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Body growth in primary de Toni-Debré-Fanconi syndrome

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Abstract. Body growth in nine children with primary de Toni-Debré-Fanconi syndrome was followed from birth to adolescence or adult life. At the time of diagnosis, corresponding to the start of treatment, the median age was 2.3 (range 0.4–13.9) years and height standard deviation score (SDS) was always decreased (median −3.5, range −6.8 to −2.1). Despite continuous electrolyte and bicarbonate supplementation only four patients showed a slight improvement in growth. At the time of the last observation at the age of 17.2 (4.5–20.1) years median height was −4.7 (−5.9 to −1.8) SDS. The median difference between height at last observation and target height was −4.5 SDS. Final height ($n = 5$) ranged between −1.8 and −5.5 (median –4.3) SDS. The pubertal growth spurt was absent in two children. Metabolic acidosis was identified as a significant growth-retarding factor. Mean serial blood bicarbonate levels and height SDS at the last observation were correlated ($r = -0.87$, $P < 0.01$). No correlation was observed between last height SDS and the degree of hypokalemia, hypophosphatemia, or hypercalciuria. In conclusion, patients with primary de Toni-Debré-Fanconi-syndrome present severe growth failure at the time of diagnosis which persists into adult life. Supportive therapy is frequently unable to prevent further loss of relative height.

Key words: Primary de Toni-Debré-Fanconi syndrome – Body growth – Acidosis – Final height – Growth hormone – Potassium

Introduction

Idiopathic or primary de Toni-Debré-Fanconi syndrome (FS) is characterized by generalized dysfunction of the proximal tubule, leading to excessive urinary loss of amino acids, glucose, phosphate (P), bicarbonate (HCO_3)and other substances handled by the proximal tubule in absence of a known underlying cause or systemic disease [1, 2, 3]. In some instances FS is hereditary [4]. According to early reports, growth retardation appears to be a common feature of FS in children [5], but only a few data have been presented on longitudinal growth [4–9]. The pathophysiology of growth failure in FS has not been investigated systematically. This retrospective study describes nine children with FS, most of whom were followed from birth to adolescence or adult life. By using modern auxological evaluation we have related long-term growth to clinical, biochemical, and radiological findings and treatment in FS.

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Patients and methods

The nine patients reported here were followed at the University Children's Hospital Heidelberg between 1962 and 1995 (Table 1). Six were of German origin and three Mediterranean. All patients showed complex tubular dysfunction with persistent hyperaminoaciduria, glucosuria, and hypophosphatemia/hyperphophaturia. Excessive renal loss of potassium (K), calcium (Ca), and (HCO_3), leading to acidosis, was found in seven, eight and seven patients, respectively. In addition, eight patients had polyuria and in three of these a renal concentrating defect was proven. Defined inborn errors of metabolism were excluded. Detailed data on patients 1 [10], 4 [11], and 9 [12] have been published earlier.

Table 1 gives clinical data at the time of diagnosis corresponding to the start of treatment. All children were born at term and had normal weight (median 3.0 kg, range 1.5–5.2 kg) and length (median 49 cm, range 30–51 cm) at birth, except patient no. 8 who was born prematurely with a gestational age of 29 weeks. In most patients growth data were available from birth, i.e. before the diagnosis of FS was mode. Longitudinal growth was analyzed over a median period of 13.2 (4.5–19.7) years from the first to the last documented height measurement (in adult patients corresponding to the time when final height was reached). The median period from the time of diagnosis to the last observation was 9.1 (range 4.1–18.9) years. The median age at the last observation was 17.2 (4.5–20.1) years. Five patients reached their final height (Table 1). Two patients died due to electrolyte and fluid disturbances during gastroenteritis.

Table 2 provides details on glomenular filtration rate (GFR), the presence of nephrocalcinosis, bone changes, renal histology and

Table 1. Age and standard deviation scores (SDS) of height and weight in nine children with de Toni-Debré-Fanconi syndrome (FS) at the time of diagnosis (corresponding to the start of treatment) and at the time of last observation[a, b, c]

