Can We Prevent Chronic Renal Failure in Children?

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Abstract The management of children with chronic renal failure is primarily the responsibility of paediatric nephrologists, but doctors at all levels of care can help to prevent its onset and delay its progression to endstage renal failure. In Hong Kong, chronic renal failure in children are caused by three main groups of diseases: chronic pyelonephritis (36%), chronic glomerulonephritis (26%), heredofamilial diseases (16%). The first group involved patients with complex congenital urological anomalies with renal dysplasia and superimposed pyelonephritis. The second group included focal segmental glomerulosclerosis, IgA nephropathy, membranoproliferative or membranous nephropathy, ANCA-associated crescentic GN or lupus nephritis. The third group included Alport syndrome, polycystic kidneys, and juvenile nephronophthisis. Universal urine and ultrasound screening have been practised in Japan, Taiwan and Korea. An alternative strategy is early detection/treatment of specific treatable diseases, and institution of non-specific renal protective management for those with progressive renal insufficiency. For the chronic pyelonephritis group, antenatal ultrasound abnormalities and infantile febrile UTI offer an opportunity to treat obstructive uropathy by surgery, VUR by antibiotic prophylaxis +/- circumcision +/- treatment of voiding dysfunction +/- antireflux surgery. Patients in the chronic GN group present with atypical or steroid resistant nephrotic syndrome, or proteinuria/haematuria/hypertension/renal impairment. Timely referral and renal biopsy allow early diagnosis and immuno-suppressive treatment. Even diseases with no specific treatment, control of hypertension, hyperphosphataemia, proteinuria and hypercholesterolaemia may retard the progression to end-stage renal disease. Such strategy calls for cooperation of all paediatricians, to identify high risk patients and refer early at the primary care level, proper workup and diagnosis at the secondary level, specific or nonspecific renoprotective treatment at the tertiary level.

Key words Chronic renal failure; Health care delivery; Prevention

Introduction Chronic renal failure (CRF) is the most devastating of all renal diseases in childhood because it is irreversible, lethal if untreated, and most resource consuming. As the glomerular filtration rate (GFR) decreases to less than 50% of normal, patients are considered to be in the stage of chronic renal insufficiency. They are asymptomatic but have biochemical disturbances such as acidosis or raised serum urea especially at times of stress. When the GFR falls to less than 25% of normal, CRF is diagnosed. Patients will experience uraemic complications and require medical treatment especially for anaemia or renal osteodystrophy or electrolyte disturbances. When the GFR is below 10%, patients will suffer from end-stage renal disease (ESRD), and they cannot survive long without undergoing renal replacement therapy.1 Children with CRF will likely develop other complications including short stature, anaemia, bone disease, fluid and electrolyte problems. Worse still, once the kidney
is damaged, it will enter a vicious cycle of progressive renal damage even though the primary insult has passed or has been treated. This was believed to be due to intraglomerular hypertension and hyperfiltration or abnormal flux of proteins through the mesangial areas. Other factors associated with interstitial fibrosis may also contribute.\textsuperscript{1,2}

A local review in 1993 indicated that the incidence of ESRD in Hong Kong was at least 4 per million childhood population per year, and the prevalence was 13.1 per million childhood population in 1992. There were three major groups of diseases causing CRF in Hong Kong children. Chronic pyelonephritis, together with congenital renal hypo/dysplasia, constituted 36% of all cases. Chronic glomerulonephritis such as focal segmental glomerulonephritis (FSGS) accounted for 26%. While heredofamilial diseases such as Alport syndrome, familial juvenile nephronophthisis accounted for another 16%.\textsuperscript{3}

**Prevention of Urological Causes of CRF**

The first group of disorders involved patients with complex congenital urological anomalies commonly associated with renal agenesis or dysplasia, obstruction or vesicoureteral reflux. There may also be superimposed pyelonephritis and acquired scarring as well. Together they accounted for about 30-40% of ESRD patients in European or American registries.\textsuperscript{4,5} Although the congenital problem cannot be prevented, there are opportunities for their early detection, and hence prevention of further deterioration by relieving obstruction or preventing further pyelonephritic scarring.

