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Ching-Yuang Lin · Chia-Chang Hsieh
Wei-Perng Chen · Ling-Yoeu Yang · Hsin-Hui Wang

The underlying diseases and follow-up in Taiwanese children screened by urinalysis

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Abstract To date, the underlying diseases and follow-up of Taiwanese children screened by urinalysis have not been reported. The grading of urine abnormalities varied from grade A (microscopic hematuria only), grade B (light proteinuria only), grade C (light proteinuria and microscopic hematuria) to grade D (heavy proteinuria). From January 1991 to August 1998, 630 students, aged 6–15 years and with positive urinary screening, were admitted to our hospital for further evaluation. Of these, 573 students had confirmed abnormal findings, 298 were boys, 275 were girls, and 294 students received a renal biopsy and have had regular follow-up visits. This study was designed to retrospectively elucidate: (1) the relationship between grading of urine abnormality and underlying disease; (2) the relationships among hypertension, grading of urine abnormality, and underlying disease; (3) the underlying disease of low serum C3 level; and (4) to determine whether urinary screening progressively decreased the number of students with end-stage renal disease (ESRD) annually. The results show that glomerular nephritis (GN) is still one of the major causes of urinary abnormalities. The most-important secondary GN was systemic lupus erythematosus (SLE) with lupus nephritis. One-quarter of the patients fulfilled at least four of the revised American Rheumatology Association (ARA) criteria for SLE at first administration, while the others who fulfilled only two to three of the revised ARA criteria had gradually developing signs and symptoms of SLE at follow-up. The percentage of SLE patients amongst anti-nuclear antibody (ANA) positive children was 72%. Membranoproliferative GN is very rare. The distribution of hypertension was 8.2% in grade A, 10.7% in grade B, 9.7% in grade C, and 28.9% in grade D urinary abnormality. There were statistical differences between grade D and either grade A or B or C ($P<0.05$). Lower serum C3 levels were found only in a minority of patients, including those with SLE. In this series, focal segmental glomerular sclerosis (FSGS) and active class IV lupus nephritis patients were found early enough to receive methylprednisolone pulse plus cyclosporine A therapy. To date there have been only 2 cases (5%) of FSGS with impaired renal function, and none of the lupus nephritis patients are in the predialysis stage. In conclusion, GN is still the major cause of urinary screening abnormality. ANA study is indicated in all Chinese students with abnormal urinary screening. The correlations between the severity of proteinuria and hypertension showed more-severe proteinuria in patients with nephritis as well as in those with hypertension.

Keywords Mass urinary screening · Proteinuria · Hypertension · Chronic renal insufficiency · Systemic lupus erythematosus

C.-Y. Lin (✉) · C.-C. Hsieh · W.-P. Chen · L.-Y. Yang
H.-H. Wang
Department of Pediatrics, Taipei Veterans General Hospital,
Shih-Pai, Taipei, Taiwan, 11217, Republic of China
e-mail: cylin2@vghtpe.gov.tw
Tel.: +886-2-2875-7140, Fax: +886-2-2873-9019

C.-Y. Lin · W.-P. Chen · L.-Y. Yang
National Yang-Ming University,
Taipei, Taiwan, Republic of China

Introduction

Mass urinary screening for school children has been performed in Taiwan Province by The Chinese Foundation of Health twice a year since August 1990 [1, 2]. Students who test positive receive a second urinary screening 10–15 days later. The students with abnormal urinary screening are advised to go to the hospital for advanced examination and/or adequate treatment. To date, the underlying diseases have not been reported.

Hypertension is a known factor in progression of renal disease [3]. Blood pressure measurement is performed by public health nurses on each student with positive urinary screening using the oscillometric method at health stations located in each township and district. The relationship between hypertension and each grade of urinary screening abnormalities has not been studied. C3 is measured in the sera of students who test positive. Sev-

eral types of nephritis may cause decreasing levels of serum C3 [4]. Likewise, the types of nephritis with decreasing serum C3 levels during urine screening have also not been studied in Taiwanese children. Also, the relationship between serum IgA level and IgA nephropathy (IgAN) has not been studied in Taiwan [5].

