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CASE REPORT

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Sudden death due to auto-immune Addison's disease in a 12-year-old girl

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Abstract A 12-year-old female suffering from adreno-cortical insufficiency showed symptoms similar to a gastro-enteritis, and severe electrolytic and acid/base disturbances which progressed into cerebral oedema and death. Autopsy findings included depletion of the adrenal cortex, with enlargement and eosinophilia of surviving cells. In ante-mortem blood, anti-adrenal auto-antibodies were found and elevated levels of ACTH and cortisol with a low level of aldosterone.

Key words Addison's disease · Adreno-cortical insufficiency · Adrenal glands · Childhood

Medical history

A 12-year-old Caucasian girl was admitted to hospital following a 2-day history of recurrent vomiting. There was a suggestion that a 'virus infection' was going round her school over the previous week; several of her friends had been similarly affected but most had recovered within 3 days. Her family doctor had found her to be significantly dehydrated when he had visited at her home and referred her as an emergency to hospital.

On admission she was initially conscious, talking and able to walk although feeling faint. Her blood pressure was unrecordable and there was marked peripheral vaso-constriction with cold peripheries. At the Emergency Department 1 L of dextrose saline (0.45% saline and 2.5% dextrose) was administered by intravenous drip following which the blood pressure improved to 60 mm Hg (systolic). The girl then started to complain of abdominal pain and there was some muscle guarding on abdominal examination.

On arrival on the ward about 30 min later, the patient was still hypotensive and a further volume load of plasma was given in an appropriate dose of 20 ml/Kg (approximately 800 mls). Following this there was some brief improvement in blood pressure to 115 systolic but thereafter her blood pressure was only maintained at 60–70 mm Hg systolic. The initial blood tests showed elevated urea and creatinine levels indicating a degree of renal shut-down together with significant dehydration. A further dextrose-saline infusion was set up (0.45% saline and 5% dextrose), following which, it was noted that the child's breathing had become deep and sighing; the arterial blood gas analysis showed a moderate degree of metabolic acidosis. Electrolytes taken at the same time as the arterial blood gas sample showed a low sodium level at 122 mmol/L and a blood glucose level which has risen from 3 mmol/L on admission to 20 mmol/L. The urine was shown to contain glucose and ketones. Ketoacidosis due to undiagnosed uncontrolled diabetes mellitus was suspected and transfer to a specialist unit was arranged. During transfer in the ambulance, the patient suffered a generalized convulsion followed by bradycardia and was resuscitated with bag and mask ventilation. A chest X-ray taken on arrival at the specialist centre showed diffuse haziness of both lungs consistent with pulmonary oedema or an aspiration pneumonia. The pupils were fixed and dilated on arrival. The patient was transferred to the intensive care unit and given progressively increasing doses of dopamine, dobutamine and adrenaline to try and improve blood pressure and cardiac output, but at this stage the myocardium appeared completely resistant to these drugs and her blood pressure remained around 60–65 mm Hg (systolic). A single dose of dexamethasone was given, also without any major effect. In view of the fixed dilated pupils and evidence of brain swelling with congested retinal veins on ophthalmoscopy, mannitol and frusemide were given intravenously. There was a modest diuresis but no improvement in her clinical condition.

Clinical examination carried out on two occasions showed no evidence of any remaining brain stem function. An EEG was also performed and showed no evidence of cortical activity. After full discussion with the parents, she was extubated and died immediately.

Autopsy findings

Post-mortem examination revealed a well developed and well built Caucasian girl with normal external and internal sexual development consistent with her stated age. There were no external features of natural disease in particular no evidence of excessive skin or mucosal pigmentation. Internal examination was unremarkable except for marked pulmonary and cerebral oedema. The adrenal glands were grossly unremarkable; the right weighed 4.3 g and the left 4.5 g. All other endocrine organs were grossly unremarkable.

Histopathology revealed depletion and atrophy of the adrenal cortex, with enlargement and eosinophilia of surviving cortical cells, with a prominent round cell infiltrate composed mostly of lymphocytes; the medulla appeared normal (Fig. 1). In addition, there was a mild chronic lymphocytic thyroiditis (Fig. 2). Other organs were unremarkable except for the marked pulmonary congestion and oedema with early basal pneumonic changes and cerebral oedema.

Bacteriological and virological examination of the contents of the small and large bowel failed to grow any pathogens and no significant inflammatory mucosal changes were identified.

