Successful Treatment of Dwarfism Secondary to Long-term Steroid Therapy in Steroid-Dependent Nephrotic Syndrome

Linlin Sun, Dongping Chen, Xuezhi Zhao, Chenggang Xu and Changlin Mei

Abstract

Prolonged steroid therapy is generally used for steroid-dependent nephrotic syndrome in pediatric patients. However, dwarfism secondary to a long-term regimen and its successful reverse is rarely reported. The underlying mechanism of dwarfism is still poorly understood, as both long-term steroid use and nephrotic syndrome may interact or independently interfere with the process of growth. Here, we present a 17-year-old patient with dwarfism and steroid-dependent nephrotic syndrome and the successful treatment by recombinant human growth factor and cyclosporine A with withdrawal of steroid. We also briefly review the current understanding and the management of dwarfism in pediatric patients with nephrotic syndrome.

Key words: dwarfism, nephrotic syndrome, recombinant human growth factor, steroid

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Introduction

Although growth retardation is a documented complication associated with prolonged steroid treatment, dwarfism, however, is a rare adverse effect of the long-term regimen to induce and maintain remission of steroid-dependent nephrotic syndrome in pediatric patients. The underlying mechanism of dwarfism in steroid-dependent nephrotic syndrome patients is still poorly understood, as both long-term steroid use and nephrotic syndrome may interact or independently interfere with the process of growth, which is regulated by the growth hormone—Insulin-like growth factor-1—Insulin-like growth factor binding protein axis (1). Cyclosporine A is indicated as a safe and potent option replacing long-term steroid prescription in steroid-dependent nephrotic syndrome patients, while exogenous growth hormone treatment is suggested to overcome growth retardation and to markedly increase growth velocity by increasing the serum Insulin-like growth factor-1 and Insulin-like growth factor binding protein-3. We present a steroid-dependent nephrotic syndrome patient with dwarfism successfully treated by recombinant human growth hormone and cyclosporine A with withdrawal of steroid, this patient achieved remission of proteinuria without relapse and marked catch-up growth during the 3-year follow-up.

Case Report

A 17-year-old Chinese boy was admitted to our renal division in August 2005 for the first time with recurrent proteinuria and severe growth retardation over 15 years. At age 26 months, he was admitted to a hospital with generalized edema and ascites. Laboratory tests indicated a nephrotic syndrome with proteinuria of 2.2 g/d, serum albumin 23 g/L and cholesterol 7.32 mmol/L. Light microscopic examination of the first kidney biopsy in 1990 revealed that glomeruli, tubules and interstitium were nearly normal. No immunofluorescence microscopy or electron microscopy examination was applied at that time. The patient did not respond to the oral prednisolone (2 mg/kg/d) for 10 weeks and still did not respond to prednisolone plus cyclophosphamide (1.5 mg/kg/d) treatment during the subsequent 4 weeks. Intravenous methylprednisolone (2 mg/kg/d) was then applied and the proteinuria was relieved in 6 weeks; steroid was then tapered gradually by subsequent oral prednisone. However, proteinuria came back once the steroids were reduced to 10 mg per day. Nephrotic syndrome would remit after the dose of steroids was re-increased to 30 mg/d. Thus, steroids were continually used to prevent proteinuria
Figure 1. Typical images of the Chinese boy. A: Short stature, Cushing face with buffalo hump and thinner skin were detected in the 17-year-old patient (left boy in black). B: nearly normalized height and appearance with mild hairiness of the patient (in black) after 3 years’ treatment.

