Pediatr Nephrol (1994) 8: 466–471

Pediatric Nephrology

Original article

Progression of chronic renal failure in a historical group of patients with nephropathic cystinosis

Friedrich Manz[1] and Norbert Gretz[2] for the European Collaborative Study on Cystinosis*

[1] Research Institute of Child Nutrition, Heinstück 11, D-44225 Dortmund, Germany
[2] Clinic of Nephrology, Klinikum Mannheim, University of Heidelberg, D-68167 Mannheim, Germany

Received April 15, 1993; received in revised form February 16, 1994; accepted February 17, 1994

Abstract. In a historical group of 205 patients with infantile or adolescent cystinosis treated without cysteamine, the rate of deterioration of renal function was analysed retrospectively. Patient survival curves and renal survival data are presented. Longitudinal data of serum creatinine values (n = 3280) in 157 patients were plotted for each patient, smoothed by the method of the running medians and grouped into 12 serum creatinine classes. In every patient the age at the last smoothed serum creatinine value observed in each serum creatinine class was determined. These virtual age values were then summarized per serum creatinine class, expressed as median and centiles and plotted, thus describing the "natural" course of the disease. In 9 pairs of affected siblings the rate of progression showed a median difference of about 12 months. Our data describe the "natural" course of nephropathic cystinosis and can be used as a prognostic aid for recently detected patients. The data can also be applied for the assessment of the influence of new therapeutic strategies on the rate of progression of renal failure in cystinotic patients.

Key words: Cystinosis – Chronic renal failure – Serum creatinine – Siblings

Introduction

Cystinosis is a rare autosomal recessive metabolic disease characterized by intralysosomal storage of cystine in the body tissues [1]. Patients with nephropathic cystinosis develop proximal tubular dysfunction and chronic renal failure. Before 1968, most patients died due to uncontrolled disturbances of water and electrolyte metabolism before reaching terminal renal failure [2]. Nowadays, other causes than uraemia are rare and most patients with terminal renal failure enter a renal replacement programme [2]. Today delaying progression of chronic renal failure is the major therapeutic challenge. In the 1970s several therapeutic trials to improve renal function, e. g. with a diet restricted in methionine and cystine or with supplements of vitamin C, showed no obvious clinical benefits [3, 4]. Recently, chronic cysteamine therapy has been claimed to preserve renal function in cystinosis [5–7]. The major problem, as with any such trials, is that adequate control data against which to assess the effect of an intervention on the progression of chronic renal failure are largely missing [8, 9].

We have, therefore, in this collaborative study collected longitudinal data of serum creatinine retrospectively in patients with nephropathic cystinosis to analyse the "historical" progression of chronic renal failure in the 1960s and 1970s. Theoretical models have been developed to evaluate the influence of new therapeutic strategies on the rate of progression of chronic renal failure.

Patients and methods

The clinical course of 205 patients with infantile or adolescent cystinosis from six European countries was analysed retrospectively. The data were collected before 1982. Most patients received a symptomatic replacement treatment based on supplements of water, electrolytes and vitamin D [10]. In several patients, tubular transport was improved by the use of hydrochlorothiazide or indomethacin [11, 12]. Only some patients received a "specific" therapy with vitamin C [4] or a diet low in cystine and methionine [3]. No data have been included from patients receiving cysteamine.

* European Collaborative Study with the participation of the following centres of six European countries: *France:* Paris (M. Broyer), Strasbourg (J. Geisert); *Germany:* Bocholt (K. Grote), Bonn (H. P. Weber), Coburg (H. Hennemann), Düsseldorf (H. J. Bremer), Erlangen (D. Michalk), Essen (C. Feldhoff, K. Pistor), Freiburg (B. Geschöll-Bauer, F. Schindera), Giessen (H. Wolf), Hamburg (C. Bender-Götze, R. Grüttner), Hannover (J. Brodehl, J. H. H. Ehrich), Heidelberg (E. Harms, F. Manz, K. Schärer, H. Schmidt), Köln (M. Bulla), Mainz (H. Schulte-Wissermann), Marburg (M. Brandis, U. Willenbockel), München (W. Endres, B. Klare), Münster (L. Diekmann), Reutlingen (J. Rau), Stuttgart (R. Augustin, W. Hagge), Ulm (D. Leupold), Wolfsburg (H. Löhr), Würzburg (D. Gekle, F. Ott); *Great Britain:* Cardiff (K. Verrier-Jones), London (T. M. Barratt, C. Chantler, M. J. Dillon, G. B. Haycock); *Portugal:* Porto (A. Oliveira); *Spain:* Barcelona (L. Callis); *Switzerland:* Basel (F. Egli), Winterthur (A. Fanconi)