The aim of this study was to retrospectively evaluate the underlying diseases causing abnormal urinary screening of students who were then referred to our hospital. We analyzed patients with hypertension in each grade, the underlying disease with decreased serum C3 level, and the serum IgA levels in IgAN patients. To our knowledge, this study is the largest follow-up study of mass urinary screening in Taiwan.

Materials and methods

Patient population

Mass urinary screening for children has been performed in Taiwan province since August 1990 [2]. This program is carried out each semester, i.e., twice a year for elementary and junior high-school students aged 6–15 years. Each year the total number of those screened is approximately 2.7 million. Medical technologists test the urine samples for: pH, protein, occult blood, and glucose by semi-automated machines (Ames CTK-200) [6]. Around 0.3% of students showed abnormality in mass urinary screening [7]. The positive students receive a second urinary screening 10–15 days later. Blood pressure is measured by the oscillometric method and serum samples are then obtained by public health nurses at the health stations located in each township and district. All samples are kept at –20°C and transferred to the main laboratory for measurement of total protein, albumin, A/G ratio, blood urea nitrogen, creatinine, anti-streptolysin O titer, C3, cholesterol, hepatitis B surface antigen (HBsAg), IgA, and fasting blood sugar by automatic analyzer (RA2000 Serum Analyzer). Urine specific gravity was also measured. For proteinuria the urine specific gravity is at least 1.015. Specialists in pediatric nephrology analyze and identify the grades of abnormalities from A to E based on all results. Grade A is microscopic hematuria without proteinuria, grade B is light proteinuria (30–100 mg/dl) without hematuria, grade C is microscopic hematuria with light proteinuria, grade D is heavy proteinuria (over 100 mg/dl) with or without microscopic hematuria, and grade E is glucosuria. All the procedures of mass urinary screening, including sample collection, examination, reporting of results, and follow-up are performed by the Chinese Foundation of Health. It is conducted by the Department of Health, in cooperation with the Department of Education, Taiwan Provincial Government.

Each year around 6,000 elementary students and 4,000 junior high-school students, or around 0.3% of the screened students, have tested positive upon urinary screening. Of these, 34.8% were grade A, 35.0% grade B, 20.6% grade C, and 7.4% grade D. Of these, from January 1991 to August 1998, 630 students, aged 6–15 years, were admitted for at least 1 day for evaluation to the Department of Pediatrics, Taipei Veterans General Hospital. Five hundred and seventy-three students with confirmed abnormal findings have had regular follow-up. The age range is from 6 to 17 years (mean 10.21±2.8 years) and the sex distribution is 298 males and 275 females. Their follow-up time ranges from 24 to 116 months (mean 82 months).

Hypertension was defined as both systolic and diastolic blood pressure greater than 95th percentile for the respective age groups (118/78 mmHg for age 6–10 years, 124/82 mmHg for age 11–13 years, and 136/86 mmHg for age 14–18 years) [8]. Two hundred and ninety-four students had a renal biopsy. Under sonographic guidance, suction needle biopsies were performed [8]. The specimens were processed for light, immunofluorescent, and electron microscopy as described previously [9].

Indications for renal biopsy were: (1) candidates with nephrotic syndrome (NS) for cytotoxic drugs due to a frequent relapsing, steroid-dependent course or steroid nonresponsiveness; (2) NS with concomitant hypertension, hypocomplementemia, gross hematuria, or persistently decreased renal function; (3) proteinuria with or without hematuria with renal insufficiency; (4) persistent or relapsing heavy proteinuria where the diagnosis could only be determined by renal biopsy; (5) NS with heavy proteinuria in conjunction with HBsAg; and (6) persistent microscopic hematuria and/or exacerbation of unknown cause or with a family history of uremia.

NS was defined as (1) proteinuria greater then 40 mg/m^2 per hour determined quantitatively on a 24-h overnight urine collection; (2) puffy face or generalized edema; and (3) hypoalbuminemia less than 2.5 g/dl [10]. Heavy proteinuria was defined as proteinuria greater than 40 mg/m^2 per hour determined quantitatively on a 24-h overnight urine collection [10].

