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ORIGINAL ARTICLE

Lesley Rees · Geraldine Ward · Susan P.A. Rigden

Growth over 10 years following a 1-year trial of growth hormone therapy

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Abstract The growth of short children with chronic renal failure (CRF) and renal transplants was assessed over 10 years following entry into a 1-year trial of recombinant human growth hormone (rhGH) therapy. Patients were divided into three groups: 6 prepubertal patients with CRF (group 1), mean (range) age at start of trial 7.7 (5.0–10.4) years; 6 prepubertal patients with renal transplants (group 2), age 11.9 (9.5–14.6) years; and 6 pubertal patients with renal transplants (group 3), age 15.6 (14.1–18.3) years. In group 1, the mean (range) height standard deviation score (Ht SDS) increased from –2.9 (–3.7 to –2.2) to –1.9 (–2.9 to –0.5) over 4.0 (0.3–9.1) years of rhGH (P=0.04), and was –1.6 (–2.9 to –0.4) after 10 years of follow-up (NS). In group 2 Ht SDS increased from –3.3 (–4.5 to –1.9) to –2.9 (–5.4 to –0.5) over 2.7 (1.0–6.0) years and was –3.0 (–6.3 to –0.1) at final height (NS). In group 3 Ht SDS increased from –3.4 (–4.3 to –2.6) to –3.0 (–3.4 to –2.2) over 1.4 (0.2–2.3) years (NS) and was –2.5 (–3.0 to –1.9) at final height (P=0.03 from stopping rhGH to final height). Final height was attained in 13 patients, in whom Ht SDS increased from –3.2 (–4.3 to –1.9) to –2.6 (–3.9 to –0.5) on rhGH (P=0.004) and to –2.2 (–4.4 to –0.1) after stopping treatment (P=0.04). Four patients died, 2 have chronic hepatitis C, and 1 has had surgery for parathyroid adenomata. In conclusion, the majority of patients had an improvement in Ht SDS while on rhGH, which was maintained after stopping treatment.

Key words Growth hormone · Chronic renal failure · Post transplant · Final height

L. Rees (✉)
Nephrourology Unit,
Great Ormond Street Hospital for Children NHS Trust,
London WC1N 3JH, UK
e-mail: L.Rees@ich.ucl.ac.uk
Tel.: +44-171-813-8346, Fax: +44-171-829-8841

G. Ward · S.P.A. Rigden
Paediatric Renal Unit, Guy's Hospital, St Thomas Street,
London SE1 9RT, UK

Introduction

It is now 10 years since the beginning of the first United Kingdom trial of the use of recombinant human growth hormone (rhGH) in children with growth retardation due to chronic renal failure (CRF) and after renal transplantation [1]. This trial showed that rhGH is effective in the short term, and there have been many reports since showing similar results [2]. Data from long-term studies are now becoming available, and suggest continuing benefit of rhGH over 5 years of treatment [2–6]. However, the deficiency in the studies is that none are controlled, so that it is not known whether the final height achieved by these patients is better than if they had not received rhGH. We have analysed the growth of the 18 children and adolescents who participated in the United Kingdom trial 10 years ago, to investigate both the subsequent growth of the children who only received a short course of rhGH and the growth of children who received prolonged treatment [1].

Patients and methods

Details of the patients have been published previously [1]. There were three groups of children at the start of treatment, with 6 patients in each group. Group 1 comprised prepubertal children with CRF. The mean (range) age was 7.7 (5.0–10.4) years and the mean glomerular filtration rate (GFR) was 18 (10–27) ml/min per 1.73 m^2; 1 was a girl (patient 2) and their diagnoses were infantile polycystic kidney disease (patients 3 and 4), posterior urethral valve (patient 1) and renal dysplasia (patients 2, 5 and 6). Group 2 comprised prepubertal children with renal transplants. The mean (range) age was 11.9 (9.5–14.6) years and the mean GFR was 66 (27–108) ml/min per 1.73 m^2; 3 were boys (patients 8, 11 and 12) and their diagnoses were posterior urethral valve (patient 8), renal dysplasia (patient 11), focal segmental glomerulosclerosis (patient 9), cystinosis (patients 10 and 12) and unspecified glomerulonephritis (patient 7). Group 3 comprised pubertal patients with renal transplants. The mean (range) age was 15.6 (14.1–18.3) years and the mean GFR was 70 (35–90) ml/min per 1.73 m^2; 4 were boys (patients 15, 16, 17 and 18) and their diagnoses were posterior urethral valve (patient 16), renal dysplasia (patient 15), reflux nephropathy (patient 14), juvenile nephronophthisis (patient 17),

