CASE REPORT

Congenital adrenal hypoplasia presenting as a chronic respiratory condition

K Schwarz, R Thwaites, A Minford, C Day, G Butler

Arch Dis Child 2003;**88**:261–262

We describe two children with oxygen dependence, which resolved when congenital adrenal hypoplasia was diagnosed and treatment initiated. Chronic respiratory distress can be a symptom of adrenal hypoplasia and this should be taken into consideration when investigating a child with unexplained chronic respiratory difficulties. Respiratory symptoms resolve very quickly when the underlying condition is recognised and treated.

Compared with the more familiar congenital adrenal hyperplasia, congenital adrenal hypoplasia is a rare cause of primary adrenocortical failure. The features are of complete adrenal insufficiency, which usually presents early in life with collapse or convulsions, or slightly later with vomiting and poor weight gain. Typical biochemical disturbances are hyponatraemia, hyperkalaemia, hypoglycaemia, and metabolic acidosis. Cortisol concentrations are low or undetectable with no response to stimulation with ACTH. ACTH concentrations are high and 17-OH-progesterone concentrations are normal.¹

Prolonged respiratory symptoms have not been described as a presenting feature of congenital adrenal hypoplasia. We describe two children whose respiratory symptoms resolved when congenital adrenal hypoplasia was diagnosed and treatment with hydrocortisone initiated.

CASE 1

A 2 month old baby girl was admitted with cough and breathlessness. She was the first child of related Pakistani parents and was born at term with a birth weight of 2.9 kg. She had required admission to the special care baby unit shortly after birth for hypoglycaemia.

On admission she was tachypnoeic and recessing. Lung fields were clear on auscultation and chest x ray examination was normal. Over the following two weeks her respiratory distress increased and she became oxygen dependent. She required around 30% headbox oxygen to maintain normal oxygen saturations. Repeat chest x ray examination showed patchy infiltrative changes; she remained unwell despite treatment with intravenous antibiotics. The following investigations were normal: nasopharyngeal aspirate for respiratory syncytial virus, antibodies for respiratory viruses, mycoplasma titre, pernasal swab for pertussis, mantoux test, serum α_1 antitrypsin, serum immunoglobulins and IgG subclasses, T cell function, barium swallow, pH studies, sweat test, and echocardiogram. A computed tomography scan of her chest performed because of persistent symptoms showed bilateral areas of collapse and consolidation. A lung biopsy showed mild pulmonary oedema but no other abnormality.

She developed hyponatraemia and hyperkalaemia while on intravenous fluids (4% dextrose/0.18% saline) and had a hypoglycaemic seizure with a blood glucose of <0.5 mmol/l when her fluids were restricted to 80 ml/kg/24 h.

Three days later she had a further seizure while on full enteral feeds. Serum sodium was 113 mmol/l, potassium 6.5 mmol/l, and blood sugar 1.6 mmol/l. This resulted in cerebral oedema necessitating ventilation on the paediatric intensive care unit. A preliminary diagnosis of severe adrenal dysfunction was made and she improved when started on hydrocortisone.

Further endocrinological investigations revealed a low random cortisol (<25 nmol/l, normal range 100–600 nmol/l), a normal 17-OH-progesterone (<2.0 nmol/l, normal range 0–12.0 nmol/l). ACTH and plasma renin activity could not be assayed but subsequently showed increased levels even after hormone replacement was initiated. Cortisol concentrations were undetectable before and after Synacthen. Serum FSH, LH, TSH, and androstendione were all normal. Thyroxine concentrations were marginally low but subsequently normalised on recovery. Abdominal ultrasound scan and magnetic resonance imaging of the head showed normal adrenals and pituitary gland. The results of these investigations were thought to be consistent with congenital adrenal hypoplasia.

Treatment with hydrocortisone and fludrocortisone resulted in a rapid improvement in her clinical state and complete resolution of her respiratory symptoms. Two weeks after starting treatment she was bottle feeding normally and in air after having been oxygen dependent and unable to feed for the previous five weeks.

At the age of 5 years she has remained well on hydrocortisone and fludrocortisone and has had no recurrence of her respiratory symptoms. Her growth and development are normal.

CASE 2

This patient was the first child of Pakistani consanguineous parents. She was born post-term, weighing 2.5 kg. At 6 hours of age she became hypothermic and hypoglycaemic. Examination and initial septic screen were normal. Her blood sugars were easily maintained on 10% dextrose and then on milk feeds.

On day 4 she was tachypnoeic and required oxygen. She was treated with intravenous antibiotics but failed to improve. Echocardiogram revealed a normal heart. On day 7 she was noticed to have increased skin pigmentation, hyponatraemia, hyperkalaemia, and a persistent oxygen requirement (maximum 33% headbox oxygen). She remained oxygen dependent for 18 days.

Three chest x ray examinations were performed during the course of her illness. All showed clear lung fields. Culture of nasal secretions grew normal respiratory flora only. Serum α_1 antitrypsin, immunoglobulins, and IgG subclasses were all normal. Endocrine investigation revealed a random cortisol <20 nmol/l (normal range 100–600 nmol/l), ACTH >1200 ng/ml (normal range 0–47 ng/ml), and 17-OH-progesterone <2.0 nmol/l (normal range 0–12 nmol/l). No steroids were identified in her urine. A short Synacthen test confirmed adrenal hypofunction with a cortisol concentration of

<20 nmol/l 30 minutes post-Synacthen. Plasma renin early in treatment was increased at 18.1 pmol/ml/h. An abdominal ultrasound scan showed a normal right adrenal, but the left adrenal was not visualised. Magnetic resonance imaging scan of her brain was normal.

