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Early age-dependent growth impairment in chronic renal failure

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Abstract. We report early linear growth in 73 children (51 boys, 22 girls) with early onset of chronic renal failure (CRF). The inclusion criteria was onset of CRF before 6 months of age, two or more height measurements during the 1st year of life, follow-up for at least 3 years and continuously impaired renal function with a glomerular filtration rate below 50 ml/min per 1.73 m^2 at 1 year or later. Only height measurements taken during conservative treatment or dialysis were included. The data were analysed in terms of the infancy-childhood-puberty growth model. There was an age-dependent growth failure in early life leading to an attained height of –3 standard deviation score (SDS) at 3 years of age. Approximately one-third of the reduction in height occurred during fetal life and one-third during the first postnatal months. Between 0.75 and 1.5 years of age height also decreased by 1 SD as a consequence of a delayed onset of the second, the 'childhood', phase of growth in 36% of the patients and by an 'offset childhood' growth pattern – i.e. a return to the infancy phase pattern after onset of the childhood phase – in 60% of the patients. Growth between 0.25–0.75 and 1.5–5 years of age was generally percentile parallel and thus less likely to be affected in CRF with early disease onset. The glomerular filtration rate was not related to the height gain in early life. We speculate that the growth failure during fetal life and the first postnatal months reflects metabolic and/or nutritional influences and the impaired growth at 0.75–1.5 years of age is related to a partial insensitivity to growth hormone.

Key words: Kidney disease – Chronic renal failure – Height – Longitudinal growth – Growth hormone insensitivity

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Introduction

Congenital kidney disorders lead to growth retardation which can occur, even without reduction in glomerular function, as a consequence of wasting, electrolyte and acid-base imbalances and altered calcium metabolism [1–3]. When chronic renal failure (CRF) is present, a markedly age-dependent pattern of growth failure is observed, with reduced growth rates in the early years and again during puberty [4–9]. In patients with untreated early-onset CRF, the loss in relative height during the 1st year of life has been estimated to be as much as 0.6 standard deviation (SD)/month [4, 5]. Prevention of CRF-associated growth failure in early life is thus of major concern, and more detailed information about the early growth pattern may be useful in this achievement.

The Infancy-Childhood-Puberty (ICP) model describes the human growth curve as a sequence of three distinct, overlapping phases of growth, each of which is believed to be dominated by specific physiological growth-promoting factors [10–12]. The aim of this study was to describe early statural growth by means of the ICP model in a major population of early-onset CRF patients in order to identify the mechanisms by which the growth process may be altered in uraemia.

Patients and methods

Patients. The growth data were obtained from a multi-centre retrospective study in which growth was evaluated in more than 500 CRF

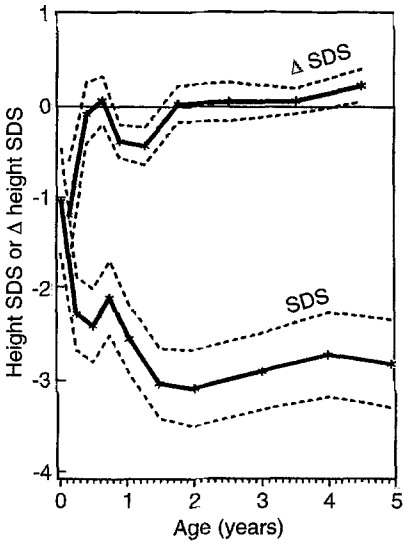

Fig. 1. Evolution of height standard deviation score (*SDS*) in total sample ($n = 73$, sexes combined) of patients with early onset of chronic renal failure (CRF). Data are shown as mean and 95% confidence interval (1.96 SEM) of height SDS and Δ height SDS

