ADDISON'S DISEASE IN INFANCY

BY

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Addison's disease may occur in infants with the adrenogenital syndrome, the adrenals being structurally intact and larger than normal. However, Addison's disease comparable with that occurring in adults also occurs in infants whose adrenal glands are hypoplastic or diseased. These infants fail to gain weight and are in a poor state of hydration despite a theoretically adequate caloric and fluid intake. They also have weakness, diarrhoea, vomiting and skin pigmentation as features of their illness. Death may be sudden following circulatory failure in a typical 'Addisonian crisis' if the condition is not recognized and treatment instituted. We have been able to find in the English literature records of only nine infants with Addison's disease due to adrenal hypoplasia or adrenal destruction.

This paper summarizes the literature, and records four additional cases. Three of these infants died suddenly, the terminal illness in each case suggesting acute adrenal insufficiency. The fourth is at present under treatment and progressing satisfactorily.

Case Reports

Case 1. A.S., a boy, was aged 10 weeks and weighed 7 lb. 5 oz. when admitted to the Royal Children's Hospital, Melbourne. Pregnancy and labour had been uneventful, and his birth weight was 7 lb. 7½ oz. His mother thought the baby was thriving until she took him to a health centre when he was 4 weeks of age and found his weight to be 7 lb. 5 oz. He was taking 4-5 oz. of breast milk seven or eight times daily. Seven weeks later because his weight was unchanged he was referred to hospital. A week before admission he had diarrhoea with three or four green watery stools daily. When examined he was mildly dehydrated, the tissue turgor being diminished and his tongue dry. Pigmentation of the scrotal, perianal and areolar skin was noticed but its significance was not initially appreciated as the baby's parents were dark-skinned Italians. The blood pressure was 80/60 mm. Hg. No definite diagnosis was made, and the babe was observed.

For the first eight days he took feeds well but although his intake was greater than his estimated requirements he did not gain weight. On the eighth day he developed slight diarrhoea, became lethargic and required gavage feedings. The next day he was found moribund with circulatory failure and gross dehydration. Twitching developed and he was given phenobarbitone with little response. Clinical signs suggested that he had developed acute bronchopneumonia and he was given intravenous saline and tetracycline. Over the next 24 hours his condition improved and intravenous therapy was suspended. However, he fed poorly and two days later, in the absence of vomiting and diarrhoea, became grossly dehydrated, again requiring intravenous fluid.

The possibility of Addison's disease was suggested by the following serum electrolyte levels.

Serum sodium	..	120 mEq. per l.
,, potassium	..	9 mEq. per l.
,, calcium	..	4·6 mEq. per l.
,, chloride	..	96·0 mEq. per l.
,, bicarbonate	..	29 mEq. per l.
,, phosphate	..	3 mEq. per l.

Other investigations gave: Haemoglobin 7·9 g. per 100 ml., W.B.C. 5,850 per c.mm. (differential cell count normal); serum proteins 6·2 g. per 100 ml. (albumin 2·56, globulin 3·64); blood urea 30 mg. per 100 ml.; fasting blood sugar (three estimations) 16, 17, 64 mg. per 100 ml.

Analysis of urine revealed a 24-hour output of 17-hydroxysteroids = 0·045 mg., and of 17-ketosteroids = 0·7 mg. The serum 17-hydroxysteroid level was less than 2 micrograms per 100 ml. (normal = 5-6 micrograms per 100 ml.). These specimens were taken one week after the baby had been given 10 mg. A.C.T.H. on alternate days.

During this period of investigation there had been no weight gain; the baby had taken feeds slowly and although obtaining theoretically adequate fluid had remained slightly dehydrated throughout.

Treatment was begun with 25 mg. cortisone by mouth twice daily. His general condition and weight remained unchanged and 10 days later he was again dehydrated.

At this stage 4 g. sodium chloride was added to the total daily feedings and the result was dramatic (Fig. 1). In the following five days he gained 1 lb. 5 oz., he was in perfect hydration and taking almost double the quantity of feeds. There was no sign of oedema, glycosuria or elevation of blood pressure and the baby was more active and a much better colour. During the next two weeks he had gained another 1 lb.

The serum electrolytes were now normal, the blood

sugar level was 100 mg./100 ml., and he was discharged from hospital.

When last seen at the age of 7 months his weight was 15 lb. He appeared normal in all respects and the pigmentation was much less noticeable. He is at present receiving 12·5 mg. cortisone daily and 3 g. sodium chloride added to his total daily feeds.

