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CASE REPORT

# Cushing's Disease in Children: Report of Three Cases

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Cushing's disease is rare in children and adolescents. We report the clinical presentations of three children with Cushing's disease. All three exhibited the typical symptoms and signs of weight gain and growth retardation. Two also demonstrated personality changes, hypertension and hypokalemia, the last of these being rarely reported in patients with Cushing's disease. Lack of diurnal changes in serum cortisol levels was the most common biochemical finding. Serum cortisol levels were suppressed by low-dose dexamethasone in one patient, which is not typical for patients with Cushing's disease. Imaging studies are essential for localizing the tumor. Transsphenoidal surgery remains the treatment of choice, and pituitary irradiation should be considered for those patients whose tumors cannot be totally removed. Careful follow-up of these patients with awareness of the possibilities of relapse and the complications of hypopituitarism is indicated.

## 1. Introduction

Cushing's syndrome, or hypercortisolism, describes the clinical manifestations of glucocorticoid excess from any sources. Cushing's disease specifically refers to hypercortisolism due to excessive adrenocorticotropic hormone (ACTH) secretion from a pituitary adenoma.<sup>1</sup> It is rare in children and adolescents.<sup>2,3</sup> The early presentations of hypercortisolism in children are weight gain and growth failure.<sup>4-9</sup> Other common symptoms include moon face, plethora,

acne, hirsutism, striae, hypertension, puberty arrest, and personality changes.<sup>4-9</sup> The last of these symptoms has been variably reported in children.<sup>3-7</sup>

Confirmation and differential diagnosis of Cushing's disease is not an easy task, especially in children. Hypercortisolism is usually manifested by the lack of a normal circadian rhythm of cortisol secretion. The localization of lesions usually relies on imaging studies and the suppressibility of the hypothalamic-pituitary-adrenal axis by dexamethasone.<sup>2-6,9-14</sup> The diagnosis and appropriate treatment

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of these children may prevent future adult height deficits and osteopenia.<sup>9,15,16</sup> Transsphenoidal pituitary adenectomy is the treatment of choice in these children, and a high cure rate has been reported.<sup>3–6,8–10</sup> Here, we report the clinical presentations, diagnosis and treatment of three children with Cushing's disease, which may help clinicians to make an early diagnosis in such patients.

## 2. Case Report

### 2.1. Case 1

This boy was diagnosed at the age of 12 years and 9 months, with a history of rapid weight gain for 10 months before admission. Insomnia, decreased appetite, weight loss, depression, and regressive behavior had also been noted for 6 months before admission. He had been treated for depression with no improvement in symptoms. An initial endocrine evaluation revealed some acne on his face, but neither moon face nor buffalo hump was noted. His growth rate was 1.1 cm/year during this period. He had a height of 148.6 cm (25–50<sup>th</sup> percentile), a weight of 34.3 kg (10–25<sup>th</sup> percentile) and blood pressure of 160/110 mmHg. He had signs of puberty; both testes had volumes of 8 mL and pubic hair was at Tanner stage I. His bone age was between 12 years 6 months and 13 years.

Laboratory tests showed serum sodium of 146 mmol/L, potassium of 2.4 mmol/L, and chloride of 101 mmol/L. His plasma ACTH level was 73.9 pg/mL (16.3 pmol/L), and serum cortisol levels were 43.3 µg/dL (1195 nmol/L) at 8 AM and 26.6 µg/dL (734 nmol/L) at 11 PM. His serum cortisol [ $>50$  µg/dL ( $>1329$  nmol/L)] was not suppressed by a low-dose dexamethasone suppression test (dexamethasone 20 µg/kg/day); however, a subsequent high-dose dexamethasone suppression test (dexamethasone 80 µg/kg/day) suppressed the patient's serum cortisol level to 26.1 µg/dL (720 nmol/L). Magnetic resonance imaging (MRI) of the sella turcica disclosed a 0.8-cm pituitary adenoma (Figure 1). The patient underwent transsphenoidal pituitary adenectomy, and transient rhinorrhea of the cerebrospinal fluid was noted. An ACTH-secreting pituitary adenoma was confirmed by pathologic examination. The symptoms, including the psychological problems, improved gradually after surgery.

