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Table of Contents

Growth hormone therapy in chronic kidney disease

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ABSTRACT

Chronic kidney disease (CKD) in growing children leads to a state of impaired growth due to altered metabolic status and defective growth hormone action. This requires direct intervention over and above the management of the renal disease. The physical deficit of short stature has significant impact on the psychological well-being and quality of life. With increasing availability of recombinant human growth hormone (GH) and its approval in CKD patients with significant short stature, it has been increasingly used in short children with CKD. GH therapy in these patients has significantly improved the final adult height achieved. Two prepubertal children with CKD and severe short stature who were treated with GH for approximately 2 years achieved significant growth benefits and one of them attained satisfactory adult height.

Key words: Chronic kidney disease, growth hormone, growth retardation

Introduction

Chronic kidney disease (CKD) is well-known to manifest with varying degree of alterations in various hormones and their action. This leads to a state of disturbed homeostasis that requires direct intervention over and above the management of the renal disease. In children with CKD, normal growth is invariably impaired, thereby leading to reduced adult height. With advancements in the field of renal replacement therapies and improved longevity of these patients, the physical deficit of short stature has significant impact on the psychological well-being and quality of life. With increasing availability of recombinant human growth hormone (GH) and its approval in CKD patients with significant short stature, it has been increasingly used in these patients in the recent years. Growth hormone therapy in these patients has significantly improved the final adult height achieved.[1] We present two prepubertal children with CKD and severe short stature who were treated with GH with significant benefits. The existing literature on the subject has been reviewed.

Case Reports

Case 1

An 8-year-old female child was evaluated for severe short stature and genu valgum. Her height was 92 cm, corresponding to that at 3 years, with upper and lower segment ratio. The weight was 13 Kg and the bone age was 7 years. Blood urea and serum creatinine were 93 mg/dl and 3.7 mg/dl, respectively. Serum potassium was 3.6 mEq/L, HCO_3: 9.4 mEq/L, calcium: 10.7 mg/dl, phosphorus: 4.2mg/dl, alkaline phosphatase: 687IU/l and intact parathormone: 398 pg/ml. Hemoglobin was 10.2 g/dl, and the thyroid profile was normal (TSH: 3.0 mIU/L, T4: 12 ng/ml). The ultrasound of the kidneys showed bilateral shrunken kidneys, and the work-up for renal tubular acidosis showed a wide anion gap metabolic acidosis (AG = 18) with urine pH = 6.2. Skeletal survey showed features of renal rickets. Initially, she was prescribed iron, Vitamin B12 and folate supplements along with calcium, calcitriol and sodium bicarbonate. On follow-up, she was 96.8 cm tall after 10 months (a gain of 4.8 cm).

In view of the severe short stature with CKD with poor growth despite the correction of anemia, acidosis and calcium – vitamin D status, GH therapy was started at a dosage of 0.25 mg/kg/week in divided daily doses. On GH therapy, at the end of the first year, her height was 107 cm (a gain of 10.2 cm) and in the following year, it was 112 cm (a gain of 5 cm) [Fig. 1]. The total height gain during GH therapy was 15.2 cm over 2 years. Height SD score changed from –4.6 SDS to –3.3 SDS, a gain of 1.3 SDS over the 2 years of GH treatment. Her renal and metabolic parameters on follow-up were as follows: blood urea: 107 mg/dl, serum creatinine: 3.8 mg/dl, calcium: 8.6 mg/dl, phosphorus: 5.7 mg/dl and alkaline phosphatase: 280 IU/L. No adverse effects of GH therapy were observed.