Correspondence to: F. Manz

Table 1. Example for smoothing of longitudinal data of serum creatinine using the method of the running medians with triplets of serum creatinine values [15] in a patient with chronic renal failure born on 11 July 1976

Date of investigation	13.05.80	16.06.80	10.07.80	09.08.80	19.09.80	25.10.80	20.11.80	09.12.80	20.12.80	13.01.81
Age (years)[a]	3.839	3.932	3.998	4.080	4.192	4.291	4.362	4.414	4.444	4.510
Original serum creatinine values (mg/dl)	1.1	0.8	2.2	0.9	1.4	2.3	1.7	2.0	1.6	2.4
Triplets of original serum creatinine values (mg/dl) with their respective *medians* and each medians final position in the triplet[b]	*1.1*	0.8[b]	2.2							
		0.8	2.2[b]	*0.9*						
			2.2	0.9[b]	*1.4*					
				0.9	*1.4*[b]	2.3				
					1.4	2.3[b]	*1.7*			
						2.3	1.7[b]	*2.0*		
							1.7	2.0[b]	1.6	
								2.0	1.6[b]	2.4
Smoothed serum creatinine values (mg/dl)										
after the first run	1.1[c]	1.1	0.9	1.4	1.4	1.7	2.0	1.7	2.0	2.4[c]
after the second run	1.1	1.1	1.1	1.4	1.4	1.7	1.7	2.0	2.0	2.4
after the third run	1.1	1.1	1.1	1.4	1.4	1.7	1.7	2.0	2.0	2.4

[a] In decimals of year according to Tanner et al. [16]
[b] Final position of the median in the triplet and the smoothed longitudinal data file of serum creatinine values
[c] The first and the last value remain outside the smoothing procedure

Survival curves. Patient survival curves and renal survival data – first presented in 1982 [13] – were re-evaluated in order to provide survival curves additionally depicting the respective 5% and 95% confidence intervals. Calculation of the survival curves was performed using the SAS procedure PROC LIFE TEST [14].

Evaluation of longitudinal serum creatinine values. In 157 patients, 3280 longitudinal data of serum creatinine were obtained. The processing of the data was divided into three parts: smoothing of each longitudinal data set of original serum creatinine values, identification of the precise age at which a given serum creatinine level was passed in each patient and descriptive statistics of these virtual age values in our group of cystinotic patients.

The time course of serum creatinine in the individual patient exhibited a considerable scattering. Therefore, longitudinal data of serum creatinine values were plotted for each patient and smoothed by the method of the running medians using triplets of serum creatinine values [15] (Table 1). In a first step the median of the first triplet (1st, 2nd, 3rd) of the longitudinal data of serum creatinine values was calculated. This value replaced the original second creatinine value while the first was unchanged. In a second step the median of the next triplet of original serum creatinine values (2nd, 3rd, 4th value) was calculated and the result placed at the position of the 3rd creatinine value. In further steps the same procedure always using triplets of data was repeated to the last three data. The last serum creatinine value remained unaltered. Now the file of data of the first run was smoothed once more by the method of the running medians using triplets of serum creatinine values (2nd run), by a 3rd run or even a 4th run, always using the same procedure until there was no further change within the data file.

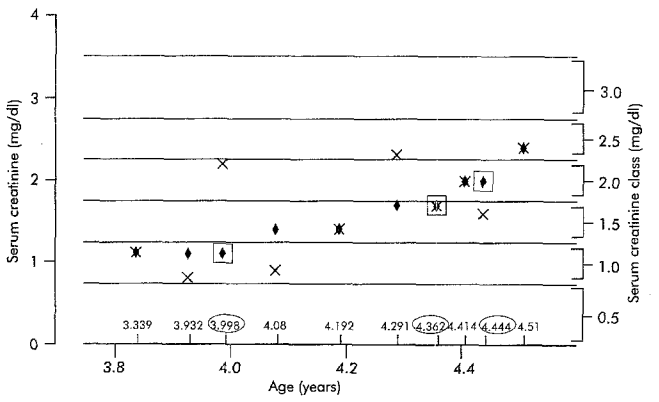

Fig. 1. Original serum creatinine values [×], smoothed serum creatinine values [◆], last smoothed serum creatinine values in defined serum creatinine classes [◈], designated values of serum creatinine by class (called creatinine class value) and identification of virtual age values (○, age at the last smoothed serum creatinine value observed in a defined serum creatinine class) within an uninterrupted chronological file of longitudinal smoothed serum creatinine values

