Congenital adrenal hyperplasia

Report of a case with neurological complications

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Little is known about the neuropathological changes associated with congenital adrenal hyperplasia. Referring to their 8 fatal cases, Cleveland, Green, and Wilkins (1962) reported that 3 had no demonstrable brain abnormalities (2 salt-losing, 1 virilizing type) and 2 showed such abnormalities (1 salt-losing, 1 hypertensive type). The changes in the hypertensive patient (C-11-hydroxylase deficiency) were those of embolism from a mural thrombus in the left ventricle of the heart, the child having had a cardiac arrest during anaesthesia for tonsillectomy. In the salt-losing case there was a generalized disturbance of the cortical architecture and cellular degeneration, most marked in the hippocampus and cerebellum. The pathologist’s impression was one of ‘postinfectious encephalitis with superimposed anoxic changes in the brain’. In the other 3 cases the state of the CNS is not mentioned.

We present below a case report of another child with the salt-losing type of the disease, whose brain presented a form of encephalopathy hitherto unreported in this condition.

Case report

The patient was a daughter of healthy unrelated parents. Her older brother was known to have the salt-losing type of adrenogenital syndrome.

At birth she weighed 3·45 kg and was noted to have an enlarged clitoris with a urethral orifice on its ventral surface, and fused labia majora having a scrotal appearance. No gonads were palpable. There were no other abnormal physical signs.

The infant fed satisfactorily, did not vomit, and had regained her birthweight by the 15th day of life.

Investigations. Buccal smear, chromatin positive. 17-Ketosteroids: 4·4 mg/24 hr (3rd day of life), 6·9 mg/24 hr (4th day of life), 5·8 mg/24 hr (6th day of life) (normal in neonates up to 2 mg/24 hr). Plasma sodium: range 135 to 139 mE/I. in the first week. Plasma potassium: range 6·1 to 7·5 mE/I. in the first week. Plasma chloride: range 105 to 112 mE/I. in the first week.

Progress and treatment. The diagnosis of adrenogenital syndrome was made on the basis of the family history, the characteristic abnormal genitalia in a chromatin positive female infant, and the raised urinary 17-ketosteroids. The hospital laboratory was not able at that time to estimate the urinary pregnanetriol.

On the 6th day of life treatment with cortisone (5 mg by mouth 3 times in 24 hours) was started. The plasma sodium, potassium, and chloride were estimated daily in view of the brother’s history. During the first 10 days of life there was no vomiting or other untoward symptoms, but the plasma sodium fell to 132 mE/I. on the 10th day of life, 130 mE/I. on the 11th day, and 125 mE/I. on the 12th day. Though there was no significant fall in the plasma chloride (103 mE/I. on the 12th day) or rise in the plasma potassium (6·9 mE/I. on the 12th day), it was considered wise to treat the child as though she had the salt-losing syndrome on the basis of the family history and the falling plasma sodium level. Accordingly, she was given 4 g salt daily by mouth and 6 mg desoxycorticosterone acetate (DOCA) twice daily by mouth from the 12th day of life.

At the age of 10 months she was feverish one morning.
and no drugs were given by her mother. At 10 a.m. she suddenly became much worse, her breathing was difficult, and she went still with staring eyes. She was admitted to hospital at 11 a.m. and given 50 mg hydrocortisone immediately. At this time she was unconscious but responding to stimuli, with increased muscle tone in all limbs, generalized convulsive movements, temperature 40·6 °C, and dehydration. There was no evidence of a focus of infection.

On the assumption that the child was in an adrenal crisis with hyponatraemic dehydration secondary to an infection, she was started on an intravenous drip with 100 ml 0·9% sodium chloride, and was given hydrocortisone 50 mg 6-hourly and desoxycorticosterone acetate (DOCA) 5 mg 12-hourly intramuscularly, and phenobarbitone and ampicillin.

The results of laboratory investigations on the day of admission are in the Table.

