CALCIFICATION OF THE ADRENAL GLANDS IN YOUNG CHILDREN

A REPORT OF THREE CASES WITH A REVIEW OF THE LITERATURE

BY

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Calcification of the adrenal glands occurs in other mammals besides man, for it has been recorded after distemper in cats and has also been observed in dogs, rats and monkeys (Marine, 1926; Ross, Gainer and Innes, 1955). Not unnaturally its occurrence in man has been more completely tabulated; it may be produced by tumours or cysts, and its association with haemorrhage, trauma and burns is well documented. So far as tumours are concerned, ganglioneuromas, neuroblastomas, phaeochromocytomas and adenocarcinomas have all been involved in the process (Schwartz and Fink, 1956). It is probable that any of these may be associated with cyst formation and this in turn may encourage haemorrhage into the cyst. Williams (1955), indeed, came to the conclusion that, in the cystic adrenal, haemorrhage was probably the precursor of calcification. Its occurrence as a rare complication in the lipoidoses (Abramov, Schorr and Wolman, 1956) requires a different explanation, and Alexander (1946) suggested that in this condition the calcific deposition could be explained by supposing that the fatty acids released by the hydrolysis of cholesterol esters were saponified by calcium.

With regard to the part infection may play in the production of such calcification, the condition most often thought of is tuberculosis. Other infections, however, have been recorded, the more notable being severe cases of meningococcal, and less often pneumococcal, septicaemia (Prior, 1953). It seems likely that in infection, and where calcification follows severe burning, the common link is the occurrence of haemorrhage into the gland for such bleeding is a common enough complication in all of them.

The importance of haemorrhage is further underlined by the fact that it is known to be a rare complication in the infant as a result of difficult labour and of prematurity. Occasionally the haemorrhage is diagnosed clinically, because of the severe collapse of the newborn infant and in some cases a tumour may be felt in the abdomen. Hill and Williams (1959) reported such a case and listed 25 instances in which massive fatal adrenal apoplexy occurred under such circumstances and another nine who survived the incident.

The fact that it is possible to survive the haemorrhagic incident must suggest that haemorrhage need not always be severe; and it is reasonable to assume that minor degrees of bleeding may escape clinical detection. Snelling and Erb (1935), for example, reported a series of 3,637 consecutive autopsies on infants and on children, in 43 of which (1.19%) haemorrhage into the adrenal gland was found. In only one had it been suspected clinically. Of the total, 15 occurred in infants and 28 in older children. Eight of the total showed evidence of calcification as well as of haemorrhage, one of which was a baby who was 6 days old at the time of death. Seligman (1928) analysed a series of 1,185 autopsies on adults with special reference to the appearance of the adrenals, and found four cases with evidence of calcification in the cortex. He was unable to explain the occurrence satisfactorily and postulated that sublethal haemorrhage might have occurred during the immediate neonatal period.

In trying to understand why haemorrhage should occur in these infants, a number of interrelated factors may be involved. It is well known that the adrenal gland of the newborn infant is relatively large compared to that of the adult and is especially so when the child is premature. The gland undergoes a rapid involution after birth, but before this its size and immaturity must render it more liable to damage. This may occur in relation to an abnormally large presentation and the breech variety seems particularly vulnerable (Stevens and Tomskyoski, 1954; Wilkins, 1959). The fact that traction has been applied to the flanks is probably the reason. Then
again, when there has been foetal distress, the too vigorous application of certain types of resuscitation might easily inflict damage. Finally, the presence of some haemorrhagic disease of the newborn or of asphyxia neonatorum are further aetiological possibilities because of the alterations in the vascularity of the gland which they may produce. That trauma of itself may play a part is suggested by Rack and Eiben (1951) who reported a case of a 2½-year-old child with unilateral haemorrhage and calcification of the adrenal. They postulated that trauma at the time of a severe thrashing known to have been administered six months previously might have been responsible.

Thus the survival of the child seems possible when the haemorrhage has not been severe. Such children may not always show clinical evidence of the condition. In these symptomless cases the diagnosis will usually be made by chance when a radiograph, usually of the chest, which has been taken for other reasons, reveals the abnormality. The three cases which we wish to report fall into this category.

Case Reports*

Case 1. A female child, aged 7 weeks, was admitted on March 11, 1958, as a case of bronchopneumonia. She had been ill for two days with an upper respiratory infection and had then developed a cough, cyanosis and vomiting. Clinical and radiological examination confirmed the presence of pneumonia and the child responded well to chemotherapy. The chest radiograph was of sufficient size to take in the upper abdomen where bilateral calcified adrenal glands were seen (Fig. 1). Clinical reappraisal in the light of this finding showed no obvious sign of adrenal insufficiency. The Mantoux reaction was positive, but the child had been given B.C.G. at birth. Serum tested for toxoplasmosis gave negative results. The child was discharged well on April 6, 1958.

The obstetric history was normal. The child was a vertex delivery after a surgical induction done just before term because of contracted pelvic outlet. Labour lasted seven and a half hours, but no foetal or maternal distress was noted. The birth weight was 7 lb.

