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Body growth in urinary tract malformations

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Abstract. Body height and height velocity were analysed in 54 children with obstructive urinary tract malformations over a mean period of 8.7 years, using new auxological methods. At the time of diagnosis, 9% of patients had a height of more than 2 standard deviations below the normal mean. Mean relative height changed significantly from the first to the last observation, the standard deviation score (SDS) increasing from –0.16 to +0.36 in patients with hydronephrosis compared with normal children ($P < 0.05$) and from –0.63 to +0.02 SDS in those without hydronephrosis ($P < 0.005$). The pathogenesis of the described growth disturbance is not clear. Stepwise multiple regression analysis pointed to a possible link between the duration of antibiotic treatment and the recovery of growth capacity, but improved growth could not clearly be attributed to any medical or surgical treatment. The synchronized average growth velocity curve was similar to that of healthy children and showed a normal pubertal spurt. Final height and target height calculated from parents' height differed only slightly from that of the normal population.

Key words: Body growth – Urinary tract malformations – Hydronephrosis

Introduction

Retardation of body growth has been described in a number of congenital tubular disorders in the absence of reduced glomerular filtration rate [1, 2]. It has been related to impaired concentrating ability, urinary loss of electrolytes and acidosis [1–4]. Since tubulointerstitial lesions are frequently associated with urinary tract malformations (UTM) due to chronic pyelonephritis, it is conceivable that children affected by this form of kidney disease may develop growth retardation as suggested by Uttley et al. [5].

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In a retrospective study, we have investigated the long-term growth of children with UTM, applying new statistical methods [6–8]. In our experience with children suffering from chronic renal failure, these sensitive techniques allow a better detection of subtle changes in growth compared with conventional auxological methods [9]. Our aim was to detect growth abnormalities in relation to the severity of UTM and to identify changes associated with long-term use of antibiotics or with reconstructive surgery. In addition, we analysed final height in a selected group of adult patients.

Patients and methods

All children recorded at the University Children's Hospital Heidelberg with major forms of UTM during the period from October 1969 to September 1989 were accepted for the study when they fulfilled the following criteria [10]:

1. Recurrent urinary tract infections associated with unilateral or bilateral UTM proven radiologically
2. Date of birth before 1970 and observation during a period of at least 3 years from the time of diagnosis
3. Serum creatinine levels consistently <1.3 mg/dl and 24-h creatinine clearance >80 ml/min per 1.73 m^2.

The patients were divided into two groups: *group A* consisting of 30 children (16 males, 14 females) with a definite dilatation of the upper urinary tract by X-ray, designated as *hydronephrotic* group and *group B* consisting of 24 children (6 males, 18 females) without significant dilatation of the upper urinary tract, defined as *non-hydronephrotic* group. The age of the patients, the time of observation and the types of lesions observed are given in Table 1. No significant differences in these parameters were noted between groups A and B. However, the proportion of patients who underwent reconstructive surgery was higher in group A (93% in A vs. 62% in B).

The following operations were performed in groups A and B, respectively: unilateral nephrectomy 11/1, heminephrectomy 0/3, ureteropelvic reconstruction 15/2, reimplantation of ureter 9/2, anti-reflux surgery (Politano Leadbatter procedure) 4/5, urethral valve resection or urethrotomy 1/2, urethroplasty 0/4 (numbers refer to renal units). Some patients had several operations but only the time of the last reconstructive surgery was taken for calculation. Antibiotic treatment or prophylaxis ($n = 24$ in group A, $n = 21$ in group B) was commenced in most patients at the time of diagnosis and was continued for 4.1 ± 3.9 years (range 0.1–18.0 years) for both groups combined.

Table 1. Age, duration of disease (in years) and types of urinary tract malformations

	Group A with hydronephrosis	Group B without hydronephrosis
No. of patients	30	24
No. of patients with reconstructive operations	29	15
Age at diagnosis (mean ± SD)	4.3±3.5	5.9±2.3
Age at last observation (mean ± SD)	13.1±4.2	14.2±2.3
Time of observation (mean ± SD)	8.9±4.7	8.4±3.6
Number of malformations		
duplication	8	2
ureteropelvic stenosis	17	4
vesicoureteral stenosis	9	–
vesicoureterorenal reflux		
degree 2 or 3	2	12
degree 4 or 5	6	–
ureterocele	2	2
meatal stenosis	–	12
urethral valve	2	–
renal hypoplasia/dysplasia	4	1

The clinical course including data on urinary findings, serum chemistry, X-rays and ultrasound assessments were obtained from hospital files. Special care was taken to include all available height measurements. Height was measured using a Harpenden stadiometer in 84% of all measurements (since 1972). The mean number of height measurements per patient amounted to 17 (range 6–41).

