ADRENAL CORTICAL HYPOPLASIA IN SIBLINGS

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There have been two reports recently of adrenocortical insufficiency in infant siblings. Mitchell and Rhaney (1959) reported it in two brothers, the first dying at 53 days and showing hypoplasia of the adrenal glands as the only apparent cause of death. The brother was born three years later, and exhibited a similar clinical picture of vomiting, wasting and dehydration shortly after birth. Biochemical studies were attempted but it became necessary to treat the child with adrenocortical hormones and with sodium chloride added to his feeds. The child has remained alive to date, and it is assumed that he also suffers from adrenocortical hypoplasia. Shepard, Landing and Mason (1959) reported adrenocortical deficiency in two sisters. The first was well until 10 months and then developed a typical clinical picture. She died at 30 months and autopsy showed very small adrenal glands. There was no evidence of tuberculosis. The sister has remained healthy until the age of 10 years, and has remained alive to date, and it is assumed that he also suffers from adrenocortical hypoplasia.

Case Reports

In 1953, the mother became pregnant for the first time, but had a spontaneous miscarriage at 4½ months. The cases reported were the result of second and third pregnancies.

Case 1. This male infant was born in hospital on May 4, 1955, as a spontaneous vertex delivery at full term after a normal pregnancy. The birth weight was 7 lb. 12 oz. (3.52 kg.). "Physiological" jaundice appeared for a few days. Before dismissal, there had been occasional vomiting after breast feeding, but the condition subsided. The baby was well for his first four days at home, and then his condition deteriorated, and he was admitted to the Royal Hospital for Sick Children, Glasgow, on May 17, 1955. On that day his motions were green and very loose. He was dehydrated, with poor muscle tone, although he was 113% of his expected weight. Lumbar puncture gave a clear cerebrospinal fluid. Rectal swabs revealed no pathogenic organisms. Four days later his general condition was improved but he remained rather listless. On May 23, 1955, he collapsed suddenly with copious green vomitus. ‘Eucortone’ 0.5 ml. was given every four hours. Surgical opinion was sought, and at laparotomy a volvulus was found involving the caecum and ascending colon. This was reduced and an obstructing band was divided. 140 ml. of quarter-strength normal saline with 5% glucose was given intravenously over the next six hours. Oral fluids were started four hours postoperatively and ‘eucortone’ was stopped on the fifth postoperative day. His condition improved over seven postoperative days, but on the eighth day (June 1, 1955) he went off his feeds once more, became marasmic and he died on June 2, 1955, at 4 weeks of age.

At necropsy the child weighed 5 lb. 10 oz. (2.55 kg.).
infusion of quarter-strength normal saline with 5% glucose was set up. 100 mg. of hydrocortisone were placed in the contents of the first bottle. In addition, intramuscular hydrocortisone injections of 25 mg., and intramuscular tetracycline 25 mg. were given every six hours. The child died eight hours after admission.

At necropsy the child weighed 7 lb. 3 oz. (3·26 kg.). There was no abnormality of the respiratory passages, lungs, heart (29 g.), great vessels, the alimentary tract, liver (150 g.), pancreas, spleen (6 g.), the genito-urinary or central nervous systems. The only abnormality was the presence of unusually small adrenal glands. Together they weighed 0·9 g. (Fig. 1), and no adrenal tissue was found at any other site.

There was no family history of adrenal cortical hypofunction either in the grandparents, the parents or in their sibs.

**Histological Features.** The histological details of the two cases are similar and are considered together.

**Adrenal Glands.** Sudanophilic material is present in the zona reticularis of the adult cortex and in individual cells of the almost completely invovled foetal zone (Fig. 2). The features are the same in both cases, and are accompanied by cytomegaly in the foetal zone. The columns of the zona fasciculata are not normal for a resting gland (Fig. 3). Fig. 4 shows that there is barely any zona glomerulosa, and the cells of the zona fasciculata show much variability in size, and in nuclear and cytoplasmic staining properties. There is no evidence of the more insidious cytolytic necrosis seen in adult cases of Addison's disease (Crooke and Russell, 1935).

Professor T. Symington, Department of Pathology, Royal Infirmary, Glasgow, has examined one gland from each case by histological and by histochemical methods, and reports that both glands have been very active, and that he is unable to find any abnormality of function by these investigations.