Periodic assessment since dismissal has shown that the child is thriving. There seems, however, to be an increased susceptibility to upper respiratory tract infections. Radiographs taken recently suggested that the suprarenal calcification may have increased. In order to gain some objective evidence of adrenal function blood steroid levels and circulating eosinophils were measured before and four hours after an intramuscular injection of 40 international units of A.C.T.H. with the following results:

<table>
<thead>
<tr>
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<th>Before A.C.T.H.</th>
<th>Four hours after A.C.T.H.</th>
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<tbody>
<tr>
<td>(1) Plasma 17-OH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>corticoids</td>
<td>0 μg./100 ml.</td>
<td>37.5 μg./100 ml.</td>
</tr>
<tr>
<td>of serum</td>
<td></td>
<td></td>
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<tr>
<td>(2) Eosinophil</td>
<td>22 per ml.</td>
<td>6 per ml.</td>
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* In these case notes no reference has been made to any blood pressure readings. These were done by using an appropriate size of sphygmomanometer cuff, the levels being measured by auscultation and the flush technique. The readings were as a rule higher than one might expect at the appropriate ages, but as readings are notoriously difficult to assess accurately in young children without direct arterial puncture, the figures have been omitted from the text.
Case 2. A female child, aged 2 years, was admitted on May 12, 1958, for investigation of an unexplained fever. Clinical and radiological examination revealed a left basal pneumonia; penicillin was given and rapid improvement ensued. As in Case 1, the chest radiograph took in sufficient of the upper abdomen to show bilateral adrenal calcification (Fig. 2). No evidence of adrenal insufficiency could be found and Mantoux skin tests were negative. She was discharged well on June 2, 1958.

The obstetric history showed the child to have been five weeks premature and a brow presentation. Delivery was spontaneous; the birth weight, $3\frac{1}{2}$ lb. She was initially cyanosed and slow to respond to resuscitation and as a result was kept in a premature baby nursery where recurrent cyanotic episodes were noted. Finally, however, she thrived.

She has kept fairly well since dismissal, although there have been frequent episodes of upper respiratory infection and an attack of whooping cough.

Between November 18, 1959 and December 3, 1959, she was readmitted for further assessment. On this occasion it was noted that the skin was dry and that there was some flattening of the vault of the skull. Observation over this period also showed that she had an ataxic gait and appeared mentally retarded. There were, however, no localizing signs on examination of the central nervous system.

Radiographs of the skull were normal and an E.E.G. was regarded as within the normal limits for her age. An intravenous pyelogram was normal and confirmed the calcification to be adrenal in site. Biochemical assessment included liver function tests, serum electrolytes, calcium, phosphate, cholesterol and urea levels, all of which were normal. Fasting blood sugar was 80 mg./100 ml. Electrophoresis of the serum proteins and chromatography of the urine were normal. The urine was also normal on chemical and microscopic examination. Serum tested for toxoplasmosis was negative.

As in Case 1, the response to an intramuscular injection of 40 international units of A.C.T.H. was assessed and in this case steroid levels in the urine were also measured.

<table>
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<th>Before A.C.T.H.</th>
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<tbody>
<tr>
<td>(1) Plasma 17-OH corticoids</td>
<td>10 $\mu$g./100 ml. 21 $\mu$g./100 ml.</td>
</tr>
<tr>
<td>(2) Eosinophil count</td>
<td>154 per ml. 90 per ml.</td>
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24-hour collection of urine before the test:
- Total volume, 615 ml.; 17-ketosteroids, 0·75 mg. per day; total 17-OH corticoids 4·3 mg. per day.

24-hour collection of urine after A.C.T.H.:
- Total volume, 590 ml.; 17-ketosteroids, 0·8 mg. per day; total 17-OH corticoids, 5·4 mg. per day.

Case 3. A male child, aged $1\frac{1}{2}$ years, was admitted on May 7, 1959, suffering from measles complicated by bronchopneumonia. It was noted at this time that he had a dry eczematous skin and that the liver was enlarged to about two-finger breadths below the right costal margin. Response to penicillin was poor and as the radiographic appearances suggested the possibility of a staphylococcal pneumonia, a combination of chloramphenicol and erythromycin was given with satisfactory resolution.

The enlargement of the liver subsided with recovery.

Fig. 2.—Radiograph of abdomen in Case 2. This shows a rather different pattern of distribution of the calcification, the film being taken at the time of an intravenous pyelogram. Fig. 2a is an enlarged outline.
from the infection, but a radiograph of the abdomen showed bilateral calcification of the adrenal glands (Fig. 3). Since there was no evidence of associated adrenal insufficiency he was dismissed on August 13, 1959. Mantoux skin test was negative as was examination of the serum for antibodies to toxoplasma.

Obstetric history showed that the child was a normal presentation with an uneventful labour. The child was, however, three weeks premature, weighing 4 lb. 12 oz. He was treated in a premature baby unit, but no asphyxia was reported.

