Pediatr Nephrol (1995) 9: 549–552

Pediatric Nephrology

Original article

Etiology of chronic renal failure in Turkish children

Aydan Şirin, Sevinç Emre, Harika Alpay, Ahmet Nayır, Ilmay Bilge, and Faik Tanman

Department of Pediatric Nephrology, Medical Faculty of Istanbul, TR-34390 Çapa, Istanbul, Turkey

Received November 2, 1994; received in revised form and accepted April 13, 1995

Abstract. The etiology of chronic renal failure (CRF) was studied in 459 Turkish children (205 girls, 254 boys) for the period January 1979–December 1993. Their mean age at onset of CRF was 9.5±4.2 years (range 1–16 years); CRF was defined as a glomerular filtration rate (GFR) below 50 ml/min per 1.73 m^2 for at least 6 months. When a GFR determination was not available, the serum creatinine concentration was used: greater than 1 mg/dl for children aged 1–3 years, greater than 1.5 mg/dl for those 3–10 years and greater than 2 mg/dl for those 10–16 years. Primary renal disorders were as follows: reflux nephropathy 32.4% glomerular diseases 22.2%, hereditary renal disorders 11.4%, amyloidosis 10.6%, urinary stones 8% and other renal disorders 15.4%. Twenty-three cases of reflux nephropathy (15.4%) were associated with neural tube defects (NTD) and 20 (13.4%) were caused by infravesical obstruction. CRF caused vesicoureteral reflux associated with NTD and amyloidosis are more frequent in our series compared with west European and Nordic countries.

Key words: Chronic renal failure – Primary renal disorders

Introduction

Primary renal diseases that lead to chronic renal failure (CRF) are quite different in children compared with adults because of the higher proportion of congenital and hereditary nephropathies [1–6]. Geographical location may also influence the distribution of the diseases which lead to CRF [4, 7–21]. In this study we retrospectively investigated the primary renal diseases in Turkish children with CRF.

Patients and methods

We reviewed the records of 459 children (205 girls, 254 boys) with CRF admitted to our hospital between January 1979 and December 1993. Their mean age was 9.5±4.2 years (range 1–16 years). Most patients had been treated by other physicians and then referred to our hospital (which is one of the major reference hospitals in Turkey).

We defined CRF as glomerular filtration rate below 50 ml/min per 1.73 m^2 for at least 6 months or a serum creatinine level above 1 mg/dl for children aged 1–3 years, 1.5 mg/dl for those 3–10 years and 2 mg/dl for those 10–16 years. The history, standard laboratory investigations, radiological and radionucleide tests and renal biopsy findings were re-evaluated for the classification of primary renal disorders.

Correspondence to: A. Şirin

Results

Primary renal disorders in the study group are presented in Table 1.

Reflux nephropathy

One hundred and forty-nine children (32.4%) (65 girls, 84 boys, aged 14 months to 12 years) with CRF had vesicoureteral reflux (VUR). A total of 114 patients had bilateral VUR (76.5%) and 16 (13.4%) had associated infravesical obstruction (all male). Twelve patients (8%, 2 girls, 10 boys) had a solitary kidney and VUR and 23 children (15.4%) with bilateral VUR had neural tube defects (NTD) and neurogenic bladder. The age range was 1–12.5 years in the patients with CRF associated with NTD and bilateral VUR and the female/male ratio was 17/6 in this group. Non-neurogenic neurogenic bladder was diagnosed in 14 of 18 patients with bilateral VUR who had signs and symptoms related to bladder dysfunction after 1990.

Glomerular diseases

There were 102 children (48 girls, 54 boys, aged 2–16 years) with CRF caused by various glomerular disorders; 85% had presented with nephrotic syndrome. Percutaneus renal biopsies were performed in all 102 children and the results of histopathological evaluation are presented in Table 1. Chronic glomerulonephritis was the predomi-

