Prenatal Cushing’s Syndrome Secondary to Nodular Adrenocortical Hyperplasia with Unsuppressed Plasma ACTH Levels

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ABSTRACT

We report a newborn girl (36th week of gestation, birth weight 1,054 g) with Cushing’s syndrome secondary to nodular adrenocortical hyperplasia with normal plasma ACTH levels. From birth she was hypertensive, hyperglycaemic and slightly hirsute. Hypercortisolism (<1,380 nmol/l) was accompanied by normal plasma ACTH levels (8.64-23.9 pg/ml). A 48-h dexamethasone suppression test decreased plasma cortisol by 35%, indicating some degree of ACTH dependency. However, there was no ACTH rise on CRF test. MRI showed enlarged adrenal glands with a possible cyst on the right; the pituitary gland was normal. At the age of 6 weeks she underwent bilateral adrenalectomy. Histology showed enlarged adrenals with multiple non-pigmented nodules (up to 5 mm) in both glands. However, over the next few weeks she developed liver failure and sepsis. She died at the age of 3 months. Post mortem examination confirmed the diagnosis. Nodular adrenocortical hyperplasia may present at birth with severe Cushing’s syndrome and unsuppressed ACTH levels, indicating some degree of ACTH dependency in this condition.

KEY WORDS

Cushing’s syndrome, nodular adrenocortical hyperplasia, newborn, ACTH-dependent

INTRODUCTION

Cushing’s syndrome is an uncommon disorder in children. Most cases of Cushing’s syndrome in newborns and infants are ACTH independent, the majority of them caused by adrenocortical carcinoma. Other causes of childhood ACTH-independent Cushing’s syndrome include primary pigmented nodular hyperplasia which often forms part of the familial autosomal dominant condition called Carney complex, McCune-Albright syndrome and ACTH-independent nodular adrenal hyperplasia. In the last case the pathogenesis is unknown, but in one infant an activating mutation in the stimulatory G-protein was detected.

ACTH-dependent Cushing’s syndrome is extremely rare in infants. In older children and adults, when inorganic causes are excluded, the commonest causes of ACTH-dependent Cushing’s syndrome are Cushing’s disease and ectopic ACTH syndrome accounting for 70% and 15% of cases, respectively. ACTH-dependent macronodular adrenal hyperplasia associated with one or more nodules from 0.5 to 5 cm in diameter have been described in adults. These patients tend to be older and have had symptoms for a longer time, but otherwise present with the classical clinical features of Cushing’s syndrome, such as obesity, moon face, hirsutism and hypertension. In children, the earliest and most reliable indicators of hypercortisolism are weight gain and growth arrest. Here we describe an unusual case of Cushing’s syndrome presenting at birth with severe intrauterine growth retardation, hypertension and hyperglycaemia, whose diagnosis was complicated due to unexpected plasma ACTH levels.

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VOLUME 18, NO. 11, 2005
PATIENT REPORT

A baby girl with severe intrauterine growth retardation (IUGR) (birth weight 1,054 g, <-3 SD) was born at the 36th week of gestation by emergency Caesarean section due to breech presentation and signs of foetal distress. Severe asphyxia and metabolic acidosis were diagnosed at birth. IUGR was diagnosed at the 20th week of gestation, but no reason was found. The mother had been in good health. Family history revealed three cases of renal tumours with arterial hypertension - the infant's grandmother and twin aunts, who had all been operated. The leading clinical symptoms were hypertension from birth and hyperglycaemia from the second day of life. She had some features of Cushing's syndrome, such as moon face, muscle weakness and slight hirsutism on her back. The skin was paper-thin, with no patches or spots of skin pigmentation indicating McCune-Albright syndrome or Carney complex. There were no signs of cholestasis.

Clinical investigations

At first hyperglycaemia was thought to be due to transient diabetes mellitus of the newborn, but both C-peptide and insulin levels were normal (0.39 nmol/l and 10.7 mU/ml, respectively). Repeated hormonal investigations, in the second and third weeks of life, showed hugely elevated plasma cortisol levels with no diurnal variation (all samples >1,380 nmol/l), whereas plasma ACTH levels (8.64, 23.9 and 27.5 pg/ml) remained in the normal range. Serum DHEAS (>27.1 mmol/l), testosterone (41.4 nmol/l), androstenedione (223 nmol/l) and 24-hour urinary free cortisol levels (UFC, 240 mmol/24 h) were all increased. Serum TSH, free triiodothyronine and eaeotholamine levels were all normal.

