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Pubertal Growth in Chronic Renal Failure

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ABSTRACT. We evaluated the growth records of 15 boys and 14 girls who developed end-stage renal failure before or during puberty and who were regularly followed from the onset to the end of their pubertal growth spurt. Height data were smoothed by using the kernel estimation method. Mean values for age, height, and height velocity at defined points of the pubertal growth period were compared with those of normal children entering puberty both at an average and late age. The start of the pubertal growth spurt was delayed by 2.5 y in both sexes. Its duration and intensity were significantly reduced. Mean pubertal height gain was 17.3 cm in boys and 13.9 cm in girls, *i.e.* 58 and 48% of that observed in the late maturing control group. Mean height at the onset of the pubertal spurt in the patients was the same as that in the late maturing healthy girls and 1.0 SD below that of corresponding boys. During the pubertal growth spurt, mean height declined to −2.9 SD in boys and −2.3 SD in girls. Although skeletal maturation was increasingly retarded, we did not observe accelerated growth velocity during late puberty. Our data indicate that most patients reaching end-stage renal failure before or during puberty irreversibly lose growth potential during this period. Renal transplantation did not consistently improve pubertal growth. (*Pediatr Res* 28: 5–10, 1990)

Abbreviations

CRF, chronic renal failure
HD, regular hemodialysis
TP, renal transplantation
Scr, serum creatinine
MHV, minimal prespurt height velocity
PHV, peak height velocity
EHV, end-point height velocity
SDS, standard deviation score

CRF is frequently associated with growth retardation, often leading to permanent stunting despite optimal therapy including successful TP (1, 2). The degree of growth retardation is influenced by the primary kidney disease, the clinical course, malnutrition, abnormalities of acid-base and electrolyte status, and endocrine growth factors. It has been emphasized that, during the critical period of infancy, there is a rapid loss of growth potential that is rarely regained in later childhood (3). Our report presents data suggesting that the pubertal period is similarly sensitive to the growth retarding effects of uremia and its treatment.

Previous investigations on pubertal growth under pathologic conditions have generally been hampered by methodologic problems (4). In our report, we introduce the kernel estimation technique as a new method that allows objective definition of characteristic points of the pubertal growth spurt, thus facilitating analysis and comparison with control data (5, 6).

MATERIALS AND METHODS

Study population. Data were reviewed from 15 boys and 14 girls with CRF who had been regularly observed at 3- to 6-month intervals at the Heidelberg University Children's Hospital between 1968 and 1988. The patients had the following primary renal disorders: focal-segmental glomerulosclerosis ($n = 6$), obstructive uropathy ($n = 6$), renal hypoplasia ($n = 5$), nephronopthisis ($n = 4$), Schönlein-Henoch nephritis ($n = 2$), rapidly progressive glomerulonephritis ($n = 2$), others ($n = 4$).

The patients were followed from 0.5 to 11.8 (median 3.3) y before the onset of the pubertal growth spurt, as defined by the MHV (see below), until pubertal growth had ceased. Median ages (range) at initial and at final observation were 9.3 (0.5–11.8) and 20.2 (16.3–25.2) y, respectively. At initial observation, 24 patients did not manifest any clinical signs of pubertal development, and two boys and three girls had reached Tanner pubic hair (PH) and/or genital (G) or breast stage 2. At final observation, all patients had attained puberty stage 4 or 5 except one boy who was stage PH3/G3. Hand epiphyses were closed in all patients except for four boys with bone ages of 16.3–17.5 y and two girls with bone ages of 14.6 and 15.6 y, respectively.

The onset of CRF was defined by the first record of an increased Scr level ≥1.3 mg/dL. At first observation, 27 patients had Scr levels ranging from 0.4 to 9.2 mg/dL (median 2.2) and two were undergoing HD. The treatment modalities at defined points of the growth spurt are shown in Figure 1. At last observation, 21 patients had a functioning TP (median Scr 1.9 mg/dL, range 0.9–6.0), seven were on HD after TP failure, and one had never received a TP.