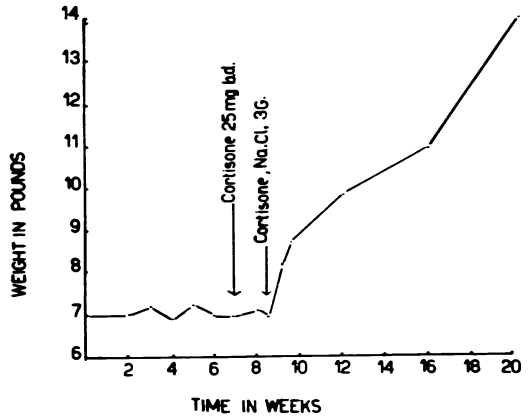

FIG. 1.—Case 1: Chart showing gain of weight following treatment with cortisone and sodium chloride.

Case 2. K.C., a 13-month-old girl, was admitted to the Royal Children's Hospital, Melbourne, in December, 1948, in a moribund condition. Heat wave conditions were prevailing at the time. She had been born at term after an uncomplicated labour, the birth weight being 8 lb. 13 oz. She had thrived since birth until her present illness which began 36 hours before admission with vomiting and refusal to take feeds. These symptoms persisted and were accompanied by intermittent crying until admission.

When examined the baby was pale and comatose. Generalized twitching was noted and the temperature was 108° F. A definite diagnosis was not possible and the baby died one hour after admission.

At necropsy the only abnormalities noted were that the lungs were congested and slightly oedematous, and both adrenals were small and contained areas of calcification. Microscopically, little cortical and no medullary tissue was present. A large area of amorphous material was surrounded by a fibrous capsule in which groups of cortical cells were present (Fig. 2). Abundant haemosiderin pigment and calcium could be seen in this fibrous tissue.

In summary, this infant had progressed normally despite extensive destruction of both adrenals until the age of 13 months. The combination of a respiratory tract infection and extremely hot weather caused death in an Addisonian crisis.

Case 3. R.G., a boy, was admitted to this hospital at the age of 4 weeks in July, 1948. He was said to have been two weeks postmature at birth and was noted to be very feeble. At the age of 2 weeks the baby began

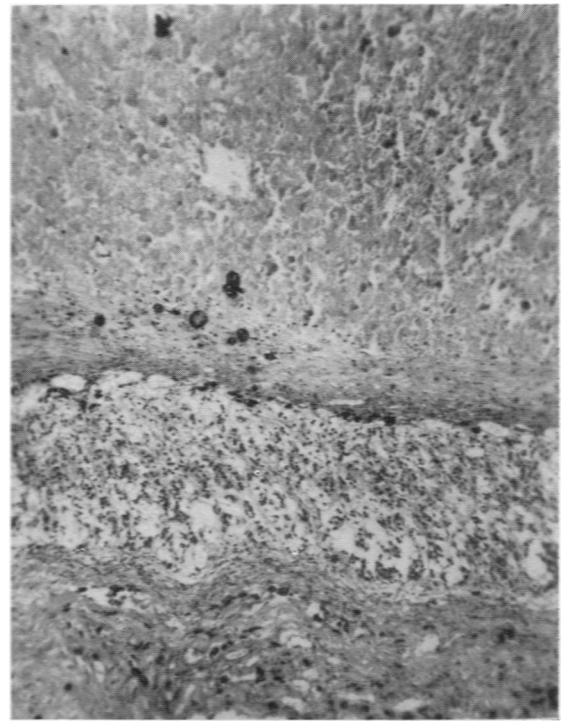

FIG. 2.—Case 2: A small amount of adrenal cortex is shown in thick fibrous tissue capsule. Haemosiderin and calcium are present in fibrous tissue and in underlying amorphous material. (Haemotoxylin and eosin × 90.)

to vomit and became dehydrated. The vomiting persisted and at times appeared projectile. For this reason he was admitted to hospital for investigation. The birth weight was 6 lb. 7 oz. and the weight on admission 5 lb. 12 oz. A fine papular rash covered most of the body but apart from this no abnormality was noted. Vomiting persisted and feeds were taken very slowly, and an intragastric drip was required. Ten days after admission, the baby suddenly became grossly dehydrated. This occurred in the absence of vomiting and diarrhoea. The hydration was restored with intravenous therapy, but could not be maintained and death was sudden 18 days after admission.

