Role of Urinary Screening Programmes in Children in the Prevention of Chronic Kidney Disease

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Abstract

Introduction: This article reviews published literature on the usefulness of population-based urinary screening in the Asian paediatric population. Methods: Articles were found in the Medline database using the key words "paediatrics", "urine screening", "proteinuria", "haematuria" and "population". The Asian countries which had carried out population-based urinary screening of the paediatric population included Taiwan, Japan and Korea. One study was found on urinary screening in a select population in Malaysia. Preliminary results of the urinary screening of school children in Singapore are presented and compared with the results found in the above-mentioned countries. Results: Overall, the proportion of children found to have urinary abnormalities ranged from less than 0.1% of the population screened to almost 50% of a select cohort referred from the screening programmes for the evaluation of urinary abnormalities. In the pilot Singapore school screening programme, the prevalence of clinically significant proteinuria was 1.25 per 1000 children screened. Multivariate analysis showed that low body weight was associated with a 1.8-fold greater risk for proteinuria. The major cause of haematuria and proteinuria in those studies where renal biopsies were performed was glomerulonephritis. The Taiwanese experience also showed a reduction in the incidence of end-stage renal failure diagnosed in children after the onset of urine screening. Conclusion: These studies showed that urinary screening programmes in school children allow the early detection of disease. The cost-benefit ratio for specific populations should be determined before the implementation of such programmes.

Ann Acad Med Singapore 2005;34:3-7

Key words: Asia, Haematuria, Population, Proteinuria

Introduction

Singapore has an estimated annual incidence of end-stage renal disease (ESRD) of 158 per million population.[1] However, the number of children who develop renal failure, and requiring renal replacement therapy, is relatively low compared to adults. The incidence of ESRD in children ranges from 5 to 6 per million children under the age of 15 years in Europe, Australia and Japan, to 10 to 11 per million children in the United States. In Singapore, with an estimated mid-year population of 4.18 million in 2003, of whom 715,000 were under the age of 15 years, the estimated incidence of ESRD is similar to that in the developed countries at 5 to 6 per million children per year.

Several studies have demonstrated that the factors that contribute to progressive renal deterioration in chronic kidney disease include hypertension and proteinuria.[2-5] The initial reduction in nephron number progressively damages the remaining ones, which suffer the consequences of adaptive increases in glomerular pressure and flow. Glomerular capillary hypertension is normally accompanied by enhanced transglomerular protein traffic. Therefore, early detection of chronic kidney disease, with appropriate management of the risk factors for progression, may slow the development of end-stage renal failure. In a paediatric multi-centre study, a casual systolic blood pressure (BP) >120 mm Hg was shown to be a significant risk factor for the progression of renal failure.[6] Similarly, moderate proteinuria of >50 mg/kg/day was shown to be a significant risk factor for progression to renal failure. This was supported by the study by Litwin[7] showing that in children with chronic renal failure, proteinuria and arterial hypertension differed significantly between patients with

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progression of chronic renal failure and those with stable or improved renal function. Thus the progression of renal failure in children with reduced renal mass appeared to be correlated to the same risk factors as in adults.

Urinary Screening Programmes in Asia

In Asia, Japan was the first country to start a national urinary screening programme for school children aged 6 to 14 years on an annual basis in 1973.[8] Taiwan initiated a national programme in 1990[9] covering children from 6 to 15 years old, while Korea's programme began in 1998 for children from 6 to 18 years.[10] Malaysia does not have a national screening programme, but a study was carried out in Kelantan between 1988 and 1994 for children aged 7 to 12 years.[11] The process of screening was similar in all the studies. Urine collected from the children were tested using urine dipstick. Those children with proteinuria and/or haematuria underwent a second urinary screen. Those with persistent abnormalities were then referred to a paediatrician or nephrologist for further investigations.