Normal medullary tissue is present, but it is difficult to assess whether or not this is present in normal amount.

**The Pituitary Gland.** The glands were normally situated in both cases. Gomori's aldehyde-fuchsin method (Gomori, 1950) shows that basophil cells are present in increased numbers in both glands (Fig. 5). This finding has been confirmed by Lieb's phosphotungstic acid haematoxylin (Lieb, 1948), and modified trichrome and P.A.S. methods. Normally, basophils are present singly or in clumps of two or three cells. Fig. 5 shows marked hyperplasia in both cases, and, if anything, a tendency to become nodular in Case 1, which survived the longer.

Thus, adrenal hypoplasia is the primary defect and not the result of pituitary hypofunction in both of these children. Conclusive evidence is obtained from histological study of the other endocrine organs.

**The Thyroid Gland.** The thyroid gland in Case 2, who lived for 10 days, shows no abnormality (Fig. 6b). The gland of Case 1 who lived for four weeks, shows collapsed acini devoid of colloid (Fig. 6a), an appearance
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Fig. 2.—Low power view of adrenal glands of Case 1, (a), and of Case 2, (b), stained with Sudan III and IV. The difference in quality of the two photographs is due to the gland of Case 1 being embedded in gelatin. (x 60.)

Fig. 3.—Low power view of adrenal cortex of Case 1, (a), and of Case 2, (b), showing disorganization of cortical structure. (Masson's trichrome x 100.)
Fig. 4.—High power view of adrenal cortex of Case 1, (a), and of Case 2, (b), showing poor zona glomerulosa and moderate pleomorphism of cells of zona fasciculata. (Masson's trichrome × 413.)

Fig. 5.—Pituitary gland of Case 1, (a), and of Case 2, (b). The basophil cells are dark. (Gomori's aldehyde fuchsin × 100.)
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FIG. 6a—Thyroid gland of Case 1, (a), and of Case 2, (b). The gland of Case 1 shows a thyrotrophic hormone-like effect. (Haematoxylin and Eosin x 100.)

FIG. 7a—Parathyroid gland of Case 1, (a), and of Case 2, (b). The gland of Case 1 shows some upset which is difficult to interpret. (Haematoxylin and Eosin x 100.)
FIG. 8a.

FIG. 8b.

FIG. 8.—Pancreas of Case 1, (a), and of Case 2, (b). Both are normal. (Haematoxylin and Eosin × 100.)

FIG. 9a.

FIG. 9b.

FIG. 9.—Testis of Case 1, (a), and of Case 2, (b). The gland of Case 1 shows tubular atrophy with reduced spermatogenic activity. There is no detectable abnormality of the interstitial cells in either case. (Haematoxylin and Eosin × 100.)
which may result from over-production of thyrotrophic hormone (Sclare, 1956).

The Parathyroid Glands. In neither case do the glands appear to be unusually large or small. The gland of the shorter lived infant (Case 2) shows no histological abnormality (Fig. 7b). The gland of Case 1, however, shows an increased number of smaller cells with more hyperchromatic (or pyknotic) nuclei (Fig. 7a). We find it impossible to conclude from this whether the gland is undergoing atrophy or hyperplasia. In favour of atrophy is the apparent increase in condensation of blood vessels per field. On the other hand, Greene (1948) cites experimental evidence in favour of a parathyrotopic hormone. Study of a section of rib from each case fails to demonstrate bone absorption, and a section of kidney from each case fails to show evidence of nephrocalcinosis by Von Kossa's stain. It may be that neither infant lived long enough to exhibit these changes.

The Islets of the Pancreas. Islet tissue appears to be present in normal amount (Fig. 8) and α and β cells are present in both cases.

The Testis. The testis of Case 2 shows a normal degree of spermatogenesis (Fig. 9b). The testis of Case 1 shows a relative degree of atrophy of the seminiferous tubules (Fig. 9a) with markedly reduced spermatogenic activity, although artefact is present as a result of unsatisfactory fixation. This finding is consistent with the records of testicular atrophy in pituitary basophilism in the adult. Interstitial cells appear to be present in normal numbers in each case.