Patient no.	Sex	At diagnosis					At last observation								
		Age (years)	Height (cm)	(SDS)	Weight (kg)	(SDS)	Age (years)	Height (cm)	(SDS)	Target height (cm)	Δ Target height[f] (SDS)	Weight (kg)	(SDS)	Bone age (years)	Age at PH_2/PH_5 -years)
1	F	2.0	78.0	–3.5	7.1	–3.1	11.9	110.0	–5.9	156.0	–4.3	17.4	–0.4	9.1	(PH_1)
2	F	13.9	124.3	–5.9	24.0	0.3	18.4	132.0[e]	–5.5	171.4	–6.6	34.5	1.4	Adult	12.5/16.5
3	F	4.0	89.6	–3.6	12.7	0.3	13.8	132.5	–4.3	165.6	–4.5	29.9	0.3	7.5	13.2/–
4	M	10.3	120.0	–3.4	24.8	0.8	20.1	148.3[a]	–4.3	176.3	–4.1	49.0	1.9	Adult	Unknown
5	F	2.3	72.0	–6.8	8.0	–2.7	13.2[d]	126.0	–4.8	164.1	–4.7	17.1	–2.4	10.7	12.8/–
6	F	0.8	66.2	–2.6	6.3	–1.3	17.4	136.7[e]	–4.7	165.8	–4.9	40.8	2.1	Adult	13.4/17.0
7	M	0.8	61.0	–4.9	4.8	–1.4	19.7	160.2[e]	–2.6	175.7	–2.3	48.8	0.5	Adult	13.0/15.8
8	M	5.0	101.0	–2.1	16.0	0.0	17.2	163.8[e]	–1.8	182.4	–2.4	64.3	1.7	Adult	12.3/16.1
9	F	0.4	57.0	–3.3	4.2	–1.4	4.5[d]	86.0	–5.4	162.6	–5.1	9.7	–2.0	2.8	(PH_1)
Median		2.3		–3.5		–1.3	17.2		–4.7	165.8	–4.5		0.5		

PH, Pubic hair stage according to Tanner
[a] In adult patients last observation corresponds to the time when final height was reached
[b] Heights are given as real (non-smoothed) values
[c] SDS of weight are corrected for height
[d] Died
[e] Final height
[f] Difference between target height and individual height at last observation

Table 2. Inulin clearance (C_{in}), nephrocalcinosis (NC), rickets (R), leg deformities (D), total numbers of fractures (F), renal histology, and occurrence of extrarenal manifestations in nine children with FS

Patient no.	C_{in} ml/min per 1.73 m² (age at assessment in years)	NC score[a] at last observation	Bone changes at any time of disease			Renal histology	Extrarenal manifestations
			R[a]	D[a]	F		
1	83 (2.1)	0	+	+	0	PTHY	DM, exocrine pancreas deficiency, retinopathy, ptosis, cardiomyopathy
2	78 (19.4)	2+	2+	2+	4	PTA, MC	–
3	82 (13.4)	+	+	0	0	Not done	–
4	83 (20.3)	0	2+	+	0	PTA	Epilepsy
5	80 (11.1)	0	+	+	1	MC	Liver cirrhosis, mental retardation
6	58 (1.8)	0	+	+	0	Normal	DM, spastic diplegia
7	37 (9.1)	+	+	0	0	GCL	DM, celiac disease, IgA deficiency
8	78 (17.2)	+	+	0	0	PTA, IF	–
9	60 (4.1)	0	2+	+	1	BBL	Mental retardation, epilepsy

PTA, Proximal tubular atrophy; PTHY, proximal tubular hypertrophy; IF, interstitial fibrosis; MC, enlarged or distorted mitochondria; GCL, glomerulocystic lesions; BBL, loss of proximal tubular brush border; DM, diabetes mellitus
[a] 0, Absent; +, mild; 2+, severe

extrarenal manifestations. Serum creatinine levels studied at last observation were normal in all patients except no. 7 who showed an increase to 1.7 mg/dl. This and a further patient (no. 2) are the only ones known to have developed progressing renal failure later in adult life.

Treatment consisted of oral substitution of K-($n=7$), P-($n=9$), Ca-($n=5$), magnesium-($n=2$) and HCO_3-($n=7$) containing salts and water ($n=9$). The median dosage of HCO_3 was 6.2 (range 3.1–12.5) mmoI/kg per day. In addition, seven patients received vitamin D_3 in supraphysiological doses up to 5000IU/day or calcitriol. Patient 1 was also treated with indomethacin from the age of 2.0 years and pancreatic enzymes from the age of 5.2 years. Patient 3 was started on recombinant human growth hormone (4 IU/m² per day s.c.) at the age of 8.3 years until the last observation. Patient 6 received hydrochlorothiazide from the age of 10.5 years. Patient 7 was on a gluten-free diet from the age of 4.6 years. Patient 9 required tube feeding from the age of 3.9 years. Three diabetic patients received insulin from 5.2, 16, and 14.5 years, respectively. Carnitine supplementation was given to two patients.