After TP, patients received immunosuppression with azathioprine and (usually daily) methyl-prednisolone or prednisone. The mean methyl-prednisolone equivalent dosage given was 6.1 ± 0.7 mg/m^2/d. Cyclosporin A was given to only one patient.

Analysis of growth. Height was measured with standard methods (7) by trained personnel using a Holtain stadiometer (Holtain Ltd., Crymych, Dyfed, UK). Height was usually recorded at 3-mo intervals; thus, a total of 959 data points were available for analysis. Pubertal status was evaluated according to Tanner (8) by the examining physician. Hand x-rays were obtained at approximately 6-mo intervals. Bone age was determined ($n = 180$) according to the TW2 method (9) by a trained observer with an intraobserver variation of ±0.5 y (95% confidence limit) (7).

To minimize the influence of measurement errors, height data were smoothed by the kernel estimation method (5, 6). This is a

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mathematical procedure applying a moving weighted average with raw data. It estimates a function at time t by

$$\hat{r}(t;b) = \Sigma\, g_i(t) \cdot y_i$$

where y_i = measurement at time t_i, $g_i(t) = 1/b \cdot \int_{s_{i-1}}^{s_i} w((t_i - u)/b)du$, $s_i = (t_{i+1} - t_i)/2$, w = kernel (or wt) function, b = bandwidth or smoothing parameter.

In contrast to parametric regression methods (10), kernel estimation makes no assumption on the shape of the true curve. This principle is essential in the evaluation of pathologic growth curves as in CRF, where abrupt changes due to clinical events may be expected. Moreover, choice of appropriate weighting functions allows direct estimation of derivatives of the height curve, *i.e.* of the corresponding height velocity and acceleration curve. The degree of smoothing was chosen data-adaptively by minimizing the mean square error (Gasser T, Köhler W, Kneip A, unpublished manuscript).

The point at which the derived smooth height velocity curve reached a maximum during puberty was defined as the PHV. It represents the growth increment during a time period spanning six mo to either side of this time point. The preceding minimum of the height velocity curve was defined as MHV and used as the starting point of the pubertal growth spurt (6). The end of the pubertal growth spurt was defined as the age at which the late ht velocity curve permanently declined below 1 cm/y (EHV). The pubertal growth period was defined by the time interval between MHV and EHV.

The individual growth curves obtained by the kernel estimation procedure were centered on MHV, PHV, and EHV. For this purpose, we used a synchronization program that transforms the time scale of each individual curve monotonously to align the characteristic points with the respective means (Kneip A, Gasser T, unpublished manuscript).

Control data were from the First Zurich Longitudinal Growth Study, comprising 232 healthy children (120 boys, 112 girls) who were followed longitudinally throughout the growth period (control group A) (13). Because the growth spurt characteristics depend on the "tempo" of the maturing process and the patients under study represent a late maturing population, we analyzed separately those 70 children (35 boys, 35 girls) in the Zurich Longitudinal Growth Study who had the latest pubertal growth spurt (control group L).

Mean values for MHV, PHV, and EHV and for the ages at which these parameters were reached were calculated for the CRF patients and both control groups. Data are given as mean ± SD. Because the distributions of height and ages in the control groups were approximately gaussian, the degrees of deviation from the normal means were expressed as SDS. The definitions of MHV, PHV, and EHV allowed calculation of conditional SDS related to the respective points of the pubertal growth spurt rather than to chronologic age or bone age. Differences between the patients and the control group data were checked with paired *t* test for statistical significance.