Table 1. Results of Blood Analyses on Admission

<table>
<thead>
<tr>
<th>Laboratory parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Red blood cell count</td>
<td>4.87×10¹²/L</td>
</tr>
<tr>
<td>Hemoglobin level</td>
<td>162g/L(16.2g/dL)</td>
</tr>
<tr>
<td>White blood cell count</td>
<td>8.23×10¹²/L</td>
</tr>
<tr>
<td>Platelet count</td>
<td>293×10⁹/L</td>
</tr>
<tr>
<td>Total serum protein</td>
<td>68g/L</td>
</tr>
<tr>
<td>Serum albumin</td>
<td>39g/L</td>
</tr>
<tr>
<td>Serum globulin</td>
<td>29g/L</td>
</tr>
<tr>
<td>Blood urea nitrogen</td>
<td>3.6mmol/L(10.1mg/dL)</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>20μmol/L(0.2mg/dL)</td>
</tr>
<tr>
<td>Serum uric acid</td>
<td>9.36mmol/L(361.4mg/dL)</td>
</tr>
<tr>
<td>Serum triglycerides</td>
<td>2.35mmol/L(208.0mg/dL)</td>
</tr>
<tr>
<td>Serum low-density lipoprotein</td>
<td>5.74mmol/L</td>
</tr>
<tr>
<td>C-reactive protein</td>
<td>3.2mg/L</td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate(ESR)</td>
<td>5 mm/hr</td>
</tr>
<tr>
<td>Serum IgA</td>
<td>1.99g/L</td>
</tr>
<tr>
<td>Serum IgG</td>
<td>5.98g/L</td>
</tr>
<tr>
<td>Serum IgM</td>
<td>1.01g/L</td>
</tr>
<tr>
<td>Serum complement component C3</td>
<td>1.15g/L</td>
</tr>
<tr>
<td>Serum complement component C4</td>
<td>0.329g/L</td>
</tr>
<tr>
<td>Serum κ-light chain</td>
<td>1.06g/L</td>
</tr>
<tr>
<td>Serum γ-light chain</td>
<td>0.75g/L</td>
</tr>
<tr>
<td>Serum M protein</td>
<td>0g/dL</td>
</tr>
</tbody>
</table>

for 15 years. The patient’s blood pressure began to become mildly elevated in 2002 and he was then treated with monopril (and sometimes nifedipine). Since the onset of the disease and long-term use of steroids, the height of the patient was apparently retarded with an annual increment of only 2-3 cm.

The patient was a normal natural full-term delivery infant at birth with no family inherited disease. On admission to our hospital in August 2005 at age 17, his height was 113.4 cm, sitting height was 62 cm, and body weight was 30 kg (Fig. 1A) with 23.3 kg/m² of BMI. Intellectual development was normal. Cushing face with buffalo hump and thinner skin were detected. The secondary sexual characteristics were undeveloped. Testes were 3 cm in diameter and penis 3 cm in length.

Results of blood tests on admission are presented in Table 1. Urinalysis showed a urine protein level of 2+ with rare erythrocytes in sediment, and a 24-hour urine collection showed 1,590 mg of protein. Measurement of serum cortisol was 52 μg/L (normal range 50-250 ug/L); estradiol 10 ng/L (normal range 0-77 ng/L); testosterone 7 ng/dL (normal range 260-1,320 ng/dL); ACTH 9.9 ng/L (normal range 25-65 ng/L); aldosterone 31.6 ng/L (normal range 59.5-173.9 ng/L); T₃ 0.71 ug/L (normal range 0.45-1.5 ug/L); T₄ 53.8 ug/L (normal range 45-120 ug/L); FT₃ 2.02 ng/L (normal range 1.45-3.48 ng/L); FT₄ 10.5 ng/L (normal range 7-18.5 ng/L); TSH 1.99 mIU/L (normal range 0.5-5 mIU/L). Fast ing growth hormone level was normal with 2.5 ug/L, while insulin-like growth factor-1 reduced to 347.1 μg/L and insulin-like growth factor binding protein-3 reduced to 4242 μg/L. No auto-antibodies (ANA, ENA, ds-DNA, ANCA and Sm) were detected. His bone-age was that of a 6-year-old by hand-wrist x-ray examination (Fig. 2). His skull and pituitary gland was normal based on MRI findings.