Table 1. Primary renal diseases in 459 children with chronic renal failure

	n	%
Vesicoureteral reflux (VUR)	149	32.4
Bilateral VUR	137	
with infravesical obstruction	20	
without infravesical obstruction	94	
NTD and VUR	23	
Solitary kidney and VUR	12	
Glomerular diseases	102	22.2
Mesangioproliferative glomerulonephritis	16	
Membranoproliferative glomerulonephritis	12	
Focal glomerulosclerosis	7	
Rapidly progressive glomerulonephritis	4	
Renal involvement with collagen disease	11	
Hereditary renal disorders	52	11.4
Alport's diseases	13	
Juvenile nephronophthisis	11	
Polycystic disease	13	
Congenital nephrotic syndrome	3	
Renal tubular acidosis	4	
Oxalosis	1	
Laurence-Moon-Biedl syndrome	1	
Unclassified hereditary disorders	6	
Renal amyloidosis	48	10.6
Urinary stones	37	8.0
Other renal disorders	71	15.4
Associated with pyelonephritis		
Bilateral ureterovesical junction stenosis	8	
Bilateral hypo-/dysplasia	14	
Bilateral ureteropelvic stenosis	1	
Bilateral small kidney	31	
Solitary kidney	4	
Solitary kidney and ureteral stenosis	1	
Horseshoe kidney	4	
Without pyelonephritis		
Interstitial nephritis	3	
Vascular nephropathies		
HUS	3	
Circulation disturbance due to sepsis	1	
Cornelia de Lange syndrome	1	
Total	459	100

NTD, Neural tube defects; HUS, hemolytic uremic syndrome

nant pathological finding with mesangioproliferative glomerulonephritis the second most common renal lesion, occurring in 16 patients. There were 7 patients with Henoch-Schönlein nephropathy, 3 with systemic lupus erythematosus and 1 with scleroderma in the group of patients with renal involvement with collagen disease.

Hereditary renal disorders

Fifty-two (22 female, 30 male) patients (12%) with CRF had hereditary renal disorders. This group consists of 13 patients with Alport's disease, 11 with nephronophthisis, 13 with polycystic disease, 3 with distal renal tubular acidosis, 3 with congenital nephrotic syndrome, 6 with unclassified hereditary renal disorders, 1 with oxalosis and 1 each with cystinosis and Laurence-Moon-Biedl syndrome.

Table 2. Amyloidosis in children with chronic renal failure

n	Age (years)	Sex		FMF *n*	TBC *n*	JRA *n*	UD *n*
		boys	girls				
48	7–16	27	21	38	2	1	7

FMF, Familial Mediterranean fever; TBC, tuberculosis; JRA, juvenile rheumatoid arthritis; UD, undetermined

Renal amyloidosis

There were 48 patients (aged 1–16 years, 21 females, 27 males) with biopsy-proven renal amyloidosis in our series. All had amyloidosis of the AA type. The underlying diseases that led to amyloidosis in these patients are shown in Table 2. The vast majority of the cases had familial Mediterranean fever (FMF) and there were 6 patients with amyloidosis of undetermined origin.

Urinary stones

Urinary stone formation associated with pyelonephritis led to CRF in 37 patients (10 girls, 27 boys) aged 4–12 years. Thirty-six patients had bilateral pelvic and ureteral stones and only 1 of them had a solitary kidney and pelvic stone. The stones were composed of calcium oxalate in most patients.

Other renal disorders

Seventy-one patients (28 female, 43 male) with CRF had various renal disorders with or without pyelonephritis (Table 1). Bilateral small kidney associated with pyelonephritis was the commonest disorder in this group.

Discussion

The most common cause of CRF in our study group is VUR (32.4%). If VUR and other renal abnormalities associated with pyelonephritis are considered as one group, this covers approximately 46% of the patients. This result is similar to that of Esbjörner et al. [22]. The striking feature is the high percentage of NTD associated with VUR (15.4%) in our series. The urinary tract has long been recognized as one of the major sites of organ failure in patients with NTD, and VUR is a common finding in children with NTD and may be present at birth or develop in infancy or childhood secondary to high intravesical pressure and inadequate emptying of the bladder [23, 24].

The incidence of NTD is only 1 in every 1,000 live births in the United States, in 1.5–1.8 in 1,000 in Europe and 1.8–8.1 per 1,000 in Turkey [25–32]. Poor nutritional status of the mother (energy, multivitamin, folic acid and zinc deficiency) during the pre- and post-conceptional period is strongly related to the malformation of the neural tube of the fetus [33–36]. Most children with NTD in our

series were from low socioeconomic classes. Pre-natal diagnosis is now performed in pregnant women with a high risk of NTD. the incidence of NTD is expected to be reduced in the near future. The patients in this study date back to the time when pre-natal diagnosis was not possible.