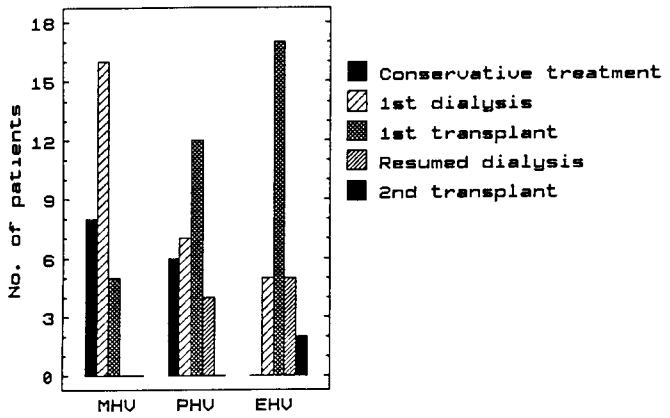

Fig. 1. Treatment of 29 children with CRF at defined points of pubertal growth.

RESULTS

All CRF patients except one girl exhibited a distinct pubertal growth spurt demonstrated by an upward turn of the height velocity curve. The spurt amplitude was less than 1 cm in three boys and two girls. The synchronized mean height velocity curves of boys and girls are shown in Figures 2 and 3, respectively.

Mean MHV occurred at 13.4 y in boys and 12.1 y in girls, which corresponds to a delay in the CRF patients by about 2.5 SD compared with control group A patients (Table 1). Age at PHV was slightly less delayed than MHV in both sexes, and the mean delay of EHV was even less than that of PHV. The delay of MHV, PHV, and EHV ($p < 0.001$) was significant when compared with control group A. This delay did not reach significance when compared with control group L, except for MHV. The mean duration of the pubertal growth period was 5.5 ± 1.6 y in boys and 4.4 ± 1.7 y in girls, which was shorter than in children of control groups A (both sexes, $p < 0.001$) and L (boys, $p < 0.02$; girls, $p < 0.01$).

The mean height and height velocities attained by the CRF patients at the defined points of the pubertal spurt compared with the two control populations are given in Table 2. Although age-related height SDS at first observation was grossly reduced in the CRF patients to −2.2 and −1.8 SDS in boys and girls, respectively, the mean heights attained at MHV were only 1.0 SD below the mean of control group L boys and at the mean of late maturing girls. At the later points of the pubertal growth

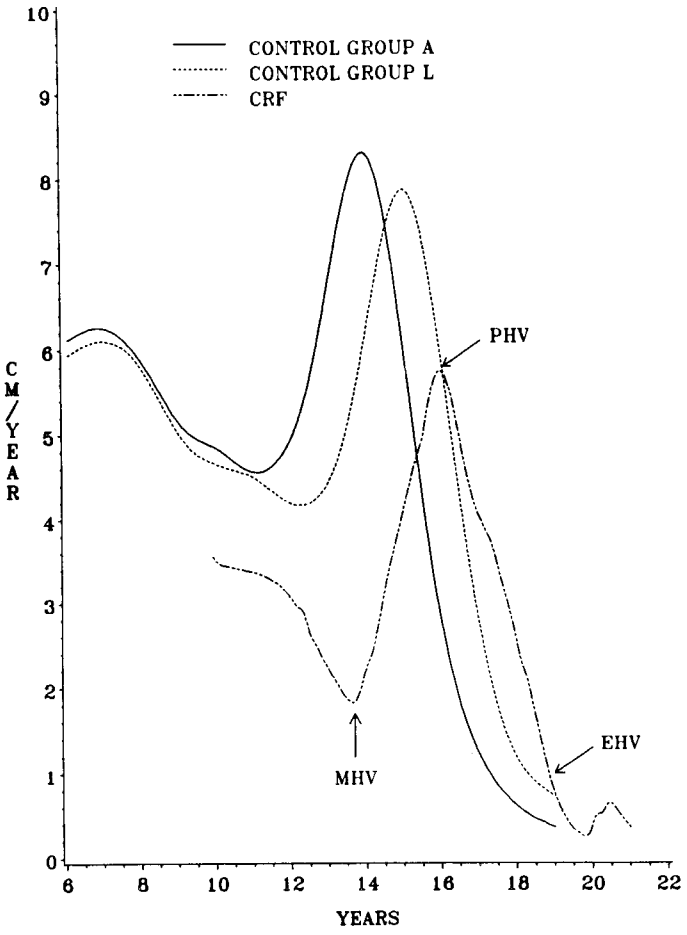

Fig. 2. Synchronized mean height velocity curves of 15 pubertal boys with CRF and healthy children maturing at average (control group A) and late (control group L) age.

