RESEARCH PAPER

Efficacy of Growth Hormone Treatment in Children With Chronic Kidney Disease: Tunisian Experience

A BOUSSETTA,[1,3] R LAAMOURI,[2,3] M JELLOULI,[1,3] O NAIJA,[1,3] T GARGAH[1,3]

From [1]Pediatric Nephrology Department, Charles Nicolle Hospital; [2]Faculty of Medicine of Tunis; [3]University of Tunis El Manar; Tunis, Tunisia.

Correspondence to:
Dr Abir Boussetta,
Pediatric Nephrology Department,
Charles Nicolle Hospital, Tunis, Tunisia.
abir.bousetta@gmail.com
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Objective: To study the effect of using recombinant human growth hormone (rhGH) in growth retarded children with chronic kidney disease (CKD) **Methods**: This was a non-randomized controlled study over 2 years including children in CKD stages 4-5 suffering from growth retardation. Children were divided into rhGH-treated or non-rhGH treated groups. **Results**: A total of 70 children (35 in each group) were enrolled. While the mean (SD) height of 35 children with CKD had increased from 109.5 (26) cm to 116 (26) cm (mean growth velocity 6.5 cm/year; *P*=0.09) prior to rhGH therapy, the same was found to increase from 116 (26) cm at the start of therapy to 125 (25) cm after one year of therapy (*P*=0.02). **Conclusions**: Therapy with rhGH was helpful in catch-up growth in Tunisian children with CKD.

Keywords: *Renal failure, Growth failure, Height velocity.*

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Chronic kidney disease (CKD) is defined as the presence of kidney damage or an estimated glomerular filtration rate (eGFR) less than 60mL/min/1.73 m^2, persisting for three months or more [1]. Growth retardation, which is a major problem for many children with CKD, can result from several causes like cachexia, chronic vomiting, metabolic acidosis, fluid and electrolyte loss, decreased levels of Insulin-like-growth factor 1 (IGF1) and its receptor, puberty delay, renal osteodystrophy and the use of certain growth-inhibiting treatments. However, random fasting serum levels of GH are normal or increased in these children with CKD [2]. The primary aim of this study was to assess whether recombinant human growth hormone (rhGH) therapy was associated with improvement of height and weight in children with CKD. Secondary aims were to assess whether serum protein, hemoglobin level and parathyroid hormone (PTH) had an impact on the growth in children with CKD receiving rhGH therapy.

METHODS

This observational study was conducted in the Pediatric Nephrology Unit of Charles Nicolle Hospital from January, 2016 to December, 2018. Children in CKD stages 4-5 with growth retardation were included and divided into rhGH-treated (Group A) or non-rhGH treated (Group B). Staging was based on eGFR, calculated by the Schwartz formula [3]. After evaluation of the history, anthropometric parameters, clinical examination and routine laboratory investigations, the children were enrolled in the study. Those with growth retardation due to a pathology other than CKD, those with severe osteodystrophy or with contraindications to rhGH were excluded.

As per recommendations for the use of rhGH for children with CKD by the National Kidney Foundation (NKF) 2005 [6], hip *X*-ray and a wrist *X*-ray for bone age estimation were performed, prior to initiation of GH therapy, in children of Group A . Also, GH therapy was not initiated until the PTH and phosphorus levels were greater than 1.5-times the upper limit for age. All rhGH-treated cases and non-rhGH-treated controls were pre-pubertal at study entry. Children with CKD stage 4-5 in regular follow-up, who did not receive rhGH treatment because of socioeconomic issues, or because parents refusal, were enrolled as controls (Group B).

Both cases and controls were regularly followed up by an experienced dietician, ensuring adequate nutritional intake of 100% of the recommended energy intake and 100-120% of the recommended protein intake [4]. Metabolic acidosis and anemia, were treated as per the recommendations of the KDOQI Guidelines [4,5]. Thyroid function was evaluated at the beginning as well as during the course of the study for both groups.

Statistical analysis: Analysis was done on SPSS software, version 23. Unpaired independent *t* test was used to compare the two groups, taking a *P*-value <0.05 as statistically significant.

Parental consent was taken and approval from hospital's ethics committee was obtained before starting the study.

RESULTS

Thirty-five children in each of group A and group B were included in our study. Baseline characteristics of both groups are represented in **Table I**. While the rate of increase in mean height, over the one year prior to initiation of GH therapy was 7.2 cm/year, the rate increased significantly (9 cm/year) after therapy (P=0.02) (**Table II**). Infants had the highest growth rate (13.5 cm/y), followed by children aged over the age of 12 years (7.35 cm/y). The statural gain was 7.27 cm/y for children aged 4 to 12 years, and 6.5 cm/y for children aged 2 to 4 years. This difference in growth rate across age groups was statistically significant (P=0.036). We also noted an increase of 3.9 kg in weight after one year of treatment (P=0.39). The increase in height and weight was significantly greater in treated children compared to the untreated group (**Table II**). Two children from group A, and 5 children from group B entered puberty, the average delay was 10 months for treated children and 16.25 months for the control group. The mean statural gain was 6.25 cm/y for group A and 5.5 cm/y for group B (P=0.7).