As soon as the initial biochemical results were available, revealing hypernatraemia, metabolic acidosis, and hypoglycaemia, the intravenous normal saline was replaced by glucose and bicarbonate. As shown in the Table, the plasma sodium was normal and the hypoglycaemia was corrected within 6 hours. After 24 hours the blood chemistry was normal and remained so. However, the patient remained unconscious with repeated fits and generalized spasticity. This neurological state persisted virtually unchanged for the remainder of the child's life. She developed optic atrophy with no pupillary response to light and occasional rapid vertical nystagmus.

At 10½ months EEG was abnormal with paroxysmal features; high voltage fast activity with θ and δ frequencies, frequent high voltage sharp waves with phase reversal in the parasagittal regions were more marked posteriorly.

The patient survived for 4 months with no further biochemical disturbance. After many respiratory tract infections she died aged 14 months.

Results

Pathological findings. At necropsy the body weighed 5·69 kg, with crown-heel length of 74 cm and head circumference of 40·5 cm (approximate average for age is 47·4 cm, SD 1·2). There was marked lumbar lordosis, bilateral pes cavus, and pigeon chest with a deviation of the sternum to the right. The external genitalia were masculinized, as already described. The ovaries and uterus were normal. A narrow vagina opened onto the tip of a large verumontanum 3 cm above the perineal opening of the urogenital sinus. The adrenals weighed together 20 g, compared with 7 to 16 g for the normal. They were excessively convoluted and creased externally, while their cut surfaces showed conspicuous thickening of the cortex which was apparently depleted of lipids. The medullae were of normal size. Histologically, the cortex showed excessive coiling and nodularity. The zona glomerulosa was ill-defined and appeared to be missing in some areas. The zona fasciculata was somewhat hyperplastic and there was considerable thickening of the zona reticularis. Individual cells of the adrenal cortex seemed normal, showing only lack of the usual 'lipid' vacuolation.

Gross bronchopneumonia was confirmed histologically.

The brain weighed 403 g (average normal for age 944 g), the cerebellum together with brainstem accounting for 48 g. It was symmetrical and dolichocephalic, showing bilateral opercular defects. Over the vertex of the brain, especially the frontal and parietal lobes, some of the gyri were depressed below the level of their neighbouring gyri. The pattern of gyri seemed to be within normal limits, but obvious ulegeria was present in the occipital lobe. Under the soft cortex the cerebral white matter seemed somewhat indurated. The cranial nerves and the main blood vessels at the base of the brain were normal.

When the brain was cut coronally it showed varying degrees of cortical atrophy in all but the anterior parts of the frontal lobes. Parts of the cortex were extremely thin and many areas showed

| TABLE |
| Investigations on day of admission |
|---|---|---|---|---|
| Plasma sodium (mE/l.) | 158 | 159 | 139 |
| Plasma potassium (mE/l.) | 7·5 | 3·3 | 3·2 |
| Plasma chloride (mE/l.) | 131 | 121 | 15·4 |
| Plasma standard bicarbonate (mE/l.) | 13·0 | 10·6 | 15·4 |
| Serum calcium (mg/100 ml) | | | |
| Blood urea (mg/100 ml) | | 107 | |
| Blood glucose (mg/100 ml) | 18·0 | 7·47 | |
| Blood pH | 3·3 | | |
| Blood Pco₂ (mmHg) | 14·3 | | |

Urine: normal
CSF: protein 10 mg/100 ml 15 cells/mm³
Blood cultures (2): sterile
rarefaction or a line of frank cavitation coursing parallel to the brain surface. The white matter was uniformly ivory white in colour. The nuclear markings of the basal ganglia were blurred. The whole ventricular system was moderately dilated. The ependymal surface was smooth. The brainstem showed mild narrowing of its basal part but no other ascertainable naked-eye abnormality. The spinal cord showed no unequivocal change. The cerebellum presented generalized sclerosis with marked atrophy of the folia and blurring of the dentate nucleus.