A summary of the biochemical changes is given in Table 3. Data were obtained at intervals of up to 1 year. To evaluate the disease activity we assessed the proportion of pathological levels of serum K, P, and HCO_3, and of calciuria and urine volume observed from the start of treatment to the last observation.

In infants, length was measured in the supine position using an infantometer. In older children a Harpenden stadiometer was used for measurement of height, except in two patients (nos. 2 and 4) observed in the 1960s. The median number of height measurements from the first observation (corresponding to birth in 7 patients) to the last observation was 24 (range 8–83) per patient. Standard deviation scores (SDS) of height and weight were related to the growth standards of the first Zürich Longitudinal Study of Growth and Development [13]. In patient 8 height SDS was calculated after correction for prematurity by subtracting the time of prematurity from the chronological age [14]. Final height was defined as epiphysial closure on hand X-rays and/or a height increment of less than 1 cm/year in the preceding year. Body mass index (BMI) SDS was calculated using the standards of Rolland-Cachera et al. [15]. To account for the observed growth retardation, standards for weight and BMI were corrected for

Table 3. Mean potassium (K), phosphate (P), and bicarbonate (HCO_3) levels, calciuria, and urine volume in nine children with FS from the start of treatment to last observation[a]

Patient no.	Serum K[b]			Serum P[c]			Blood HCO_3[d]			Calciuria[e]			Urine volume[f]		
	Mean mmol/l	n/d	%	Mean mmol/l	n/d	%	Mean mmol/l	n/d	%	Mean mg/kg per day	n/d	%	Mean l/m^2 per day	n/d	%
1	3.9	7/20	35	1.7	0/13	0	18	9/16	56	2.7	3/7	42	1.2	2/9	22
2	3.4	4/9	44	0.9	7/14	50	18	7/8	88	6.8	8/9	89	2.8	8/9	89
3	3.6	13/41	32	1.1	14/42	33	19	16/39	41	10.9	11/13	85	2.5	20/23	87
4	3.7	3/10	30	0.6	13/14	93	20	0/5	0	2.3	0/4	0	1.8	0/4	0
5	3.6	22/51	43	0.9	24/30	80	21	13/32	40	9.5	5/5	100	2.6	3/4	75
6	4.0	10/32	31	1.0	22/31	71	20	9/22	41	5.9	3/4	75	2.7	9/12	75
7	4.4	0/36	0	1.4	7/33	21	23	4/23	17	2.0	1/10	10	3.4	12/12	100
8	3.9	2/10	20	1.3	0/8	0	23	0/6	0	8.0	4/4	100	3.6	6/6	100
9	4.5	0/13	0	0.9	14/15	93	16	11/14	79	2.1	2/6	33	2.2	4/6	67
Median	3.9		31	1.0		50	20		41	5.9		75	2.6		75

[a] For each variable the nominator (n) indicates the number of pathological values and the denominator (d) the number of all determinations measured in individual patients
[b] Lower normal limit of serum K 3.6 mmol/l
[c] Lower normal limits of serum P according to age [42]
[d] Lower normal limit of blood HCO_3 20 mmol/l
[e] Upper normal limit of calcium excretion 4 mg/kg per day
[f] Upper normal limit of urinary volume assumed to be 2 l/m^2 per day

height age, i.e., the corresponding mean age in the normal population for individuals of the same height as the patients.

To minimize the influence of measurement errors, height data were smoothed by the kernel estimation method, which is a mathematical procedure applying moving weighted averages to raw data [16, 17]. The degree of smoothing was chosen by minimizing the mean square errors. Bone age was assessed according to Greulich and Pyle. Target height was calculated from mid-parental height (MPH) plus 10 cm for boys and MPH minus 2.6 cm for girls [18]. Pubertal stages were assessed according to Tanner and evaluated by Swiss standards. GFR was determined by inulin clearance (C_{in}). Nephrocalcinosis was evaluated by ultrasound and graded [19]. Ricketic lesions on x-ray and leg deformaties were quantified using the following scores (0 absent, + mild, 2+ severe lesions).

Statistics. Differences in height SDS were calculated for different time points of observation using the Wilcoxon sign rank test for dependent variables. The mean biochemical values and the proportion of pathological data were related to height SDS at last observation using correlation analysis. A P value below 0.05 was assessed to be statistically significant.