neonatal cortical necrosis (patient 13) and membranoproliferative glomerulonephritis (patient 18).

Children fulfilled the following criteria on entry to the study in 1988: they had attended the clinic for at least 18 months; they were short with height standard deviation scores (Ht SDS) more than 2 SDs below the mean (n=17) or height velocity SD scores more than 1 SD below the mean (n=12); and none had diabetes, uncontrolled bone disease, nephrotic syndrome, or abnormal liver or thyroid function tests. All patients with transplants were receiving prednisolone on alternate days in the morning. The mean (range) doses were: group 2, 14.9 (10.1–17.6) mg/m^2 and group 3, 11.0 (8.6–19.4) mg/m^2.

rhGH (30 units/m^2 per week) was given in daily doses subcutaneously for a median (range) of 0.98 (0.25–0.99) years in the initial study. Patients were then offered the possibility of continuing with rhGH if they wished. The dose was maintained with growth. Height was measured by the same observer (G.W.) at each visit in all patients (whether on rhGH or not) while in the paediatric clinic. Final height, defined as no measurable increase in height over 1 year, was obtained from the appropriate adult unit. Changes in management, renal function and adverse events were recorded over the 10 years. Ht SDS before and after rhGH and after 10 years were compared using paired t-tests.

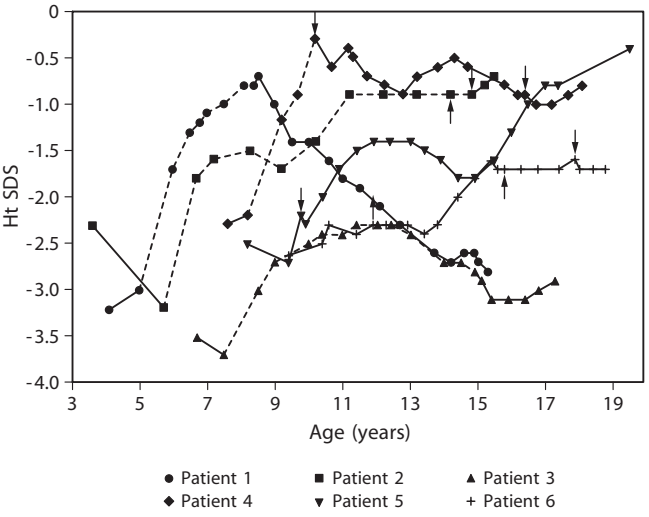

Fig. 1 Height standard deviation score (*Ht SDS*) of the children in group 1. The duration of recombinant human growth hormone (rhGH) is shown by a *dotted line*; ↓ represents time of transplantation; ↑ represents start of dialysis

Results

Group 1 (Fig. 1, Table 1)