On November 3, 1959, he was readmitted because of obstinate bronchospasm which settled after treatment with a variety of antispasmodics. A further chest radiograph showed signs of early emphysema and clinically the thorax was becoming barrel-shaped. Biochemical assessment showed normal values for the serum electrolytes, urea, calcium and phosphate, and liver function tests. The electrophoretic pattern was normal and a fasting blood sugar 123 mg./100 ml.

The response to 40 international units of A.C.T.H. in this case was as follows:

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<tr>
<td>(1) Plasma 17-OH corticoids</td>
<td>5 μg./100 ml.</td>
</tr>
<tr>
<td>(2) Eosinophil count</td>
<td>36 per ml.</td>
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**Discussion**

In the three cases described above, bilateral adrenal calcification has been found by chance and, in view of the age of the patients and the lack of evidence to indicate another aetiological factor, it seems reasonable to suggest that haemorrhage at, or just after, birth was the initial cause. None of our cases has shown clinical evidence of hypo-adrenocorticism, and although adrenal function tests are difficult to perform in young children and there is a wide range of normality, our own figures after A.C.T.H. stimulation do not indicate any gross deficiency. Perhaps one should not suspect any impairment of adrenal function since the presence of the calcification does not necessarily imply widespread destruction of adrenal tissue. Even if it did, Sézary (1923) has suggested that up to 90% of adrenal tissue can be destroyed and survival can still be possible. A certain amount of functioning adrenal tissue can be found in the testes and ovaries and this may play a part in offsetting the loss of the adrenal glandular secretions. Despite the present good health of our own cases, it is important to appreciate that this condition has been reported in association with a variety of clinical pictures and in a few instances it has been claimed to have caused death. A continued follow-up of our own cases is, therefore, desirable.

A survey of the literature indicates that the condition may not always be benign. Death in coma after convulsions, sometimes of an epileptiform nature, has been reported in three instances (Newsan (1924) in a child of 2½ years; Lintz (1943) in a child of 11 years; Minder (1954) in a case aged 28 months). Gardner (1957) reported two living examples; one
of these had skin pigmentation and required hydrocortisone supplements during any infectious episodes. This case, a premature breech delivery complicated by asphyxia, had low serum steroid levels which rose, however, after A.C.T.H. stimulation. His second case, with a normal obstetric history, also had crisis-like episodes with infection and in this case there was associated hypoglycaemia.

Does the calcification persist or increase with the chance of trouble later on? Seligman (1928) suggested that the calcification he found in his four adults may have been there throughout life. On the other hand, Drucker and Rodriguez (1955) thought the calcification in their case increased over some months before the child died from a respiratory infection and Lintz’s case had signs of adrenal insufficiency from the age of 2½ years before finally dying at the age of 11. In our own Case 1 serial radiographs suggest a slight degree of extension, though this could be simply a redistribution of calcium with growth.

The case reported by Schwartz and Fink (1956) was of special interest to us. A 9-month-old baby was admitted with fever, vomiting and respiratory difficulty, and subsequently died. At autopsy, calcification and ossification of the adrenal glands were found and the lungs showed acute generalized obstructive emphysema. We have been impressed by the early development of emphysema in our own Case 3 and have wondered whether there is a cause-and-effect relationship. It is true that many of the cases reported with this adrenal abnormality had an associated respiratory infection, and this is true of our own three cases; this association might be explained quite simply by the fact that the chest radiograph often brings the calcification to light.

In view of the reported association of haemorrhage and calcification, it was considered of interest to review some cases of severe adrenal haemorrhage (Waterhouse-Friderichsen syndrome) treated in this hospital for meningococcaemia. Accordingly, we carried out a review of 21 cases treated over the past six years. These patients had shown extensive skin haemorrhages associated with collapse and required steroid therapy during the acute phase of the illness. Their ages ranged from 5 months to 14 years at the time of the fulminating infection. In none did we find any evidence of adrenal insufficiency and on the radiographs none showed evidence of calcification.

In conclusion it might be worth suggesting that some cases can be prevented by such measures as care in dealing with abnormal, and especially breech, presentations, by the avoidance of undue force in measures of resuscitation and by the prompt treatment of any asphyxia.

Summary

Three cases of bilateral calcification of the adrenal glands in infants are described. The pathogenesis of the condition is discussed and the most usual cause is thought to be haemorrhage at, or about the time of, birth.

Factors such as prematurity, abnormal presentations and abnormal labour, asphyxia, or a combination of any of these, seem to predispose to such haemorrhage and some cases could probably be prevented by good obstetrics.

In those cases where the finding has been made during life it has usually been unsuspected. While it may often be of little importance in some children, it seems to be associated with definite signs and symptoms which may declare themselves in the form of an increased response to infection or stress of any kind, by focal or generalized epileptiform seizures, by hypoglycaemia and as classical Addison’s disease with pigmentation.

It is hoped to maintain contact with the patients in order to observe their progress.

We would like to thank Professor T. Anderson and Dr. J. H. Lawson for permission to publish these cases. We are also indebted to Dr. W. G. Whyte of the Royal Infirmary, Glasgow, for the blood steroid estimations.

REFERENCES