A 48-h low-dose dexamethasone suppression test (20 μg/kg) decreased plasma cortisol by 35% (3,650 to 2,389 nmol/l), UFC by 72% (719 to 202 nmol/24 h) and ACTH from 27.5 to 8.1 pg/ml. However, as the patient became very hypertensive and her general condition deteriorated during the test, we did not perform the high-dose dexamethasone suppression test. There was no ACTH response to a CRF test (Table 1), which should exclude pituitary Cushing's disease. Ectopic ACTH syndrome was still possible, but the basal ACTH level was too low for that. Thus an adrenal tumour was the most likely diagnosis. Ultrasound scans and MRI showed enlarged adrenal glands (20 x 10 mm), with a possible small (4 mm) cystic lesion on the right. MRI of the head including the pituitary gland was normal.

The infant failed to thrive and showed poor tolerance to enteral feeds. She received 18 days of additional parenteral feeding and by the end of her third week of life she had gained 330 g in weight. Over the first 6 weeks both blood glucose and arterial blood pressure figures were difficult to control in spite of insulin infusion (1.2-1.4 U/kg/day) and different antihypertensive medications (enalapril, propranolol). Ketoconazole, the only available drug for Cushing's syndrome in our country, was considered for medical treatment. However, due to the limited information about the efficacy of ketoconazole in children with Cushing's syndrome, abnormal liver function tests in a patient and a recent report of fatal liver failure to ketoconazole, surgical intervention was considered more favourable.

At the age of 6 weeks (weight 1,750 g) bilateral adrenalectomy was performed. The operation was complicated by major bleeding from the liver and the left adrenal gland could not be totally removed. During the weeks following the operation her plasma cortisol levels remained moderately elevated (678-1,113 nmol/l) without any glucocorticoid replacement therapy. She became normotensive and euglycaemic. However, the postoperative course was complicated by necrotising enterocolitis and several episodes of infection. Over the following weeks her liver function gradually deteriorated, and at the age of 3 months she died of sepsis.

Post mortem pathological examination showed enlarged adrenal glands; the left, in two pieces, measured 3.0 x 2.0 x 0.7 cm, and the right 2.7 x 2.0 x 1.0 cm. The zona fasciculata was characterised by proliferated cells that formed non-pigmented multiple nodules in both glands with diameter up to 5 mm. Adjacent adrenal tissue between the nodules was normal with some degree of hyperplasia. There were no signs of malignancy. Histology of the liver showed haemochromatosis.

JOURNAL OF PEDIATRIC ENDOCRINOLOGY & METABOLISM
TABLE 1
The results of corticotropin-releasing factor (CRF) stimulation test (1 µg/kg)

<table>
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<th>Time</th>
<th>-15 min</th>
<th>0 min</th>
<th>+15 min</th>
<th>+30 min</th>
<th>+45 min</th>
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<td>ACTH (pg/ml)</td>
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<td>24.7</td>
<td>31.8</td>
<td>19.9</td>
<td>17.6</td>
<td>23.8</td>
</tr>
<tr>
<td>Cortisol (nmol/l)</td>
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<td>4.55</td>
<td>4.66</td>
<td>4.71</td>
<td>4.39</td>
<td>3.51</td>
<td>3.75</td>
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</tbody>
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DISCUSSION

We have described an unusual case of prenatal Cushing's syndrome secondary to nodular adrenocortical hyperplasia. The most striking finding in this case was the normal plasma ACTH levels whereas one would expect to see suppressed ACTH levels.

Cushing's syndrome in children is rare. The most common cause is Cushing's syndrome in infants under 1 year of age is adrenal tumours, especially adrenal carcinomas accounting for 52%, and adrenal adenomas accounting for 42% of all adrenal tumours in infancy. Thus our first hypothesis was an adrenal tumour, particularly bearing in mind that they are 3-4 times more common in girls than in boys. However, with an adrenal tumour one would expect to find suppressed plasma ACTH levels, while in our child they were in the normal range. In addition, ACTH levels were not above the normal range, as seen in Cushing's disease or ectopic ACTH syndrome, in which the values can be elevated up to 700 pg/ml. In addition, there was no significant rise in ACTH or cortisol levels during the CRF test, indicating the adrenal glands as the primary cause of the disease.

