Growth hormone treatment of renal growth failure during infancy and early childhood

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Abstract Despite major progress in dialysis, nutrition and drug treatment in the past 20 years, growth of infants and toddlers with chronic kidney disease (CKD) remains a major challenge in paediatric nephrology. Our hypothesis is that early growth deficit is one of the most important factors for impaired final height in children with CKD, and we conclude that early implementation of recombinant human growth hormone (rhGH) therapy should be offered to infants with growth failure. Infants with delayed growth, adequate caloric intake and stable parameters of bone metabolism are candidates for rhGH therapy. One predictive factor for the selection of infants for rhGH treatment may be growth retardation at birth. Our conclusion from the limited published data is that the use of rhGH in young children with CKD is effective and safe. Compared with its use in older children, the early use of growth hormone requires lower absolute dosages of rhGH, which therefore reduce the annual treatment costs and allow earlier renal transplantation. Furthermore, an early start on rhGH improves the psychosocial situation later in childhood and may lead to a further improvement in adult height. A multi-centre randomised controlled study should be initiated to analyse the short-term and long-term effects of early rhGH therapy on infants with CKD.

Keywords Growth retardation · Growth hormone · Growth therapy · Chronic kidney disease · Infants

Remark from the Editors

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Introduction

Impairment of linear growth during chronic kidney diseases (CKD) reflects both the severity of renal diseases 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 [1–5]. More than 60% of adults with childhood onset of CKD had a height less than –2 standard deviation score (SDS) [6]. One-third of CKD patients who had received transplants in childhood and had maintained good graft function developed an adult height below the 3rd centile due to reduced pubertal height gain and the pre-existing height deficit at the time of transplantation [7].

What is the challenge?

Between 1988 and 2008 the adult height of European children undergoing renal replacement therapy improved by a mean of 1.8 SDS, reflecting substantial improvement in health care. However, for children under 4 years of age, this improvement in height was only 0.4 SDS [8]. We therefore regard the growth deficit acquired in early childhood as one of the most important factors for impaired final height in children with early onset renal failure. Thus, there is a strong need for further amelioration of catch-up growth in infancy and early childhood.

Children with an early onset of CKD may suffer from prenatal and postnatal growth failure, leading to severe growth retardation even before the age of 3 years (Fig. 1) [2, 4, 5, 9]. The pathophysiology of growth failure in CKD is multi-factorial; thus, combined causal and symptomatic treatment, including hormonal, metabolic and nutritional

Fig. 1 Mean standard deviation score (SDS) for body height according to age cohorts for 190 boys with chronic kidney disease

therapeutics, is required to improve growth. Recombinant human growth hormone (rhGH) therapy in supraphysiological doses has become a mainstay in the treatment of growth failure in pre-pubertal children with CKD. The rationale for the use of rhGH is based on the finding that children with CKD suffer a lack of endogenous GH efficacy. In the late 1980s, 65% of European specialised paediatric nephrology centres and 93% of non-paediatric centres treating 736 children over 3 years of age with renal replacement therapy (RRT) were not using rhGH at all [10]. Only 3% of specialised paediatric nephrology centres were prescribing rhGH for most children and 32% for some children on RRT. The 1992 data from the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS) reported a usage of rhGH for 9% of American children on peritoneal dialysis and 5% for children on haemodialysis [11]. During 2000 to 2008, rhGH was given to 38% of 500 children with CKD in two German paediatric nephrology centres (Hannover and Berlin). At our centre growth hormone was given to 42 children under 3 years of age. Those 17 children receiving rhGH for more than 1 year showed a significantly ($P<0.05$) higher annual change in body height SDS than did 29 children that were not given rhGH therapy (Fig. 2). The mean annual height gain was 66 mm for children not on rhGH and 85 mm for children receiving rhGH (Fig. 3). Živičnjak et al. [5] identified age as the most important factor determining growth in children with CKD, especially in early childhood and in puberty. Reports describing a marked improvement in height SDS after the use of rhGH in infants and toddlers are scarce [3, 6, 12]. There is a need for long-term follow-up data before any conclusion can be reached concerning the benefit of early rhGH treatment on adult height.

Fig. 2 Mean annual change in body height standard deviation score (SDS) for 46 children with chronic kidney disease undergoing ($n=17$) and not undergoing ($P=29$) rhGH treatment in early childhood (2–3 years old and 3–4 years old)

What is the dogma?