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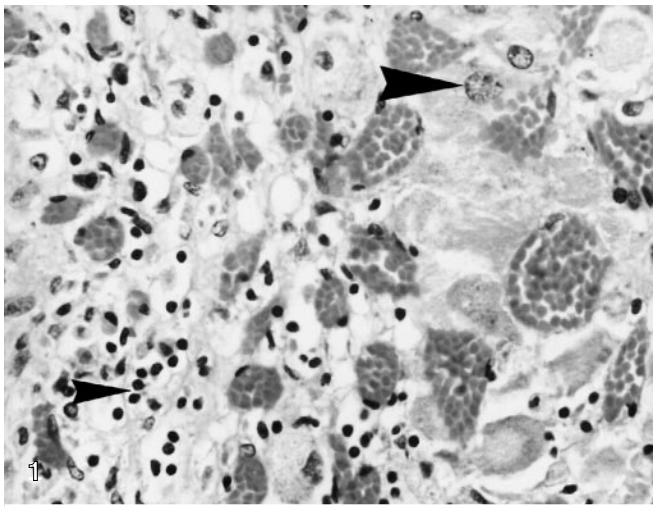

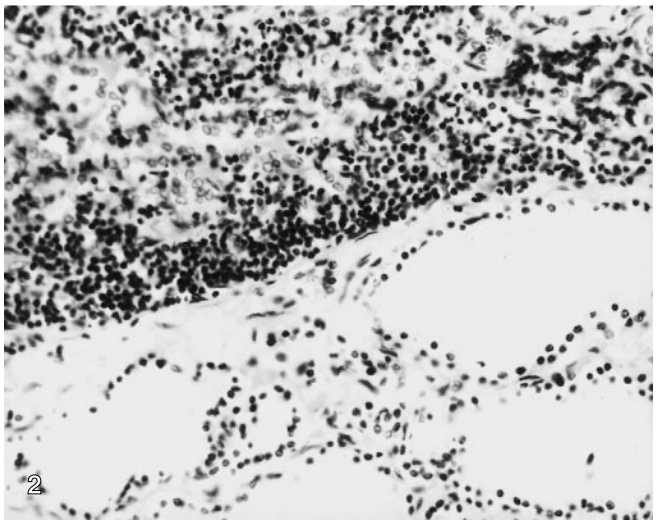

Fig. 1 Adrenal gland showing disorganization of cortex with large persistent cortical cells (large arrowhead) and lymphocytic infiltrate (small arrowhead) H & E × 400

Fig. 2 Thyroid gland showing well preserved follicles adjacent to interstitial lymphocytic infiltrate H & E × 250

Subsequent to the finding of the adrenal and thyroid lesion, the initial blood sample obtained at the time of the original admission was studied. Anti-adrenal and anti-thyroid antibodies were identified. No other organ-specific antibodies were demonstrable. There was an elevated serum ACTH and unusually low levels of cortisol and aldosterone. Glycosylated haemoglobin was normal and the glucose and sodium levels were low.

Discussion

Chronic adrenal insufficiency (Addison's disease) can be defined as any disorder which ultimately leads to destruction or atrophy of the adrenal cortex with the clinical symptoms of insufficient glucocorticoid and mineralocorticoid activity [9]. This disorder was first noted by Addison in 1855 who observed that some cases were due to such identifiable causes such as tuberculosis, histoplasmosis, and metastatic disease; others were labelled as "idiopathic" [4].

Addison's disease is rare in children [18] and its maximum incidence is in the 4th and 5th decades. Its exact incidence has not been accurately recorded but it is estimated at 0.04% of all deaths in Britain [18]. Between 1990 and 1992, 141 cases of fatal cortico-adrenal insufficiency were recorded in England and Wales, whereas in Scotland there were only 19 cases; all these cases occurred after the second decade and none between the ages of 5 and 20 years. [19, 22]. Addison's disease is 2 to 3 times more common in females than males [3, 12] and all ethnic groups can be affected although the prevalence of tuberculosis or other infections in particular populations results in a higher incidence [3].

With effective control of active tuberculosis, the proportion of cases due to this disease have declined [12], and auto-immunity is currently the leading cause of Addison's disease [9, 26]. Among other rarer causes are histoplasmosis, coccidioidomyocosis, torulosis, myocosis fungoides, amyloidosis [14], X-linked congenital adrenal hypoplasia in the neonatal period, [1, 10, 15, 25], X-linked adrenoleukodystrophy [3, 8, 13], and local hemorrhage and dystrophic calcification [9].