Another possible cause we considered was primary pigmented nodular hyperplasia which often forms part of the Carney complex. Carney complex is a multiple neoplasia syndrome featuring cardiac, endocrine, cutaneous and neural tumours, as well as a variety of pigmented lesions of the skin and mucosa. It is inherited as an autosomal dominant trait. In five patients the diagnosis was made at birth. However, our patient did not have any spotty skin pigmentation, myxomas, or other signs of this syndrome. Histology of the adrenal gland in our patient showed non-pigmented nodules with normal adrenal tissue with some degree of hyperplasia between the nodules, whereas in primary nodular hyperplasia the nodules are pigmented and adjacent adrenal tissue is atrophic.

Several cases of Cushing's syndrome associated with McCune-Albright syndrome have been reported, but neonatal presentation seems rare. A recent study of 113 children with McCune-Albright syndrome revealed seven children with hypercortisolism with earliest presentation at the age of 6 months. Classic presentation, with the triad of precocious puberty, skin lesions and osteotis fibrous dysplasia, occurred in two children, and another two patients had two signs of the triad. Two girls with hypercortisolism did not have any signs of the triad nor did they have the Arg251 mutation in the G-protein α-subunit. Thus McCune-Albright syndrome may still be a possible cause, but the very early onset of the disease and the unsuppressed ACTH levels makes a diagnosis of McCune-Albright syndrome unlikely. Another interesting case of Cushing's syndrome caused by an activating mutation in the stimulatory G-protein was described in a 3-month-old infant. He was a healthy neonate with normal birth weight and length. At 3 months of age he was growing poorly, and hypercortisolism with suppressed ACTH levels was found. Histology showed non-pigmented adrenocortical hyperplasia. He had no evidence of cafe-au-lait pigmentation. However, he had asymptomatic fibrous dysplasia in the proximal femur and humerus. Plasma ACTH levels were constantly suppressed and the high dose dexamethasone test did not suppress serum cortisol levels, indicating ACTH-independent Cushing's syndrome.

The leading clinical symptom and problem to control was hypertension. Hypertension is a prominent feature of Cushing's syndrome, occurring in up to 75% of cases. ACTH-dependent macro-nodular adrenal hyperplasia is a condition in which hypertension is particularly frequent and severe.
However, this disease has been described only in adults, especially in older people. Macronodular hyperplasia is thought to result from long-standing adrenal ACTH stimulation that leads to autonomous adrenal adenoma formation. Thus the adrenals become more hyperplastic and secrete more cortisol for a given ACTH level and this may lead to autotumour suppression. Macronodular adrenal hyperplasia has been regarded as an ACTH-dependent form of Cushing's syndrome, even though ACTH levels may be relatively low and dexamethasone suppressibility less marked than in other cases of Cushing's disease. We could not perform the high-dose dexamethasone suppression test because the patient's general condition deteriorated (she became very hypertensive) during the low-dose dexamethasone suppression test. At the end of the 48 h low-dose dexamethasone suppression test plasma cortisol decreased by 33% and UFC by 72%. These test results are consistent with reports from adults with macronodular adrenal hyperplasia in whom cortisol levels are less suppressed than in pituitary-dependent Cushing's disease, but are more suppressed than in adrenal tumours. We suggest that in those her hypothalamo-pituitary hyperfunction preceded the development of nodular adrenal disease and after birth she was left with some degree of pituitary dependency.

The unfavourable post-operative course may be explained by the very high and long-lasting cortisol levels, suggesting an inadequate cure, and probably also by severe changes in all organs already presenting before the operation. Though cortisol levels decreased to near normal and the patient became euglycaemic and normotensive after the operation, she suffered several episodes of infection, suggestive of immunosuppression. She died at the age of 3 months of sepsis.

CONCLUSIONS

Nodular adrenocortical hyperplasia may present at birth with severe intrauterine growth retardation, hypertension and hyperglycaemia. Differentiation between ACTH-dependent and ACTH-independent disease may present significant difficulties because measurable levels of ACTH may be seen. Early severe hypercortisolism affects all organ systems and thus likely carries an unfavourable prognosis.

REFERENCES