While the baby was in hospital the following investigations were performed and results found to be normal: Chemical and microscopic examination of urine and cerebrospinal fluid; radiographic examination of heart and lungs; a barium meal and a peripheral blood examination.

Post-mortem examination revealed minimal bronchopneumonia. The only other abnormality detected on macroscopic or microscopic examination was the presence of extremely small adrenal glands (approximately one-sixth the volume for normal glands at this age. On histological examination the adrenal cortex appeared well differentiated and was separated from well

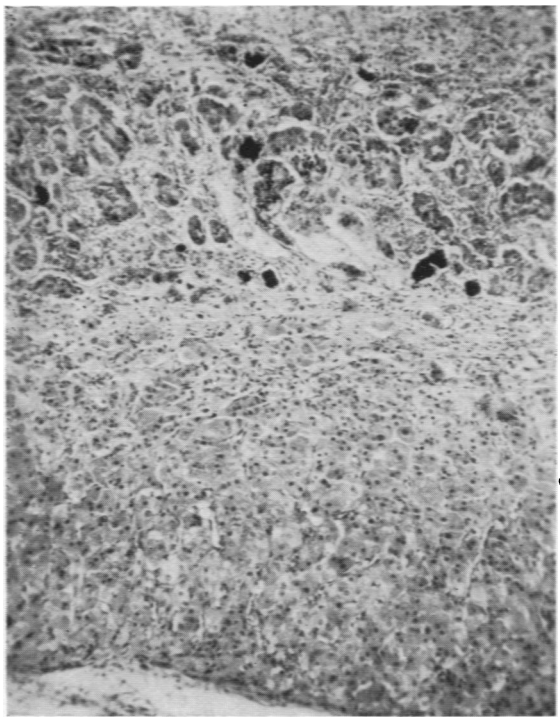

FIG. 3.—Case 3: Calcium and haemosiderin granules in fibrous tissue adjacent to well formed medulla. (Haemotoxylin and eosin × 105.)

formed medullary tissue by a thin layer of fibrous tissue. In this tissue deposits of calcium and haemosiderin were present (Fig. 3).

It would appear that in this child the symptomatology of adrenal insufficiency began shortly after birth and that death occurred in an Addisonian crisis.

Case 4. K.F., a girl, was aged 2 days when admitted to this hospital in July, 1951. Birth was normal, but some hours later vomiting began. The only abnormalities noted on examination were a mild degree of jaundice and a palpable spleen. The provisional diagnosis of erythroblastosis foetalis was not confirmed by serological investigation. The jaundice completely subsided in about one week, but the baby remained lethargic, vomited persistently and refused feeds. Investigations included chemical and microscopic examination of urine, radiography of the skull and chest: blood urea and a barium meal were normal. Two weeks after admission the baby had become dehydrated, the skin was noted to be a dirty grey colour and intravenous therapy was begun. The baby developed acute bronchopneumonia and died 24 hours later.

At necropsy extensive bronchopneumonia was present. Both adrenals were hypoplastic, approximately one-quarter of their normal size. Microscopic examination revealed a well formed definitive cortex, immediately adjacent to medullary tissue. The zone of connective tissue representing condensation of stroma of the foetal zone which is usually seen at this age was absent. There was no evidence of calcification or haemorrhage.

This history is compatible with adrenal insufficiency, death being precipitated by acute bronchopneumonia.

Discussion

From the clinical notes of our own and the recorded cases (Table 1) a definite syndrome emerges. The features are failure to gain weight, dehydration despite a theoretically adequate fluid intake and skin pigmentation. These infants are sluggish, feed poorly and are subject to episodes of vomiting and diarrhoea. Addison's disease should be considered in any infant whose illness manifests this combination of features. Diagnosis and institution of treatment should be made without delay as sudden circulatory collapse followed by death may occur. In two of our cases and seven of the nine recorded cases death occurred suddenly in an Addisonian crisis.

Diagnosis of Addison's disease in an infant is suggested by the demonstration of a typical electrolyte pattern in the serum and confirmed by a low 17-hydroxysteroid level in the urine. The levels of sodium, chloride and bicarbonate in the serum are low and that of potassium elevated. These deviations from normal are more pronounced in a crisis. A similar serum electrolyte pattern is occasionally seen in some forms of renal disease, which should be excluded by examination of urine and blood urea estimation.