The clinical diagnosis of Addison's disease is difficult because the initial clinical symptoms are vague and nonspecific and thus there is often delay in making the diagnosis [3, 10, 12]. Symptoms develop insidiously with the patient complaining of tiredness and general malaise with both physical and mental asthenia, anorexia and weight loss. In some patients the skin and mucous membranes may show hyperpigmentation, and the skin may also be dry and brittle. Nausea and constipation alternating with diarrhoea occur with increasing frequency with progression of the disease; some patients may also show an abnormal preference to salt (salt craving). Genital examination usually reveals normal pubertal development in contrast to the delayed puberty due to gonadotrophin deficiency which is a feature of familial adrenal hypoplasia [3, 6, 9, 10, 12].

In children an 'acute adrenal crisis' can often be the presenting feature, often initiated by a mild acute infection or other stress. The patient is usually very ill, may be pale and cyanotic, comatose or delirious with dehydration and severe gastrointestinal symptoms which may simulate an 'acute abdomen' or an acute gastro-enteritis. Biochemical abnormalities include decreased serum sodium and chloride levels increased serum potassium, hypercalcaemia, haemoconcentration, hypoglycemia and metabolic acidosis. Decreased intra-vascular volume is responsible for a small cardiac shadow radiologically and a decreased cardiac output, with a small and retarded pulse and low blood pressure [3, 6, 9, 14, 27]. Hyperpigmentation caused by high levels of circulating ACTH and MSH-related peptides affects the whole body but especially areas exposed to light, physiologically pigmented areas – the areolae, peri-anal region or genitalia, and areas submitted to friction – skin folds or creases and operative scars [3]. In the present case no pigmentation was detected on the skin or mucous membranes, but this is not an unusual finding in children. Hypoglycemia is a very frequent symptom (> 90%) in children and is attributed to

the low levels of circulating cortisol which is an insulin-antagonist hypoglycemia [3, 5, 12].

Circulating organ-specific anti-adrenal auto-antibodies (mostly IgG) are found in about two-thirds of cases of Addison's disease; antibodies reactive with zona glomerulosa cells alone seem to be associated with a benign course, whereas those patients with auto-antibodies to all cortical layers especially to the fasciculata layer, are more likely to be associated with clinical Addison's disease. These antibodies precede the clinical onset of adrenal insufficiency and discovery allow the early diagnosis of subclinical adrenocortical failure. They are usually absent in cases of tuberculous Addison's disease. The presence of adrenal auto-antibodies does not correlate with disease duration or age of onset [3, 4].

In the present case, the patient was misdiagnosed as having diabetic keto-acidosis. It is believed that her hyperglycemic state was essentially due to the administration of large quantities of intra-venous dextrose/saline. The normal histological appearance of the pancreas and the absence of any pancreatic auto-antibodies, and normal HbA/C (glycosylated haemoglobin) level support this contention. Autoimmune Addison's disease may occur as an isolated entity, it may also be associated with other organ-specific auto-immune diseases such as hypoparathyroidism, primary hypogonadism, pernicious anaemia, autoimmune thyroid disease, vitiligo, insulin-dependent diabetes mellitus and chronic active hepatitis [3, 9,11,16, 20, 21, 24]. These diseases are more common in adult patients and predominate in females [3, 21].

Familial occurrence in auto-immune Addison's disease is frequent and results from inherited abnormalities of the immune response mechanism thought to be largely autosomal dominant, although females are more affected. In such cases, all patients and family members should be carefully evaluated for associated entities. This was done and no other family members were found to be affected.

Histological examination of the adrenals confirmed the diagnosis; in auto-immune Addison's disease, only the cortex is involved, with sparing of the medulla, in contrast to the destruction of the whole gland in other types of Addison's disease e.g. tuberculous. Characteristically, the glands are very small and may be misshapen, and in some instances no adrenal tissue can be found. Microscopically the adrenal cortex is atrophied and replaced by islands of large eosinophilic compact-type cells surrounded by the collapsed vascular reticulin framework of the original cortex but no fibrosis is seen. There may be a moderate lymphoid infiltration with some involvement of the medulla, which is otherwise normal [2, 4]. These changes contrast sharply with the findings in the adrenal glands in the sudden infant death syndrome [23].

The prognosis of Addison's disease depends on early recognition and prompt treatment and with adequate correct therapy and parental support patients will have a normal life and normal life span [3, 5].

The child in the present case died from cerebral and pulmonary oedema likely to be due to an acute episode of hyponatraemia, the result of aldosterone deficiency and aggravated by fluid overload. A state of hypo-osmolality leading to swelling of brain cells causing encephalopathy with peri-cellular brain oedema and increased intracranial pressure [7, 17].

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