patients in 22 paediatric nephrology centres in 11 European countries [13]. The selection criteria in the present study were: (1) onset of CRF within the first 6 months of life, (2) two or more height measurements during the 1st year of life, (3) regular height recordings until 3 years of age, (d) continuously impaired renal function as defined by a glomerular filtration rate (GFR) of 3 SD below the age-approximated mean (i.e. < 16 ml/min per 1.73 m^2 during the first 4 months, < 35 ml/min per 1.73 m^2 during the 4th–12th month and < 50 ml/min per 1.73 m^2 beyond the age of 1 year) [14]. GFR was estimated by the calculated creatinine clearance using the age-specific k values published by Schwartz et al. [15]. Only height measurements taken during conservative treatment or dialysis were included in the analysis, while data obtained after transplantation were excluded. These criteria were met by 51 boys and 22 girls. The underlying kidney disorders included mainly renal hypoplasia or dysplasia, obstructive uropathy and reflux nephropathy. Patients with systemic metabolic disorders such as nephropathic cystinosis or oxalosis were excluded. The mean (SD) GFR was 23.6 (10) ml/min per 1.73 m^2 with a range from 5.8 to 44 ml/min per 1.73 m^2. The average duration of observation was 7.3 (range 3–16) years and the mean number of height measurements was 14 (range 4–29).

Methods. One height measurement per patient was selected, if available, at each of the following 10 ages: at birth, 0.25, 0.50, 0.75, 1, 1.5, 2, 3, 4 and 5 years of age. The average number of observations was 7.2 (range 3–10). Height was converted into standard deviation scores (SDS) using the ICP growth reference based on Swedish normal children, since this allowed growth to be viewed in terms of both total growth and the infancy and childhood phases of growth in early life [10–12]. These reference mean and SD values of length/height are virtually the same as those of the Swiss growth reference [16], which otherwise would have been the growth reference of choice for the multinational European patients studied here. The change in height SDS was computed as the difference in height SDS between the adjacent selected ages.

The individual growth pattern was plotted out in the ICP growth charts for 32 boys and 15 girls with longitudinal height series during the first 3 years of life [11, 12]. The age at onset of the childhood component was determined as an abrupt increase in height velocity at the end of the 1st year of life or during the 2nd year of life [11, 12]. Normal children attain the onset of the childhood phase before 1 year of age; therefore, the percentage of patients with an onset after 1 year was computed. A delayed onset has been observed in several disorders affecting growth [17]. The statistical analysis included the one-sample *t*-test, bivariate correlation (Pearson) and multiple linear regression analysis.

Results

Table 1 gives the mean and SD values for height SDS and Δ SDS over the ages together with the *P* value of the one-sample *t*-test based on the total sample ($n = 73$). The mean values with the 95% confidence limits are shown for height SDS and Δ height SDS in Fig. 1. The mean values of this

Table 1. Height standard deviation score (SDS) and change in height SDS between adjacent age intervals[a]

Age group (years)	Mean age (years)	*n*	Mean (SD) height SDS	*P* value*	Mean age (years)	*n*	Mean (SD) change in height SDS	*P* value*
0.00	0.00	36	−1.05 (1.80)	0.002				
					0.13	23	−1.20 (1.50)	0.001
0.25	0.25	50	−2.29 (1.43)	0.00001				
					0.37	47	−0.08 (1.15)	0.65
0.50	0.49	52	−2.42 (1.45)	0.00001				
					0.61	47	0.07 (0.88)	0.61
0.75	0.74	55	−2.12 (1.52)	0.00001				
					0.88	51	−0.38 (0.66)	0.0002
1.00	1.04	60	−2.56 (1.44)	0.00001				
					1.26	55	−0.42 (0.79)	0.0003
1.50	1.48	59	−3.03 (1.48)	0.00001				
					1.68	53	0.03 (0.70)	0.74
2.00	2.01	58	−3.09 (1.60)	0.00001				
					2.49	56	0.06 (0.77)	0.59
3.00	3.00	61	−2.90 (1.63)	0.00001				
					3.48	52	0.06 (0.49)	0.35
4.00	4.00	55	−2.72 (1.70)	0.00001				
					4.47	43	0.23 (0.58)	0.02
5.00	4.95	46	−2.82 (1.63)	0.00001				

* The *P* value for the one-sample *t*-test with an expected value of zero is also included