To minimize the influence of measurement errors, height data were smoothed by the kernel estimation method [6, 8]. This is a mathematical procedure applying moving weighted averages to raw data. The degree of smoothing was chosen by minimizing the mean square errors. The individual growth curves obtained by the kernel estimation procedure were centered on: (1) the time of diagnosis, (2) the end of antibiotic treatment, (3) the time of last reconstructive surgery and (4) the last observation, to obtain a "structural average growth curve" for groups of patients [7]. For this purpose a synchronization procedure to align the defined points with the respective means was used. The kernel estimation smoothing and the synchronization procedure were performed using a Fortran programme on an IBM 3090 mainframe computer located at the University of Heidelberg. Standard deviation scores (SDS) of height and of 12-month height velocity (HV) were related to the growth standards of the first Zurich Longitudinal Study of Growth and Development [11].

Final height was defined as a growth rate of less than 1 cm in the previous year. Except for 5 patients, it was obtained from questionnaires returned by the patients. Target height was calculated using two formulae: (1) mid-parent height (MPH)+6.5 cm for boys and MPH –6.5 cm for girls [12] and (2) MPH +10.6 cm for boys and MPH –2.6 cm for girls [13].

Statistics. Differences in SDS of height and of HV were calculated for different time points or intervals of observation using the *t*-test for dependent variables. For comparison between the disease groups and between sexes, the *t*-test for independent samples was used. In order to assess the relative impact of various patient characteristics on the changes in relative height, we performed a stepwise multiple regression analysis which was applied both to the total population under study and to groups A and B separately. The cut-off level of significance for accepting a variable in the multi-regression model was $P < 0.15$ as calculated by the F-test. For all calculations the SAS-package was used [14, 15].

Results

At the time of diagnosis 5 of the 54 patients had a height 2 SD or more below the mean of controls. In group A body height at the time of diagnosis and at last observation was –0.16±1.61 SDS and +0.36±0.95 SDS, respectively (mean values ± SD, $P < 0.05$). In group B the relative height increased from –0.63±0.92 SDS at the time of diagnosis to +0.02±0.75 SDS at last observation ($P < 0.005$). The difference in the increase of SDS of height was not significant.

Figure 1 and Fig. 2 demonstrate the smoothed height data in the two groups of patients, expressed as SDS compared with healthy children. At the time of diagnosis, 3 of 30 patients in group A (all below 2 years) and 2 of 24 in group B were found to have a height of 2 SD or more below the mean of controls. The proportion of patients with a height below average was obviously greater in group B than in group A. As shown by the SDS height curves, there was an upward trend of height SDS with time in both groups, although at a lower level for group B than for group A.

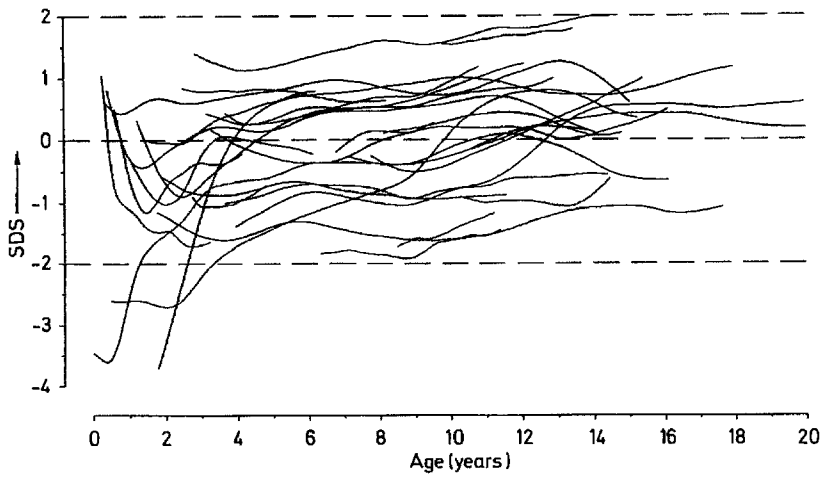

Fig. 1. Changes in height of 30 patients with urinary tract malformations (group A). Height is expressed in standard deviation score (*SDS*) compared with normal children (11)