Unfortunately, recurrence of Cushing's syndrome was noted 1 year after surgery, with symptoms of weight gain, moon face, and emotional instability. Transcranial tumor excision was performed 11 months later, and transient neurologic diabetes insipidus was noted postoperatively. Because residual tumor was detected after surgery, the patient underwent



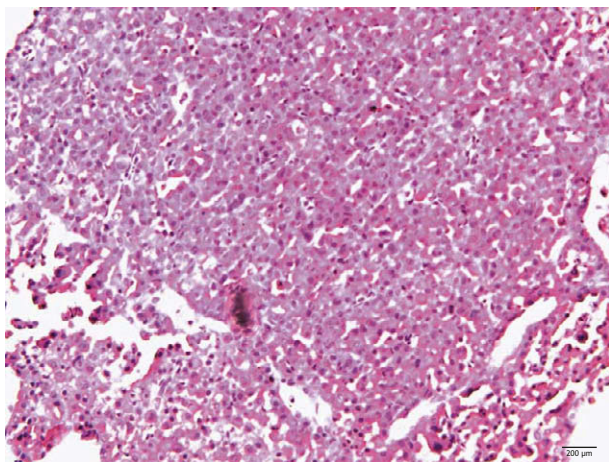
**Figure 1** Magnetic resonance image of case 1. Coronal T1-weighted image with gadolinium enhancement showed a 0.8-cm pituitary adenoma.

radiotherapy with a total dose of 5000 cGy. The signs and symptoms improved, though panhypopituitarism was noted 4 years after the second operation and radiotherapy. The patient received continuing treatment with eltroxin, cortisone acetate, and testosterone cypionate, with no evidence of recurrence after 13 years' follow-up.

### 2.2. Case 2

This girl presented at the age of 11 years and 3 months. She had experienced rapid weight gain from 31 kg to 65 kg, but had only grown by 7 cm in height in 2 years. Acne and facial flushing were also noted. No previous medication had been prescribed. The patient had initially ignored the symptoms, but frequent poor appetite, nausea, vomiting, and abdominal pain developed 6 months prior to attendance at our pediatric endocrine clinic. Moon face, buffalo hump, generalized obesity, and purpuric striae were noted. She had a height of 149.8 cm (75–90<sup>th</sup> percentile), weight of 65 kg (above the 97<sup>th</sup> percentile), and blood pressure of 114/80 mmHg. Her breasts were Tanner stage III, and pubic hair was Tanner stage II. She had not yet undergone menarche. Her bone age was between 12 and 13 years.

Blood chemistry analysis demonstrated a lack of changes in diurnal serum cortisol levels, with 15.4 µg/dL (425 nmol/L) at 8 AM and 15.2 µg/dL (419 nmol/L) at 8 PM. A low-dose dexamethasone suppression test reduced her serum cortisol levels from 23.45 µg/dL (647 nmol/L) to 0.29 µg/dL (8 nmol/L). However, MRI of the sella turcica showed a 0.5-cm mass at the left inferior adenohypophysis. Transsphenoidal pituitary adenectomy was performed, and pathology revealed an ACTH-secreting adenoma, which was immunoreactive for ACTH by immunochemical stain (Figure 2). Transient central diabetes insipidus



**Figure 2** Pathological examination of patient presented in case 2 showed nests of adenomatous tumor cells characterized by vesicular nuclei with nucleoli and acidophilic cytoplasm (Hematoxylin & eosin stain, original magnification, 200 $\times$ ).

and rhinorrhea of cerebral spinal fluid were noted postoperatively. However, the symptoms subsided after surgery, and there was no evidence of recurrence during 12 years' follow-up.

### 2.3. Case 3

A girl aged 10 years and 9 months experienced rapid weight gain from 23 kg to 36.4 kg, with an increase in height of only 3.5 cm in 2 years. No specific drugs had been prescribed previously. Although she had visited other hospitals, no diagnostic conclusion had been reached. She also experienced regressive behavior, depression, and poor school performance during this period. The patient presented at our outpatient clinic with a presentation of moon face with plethora, buffalo hump, acne over the face, and purpuric striae over her thighs. She had a height of 122.5 cm (below the 3<sup>rd</sup> percentile), weight of 36.4 kg (50–75<sup>th</sup> percentile), and a blood pressure of 159/109 mmHg. Her breasts were Tanner stage III and pubic hair was Tanner stage II, but she had not yet undergone menarche. Her bone age was 7 years and 4 months. Blood chemistry analysis showed serum sodium, 141 mmol/L; potassium, 2.9 mmol/L; and chloride, 103 mmol/L.