According to a British study, antenatal ultrasound screening have picked up renal anomalies in 0.65% of pregnancies (which were confirmed postnatally).\textsuperscript{6} The majority were benign, but about 15% showed evidence of obstruction such as PUJ obstructions or ureteroceles. The most severe cases are those with bilateral PUJ obstruction or posterior urethral valves, and they may lead to in-utero renal failure. If they are detected early, some renal function can be salvaged by early surgical correction. Although a conservative approach is advocated in general, these patients have to be fully investigated and carefully monitored to detect evidence of progressive obstruction to prevent further renal damage.\textsuperscript{7,8}

The second opportunity occurs when children present with febrile urinary tract infections. Epidemiological studies have shown that about 5% of children presenting with fever, usually without other symptoms and signs, had UTI.\textsuperscript{9} This frequently signals an underlying urological anomaly. Also UTI itself may lead to renal scarring. The commonly identified risk factors for scarring include: obstruction, VUR, young age, delayed diagnosis and treatment, recurrent infections, and voiding dysfunction.\textsuperscript{10} We can prevent further renal damage by prompt diagnosis and treatment of each episode of UTI, correcting obstructive lesions if present, preventing recurrence by giving antibiotic prophylaxis, circumcision, attention to voiding problems, and, as a last resort, anti-reflux surgery.

**Prevention of CRF Due to Chronic Glomerulonephritis**

The second category of preventable causes of CRF is the chronic glomerulonephritis. This include: primary glomerulonephritis such as focal segmental glomerulosclerosis (FSGS), IgA nephropathy, membranoproliferative glomerulonephritis, or membranous nephropathy, and systemic diseases such as systemic lupus erythematosus (SLE), Henoch-Schönlein Purpura and systemic vasculitis. Of these, FSGS, IgA nephropathy and SLE nephritis are the commonest in our locality.\textsuperscript{3}

Although treatment for glomerulonephritis are still unsatisfactory, much advances have been made in recent years to improve the outcomes of these patients. For instance, FSGS, which usually presents as steroid resistant nephrotic syndrome, carries a poor prognosis with reported ESRD rates of 15-75%. Current advances of treatment include a regimen of repeated pulses of intravenous methylprednisolone, which was reported to achieve a remission rate of 50% and ESRD rate of 5% only.\textsuperscript{11} An alternative regimen is the use of steroid plus cyclosporine A which was reported to have ESRD rates of about 20-24%.\textsuperscript{12}

Similarly treatment of SLE nephritis have improved steadily over the past decades with renal 5-year survival rates of 65% in the 1970's and 80-90% in the late 1980's.\textsuperscript{13,14} The treatment options now are fairly standardised: Either intermittent intravenous pulse cyclophosphamide plus prednisolone for 2 years,\textsuperscript{15} or sequential therapy with oral prednisolone and oral cyclophosphamide for 3-6 months followed by low dose steroid and azathioprine maintenance.\textsuperscript{16} Yet further improvements with newer and less toxic agents are being reported, for instance the use of mycophenolate mofetil in proliferative lupus nephritis.\textsuperscript{17}

The message is that these previously sinister conditions are now to some extent treatable and they have to be detected.
early. One approach of prevention is universal urine screening of school children, which has been conducted for some years in Japan, Taiwan and Korea. However their efficacy have not been proven by controlled trials. A recent publication from Taiwan reported that 0.3% of those screened showed urine abnormalities, and now most of their patients with SLE, IgA nephropathy, IgM nephropathy, and FSGS were detected in the asymptomatic stage and treated early. Compared with historical data, there have been a marked reduction in FSGS and SLE patients going into renal insufficiency.18

Short of universal urine screening programs, we can rely on the early clinical recognition of these patients, timely referral for renal biopsy and early diagnosis and treatment. In actual practice, this strategy involves recognising the presence of significant proteinuria, haematuria in our patients, or of atypical features in patients who present with acute nephritic syndrome or nephrotic syndrome, so that appropriate patients are selected for renal biopsy and histological evaluation of glomerulonephritis.19