Even today, more than half of all children with CKD and body length under the 5th centile did not receive rhGH treatment [13]. The obstacle to the use of rhGH for children less than 2 years old was that they were considered to be ‘too young’, although effectiveness of rhGH in young children has been reported [5, 12, 14].

Historical treatment philosophies, legal restrictions and financial limitations confined the use of rhGH to children below 2–3 years of age for many years, although there are almost no contra-indications to rhGH and although side effects are rare [15]. One of the reasons for the withholding

Fig. 3 Mean annual gain in body height (in millimetres) of 46 children with chronic kidney disease undergoing and not undergoing rhGH treatment in early childhood (2–3 years old and 3–4 years old)

of rhGH from infants and toddlers was the 35-year-old hypothesis that growth in early childhood was mainly dependent on adequate nutrition [9, 16] and not on growth hormone. It was speculated that growth failure during foetal life and the postnatal months is related to a partial insensitivity to growth hormone [9]. Children of all ages with CKD suffer from lack of appetite, and feeding is most difficult in infants and toddlers with CKD. Therefore, many paediatric nephrologists focused on adequate dietary treatment by tube feeding, and some reports showed that young children with CKD grew better when adequate tube feeding was performed [17–20]. Only Abitbol et al. [2] did not report a correlation between growth and caloric intake. We agree that adequate nutrition is a prerequisite for normal growth. However, conservative treatment or forced feeding policies alone may lead to a prolonged watchful waiting policy, with the result of a severe growth deficit in infancy that can never be caught up in the remaining growth period.

It is unclear if all young children that underwent intensified tube feeding reached their optimum of catch-up growth. To the best of our knowledge, there is no prospective randomised controlled study of infants with CKD available that compares the efficacy of a combined treatment using rhGH plus adequate nutrition with dietary monotherapy.

Mencarelli et al. [14] should be congratulated on having started treating young renal patients with rhGH and showing its positive additional effect on growth superimposed on the benefits of all other causal and symptomatic therapies. This retrospective non-randomised study of 12 infants receiving rhGH therapy may serve as a pilot study for future randomised controlled trials.

The early treatment of young children with CKD and growth failure below the 3rd percentile, using rhGH, may have several advantages if compared with the later initiation of rhGH therapy:

1. The use of rhGH for young children requires lower total dosages of rhGH, thereby reducing the annual treatment costs and allowing earlier renal transplantation.
2. Children will enter the relatively stable phase of growth at 5–10 years with a better height, thus improving their psychosocial situation when entering school.
3. Early implementation of rhGH therapy may lead to a further improvement in adult height.

It may be argued that children who have received rhGH early in life may benefit less from a repeat treatment with rhGH than those older children receiving rhGH for the first time. This argument is based upon the findings that the annual benefit of rhGH decreases with time. However, this effect may not be explained alone by a loss of efficacy, but also by the increase in height gained. To the best of our knowledge, there are no data available that answer the

question of whether previous rhGH therapy will influence further treatment courses after a longer treatment pause.

Who should receive early rhGH treatment?

In our opinion infants with a delayed growth velocity, adequate caloric intake and stable bone metabolism parameters should be candidates for rhGH therapy. One predictive factor for the selection of infants for rhGH treatment may be growth retardation at birth. We would like to encourage all paediatric nephrologists to start a multi-centre prospective trial on the use of rhGH in the treatment of infants and toddlers with CKD and growth failure.

Children with CKD may not reach their target height because of various factors (e.g. lack of adequate nutrition and/or overdose of drugs affecting growth). Therefore, previous data on the use of rhGH therapy for infants with CKD should be analysed firstly to identify and select those infants requiring rhGH in addition to standard treatment. Secondly, the stratification of infants from the new study into two treatment groups should include one group of infants receiving rhGH in addition to standard therapy and the other group not receiving rhGH. Growth hormone should be given until the patients reach the percentile of their target height, which should be estimated according to parental height, or until successful renal transplantation. Thirdly, all study patients should be followed up for 20 years by annual documentation of height and weight, stage of CKD and methods of treatment to allow detailed conclusions to be drawn on the long-term effect of early rhGH therapy.

The international discussion on the use of rhGH for young and older children is biased by the inadequacy of access to this expensive drug treatment and the decision pro or contra does not always lie in the hands of paediatricians. However, normal final height is regarded by the CKD patients themselves as one of the major criteria for good rehabilitation. Therefore, paediatricians must provide a solid basis for the discussion on the use of rhGH for infants by an adequate multi-centre trial, regardless of treatment costs.

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