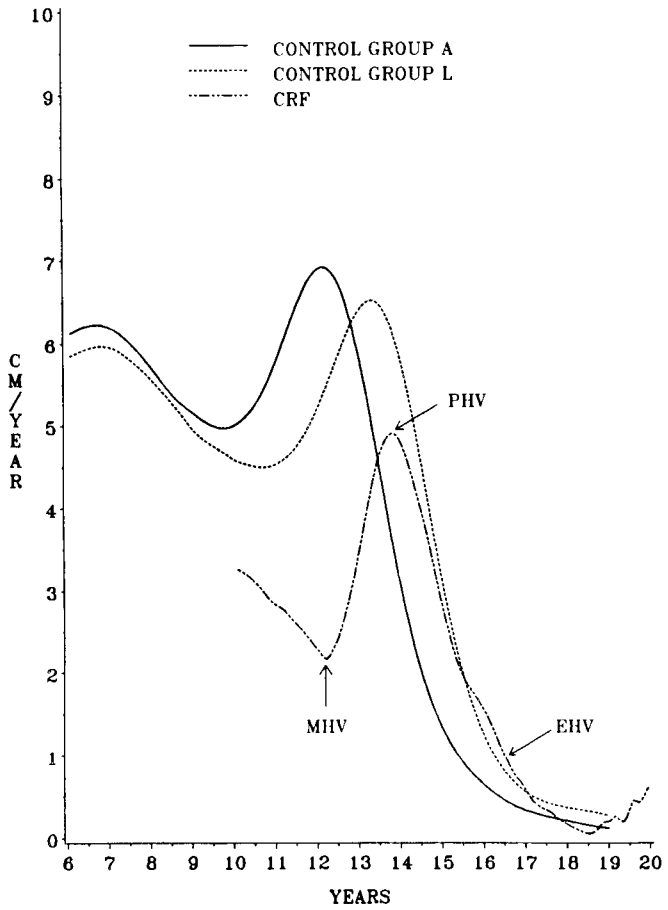

Fig. 3. Synchronized mean height velocity curves of 14 pubertal girls with CRF and healthy children maturing at average (control group A) and late (control group L) age.

spurt, conditional height SDS decreased to a final SDS of −2.9 in boys and −2.3 in girls.

Mean MHV was 1.9 cm/y in boys and 2.0 cm/y in girls, which is more than 5 SD below the mean of control group A ($p < 0.001$). The magnitude of PHV reduction was relatively less, averaging 5.5 cm/y in boys ($p < 0.001$) and 5.0 cm/y in girls ($p < 0.01$). The increase of height velocity SDS from MHV to PHV was significantly greater in girls (+5.4 SDS) than in boys (+1.9 SDS) ($p < 0.05$). The magnitude of MHV and PHV was reduced in the CRF patients also when compared with control group L ($p < 0.001$). Only seven of 15 boys and nine of 14 girls achieved a PHV within 2 SD from the mean of control group L children.

Pubertal growth was also analyzed with respect to skeletal maturation (Table 1). At MHV, the bone age related to chronologic age was retarded by 2.9 y in boys and 1.3 y in girls; during puberty the bone age progressed slightly slower than chronologic age with a mean ratio of advance in bone age/chronologic age of 0.9 ± 0.3 y. Comparison with the control groups is not possible because data on skeletal maturation were not available for the latter. Under the assumption that bone age in control group A corresponds to chronologic age, PHV and EHV in the CRF patients occurred at an increasingly earlier stage of skeletal maturation.