In an effort to detect and treat chronic kidney disease in children while still in the asymptomatic phase, the National Kidney Foundation, in conjunction with the Shaw-NKF Children's Kidney Centre, National University Hospital and the School Health Service, Ministry of Health, have undertaken a programme of detecting asymptomatic renal disease in 12-year-old school children in Singapore by urinary screening for haematuria, proteinuria as well as blood pressure monitoring.[12,13] This programme began in 1999. This age group was chosen as there is a well-recognised increase in the prevalence of urinary abnormalities and hypertension as age increases.[14] Moreover, the urinary screening process was coordinated with the routine medical examination carried out by the School Health Service, Ministry of Health, on this age group. Briefly, a comprehensive questionnaire was given to each student that surveyed the home environment, past medical histories of the family for hypertension, renal disease and diabetes, and lifestyle patterns. First-morning urine samples were tested using urine dipstick for haematuria and proteinuria. For those with abnormalities, a second screen was performed, and those with persistent abnormalities were referred to the Paediatric Nephrology Clinic for further investigations and follow-up.

Isolated Haematuria

Over a 13-year period of urinary screening in Japanese school children in Tokyo from 1974 to 1986,[8] almost 5 million children aged 6 to 11 years and 2,400,000 children aged 12 to 14 years were screened. Of these, the mean prevalence of haematuria on the second urine screen in the 6- to 11-year age group was 0.54%, and the 12- to 14-year age group was 0.94%. Renal biopsy in patients 6 to 14 years with haematuria persisting for 1 year or more revealed the presence of glomerulonephritis in 25.4%.

The mass urinary screening programme for children in Taiwan screened approximately 2.7 million children annually, of whom 0.3% were positive for either haematuria or proteinuria or both.[9] Of these, 34.8% had microscopic haematuria alone. Evaluation of these patients at a tertiary referral centre identified glomerulonephritis as a cause in 52.3%, whereas 17.7% had familial benign haematuria or thin membrane disease. In 12% of cases, no known cause was identified. The main causes of glomerulonephritis in this group of children were lupus nephritis (31.6%) and IgA nephropathy (11.7%).

In the Korean school screening programme between 1998 and 2000, of the 452 children detected with abnormal urinary findings, 50.4% had microscopic haematuria alone.[10] However, only 43.7% of patients in this group had significant pathology on further evaluation. By contrast, the Malaysian study[11] only detected persistent haematuria on urine testing on two separate occasions in 0.21% of the initial sample. Of these, only 0.03% of the initial sample persisted with haematuria on the third episode of testing. Haematuria was more common in girls than in boys.

In the pilot school screening programme for urinary abnormalities in Singapore conducted between 1999 and 2000, where 2325 12-year-old school children were examined, the prevalence of clinically significant isolated haematuria was 6.8% based on the first urinary screen. Evaluation of these children at a tertiary centre for isolated haematuria showed that 22.2% had more than 30% dysmorphic red cells on phase-contrast microscopy, suggestive of some form of glomerulonephritis as the underlying aetiology.[12,13] The results of the urinary screening programmes for isolated haematuria are summarised in Table 1.

Isolated Proteinuria

In the Japanese school screening study which looked at almost 5 million children, the prevalence of proteinuria was much lower than that for isolated haematuria, with 0.08% students in the 6- to 11-year age group having persistent proteinuria on second screening.[8] This proportion increased to 0.37% in the 12- to 14-year olds. The Taiwanese study showed a prevalence of 4.9% for mild proteinuria of 30 to 100 mg/dL,[9] of whom 60.7% had evidence of a significant glomerulopathy, the most common of which was lupus nephritis. On the other hand, the Korean study showed a prevalence of 21.7% for persistent proteinuria without haematuria in children referred for urinary abnormalities.[10] In the Malaysian study, 1.9% of those screened had a positive second sample, but on further evaluation at the tertiary centre, only 0.12% were found to

Table 1. Results of School Screening Programmes for Isolated Haematuria

Study	Country	Period covered (y)	Age (y)	No. of children in study	No. positive
Murakami et al[8]	Tokyo, Japan	1974-1986	6-11	4,929,524	26,388 (0.54%*)
Murakami et al[8]	Tokyo, Japan	1974-1986	12-14	2,420,404	22,870 (0.94%*)
Lin et al[9]	Taipei Veterans General Hospital, Taiwan	January1991-August 1998	6-15	573 with confirmed urinary abnormalities	266 (46.4%**)
Cho et al[10]	Kyung-Hee University Hospital, Korea	1998-2000	6-18	452 with persistent urinary abnormalities	228 (50.4%**)
Zainal et al[11]	Kelantan, Malaysia	1988-1994	7-12	45,149	97 (0.21%*)
Ramirez et al[12]	Singapore	1999-2000	12	2325	158 (6.8%***)