Results

At the time of diagnosis, all children had a height less than 2 SD below the normal mean (Table 1). Weight according to height was normal except for patients 1 and 5. Corrected BMI was normal in all children (median −0.4 SDS, range −1.7 to 0.6). Figure 1 shows the smoothed growth curves of boys and girls with FS compared with standards [13]. Despite treatment, all children beyond infancy were growing below the 3rd percentile, except patient 8 for a short period.

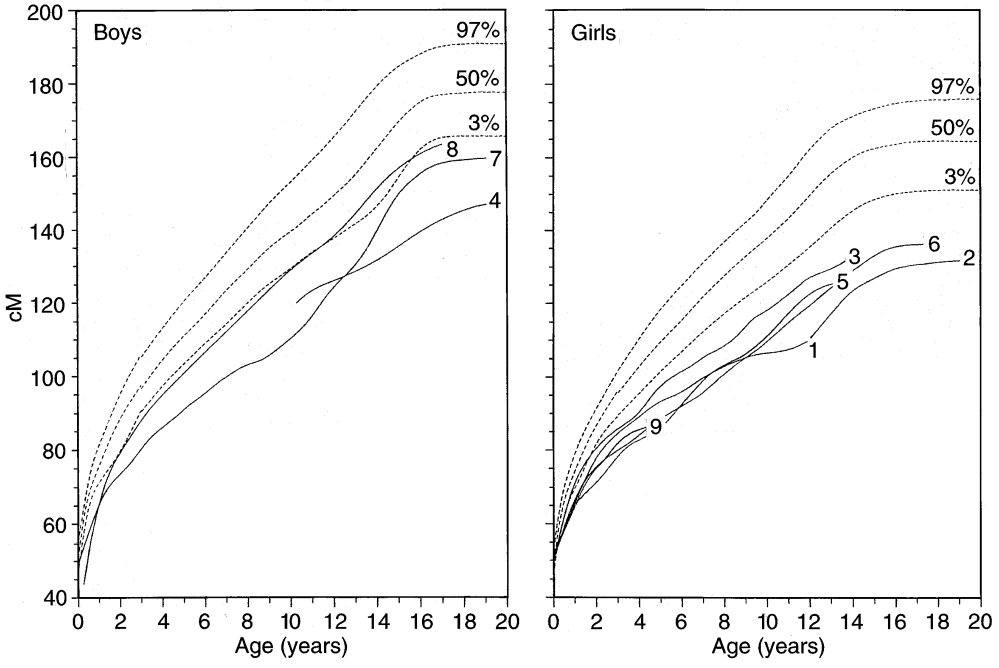

Fig. 1. Changes in body height of three boys and six girls with de Toni-Debré-Fanconi syndrome (FS). Normal percentile curves are according to Prader et al [13]. The *numbers* attached to the growth curves relate to the individual patients (Table 1)

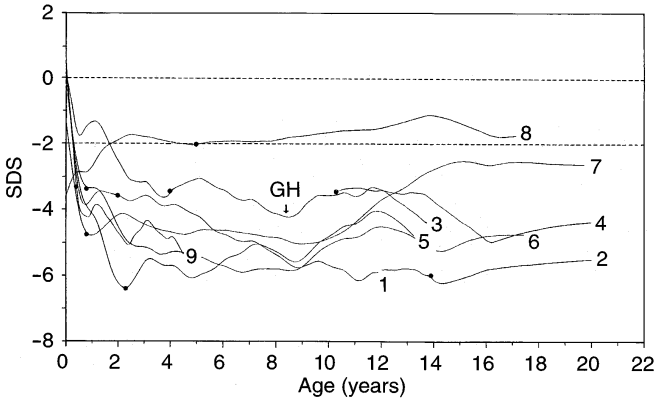

Fig. 2. Changes in height standard deviation score (*SDS*) of nine children with FS compared with normal standards [13]. The *numbers* attached to the growth curves relate to the individual patients (Table 1). The *dots* indicate the time of diagnosis corresponding to the start of treatment. *GH*, Start of treatment with recombinant human growth hormone