A diagnosis of congenital adrenal hypoplasia was made, and sodium supplements and hydrocortisone were commenced on day 20, which led to a rapid improvement and resolution of her respiratory symptoms. Her electrolytes normalised when treatment with fludrocortisone was commenced.

She was discharged on day 27, gaining weight on demand bottle feeds, with no respiratory symptoms and normal oxygen saturations. She was last reviewed aged 14 months making good progress on fludrocortisone and hydrocortisone. She has had no further respiratory symptoms and her development is progressing normally.

DISCUSSION

Congenital adrenal hypoplasia is a well known condition that was first described in 1948.¹ The hereditary forms can be X-linked or autosomal recessive,¹ and the gene for the X-linked form (DAX-1 gene) has recently been described.² Clinical symptoms are usually those of complete adrenal insufficiency presenting early in life, but do vary slightly according to the underlying aetiology.¹ The X-linked type can be associated with Duchenne muscular dystrophy and/or glycerol kinase deficiency as this is part of a contiguous gene syndrome.³ Other unusual presentations with progressive high frequency hearing loss,⁴ profound hyperpigmentation,⁵ and monosomy 7⁶ have also been described.

Both our cases are girls, making it likely that they have the autosomal recessive form of congenital adrenal hypoplasia. Most research has been carried out on the X-linked form of congenital adrenal hypoplasia, but we are not aware of case reports linking chronic respiratory symptoms with any type of congenital adrenal hypoplasia. Both of our cases were born at full term and had chronic respiratory symptoms with an oxygen requirement for which no cause could be found despite extensive respiratory investigations. Symptoms resolved very quickly after initiation of treatment with steroids.

It could be argued that symptoms resolved because of treatment with steroids regardless of the underlying condition, but doses used for treatment of adrenal hypoplasia are very small compared with steroid doses used for treatment of lung conditions and symptoms resolved very quickly without recurrence.

There is some evidence that preterm babies with a poor cortisol response to stimulation with ACTH develop more severe bronchopulmonary dysplasia. It is thought that an insufficient

cortisol excretion in times of stress leaves these infants more vulnerable to continuing lung injury.^{7,8} A similar mechanism may be responsible for the respiratory difficulties in our patients with adrenal hypoplasia although these babies did not have immature lungs. Previous research has shown that endogenous glucocorticoids play an important role in the development of the lungs and in lung repair,⁷ and future research may help to clarify this role.

We conclude that chronic respiratory distress can be a symptom of adrenal hypoplasia and that this should be taken into consideration when investigating a child with unexplained chronic respiratory difficulties, particularly if these symptoms are associated with electrolyte disturbances and/or hypoglycaemia. Baseline endocrinological investigations, including cortisol and ACTH, can easily be performed, and respiratory symptoms appear to resolve very quickly when the underlying condition is recognised and treated.

.....

Authors' affiliations

K Schwarz, R Thwaites, A Minford, C Day, Paediatric Department, Bradford Royal Infirmary, UK

G Butler, Paediatric Endocrinology, Leeds General Infirmary, UK

Correspondence to: Dr K Schwarz, Consultant Paediatrician, Huddersfield Royal Infirmary, Acre Street, Lindley, Huddersfield HD3 3EA, UK

Accepted 14 August 2002

REFERENCES

- 1 **Brook CD**. Congenital adrenal hypoplasia. In: *Clinical paediatric endocrinology*. Oxford: Blackwell Scientific Publications, 1989:371–4.
- 2 **Peter M**, Viemann M, Partsch CJ, *et al*. Congenital adrenal hypoplasia: clinical spectrum, experience with hormonal diagnosis, and report on new point mutations of the DAX-1 gene. *J Clin Endocrinol Metabol* 1998;**83**:2666–74.
- 3 **Cole DE**, Clarke LA, Riddell DC, *et al*. Congenital adrenal hypoplasia, Duchenne muscular dystrophy, and glycerol kinase deficiency: importance of laboratory investigations in delineating a contiguous gene deletion syndrome. *Clin Chem* 1994;**40**(11 pt 1):2099–103.
- 4 **Zachmann M**, Fuchs E, Prader A. Progressive high frequency hearing loss: an additional feature in the syndrome of congenital adrenal hypoplasia and gonadotrophin deficiency. *Eur J Pediatr* 1992;**151**:167–9.
- 5 **Jones D**, Kay M, Craigen W. Coal-black hyperpigmentation at birth in a child with congenital adrenal hypoplasia. *J Am Acad Dermatol* 1995;**33**(2 pt 2):323–6.
- 6 **Le SQ**, Kutteh WH. Monosomy 7 syndrome associated with congenital adrenal hypoplasia and male pseudohermaphroditism. *Obstet Gynaecol* 1996;**87**(5 pt 2):854–6.
- 7 **Watterberg KL**, Scott SM. Evidence of early adrenal insufficiency in babies who develop bronchopulmonary dysplasia. *Pediatrics* 1995;**95**:120–5.
- 8 **Watterberg KL**, Scott SM, Backstrom C, *et al*. Links between early adrenal function and respiratory outcome in preterm infants: airway inflammation and patent ductus arteriosus. *Pediatrics* 2000;**105**:320–4.