Kidney International, Vol. 67, Supplement 94 (2005), pp. S23–S27

Proteinuria screening for children

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Proteinuria screening for children.

Background. In Japan, urine screenings are performed annually at school for proteinuria and hematuria, but the effectiveness of this practice has not been clarified.

Methods. Urine screening at school was performed, and we investigated the prevalence of urine abnormalities and incidence and the causes of their diseases. Therefore, we studied effectiveness of the school-screening program.

Results. The prevalence of urinary abnormalities was 0.52% among elementary school children and 0.75% among junior high school children. The incidence was 0.24% among elementary school children. The school-screening program is effective in early detection of glomerulonephritis, so the number of new end-stage renal disease (ESRD) patients starting treatment has been changing.

Discussion. The school-screening program is effective for early detection of glomerulonephritis. In case of generations who underwent the school-screening program, the age that one develops ESRD has been rising year by year, and the number of new ESRD patients starting treatment before 20 years old is lower in Japan than in America.

Conclusion. The school-screening program in Japan represents a highly effective mass screening technique.

In Japan, the school-screening program is used to screen for proteinuria and hematuria in school-aged children. Since a 1973 revision in the School Health Law, urine screening has been performed every year since 1974 in elementary and junior high schools for the early detection of nephropathies and uropathies.

The present study investigated whether this screening program is effective in reducing the number of patients requiring renal replacement therapy (RRT).

METHODS

Prevalence and incidence of urinary abnormalities in elementary and junior high school children in Japan

Since 1974, we have been conducting screening by using reagent strips produced by the same manufacturer (Bayer Corporation, Elkhart, IN, USA), and analyzed using the same standards [1]. In the first screening, elementary and junior high school children are instructed to completely empty the bladder at night, and early morning urine is sampled to screen for urinary protein and occult blood. For both proteinuria and hematuria, positive reactions are defined as ± or above. A sulphosalicylic acid test is used to confirm proteinuria, while microscopy is performed to confirm occult hematuria. Children who gave positive results in the first test were examined again 10 to 20 days later using the same methods. If both of the sets of tests are positive, children will undergo a second screening. In this second screening, besides urinalysis, each child is interviewed and examined by a physician, a blood sample is taken, and blood pressure is measured. Based on the results of these tests, further tests are ordered as necessary.

To ascertain the incidence of urinary abnormalities, 31,552 elementary school children who began attending elementary school in 1987 were followed for six years. Urine screening was performed over the six-year period on more than 96% of the elementary school children. The first urinalysis was conducted soon after entering elementary school, and incidence of urinary abnormality was monitored annually for the next five years.

Final diagnosis for children with positive test results

Precise tests were conducted on a total of 425 children who visited Nippon Medical School hospital. They were diagnosed with urinary abnormality based on results of the second screening, which has been conducted for the last 29 years using the same reagent strips and standards. The next examination step for children found to have positive finding on the second screening should be one that enables a definitive diagnosis to be made. That is to say, measurements of serum complements, serum IgA, urine β2-microglobulin, urine Ca/creatinine, and renal sonography are added to routine test. Kidney biopsy was conducted for children satisfying the following criteria: (*1*) proteinuria ≥100 mg/dL (early morning urine); (*2*) abnormal clinical or serum findings (e.g., edema, hypertension, renal dysfunction, hypoproteinemia, hypocomplementemia); (*3*) senior elementary school children (over 9 years old) and junior high school students with proteinuria and hematuria; and (*4*) macroscopic

Key words: urine screening at school, proteinuria, hematuria, ESRD.