Twelve classes of serum creatinine values (<0.75 mg/dl, 0.75–1.24 mg/dl, 1.25–1.74 mg/dl, 1.75–2.24 mg/dl, 2.25–2.74 mg/dl, 2.75–3.4 mg/dl, 3.5–4.4 mg/dl, 4.5–5.4 mg/dl, 5.5–6.4 mg/dl, 6.5–7.4 mg/dl, 7.5–8.4 mg/dl, 8.5–9.4 mg/dl) were defined and each class designated by a so-called serum creatinine class value which in most classes corresponds to the mean value of the range of serum creatinine of this class (e. g. <0.75 mg/dl = 0.5 mg/dl, 0.75–1.24 mg/dl = 1 mg/dl, 2.75–3.4 mg/dl = 3 mg/dl, 8.5–9.4 mg/dl = 9 mg/dl) (Fig. 1). The linear scale of original serum creatinine values on the *y* axis was replaced by ordered categories of serum creatinine class (henceforth denoted "creatinine class") values. In every patient the age at the last smoothed serum creatinine value observed in one defined creatinine class within an uninterrupted chronological file of longitudinal smoothed serum creatinine values was identified (henceforth denoted "virtual age"). A virtual age at a creatinine class value of ≤4 mg/dl was rejected if the corresponding smoothed serum creatinine value was the last value of the longitudinal data file or if the time from the corresponding smoothed serum creatinine value to the next one was 6 months or more. If the last value of a file of smoothed serum creatinine data was 4.5 mg/dl or more, the corresponding virtual age value at a creatinine class value of ≥5 mg/dl was also accepted (e. g. if the last serum creatinine value is 4.5 mg/dl determined at 3 February 1978, then the serum creatinine class value is 5 mg/dl and the virtual age is 3 February 1978).

Analysing the scattering of the time of the individual periods between the age at a creatinine class value of 2 mg/dl and the age at a creatinine class value of 4 mg/dl, we observed that the median length of 12 periods in 12 patients calculated on the basis of original serum creatinine values of about 2 mg/dl determined before 1974 was much longer (2.3 years) than the median length of 29 periods in 29 patients using more recent original serum creatinine values (0.8 years). There-

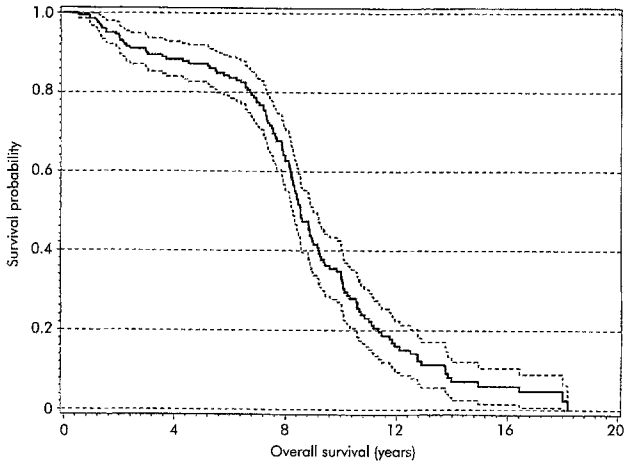

Fig. 2. Overall survival time (patient's death or age at starting renal replacement therapy) and the respective 5%–95% confidence interval in 205 cystinotic patients

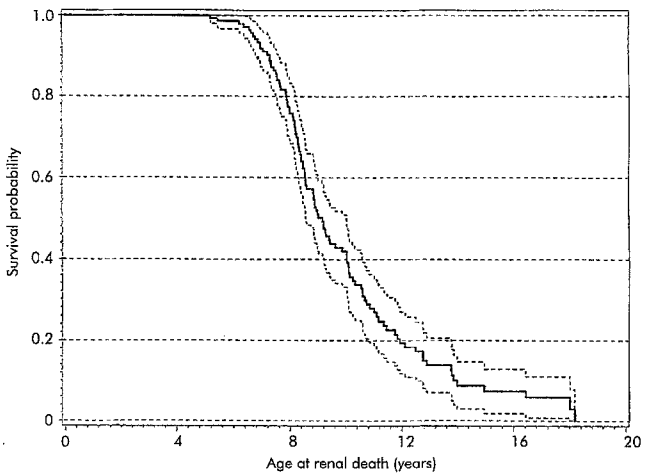

Fig. 3. Survival time and the respective 5%–95% confidence interval of 106 cystinotic patients suffering from renal death (age at death due to uraemia or age at starting renal replacement therapy)