Chronologic age at MHV and PHV was inversely correlated with the duration of CRF (MHV: $r = -0.63$, $p < 0.0005$; PHV: $r = -0.70$, $p < 0.001$). No association was noted, however, between the duration of CRF and the magnitude of MHV and PHV or the duration of the growth spurt.

At first observation, CRF patients with congenital or hereditary nephropathies (height SDS compared with control group A, −2.2 ± 1.1) were significantly shorter than those with acquired renal disease (height SDS, −1.1 ± 1.5; $p < 0.05$). This difference disappeared during the further course of CRF. No relationship between the type of primary renal disease and the timing, size, or duration of the pubertal growth spurt was found.

The mean total height gain achieved during the pubertal period amounted to 17.3 ± 5.8 cm in boys and 13.9 ± 9.0 cm in girls compared with 29.8 ± 7.2 cm and 29.0 ± 10.0 cm, respectively, in control group L ($p < 0.001$). The pubertal height gain was greater in children who were still preterminal at MHV (21.4 ± 6.0 cm) than in those who had reached end-stage renal failure (13.5 ± 7.0 cm) ($p < 0.01$). It was inversely related to the ratio of the entire time period spent on HD and the duration of the pubertal growth period ($r = -0.57$; $p < 0.002$). In contrast, no association was observed between pubertal growth and the time the patients had a functioning graft. Patients who received a TP before PHV did not gain significantly more height during puberty than those who had transplantations later (15.2 ± 7.3 cm *versus* 13.9 ± 7.7 cm). The height gain of the seven TP patients with a bone age of ≥12 yr at PHV was 6.8 ± 3.9 cm between PHV and EHV compared with 6.2 ± 4.4 cm from MHV to PHV.

Individual values for MHV and PHV expressed as SDS according to the mode of treatment are shown in Figure 4. MHV tended to be more suppressed in the HD and TP patients combined than in the preterminal stage patients ($p = 0.10$). No significant difference of PHV was found between the three treatment groups, although the most severe growth suppression was observed in the HD patients.

We also analyzed the impact of corticosteroid treatment on PHV (related to control group L) in TP patients. PHV SDS were inversely correlated with the dose of steroids consumed in the 12 mo spanning the PHV ($r = -0.68$; $p < 0.02$) (Fig. 5). In contrast, renal function as estimated by the mean of serial Scr levels

Table 1. *Chronological age and bone age at successive points of pubertal growth spurt in 29 children with CRF compared with average (A) and late (L) maturing control population (mean ± SD)*

	CRF		Control group A	Difference	Control group L	Difference
	Chronologic age (y)	Bone age (y)	Chronologic age (y)	A–CRF* (SDS)	Chronologic age (y)	L–CRF* (SDS)
Boys ($n = 15$)						
at 1st observation	8.1 ± 3.0					
at MHV	13.4 ± 1.4	10.5 ± 1.9	10.9 ± 1.0	2.6 ± 1.4	12.0 ± 0.6	2.0 ± 2.4
at PHV	16.0 ± 2.1	12.4 ± 1.6	13.9 ± 0.9	2.3 ± 2.4	15.0 ± 0.7	1.4 ± 4.3
at EHV	18.9 ± 1.8	15.6 ± 0.8	17.4 ± 0.9	1.7 ± 2.0	18.2 ± 0.7	1.0 ± 2.6
Girls ($n = 14$)						
at 1st observation	9.5 ± 2.3					
at MHV	12.1 ± 2.0	10.8 ± 2.3	9.6 ± 1.0	2.5 ± 2.0	10.6 ± 0.8	1.9 ± 2.5
at PHV	13.9 ± 2.1	12.3 ± 1.4	12.0 ± 0.9	1.9 ± 1.9	13.1 ± 0.6	1.3 ± 3.2
at EHV	16.5 ± 1.4	14.7 ± 0.8	15.5 ± 0.9	1.1 ± 1.5	16.3 ± 0.6	0.4 ± 2.2

* Mean age difference between CRF patients and control group A or L expressed as SDS.