Renal hypoplasia or dysplasia may also be associated with VUR, but these malformations were not evaluated radiologically in our patients. Glomerulopathies are the most common cause of CRF in some series [11–14]. Reports from developing countries have shown that glomerulonephritis is nearly twice as common as pyelonephritis as a cause of CRF in children [12, 13]. Focal glomerulosclerosis, chronic glomerulonephritis and nephrotic syndrome with minimal glomerular changes were reported as primary renal pathologies in the patients with end-stage renal disease [4, 37]. In our study, glomerular diseases were the second most common cause of CRF and the majority of the cases had chronic glomerulonephritis. Mesangioproliferative glomerulonephritis and membranoproliferative glomerulonephritis are also common in our patients compared with other series [2, 22]. No patient in our study developed CRF as a result of minimal change nephrotic syndrome or acute post-streptococcal glomerulonephritis.

We found amyloidosis to be quite a common cause of CRF in Turkish children. FMF was the predominant underlying disease. All patients had amyloidosis of the AA type. Six patients with amyloidosis of undetermined origin may also have FMF phenotype II in which the first manifestation is the accumulation of amyloid material in the organs. These findings correlate with the geographical location of Turkey. As a result of early recognition and treatment of infectious diseases which lead to amyloidosis, FMF has replaced the chronic suppurative diseases as the major cause of amyloidosis in this country [38]. Colchicine therapy may prevent the development of amyloidosis in patients with FMF [39]. None of the children with amyloidosis in our study had received colchicine during the course of their disease. Probably in the near future this therapy will lead to a decline in the number of children with CRF caused by amyloidosis.