Prevention of CRF Due to Heredofamilial Causes

The third major category of CRF in our children include Alport syndrome, juvenile nephronophthisis and autosomal recessive polycystic kidney diseases.3 The other hereditary diseases such as cystinosis and Finnish type of congenital nephrotic syndrome are rare in our population. These conditions are usually considered to be not amenable to specific cure. However novel therapies are being reported, though not yet proven or generally accepted. For instance, there have been studies on the use of tyrosine kinase inhibitors to retard the cyst formation and parenchymal injury associated with autosomal dominant polycystic kidney diseases.20 Another group of workers have reported their 8 year follow up study on the use of cyclosporine A to reduce proteinuria and maintain renal function in patients with Alport syndrome.21

Non-specific Renoprotective Strategy

Even if there is no effective specific treatment for the primary cause of renal damage, we can adopt a non-specific renal protective strategy of management to slow down the progression of renal failure. The basic components of such an approach, including dietary protein restriction, control of blood pressure, treatment of hyperlipidemia were discussed in an evidence-based review of the literature by Burgess.22

It was demonstrated in early randomised controlled trials (RCT) that protein restriction to the level of 0.4-0.6 g/kg/day (about 0.2 g below the minimal protein intake of 0.6 g/kg/day to sustain nitrogen balance in adults) can retard progression to end-stage renal failure.23,24 This was also confirmed by a recent meta-analysis of RCTs in adult patients.25 However, protein restriction to such degree could result in malnutrition and strict compliance to such a diet is not possible as demonstrated in later clinical trials.26 In addition, allowance for growth must be considered in children. Previous clinical studies have all prescribed protein intakes no lower than the recommended daily allowance (RDA) for age. Two recent RCTs were reported by Kist-ven Holthe et al27 and Wingen et al.28 They compared a restricted protein group (taking 0.8-1.1 g/kg/day adjusted for age) of children aged 2 to 18 years old with GFR from 15-60 ml/min/1.73 m2 versus a control group of children with unrestricted protein intake. They found that there were no significant differences in the growth parameters, and also in the rates of decline of GFR over a period of 1-3 years. As expected, analysis of actual protein intake by urine urea: creatinine analysis and diet history indicated significant dietary non-compliance in the treatment group patients. The current consensus is to give adequate but not excessive protein intake (to the level of RDA for different ages) when the GFR is less than 50% of normal.1

As regards to the control of blood pressure, early retrospective studies have found that diastolic hypertension was associated with a faster rate of renal deterioration. Subgroup analyses of RCTs showed that tight BP control (to <125/75 mmHg in adults) can slow renal deterioration in patients with heavy proteinuria (of >1 g/day) and renal impairment (with GFR<55 ml/min).24,29 It is thus advisable to achieve tighter control of hypertension to the 90th percentile for age and sex rather than the 95th percentile in children with heavy proteinuria and renal insufficiency.

In patients with chronic renal disease, the renin-angiotensin-aldosterone system has been implicated in the pathogenesis of not only systemic hypertension but also progressive glomerulosclerosis due to intraglomerular hypertension and various cellular and cytokine stimulation. Angiotensin converting enzyme inhibitors (ACEI) have been demonstrated in animal studies and clinical trials to reduce proteinuria by generally 35-40%, and to slow the progressive decline in GFR. In adults several large RCTs30-32
and a recent meta-analysis have shown that, even with the same degree of hypertension control, angiotensin-converting enzyme inhibitors (ACEI) such as benazepril and ramipril conferred greater benefit than conventional antihypertensives (such as beta-blockers, diuretics) or placebos, in terms of reduction in proteinuria, significant reduction in rates of doubling of serum creatinine or progression to end-stage renal failure. This clinical benefit is greatest in patients with massive proteinuria of >3 g/day) and those with early renal insufficiency, but also significant in patients with less proteinuria of >1 g/day or more advanced renal impairment. Unfortunately experience in paediatric patients were so far limited to case series. For instance, Soergel et al had shown successful control of hypertension and reduction of proteinuria by ramipril in 14 children with hypertension due to various nephropathies.

In a recent review article, Massy and colleagues pointed out that the clinical benefits of HMG-CoA reductase inhibitors, or the "statins", were greater than expected from the simple lowering of blood lipid levels or the improvement in atherosclerotic lesions. From many in vitro and in vivo studies, the possible mechanisms were postulated to be their ability to inhibit proliferation and promote apoptosis, prevent thrombosis, reduce inflammation and improve the endothelial dysfunctions. All of these factors may contribute to the process of progressive glomerulosclerosis, and hence may be improved by the "Statins".