The most conspicuous histological changes were degeneration of the cerebral and cerebellar cortex and appearances identical with those in sudanophil leucodystrophy of the white matter (Fig. 1 and 2). In the cerebrum the process was most marked in the parietal, occipital, and temporal lobes, the frontal one being relatively spared. The affected cortex showed wasting, severe or total loss of nerve cells, diffuse and focal accumulation of lipophages, astrocytic hyperplasia, and spongiform transformation (Fig. 3), which was most marked in layer 3 but was also present in some areas beneath the cortex. Large amounts of sudanophil material could be shown in appropriately stained sections in microglial cells, which contained also some PAS-positive granules. As mentioned, the temporal lobe was as severely affected as the other areas but the hippocampus showed only moderate neuronal loss, especially in the Sommer sector. The cerebral white matter presented widespread demyelination and gliosis. Though the U-fibres were spared in some places, they showed considerable depletion of myelin in the frontal part of the brain. Only a few myelinized fibres were present in the centrum semiovale. Near the cortex and in its deeper layers the fibres were generally better preserved but nearly all showed degenerative changes. Massive quantities of sudanophil lipids were stored in microglial cells sometimes accumulated around the blood vessels.

The thalamus showed neuronal atrophy and astrocytic overgrowth, which was accentuated in some areas. The corpus striatum was somewhat better preserved, presenting also some neuronal loss and astrocytic hyperplasia. Focal spongiform change and small foci of calcification were present in the thalamus and pallidum. The hypothalamus was gliotic but the supraoptic and paraventricular nuclei were rather well preserved.

Relatively minor changes were seen in the brainstem. The cerebral peduncles showed demyelination of the frontopontine and temporo-pontine tracts. The corticopontospinal tracts showed some atrophy at the level of the pons. The crossing fibres of the pons were also somewhat atrophic, while the pontine nuclei appeared to be normal. Some neuronal loss and fibrous gliosis were present in the inferior olives. The pyramids were rather small presenting some loss of myelin with sudanophilic degeneration. Cranial nerve nuclei were not affected. In the spinal cord there

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**Fig. 1.**—Occipital lobe. *Atrophy and spongiform change of the cortex.* (H. and E. ×3.)

**Fig. 2.**—Cerebellum. *Widespread cortical atrophy with sparing of the palaeocerebellum.* (H. and E. ×2.)
was marked degeneration of the dorsal columns, the products of myelin breakdown staining strongly with Sudan dyes. The lateral corticospinal tract showed some loss of nerve fibres and myelin. A peripheral nerve presented focal breakdown of myelin with liberation of sudanophil material. Attempts to show segmental demyelination in teased preparations were unsuccessful.

Generalized cortical atrophy and gliosis were present in all parts of the neocerebellum, being less pronounced in the palaeocerebellum. The Purkinje cells and those of the granular layer had almost entirely disappeared and there was a correspondingly marked proliferation of Bergmann glia. Microglial proliferation was present in the molecular layer and many of these cells were laden with sudanophilic material (Fig. 4). The cerebellar white matter showed marked gliosis with considerable loss of myelin sheaths. However, some fibres were preserved in the more central parts. A large
number of microglial cells contained sudanophilic material. Neuronal loss and glial overgrowth were present in the dentate nucleus.

**Comment**

This patient was born with the adrenogenital syndrome and the diagnosis was proved by the finding of raised urinary 17-ketosteroids which fell in response to cortisone therapy. On the basis of a sib with the salt-losing syndrome and the finding of a significantly low plasma sodium on three occasions at the age of 10 days, the patient was considered to have the salt-losing type of the disease. She progressed reasonably well for the first 10 months in spite of some intercurrent illness, feeding difficulties, and management problems at home. Her developmental progress was normal. She suddenly became seriously ill for no obvious cause at the age of 10 months with hypernatraemia and hypoglycaemia. Though the true nature of this biochemical disturbance was not immediately appreciated and appropriate treatment was therefore delayed for a few hours, it seems likely that she had already sustained irreversible brain damage by the time she was admitted to hospital.