Table 2. *Body height and height velocities attained at successive stages of pubertal growth spurt in 29 patients with CRF compared with average (A) and late maturing (L) control population (mean ± SD)*

	CRF (cm)	Control group A (cm)	Difference A-CRF* (SDS)	Control group L (cm)	Difference L-CRF* (SDS)
Boys (n = 15)					
at 1st observation			−2.2 ± 1.5		
at MHV	139.6 ± 10.6	144.0 ± 7.6	−0.5 ± 1.4	146.9 ± 7.4	−1.0 ± 0.4
at PHV	147.3 ± 11.3	161.1 ± 6.9	−2.0 ± 1.6	162.7 ± 7.0	−2.2 ± 1.6
at EHV	156.9 ± 11.0	176.7 ± 6.9	−2.9 ± 1.6	176.7 ± 6.9	−2.9 ± 1.6
at last observation	157.8 ± 11.6	178.4 ± 7.0	−2.9 ± 1.6	178.4 ± 7.0	−2.9 ± 1.6
	(cm/y)	(cm/y)	(SDS)	(cm/y)	(SDS)
MHV	1.9 ± 1.4	4.7 ± 0.5	−5.5 ± 2.9	4.3 ± 0.5	−4.7 ± 2.9
PHV	5.5 ± 2.2	7.8 ± 0.8	−2.9 ± 2.8	7.4 ± 0.7	−1.8 ± 2.2
Girls (n = 14)					
at 1st observation			−1.8 ± 1.2		
at MHV	136.2 ± 9.3	135.0 ± 9.8	0.1 ± 0.9	136.6 ± 13.4	−0.0 ± 0.7
at PHV	142.3 ± 7.2	149.2 ± 5.8	−1.2 ± 1.2	152.6 ± 6.2	−1.7 ± 1.2
at EHV	150.1 ± 7.4	163.7 ± 5.9	−2.3 ± 1.3	165.6 ± 6.6	−2.3 ± 1.1
at last observation	150.8 ± 7.5	165.3 ± 6.0	−2.3 ± 1.2	166.3 ± 6.2	−2.3 ± 1.1
	(cm/y)	(cm/y)	(SDS)	(cm/y)	(SDS)
MHV	2.0 ± 1.7	5.2 ± 0.6	−5.3 ± 2.8	4.7 ± 0.4	−6.6 ± 4.1
PHV	5.0 ± 2.0	6.5 ± 0.9	−1.8 ± 2.2	6.2 ± 1.0	−1.2 ± 2.0

* Mean difference in height and height velocity between CRF patients and control group A or L expressed as SDS. At the initial observation, age was highly variable; therefore, height at this point is expressed only as age-related SDS.