We can also improve the quality of life of children with CRF by giving them aggressive treatment such as erythropoietin for anaemia, adequate nutrition, growth hormone therapy for short stature, psychological and social support, and when the time comes, adequate dialysis and renal transplantation.

**A Shared Care Approach to the Prevention of Chronic Renal Failure**

Thus, chronic renal failure can be "prevented" by appropriate management at different levels of the health care system. At the primary care or clinic level, at risk cases are identified early so that referrals are made at the appropriate time. Colleagues working in hospitals can perform appropriate initial investigations and make specific diagnosis, and, when indicated, refer to nephrologists for specific treatment. At the tertiary care facilities, children with CRF can be treated so that their renal deterioration is slowed or their quality of life is improved.

This approach requires doctors at all levels to get together and work out clinical protocols of common nephrological problems, so that colleagues at different levels know what to do and know what they are expected to do. This will prevent overloading the referral system and the management of patients can be more coordinated. Thus, in line with the above strategy to prevent the major causes of CRF, we should have agreed guidelines to deal with antenatally detected urological abnormalities, febrile urinary tract infections in young children, and abnormal urinalysis findings at the primary care level. At the secondary care level, we should have clinical protocols to workup significant proteinuria/haematuria, and to treat various glomerulonephritis.

At the primary care level, patients will be benefited if UTI is suspected in all febrile infants with no identifiable focus of infection, but care should be taken to distinguish contaminated urine cultures from genuine infection. Infants with confirmed UTI should be investigated for underlying urological problems and followed for recurrences.

Secondly, haematuria and proteinuria may be due to various causes, but those with combined haematuria and proteinuria, with massive proteinuria of >40 mg/m²/hour or with associated nephritic or nephrotic features (such as renal impairment, hypertension, oedema) will most likely have glomerulonephritis. They should be referred for renal biopsy so that early diagnosis and treatment can be given. Other patients with persistent isolated haematuria or proteinuria should also be referred for nephrologist evaluation. When urological causes have been excluded, persistent isolated haematuria commonly indicates Alport syndrome, IgA nephropathy or thin membrane disease. Persistent isolated proteinuria may be due to chronic glomerulonephritis including focal segmental glomerulosclerosis.

Patients with mild acute nephritic syndrome can be managed symptomatically in general paediatric units. However those with rapidly progressive renal impairment should be referred to nephrology centres for urgent renal biopsy because there are other differential diagnosis with a similar clinical picture, such as lupus nephritis, vasculitis or ANCA-associated crescentic glomerulonephritis or anti-GBM nephritis. These latter diseases required early aggressive treatment depending on the histologic findings.

The child with typical nephrotic syndrome can be treated with an empirical course of prednisolone in general paediatric units. But those with atypical features at presentation, or those who are resistant to steroid treatment, should be referred to units with nephrologists for renal
biopsy and further treatment. The atypical features at disease onset include the age of onset before 6 months, the presence of gross haematuria, or of microscopic haematuria plus persistent hypertension, renal impairment not due to other causes, or low serum complement C3 levels. It is also advisable to do a renal biopsy for the steroid dependent nephrotic child before starting therapy with third line drugs such as cyclosporine A.43

The central idea is to form a service network for all children with renal diseases based on the following principles. Firstly, there are agreed protocols which are developed and supported by the joint efforts of doctors from all levels, so that patients can get equal and up-to-standard treatment in any clinics or hospitals in the territory. Secondly, the planning of services should reflect a balance of easy accessibility for patient convenience, and the need for economy of resources and building up of expertise in managing rare diseases. Thus every paediatric unit should be able to provide nephrology services, but expensive setup like haemodialysis and renal transplantation should be concentrated in a few Renal Centres.

With such a shared-care approach and referral system, we can provide a better nephrology service for our children. Although many diseases causing CRF are still beyond our control, we can do much by making earlier diagnoses and delaying the onset of CRF and the progression to endstage renal failure.

References