We found that none of the parameters like serum protein, hemoglobin, or PTH levels had an influence on growth (P=0.367, P=0.203, and P=0.841, respectively).

Table I Baseline Characteristics of Children With CKD

	rhGH-treated cases (n=35)	*Non-rhGH-treated controls (n=35)*
Age at baseline (y)	9.7(1.1)	9.4 (1.8)
Males[a]	20 (57.1)	26 (74.3)
Age groups[a]		
< 2 y	3 (8)	2 (5)
2-4 y	2 (7)	3 (10)
4-12 y	18 (50)	23 (65)
> 12 y	12 (35)	7 (20)
Dialysis[a]	HD: 11 (33)	HD: 14 (40)
Height SDS at baseline	-2.5 (1.2)	-2.3 (1.02)
Height <-2 SDS (%)[a]	30 (85)	29 (83)
BMI SDS	-0.7 (1.25)	-0.65 (1.13)
Etiologies of CKD[a]		
CAKUT	26 (74)	31 (85.7)
Glomerular nephropathies	2 (6)	1 (2.8)
Hereditary nephritis	4 (11)	1 (2.8)
Urea (mg/dL)	172.3 (3.0)	163 (2.4)
Creatinine (mg/dL)	5.27 (1.9)	4.68 (1.6)
Hemoglobin (g/dL)	9.9 (1.3)	9.58 (1.0)
Serum total protein (g/L)	69.2 (5.2)	67 (4.3)
Serum albumin (g/L)	37.2 (2.4)	36 (1.9)
PTH (pmol/L)	456 (23.9)	389 (22.0)

Values in mean (SD) or [a]no. (%). All P values>0.05. Unknown etiology in 3 and 2 children in the two groups, respectively. CAKUT: congenital anomalies of kidney and urinary tract, CKD: chronic kidney disease, BMI: body mass index, PTH: parathyroid hormone. HD:hemodialysis.

DISCUSSION

Impairment of linear growth in children with CKD reflects both the severity of renal disease and the quality of health care. Failure to grow is most pronounced if renal diseases arise during those vulnerable phases of life when growth velocity in healthy children is at its maximum: during the first year of life and during puberty [7-8]. We found that, without use of rhGH, our patients gained a mean of 7.2 cm/year in height and mean of 2.2 Kg/year in weight, which is the result of comprehensive management including nutritional and conservative treatment [9]. After receiving rhGH, patients gained height at a mean velocity of 9 cm/year, higher than the normal velocity of 5 cm/year. Our results are comparable to the report published by the Food and Drug Administration in 1987, where the annual growth velocity increased from 4.94 (1.4) cm/year for the year before treatment to 10.08 (1.97) cm/year after treatment (P<0.01). A subsequent report published in 1989 noted that the actual velocity after one year of treatment in these five children was 9.8 (1.2) cm/year (P=0.006).

Our study shows significant increase in mean weight after rhGH therapy, of 3.9 kg/year, indicating that GH might help in improving weight, though nutritional care remains the cornerstone for optimal weight gain. Moreover, by comparing the rate of increase in weight in the year before

Table II Comparison of Changes in Height and Weight in Treated and Control Groups

Time point	*Height (cm)*		*Weight (kg)*	
	Group A n=35	*Group B n=35*	*Group A n=35*	*Group B n=35*
1 y before initiation of therapy	109.5 (26)	110 (15)	18.9 (9)	18.1 (7)
At initiation of therapy	116 (26)	115 (9)	21.1 (9)	20.7 (7.05)
After 6 mo of therapy	122.5 (25)	120 (20)	23.6 (10)	22.2 (8)
After 1 y of therapy[a]	125 (25)	120.7 (21)	25 (11)	22.9 (8.1)

Values in mean (SD). [a]P=0.03 both for height and weight comparison between the groups.

WHAT THIS STUDY ADDS?

- This study documents the favorable response of recombinant growth hormone therapy in Tunisian children with chronic kidney disease.

and after therapy, it appears that the nutritional care and routine treatment given to those patients are the main determinants of the weight gain and growth hormone therapy only affects it to a minor degree, in comparison to its effect on height velocity effect [10-13]. As GH therapy raises serum level of PTH, it is advisable to have a close follow-up of PTH levels and readjustment according to the NKF recommendations [14,15].

The limitation of our study is the small number of patients and a non-randomized recruitment design of the study.

To conclude, growth retardation is a major complication of children with CKD. In our study, we found that giving rhGH to children with CKD in Tunisia helps them to catch up their growth due to an increase in the growth velocity. rhGH therapy may be considered in the treatment regimen of these children, provided other factors exacerbating growth retardation are corrected prior to initiation of therapy.

Ethics clearance: Ethic committee of Charles Nicolle Hospital; No. Tun23032016, dated March 23, 2016.
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