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Febrile Proteinuria in Children: an Evaluation of Causes and Finding

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Abstract

Introduction. Transient proteinuria can be caused by high fever. It does not involve underlying kidney disease. Present study was designed to evaluate the prevalence of transient proteinuria in pediatrics with febrile diseases.

Method. One hundred eighty six febrile children were studied in one year according to enumeration method between August 2017 and 2018. Patients with renal diseases were excluded. The urine analysis was taken at the time of admission and after the fever improvement. A blood sample was taken and CRP, ESR and WBC were evaluated.

Results. Proteinuria was detected in 21 patients (11.4%). Among them 8 patients (38%) were male and 13 patients (62%) were female with the average age of 1.87±1.94 years. There was no difference between sex and age in patients with or without proteinuria ($p>0.05$). The intensity of proteinuria at the time of admission in 4 patients (19%) was trace, in 12 patients (57%) was one plus (+), in 4 patients (19%) was two plus (++) and in 1 patient (5%) was three plus (+++). Proteinuria disappeared after fever improvement in all patients. Febrile convulsion and gastroenteritis were the common diagnosis. The mean of fever, SG, ESR and WBC in children with proteinuria were 38.78±0.56 ^{0}C, 1017.58±8.58, 45.05±10.92 and 13247.05±6501.06 cell/mm^3 respectively. CRP was positive in 16 patients (76%) and 73 patients (44.24%) with and without proteinuria. Difference was significant ($p=0.01$).

Conclusion. Prevalence of proteinuria in febrile children was 11.4%. Gastroenteritis and febrile convulsion were the most common diseases in febrile children with proteinuria.

Key words: child, fever, proteinuria

Introduction

The excretion of protein in urine is a usual laboratory finding in pediatrics [1]. In spite of proteinuria is generally benign, but it can be a sign for a major systemic disease or renal disorder [2,3]. Proteinuria is defined as urinary protein excretion more than 150 mg/day [4]. It may result from non-pathological (stress, fever, exercise) or pathological (kidney diseases) conditions. Asymptomatic proteinuria may be transient or persistent [5]. While transient proteinuria is a benign state and almost requires no intervention, persistent proteinuria can be the first marker of kidney disease [1].

The relationship between proteinuria and fever was first described many years ago. In spite of its importance the pathogenesis are not fully understood, it is usually considered to be a benign and transient occurrence [6]. Despite transient proteinuria being often benign, persistent proteinuria can be a marker of progressive kidney disease and is related with increased cardiovascular morbidity [7]. So, proteinuria presents a challenge to the primary care physician in regards to distinguishing benign proteinuria and proteinuria that requires referral to the nephrologists [8]. The glomerular basement membrane provides the barrier between the urinary space and blood. This barrier is negatively charged because the existence of glycosaminoglycans and glycocalyx [9]. Therefore, the nature of the crossable particles is dependent to the molecular size and the charge of the particle. The major of the proteins that are filtered through the barrier are reabsorbed by the proximal tubule, and the residuals are degraded and so excreted as low-molecular weight proteins. Albumin, transferrin and macroglobulin constitute 30% of proteins. The remaining (70%) is the Tamm-Horsfall protein which are secreted by the Henle loop. Increased urinary protein excretion can result from increased filtration across the glomerular barrier (glomerular proteinuria), decreased reabsorption from the proximal tubule (tubular proteinuria) or increased secretion of protein from the tubules (secretory proteinuria) [9].

Present study was carried out to determine the prevalence, causes, clinical and laboratory symptoms of proteinuria in febrile children referred to emergency room of Dr. Sheikh hospital, Mashhad University of Medical Sciences, Mashhad, Iran from August 2017 to 2018.