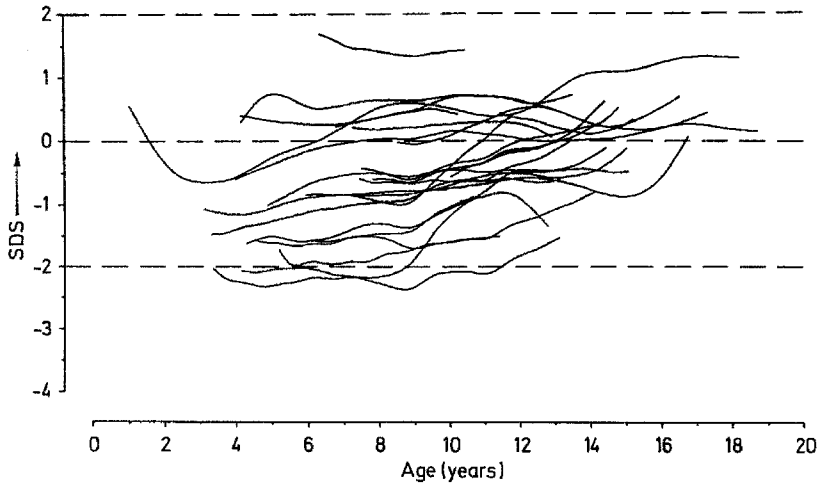

Fig. 2. Changes in height of 24 patients with urinary tract malformations (group B). Height is expressed in SDS compared with normal children (11)

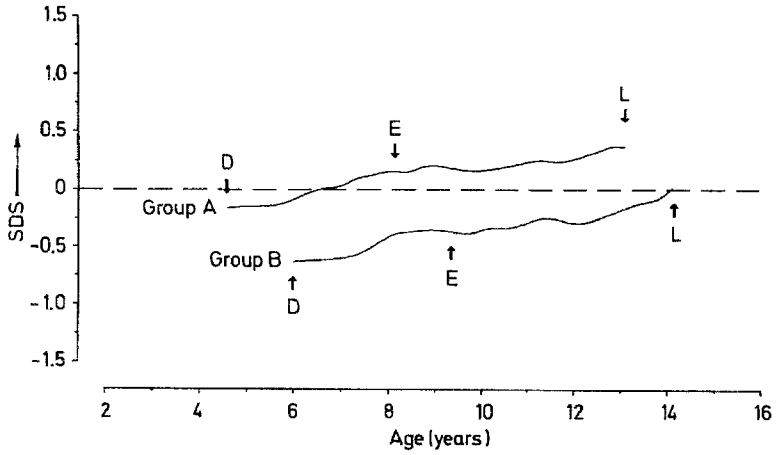

Fig. 3. Changes of mean body height of 24 children with urinary tract malformations with hydronephrosis (group A) and 23 children without hydronephrosis (group B) centered on the time at diagnosis (coinciding with start of antibiotic therapy (*D*), end of antibiotic therapy (*E*) and last observation (*L*). The data are expressed in SDS of normal body height (11) obtained from individual growth curves smoothed by the kernel estimation method

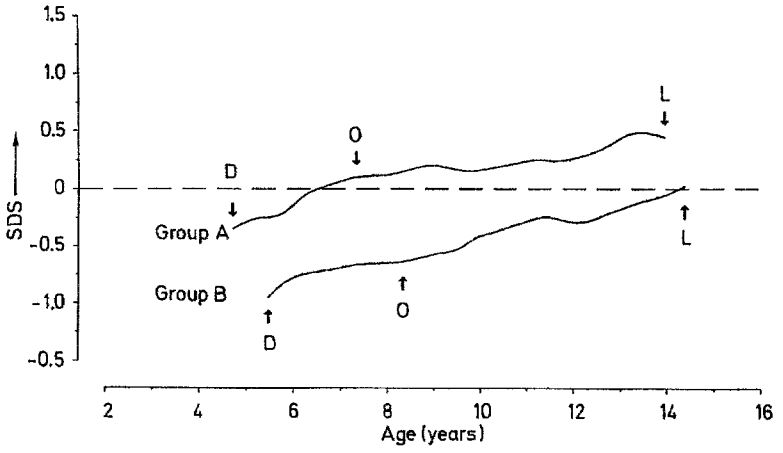

Fig. 4. Changes in SDS of body height of 20 children with urinary tract malformation with hydronephrosis (group A) and 11 children without hydronephrosis (group B) centered on the time at diagnosis (D), at last reconstructive operation (*O*) and at last observation (L)

The growth during antibiotic treatment is displayed in Fig. 3. Significant differences were found between SDS of height at the beginning and at the end of antibiotic therapy in group B ($P < 0.005$) and between SDS of height at the end of the antibiotic period and at last observation in groups A ($P < 0.05$) and B ($P < 0.001$). However, the yearly change in height SDS during and after discontinuation of antibiotic treatment was not significantly different. This applied also to a group of 9 children from group B who did not receive surgery.