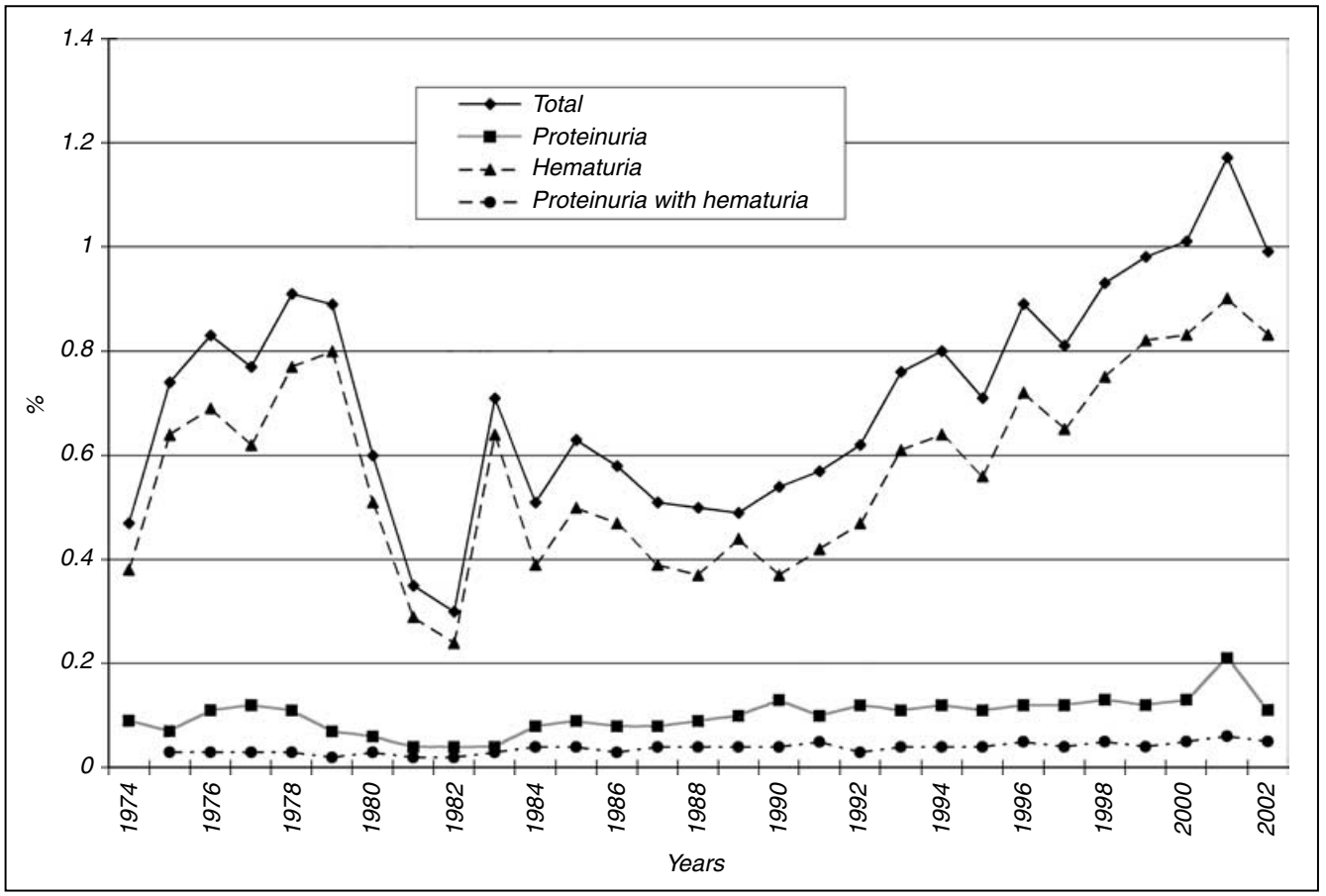

Fig. 1. Prevalence of the first screening (elementary school child).

hematuria without urologic disease, left renal vein entrapment syndrome, or hypercalciuria.

RESULTS

Prevalence and incidence of urinary abnormalities in elementary and junior high school children in Japan

Since 1974, we have conducted urine screenings on more than 200,000 elementary school children (6 to 11 years old) and 100,000 junior high school children (12 to 14 years old) each year. Figures 1 and 2 show results for the first screening in elementary and junior high school children from 1974 to 2002. In 2002, urinalysis was conducted for 246,368 elementary school children and 115,736 junior high school children. In the first screening, positive rates of proteinuria, proteinuria with hematuria, and hematuria were 0.11%, 0.05%, and 0.83%, respectively, among elementary school children, and 0.6%, 0.10%, and 1.10%, respectively, among junior high school children. In the second screening, positive rates of proteinuria, proteinuria with hematuria, and hematuria were 0.06%, 0.01%, and 0.45%, respectively, among elementary school children, and 0.32%, 0.03%, and 0.40%, respectively, among junior high school children.