The lesions were histologically classified according to the World Health Organization (WHO) classification [11]:

(a) Minimal change NS (MCNS) [11, 12].
(b) Focal segmental glomerular sclerosis (FSGS) [13].
(c) IgAN or Berger disease [9].
(d) IgM mesangial nephropathy (IgMN). Criteria included: (1) a diffuse increase of mesangial cellularity with more than four mesangial cells in each cluster; (2) immunofluorescence that demonstrated at least two different sources of fluorescein isothiocyanate (FITC)-labelled anti-IgM sera deposits in the mesangium; and (3) electron-microscopic studies also showing electron-dense mesangial deposits corresponding to the immunofluorescence findings [14].
(e) Hepatitis B virus membranous nephropathy (HBVMN) [15].
(f) Lupus nephritis (LN). Criteria were: (1) fulfillment of at least four of the revised American Rheumatism Association (ARA) criteria for the diagnosis of systemic lupus erythematosus (SLE); (2) renal lesion classified according to the WHO system [11] if renal biopsy was performed.
(g) Purpura nephritis (PN) [16].
(h) Rapidly progressive glomerulonephritis (RPGN): defined as deterioration to renal failure within 3 months from normal creatinine clearance (C_{Cr}) to C_{Cr} less than 10 ml/min [17].

Chronic renal insufficiency (CRI) was defined as: serum Cr over 1.7 mg/dl before end-stage renal disease (ESRD) (C_{Cr} less than 20 ml/min per 1.73 m^2); structural renal abnormalities being excluded.

Low serum C3 level was defined as lower than 67 mg/dl, based on half level from our laboratory of normal values [18].

Benign hematuria was defined as persistently normal serum Cr and renal function (C_{Cr}) with no family history of CRI or ESRD and normal light microscopic findings on renal biopsy if performed. Thinning of the basement membrane on electron-microscopic examination was also included. The children with glucosuria (grade E) were not included in this study.

Statistical analysis

For statistical analysis, self-constant estimation, Student's *t*-test, Wilcoxon rank sum test, chi-squared test, and logistic regression analysis were used. For studying the relationship between serum IgA level in each age group and IgAN, the Pearson correlation coefficient was used.

Table 1 The diagnosis of patients with grade A, B, C, and D abnormalities on mass urinary screening (*SLE* systemic lupus erythematosus, *IgAN* IgA nephropathy, *IgMN* IgM mesangial nephropathy, FSGS focal segmental glomerulosclerosis, *HBVMN* hepatitis B virus membranous nephropathy, *MCNS* minimal change nephrotic syndrome, membranoproliferative glomerulonephritis, *APGN* acute post-streptococcal glomerulonephritis, *UTI* urinary tract infection, *VUR* vesicoureteral reflux, *ATN* acute tubular necrosis, CHD coronary heart disease, *UPJ* ureteropelvic junction, *RPGN* rapidly progressive glomerulonephritis)

	A	B	C	D	Total
SLE	84	7	30	48	169
IgAN	31	1	12	17	61
IgMN	1	2	3	32	38
FSGS	1	0	2	35	38
HBVMN	1	1	2	9	13
MCNS	1	2	0	11	14
Thin basement membrane disease	9	0	1	0	10
MPGN	1	0	0	1	2
Mesangial proliferative nephropathy	1	0	0	0	1
Chronic GN	0	0	0	1	1
Diffuse crescentic GN	0	0	0	1	1
APGN	5	0	2	2	9
Nephritis (unknown origin)	13	2	5	2	22
UTI	18	0	0	4	22
VUR	1	0	2	2	5
Hypercalciuria	17	0	1	0	18
Benign hematuria	38	0	2	0	40
Purpura nephritis	3	1	0	6	10
Orthostatic proteinuria	0	8	8	7	23
Cystitis	2	1	0	0	3
Hydronephrosis	1	0	0	0	1
Blunt injury	1	0	1	0	2
Hemophilia	1	0	0	0	1
Diabetic insipidus	1	0	0	0	1
Broncho-pulmonary dysplasia	1	0	0	0	1
Turner syndrome	1	0	0	0	1
Renal dysgenesis	1	0	0	0	1
ATN	0	0	1	0	1
Hemolytic uremic syndrome	0	0	0	2	2
Uremia with CHD	0	0	0	1	1
Polycystic kidney	0	0	0	1	1
UPJ stenosis	0	1	0	0	1
Alport syndrome	0	0	0	4	4
Hypertensive nephropathy	0	0	0	2	2
RPGN	0	1	5	1	7
Unknown	32	1	5	8	46
Total	266	28	82	197	573
Percentage	46.4%	4.9%	14.3%	34.4%	100%