In order to detect influences of reconstructive surgery, we compared height before and after the last operation, irrespective of antibiotic therapy (Fig. 4). Whereas differences were observed between height SDS at the time of diagnosis and at last operation in group B ($P < 0.05$) and at time of last operation and last observation ($P < 0.05$ group A, $P < 0.001$ group B), we failed to detect a significant difference in the yearly change of height SDS following surgery.

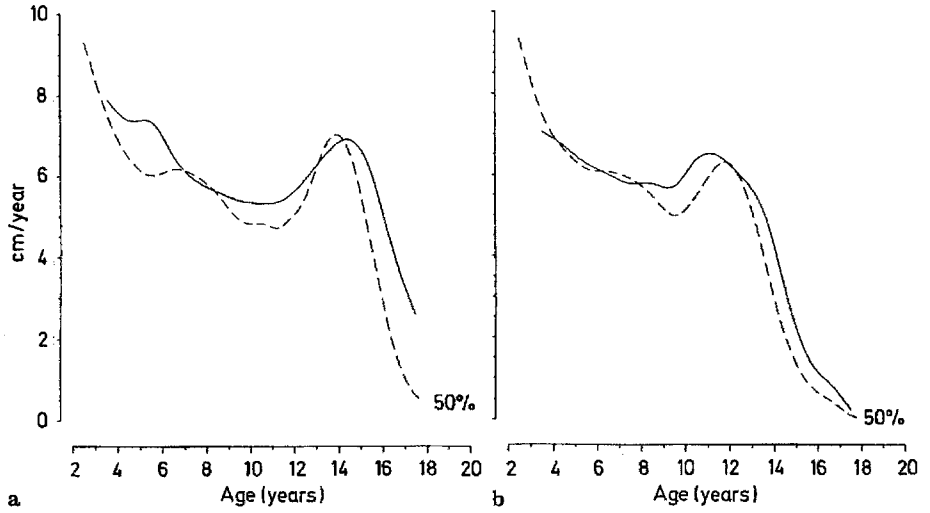

Fig. 5. Mean height velocity of **a** 22 boys and **b** 32 girls with urinary tract malformation, both groups together (———). The curve was obtained by using the smoothing and synchronization procedures described in the text. – – – –, Normal children (50th percentile)

Mean HV was similar to the average normal curve for both groups in both sexes, as demonstrated in Fig. 5 for groups A and B together. In particular, the pubertal height spurt had a similar size and appearance as in healthy children. Mean HV calculated over 1 year before and after the last reconstructive operation increased from +0.31 (–2.80 to +5.19) SDS to +0.81 (–0.97 to +6.29) SDS (NS).

In the multiple regression analysis procedure, sex, disease group, age at diagnosis, height SDS at the time of diagnosis, duration of antibiotic prophylaxis and treatment, as well as duration of the observation period, were offered as independent factors for stepwise variable selection. The dependent variable was the change in height SDS from the time of diagnosis to the time of last observation. For the study population as a whole, initial height SDS was the main predictor of the change of height SDS throughout the observation period (partial $r^2 = 0.54$, $P < 0.0001$), implying a more severe initial retardation of height being associated with improved subsequent growth. In addition, a longer duration of antibiotic treatment contributed significantly to an increased height SDS (partial $r^2 = 0.07$, $P < 0.005$). Furthermore, sex had a weak but significant influence on the development of relative height, girls showing a greater growth improvement than boys (partial $r^2 = 0.03$, $P < 0.05$). When the disease groups were considered separately, an even closer association between height SDS change and initial height SDS was found in group A (partial $r^2 = 0.64$, $P < 0.0001$), whereas the length of the observation period mainly influenced growth change in group B (partial $r^2 = 0.30$, $P < 0.005$).