Ht SDS (British height data [7]) for each child, duration of rhGH therapy and age at onset of peritoneal dialysis and transplantation are shown in Fig. 1. Clinical details are shown in Table 1. Two patients stopped rhGH within the 1st year: patient 5 at 0.4 years because of rapidly declining renal function and patient 6 at 0.3 years because of fear of needles. All children reached end-stage renal failure (ESRF): patients 1,3,4 and 5 were transplanted pre-emptively at 8.5, 15.1, 16.4 and 9.9 years, respectively; and patients 2 and 6 received peritoneal dialysis at ages 13.5 and 15.6 years and were transplanted at 14.8 and 18.0 years, respectively. Patient 1 returned to dialysis at 12.7 years. The mean (range) change in Ht SDS from transplant until final follow-up or dialysis was 0.0 (–1.6 to 1.5). The mean (range) creatinine of patients 2–6 at last follow-up was 137 (75–278) µmol/l. The mean (range) Ht SDS at the start of rhGH was –2.9 (–3.7 to –2.2), at the end of rhGH therapy –1.9 (–2.9 to –0.5) (P=0.04) and after 10 years of follow-up –1.6 (–2.9 to –0.4) (P=0.28). Patient 1 developed chronic hepatitis C at 11.5 years of age and is being treated with interferon. Patient 2 was found to have parathyroid adenomata at age 14.8 years and had surgery at 15.6 years of age. There were no other adverse events. Ht SDS improved in all patients while on rhGH, except for patient 1 during his second course, and continued to increase in half of the patients after stopping treatment. Final height was obtained in patients 5 and 6 and was within the normal range.

Group 2 (Fig. 2, Table 2)

Ht SDS for each child and duration of rhGH therapy is shown in Fig. 2. Clinical details are shown in Table 2. Patient 12 died shortly after the end of the 1st study year, when his third graft failed and he refused further renal replacement therapy. Patient 7 received a second renal transplant at the end of the trial year, but restarted rhGH after a further 3 years because of a declining

Table 1 Clinical details of patients in group 1 (*Ht SDS* height standard deviation score, *rhGH* recombinant human growth hormone)

Patient	Age (years) at start of rhGH	Ht SDS at start of rhGH	Duration (years) of rhGH	Ht SDS on stopping rhGH	Ht SDS at 10 years
1	5.0 course 1	–3.0	3.5	–0.7	
	12.7 course 2	–2.3	2.6 (still on)	–2.8	–2.8
2	5.7	–3.2	9.1	–0.9	–0.7
3	7.5	–3.7	7.6	–2.9	–2.9
4	8.2	–2.2	3.1	–0.5	–0.8
5	9.4	–2.7	0.4	–2.2	–0.4
6	10.4	–2.5	0.3	–2.3	–1.8
Mean (SD)	7.7 (2.1)	–2.9 (0.5)	4.4 (3.7)	–1.9 (1.0)*	–1.6 (1.1)

*P=0.04 from baseline

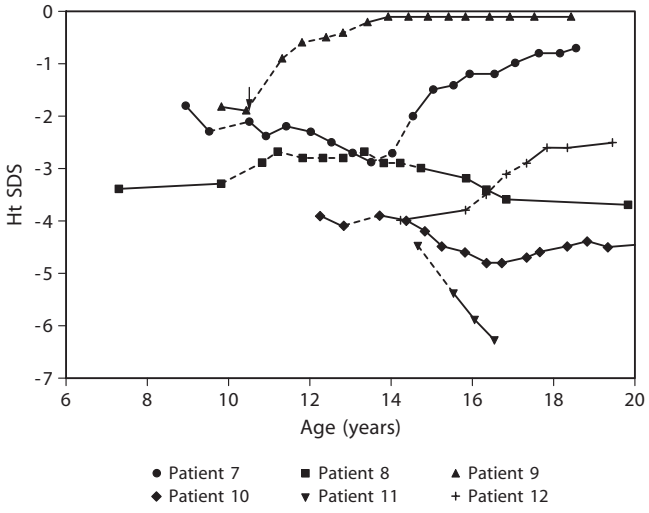

Fig. 2 Ht SDS of the children in group 2. The duration of rhGH is shown by a *dotted line*; ↓ represents time of transplantation