Results

The correlations between underlying disease and urine abnormality

After regular follow-up, the distribution of grades according to the classification of mass urinary screening and underlying disease in children is shown in Table 1. There were 266 cases (46.4%) assessed as grade A with microscopic hematuria only, 28 cases (4.9%) were grade B with light proteinuria only, 82 cases (14.3%) were grade C with microscopic hematuria and light proteinuria, and 197 cases (34.4%) were grade D with heavy proteinuria.

The most-important secondary nephritis in our study was SLE. All the patients diagnosed with SLE had initial urinary abnormalities with positive anti-nuclear antibody (ANA) assays. One-quarter of the patients fulfilled at least four of the ARA criteria at first presentation, others who fulfilled only two or three ARA criteria had gradually developing signs and symptoms of SLE at follow-up, especially doing adolescence. The most-frequent extrarenal findings were hematological involvement, and skeletal and joint involvement. The percentage of SLE in ANA-positive children was 72%. The correlations between histological classification and mass urinary screening findings of these patients are shown in Table 2. More than half of each grade of SLE patients with mass urinary screening abnormalities received a renal biopsy. Even lupus patients with grade A urinary abnormality could have histological findings of class III or class IV. Of course, the majority of lupus patients with grade D urinary abnormality had higher histological classifications than grade A, B, and C patients.

In grade A urinary abnormality, the majority of underlying diseases were IgAN and benign hematuria. Most children with a family history of benign hematuria did not progress to ESRD. We have proved by renal biopsies that some of the cases were thin basement membrane disease. In grade B urinary abnormality, orthostatic proteinuria was the most-important underlying disease. In grade C, IgAN and SLE nephritis were the major causes. Various types of primary and secondary GN were the major causes of grade D urinary abnormality. Secondary

Table 2 The distribution of histological classification and mass urinary screening findings in children with SLE who received renal biopsy

Patient no.	Mass urinary screening abnormality			
	Grade A	Grade B	Grade C	Grade D
Class IIa	1	0	0	0
Class IIb	41	4	15	8
Class III	2	0	1	3
Class IV	2	0	0	14
Class V	0	0	0	5
Total	46	4	16	30

GN included lupus nephritis, HBVMN, and PN. RPGN is not common in Chinese children. However, the initial presentation is like nephritis and always found in grade C urinary abnormality.

Correlations among hypertension, underlying disease, and urine abnormality

Ninety cases (15.7%) were accompanied by hypertension evident at both urinary screening and admission. The distribution was 22 cases in grade A, 3 cases in grade B, 8 cases in grade C, and 57 cases in grade D urinary abnormality. The majority of underlying diseases were GN (65%), including SLE (29%) and primary GN (26%). There were statistical differences between grade D and either grade A or B or C ($P<0.05$). The correlation between severity of proteinuria and hypertension showed more-severe proteinuria in patients with nephritis as well as in those with hypertension. Controlling for the covariates via logistic regression analysis, the adjusted odds ratio (OR) was calculated. The results showed that heavy proteinuria with hypertension of systolic pressure over 130 mmHg and diastolic pressure over 90 mmHg were significant factors in disease progression to CRI (OR 5.24 and 6.08 respectively, $P<0.001$).

The correlation between serum IgA level and IgAN

The distribution of IgAN included all grades. Of the 61 cases of IgAN, 26 had elevated serum IgA levels. There was a positive correlation between serum IgA levels of IgAN patients and their ages. There were 12 patients with grade A, 6 with grade C, and 8 with grade D. There was no patient with grade B. There was no correlation between grade of IgAN and serum IgA level. However, 2 cases with very high serum IgA levels were noted; 1 in grade A with a serum IgA level of 928 mg/dl and the other in grade C with a serum IgA level of 955 mg/dl. Renal biopsy demonstrated IgAN in both cases.