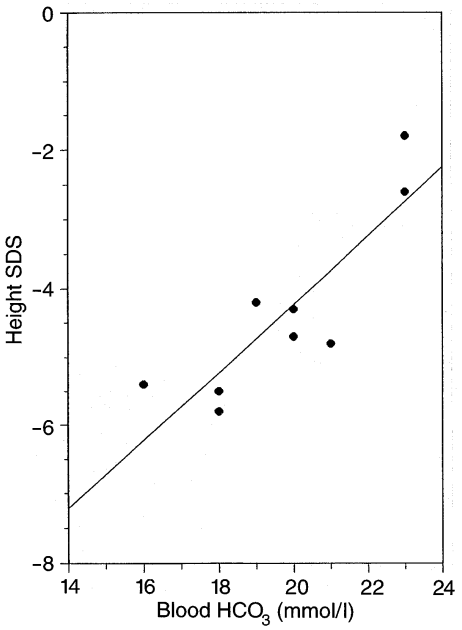

Fig. 3. Relationship between mean individual blood bicarbonate (HCO_3) levels during treatment and height SDS at last observation in nine children with FS ($r = 0.87$, $P < 0.01$)

Figure 2 shows the growth curves for both sexes combined, expressed as height SDS. From the first observation until the time of diagnosis height SDS dropped in all patients, except patient 8 who was born prematurely. In four children (nos. 3, 5, 7, and 8), a small partial catch-up growth was observed after the start of treatment, which was sometimes delayed and interrupted by a transient fall in height SDS. Four patients (nos. 2, 5, 7, and 8) finally achieved a height SDS exceeding that at the start of treatment (Table 1). In five patients (nos. 1, 3, 4, 6, and 9), the latest height SDS was lower than at the start of treatment. The median change in height in all patients from the start of treatment to the last observation was −0.7 (−2.4 to +2.3) SDS. There appeared to be no relationship between age at the start of treatment and the change in height SDS. Growth hormone treatment in patient 3 prevented a further decrease in height SDS only transiently.

Final height was reached in five patients at a median age of 18.4 years and ranged between −5.5 and −1.8 (median −4.3) SDS (Table 1). The median difference between height at the last observation and target height was −4.5 SDS. SDS of weight increased from the first to last observation in almost all patients ($P < 0.05$). SDS of BMI increased only slightly from −0.4 to 0.2 (−1.3 to 0.5) (NS).

Bone age was markedly retarded in all children. Clinical signs of puberty were noted in seven patients. In three of five patients (nos. 3, 5, and 6) with sufficient data pubertal development was retarded. In two patients (nos. 2 and 6), an adequate pubertal growth spurt appeared to be absent (Figs. 1, 2).

Table 3 summarizes some biochemical data in blood and urine. There was no significant correlation between height SDS at the last observation and mean levels or percentage subnormal values of serum K and P. It is, however, noteworthy that the two patients (nos. 7 and 8) attaining the tallest final height never required K supplements, in contrast to all other patients. Relative height at last observation correlated well with the mean blood HCO_3 levels ($r = 0.87$, $P < 0.01$) determined from the start of treatment to the last observation (Fig. 3) and with the proportion of HCO_3 levels below 20 mmol/l ($r = -0.80$, $P < 0.01$). A correlation was also found with mean urine volume ($r = 0.76$, $P < 0.05$), but not with urinary calcium excretion and C_{in} measured concomitantly or with the presence of nephrocalcinosis. Patients 7 and 8 who had the mildest bone changes also showed the mildest degree of growth retardation (Tables 1, 2).

Discussion

There is no general agreement on the definition of FS, but most authors agree that it includes a generalized dysfunction of the proximal tubules without obvious cause and independent of the presence of extrarenal manifestations. In the past, some cases described as primary FS might have been due to mitochondrial respiratory chain disorders, such as Pearson or Kearns-Sayre syndrome, that may result in similar disturbances of tubular transport [20, 21]. In our report we included one such patient (no. 1) who first presented with isolated kidney disease [10].

Growth has rarely been investigated in FS. In an early review, Illig and Prader [5] noted that only 1 of 16 patients with FS had a normal height. Since the appearance of that paper we know of 12 further published studies of body height in 20 pediatric patients, 7 of whom attained final height [4, 6–9, 22–28]. The median height reached by these 20 patients at the last observation was −3.7 (−1.9 to −6.4) SDS using Swiss standards [13], compared with −4.7 SDS in our series.

This paper describes long-term growth over a median period of 13 years in a representative series of children with FS. In all patients we observed severe growth retardation.