Out of the 31,552 elementary school children who began to attend school in 1987, 384 children (1.22%), comprising 131 boys (0.8%) and 253 girls (1.66%), were found to have urine abnormalities over the six-year period. Breakdown of urinary abnormalities was as follows: proteinuria ($N = 54$; 14.1%), proteinuria with hematuria ($N = 30$; 7.8%), and hematuria ($N = 300$; 78.1%). Based on these findings, annual incidence of urinary abnormality in elementary school children from 6 to 10 years old is 0.03% for proteinuria, 0.02% for proteinuria with hematuria, and 0.19% for hematuria [2].

Final diagnosis for children with positive test results

Breakdown of pathologies for the 425 children was: proteinuria, $N = 96$; proteinuria with hematuria, $N = 49$; proteinuria with leukocyturia, $N = 5$; and hematuria, $N = 275$. Table 1 shows final diagnoses. Final diagnosis was made in 9.4% of children with proteinuria, 67.3% of children with proteinuria with hematuria, 80% of children with proteinuria with leukocyturia, and 4.7% of children with hematuria. We diagnosed children who were not

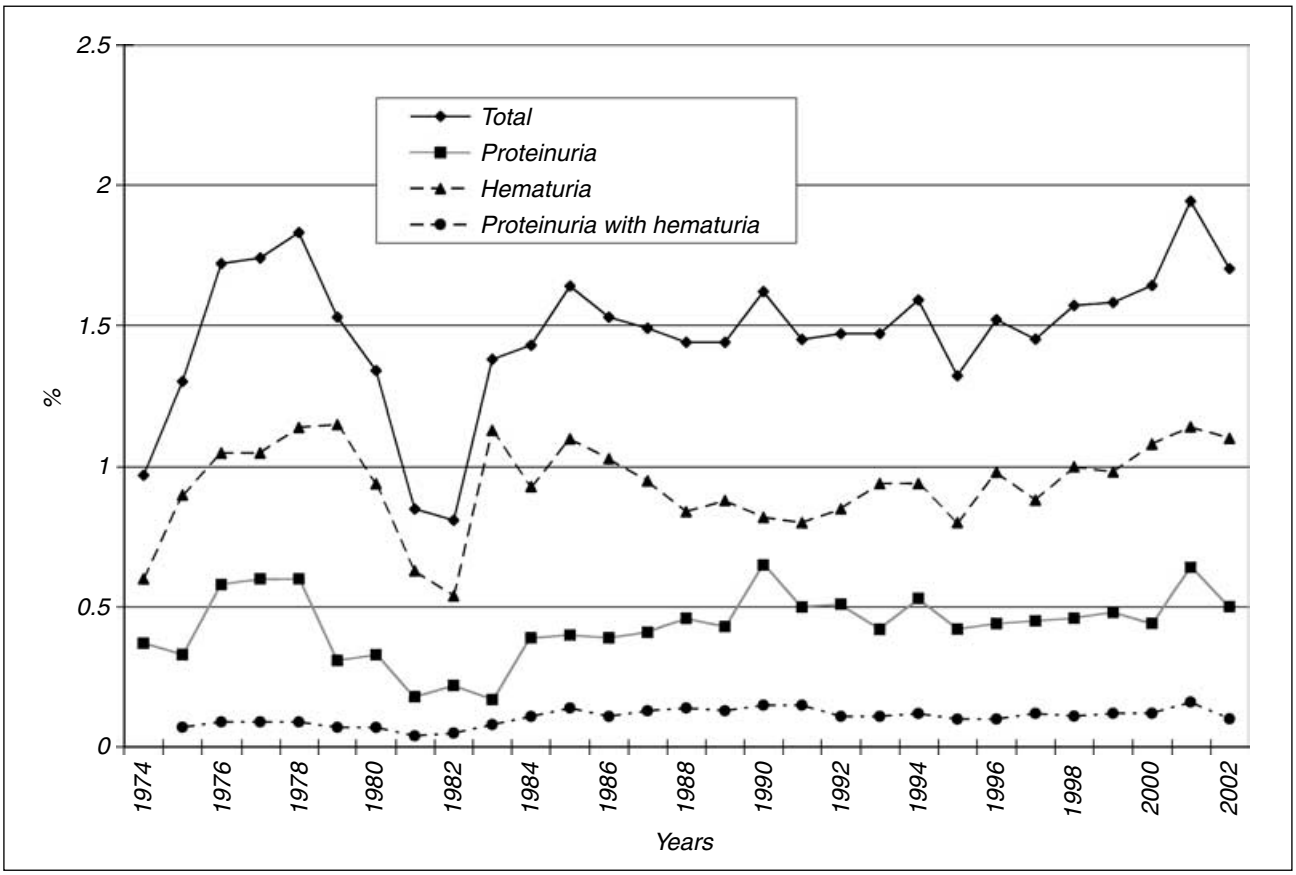

Fig. 2. Prevalence of the first screening (junior high school child).

Table 1. Final diagnosis of the positive cases

	Isolated proteinuria	Proteinuria with hematuria	Proteinuria with leukocyturia	Isolated hematuria
N	96	49	5	275
No abnormal urine[a]	1			40
Postural P	44		1	
Asymptomatic P	42			
Asymptomatic H		7		220
Asymptomatic P and H		9		2
Urinary tract infection	1	1	4	
Urinary tract malformation	4	1		5
Glomerulonephritis	1	30		6
Others	3	1		2

Abbreviations are: P, proteinuria; H, hematuria; P and H, proteinuria and hematuria.
[a]The patients had urinary abnormalities in the second screening.

given the name of diseases as isolated proteinuria, asymptomatic proteinuria with hematuria, or isolated hematuria [3].

Histologic examination of the kidney was conducted for 54 children (Table 2)[3]. In the second screening, excluding those with minor glomerular abnormalities, positive rates of glomerulonephritis was 1.0% for children with proteinuria, 61.2% for children with proteinuria with hematuria, and 2.2% for children with hematuria. Based on these findings and the above incidences of urinary abnormalities, incidence of glomerulonephritis in school children from 6 to 10 years old was estimated at 0.016% (5.1/31,552 children) per year.

DISCUSSION