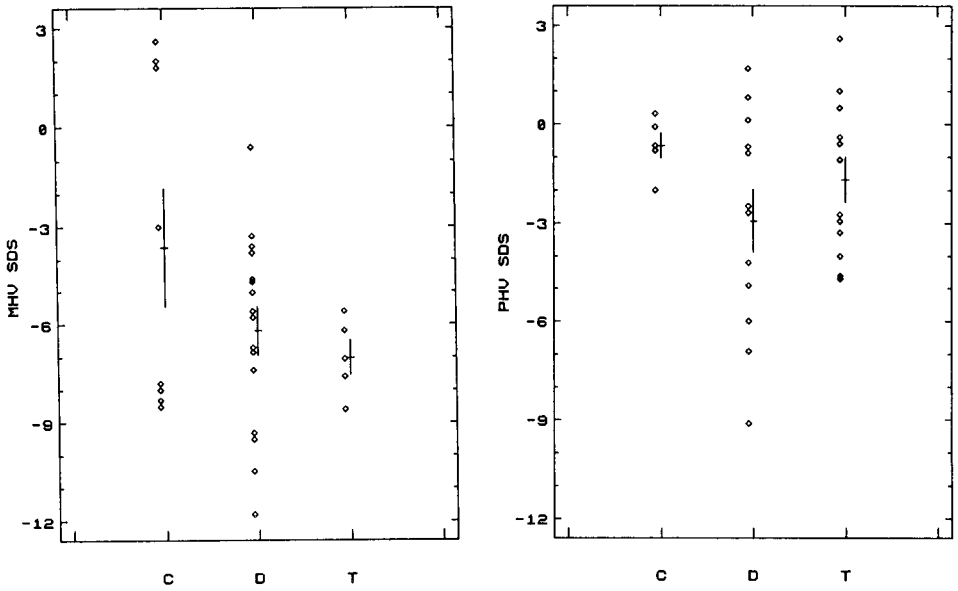

Fig. 4. Size of MHV and PHV in 29 children with CRF, expressed in SDS of control group L. Individual values are shown by ◇, and the means (±2 SEM) by *vertical lines*. The treatment modalities at MHV and PHV are indicated at the bottom: *C*, conservative treatment (preterminal CRF); *D*, dialysis; *T*, transplantation.

(median 1.2 mg/dL, range 0.5–2.9) during the same period was not correlated with height velocity at PHV expressed as SDS.

DISCUSSION

The aim of our study was to evaluate the pubertal growth characteristics of children with advanced CRF. Previous studies on pubertal growth in CRF have been limited by several methodologic problems such as small numbers of patients and height recordings, short follow-up periods, or the use of inadequate control populations (3, 14–21). In addition, the onset of puberty was often poorly defined (*e.g.* only by a fixed chronologic or bone age), resulting in a bias by the inclusion of variable periods of prepubertal growth. No precise definition of the start, the peak, and the end of the pubertal growth spurt had been used. Another previous methodologic problem was the lack of adequate smoothing and synchronization of individual longitudinal height data. The use of kernel estimation, a moving average principle (5, 6), in our study allowed a smoothed reproduction of the individual growth curves closely following the changes of growth velocity induced by puberty, by the disease, or by treatment (22). The synchronization of the individual data to mean growth curves that were centered on defined points of the pubertal growth curve enabled us to compare ages, height, and growth velocities of the CRF patients at these time points with those of normal children assessed by the same techniques. The large

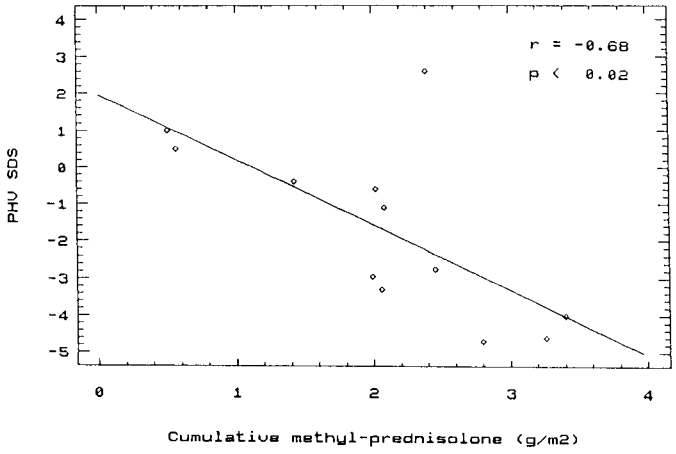

Fig. 5. PHV SDS related to cumulative dosage of methyl-prednisolone consumed during the year of measurement. There is a significant inverse relationship in 11 patients with a functioning transplant.

amount of material of the Zurich Longitudinal Growth Study (13) also allowed us to select a group of late-maturing healthy children to compare with our patients. Thus, the influence of CRF on the pubertal growth spurt could be analyzed independent of the effects of delayed maturation per se.