The cause of the acute illness and the development of hypernatraemia and hypoglycaemia remains obscure. The usual biochemical disturbance in an acute adrenal crisis precipitated by infection is hypernatraemia. It was known that the parents were emotionally disturbed throughout the period of the child's life and it is not impossible that some major and disastrous changes were made in the child's therapy in the 24 hours or so before her collapse. The hypernatraemia could be explained by overdoses of salt and/or the salt-retaining hormones.

Pathologically, the brain showed gross and possibly progressive cortical cerebral and cerebellar degeneration with areas of spongiform change, widespread gliosis, some focal atrophy of the basal ganglia, demyelination of long tracts in the brainstem and cerebellum, and degenerative change of some peripheral nerve fibres. This clinical and pathological picture resembles closely that of Alpers' disease or poliodystrophia cerebri progressiva (Alpers, 1931; Christensen and Krabbe, 1949). According to Ford, Livingstone, and Pryles (1951), Alpers' disease occurs in two forms: infantile and juvenile. The infantile form is characterized by early onset, mental retardation, convulsions, spasticity, choreoathetosis, ataxia, myoclonic jerks, blindness, and optic atrophy (Alpers, 1960; Greenhouse and Neubuerger, 1964). The main pathological change is cortical atrophy with or without cerebellar involvement. Neuronal loss is generalized, being more marked in the posterior parts of the brain. The hippocampus is likewise less severely involved. As a rule, the midbrain, pons, medulla, and spinal cord show no gross change (Wolf and Cowen, 1954; Noetzel, 1957; Greenhouse and Neubuerger, 1964; Laurence and Cavanagh, 1968). Other pathological aspects have been discussed by Ford et al. (1951) and Blackwood et al. (1963). In particular, spongiform degeneration has been frequently mentioned (Kramer, 1953; Wolf and Cowen, 1954; Ulrich and Cunz, 1966). It is thus obvious that were it not for the associated adrenal condition the present case might well be regarded as one of Alpers' disease.

The causes of Alpers' disease are still unknown. Hypoxia, infection, metabolic or genetic factors have all been discussed by the authors mentioned above and by Dreifuss and Netzky (1964). It seems certain that the condition is not an aetiologically homogeneous group. Identical neuropathological changes have been observed, for example, in Addison's disease, Cockayne's syndrome, and juvenile diabetes mellitus (Crome and Stern, 1967). Laurence and Cavanagh (1968) thought that their 5 cases differed neurologically from Alpers' disease. However, the association of congenital adrenal hyperplasia with this particular type of encephalopathy has not previously been reported.

It is only possible to speculate on the actual cause of the encephalopathy in the present case. The patient had had fits during the period of acute metabolic disturbance. The acute episode of hypernatraemia and hypoglycaemia may have been decisive in causing the cerebral damage, since all of these are well known to be potentially encephalopathic. The pathogenetic effects of hypernatraemia, particularly cerebral haemorrhage, have been discussed by a number of authors (Finberg, 1969). Other authors dealing with this subject include Allott (1939, 1957), Rapoport (1947), Finberg (1959), Finberg and Harrison (1955), Finberg, Kiley, and Luttrell (1963), Finberg, Luttrell, and Redd (1959), Weil and Wallace (1956), Macaulay and Blackhall (1961), Macaulay and Watson (1967), Morris-Jones, Houston, and Evans (1967), and Ahmed and Agusto-Odutola (1970). The effects of hypoglycaemia have also been described by a number of workers (Adams et al., 1966; Anderson, Milner, and Strich, 1966; Banker, 1967). None of the changes described in these reports resembles the encephalopathy in the present case. In addition to the close resemblance to Alpers' disease, there was demyelination with release of sudanophil lipids which were stored.
mainly in microglial cells. These changes were generalized throughout the brain and spinal cord and involved also the peripheral nerves. In recent years the association of sudanophil leucodystrophy with adrenal cortical atrophy has become recognized as a distinct syndrome (Hoefnagel, Van den Noort, and Ingbar, 1962; Fanconi et al., 1963; Gordon and Marsden, 1966; Blaw, 1970; Forsyth, Forbes, and Cumings, 1971). The possibility that the adrenal dysfunction played a role in the present case must therefore remain open.

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References


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