Journal of the Formosan Medical Association (2017) xx, 1–9

Available online at www.sciencedirect.com

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journal homepage: www.jfma-online.com

Original Article

A large retrospective review of persistent proteinuria in children

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Received 5 April 2017; received in revised form 13 August 2017; accepted 5 September 2017

KEYWORDS
Proteinuria;
Dipstick urinalysis;
Prevalence

Background: Proteinuria is a common finding in children. It may be due to a benign cause, but it can also represent early renal injury. Of children with persistent proteinuria noted in mass urine screening programs, 35% have a urine protein level greater than 100 mg/dl and many of them are associated with many underlying renal diseases. The aim of this study was to identify the etiology and prognosis of persistent proteinuria in children.
Methods: We collected data on urine protein from January 2011 to December 2016 in a tertiary medical center. During this 6-year period, 37,645 children received urinalysis, and 2.3% were found to have persistent proteinuria. We reviewed their medical charts for clinical diagnoses and renal function. According to the level of persistent proteinuria, we divided the children into three groups (mild, moderate, and severe).
Results: Most clinical diagnoses in the mild persistent proteinuria group were not readily identifiable. In the moderate and severe groups, acute kidney injury was the leading cause of significant proteinuria, followed by systemic lupus erythematosus, steroid-sensitive nephrotic syndrome, and congenital urogenital tract anomalies. There were significant differences in the rate of chronic renal insufficiency among the three groups. Prematurity with extremely low birth weight was also a major factor associated with pediatric chronic renal insufficiency.
Conclusions: Assessing persistent proteinuria in children is important due to the diverse range of associated diseases or mortality.

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http://dx.doi.org/10.1016/j.jfma.2017.09.004

Introduction

Proteinuria is a common laboratory finding in children. It can be a transient condition during a fever, dehydration, exercise, or stress, however it can also be persistent. Orthostatic proteinuria is the most common condition in persistent proteinuria. Chandar et al. reported that after excluding transient proteinuria in children with isolated proteinuria, 72% had orthostatic proteinuria.[1] Furthermore, persistent proteinuria not explained by orthostatic proteinuria can increase the risk of underlying renal diseases.[2,3]

In a study conducted by Lin et al. in Taiwan, a mass urinary screening program among students aged 6−15 years showed that 7% had abnormal results in second urinalysis from samples collected in the morning.[4] In follow-up, 35% of these children with persistent proteinuria had a urine protein level greater than 100 mg/dl (equivalent to 2 + in a dipstick test) with or without concomitant hematuria, and they also had many different underlying renal diseases.[5]

Simple dipstick and sulfosalicylic acid (SSA) tests are convenient methods to detect urine protein. However, false-positive results can still occur with the SSA test in children due to contaminated specimens, prescriptions of certain antibiotics (penicillin, cephalosporin or sulfonamide), or after the administration of radiographic dyes.[2]

To the best of our knowledge, no large-scale study has focused on the etiology of proteinuria among children at a hospital. Thus the aim of this study was to review all urinalysis results of children under 18 years of age at our hospital over a 6-year period, and evaluate the spectrum of diagnoses in those with significant persistent proteinuria.

Methods

Study population

We obtained urinalysis results of all patients aged less than 18 years from the database of National Taiwan University Hospital (NTUH), a tertiary medical center in Taiwan, from January 2011 to December 2016. The children with a dipstick test (Aution Sticks 10 EA; Arkray, Kyoto, Japan) result showing urine protein 1 + or greater with a urine pH 8.0 or higher received further urine protein verification with the SSA test. The children with proteinuria 1 + or greater received repeat urinalysis in the morning, and further quantitative assessments including timed urine collection of urine protein or spot morning urine protein to creatinine ratio were performed in some cases. For persistent proteinuria other than orthostatic proteinuria, additional studies were arranged. The study protocol was approved by the Institutional Review Board of National Taiwan University Hospital (201608049RIN).

The two urine samples showing proteinuria had to be taken at least 2 weeks apart to rule out transient proteinuria and confirm persistent in this study. We reviewed the medical charts of all children with persistent proteinuria to identify their clinical diagnoses. A 1 + urine protein result may not reflect a serious underlying disease as it could be transient proteinuria or a false-positive result; therefore, we defined proteinuria ≥2 + as significant proteinuria. To explore whether the severity of proteinuria was correlated with abnormal renal function, we further divided the children into three persistent groups: persistent 1 + group as mild-persistent group, persistent ≥3 + group as severe-persistent group and moderate-persistent group was the severity of proteinuria in the between with the former two. All of the urine protein data in the latter two groups was defined as being significant proteinuria. We then compared the prevalence of abnormal renal function in the past 1 year among the three groups. The serum creatinine level was measured using a chemical analyzer (Beckman Coulter AU5800) with the compensated Jaffe method traceable to isotope dilution mass spectrometry. We used the bedside Schwartz formula to obtain the estimated glomerular filtration rate (eGFR).[6] For the children who turned 18 years of age during the follow-up period, eGFR was obtained using the Modification of Diet in Renal Disease (MDRD) study equation. We apply KDIGO guideline to define acute kidney injury (AKI). Chronic renal insufficiency (CRI) was defined as eGFR < 90 ml/min/1.73 m^2 for children above 2 years of age, or a serum creatinine level above normal range for those below 2 years of age for over three months. GFR categories were assigned as KDIGO guideline.

All the number in our table represented person and the number in parentheses following each number was the percentage in each group; the number of our result in each subgroup was presented by mean ± standard deviation.

Statistical analysis

Age was presented as median with interquartile range. Pearson's chi-square test with Yates' continuity correction was used to compare frequencies. Statistical analyses were performed using Microsoft Excel (2011), version 14.4.6. A P value < 0.05 was considered to be statistically significant.

Results

In total, 37,645 children underwent urinalysis at our hospital in the 6-year study period, including 21,832 (58.0%) boys and 15,813 (42.0%) girls. Of these children, 6507 (17.2%) had proteinuria on at least one occasion. Proteinuria was first noted in the following situation: outpatient clinic visit (37.8%), emergency room (30.3%), and hospitalization (31.9%). Of these 6507 children, 4876 had urinalysis only once and 776 had two or more urine samples but not in an appropriate time frame to present persistency, and thus they were excluded. The remaining 855 (2.3%) children had persistent proteinuria, including 303 (0.8%) with mild-persistent proteinuria, 410 (1%) with moderate-persistent proteinuria, and 142 (0.4%) with severe-persistent proteinuria (Fig. 1). The median age at presentation with significant proteinuria was 10.2 years. The prevalence was higher in girls (2.4%) than in boys (2.2%). The mean follow-up duration of children with moderate persistent proteinuria and severe persistent proteinuria was respectively 1158.26 ± 710.9 days and 1287.94 ± 604.08 days. There was no significant difference between both groups. We were unable to identify the underlying diagnoses in most of the mild-persistent group, and thus only the final diagnoses of the moderate-persistent and severe-persistent groups are

Please cite this article in press as: Chang-Chien C, et al., A large retrospective review of persistent proteinuria in children, Journal of the Formosan Medical Association (2017), http://dx.doi.org/10.1016/j.jfma.2017.09.004