The underlying disease of patients with low serum C3 level

Only 30 patients with underlying diseases of SLE, HBVMN, acute post-streptococcal GN, FSGS, and hemolytic uremic syndrome had serum C3 levels lower than 67 mg/dl.

The efficacy of mass urinary screening

Before mass urinary screening, all RPGN cases progressed to ESRD. In this series, 2 cases (28.5%) were discovered early enough to preserve renal function. These two patients received methylprednisolone pulse therapy and plasmapheresis. After the disease was stabilized, cyclosporine A (CsA) was used for maintenance therapy.

For each screened child, we routinely checked ANA. When patients were ANA positive, they were regularly followed in our outpatient clinic. If patients had heavy proteinuria or progressively increasing serum Cr levels, renal biopsy was performed to estimate the severity of renal involvement [19]. The choice of therapies depended on the clinical status. During acute exacerbation, methylprednisolone pulse therapy followed by intravenous cyclophosphamide was used [19]. If the patients showed no response to the above treatments or the clinical course was complicated with severe leukopenia, high-dose intravenous immunoglobulin was given after being proven to be effective in the in vitro test [20]. For those with severe edema and refractory to treatments with albumin and diuretics, we tried intravenous prostaglandin E_1 therapy [21]. For the prevention of growth retardation induced by corticosteroid, we used CsA instead of prednisolone and cyclophosphamide when the serum Cr was lower than 1.5 mg/dl. In patients with serum Cr over 1.5 mg/dl, we used mycophenolate mofetil (CellCept) instead of CsA [19]. Therefore, before mass urinary screening, around 20% of patients with class IV nephritis progressed to CRI in the 10-year follow-up. After mass urinary screening, no lupus nephritis patient progressed to CRI.

Before mass urinary screening, around 50% of FSGS patients progressed to CRI or ESRD in the 10-year follow-up. After mass urinary screening, FSGS patients were given methylprednisolone pulse plus CsA therapy.

To date, only 2 patients (5%) have progressed to CRI and no patient needs dialysis.

Discussion

Previous data from the Chinese Foundation of Health showed that urinary abnormalities were present in 0.39% of students tested by mass screening. Of these, 34.8% were grade A, 35.0% grade B, 20.6% grade C, 7.4% grade D, and 2.14% grade E with glucosuria in 1997. This distribution of grades A to D is different from ours. One reason for this difference may be that some parents did not heed the recommendations for follow-up, another reason may be that patients with serious renal problems always went to our pediatric nephrology section. Therefore, we have more grade D patients.

According to our results, SLE with lupus nephritis is the most-important disease resulting in a urinary abnormality detected by mass screening. Before adolescence, these children are mostly without butterfly facial rash or other atypical skin lesions. Renal and hematological involvement are two of the most-frequent initial manifestations in Chinese SLE patients. The prevalence of SLE in Taiwan is unknown, as there has been no nationwide study. However, in our section of pediatric immunology and nephrology, we have more than 300 SLE patients who are regularly followed in our outpatient clinic. There are also around 2,000 SLE patients regularly followed in our adult rheumatology outpatient clinic. SLE is still the most-important autoimmune disease in Taiwan. Therefore, each child with abnormal urine needs to have an ANA assay. Ten years ago, the second most-prevalent secondary GN in Taiwan was HBVMN [15]. After nationwide hepatitis B vaccination began in 1984, both HBV carrier and HBVMN patients have decreased dramatically. Henoch-Schönlein purpura nephritis is also an important cause of ESRD in Japan [3,4]. In our experience, anaphylactoid purpura is not uncommon in Taiwan [7]. However, renal involvement either with nephritic or nephrotic syndrome is less than that seen in Japan [7]. MPGN is also very rare in Taiwan [7].

In the present study SLE was the most-common cause of hematuria, benign hematuria was the second cause, and IgAN was the third. Even after a series of studies, 32 patients in class A still have no proper diagnosis. This is similar to the report of Boineau and Lewy [22].