To ascertain the kidney pathologic lesion, a repeat-biopsy was applied upon admission to our division in 2005. Mild
Figure 2. Hand-wrist x-ray examination showed bone-age of 6-year-old.

Figure 3. Growth curve (filled triangles) of the patient during the 3-year follow-up. He has been continuously treated with cyclosporine A (filled circles) and recombinant human growth factor (1μ/kg/wk).

Discussion

Blodgett et al (1) first described the impairment of childhood growth with long-term glucocorticoids almost 50 years ago (1956). Doses commonly used for physiological replacement of prednisone (3-5 mg/m²·d; 0.075-0.125 mg/kg·d) can be sufficient for this impairment (2). Children with steroid-dependent nephrotic syndrome usually need prolonged steroid treatment which exposes them to the risk of growth retardation. Here, we present a patient who suffered from dwarfism, the rarely reported severe growth retardation secondary to 15 years of steroid therapy and the marked reverse after treatment with over three years of follow-up.

The pathologic result of this patient’s renal re-biopsy deserves discussion. As in this case, it seems that two common pathologic manifestations coincided: minimal change disease mesangial proliferation was observed by light microscopy. No fibrosis or mononuclear cell infiltration in the interstitium was detected. IgA was predominantly deposited in the mesangial area based on immunofluorescence staining results. Ultra-structural evaluation revealed that electron dense deposits in the mesangial area and the thickness of the basement membrane were normal.

The patient was treated with cyclosporine A (4 mg/kg/d) and prednisone (1 mg/kg/d). After the proteinuria disappeared, the steroid was gradually tapered, maintained at 7.5 mg/d for one year, and then stopped. The dosage of cyclosporine A was gradually reduced to 2.5 mg/kg/d and maintained for over 3 years without recurrence of proteinuria. Recombinant human growth factor (1 μ/kg/wk) was also prescribed. The regimen turned out to be successful and the disease remained in complete remission. Serum levels of Insulin-like growth factor-1 and Insulin-like growth factor binding protein-3 returned to the normal level (412.5 μg/L and 4725.2 μg/L, respectively) after a half year of treatment. The height of the patient increased from 113.4 cm to 161.5 cm (Fig. 1B, Fig. 3) and bone-age to 14 years old after over 3 years of follow-up. Low-dose cyclosporine A (2.5 mg/kg/d) has been maintained to prevent the recurrence of proteinuria and no obvious side effect was found.
and mesangial IgA deposition. This is a very rare finding and there has been no consensus on nomenclature and categorization of this entity (3). From the clinical point of view, no single episode of hematuria was experienced, mesangial IgA deposition in this case has to be regarded as a minimal change nephrotic syndrome with asymptomatic mesangial deposition, although histological diagnosis of mesangial deposition of IgA may comprise different pathogenetic entities. However, the IgA deposition indicates a frequently relapsing course as in our case. A regimen appropriate for minimal-change disease with nephrotic syndrome and preserved renal function was suggested.

Children in first episode of nephrotic syndrome are recommended to be first treated with steroid up to seven months with an increase in benefit (4). For patients who frequently relapse, other immunosuppressive agents should be considered to replace corticosteroid and existing trial evidence is the strongest for cyclophosphamide and cyclosporine A (5). Cyclosporine A is reported to reduce proteinuria in 70-100% of children with steroid-dependent nephrotic syndrome and it is recommended in pediatric patients. Combination therapy using intravenous pulse methylprednisolone and cyclosporine A has been reported to achieve a long-term benefit (6). The present patient attained a good response with this regimen and it was generally well tolerated and safe (7), and the steroid could be gradually tapered until it was stopped without proteinuria recurrence in over 3 years.