Final height was available for 25 patients (14 in group A, 11 in group B). Mean final height was 177.7±6.3 cm (range 164.8–186.0 cm) in 11 males and 165.9±5.2 cm (156.0–173.0 cm) in 14 females, corresponding to –0.10 SDS and +0.24 SDS of the control population, respectively. For patients in group A, mean final height was similar (–0.14 SDS) to that in group B (+0.33 SDS). Mean final height for groups A and B combined was +0.10 (–1.94 to +1.45) SDS, compared with an initial height of –0.65 (–3.87 to +2.02), respectively; this increase was significant ($P < 0.01$).

Mean target height calculated from parents' height by the classical formula of Tanner et al. [12] was +0.4 (–3.6 to +6.0) cm related to the expected value in boys ($n = 8$) and +1.4 (–2.5 to +7.5) cm in girls ($n = 9$), corresponding to +0.10 and +0.24 SDS. When the formula of Molinari et al. [13] (which considers the secular trend and the present growth status of our normal population more adequately) was applied, mean final height was –3.3 (–7.3 to +2.3) cm related to the target in boys and –2.5 (–6.4 to +3.6) cm in girls, with a small difference between groups A (–4.4 cm) and group B (–1.5 cm).

Discussion

Precise retrospective assessment of longitudinal growth in a diseased population is a difficult task, especially when differences from the normal population are expected to be small and the points of height measurements do not correspond to the time periods required for meaningful analysis. The kernel estimation method for smoothing growth curves [6] and the synchronization procedure for obtaining "structural average data" at defined points of observation [8] were used in this study to meet the requirements of an adequate growth analysis. We previously used these methods in a group of patients with chronic renal failure where a large number of height measurements was available which were taken at more or less short and regular intervals [9]. The application of these auxological methods in patients with UTM, who obviously have a less severe clinical course, appeared to be suitable because height data were obtained at less regular intervals although over longer periods of time. Under these circumstances, external influences, e.g. measurements by multiple observers, become more important.

Our study revealed some alterations of long-term growth in UTM, although the differences from controls were small. At the time of diagnosis we found a distinct decrease of the relative height in the non-hydronephrotic group compared with the normal population. In both groups, patients with lower initial scores had a better sub-

sequent growth than those with normal scores. The improved height cannot fully be attributed to a transient physiological rise in height SDS during puberty because it was found both in patients who remained prepubertal and in those who had attained final height at the time of the last observation.

The pathogenesis of the growth changes observed is difficult to evaluate. It must be stressed that our study was restricted to patients with UTM without obvious change of renal function. Although tubular function was not studied systematically, we assume that it was affected at least during early periods of the disease, when signs of urinary tract obstruction and infection were frequently present. It is well known that these conditions may result in tubular dysfunction [16] such as decreased concentrating ability, sodium loss and acidosis, i. e. conditions known to interfere with normal growth [3, 4].

The reason for the lower height SDS in non-hydronephrotic patients compared with those with hydronephrosis is not clear. We would speculate that, despite the less obvious structural changes of the urinary tract, group B presented a more severe degree of renal dysfunction, e. g. by protracted urinary tract infections, affecting growth more severely. Furthermore, it is notable that patients in group B were slightly older at the time of diagnosis than those in group A.

The significant increase in height SDS from diagnosis to last observation and to final height in both groups of patients may reflect the correction of growth-depressing factors. A minor influence of antibiotic prophylaxis on growth may be inferred from our multiple regression analysis, although the possibility remains that a similar improvement may have occurred without intervention. In the only similar study reported in the literature, growth of girls with recurrent urinary tract infections did not significantly differ from that of normal children and was independent of anti-microbial prophylaxis with co-trimoxazole [17].

Reconstructive surgery was followed by a significant increase in relative height in both groups of our patients which was similar to that observed before surgery. Two earlier investigations reported on an increased growth spurt following successful anti-reflux operation [18, 19], but the auxological methods used in the first of these studies may be questioned. Despite the application of a more sensitive method to test the effectiveness of treatments, our data do not allow us to attribute a growth-promoting influence either to antibiotic treatment or to reconstructive surgery. The improved growth of our patients may well have been the result of the natural history of the disease. Final height of our patients was almost the same as that of the reference population indicating an inherent capacity for catch-up growth. This was confirmed by the calculations of target height from parents' height.

In conclusion, our study demonstrates that some children with UTM have a slight degree of growth retardation which corrects itself with time and/or operative intervention. The significant increase in relative height from the first to the last observation and to final height cannot be clearly related to any form of treatment. The overall normal growth velocity curve and final height observed indicate that, despite the low initial height SDS, at least in the non-hydronephrotic group, overall growth reached its genetically determined curve.

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