The Thymus. This organ is generally considered to be an endocrine gland, although in hypofunction of the adrenal cortex it appears to behave in the same manner as lymphoid tissue elsewhere in the body (Crooke and Russell, 1935). In the present two cases, the weight of the thymus was at the upper end of the scale of normal limits, and it must be assumed that the episode of adrenal hypofunction was too acute to allow time for the glands to show hyperplasia, regeneration or a reduced rate of involution.

Discussion

Hypoplasia of the adrenal glands is well known in association with anencephaly (Angevine, 1938) and in association occasionally with other congenital deformities of the central nervous system. In another group, however, adrenal hypoplasia is the only abnormality (Sikl, 1948; Deamer and Silver, 1950; Geppert, Spencer and Richmond, 1950; Provenzano, 1950; Welsh and Mehlin, 1954; Williams and Robinson, 1956; Harlem and Myhre, 1957; and MacMahon, Wagner and Weiner, 1957), and some of these cases have responded well to hormone therapy (e.g. Case 1 of Williams and Robinson, 1956). Some authors emphasized that the survival of these children was precarious, with sudden irrecoverable collapse if therapy were stopped even for a short period, and for this reason Mitchell and Rhaney (1959) felt that it was unjustified to investigate their second case fully while denying the infant the chance of recovery with replacement therapy. The histological appearances of the adrenal cortex of the brothers reported here resemble very closely those of Case 1 of Mitchell and Rhaney (1959) even to the presence of cytomegaly (Kampmeier, 1927; Beatty and Hawes, 1955). It should be stated that we are aware of endocrine gland involution during replacement therapy, but that we do not consider this process to be important in our cases, nor in the similar cases reviewed by us, because the adrenal glands are hyperactive. We believe that their small size is a congenital anomaly. It is essential in such cases, however, to make a thorough study of the whole endocrine system.

For example, Blizzard and Alberts (1956), Brewer (1957) and Ehrlich (1957) have described congenital aplasia or hypoplasia of the pituitary gland, and Mosier (1956) has recorded the condition, which is accompanied by hypoplasia of the adrenal glands, in siblings.

Further, our study of the literature reveals several familial syndromes which involve adrenal gland hypofunction: (1) The syndrome of hypoparathyroidism, adreno-cortical insufficiency and chronic moniliasis brought to general notice by Sutphin, Albright and McCune (1943) and followed by several reports, all from America (Leonard, 1946; Collins-Williams, 1950; Leifer and Holland, 1953; Baker, 1954; Papadatos and Klein, 1954; Craig, Schiff and Boone, 1955; Whitaker, Landing, Esselborn and Williams, 1956; and DiGeorge and Paschakis, 1957); (2) the association of Addison's disease with thyroid gland changes in some instances (Wells, 1930; Anderson, Goudie, Gray and Timbury, 1957), and the well-known familial tendency to hyperthyroidism (Martin and Fisher, 1945), or to hypothyroidism as in sporadic non- endemic goitrous cretinism (Hutchison and McGirr, 1956), make a study of the thyroid gland essential; (3) the coincidence of diabetes mellitus and Addison's disease was described by Bloomfield (1939) and by McNicol and McNicol (1960) and since a familial tendency in diabetes is now well known, a familial tendency to both conditions simultaneously may be reported in the future; and (4) the syndrome of Addison's disease in association with familial spastic paraplegia has been recorded recently by Harris-Jones and Nixon (1955).

The existence of these conditions makes it necessary to examine not only these endocrine organs, but to examine the gonads histologically.
in order to exclude the presence of ectopic adrenal tissue at this site, and also to examine the central nervous system, mainly to exclude a congenital abnormality of the fore-brain. We were unaware of the existence of the association between Addison’s disease and familial spastic paraplegia and therefore a histological examination of the spinal cord was not made.

The findings suggest that our cases exhibit primary adrenal gland hypoplasia with secondary pituitary basophilism, although it is not possible to state categorically that the infants would not have developed later one or other of the syndromes referred to above, had they survived.

**Summary**

Congenital adrenal hypoplasia is recorded in two brothers who died in the neonatal period.

Two previous examples of this condition in infants have been reported; one sibling has been maintained alive by replacement therapy in each.

Histological study suggests that the present two cases suffered from primary adrenal gland hypoplasia with secondary pituitary basophilism, the effects of which are demonstrable on the other endocrine glands.

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**References**