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Materials and methods

A cross sectional study was performed in emergency room of Dr. Sheikh hospital, Mashhad University of Medical Sciences, Mashhad, Iran from August 2017 to 2018. This study was approved by Mashhad University Medical Ethics Committee (code: IR.MUMS.fm.REC. 1396.803). The study participants included were 186 admitted febrile children, aged less than 18 years. Fever was defined as a temperature rise above 38^0C axillary. Parental informed consent was obtained prior to the study. Since renal diseases in general are associated with abnormal urinalysis, patients with renal disease diagnosis were excluded on the basis of the physical examination and normal urinalysis, either at the time of the fever or after. Therefore 5 patients with febrile UTI were excluded in spite of positive proteinuria. Temperature, duration of fever and pulse rate was checked for all patients. Also a blood sample was taken and parameters including WBC (using Sysmex kx-21N, automated hematology analyzer), ESR (through infrared technique using Sed rate device (Lena)) and CRP (qualitative assessment by agglutination latex) were measured for each patient at the time of admission. A midstream, clean-catch specimen was collected in toilet trained patients and in non toilet trained subjects, the sample was collected using urine bag or urethral catheterization. All urine samples were sent to the laboratory within an hour. Urinalysis was done at the time of admission and after fever improvement. The urine protein was assessed according to dipstick method. False positive samples were excluded using sulfosalicylic acid 3%. The WBC more than 15000 cell/mm^3 was considered abnormal.

Sample size

The sample size study population was 186 patients in one year according to enumeration method between August 2017 and 2018.

Analysis

Statistical analysis was performed using SPSS windows program version 16 (SPSS Institute, Inc., Chicago, IL, USA). All experimental values are presented as Means ± standard deviation (SD). Two groups were compared using independent student t test or nonparametric equivalent. Relationship between qualitative variables was evaluated by chi-square test. P values less than 0.05 was considered statistically significant.

Table 1. Demographic characteristics of febrile patients

Variable	Positive proteinuria (n=21) Frequency/mean±SD	Negative proteinuria (n=165) Frequency/mean±SD	P value
Sex			
Male	8	93	0.12*
Female	13	72	
Age (year)	1.87±1.94	1.99±1.84	0.83#

*Chi square, # Independent t test

Table 2. Characteristics of patients with febrile proteinuria

Case number	Age	Gender	Temperature (^{0}C)	Urine protein	Diagnosis
1	8 M	F	38.5	1+	Kawasaki
2	8 M	F	38.5	1+	Febrile convulsion
3	6 M	M	39	1+	Others
4	7 M	M	38.5	1+	Gastroenteritis
5	2 M	M	38.9	1+	Gastroenteritis
6	5.5 Y	F	38.2	1+	Febrile convulsion
7	1.2 Y	F	38.5	1+	Febrile convulsion
8	1 Y	F	40.5	1+	Febrile convulsion
9	6 Y	F	38.5	1+	Gastroenteritis
10	3 Y	F	39.5	1+	Pneumonia
11	7 M	F	38.5	1+	Febrile convulsion
12	1.5 Y	F	38.8	1+	Gastroenteritis
13	2.5 Y	M	38.5	2+	Gastroenteritis
14	9 M	F	38.5	2+	Febrile convulsion
15	7 M	M	38.5	2+	Gastroenteritis
16	3 M	F	39.4	2+	Gastroenteritis
17	8 M	M	38.5	3+	Febrile convulsion
18	4 Y	F	38.7	trace	Pneumonia
19	8 M	M	38.5	trace	Gastroenteritis
20	7 M	F	39.5	trace	Viral infection
21	3.5 Y	M	38.5	trace	Febrile convulsion

M= month, Y= year, F= female, M= male

Results

Of the 186 included children, 85 cases (45.7%) were female and 98 cases (54.3%) were male. The average age of patients was 1.98±1.84 years. The minimum age was 40 days and the maximum was 9 years. The mean fever temperature and pulse rate were 38.66±0.56ºC and 125.49±19.9 pulse/minute respectively. Duration of fever in 112 patients (63%) was 48 hours or less.
Proteinuria was detected in 21 cases (11.4%). Among the 21 patients with proteinuria 8 patients (38%) were male and 13 patients (62%) were female with the average age of 1.87±1.94 years. There was no significant difference between sex and age in patients with or without proteinuria (p=0.12 and p=0.83 respectively). Demographic characteristics were presented in table 1. The intensity of proteinuria at the time of admission in 4 patients (19%) was trace, in 12 patients (57%) was one plus (+), in 4 patients (19%) was two plus (++) and in 1 patient (5%) was three plus (+++). Characteristics of patients with febrile proteinuria were presented in table 2. A second UA was obtained from 19 cases with proteinuria a week after fever improvement (Two patients did not return for follow up). Proteinuria disappeared after fever improvement in all patients.
Final diagnosis in febrile patients with or without proteiuria was present in table 3. Febrile convulsion and gastroenteritis were the most common diagnosis in the patients. There was not significant relationship between proteinuria and final diagnosis (p=0.21).