Case 2

A 12-year-old female child with CKD secondary to bilateral

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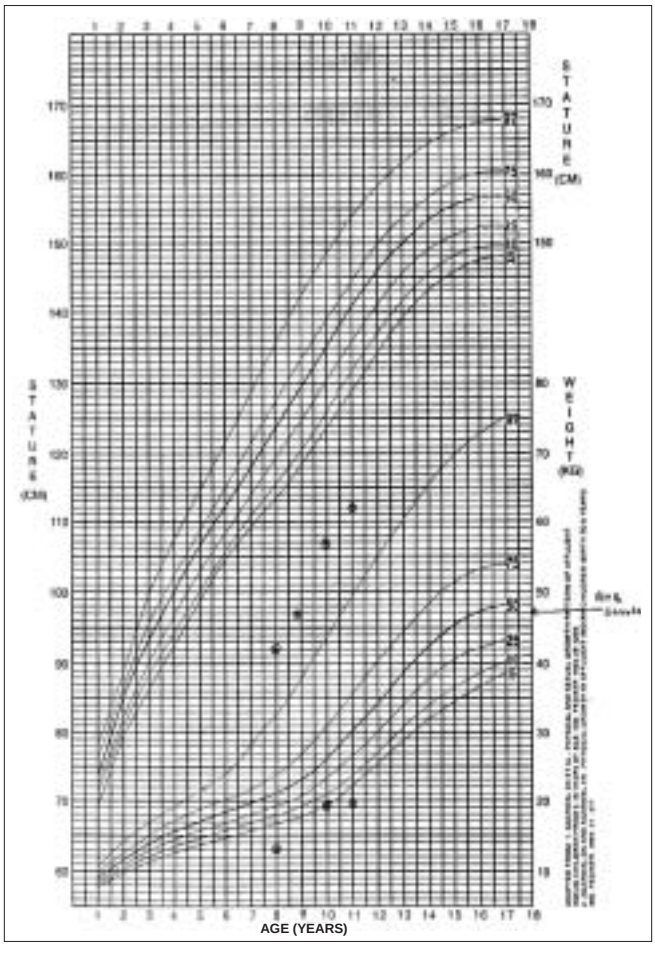

Fig. 1: Growth Chart of the patient in Case 1

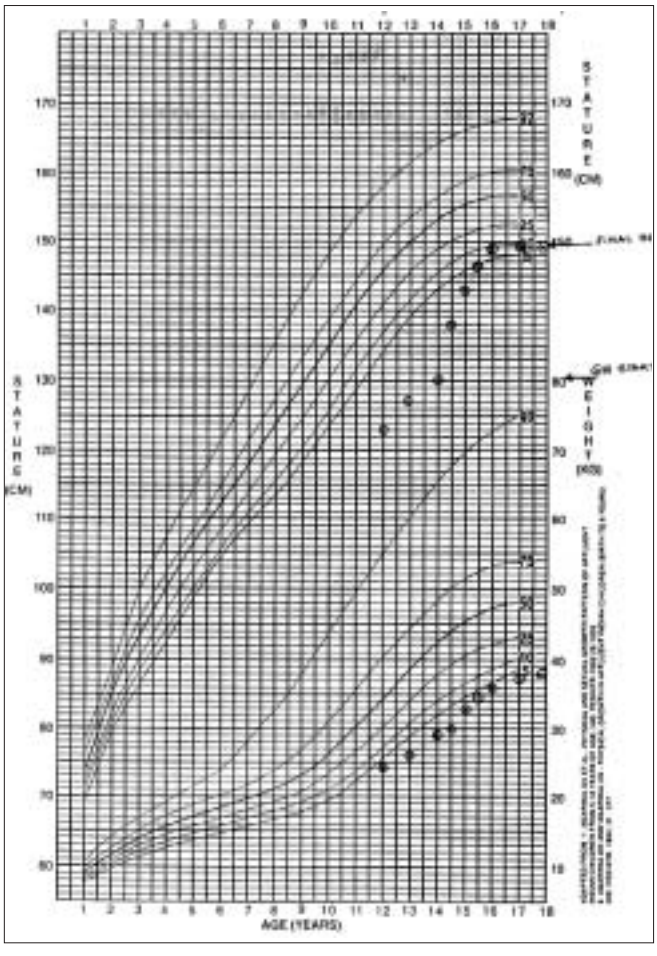

Fig. 2: Growth Chart of the patient in Case 2

vesicoureteric reflux presented with complaints of painful proximal muscle weakness, bone pains and short stature. Her height was 123 cm (height age: 8 years) and weight was 24 kg (weight age: 8 years). Blood urea was 77 mg/dl, serum creatinine: 3.6 mg/dl, calcium: 9.2 mg/dl, phosphorus: 2.4 mg/dl, ALP: 680IU/L and intact PTH: 490 pg/ml. Serum potassium was 3.2 mEq/L, chloride: 104 mEq/L and bicarbonate: 15 mEq/L. She had a wide anion gap metabolic acidosis and a urine pH of 5.9. Thyroid function status was normal. Skeletal survey revealed features of mixed renal osteodystrophy. Supportive treatment was optimized with calcium, calcitriol, iron and vitamin B12 supplements, phosphate binders and sodium bicarbonate. On follow-up, her height increased to 130 cm (a gain of 7 cm) over 2 years. GH therapy was started at a dosage of 0.25 mg/kg/week in divided doses. She received GH for next 2 years till the chronological age of 16 years, during which she gained a total of 19 cm (13 cm in the first year and 6 cm in the second year). At 18 years of age, she attained a final height of 149 cm and her weight was 38 kg (weight gain: 14 kg) [Fig. 2].