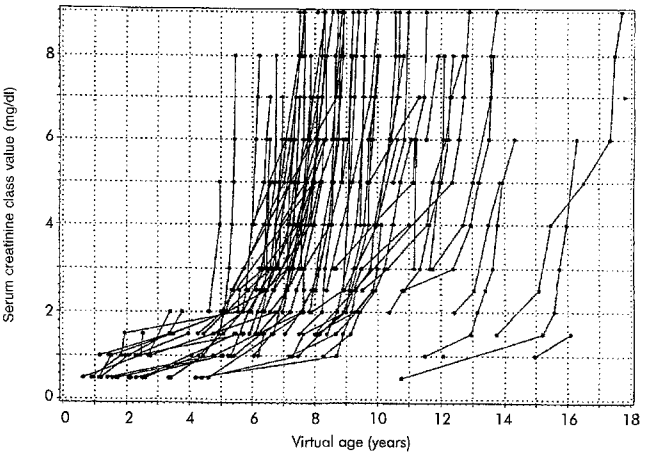

Fig. 4. Individual courses of serum creatinine class values ($n = 453$) at each virtual age in 117 patients with nephropathic cystinosis

fore all virtual age values at creatinine class values of 2 mg/dl or below measured before 1974 were excluded from the study, with the exception of the data from Heidelberg, the centre in which the author (F. M.) was working. There were indications that methodological problems in creatinine determination at serum creatinine values of ≤2 mg/dl existed in several centres before 1974, but not in Heidelberg.

For any one patient there was only one virtual age value at a defined serum creatinine class. In order to describe the rate of progression of renal failure in our group of cystinotic patients, the data of all patients had to be treated as a whole. Therefore all virtual age values were summarized and expressed as median and centiles [17]. Finally the 12 results of one centile, each corresponding to the scattering of virtual age values of 1 of the 12 serum creatinine classes, were smoothed using the spline function SMxx (xx = 80) of SAS/GRAH [18].

Results

Patient survival curves to calculate cystinotic patient death or end-stage renal failure are shown in Fig. 2, renal survival data are shown in Fig. 3. Longitudinal data of serum creatinine values of 157 patients with infantile and adolescent cystinosis were plotted for each patient, smoothed by the method of the running medians and grouped in 12

Table 2. Centiles of virtual age values at 12 defined serum creatinine classes in 117 patients with cystinosis

Serum creatinine class (mg/dl)	Number of time points	Virtual age (years) at defined serum creatinine class values (median, centiles)						
		5%	10%	25%	50%	75%	90%	95%
0.5	25	0.9	1.0	1.4	2.1	3.4	4.4	4.6
1.0	33	1.4	1.5	2.4	4.8	6.2	8.7	12.1
1.5	38	2.5	3.4	4.8	6.2	8.2	12.9	15.2
2.0	40	4.2	5.0	5.6	6.9	9.0	9.9	12.8
2.5	35	5.4	5.8	6.5	7.6	9.5	10.8	13.4
3.0	41	6.2	6.4	6.7	7.5	9.8	11.7	12.4
4.0	51	6.0	6.4	7.2	8.0	10.0	12.7	13.8
5.0	46	6.4	6.6	7.7	8.4	10.5	13.0	13.9
6.0	52	6.5	7.1	7.3	8.6	10.8	12.3	14.3
7.0	34	6.6	7.4	7.9	8.7	10.0	12.3	13.6
8.0	33	6.2	7.5	8.3	9.2	10.8	12.8	13.7
9.0	25	7.6	7.7	8.3	8.9	10.6	12.9	13.8

Table 3. Median time (years) for any patient's serum creatinine class value to rise to a higher class value[a]