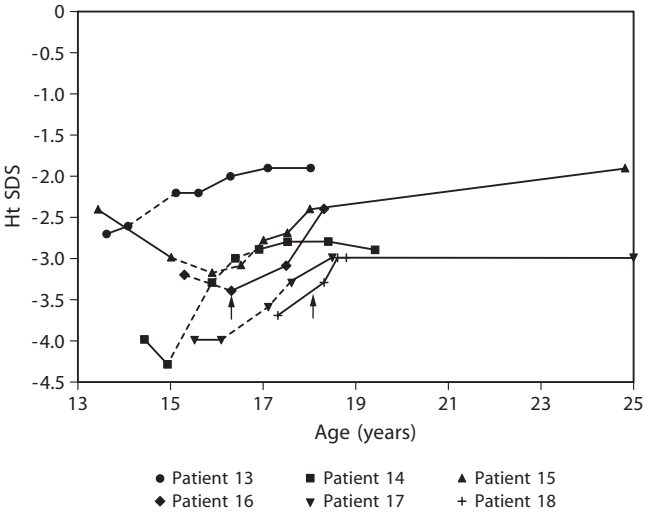

Fig. 3 Ht SDS of the adolescents in group 3. The duration of rhGH is shown by a *dotted line*; ↑ represents start of dialysis

growth velocity despite good graft function. She was the only patient to receive a second transplant. The other four transplants functioned well throughout. The mean (range) creatinine at final follow-up (excluding patient 12) was 90 (65–114) µmol/l. The mean Ht SDS at the start of rhGH was –3.3 (–4.5 to –1.9), at the end of rhGH therapy –2.9(–5.4 to –0.5) (P=0.27) and at final height (which was achieved in all but patient 12, who has therefore been excluded) –2.3 (–4.4 to –0.1) (P=0.75). Patient 9 was found to be hepatitis C positive at 13.9 years. Patient 10, who has cystinosis, developed a persistently elevated blood sugar requiring treatment with oral hypoglycaemic therapy when he had been off rhGH for 6 months. Patient 11 was murdered at age 22 years. There were no other adverse events. Ht SDS increased during rhGH therapy in all but patient 12, and continued to increase in half of the patients after stopping treatment.

Group 3 (Fig. 3, Table 3)

Ht SDS for each patient and duration of rhGH therapy are shown in Fig. 3. Clinical details are shown in Table 3. Pa-

Table 2 Clinical details of patients in group 2 (†: died)

Patient	Age (years) at start of rhGH	Ht SDS at start of rhGH	Duration (years) of rhGH	Ht SDS on stopping rhGH	Final Ht SDS
7	9.5 course 1	–2.3	1.0	–2.1	–0.7
	13.5 course 2	–2.9	1.0	–2.0	
8	9.8	–3.3	6.0	–3.0	–3.7
9	10.4	–1.9	4.0	–0.5	–0.1
10	12.8	–4.1	1.0	–3.9	–4.4
11	14.2	–3.8	2.0	–2.6	–2.5 († age 22)
12	14.6	–4.5	1.0	–5.4	–6.3 († age 16.5)
Mean (SD)	11.9 (2.3)	–3.3 (1.0)	2.9 (1.6)	–2.9 (1.7)	–3.0 (2.3)

Table 3 Clinical details of patients in group 3 (†: died)

Patient	Age (years) at start of rhGH	Ht SDS at start of rhGH	Duration (years) of rhGH	Ht SDS on stopping rhGH	Final Ht SDS
13	14.1	–2.6	1.0	–2.2	–1.9
14	14.9	–4.3	2.3	–3.0	–2.9
15	15.0	–3.0	2.2	–2.8	–1.9
16	15.3	–3.2	1.0	–3.4	–2.4 († age 19)
17	16.1	–4.0	1.8	–3.2	–3.0
18	18.3	–3.3	0.2	–3.3	–3.0 († age 27)
Mean (SD)	15.6 (1.5)	–3.4 (0.6)	1.4 (0.8)	–3.0 (0.4)	–2.5 (0.5)*

*P=0.03 from stopping rhGH

tient 18 died after 6 years on dialysis. Patient 16 died of surgical complications post transplant approximately 3 years later. Patients 13, 14, 15 and 17 maintained good transplant function throughout. Their mean (range) creatinine at final follow-up was 110 (74–189) μmol/l. The mean Ht SDS at the start of rhGH was –3.4 (–4.3 to –2.6), at the end of rhGH therapy –3.0 (–3.4 to –2.2) (P=0.12) and at final height –2.5 (–3.0 to –1.9) (P=0.03). The growth velocity of the 5 patients who were treated for a mean (range) of 1.5 (1.0–2.3) years was 4.9 (4.5–5.9) cm/year. Patient 18 (who did not receive rhGH) grew at 3.8 cm/year. There was a mean overall height gain of 4.4 (0–9.1) cm after stopping rhGH. Patient 13 is pregnant and patient 14 has had a healthy baby. There were no known adverse events. Ht SDS increased during rhGH therapy in 4 patients, and continued to increase after stopping in all patients.