In these results, annual incidence of urinary abnormality in elementary school children from 6 to 10 years old is 0.03% for proteinuria, 0.02% for proteinuria with hematuria, and 0.19% for hematuria [2]. Further, incidence of

Table 2. Details of glomerulonephritis

	Isolated proteinuria	Proteinuria with hematuria	Isolated hematuria
N	7	34	13
MGA	6	4	7
IgA nephropathy		21	6
Non-IgA mes. PGN		1	
MPGN		4	
MN	1	3	
FSGS		1	

Abbreviations are: MGA, minor glomerular abnormalities; mes. PGN, mesangial proliferative glomerulonephritis; MPGN, membranoproliferative glomerulonephritis; MN, membranous nephropathy; FSGS, focal segmental glomerular sclerosis.

glomerulonephritis in school children from 6 to 10 years old was estimated at 0.016% (5.1/31,552 children) per year. These results suggest that the school-screening program is, thus, effective for early detection of glomerulonephritis.

Comparing Japan, with its mandatory school screening program, and America, which does not have any such program, 29 children <20 years old developed end-stage renal disease (ESRD) from primary glomerulonephritis in 1999 in Japan [4], while an average of 311 children <20 years old developed ESRD each year between 1996 and 1999 in America [5]. Adjusted for population, the value of ESRD in America is 111, about 4-fold higher than in Japan.

Regarding therapeutic responsiveness of early-stage glomerulonephritis, studies have been conducted on membranoproliferative glomerulonephritis (MPGN) and IgA nephropathy, which are often asymptomatic.

Iidaka et al studied therapeutic outcomes for 41 Japanese children with MPGN, including 29 children diagnosed with MPGN based on the results of school screenings, and reported that only one child developed ESRD [6]. According to Iidaka et al, outcomes for MPGN patients were superior compared to other studies due to earlier detection and treatment. We have followed 20 patients who were diagnosed with type I MPGN based on the results of school screenings for more than 10 years, and none of these children have yet developed ESRD. Yoshikawa et al studied children with IgA nephropathy; among them, about 70% were diagnosed based on results of school screenings. And they concluded that in case of the patients with early detection and treatment, the disease would be delayed [7]. These findings suggest that early detection led to early treatment with lower incidence of ESRD complicated.