References

1. Scharer K (1971) Incidence and causes of chronic renal failure in childhood. Proc Eur Dial Transplant Assoc 7: 211–214
2. Habib R, Broyer M, Benmaiz H (1973) Chronic renal failure in children. Nephron 11: 209–220
3. Leumann E (1976) Die chronische Niereninsuffizienz im Kindesalter. Schweiz Med Wochenschr 106: 244–250
4. Helin I, Winberg J (1980) Chronic renal failure in Swedish children. Acta Paediatr Scand 69: 601–607
5. Arbeitsgemeinschaft für Paediatrische Nephrologie (1985) Children with chronic renal failure in Federal Republic of Germany. I. Epidemiology, mode of treatment, survival. Clin Nephrol 23: 272–277
6. Arbeitsgemeinschaft für Paediatrische Nephrologie (1985) Children with chronic renal failure in Federal Republic of Germany. II. Primary renal diseases, age and intervals from early renal failure to renal death. Clin Nephrol 23: 278–284
7. Chantler C, Carter JE, Bewick M, Counahan R, Cameron J, Ogg CS, Williams DG, Winder E (1980) Ten years experience with regular hemodialysis and renal transplantation. Arch Dis Child 55: 435–445
8. Leumann, EP, Egli F, Fanconi A, Guignard JP, Koegel R, Oetliker O, Paunier L (1984) Outcome of pediatric patients with end-stage renal disease in Switzerland 1973–1982. Int J Pediatr Nephrol 5: 155–159
9. Offner G, Aschendorf C, Hoyer PF, Krohn HP, Ehrich JHH, Pichlmayer R, Brodehl J (1988) End stage renal failure: 14 years experience of dialysis and renal transplantation. Arch Dis Child 63: 120–126
10. Gusmano R, Perfumo F (1993) Worldwide demographic aspects of chronic renal failure in children. Kidney Int 43: Suppl 41 s31–s35
11. Choı Y, Kim JD, Ko KW, Lee JS, Kim PK, Ko JH (1986) Chronic renal failure in children. J Korean Pediatr Assoc 29: 29–33
12. Abdurrahaman MH, Al Mugeren M, Al Rasheed SA (1990) Chronic renal failure in children in Saudi Arabia. J Nephrol 2: 93–96
13. Srivastava RN, Marwaha RK, Koehar GS, Choudry VP (1983) Incidence and causes of irreversible renal failure. Indian Pediatr 20: 95–98
14. Rama De Nefrologia (1983) Sociedad Chilena de Pediatria. Insufficiencia renal cronica. Encuesta Rev Chil Pediatr 54: 141–143
15. Potter D, Holliday M, Piel CF, Feduska NJ, Belzel FO, Salvatierra O (1980) Treatment of end-stage renal failure in children: a 15 year experience. Kidney Int 18: 103–109
16. Trachtman H, Hackney P, Tejani A (1986) Pediatric hemodialysis: a decade's (1974–1984) perspective. Kidney Int 30: 15–22
17. Zilleruelo G, Andia J, Gorman HM, Strauss J (1980) Chronic renal failure in children: analysis of main causes and deterioration rate in 81 children. Int J Pediatr Nephrol 1: 30–33
18. Arbus GS, DeMaria JE, Galiwango J (1980) The first 10 years of dialysis-transplant program at the Hospital for Sick Children, Toronto: predialysis and dialysis. Can Med Assoc J 122: 655–659
19. Alexander SR, Lindblad AS, Nolph KD, Novak JW (1990) Pediatric CAPD/CCPD in United States. A review of the experience of the national CAPD Registry's Pediatric Patient population for the period of January 1, 1981 to August 31, 1986. Contemp Issues Nephrol 22: 231–255
20. Alexander SR, Arbus GS, Butt KMH, Conley S, Fine RN, Greifer I, Gruskin AB, Harmon WE, McEnery PT, Nevins TE, Nogueira N, Salvatierra O Jr, Tejani A (1990) The 1989 report of the North America Pediatric Renal Transplant Cooperative Study. Pediatr Nephrol 4: 542–553
21. Avner ED, Harmon WE, Grupe WE, Ingelfinger JR, Eraklis AJ, Levey RH (1981) Mortality of chronic hemodialysis and renal transplantation in pediatric end-stage renal disease. Pediatrics 67: 412–416
22. Esbjörner E, Aranson S, Berg M, Jodal M, Linne T (1990) Children with chronic renal failure in Sweden 1978–1985. Pediatr Nephrol 4: 249–252
23. Allen TD (1985) Vesicoureteral reflux and unstable bladder. J Urol 134: 1180–1182
24. Mundy AR (1984) The prognosis of the neuropathic bladder in childhood. In: Brodehl J (ed) Proceedings of the 6th International Symposium of Pediatric Nephrology. Springer, Berlin Heidelberg New York, pp 350–352
25. Rhoads GG, Mills JL (1986) Can vitamin supplements prevent neural tube defects? Current evidence and ongoing investigations. Clin Obstet Gynecol 29: 569–579
26. Laurence KM (1967) Major central nervous system malformations in South Wales. I. Incidence, local variations and geographical factors. Brit J Prev Soc Med 22: 146–160
27. Koch M, Furmann W (1984) Epidemiology of neural tube defects in Germany. Hum Genet 68: 97–103
28. Çavdar AO, Arcasoy A, Babacan E (1983) Zinc levels of serum, plasma, erythrocytes and hair in Turkish women with anencephalic babies. In: Prasad AS, Çavdar AO, Brewer J, Agget P (eds) Zinc deficiency in human subjects. Liss, New Yor, pp 99–106
29. Say BE, Tunçbilek E, Balcı S (1973) Incidence of congenital malformations in a sample of the Turkish population. Hum Hered 23: 434–438

30. Buckley WR, Erten J (1979) The epidemiology of anencephaly and spina bifida in Izmir, Turkey in the light of recent etiological theses. J Epidemiol Community Health 33: 186–188
31. Ilter O, Atasu T, Aksu MF (1978) Central nervous system abnormalities in Istanbul. Med Bull Istanbul 11: 160–166
32. Akar N, Çavdar AO, Arcasoy A (1988) High incidence of neural tube defects in Bursa, Turkey Paediatr Perinat Epidemiol 2: 89–92
33. Smithells RW (1981) Vitamin supplementation and neural tube defects. Lancet II: 1425–1427
34. Smithells RW (1983) Further experience of vitamin supplementation for prevention of neural tube defects recurrences. Lancet I: 1027–1031
35. Smithells RW (1984) Rational use of vitamins. Lancet II: 1295
36. Milunsky A, Jick H, Bruell CL (1989) Multivitamin/folic acid supplementation in early pregnancy reduces the prevalence of neural tube defects. JAMA 262: 2847–2852
37. Arbus GS, Geary DF, McLorie GA, Major MI, Berdock SE, Freedman L, Baumai R (1986) Pediatric renal transplant: a canadian perspective. Kidney Int 30: 31–34
38. Çoruh M (1971) Renal amyloidosis as a complication of familial Mediterranean fever in children. Turk J Pediatr 14: 99–103
39. Zemer D, Pras M, Sohar E (1986) Colchicine in the prevention and treatment of the amyloidosis of familial Mediterranean fever. N Engl J Med 314: 1001–1005