Effect of duration of rhGH

Overall, the mean (range) increase in Ht SDS while on rhGH was 0.6 (–0.9 to 2.3) and after stopping rhGH it was 0.3 (–0.9 to 1.8). Eight patients achieved a height within the normal range [mean, range Ht SDS –1.1 (–1.9 to –0.1) after 2.8 (0.3–9.1) years of rhGH]. The 10 patients who were below the normal range for height [Ht SDS –3.4 (–6.3 to –2.4)] received 2.9 (0.2–7.6) years of rhGH.

Final height

Thirteen patients attained final height. Their mean (range) Ht SDS on starting rhGH was –3.2 (–4.3 to –1.9), on stopping rhGH –2.6 (–3.9 to –0.5) (P=0.004 from baseline) and at final height –2.2 (–4.4 to –0.1) (P=0.04 from stopping rhGH to final height).

Discussion

Over the last few years there have been major advances in our understanding of the causes of growth failure in children with chronic renal disease. The importance of nutrition, electrolyte balance and renal osteodystrophy are well described, but the most-dramatic influence on growth management has been the identification of the endocrine abnormalities of CRF, and, in particular, Mehl's seminal work in rats showing the benefits of GH on growth in renal failure [8]. This work lead to the new therapeutic option of rhGH in renal disease, and it is now 10 years since the first children with renal disease were treated with rhGH. Since then there have been many publications describing its short-term benefits in children with CRF, on dialysis and with renal transplants [1–6].

However, despite these therapeutic advances, there are as yet few published data to suggest that growth prognosis is improving for children with chronic renal disease. This may be a result of the changing population of children with ESRF. The first growth data from the European Dialysis and Transplant Association (EDTA) were published in 1977, at a time when units were selective about children who could be accepted onto ESRF programs, and certainly there would not have been any infants, or even young children included in these data [9]. Currently, at least in the countries that report to this and other large databases, ESRF management is offered even to infants. Growth in the first 2 years of life in young children with CRF is very difficult to maintain, and height lost at this time is difficult to regain, so the increasing proportion of infants on ESRF programs may negatively affect the growth data. However, the impact of rhGH therapy may begin to positively influence growth data, so it might be expected that over the next few years growth prognosis will improve.

The Ht SDS of patients with conservatively managed CRF has recently been reported by the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS) [10]. Of the 1,701 patients on the database whose GFR was <75 ml/min per 1.73 m^2, the mean overall Ht SDS was –1.5. Half those under 5 years of age were below the normal range for height, a figure similar to 10 years previously, although this database was much smaller [11]. However, Ht SDS at presentation for dialysis seems to have improved over the last 10 years, from a mean of –4.0 in the 1988 EDTA analysis [12] to –2.0 in the Dutch study [13] and a similar figure of –1.9 for NAPRTCS [14]. Despite this improvement, a decline in Ht SDS occurs in most patients while they are on dialysis, although again there has been a slight improvement over the years [13, 14]. Ht SDS of patients post transplant has also changed little. The mean Ht SDS of patients in the 1988 EDTA database was –3.1 [12], and for NAPRTCS was –2.2 in 1987 and –2.1 in 1996 [14, 15]. The Dutch reported a mean value of –2.6, with no change to final height [13].

There is very little information available on final height. However, what is available again shows little change over the years. The Dutch study is the most recent to look at final height in 52 patients who had undergone a period of dialysis prior to transplantation but had not received rhGH. The mean Ht SDS was –2.5 [13]. These results are disappointing, and show little difference from those published by the EDTA in 1974, when the mean Ht SDS was –2.0 for males and –1.4 for females [9].