Despite normal height at birth, all children presented a rapid fall in height SDS in the 1st year of life and sometimes over prolonged periods. The *time of diagnosis* and the start of treatment in our patients with FS was rather late, despite the early observation of polyuria, recurrent dehydration, fever, and failure to thrive from birth. This might explain the severe degree of growth retardation at the time of diagnosis.

Severe growth failure, as in FS, is rarely observed in other congenital tubular disorders [14, 29–31]. However, some secondary forms of complex congenital tubular disorders present with a similar reduction of height SDS [32–34]. The *pathomechanism* of growth failure in FS is complex. In contrast to other tubular disorders [14, 29], prematurity was found in only one child. This corresponds to the literature, where prematurity was rarely reported in FS [22, 26]. In some of our patients *malnutrition* may have influenced growth, as indicated by a low SDS of weight. However, despite an increase in weight and BMI SDS with treatment, indicating an improved nutritional state height SDS rose only in four patients, which argues against malnutrition playing a decisive role in growth impairment. Similarly *glomerular insufficiency* does not seem to be a contributing factor, because C_{in} was clearly reduced in only one patient (no. 7). It is possible, however, that a transient compromise of glomerular function during infancy by fluid and electrolyte imbalances might have contributed to the rapid fall in height SDS in the 1st year of life. *Glucosuria* and *aminoaciduria* are unlikely to be responsible factors, because corresponding isolated congenital defects of tubular transport usually show normal growth [3].

Losses of electrolytes have repeatedly been proposed as causes of growth failure in congenital nephropathies [35]. Renal K loss as a growth-depressing factor is evident in the neonatal variant of Bartter syndrome [14]. In our study, no correlation was found between growth retardation and hypokalemia, but it is noteworthy that two patients who never required K supplements had the greatest height SDS at the last observation. Severe stunting may occur in the absence of hypokalemia, as demonstrated in patients 7 and 9 and in some FS patients reported in the literature [22, 27, 36].

The frequent occurrence of *hypophosphatemia* (in 7 of 9 patients) seems to be related to the severe bone changes observed in FS. Leg deformities were found mainly in patients with low serum P levels (Tables 2, 3), but no correlation between the degree of hypophosphatemia and growth retardation was found, and two of the three patients without leg deformities (nos. 7 and 8) attained the highest height SDS. Similar to children with hypophosphatemic vitamin D-resistant rickets [30], prolonged treatment with P supplements and vitamin D did not improve growth consistently in our patients.

Metabolic acidosis is known to impair growth in rats, and is probably related to a negative sodium balance [37]. In our study, a strong positive relationship was observed between blood HCO_3 levels during treatment and height SDS at the last observation, indicating a major role of metabolic acidosis in the development of growth failure in FS. Our finding is consistent with comparable observations in patients with primary distal tubular acidosis [38], but in contrast most of our acidotic patients failed to show a significant catch-up growth after the start of HCO_3 treatment. This is possibly due to a higher HCO_3 loss with proximal tubular dysfunction, which makes therapy less efficient in FS than in distal tubular acidosis. Our hypothesis is supported by persistently low blood HCO_3 levels despite high-dose supplementation in many patients.

In contrast to early reports on idiopathic hypercalciuria [31], but similar to patients with neonatal Bartter syndrome [14] we could not demonstrate a relationship between growth failure and Ca excretion. Likewise, the presence of nephrocalcinosis was not correlated with growth. Unexpectedly, the degree of polyuria was positively correlated with height SDS at the last observation, which contradicts findings in patients with nephrogenic diabetes insipidus [29].

In chronic renal failure a delay in the onset of pubertal development is usually related to depressed pubertal growth [39]. We feel that the delayed pubertal development in three of our patients might also have contributed to the depressed pubertal growth spurt and to a further loss of height SDS, resulting in reduced final height.

Six of our patients showed *extrarenal manifestations*, mainly of the gastrointestinal tract and of the central nervous system. It is possible that the dysfunction of these organs has indirectly contributed to growth failure, especially in patients 1 and 5. *Growth hormone* given to one of our patients (no. 3) led to an increased growth velocity, but the effect was only transient and less than in other tubular disorders [40, 41].

In conclusion, body growth is reduced in children with FS, as in some other complex congenital tubular disorders. Continuous electrolyte and HCO_3 supplementation is able to improve height SDS only in about half of the patients. Our analysis suggests that acidosis is the most important determinant of growth retardation in FS. We assume that earlier diagnosis and a more efficient correction of acidosis and electrolyte imbalances might contribute to improve growth and final height in this condition.

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