

Chronic Kidney Disease: The ABC of Nephrology

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To this day, in many parts of Asia, paediatricians are still grappling with the childhood problems of infectious diseases, diarrhoeal diseases and malnutrition. With improvements in public health, many countries have seen a decrease in infant mortality rates, with a shift in the causes of mortality from infections to other chronic diseases such as malignancies. This is especially significant in the adult population, which has seen a rise in the prevalence of “lifestyle” diseases such as obesity, hypertension and diabetes, resulting in increased morbidity due to cardiovascular and cerebrovascular complications as well as chronic renal failure (CRF). In fact, the incidence of end-stage renal disease (ESRD) is increasing worldwide, ranging from 75 to 350 per million population in developed countries.¹ Over the last decade, the number of patients on renal replacement therapy has more than doubled in many countries. The prevalence of ESRD is a good indicator of the burden of renal diseases, as most chronic nephropathies progress relentlessly to ESRD. In the adult population, the increased prevalence of chronic kidney disease (CKD) is due primarily to the increasing incidence of diabetic nephropathy, not only in the USA and Europe, but also in our Asian populations such as Singapore and Malaysia.² Consequent upon this high incidence of ESRD, an estimated 349,911 patients were on dialysis in Asia at the end of 2004.¹ On the other hand, the incidence of ESRD in children worldwide ranges from 3 to 15.5 per million population under the age of 19 years,¹ without the marked increases seen in the adult population. Should paediatricians then be concerned about this worldwide epidemic of ESRD in adults?

In the words of James Joyce, one of the most significant writers of the 20th century: “*I am tomorrow, or some future day, what I establish today. I am today what I established yesterday or some previous day...*”, how we care for the child of today, will impact on his well-being tomorrow when he has grown into an adult. Therefore, *pari passu* with the strides taken in improving infant and child health over the last decade, paediatricians should look beyond treating the child today, but instead focus on treating the child as the future adult. In other words, when one looks at the problem of ESRD, this is the final event of a sequence

that begins with an initial insult to the kidney, which inexorably progresses to total loss of renal function. Many of these initial insults either begin in childhood, or have their base in “lifestyle” diseases for which the foundations have been laid in childhood! Prevention of this worldwide epidemic of ESRD in adults should therefore begin in the paediatric age group.

Definition of CKD

CKD is best defined as a spectrum ranging from kidney damage with a normal glomerular filtration rate (GFR) to CRF requiring dialysis. A patient has CKD if either of the following criteria are present:³

1. Kidney damage for 3 months as defined by structural or functional abnormalities of the kidney with or without decreased GFR manifested by 1 or more of the following features:
 - a. Abnormalities in the composition of the blood or urine
 - b. Abnormalities in imaging tests
 - c. Abnormalities on kidney biopsy
2. GFR <60 mL/min/1.73 m² for 3 months with or without the other signs of kidney damage

With progression of CRF, complications such as anaemia, renal osteodystrophy and growth failure are inevitable. Hence, the principles of management of children with CKD should include:

- (A) Early detection of CKD so that appropriate monitoring and early treatment can be instituted in the hope of reversing the disease in some instances
- (B) Prevention of progression of CKD
- (C) Prevention and early treatment of the complications of CRF which can eventually lead to serious morbidity in adults.

(A) Early Detection of CKD

The rate of progression of CKD varies according to the underlying cause. Children with hypoplastic/dysplastic kidneys tend to progress slower to ESRD compared to those with glomerulonephritis.⁴ Early detection of congenital abnormalities of the kidney and urinary tract (CAKUT)

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will allow surgical correction of any obstructive element, as well as prevention of pyelonephritis with appropriate antibiotic prophylaxis. These measures, if instituted early, are important in order to stabilise renal function; and to obviate the need for future renal replacement therapy. Conditions such as posterior urethral valves and neurogenic bladders should be treated in infancy, before more severe damage occurs due to high pressures in the urinary tract.