Reports of the growth of patients who have been treated with rhGH for 5 years or more are now beginning to appear in the literature [2–6]. Tönshoff and Mehls [2] reported six children with renal transplants treated for 5 years and two treated for 6 years. All had an improvement in Ht SDS above baseline, but in half of the patients Ht SDS began to decline after approximately 3 years of rhGH [2]. The multicentre American trial reports a 5-year follow-up of 20 prepubertal patients with CRF. Ht SDS improved from –2.6 (0.8) at baseline to –0.7 (0.9) at 5 years. Eight of the patients stopped rhGH

because they had reached their target height; 4 recommenced treatment, but 4 did not. Of the latter 4, 3 demonstrated a decline in Ht SDS [3]. Yadin and Fine [4] reported six patients: two with transplants continued to improve their Ht SDS over 5 years, and two over 6 years; two with CRF maintained an improvement in Ht SDS over 6 and 8 years [4]. The French multicentre study reported eight children on haemodialysis treated for 5 years. Their Ht SDS improved from –4.2 to –2.9 [6]. Growth velocity remained above pretreatment levels for the 5 years, but, after the dramatic improvement in the 1st year, began to decline.

As yet there are few data on the effect of rhGH on final height. The Belgian group looked at final height attainment of 17 patients who had been treated with rhGH for a median of 2.9 years in the boys and 3.4 years in the girls. They found that there was a significant improvement in Ht SDS, from –3.0 on starting to –2.1 on stopping rhGH and to –1.9 at final height. Compared with a historical control group, who showed no change from –3.3 at transplant to –3.2 at final height, the boys, but not the girls, grew significantly better [5].

Whether rhGH is effective in puberty is also an unanswered question. Our results are not as dramatic as those of Hokken-Koelega et al. [16], who treated 18 adolescent transplant recipients with a comparable dose of rhGH. The height increase was 15.7 (5.1) cm over 2 years of rhGH compared with 5.8 (3.4) cm in retrospective controls. Our results are better than these controls, both during and after treatment with rhGH, but none have achieved growth rates as high as the treated group. This may be because our patients were older and less growth retarded. However, all 6 of our patients continued to grow after stopping rhGH, and 2 increased further in height by 1 SD. Unfortunately it was not possible in all patients to determine the age at which final height was reached, as this had not been carefully followed in adult units. However, it is clear that growth continues for longer than normal in some patients. Another factor affecting the growth of pubertal patients post transplant is the steroid regimen. Our results in patients transplanted during puberty, using alternate-day steroids, show catch-up growth comparable to patients treated with rhGH [17].

The mortality in our patients was high, at 22%. Previous studies have demonstrated negative psychosocial outcomes, and in particular low self-esteem, in adults with short stature [18]. Such factors might influence mortality. However, of the 4 deaths, in only 1 (patient 12) was there a possible link between his decision to refuse renal replacement therapy and his short stature. The morbidity, however, was low, as in other studies [3, 4].

Whether rhGH improves final height can only be answered definitively by a controlled trial. However, such a study would be difficult, as it would be impossible to control for variables such as rate of decline of CRF, duration of dialysis and success of renal transplantation, which are factors known to influence growth in renal failure patients. It is, therefore vital that the longitudinal height data of children treated with rhGH are collected and analysed, whether they remain on treatment or not. Although we are not describing a controlled trial, the children in each group started with similar clinical backgrounds and remained in the same centre where they were measured by the same observer and managed with similar protocols until they were transferred to adult units. The majority had an improvement in their Ht SDS while on rhGH therapy, which was maintained after stopping rhGH. What we do not know is what their final height would have been if rhGH had been continued for longer. However, most patients continued to improve their Ht SDS until final height was achieved even without rhGH, and some grew well with only short durations of rhGH treatment. In conclusion, therefore, more data are needed to answer the question of whether rhGH improves final height.