Ask the expert*

*When should essential hypertension in childhood be treated and how?***

Key words: Essential hypertension – Treatment

A pragmatic approach is best when deciding whether to treat essential hypertension in childhood, aiming to control systolic and diastolic blood pressure at or below the 90th percentile for age and size. The 1987 Task Force [1] suggests nonpharmacological therapy for mild elevations in blood pressure; and, indeed, this remains a reasonable approach for most children. Thus, I first recommend moderate reduction of salt intake, weight reduction (if the child is overweight), exercise, and stress reduction. I explore this with the patient and family to see whether such nonpharmacological steps will be acceptable to them and whether, indeed, they will try them. On the other hand, if there is more interest in pharmacology, then it is better, in my view, to embark on a plan of medication for a defined period of time, in order to see whether even a modest level of hypertension will easily be controlled [2].

If blood pressure is invariably elevated when a patient is seen in the office, and that elevation is moderate to severe, then hypotensive medications are indicated, in my view. While severe blood pressure elevations can be seen in primary hypertension, this necessitates investigation for secondary causes, along with concomitant blood pressure control.

The pharmacological treatment of primary hypertension remains problematic, as most modern hypotensive agents lack formal approval for use in children and young adolescents. Two approaches to pharmacotherapy – the "rational" and the "practical" – should be combined. A rational approach attempts to determine whether the patient's hypertension is salt sensitive or is mediated by strong vasoconstriction, and bases therapy on that determination. If the patient is salt sensitive, then treating the child with a diuretic (if the patient has not been able to reduce salt in the diet effectively) should control the hypertension. If the patient appears to have vasoconstrictor-mediated hypertension, then angiotensin-converting enzyme (ACE) inhibitors make sense as a first step. Other drug classes, such as calcium channel blockers, also make sense in this latter scenario. A "pragmatic" approach simply uses the most convenient preparation which will have the fewest side effects in the given patient. The following is a cautious, practical plan for embarking on pharmacotherapy:

1. Determine that the patient needs medication. Discuss the pros and cons of pharmacotherapy and be sure that the patient and family will be given information on the specific medication(s) chosen. Review this again at subsequent meetings.
2. Check for problems that may rule *out* using a particular class of medication, e.g., reactive airway disease precludes use of β-adrenergic blocking agents, hypokalemia precludes use of diuretics (patient should be evaluated for aldosteronism and/or glucocorticoid remediable-aldosteronism), single kidney precludes use of ACE inhibitors although whether such a patient has primary hypertension would be open to question).
3. Check whether the patient is on other medications or regimens that may be problematic when taking a particular antihypertensive medication, e.g., a patient adhering stringently to a low-salt diet may develop electrolyte abnormalities when on diuretics, a patient on lithium therapy may develop lithium toxicity if on ACE inhibitors. Be sure that the patient and family understand the importance of checking drug/drug interactions if further medication is given for any indication.
4. Outline how blood pressure levels will be followed and what constitutes a successful therapeutic trial of medication.

My aim is to achieve blood pressure control for a period of 6–12 months and then to attempt to lower and discontinue medication. This approach enlists patient and family as partners, allaying the frequent concern that the patient is doomed to a life on medication. Since some children with primary hypertension may remain normotensive for a prolonged period of time once medication is discontinued, this is an important aspect of therapy. If blood pressure does not remain normal, then longer-term therapy is indicated.

Julie R. Ingelfinger
Division of Pediatric Nephrology
Massachusetts General Hospital
MA 02114, USA

References

1. National Heart, Lung, and Blood Institute (1987) Report of the Second Task Force on Blood Pressure Control in Children. Pediatrics 79: 1–25
2. Daniels SR (1992) Management of patients with essential hypertension. In: Loggie JMH (ed) Pediatric and adolescent hypertension. Blackwell Scientific Publications. Cambridge, Mass., pp 197–201

* The editors invite questions for this section
** See also Ask the expert on page 548