On the other hand, early detection and treatment of many types of chronic glomerulonephritis may result in prevention of progressive inflammation and damage, and may potentially reverse or heal the glomerular inflammatory process. Children with focal and segmental glomerulosclerosis (FSGS) which are resistant to steroid treatment, present a difficult management problem as they often progress to end-stage renal failure. A long-term follow-up study by the International Study of Kidney Disease in Children over 5 to 15 years showed that children with nephrotic syndrome, who were initial non-responders to steroids had a significantly higher mortality than those who were steroid-responsive, with a death rate of 18.5%.⁵ In our series of children with steroid-resistant FSGS, the actuarial 5-year survival in those who responded to treatment was 80% while in those who did not respond to immunosuppressive treatment, the 5-year survival was about 35%. This was similar to reports by Ingulli et al,⁶ i.e. the actuarial 5-year renal survival for patients with steroid and cyclophosphamide-resistant FSGS treated with cyclosporine was significantly better than historical controls, with about 30% in their treated group developing renal failure compared to 80% of their historical controls.

In adults, the International Society of Nephrology (ISN) has recommended that patients diagnosed with diabetes and hypertension should have regular screening for development of kidney disease.⁷ In addition, the ISN recommended that close relatives of patients with nephropathy caused by diabetes, hypertension and glomerulonephritis should also be the primary targets for screening to detect clinically silent kidney disease. Thus screening in adults for CKD is targeted at high-risk populations. How about in children, is there a value for screening programmes?

The experience of nation-wide school screening programmes in Asia have shown that proteinuria, with or without haematuria, is detected only in approximately 0.08% to 2% of asymptomatic school children, with a higher prevalence in adolescents.⁸ Many of these studies showed that coexistent proteinuria and haematuria correlated better with the presence of significant glomerular disease in asymptomatic children.⁹ Mass urinary screening has allowed early intervention in selected cases as evidenced in the Taiwanese study where in their cohort, they have

managed to reduce the incidence of chronic renal insufficiency in their patients with focal segmental glomerulosclerosis and lupus nephritis.¹⁰ Additionally, there has been a reduction in the percentage of patients with heavy proteinuria detected by mass screening from 10.5% in 1992 to 7.1% in 1996 in the Taiwanese school screening programme. This was accompanied by a decrease in the incidence of new dialysis cases annually in children aged 6 to 15 years, from 19 per million in 1992 to 8 per million in 1997. Hence, early detection and treatment of glomerulonephritis in a school-screening programme may contribute to the decrease in the incidence of ESRD in children.

(B) Prevention of Progression of CKD

Most renal diseases continue to progress to renal failure as a consequence of hyperfiltration, which is a form of functional adaptation, after the original disease has caused a critical loss of nephron units.¹¹ The notion of renoprotection has been propounded as a strategy that aims to interrupt or reverse this process. With this in mind, what are the measures that should be taken to prevent progression of CKD in children?

Correction of acute reversible factors is important in preserving renal function in children with chronic renal impairment. This is especially important in children with renal hypoplasia or dysplasia with accompanying tubular dysfunction. Such children are often polyuric due to a tubular concentration defect, and may also have various electrolyte abnormalities such as hypokalaemia, hypomagnesaemia or hyponatraemia due to tubular loss, as well as renal tubular acidosis. Persistent dehydration, acidosis and electrolyte imbalances will result in progressive loss of residual renal function. Moreover, any uncorrected obstructive element or recurrent pyelonephritis will further aggravate the renal dysfunction.

Among the theories on the pathophysiology of progressive nephropathies, the most convincing one suggests that the initial reduction in nephron number progressively damages the remaining ones, by a vicious cycle mediated in part by glomerular hypertension. As glomerular capillary hypertension is normally accompanied by enhanced transglomerular protein traffic, both hypertension and proteinuria may contribute to the progressive loss of renal function. Data from large clinical trials and epidemiological studies indicate that hypertension is a very important risk factor for progressive renal disease. Data from the Multiple Risk Factor Intervention Trial (MRFIT) showed that high blood pressure was a strong and independent risk factor for the development of ESRD.¹² Elevated systolic blood pressure was especially predictive, and a relatively small increase doubled the risk for ESRD. Similarly, in the

European Study Group of Nutritional Treatment of Chronic Renal Failure in Childhood, a casual systolic blood pressure of more than 120 mm Hg was a significant risk factor for progressive renal failure.¹³

If one looks at the renal literature of the last 20 years, there is no question that more severe proteinuria is associated with a more rapid progression in various forms of glomerulopathy, and this correlation is even stronger for patients with nephrotic range proteinuria. That baseline proteinuria predicts a subsequent decline in renal function is amply supported by the Ramipril Efficacy in Nephropathy (REIN) Study which showed that the rate of GFR decline was significantly lower in those with the lowest baseline urinary protein excretion.¹⁴ Similarly, moderate proteinuria of >50 mg/kg/day in children was shown to be a significant risk factor for progression to renal failure.¹³ Thus the progression of renal failure in children with reduced renal mass appears to be correlated to the same risk factors as in adults.