	Serum creatinine class value (mg/dl)										
	0.5	1.0	1.5	2.0	2.5	3.0	4.0	5.0	6.0	7.0	8.0
0.5											
1.0	1.8 (11)										
1.5	2.3 (10)	0.9 (20)									
2.0	4.6 (8)	1.6 (18)	0.7 (27)								
2.5	4.7 (4)	1.6 (12)	1.0 (18)	0.3 (24)							
3.0	5.0 (5)	2.0 (13)	1.1 (19)	0.6 (24)	0.3 (23)						
4.0	5.2 (5)	2.2 (13)	1.4 (22)	0.8 (29)	0.6 (28)	0.3 (32)					
5.0	3.7 (4)	2.4 (9)	1.6 (18)	1.2 (24)	0.8 (24)	0.6 (25)	0.3 (35)				
6.0	5.4 (6)	2.8 (10)	1.7 (19)	1.2 (19)	1.2 (22)	0.6 (29)	0.4 (32)	0.2 (31)			
7.0	5.5 (3)	2.5 (5)	1.8 (13)	1.4 (15)	1.4 (17)	0.8 (17)	0.5 (24)	0.3 (24)	0.1 (22)		
8.0	5.7 (3)	2.3 (4)	1.9 (12)	1.5 (13)	1.6 (15)	0.9 (15)	0.5 (23)	0.4 (22)	0.2 (23)	0.1 (20)	
9.0	6.5 (1)	4.6 (2)	3.1 (8)	1.5 (9)	1.8 (11)	1.3 (10)	1.0 (15)	0.6 (18)	0.3 (16)	0.2 (15)	0.1 (15)

[a] Number of periods in parentheses

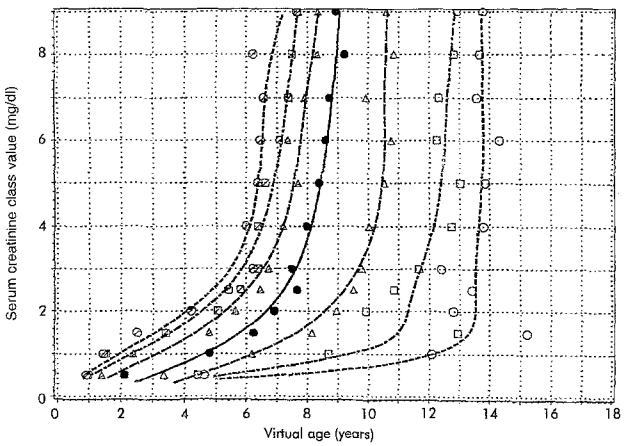

Fig. 5. Standards for serum creatinine class values at each virtual age in patients with nephropathic cystinosis. ⊘, 5%; ⊠, 10%; ⧋, 25%; ●, 50%; △, 75%; □, 90%; ○, 95%

serum creatinine classes to identify virtual age values. A total of 453 virtual age values at 12 creatinine classes in 117 patients was observed (Table 2, Fig. 4). In 40 patients we found no such time points. In 29 patients there was one time point, in 35 patients there were 2 or 3, in 31 patients 4–6, in 18 patients 7–9 and in 4 patients 10 or 11 time points. Medians and centiles of all time points at each of the 12 creatinine classes are presented in Table 2. In Fig. 5 the splined course for the different centiles is superimposed on the calculated data of Table 2. It is of note that the rise in creatinine class values in an individual patient usually occurred once the centile with a first creatinine class value of 2 mg/dl or above was reached. The median time for any patient's creatinine class to rise to another class is presented in Table 3.

There was a correlation between the virtual age values at a creatinine class value of 1 mg/dl (x, range 1.2–8.7 years) and the time (y, range 0.2–3.3 years) for the creatinine class value of 1 mg/dl to rise to the class value of 1.5 mg/dl ($y = 1.85 - 0.17\,x$, $r = -0.49$, $P < 0.05$, $n = 18$), if the data of 2 patients with adolescent cystinosis were excluded (virtual age at creatinine class value of 1 mg/dl: 11.5, 15.0 years; length of the period: 1.5, 1.1 years). A similar correlation was observed between the virtual age values at creatinine class value of 1.5 mg/dl (x, range 1.9–9.1 years) and the time for the creatinine class value of 1.5 mg/dl to rise to the class value of 2 mg/dl (y, range 0.2–3.6 years) ($y = 2.09 - 0.19\,x$, $r = -0.51$, $P < 0.01$, $n = 25$).

In 9 pairs of siblings the median time difference between virtual age values at the same creatinine class value was 0.8 years (range 0.1–2.6 years). The median time difference between age at renal death in 8 pairs of siblings was 0.9 years (range 0.0–2.7 years).

Discussion

In this co-operative study the "natural" course of the progression of chronic renal failure in a large historical group of patients with nephropathic cystinosis in a defined therapeutic situation is characterized. Our data show that in patients with nephropathic cystinosis the rate of deterioration of glomerular function is quite uniform if the serum level of creatinine is above the class value of 2 mg/dl. Deterioration of glomerular function, morphologically characterized by focal and segmental glomerulosclerosis [19], seems to be strongly determined by genetic factors. Siblings with nephropathic cystinosis show a surprisingly low time difference between virtual age at the same creatinine class value or the age at renal death [20]. The rate of deterioration of glomerular function above the creatinine class value of 2 mg/dl is very similar in patients with the infantile type of cystinosis and in patients with the adolescent type of cystinosis. This is a further argument [13] for the use of the expression nephropathic cystinosis instead of infantile or adolescent type of cystinosis.