* Percentage positive after second screening
** Percentage positive in children referred for urinary abnormalities
*** Percentage positive after first screening

Table 2. Results of School Screening Programmes for Isolated Proteinuria

Study	Country	Period covered (y)	Age (y)	No. of children in study	No. positive
Murakami et al[8]	Tokyo, Japan	1974-1986	6-11	4,929,524	3719 (0.08%*)
Murakami et al[8]	Tokyo, Japan	1974-1986	12-14	2,420,404	9063 (0.37%*)
Lin et al[9]	Taipei Veterans General Hospital, Taiwan	January 1991 - August 1998	6-15	573 with confirmed urinary abnormalities	28 (4.9%**)
Cho et al[10]	Kyung-Hee University Hospital, Korea	1998-2000	6-18	452 with persistent urinary abnormalities	98 (21.7%**)
Zainal et al[11]	Kelantan, Malaysia	1988-1994	7-12	45,149	837 (1.85%*)
Ramirez et al[12]	Singapore	1999-2000	12	2325	29 (1.2%***)

* Percentage positive after second screening
** Percentage positive in children referred for urinary abnormalities
*** Percentage positive after first screening

Table 3. Results of School Screening Programmes for Haematuria and Proteinuria

Study	Country	Period covered (y)	Age (y)	No. of children in study	No. positive
Murakami et al[8]	Tokyo, Japan	1974-1986	6-11	4,929,524	1237 (0.03%*)
Murakami et al[8]	Tokyo, Japan	1974-1986	12-14	2,420,404	1943 (0.08%*)
Lin et al[9]	Taipei Veterans General Hospital, Taiwan	January 1991 - August 1998	6-15	573 with confirmed urinary abnormalities	82 (14.3%**)† 197 (34.4%**)‡
Cho et al[10]	Kyung-Hee University Hospital, Korea	1998-2000	6-18	452 with persistent urinary abnormalities	79 (17.5%**)
Zainal et al[11]	Kelantan, Malaysia	1988-1994	7-12	45,149	25 (0.06%*)
Ramirez et al[13]	Singapore	1999-2001	12	9479	218 (2.3%*)

* Percentage positive after second screening
** Percentage positive in children referred for urinary abnormalities
† Proteinuria 30 to 100 mg/dL
‡ Proteinuria >100 mg/dL

be positive.[11] Similarly, a pilot study conducted on 2325 12-year-old school children in Singapore showed that the prevalence of isolated proteinuria was 1.2% on a single screening visit.[12] Table 2 summarises the prevalence of isolated proteinuria in the school screening programmes.

Haematuria and Proteinuria

In the Japanese study, the prevalence of proteinuria and haematuria was 0.03% amongst the almost 5 million school children aged 6 to 11 years who were screened (Table 3). This prevalence increased to 0.08% in the 12- to 14-year age group.[8] In an earlier review of 247 children referred from the school screening programme for persistent urinary abnormalities, 74 were found to have haematuria and proteinuria.[15] Of these, 66 children had evidence of glomerulopathy. Clinical and histological data identified IgA nephropathy as the most common glomerulonephritis, comprising 43.9% of the cases, followed by diffuse proliferative glomerulonephritis in 24.2% and Henoch-Schonlein nephritis in 15.2%.

In the Taiwanese study, 14.3% of children had haematuria with mild proteinuria of 30 to 100 mg/dL, whereas 34.4%

had heavy proteinuria >100 mg/dL. Of those with mild proteinuria accompanied by haematuria, 75.6% had some form of glomerulopathy on renal biopsy, the most common being lupus nephritis. In those with heavy proteinuria with or without haematuria, 87.3% were diagnosed with glomerulopathy, the most common again being lupus nephritis, followed by focal segmental glomerulosclerosis, IgM mesangial nephropathy and IgA nephropathy.[9]

In the Korean study, 17.5% of 452 school children referred for urinary abnormalities had both proteinuria and haematuria.[10] Renal biopsy was done for 173 subjects referred from the school screening programme and, of these, 21.9% were diagnosed with mesangial proliferative glomerulonephritis while 11.3% had IgA nephropathy. There was a higher proportion of children with chronic renal disease (57.7%) in those presenting with haematuria and proteinuria, as compared with those presenting with haematuria alone (43.7%) or proteinuria alone (19.4%).