[a] Both sexes are pooled

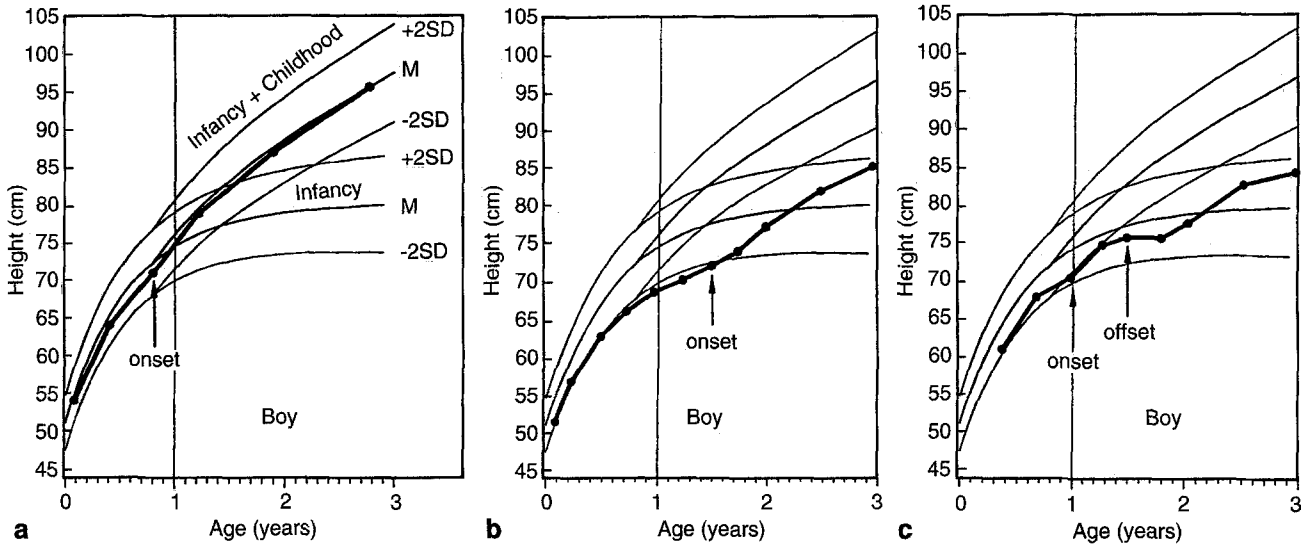

Fig. 2. Examples of normal and abnormal growth patterns observed in CRF. *Left panel:* normal growth pattern in a CRF patient. Smooth decelerating path during the infancy phase and a smooth transition into the infancy + childhood phase at about 0.75 years of age representing the age at onset of the childhood component. *Middle panel:* CRF patient with normal smooth path of growth in infancy, but with delayed childhood onset (> 1 year of age); 36% of all patients exhibited a late childhood onset (41% of boys, 27% of girls). *Right panel:* CRF patient with a childhood onset at 1 year of age followed by a childhood offset period, i.e. a growth curve returning back to the infancy growth pattern; 60% of the patients showed a childhood offset pattern (59% of boys, 60% of girls)

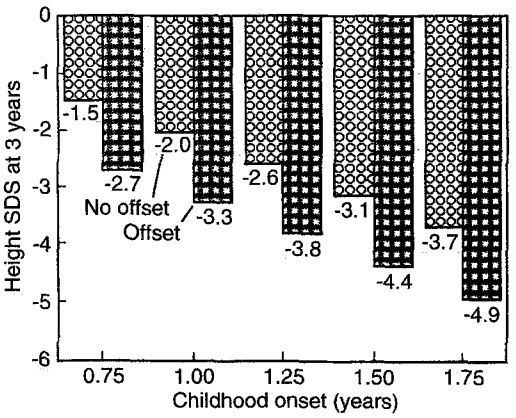

Fig. 3. Impact of the age at onset of the childhood component and the occurrence of a growth arrest after the onset (offset vs. no offset) on height SDS attained at 3 years of age

cross-sectional analysis exhibit an age-dependent pattern of growth impairment with: (1) decreased SDS values at birth, (2) a negative change in SDS values from birth to 0.25 years of age, (3) no significant change in SDS values at 0.25–0.50 and 0.50–0.75 years of age, (4) again a negative change in SDS values between 0.75–1 year and 1.0–1.5 years of age and (5) no change in SDS values between 1.5–2.0, 2–3, 3–4 and 4–5 years of age. Due to the semi-longitudinal nature of the series with some patients followed less frequently, a subgroup analysis was performed in patients with complete height data at 0.25, 0.50, 0.75 and 1 year of age (n = 39). The growth pattern observed in this strictly longitudinal subgroup confirmed the evolution of height SDS described above, with significant height SDS changes in the same age intervals as in the total sample.