The critical period for the age at renal death is the period with serum creatinine values below 2 mg/dl. In patients with the adolescent type of cystinosis the late onset of the decrease of glomerular function is well documented [21]. In three patients with infantile cystinosis, glomerular filtration rate measured longitudinally by inulin clearance showed a steep initial decline followed by a constant level of glomerular function for several years [22]. In one pa-

tient, nine determinations of inulin clearance every 6 months showed a constant level of glomerular filtration rate of 22.5 ± 4.6 ml/min per 1.73 m^2 (range 16.3–28.8 ml/min per 1.73 m^2) (B. Geschöll-Bauer, personal communication). Our finding of a significant correlation between the virtual age at creatinine class values of 1 mg/dl or 1.5 mg/dl and the time for these class values to rise to the subsequent class values support the concept of a constant level of glomerular function for years in some patients with infantile type of cystinosis. The question is whether focal and glomerular sclerosis is the only factor responsible for the steep decline and the following plateau of glomerular function in patients with infantile cystinosis. Cystinosis is the only complex tubular disorder with general impairment of proximal tubular function and dysfunction of water transport of the distal tubule. Theoretically it is possible that proximal tubular dysfunction and impaired water reabsorption of the ascending part of distal tubule result in a high luminal sodium and chloride concentration at the macula densa, activating the glomerular tubular feedback mechanism and thus decreasing glomerular filtration rate [23], as has been demonstrated in a patient with idiopathic Fanconi syndrome due to the absence of proximal tubular brush border [24].

The detailed results from this study can be used as a prognostic aid for recently detected patients. In several studies the progression of chronic renal failure of a patient has been claimed to be predictable by means of mathematical models [5, 7]. Longitudinal serum creatinine data of 1 patient were linearized by reciprocal or logarithmic transformation. From the transformed data, regression equations were calculated and used for the prediction of the course of an individual patient. Retrospective analysis of longitudinal data of serum creatinine in adults [8] or rats [9] with chronic renal failure show, however, that the prediction error has a wide range. Therefore these models should be used with caution for prediction purposes in individual patients.

There are three objections to these models. Firstly, about 50% of all patients show no linear relationship between transformed serum creatinine values and time. Systemic deviations may be caused by hypertension, urinary tract infection, diet and drugs and reduced creatinine production by muscle wasting. Secondly, clusters of serum creatinine values may give undue weight to repeated similar values. Thirdly, there is usually a high scattering of low serum creatinine values which, after being reciprocally transformed, cause a wide scattering of the prediction error [9].

In contrast to these mathematical models with a fixed notion of the mode of progression of chronic renal failure, we propose evaluating the further individual rate of deterioration of glomerular function by a comparison of the existing data of serum creatinine of a patient with the course of serum creatinine of a defined group of patients with the same disease. This purely descriptive approach takes account of the interaction of all really effective factors influencing the progression of chronic renal failure. Thus, our chart of standards for virtual age at defined serum creatinine class values may be used like a growth chart.

In the scientific literature, only semi-quantitative serum creatinine class values should be used. In clinical practice it may be helpful to use original data of serum creatinine or median values of original data in the case of clustered data to gain a rough impression of the course of the progression of chronic renal failure. However, as virtual age corresponds to the age at the last smoothed serum creatinine value observed in a creatinine class, the increase of the serum creatinine level using original data is earlier and steeper at low levels of serum creatinine.

The data may enable a theoretical model to be developed to evaluate the influence of new therapies on the progression of chronic renal failure. Four different approaches seem possible to isolate factors that influence the rate of deterioration of glomerular function in defined groups of patiens with nephropathic cystinosis. Firstly, the effect of a factor in one of two groups of patients may result in differences in survival time. Using this approach, no differences in survival time in male and female patients with cystinosis, as well as in cystinotic patients of four countries, could be demonstrated [13]. Furthermore, in the combined report on regular dialysis and transplantation of children in Europe in 1989, the age at the start of treatment in patients with cystinosis who commenced renal replacement treatment between 1977 and 1982 was not different from that of patients who started renal replacement treatment between 1983 and 1988 [25]. Secondly, our chart of standards for virtual age at defined serum creatinine classes of a historical group of cystinotic patients may be used as reference for comparison with data of other groups of cystinotic patients with a different therapeutic regimen [26]. Thirdly, comparison of standardized progression rates of chronic renal failure of different groups of patients using the median time for any patient's creatinine class value to rise to a higher class value may be a useful approach [9, 27]. Fourthly, the small difference between virtual age at the same creatinine class value or age at renal death in siblings with cystinosis may be used to quantitate the effect of different therapeutic regimens in siblings [20, 28, 29].