In Japan, a total of 229,538 patients were on dialysis in 2002, and 33,710 new ESRD patients were starting treatment. The number of new dialysis patients has increased by about 1000 each year [8]. According to the Japanese Society for Dialysis Therapy, the number of new ESRD patients starting treatment <20 years old was 174 in 1984 compared to 108 in 2002. Moreover, pediatric peritoneal dialysis has been performed more often in recent years, and the number of new ESRD patients starting treatment before 12 months old was eight in 1984 compared to 22 in 2002. We have a conclusion from this result that the number of new ESRD patients starting treatment <20 years old has not been increasing in 2002 in comparison to 1984.

Yamagata et al investigated the age distribution of patients who began maintenance RRT from 1983 to 1999 in Japan, and found that the average age of patients with ESRD has increased in recent years [9]. Their data indicate that the number of new ESRD patients starting treatment has decreased for patients <30 years old since around 1990, for patients <35 years old since around 1995, and for patients <40 years old since around 1999. Furthermore, according to Yamagata et al, among patients with glomerulonephritis, the incidence rate for Japanese was greater than those for other races in all age groups in 1983; however, in 1999, the incidence rate for Japanese patients with glomerulonephritis was lowest in the younger than 25-year-old group, and lower than in U.S. blacks in the younger than 55-year-old group. These findings suggest that Japanese children who undergo annual urine screening at school tend to develop ESRD at a later stage of life than is comparable American populations.

In Japan in 1999, age distribution for new ESRD patients starting treatment <20 years old was as follows: 3 per million among 0- to 4-year-olds; 2 per million among 5- to 9-year-olds; 5 per million among 10- to 14-year-olds; 6 among 15- to 19-year-olds. In total population <20 years old, the number of new ESRD patients starting treatment was 4 patients per million [4]. In America in 1999, this figure was 10 per million among 0- to 4-year-olds; 8 per million among 5- to 9-year-olds; 16 per million among 10- to 14-year-olds; 30 per million among 15- to 19-year-olds. In total population <20 years old, the number of new ESRD patients starting treatment was 16 patients per million [5]. Since the school screening program is conducted on school-aged children ≥6 years old, no effect is seen on children <6 years old, but differences between the two countries in the number of new ESRD patients starting treatment at higher age groups could be partially attributable to the benefits of the screening program.

CONCLUSION

The school-screening program in Japan represents an effective mass screening technique; compared to children who did not participate in the mass-screening program, nephropathies were more responsive to therapy, ESRD took longer to progress, and incidence of ESRD was lower.

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REFERENCES

1. Murakami M, Yamamoto H, Ueda Y, *et al*: Urinary screening of elementary and junior high school children over a 13 year period in Tokyo. *Pediatr Nephrol* 5:50–53, 1991
2. Ambo K, Tsuchiya M, Murakami M, *et al*: Incidence of abnormalities in urinalysis in Japanese children aged six to ten years (in Japanese). *J Jpn Pediatr Soc* 103:543–548, 1999
3. Tsugu H, Tsuchiya M, Murakami M, *et al*: The Prospective study in school-age children with proteinuria (in Japanese). *J Jpn Pediatr Soc* 101:61–66, 1997
4. Hattori S, Yoshioka K, Honda M, *et al*: The 1999 Report of the Japanese National Registry Data on Pediatric End-Stage Renal Disease Patients (in Japanese). *Jpn J Pediatr Nephrol* 14:165–173, 2001
5. US Renal Data System: Excerpts from the *2001 Annual Data Report*: Atlas of end-stage renal disease in the United States. *Am J Kidney Dis* 38:195–200, 2001
6. Iidaka K, Ishidate T, Hojo M, *et al*: Idiopathic membranoproliferative glomerulonephritis in Japanese children. *Pediatr Nephrol* 9:272–277, 1995
7. Yoshikawa N, Ito H, Sakai T, *et al*: A controlled trial of combined therapy for newly diagnosed severe childhood IgA nephropathy. *J Am Soc Nephrol* 10:101–109, 1999
8. Japanese Society for Dialysis Therapy: An overview of regular dialysis treatment in Japan as of Dec. 31, 2002 (in Japanese), Tokyo, Japan
9. Yamagata K, Takahashi H, Suzuki S, *et al*: Age distribution and yearly changes in the incidence of ESRD in Japan. *Am J Kidney Dis* 43:433–443, 2004