References

1. Rees L, Rigden SPA, Ward G, Preece MA (1990) Treatment of short stature in renal disease with recombinant human growth hormone. Arch Dis Child 65:856–861
2. Tönshoff B, Mehls O (1997) Factors affecting growth and strategies for treatment in children after renal transplantation. Pediatr Transplant 1:176–182
3. Fine RN, Kohaut E, Brown D, Kuntze J, Attie KM (1996) Long-term treatment of growth retarded children with chronic renal insufficiency, with recombinant human growth hormone. Kidney Int 49:781–785
4. Yadin O, Fine RN (1997) Long-term use of recombinant human growth hormone in children with chronic renal insufficiency. Kidney Int 51 [Suppl 58]:S114–S117
5. Janssen F, Van Damme-Lombaerts R, Van Dyck M, Hall M, Schurmans T, Herman J, Hooghe L, Van Damme B (1997) Impact of growth hormone treatment on a Belgian population of short children with renal allografts. Pediatr Transplant 1:190–196
6. Berard E, Crosnier H, Six-Beneton A, Chevallier T, Cochat P, Broyer M (1998) Recombinant human growth hormone treatment of children on hemodialysis. Pediatr Nephrol 12:304–310
7. Freeman JV, Cole TJ, Chinn S, Jones PRM, White EM, Preece MA (1995) Cross-sectional stature and weight reference curves for the UK, 1990. Arch Dis Child 73:17–24
8. Mehls O, Ritz E, Hunziger E-B, Eggli P, Heinrich U, Zapf J (1988) Improvement of growth and food utilisation by human recombinant growth hormone in uremia. Kidney Int 33:45–52
9. Broyer M, Chantler C, Donckerwolke R, Ehrich JHH, Rizzoni G, Schärer K (1993) The paediatric registry of the European Dialysis and Transplant Association: 20 years' experience. Pediatr Nephrol 7:758–768
10. Fivush BA, Jabs K, Neu AM, Sullivan EK, Feld L, Kohaut E, Fine R (1998) Chronic renal insufficiency in children and adolescents: the 1996 annual report of NAPRTCS. Pediatr Nephrol 12:328–337
11. Rees L, Ward, Rigden SPA (1989) Chronic renal failure and growth. Arch Dis Child 64:573–577
12. Rizzoni G, Ehrich J, Brunner FP, Geerlings W, Fassbinder W, Landais P, Mallick N, Margreiter R, Raine AEG, Selwood NH, Tufveson G (1991) Combined report on regular dialysis and transplantation of children in Europe, 1990. Nephrol Dial Transplant 6 [Suppl 4]:31–42
13. Hokken-Koelega ACS, Zaal MAE van, Bergen W van, Ridder MAJ de, Stijnen T, Wolff ED, Jong RCJW de, Donckerwolcke RA, Muinck Keizer-Schrama SMPF de, Drop SLS (1994) Final height and its predictive factors after renal transplantation in childhood. Pediatr Res 36:323–328

14. Warady BA, Hebert D, Sullivan EK, Alexander SR, Tejani A (1997) Renal transplantation, chronic dialysis, and chronic renal insufficiency in children and adolescents. The 1995 Annual report of the North American Pediatric Renal Transplant Cooperative study. Pediatr Nephrol 11:49–65
15. Feld LG, Stablein D, Fivush B, Harmon W, Tejani A (1997) Renal transplantation in children from 1987–1996: the 1996 annual report of the NAPRTCS. Pediatr Transplant 1: 146–162
16. Hokken-Koelega ACS, Stijnen T, Ridder MAJ de, Muink Keizer-Schrama SMP de, Wolff ED, Jong MCJW de, Donckerwolcke RA, Groothoff JW, Blum WF, Drop SLS (1994) Growth hormone treatment in growth-retarded adolescents after renal transplant. Lancet 343:1313–1317
17. Maxwell H, Haffner D, Rees L (1998) Catch-up growth occurs after renal transplantation in children of pubertal age. J Pediatr 133:435–440
18. Sartori A, Conti A, Molinari E, Riva G, Morabito F, Faglia G (1996) Growth, growth hormone and cognitive functions. Horm Res 45:23–29