Although the shape of the synchronized height velocity curve followed the typical pubertal pattern, the timing and the size of the growth spurt in the CRF patients were markedly abnormal. The delayed onset of the pubertal growth spurt is compatible with data describing the late appearance of pubertal signs and delayed increase of gonadal steroid secretion in children with CRF (14, 23). The degree of delay was correlated with the duration of CRF. Surprisingly, the mean height at MHV was only slightly decreased in CRF boys and almost the same as in healthy girls. This finding may have been biased by the fact that, due to the small number of very late maturing normal children and the shorter duration of the growth spurt in our children, a complete match between control group L and the children under study was not possible, and the age difference at MHV was about 1.5 y. Comparison with the proposed normal mean height at MHV, as estimated in the Infancy-Childhood-Puberty standards (24), suggests that "normal" children entering puberty 2.5 SD later than average might be expected to be taller than the children in control group L. Nevertheless, it is remarkable that, in spite of the severe stunting at first observation and subnormal growth rates during prepuberty, the onset of pubertal growth in children with CRF occurs at a body height similar to normal children at MHV. The successive decline of height SDS during the pubertal period demonstrates that growth potential of CRF patients was irreversibly lost during puberty, resulting in a mean final height of −2.9 SDS in boys and −2.3 SDS in girls.

The loss of growth potential may be attributed to three factors: *1*), mean MHV was reduced to only 45% of that in control group L; *2*), although a distinct growth acceleration took place during puberty, mean PHV was only 75% of that in control group L, and in 16 of 29 children, below −2 SD; *3*), comparison of the duration of the pubertal growth period in CRF patients with that of normal late maturers revealed a mean deficit of 1.0 y in boys and 1.5 y in girls. Thus, diminished magnitude and duration of the growth spurt both contribute to the diminished ht gain during puberty.

In contrast to MHV, EHV occurred at a mean bone age that was markedly lower than the chronologic age of the control population. Some growth beyond EHV cannot be completely ruled out in those six patients whose epiphyses are not yet closed; however, none of the 23 patients who reached adult height gained more than 1 cm of height beyond a mean bone age of 15.6 y in boys and 14.7 y in girls. The low bone age at EHV emphasizes the limitation of the use of bone age as a maturational parameter in patients with CRF.

The longitudinal follow-up presented in our study covers periods of growth under varying treatment regimens. Earlier studies have reported normal PHV in preterminal CRF patients, severely depressed or absent growth spurts in long-term HD patients, and suppressed or normal pubertal growth in TP recipients (3, 15, 16, 19, 21, 25). In only one of these studies (19) was a correction made for the late appearance of the growth spurt. Our data demonstrate that the pubertal height gain is greatest in patients who enter end-stage renal failure late in adolescence. We observed the most severe degrees of pubertal growth failure in patients on long-term HD; however, mean PHV after TP was similar to that of patients undergoing HD. TP before PHV did not result in a greater pubertal height gain than later TP. In contrast to another recent study on TP adolescents, which defined the start of pubertal growth by bone age (19), our analysis of the individual growth patterns revealed that the duration of the pubertal period was shorter than in the control populations even after early grafting.

Grushkin and Fine (26) proposed that limited growth was achieved after renal TP in patients with a bone age of 12 y or more. However, most patients in that study had already fused epiphyses at the time of TP. Van Diemen-Steenvoorde *et al.* (19) found "significant" growth even in patients with a bone age of 12 y or more. In our study, where PHV occurred at a bone age of around 12 y, TP patients achieved more than 50% of the pubertal height increment beyond this point.

The inverse relationship we observed between PHV and cumulative corticosteroid intake is in agreement with other reports on steroid effects on growth after TP (21, 27). In contrast, we could not demonstrate a significant association between graft function and PHV, suggesting that the major factor compromising pubertal growth in TP recipients is indeed high-dose steroid treatment.

Our study reflects the limited success of various therapeutic regimens in the past two decades to improve pubertal growth in children with advanced CRF. Recently, recombinant hGH has been used successfully in prepubertal patients (28). Although the ultimate benefit of this treatment remains to be proven, it gives hope to pubertal patients to achieve acceptable adult height. Long-term courses of patients on growth hormone treatment during puberty may be validated by use of the methodology and comparison with the data presented in our study.

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