Clinical features and laboratory findings identical with the above may be seen in infants with adrenal hyperplasia resulting in female pseudo-hermaphroditism and macrogenitosoma praecox. The former is readily recognized by the characteristic genital anomaly, but in the diagnosis of the latter estimations of urinary 17-ketosteroids may be needed. These are elevated (above 1 mg. per 24-hour specimen) in adrenal hyperplasia but are low in adrenal hypoplasia. Final proof of the correct diagnosis is shown by the disappearance of signs and symptoms with substitution therapy.

In the treatment of a crisis adequate fluid, sodium, chloride and glucose must be rapidly supplied. The most satisfactory method is via the intravenous route, amounts required depending on the state of hydration and electrolyte depletion. Cortisone alone, or in combination with D.O.C.A., is also required. Although most authorities have recommended maintenance with D.O.C.A., it is our impression that cortisone with its hyperglycaemic action is more effective. From analysis of the reported cases and from personal observations, hypoglycaemia is a feature of this illness in infants.

TABLE 1
SUMMARY OF RECORDED CASES OF ADDISON'S DISEASE IN INFANCY

Author	Age	Clinical Features	Investigations	Treatment	Mode of Death	Necropsy Findings
Jaudon (1946a)	4½ months	Anorexia, diarrhoea, listlessness, vomiting, loss of weight, pigmentation	Serum electrolytes supported diagnosis of Addison's disease. Low blood sugar. Positive Mantoux test	D.O.C.A. plus sodium chloride	—	—
Sikl (1948)	33 days	Failure to thrive, diarrhoea, pigmentation	—	—	Sudden death soon after admission	Hypoplasia of adrenals
Roberts (1949)	3 weeks	Vomiting, failure to thrive, dehydration	Serum electrolytes supported diagnosis of Addison's disease	Adrenal cortical extract and sodium chloride	Well until 6 months. Died suddenly	Hypoplasia of adrenals
Deamer and Silver (1950)	*Case 1* 2½ months	Vomiting, failure to gain weight, pigmentation	Serum electrolytes supported diagnosis of Addison's disease	D.O.C.A. and sodium chloride, pellets later implanted	Sudden death aged 6 months after fever, convulsions, diarrhoea and vomiting	Hypoplasia of adrenals
	Case 2 19 months	Anorexia, vomiting, weakness, craving for salt	Electrolytes supported diagnosis of Addison's disease	D.O.C.A. and sodium chloride	—	—
Moore and Cermak (1950)	3 weeks	Vomiting, diarrhoea, pigmentation	Serum electrolytes supported diagnosis of Addison's disease	D.O.C.A. and sodium chloride	Sudden death	Bilateral adrenal cysts
Geppert *et al.* (1950)	8 months	Vomiting, failure to gain weight, pigmentation	Serum electrolytes supported diagnosis of Addison's disease	D.O.C.A. and sodium chloride	Sudden death following convulsions	Hypoplasia of adrenals
Provenzano (1950)	11 days	Failure to gain weight, dehydration	—	Adrenal cortical extract and sodium chloride	Sudden death aged 21 days after convulsions	Hypoplasia of adrenals
Welsh and Mehlin (1954)	18 hours	Collapse and pigmentation	—	—	Sudden death at 24 hours	Hypoplasia of adrenals

Several of the recorded infants died following convulsions (Table 1). It would appear feasible that the convulsions were related to profound hypoglycaemia as low blood sugar levels were recorded in several cases. Random blood sugar estimations in our Case 1 gave low results, the level on three separate occasions being 17 mg., 18 mg. and 64 mg./100 ml. Cortisone rather than D.O.C.A. is likely to control this abnormality. In addition, cortisone has slight salt-retaining properties, and if used with additional salt in the diet allows good electrolyte control and obviates daily injections or implantation of pellets. That this therapy has been completely successful in our case is shown by the complete resolution of clinical signs and symptoms and the good biochemical control achieved. Neither long-term prognosis nor duration of treatment can be discussed from the available data as the duration of follow-up periods has been relatively short. The prognosis and duration of treatment will depend on two factors: (1) whether the adrenal lesion is progressive and (2) whether the adrenal cortex can regenerate.

The adrenal abnormality most commonly recorded in these infants has been cortical hypoplasia. This condition, which is usually associated with anencephaly, was found at necropsy in six of the recorded cases (Table 1) and in two of the three infants in our series. In Cases 3 and 4 the adrenals resembled those seen in anencephalic monsters, i.e., well formed definitive cortex, little evidence of foetal cortex and an increased amount of medullary tissue. In Case 3, in addition, haemosiderin and calcium were present in the fibrous tissue separating cortex from medulla. This appearance suggests that haemorrhage and replacement fibrosis had been at least partly responsible for the grossly diminished size of the adrenals in this infant. In view of the association with anencephaly the central nervous system and pituitary glands were studied but no abnormality was detected.