Postnatal growth is a multifactor regulating process, and it is hypothesized that growth is regulated by the growth hormone—Insulin-like growth factor-I—Insulin-like growth factor binding protein axis (8). Long-term steriod-induced growth retardation may be due to a combination of factors such as a disruption of the growth hormone—a defect in sex steroid action, a disturbance in calcium and phosphate homeostasis as well as direct effects on the growth plate (9). Long-term corticosteroid treatment alters the pulsatility and secretion of growth hormone by increasing the somatostatin inhibitor tone (10). Chronic steroid prescription also reduces the expression of growth hormone receptors in hepatocytes, leading to lower mRNA levels of Insulin-like growth factor-I in the liver (11). Long-term oral prednisolone has been reported to reduce the serum Insulin-like growth factor-I and Insulin-like growth factor binding protein-3 level (12) as in the present case. The metabolism of calcium and phosphorus could also adversely be influenced by glucocorticoid, resulting in a negative balance and inducing an obstacle to bone growth. Steroids can directly affect the growth plate and decrease chondrocyte proliferation (13) and also inhibit the transcription of the growth hormone receptor in chondrocyte cell cultures, decreasing Insulin-like growth factor-I production (14). The severity of growth retardation mainly depends on the age at disease onset, the severity of the disease and consequently the duration and dose of steroid.

It is also documented that nephrotic syndrome itself can alter growth hormone—Insulin-like growth factor-I—Insulin-like growth factor binding protein axis and can cause growth retardation. Urinary loss of Insulin-like growth factor-I and Insulin-like growth factor binding proteins has been demonstrated in nephrotic syndrome children, which has been suggested to be the cause of the growth retardation (15). The urinary excretion rate of Insulin-like growth factor-I has been reported to be enhanced by five fold and age-related serum level of growth factor-I was significantly decreased in nephrotic patients (16). In addition, there are many other related factors in serum, including calcium, 25-hydroxyvitamin D3, and thyroid hormone, which are combined and lost in urine with their associated binding proteins; all of the above exert effects on growth. Malnutrition or hypoproteinemia is another important cause of growth retardation in NS children (17), which is still poorly understood.

"Catch-up growth", known as the phenomenon that the linear growth rate usually exceeds the normal range, was observed after a period of growth inhibition. We believe in this case that it was the most important result that steroid was stopped before puberty with cyclosporine A. Amelioration of the growth retarding insult can result in a period of supranormal linear growth as described previously (18) and in our case. Growth plate function, which is responsible for catch-up growth, is thought to be appropriate for a younger child, as linear growth and bone maturation reflect longitudinal bone growth at the growth plate (19).

In addition, it was more effective by using growth hormone therapy during the secondary sexual character period when this case became steroid free. Early administration of growth hormone therapy in long-term steroid treated patients might be a better strategy (10). European and US clinical studies showed that rhGH treatment was effective and safe improving height standard deviation score in prepubertal and pubertal children (20, 21). It has been observed that the low serum concentrations of Insulin-like growth factor-1, which mainly contributes to the growth retardation, can be significantly elevated with exogenous growth hormone therapy (22). Linear growth as well as serum Insulin-like growth factor-I concentrations was observed to increase after recombinant human growth factor was given to children on chronic steroids (23). In the present case, recombinant human growth factor (1 μ/kg/wk) was prescribed with around 48.1 cm of height increased and bone-age approaching 14 years old during follow-up. Serum levels of Insulin-like growth factor-I and Insulin-like growth factor binding protein-3 gradually returned to the normal level one-half year later.

In conclusion, dwarfism secondary to long-term steroid therapy and the successful treatment with marked reverse in a pediatric patient with steroid-dependent nephrotic syndrome is rarely reported. Cyclosporine A is a safe and potent option to replace prolonged steroids in patients with minimal change nephrotic syndrome with mesangial IgA deposition. Exogenous growth hormone treatment should be...
early and given long term in pediatric patients with nephrotic syndrome (24, 25). Here, both the cessation of glucocorticoid treatment along with exogenous recombinant human growth factor played important roles in the reverse of dwarfism in this pediatric steroid-dependent nephrotic syndrome patient.

Conflict of Interest
The authors declared no competing interests.

References