Fig. 2 depicts the most common individual growth patterns found in our CRF patients in terms of the ICP model. Fig. 2a shows an unusual pattern of growth in CRF, i.e. the normal smooth pattern with an onset of the childhood component at about 0.75 years of age. Fig. 2b depicts a patient with a smooth normal infancy growth pattern, but with a delayed onset of the childhood component, i.e. after 1 year of age. Many CRF patients returned, for a period of variable duration, to the infancy growth pattern of the ICP growth charts after onset of the childhood phase of growth ('childhood offset' pattern), as illustrated in Fig. 2c. The mean (SD) onset of the childhood component was 1.10 (0.32) years in boys (n = 32) and 0.94 (0.32) years in girls (n = 15). For both sexes the mean onset time was significantly (P < 0.0001) later than for the Swedish controls, i.e. at 0.74 (boys) and 0.68 (girls) [11]. The percentage of boys with a late childhood onset (> 1 year) was 41% with 27% of girls displaying late childhood onset. A childhood offset pattern was seen in 59% of the boys and 60% of the girls.

Multiple linear regression was applied to the data at different ages with height SDS as the dependent variable and with: (1) the age at onset of the childhood component and (2) childhood offset as independent variables. Neither of the two independent variables showed any significant association with height during the 1st year of life, but from 2 years of age onward. The combined effects of the two independent variables explained 31%, 33% and 28% of the total variance of height SDS at 3, 4 and 5 years of age, respectively. The multiple regression model includes some assumptions, such as an additive effect between the independent variables and a linear relationship over the full range of values, which are not necessarily always true. Nonetheless, we would like to illustrate the importance of the childhood onset and offset measures for the height

achieved at 3 years of age; Fig. 3 is based on the estimated parameters for the multiple regression model at 3 years of age. The figure shows that CRF patients with normal timing of the childhood onset have a height SDS of –1.5 at 3 years of age. A delayed childhood onset, e. g. to 1.75 years of age, produces an average height SDS of –3.7. The effect of 'childhood offset' is a reduction in height by 1.2 SDS.

The mean GFR values increased from 9.1 (SD 4.1) ml/min per 1.73 m^2 at birth to 18.7 (7.8) at 0.75 years of age and reached a constant level at 2 years of age [26.5 (11.7) ml/min per 1.73 m^2]). The individually averaged GFR values between 0.75 and 2 years of age were not related ($P > 0.05$) to the change in height SDS during the same age period nor to the age at onset of the childhood component or the childhood offset pattern ($n = 47$ in a multiple linear regression). Non-significant ($P > 0.05$) results were also reached between GFR levels and growth during the first postnatal months of life ($n = 14$).

Discussion

In this study we evaluated early growth in 73 selected patients with CRF. The selection was made by early onset of CRF (<6 months of age) and permanent kidney dysfunction in childhood. The growth data of this cohort are the largest presented so far in patients with early onset of CRF and it is the first to be analysed in terms of the ICP growth model. The results clearly support an age-dependent early growth failure and also give hint to possible underlying mechanisms of the growth impairment.

The ICP model describes linear growth during the first 3 years of life as a combination of a sharply decelerating infancy component and a slowly decelerating childhood component, the latter acting from the second half of the 1st postnatal year onward [10–12, 17]. In puberty, a third independent component is added. Empirical evidence suggests that the three components of the ICP model can be observed in isolation and that they are additive. Each component of this model is therefore assumed to represent a separate biological phase of the growth process. The infancy component, tentatively starting in mid-gestation and continuing up to 3–4 years of age, is believed to represent the postnatal continuation of fetal growth. It is assumed that the childhood component, slowly decelerating during childhood and adolescence, is dominated by the growth-promoting effect of the somatotrophic hormone axis. What mediates the onset of the childhood phase of growth has not been elucidated yet because information about serum levels of growth factors and hormones as well as their interaction with specific plasma binding proteins and tissue receptors during this critical period is still almost completely lacking. However, the most plausible explanation is that it represents the age at which growth hormone takes over its role as the major endogenous growth-promoting agent during prepubertal life [17]. In normal children, the onset of the childhood phase is reliably detected by a transient acceleration of growth around 1 year of age [11]. If the hypotheses regarding the dominating growth-promoting mechanisms underlying the infancy and childhood phases are correct, then the ICP model permits to distinguish between the effects of nutrition and endocrine factors on growth in healthy and diseased infants.