LITERATURE ABSTRACTS

H. Trachtman · S. Futterweit · P.C. Singhal · N. Franki M. Sharma · R. Sharma · V. Savin

Circulating factor in patients with recurrent focal segmental glomerulosclerosis postrenal transplantation inhibits expression of inducible nitric oxide synthase and nitric oxide production by cultured rat mesangial cells

J Invest Med (1999) 47:114–120

Background Primary focal segmental glomerulosclerosis (FSGS) recurs in nearly 30% of patients who progress to end-stage renal disease and then receive a kidney transplant. A circulating plasma factor has been isolated from these patients that increases glomerular permeability to albumin in vitro. Because of the pivotal role of the mesangial cell in the accumulation of extracellular matrix (ECM) material within the glomerulus and the modulation of matrix protein synthesis by nitric oxide (NO), we examined the effect of the FSGS factor on inducible nitric oxide synthase (iNOS) expression and NO production by cultured rat mesangial cells (RMC).
Methods RMC were incubated with the supernatant following 70% ammonium sulfate precipitation of serum from patients with recurrent FSGS.
Results Addition of the FSGS factor to cultured RMC led to a significant inhibition of nitrite accumulation, an index of NO synthesis. There was a parallel decline in iNOS gene and protein expression. Sera obtained from control patients or those with minimal change nephrotic syndrome or diabetic nephropathy that was processed in the same manner as FSGS samples had no effect on NO synthesis or iNOS activity. The inhibitory effect of the FSGS factor on NO production persisted despite addition of indomethacin (0.1–1 μmol/L) or cyclosporine (25 μg/mL) to test media.
Conclusions These data indicate that the FSGS factor independently alters two aspects of glomerular function-permselectivity and matrix protein synthesis-by distinct: mechanisms. FSGS factor-induced disturbances in iNOS gene and protein expression, and NO production by mesangial cells may antagonize the antifibrotic effect of NO within the mesangium and contribute to progressive glomerulosclerosis in patients with primary FSGS.

S. Cazzato · F. Bernardi · C. Cinti · D. Tassinari · A. Canzi R. Bergamaschi · I. Corsini · V. Capecchi · E. Cacciari

Pulmonary function abnormalities in children with Henoch-Schönlein purpura

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Henoch-Schönlein purpura (HSP) is a widespread necrotizing vasculitis affecting small vessels characterized by non-thrombocytopenic purpura. Pulmonary involvement is a rare fatal complication with diffuse alveolar haemorrhage. The objective of this study was to evaluate possible early lung function abnormalities and to establish any relationship with the clinical activity of the disease. Fifteen children with HSP and without clinical or radiological evidence of lung involvement underwent pulmonary function study at the onset of the disease. A sample of 28 subjects matched by age, height, and weight was chosen as a control group. After a mean of 21 months (range 12–43) lung function tests were repeated in 10 of the previously studied children. During the acute phase of the disease the transfer factor for carbon monoxide, measured by steady-state (TL,COss) and single-breath (TL,COsb) methods, was found to be significantly lower in children with HSP than control subjects. There was no significant relationship between pulmonary function tests with symptoms and signs at onset, nor was there any correlation between variables and serum immunoglobulin A (IgA) concentration. In all but two patients, clinical recovery was observed within 6 weeks from the onset of the disease. In one case relapses of purpuric skin lesions were observed during the first 3 months of follow-up. The second case had relapses of purpuric skin lesions and microscopical haematuria during the 12 months following the onset of the disease with characteristic IgA mesangial deposition on renal biopsy. Although the overall mean value of TL,COsb improved from baseline to the second investigation, in both patients the recurrences of clinical signs were associated with a slight impairment of TL,COsb at the second evaluation. These data suggest an early subclinical lung impairment in children with HSP during the active phase of the disease. The presence of isolated pulmonary function abnormalities was not associated with the subsequent development of lung disease.