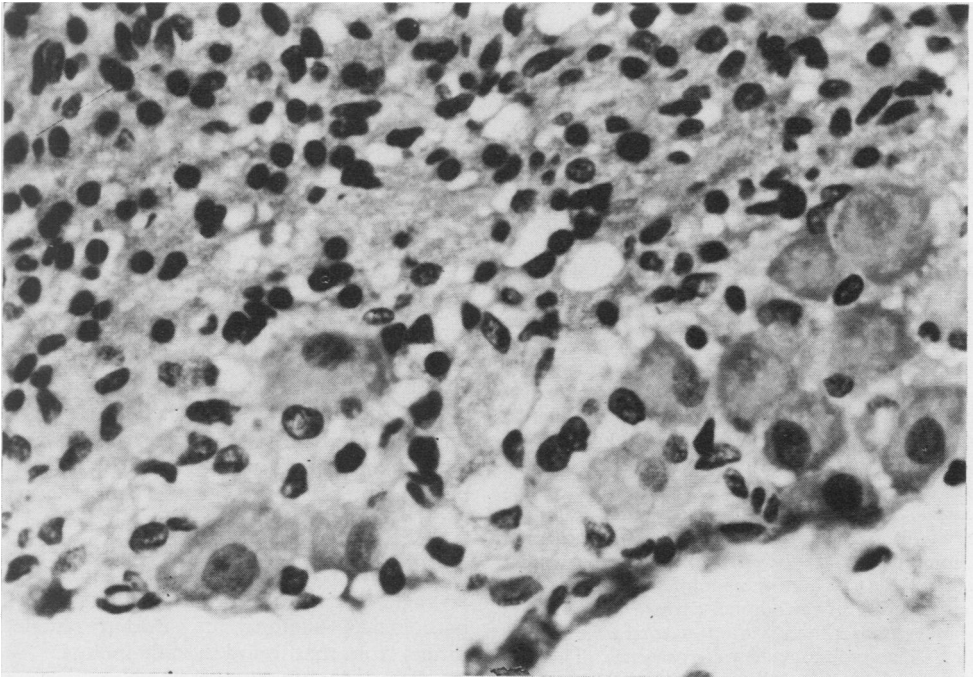FIG. 2.   The right adrenal gland showing the complete lack of organization of the cortex.   (× 175.)

FIG. 3.   The right adrenal gland showing both the small compact cells and the groups of large eosinophilic cells.   (× 830)

those in this family) not associated with tuberculosis, adrenal haemorrhage, or pituitary abnormalities. Twenty-three of these occurred in male infants (Dacou and DiGeorge, 1968; Bickham *et al.* 1968; Zondek and Zondek, 1968; Boyd and MacDonald, 1960; Stempfel and Engel, 1960; Mitchell and Rhaney, 1959; Gardner, 1957; MacMahon, Wagner, and Weiner, 1957; Harlem and Myhre, 1957; Denys, Corbeel, and Malbrain, 1955; Deamer and Silver, 1950; Provenzano, 1950; Geppert, Spencer, and Richmond, 1950; and Šikl, 1948) and five in females (Winquist, 1961; Shepard, Landing, and Mason, 1959; Williams and Robinson, 1956; Weens and Golden, 1955). Of the affected males, 15 had affected male sibs, but none had an affected female sib. Of the reported female patients there was only one sib pair (Shepard *et al.*, 1959). In this female sibship, the onset of symptoms was in the second year of life while in the males the onset was usually in the first weeks of life. One of the girls died, and at necropsy the adrenal glands were described as 'shell-like and resembled connective tissue of the surrounding area'. No cells could be found in the zona fasciculata and reticularis, but occasional clumps of cortical cells were described in the zona glomerulosa.

The adrenal glands of the female patient reported by Williams and Robinson (1956) as Case 4 had a well-formed definitive cortex with little evidence of fetal cortex. This tissue is similar to that found in anencephalic infants, though the pituitary gland was not mentioned in this report. The adrenal histology in the female patient described by Winquist (1961) is reported as, 'histologically normal glomerular and fascicular zones and a slightly more conspicuous 'permanent' reticular zone. There was no fetal reticular zone'. The adrenal cortex of Case 2, reported by Weens and Golden (1955), was described as having a thin but orderly zona fasciculata, slight evidence of the zona glomerulosa, and a normally involuting zona reticularis. Thus, histology in these female infants is distinctly different from that described for affected males, in whom there is disorganization of the cortex with scattered groups of large eosinophilic cells in haphazard arrangements. This description is consistent in all except three reports of male infants. Provenzano (1950) did not mention large cells, and described a 'mature type differentiation into glomerular and fascicular zones'. Stempfel and Engel (1960) found 'no adrenal tissue'. Gardner (1957) does not describe the histology of the adrenal gland. In our patient and presumably in his similarly affected sibs the histological picture is very similar to that found in most of the previous cases. Adrenal hypoplasia

with complete disorganization of the cortex, the absence of the normal formation of cords of cells and the presence of large eosinophilic cells is therefore characteristic of X-linked adrenal hypoplasia. This histological picture and the clinical appearance of adrenal hypofunction in the first few months of life suggests the failure of an inducer substance which normally is responsible for the formation of the adult cortex as the fetal cortex undergoes involution. A recessive gene located on a maternal X-chromosome is undoubtedly responsible for the failure of adrenal maturation and function.

Summary

Adrenal hypoplasia not associated with abnormalities of the pituitary gland has been considered to be either an autosomal recessive disease or a sporadic event. We have studied a family in which the gene for this abnormality was inherited as an X-linked recessive. A summary of previous cases supports this observation.

Three of four male sibs had adrenal hypofunction shown by clinical and biochemical determinations and failure of adrenal response to ACTH stimulation. One infant died after hernia repair, and hypoplasia of the adrenal glands in the presence of a normal pituitary gland was confirmed at necropsy. Blood group determinations established different fathers for each of the affected children. X-linked inheritance is therefore believed to be established in this family.

Of 25 additional reported cases of adrenal hypoplasia not associated with tuberculosis, adrenal haemorrhage, or pituitary abnormalities, 20 were male and 5 were female. Fifteen affected males had affected male sibs, while only one female sibship is reported. The characteristic adrenocortical histology found in males, lack of organization of the adult cortex into cords, and the presence of clumps of large pale staining cells, has not been described in females. These findings support the contention that this distinctive form of adrenal hypoplasia is inherited as an X-linked recessive. The histology suggests the failure of an inducer substance which normally stimulates formation of adult cortex as the fetal cortex undergoes involution.

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Addendum

After this manuscript was prepared a report appeared documenting two additional male sibships with the histological characteristics (Uttley, 1968).

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