In some 50% of our CRF patients the infancy growth phase was clearly affected at birth and/or during the first 3 postnatal months, but behaved normally between the 3rd and 9th month of life. About two-thirds of the observed overall reduction in height SDS in childhood occurred in early life; about half of this growth deficit was acquired during fetal life and half during the first postnatal months. This period of growth is generally believed to be dominated by nutritional factors. In this context, the observed intrauterine growth retardation is of particular interest, raising the question whether the prenatal accumulation of certain circulating substances not cleared by the placenta may compromise fetal growth. Conversely, intrauterine malnutrition could be the primary cause not only of fetal growth retardation but also, if present in the early stages of pregnancy, of abnormal renal morphogenesis. With respect to early postnatal life, it is well known that CRF during the first months of life leads to severe anorexia, the correction of which may partly reverse early infantile growth failure [6–8]. In addition, fluid, acid-base and electrolyte disturbances may have affected growth during the infancy phase. Some of the growth data analysed in this retrospective study were obtained in the late 1970s, when aggressive supplementary management was not yet commonplace in all centres. It is therefore possible that the factors mentioned may have compromised growth in the CRF infants viewed here to a greater degree than they do today. On the other hand, a recent prospective study in infants with congenital CRF documented a drop in length SDS to –2 SDS within the first 6 months of life, despite reportedly adequate nutritional and supplementary therapy [18].

The second age-dependent loss in relative height occurred between 0.75 and 1.5 years of age and affected height negatively by approximately 1 SDS unit. A delayed onset of the childhood phase was noted in 36% and a childhood offset pattern in 60% of the patients, and both contributed significantly to a poor height gain. A delayed childhood onset has been observed in other studies of growth-related disorders such as in Turner syndrome, coeliac disease and normal children with short stature [17, 19]. The mean net effect of a delayed childhood onset in CRF was 0.5 SDS (Fig. 3, SDS difference from 0.75 to 1 year of age). As many as 60% of the patients showed a transient growth arrest during the 2nd year of life, which was characterised by a return to the infancy phase of growth after the childhood phase had already started (Fig. 2c). The growth arrest was usually observed over more than one height observation, ruling out a major distorting effect of measurement errors. The impact of this irregular action of the childhood component on height at 3 years of age is 1.2 SDS (Fig. 3). This irregular growth pattern was found in 60% of our CRF patients, so the mean net effect would be around 0.7 SDS.

We can only speculate about the mechanisms underlying this phenomenon, which has not been observed in other disease groups analysed by the ICP model. In uraemia, growth hormone insensitivity is the key alteration of the

somatotrophic axis [20]. However, high doses of recombinant human growth hormone have a growth-promoting effect [21, 22], even in infants around 1 year of age [23], so the insensitivity is regarded as being partial. If the hypothesis is correct that the childhood component is predominantly driven by growth hormone, then the irregular growth observed in CRF patients during the 2nd year of life could represent changes between periods of normal (infancy plus childhood component) and impaired growth hormone action (infancy component alone). The delay of the childhood phase and/or return to the infancy phase could be related to low secretion or bioactivity of growth hormone.

In the periods 0.25–0.75 and 1.25–5 years a percentile-parallel growth pattern was observed. This may be interpreted as a less-significant interference of the growth-suppressive factors associated with CRF in these periods compared with the crucial phases described above. On the other hand, if growth was completely unresponsive to the state of CRF in these periods, one should have expected catch-up growth, as seen in other disorders (e.g. coeliac disease [19]). The absence of any catch-up growth in these periods is therefore compatible with either a persistence of the underlying mechanisms of growth disorder or with an irreversible resetting of the endogeneous growth target to a lower level. The latter is made less likely by the experience of complete catch-up growth after steroid-free kidney transplantation [24].

We conclude that early onset of CRF is associated with an age-dependent growth failure in early life leading to an attained height of –3 SDS at 3 years of age. Approximately one-third of the reduction in height occurs during fetal life and one-third during the first postnatal months, probably due to metabolic and/or nutritional disorders. Between 0.75 and 1.5 years of age relative height is further reduced by 1 SDS, possibly by partial insensitivity to growth hormone. Growth between 0.25–0.75 and 1.5–5 years of age is percentile parallel and thus less likely to be affected in early-onset CRF.

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