Orthostatic proteinuria has been reported to be the most-important cause of light proteinuria, accounting for 60% of all children and 75% of adolescents with proteinuria [23]. Our findings are similar. The most-common causes of persistent, non-orthostatic, non-nephrotic pathological proteinuria in children were MPGN, FSGS, and IgAN [24]. This is similar to our results. Because most patients with MCNS are characterized by a good initial response to corticosteroid treatment and do not require renal biopsy [25], here the percentage of MCNS is less than that of lupus nephritis and other GN.

In our study, hypertension was detected not only in grade D, but also in grades A, B, and C. Only 22 of the 266 children with hypertension were in grade A. Therefore, the significance of hypertension is difficult to assess.

The present study demonstrates that SLE is the major cause of decreasing serum C3 levels. The percentage decrease in serum C3 is low in post-streptococcal GN (PSGN), because at the time of testing the patients with PSGN were not in the acute phase. The decreased C3 levels in our PSGN patients returned to normal within 6–8 weeks of disease onset.

Serum IgA levels in the general population increase with age. In general, serum IgA levels of IgAN patients, after correcting for age, also increase with age. This finding is similar to another study in 1966 [26]. However, in our 61 IgAN patients, levels of serum IgA above 2 standard deviations for age were noted in 26 patients (42.6%), which is similar to the results of Clarkson et al. [27]. The distribution of elevated serum IgA in each class of IgAN patients was as follows: grade A, 39% (12/31); grade C, 50% (6/12); and grade D, 47% (8/17). There was no correlation between serum IgA level and pathological grading. Two patients had very high serum IgA levels (928 mg/dl and 955 mg/dl, respectively). Renal biopsy demonstrated IgAN in both cases. However, one was grade I without hypertension and the other was grade IV with focal sclerosis and hypertension. This suggests that a very high level of serum IgA with hypertension is probably a poor prognostic sign.

We aimed to ascertain whether mass urinary screening could progressively decrease the number of students progressing to ESRD and needing dialysis. Our results demonstrate that mass urinary screening improved the outcome of patients with RPGN, FSGS, and lupus nephritis. The result was especially good in lupus nephritis [2,19]. In our previous study, no lupus patient detected by mass urinary screening progressed to dialysis [2]. Our data also demonstrated that 6% of lupus nephritis patients who were not detected by mass screening progressed to ESRD [25]. In the present study, there were 7 patients with RPGN. The optimal time for the treatment of RPGN is only several weeks after onset of disease. There were only 2 patients detected early enough to stop the disease progression. The other 5 patients have already progressed to ESRD. Around 30% of the FSGS patients with grade C and D urinary abnormalities have progressed to ESRD in the past 5 years. Of the 37 screened FSGS patients with grade C and D urinary abnormalities, treated with methylprednisolone pulse therapy followed by CsA treatment and an angiotensin converting enzyme inhibitor to control blood pressure and cardiac function, so far only 2 patients have progressed to CRI. From the data of the Chinese Foundation of Health, the number and percentage of patients with heavy proteinuria detected by mass urine screening were 1,289 patients (10.5%) in 1992 and 705 patients (7.1%) in 1996, with a statistical difference of $P<0.05$ [26]. The absolute number and percentage of patients with heavy

proteinuria decreased annually. Heavy proteinuria is one of the factors causing renal disease progression to CRI. The incidence of new dialysis cases per year in children 6–15 years old in Taiwan was 19 per million in 1992 and 8 per million in 1997. The percentage of children requiring dialysis due to GN decreased from 63.2% to 47.0%. Taken together, more-severe proteinuria in patients with nephritis as well as those with hypertension predisposes to progression to CRI. Therefore, by early detection with urine screening and early treatment, we may even cure or delay the time on dialysis in these predialysis CRI patients and maintain their growth and development.

In summary, the majority of students with abnormal urinalysis detected by mass urinary screening are asymptomatic. In these Chinese students, the most-common pathology in secondary nephritis is lupus nephritis. ANA assay is indicated for each student with abnormal urinary screening. ANA is much more useful in this setting than C3 levels. GN is still the major cause of abnormal findings in these students. The correlation between severity of proteinuria and hypertension shows more-severe proteinuria in patients with nephritis, as well as in those with hypertension.

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