The change in height SD Score was from –3.8 SDS to –1.6SDS, i.e., a gain of 2.2SDS. Her renal and metabolic parameters on follow-up were: S. creatinine: 4.1 mg/dl, urea: 79 mg/dl, calcium: 9.6 mg/dl, phosphorus: 3.6 mg/dl and ALP: 271IU/L.No adverse effects were observed on follow-up 2 years after discontinuing the GH therapy.

Discussion

Chronic kidney disease is known to manifest with alterations in the endocrine system, and adversely impacts growth hormone metabolism and their action. In children with CKD, normal growth is invariably impaired, leading to reduced adult height.[1,2]

Growth deficit are some of the initial manifestations of uremia and renal tubular acidosis . The defects that are implicated in the pathogenesis include the deficient production of $1,25(OH)_2$ vitamin D3, metabolic acidosis, dyselectrolytemia, anemia, reduced caloric intake, protein loss and defective GH action. Short stature with final adult height more than –2SD below mean was observed in 60-75% of CKD children before the advent of GH therapy in CKD.[2] Even with adequate renal replacement therapies

and a successful renal transplant, growth may not be normal. Prolonged glucocorticoid therapy in some of these cases may contribute to growth defect. In a series, mean height gain after transplantation was only 0.11 SD in the first 4.5 years.[3]

The defective GH action in CKD is characterized by normal to high GH levels and low IGF-1 levels due to defective hepatic production of IGF-1 secondary to low hepatic GH receptor gene expression.[4] Another possible molecular mechanism is the reduced density of GH receptors in GH target organs in the uremic state. Low levels of GH-binding protein are observed in CKD as in the GH insensitivity states such as Laron's dwarfism, chronic malnutrition and insulin-dependent diabetes mellitus.[5] Uremia may cause a postreceptor defect in GH signal transduction by reducing the phosphorylation and nuclear translocation of GH-activated STAT proteins.[4] IGF and IGFBP-3 maybe low in protein-losing renal disease, where the IGF-IGFBP3 complexes are lost in urine.[3]

Although CKD or post-renal-transplant-associated growth disorder is not due to GH or IGF deficiency, GH therapy can accelerate skeletal growth, probably by increasing the molar ratio of IGF peptides to IGFBPs, and hence, their growth inhibitory effects are overcome.[3] Growth hormone stimulation test is not required before starting GH treatment in CKD patients. A retrospective analysis of the impact of rhGH therapy given for a mean duration of 5.3 years on linear growth in 183 patients with chronic renal failure (CRF) has showed significantly improved height standard deviation score (Ht SDS) in predialysis group from –2.6 to –2.1, in the dialysis group from –2.7 to –2.3 and in the post-transplant group from –3.1 to –2.8.[6] The benefit of rhGH therapy was apparent in both the short and long term.[7] The maximum benefit was seen in the early therapy before dialysis or transplantation when an irrecoverable loss of height potential occurs with a delay in the starting treatment.

In our first patient, a height gain of 15.2 cm was observed in 2 years (Ht SDS gain of 1.3SDS) and the first patient is still continuing on GH therapy. In the second case, a height gain of 19 cm was achieved in 2 years (Ht SDS gain 2.2 SDS) and a satisfactory final height of 149 cm was achieved.

The economic implication of prolonged GH therapy is one of the major issues, and has an overbearing impact on the management of these patients. With considerable cost burden involved in the renal replacement therapy, added cost of GH therapy imposes a tremendous financial burden. This restricts the usage of GH therapy for dosage and duration desired for optimum benefits. However, with significant improvement in height and the resultant psychological and quality of life improvements, GH therapy should be advised in all cases of significant short stature with CKD, starting as early as possible and continuing for as long as possible till the final adult height is achieved. For best results, other factors that negatively contribute to growth such as anemia, malnutrition, calcium-phosphate abnormality, acidosis and associated thyroid abnormality should be aggressively treated, and the treatment for these problems should be optimized before starting the GH therapy. The exemplary results in height gain achieved by GH therapy in these patients could effectively substitute the concept of preemptive renal transplant for catch-up growth in children with CKD.

Chronic kidney disease adversely affects the growth prospects of the child and markedly impairs the final height. Advance renal replacement therapies have significantly enhanced the lives of these patients and improved the longevity. Early initiation with adequate dosage and duration of GH therapy and a close observation on other defects contributing to short stature in these patients can help in achieving a better adult height and can go a long way in improving their overall physical and psychological well-being. GH therapy can be a satisfactory substitute for preemptive renal transplant for achieving adequate catch-up growth in uremic short children.

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