Measures to prevent progression of CKD involve lifestyle changes in the first instance,⁷ especially in adolescents. These include weight loss with physical exercise, reduced sodium intake, avoidance of smoking and avoidance of excessive alcohol. In adults with CKD, a protein-controlled diet of 0.75 to 1.0 g/kg/day is recommended.¹⁵ However, in children, the reduction of dietary protein to the lowest safe amounts recommended by the World Health Organization (WHO) (0.8 to 1.1 g/kg/day depending on age) has not been shown to decrease the progression of CKD and, hence, is not currently recommended.¹³

On the other hand, optimisation of blood pressure control is a very important measure in the prevention of progression of CKD. The results of the Modification of Diet in Renal Disease (MDRD) Study showed that lowering blood pressure in hypertensive patients at risk for or with overt renal disease preserves renal function.¹⁶ Currently, there is a large body of evidence that in many chronic progressive renal diseases, the use of angiotensin converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) may help in retarding progression of renal failure.¹⁴ In a meta-analysis, these drug classes seem to have the greatest benefit in patients with high urine protein excretion levels at baseline.¹⁷ As proteinuria is also an important independent risk factor for the progression of CKD, use of both ACEI and/or ARB to reduce proteinuria in patients with or without hypertension is highly recommended.^{7,17}

In North American studies, the cumulative incidence of end-stage renal failure in diabetics who presented in childhood or adolescence was approximately 20%.¹⁸ A strong predictor for the development of kidney failure is the level of sugar control in the first 2 decades of type 1 diabetes. The incidence of kidney failure ranges from 9.2% in the best

controlled, to 36.3% in the worst controlled patients. Microalbuminuria is the first sign of diabetic nephropathy. Sixty-seven per cent of patients with micro-albuminuria may progress to CKD. Tight glycaemic control in both type 1 and 2 diabetes has been shown to slow the progression of microalbuminuria;^{19,20} hence, diabetic patients should aim to achieve a target fasting plasma glucose of <7.2 mmol/L and a HbA1c level of <7%.⁷ Moreover, patients with diabetic nephropathy, with either microalbuminuria or macroalbuminuria with or without hypertension should also be treated with either an ACEI or ARB.

(C) Prevention and Early Treatment of Complications of CRF

In the management of children with chronic kidney failure, the outcome parameters should not be just on survival in childhood, but also long-term effects such as growth and development. Complications such as anaemia, growth failure and renal bone disease should be addressed early, so as to prevent long-term morbidity.

The long-term survival of children on dialysis is similar to transplant patients during the first 5 years. However, cumulative survival after 10 years is significantly worse in children on dialysis after 10 years. In fact, cardiovascular and cerebrovascular complications are the major causes of death in young adults with childhood onset CRF.²¹ Oh et al²¹ reported the presence of advanced coronary and carotid arteriopathy in young adults with childhood-onset CRF. The coronary calcium scores and intima-media thickness were associated with cumulative dialysis and ESRD time, as well as the cumulative serum calcium-phosphate product. Although long-standing hypertension is an important determinant of concentric left ventricular hypertrophy, hypertension also results in increase in arterial wall tension, contributing to the development of arteriosclerosis and myocardial ischaemia. However, anaemia also worsens eccentric left ventricular hypertrophy, often seen in volume overload states, by increasing the left ventricular chamber size and stroke volume. Anaemia also increases the arterial diameter, and could conceivably lead to an increase in arterial wall thickness, worsening the arteriosclerosis. In addition, metastatic calcification due to increased calcium-phosphate product will also lead to progressive coronary calcification contributing to the myocardial dysfunction. Therefore, it is important to control blood pressure, correct anaemia and control renal osteodystrophy as all these will contribute to the long-term cardiovascular morbidity.

Conclusion

In conclusion, early recognition and treatment of CKD can result in postponement of dialysis in many patients, although the ultimate goal should be remission of disease and regression of structural damage to the kidneys.

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