Acknowledgement. Dedicated to Karl Schärer on the occasion of his 65th birthday.

References

1. Schulman JD (1989) Cystinosis. Prog Clin Biol Res 305: 137–144
2. Manz F, Gretz N (1985) Cystinosis in the Federal Republic of Germany: coordination and analysis of the data. J Inherited Metab Dis 8: 2–4
3. Schmidt H, Lutz P, Bickel H (1973) Wertbeurteilung der diätetischen Behandlung der Cystinose. Monatsschr Kinderheilkd 121: 171–173
4. Schneider JA, Schlesselman JJ, Mendoza SA, Orloff S, Thoene JG, Kroll WA, Godfrey AD, Schulman JD (1979) Ineffectiveness of ascorbic acid therapy in nephropathic cystinosis. N Engl J Med 300: 756–759
5. Yudkoff M, Foreman JW, Segal S (1981) Effects of cysteamine therapy in nephropathic cystinosis. N Engl J Med 304: 141–145
6. Gahl WA, Reed GF, Thoene JG, Schulman JD, Rizzo WB, Jonas AJ, Denman DW, Schlesselman JJ, Corden BJ, Schneider JA (1987) Cysteamine therapy for children with nephropathic cystinosis. N Engl J Med 316: 971–977
7. Gahl WA, Schneider JA, Schulman JD, Thoene JG, Reed GF (1990) Predicted reciprocal serum creatinine at age 10 years as a

measure of renal function in children with nephropathic cystinosis treated with oral cysteamine. Pediatr Nephrol 4: 129–135
8. Gretz N, Manz F, Strauch M (1983) Predictability of the progression of chronic renal failure. Kidney Int 24 [Suppl 15]: S2–S5
9. Gretz N, Meisinger E, Strauch M (1986) Experimental models to assess the influence of low protein diets on the progression of chronic renal failure. Contrib Nephrol 53: 7–20
10. Manz F, Schärer K (1982) Long-term management of inherited renal tubular disorders. Klin Wochenschr 60: 1115–1125
11. Callis L, Castello F, Fortuny G, Vallo A, Ballabriga A (1970) Effect of hydrochlorothiazide on rickets and on renal tubular acidosis in two patients with cystinosis. Helv Paediatr Acta 6: 602–619
12. Parchoux B, Guibaud P, Louis J-J, Benzoni D, Larbre F (1982) Etude des prostaglandines urinaires et effets d'un traitement par l'indometacine dans la cystinose. Pédiatrie 37: 19–30
13. Gretz N, Manz F, Augustin R, Barrat TM, Bender-Götze C, Brandis M, Bremer HJ, Brodehl J, Broyer M, Bulla M, Callis L, Chantler C, Diekmann L, Dillon MJ, Egli F, Ehrich JHH, Endres W, Fanconi A, Feldhoff C, Geisert J, Gekle D, Geschöll-Bauer B, Grote K, Grüttner R, Hagge W, Haycock CB, Hennemann H, Klare B, Leupold D, Löhr H, Michalk D, Oliveira A, Ott F, Pistor K, Rau J, Schärer K, Schindera F, Schmidt H, Schulte-Wissermann H, Verrier-Jones K, Weber HP, Willenbockel U, Wolf H (1982) Survival time in cystinosis: a collaborative study. Proc Eur Dial Transplant Assoc 19: 582–589
14. SAS Institute (1985) SAS user's guide, statistics, version 5. SAS Institute, Cary, North Carolina, pp 529–558
15. Mosteller F, Tukey JW (1977) Data analysis and regression. Addison-Wesley, Reading
16. Tanner JM, Whitehouse RH, Takaishi M (1966) Standards from birth to maturity for height, weight, height velocity, and weight velocity: British children, 1965. II. Arch Dis Child 41: 613–635
17. SAS Institute (1985) SAS procedures guide for personal computers, version 6. SAS Institute, Cary, North Carolina
18. SAS Institute (1988) SAS/Graph user's guide, release 6.03. SAS Institute, Cary, North Carolina
19. Waldherr R, Manz F, Hagge H (1982) Nierenveränderungen bei infantiler und adoleszenter (nephropathischer) Cystinose. Verh Dtsch Ges Pathol 66: 297–303
20. Oberfield SE, Levine LS, Wellner D, Novogroder M, Laino P, New MI (1981) Ascorbic acid treatment in nephropathic cystinosis in identical twins. Dev Pharmacol Ther 2: 80–90
21. Manz F, Harms E, Lutz P, Waldherr R, Schärer K (1982) Adolescent cystinosis: renal function and morphology. Eur J Pediatr 138: 354–357
22. Manz F, Gretz N, Ehrich JHH, Weber HP, Pistor K, Fanconi A (1981) Cystinosis. Int J Pediatr Nephrol 2: 122
23. Blantz RC, Thomson SC, Peterson OW, Gabbai FB (1990) Physiologic adaptations of the tubuloglomerular feedback system. Kidney Int 38: 577–583
24. Manz F, Waldherr R, Fritz HP, Lutz P, Nützenadel W, Reitter B, Schärer K, Schmidt H, Trefz F (1984) Idiopathic de Toni-Debré-Fanconi syndrome with absence of proximal tubular brush border. Clin Nephrol 22: 149–157
25. Ehrich JHH, Rizzoni G, Brunner FP, Brynger H, Geerlings W, Fassbinder W, Raine AEG, Selwood NH, Tufveson G (1991) Combined report on regular dialysis and transplantation of children in Europe 1989. Nephrol Dial Transplant 6 [Suppl 1]: 42–44
26. Gretz N (1994) How to assess the rate of progression of chronic renal failure in children? Pediatr Nephrol 8: 506–511
27. Gretz N, Schärer K, Waldherr R, Strauch M (1989) Rate of deterioration of renal function in juvenile nephronophthisis. Pediatr Nephrol 3: 56–60
28. Da Silva VA, Zurbrügg RP, Lavanchy P, Blumberg A, Suter H, Wyss SR, Lüthy CM, Oetliker OH (1985) Long-term treatment of infantile nephropathic cystinosis with cysteamine. N Engl J Med 313: 1460–1463
29. Proesmans W, Baten E, Hoogmartens J, Bruyneel P (1987) Nephropathic cystinosis: effect of long-term cysteamine therapy. Clin Nephrol 27: 309–312