A series of studies were performed under the impression of Cushing's syndrome. The patient's baseline endocrine data showed ACTH level to be 41.4 pg/mL (9.11 pmol/L) in the morning, and serum cortisol levels of 28.2  $\mu$ g/dL (778 nmol/L) at 9 AM and 15.7  $\mu$ g/dL (433 nmol/L) at 11 PM. The serum cortisol level was not suppressible [27.5  $\mu$ g/dL (759 nmol/L)] by low-dose dexamethasone, but was suppressed to 10.2  $\mu$ g/dL (281 nmol/L) by high-dose dexamethasone. A 0.3-cm heterogeneously-enhanced tumor



**Figure 3** Magnetic resonance image of patient presented in Case 3. Sagittal T1-weighted image with gadolinium enhancement disclosed a nonenhanced tumor in the lower posterior portion of the anterior pituitary gland.

in the lower anterior pituitary gland was suspected on the basis of a brain MRI study (Figure 3). Transphenoidal pituitary adenectomy was performed. The pathologic findings disclosed an ACTH-secreting pituitary adenoma. Transient neurologic diabetes insipidus was noted after surgery. She lost 9.1 kg over the following 10 months. All the symptoms subsided, but panhypopituitarism was confirmed 8 months after surgery. She received treatment with growth hormone, eltroxin, and cortisone acetate and demonstrated normal growth after hormone replacement therapy. There was no evidence of recurrence after two and a half years' follow-up.

### 3. Discussion

Cushing's disease is rare in children, and its clinical presentations differ from those in adults. In children with Cushing's disease, growth retardation may be an early and the most impressive sign.<sup>4-9</sup> Other common presentations include obesity-associated moon face, buffalo hump, bruising striae, hirsutism, hypertension, and psychological disturbances.<sup>4-9</sup> Rapid weight gain and growth retardation were observed in all three patients in this study. Psychological problems, such as depression and behavioral changes, may be the major complaints in children with Cushing's disease. Two of our patients presented with such problems as initial symptoms. Thus a high index of suspicion of Cushing's syndrome is essential for its diagnosis in children with obesity, retarded growth, and behavioral changes.

Two patients (cases 1 and 3) also presented with hypertension accompanied by marked hypokalemia. Hypokalemia is often reported in patients with ectopic ACTH syndrome and macroadenoma; potassium

levels are negatively correlated with plasma cortisol levels.<sup>17,18</sup> The overproduction of cortisol, which has mineralocorticoid effects, has been proposed to explain such phenomena.<sup>19</sup> Another possible mechanism may involve increased deoxycorticosterone or corticosterone levels, as a result of chronic ACTH stimulation.<sup>20</sup> Our experience demonstrated that hypokalemia may not be a rare finding in children with Cushing's disease.

The diagnosis of Cushing's disease is based on the clinical suspicion and biochemical confirmation of hypercortisolism. Lack of a diurnal rhythm in serum cortisol levels is the most sensitive index for hypercortisolism, especially in children.<sup>6,9,21,22</sup> More than 50% of children with Cushing's disease have high serum cortisol levels in the early morning.<sup>3</sup> A relative resistance to glucocorticoid suppression of ACTH secretion has been found in patients with ACTH-dependent Cushing's disease.<sup>11,21,22</sup> Hypercortisolism that can be suppressed by high-dose, but not low-dose dexamethasone is thus the classical feature of this disease.<sup>11</sup> All three patients in this report had high serum cortisol levels with no diurnal changes. Serum cortisol levels were not suppressed by low-dose dexamethasone in two of these patients (cases 1 and 3) but serum cortisol levels were suppressed in case 2. Such a phenomenon has been reported in the literature,<sup>6,7,11,21</sup> It confirms that the recommended dosage of dexamethasone for children in the low-dose dexamethasone suppression test may be too high in some children with Cushing's disease. The results of dexamethasone suppression tests in children with Cushing's syndrome should thus be interpreted with caution. After careful analysis of the above data, imaging studies of the pituitary gland should be arranged in patients with suspected Cushing's disease.<sup>12</sup> Bilateral inferior petrosal sinus samplings with or without ovine corticotropin-releasing hormone stimulation are recommended when pituitary lesions are hard to define in imaging studies.<sup>4,5,9,10,13,14</sup>

Transsphenoidal pituitary adenectomy is the treatment of choice in patients with Cushing's disease.<sup>3-6,8-10</sup> The signs and symptoms of hypercortisolism usually improve gradually within several months following surgery. The hypothalamic-pituitary-adrenal axis usually recovers between 6 and 12 months, and substantial catch-up growth may occur.<sup>4</sup> In patients who cannot be cured by the first operation or who experience recurrence, repeated surgery or radiotherapy are considered as second-line treatments.<sup>5,23</sup> Diabetes insipidus and hypopituitarism may develop after pituitary surgery or radiotherapy.<sup>5,23,24</sup> Under such circumstances, appropriate hormone replacement therapy is indicated. In patients with growth hormone deficiency, growth hormone therapy will be beneficial in terms of their adult height.<sup>9,15</sup>

In conclusion, rapid weight gain but retarded growth in children is a clue to hypercortisolism. A high index of suspicion is important for the early and correct diagnosis Cushing's disease in children.

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