In the Malaysian study, 0.06% of those undergoing a second screen had proteinuria and haematuria, however, on further evaluation in a tertiary centre, only 0.02% were found to have both proteinuria and haematuria.[11] Similarly, of the 9479 children screened in the pilot Singapore school screening programme for urinary abnormalities, 1048 or 11.1% were found to be positive on one dipstick examination, and had a repeat test.[12,13] Of these, 218 or 20.8% were found to be still positive. On further evaluation, 51.5% were found to have persistent proteinuria, and were referred to the hospital. Quantitative 24-hour urinary protein excretion revealed that only 9 out of the 85 school children who had persistent proteinuria on repeat dipstick examination had elevated protein excretion. Eight of these 9 children had accompanying haematuria, suggesting an underlying glomerulonephritis as the aetiology, whereas 1 had reflux nephropathy with elevated serum creatinine. Hence, the prevalence of clinically significant proteinuria in the school cohort was 1.25 per 1000 children screened. Multivariate analysis looking at the predictors of proteinuria in the school population showed that low body weight, presence of persistent newly detected hypertension and a lack of sports activity were significant predictors for persistent proteinuria (Table 4).[13,16] In fact, low body weight was associated with a 1.8-fold greater risk for proteinuria after adjusting for confounding factors. There was a trend for lower birth weights in the proteinuric group, suggesting that low renal mass, together with additional environmental influences resulting in decreased body weight, may result in earlier manifestation of renal disease.[16]

Table 4. Significant Clinical Predictors for Proteinuria on Multivariate Analysis

Characteristic	Odds ratio	95% confidence interval	*P* value
Low birth weight[16] (Yes vs No)	1.8	1.27-2.64	0.0019
Newly detected hypertension[13]	15.2	9.30-24.28	<0.0001
Regular sports activity (No vs Yes)[13]	1.61	1.10-2.36	0.014

Since the onset of urinary mass screening, many cases of otherwise asymptomatic cases of glomerulonephritis have been detected in the Asian paediatric population. The Japanese experience has shown that those who were symptomatic at the time of diagnosis, e.g. nephritic syndrome, nephrotic syndrome or gross haematuria had more severe glomerular disease than those who had asymptomatic haematuria or proteinuria picked up on mass screening.[17] Most of the studies also demonstrated that coexisting proteinuria and haematuria, and the degree of haematuria correlated with the severity of the morphological alteration in the glomeruli in asymptomatic children.[18] 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.[19] 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. Moreover, 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 had been observed, and was associated with a decrease in the percentage of children requiring dialysis due to glomerulonephritis from 63.2% to 47.0%. These data suggest that early detection and treatment of glomerulonephritis in a school screening programme may contribute to the decrease in the incidence of end-stage renal disease in children.

The main objective of mass urinary screening programmes in school children is to detect renal disease in its early stages, allowing treatment so as to delay or even prevent the onset of renal insufficiency. The major disadvantage of such programmes is not only the cost, but also the anxiety that will be created in parents and children where the proteinuria or haematuria is intermittent, and where subsequent investigations show that the proteinuria or haematuria has resolved spontaneously. Additionally, the urinary screening programmes will not detect renal disease where there is no proteinuria or haematuria. There is no doubt that urinary screening programmes in school children will allow earlier detection of disease, but the cost-benefit ratio for specific populations should be determined before the institution of such programmes. An alternative would be to institute selective screening of children with low birth weight and those with lower weights as they may have an increased risk of proteinuria.

Acknowledgements

We would like to acknowledge the contribution of the National Kidney Foundation Prevention Clinical School Team, Ms Usha D/o Kumaran, Ms Toh Mei Chi and Ms Zainab Bte Ahmad. Special thanks also to Dr Kwang Yoke Ping and Dr Rose Vaithinathan, School Health Service, Health Promotion Board for their continued support of the school screening programme.

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