Literature abstract

Clin Nephrol (1993) 40: 299–307

Glomerular permselectivity to macromolecules in reflux nephropathy: microalbuminuria during acute hyperfiltration due to aminoacid infusion

R. Coppo, M. G. Porcellini, B. Gianoglio, D. Alessi, L. Peruzzi, A. Amore, M. Bianchi, R. Lace, G. Cavalli, and M. C. Amprimo

Reflux nephropathy is an important cause of chronic renal failure in children. After the parenchymal scar, the progression is thought to be mediated by glomerular hypertension in remnant nephrons resulting in modifications in permselectivity to macromolecules. Proteinuria correlates with a progressive course. The glomerular permselectivity to macromolecules in basal conditions and after acute hemodynamic stress was investigated in 28 children whose bilateral vesico-ureteric reflux (VUR) had been previously surgically corrected (meanly 5.6 years before) and with normal creatinine clearance (CrCl). Bilateral renal scarring (0 to 8 scale for both kidneys) was 4.3 ± 1.6. Albuminuria (UAE) was evaluated in basal conditions and under acute hyperfiltration induced by amino acid (Aa) infusion. After isotonic saline at 310 ml/hour/1.73 m^2, 6 mg/kg/min of Aa were infused for 2 hrs. UAE was significantly higher than controls in basal conditions ($p < 0.01$), and further increased after Aa infusion ($p < 0.02$). Microalbuminuria was detectable in 53.5% of the children in basal conditions and in 64.3% after Aa. Also urinary β_2 microglobulin significantly increased at the end of the test ($p < 0.001$). CrCl significantly increased at the first hour ($p < 0.05$). Children with severe renal parenchymal scarring had greater UAE ($p < 0.01$) and β_2M ($p < 0.02$) values after provocative test than those with mild renal damage. In 8 children GFR and ERPF were measured by means of inulin and p-hippurate clearance respectively. The variations in UAE during Aa infusion were significantly correlated with GFR dynamics ($p < 0.05$) while they were not influenced by ERPF modifications. In children with initial RN and still normal CrCl a provocative test of hyperfiltration with Aa infusion induces a significant modifications in permselectivity to macromolecules evidenced by microalbuminuria.