Destruction of adrenal tissue in Case 2 appears

to have been caused by haemorrhage, abundant haemosiderin pigment as well as fibrous tissue and calcium being present in sections. It is difficult to estimate when the adrenal haemorrhage occurred. The relative frequency with which adrenal haemorrhage occurs at birth and the knowledge that such haemorrhage is not always immediately fatal (Potter, 1952; Snelling and Erb, 1935; Emery and Zachary, 1952) suggest that it occurred at this time. Adrenal insufficiency became clinically manifest 13 months later when the presence of a respiratory tract infection and a bout of extremely hot weather coincided. During this same period of hot weather another infant aged 3 months died suddenly in this hospital. This infant was spastic, presumably following cerebral damage during birth which had been a difficult forceps delivery. He had been in hospital since birth and during that period his weight had remained stationary. He died unexpectedly 24 hours after the onset of severe dehydration accompanied by a sudden temperature rise to 107° F. Necropsy disclosed bronchopneumonia which was not extensive, and adrenals in both of which haemorrhage had occurred as judged by the presence of haemosiderin, fibrosis and calcification. There was little normal cortical tissue, the histological appearances of the adrenals resembling those of Case 2. (This infant is not included in the case reports as cerebral palsy dominated the clinical picture.)

Similarly the adrenals of Cases 3 and 4 had almost certainly been considerably diminished in size since birth and it is difficult to account for the lack of any evidence of regeneration in these adrenals with non-progressive lesions in view of the knowledge that adrenal cortex regenerates readily in experimental animals. This lack of regeneration was not only present in the hypoplastic adrenals where a functional pituitary abnormality may have been the primary cause, but also in those where haemorrhage had caused destruction of tissue.

There is evidence to suggest that temporary adrenal insufficiency may occur. Jaudon (1946b, 1948) records a series of 14 infants whose clinical and laboratory findings satisfy the diagnostic criteria of Addison's disease. They responded to substitution therapy with recurrence of clinical features upon its cessation. After periods varying from five to 29 months it was possible to stop treatment without recurrence of symptoms.

Summary

Addison's disease occurs in infancy and may be due to hypoplasia or destruction of the adrenal glands. The features of the illness are failure to gain weight, dehydration, vomiting and pigmentation. Death may occur suddenly in an Addisonian crisis.

Diagnosis is supported by detection of a typical pattern of serum electrolytes with low sodium, chloride and bicarbonate levels and elevated potassium. There is also a lowered urinary excretion of 17-hydroxysteroids.

The clinical notes are presented of an infant in whom the signs and symptoms of Addison's disease rapidly responded to treatment with cortisone and sodium chloride.

The histories of three infants in whom adrenal hypoplasia or destruction of adrenal tissue by haemorrhage was found at post-mortem examination are recorded. These lesions of the adrenals were considered responsible for features of Addison's disease during life.

A brief summary of nine similar recorded cases is tabulated.

We wish to thank Dr. S. W. Williams, under whose care A.S. (Case 1) was admitted, for permission to publish this case.

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References

Deamer, W. C. and Silver, H. K. (1950) *J. Pediat.*, **37**, 490.
Emery, J. L. and Zachary, R. B. (1952). *Brit. med. J.*, **2**, 857.
Geppert, L. J., Spencer, W. A. and Richmond, A. M. (1950). *J. Pediat.*, **37**, 1.
Jaudon, J. C. (1946a). *J. clin. Endocr.*, **6**, 558.
—— (1946b) *J. Pediat.*, **29**, 696.
—— (1948). *Ibid.*, **32**, 641.
Moore, F. P. and Cermak, E. G. (1950). *Ibid.*, **36**, 91.
Potter, E. L. (1952). *Pathology of the Fetus and the Newborn*, p. 99. Chicago.
Provenzano, R. W. (1950). *New Engl. J. Med.*, **242**, 87.
Roberts, M. H. (1949). *J. Amer. med. Ass.*, **139**, 439.
Sikl, H. (1948). *J. Path. Bact.*, **60**, 323.
Snelling, C. E. and Erb, I. H. (1935). *J. Pediat.*, **6**, 22.
Welsh, J. B. and Mehlin, G. Burch (1954). *A.M.A. Amer. J. Dis. Child.*, **87**, 319.