Table 3. Final diagnosis of febrile patients

Final diagnosis	Positive proteinuria (n=21)	Negative proteinuria (n=165)	P value*
Gastroenteritis	7 (20%)	32 (80%)	0.21
Febrile convulsion	8(8.4%)	87 (91.6%)	
Pneumonia	2 (14.3%)	12 (85.7%)	
Kawasaki	1 (33.3%)	2 (66.7%)	
Viral infection	1 (5.3%)	18 (94.7%)	
Other diseases	1 (7.1%)	13 (92.9%)	

*Chi square test

Table 4. Comparison of laboratory variables between patients with and without proteinuria

Laboratory variables	Positive proteinuria (n=21)	Negative proteinuria (n=165)	P value
Fever	38.78±0.56^{0}C	38.65±0.56^{0}C	0.37*
SG	1017.58±8.58	1012.01±7.87	0.15*
ESR	45.05±10.92	27.47±28.65	0.02*
WBC (cell/mm3)	13247.05±6501.06	11500±5961.11	0.25*
Positive CRP (%)	76%	44.24%	0.001#

SG: specific gravity, ESR: erythrocyte sedimentation rate, WBC: white blood cell, CRP: C reactive protein, *Independent t test, # Chi square test

The mean±SD of fever, SG, ESR and WBC in children with proteinuria were 38.78±0.56^{0}C, 1017.58±8.58, 45.05±10.92 and 13247.05±6501.06 cell/mm^3 respectively. The mean±SD of fever, SG, ESR and WBC in children without proteinuria were 38.65±0.56^{0}C, 1012.01 ±7.87, 27.47±28.65 and 11500±5961.11 cell/mm^3 respectively. Difference was not significant in fever and WBC (p= 0.37 and p=0.25 respectively) (Table 4).
Among studied children CRP was positive in 16 patients (76%) and 73 patients (44.24%) with and without proteinuria respectively. Difference was significant (p=0.01).
Among the 186 febrile children, microhematuria was detected in 11 patients (5.9%) in the first urine sample. Among these, 5 patients (45.45%) were diagnosed with positive proteinuria. Also microhematuria was detected in 1 patient (5.3%) with positive proteinuria in the second urine sample.

Discussion

One hundred eighty six patients were studied for the evaluation of proteinuria in their febrile conditions. Proteinuria was detected in 21 cases (11.4%) in range of trace to three plus (3+). Proteinuria disappeared after fever improvement in all patients. Gastroenteritis and febrile convulsion were the most common diagnosis in febrile children with proteinuria.
The normally excretion of protein in urine is variable. The average of urinary protein in children is about 75-100 mg/24 hours [4]. The mechanism of normal proteinuria is not fully understood. But probably it is influenced by the relative rates of protein filtration at the capillary basement membrane and the rate of proximal tubular re-absorption [10]. Proteinuria could be considered benign if it disapears when fever abates. As seen in present study, the proteinuria has been resolved after treatment in all patients indicating the importance of febrile conditions in benign proteinuria. Usually, only repeat urinalysis is necessary to confirm transient nature of this phenomenon in majority of cases.
Proteinuria has been seen in a number of conditions in which there is no identified kidney disease including

fever, exercise, stress, or cold exposure [11]. It may also be caused by hemodynamic alterations in glomerular blood flow.

Numerous hypotheses have been suggested to describe the proteinuria which may be seen with fever [1]. One theory suggests that proteinuria is occurred in response to an infectious agent that triggers an inflammatory response in the kidney [12,13]. However, Welty [14] showed that fever could lead to an increased protein excretion even in the absence of demonstrable infection. King and Baldwin [15] showed that fever induced stress caused the release of Adrenal hormones.

Similarly, Melvin *et al*. in a study on 198 febrile patients reported that 11 cases (5.6%) have proteinuria with variable causes including pneumonia, septicemia, otitis media and others [6]. The results of Melvin are in agreement with our study.

Valavi *et al*. in a study on children with febrile UTI reported that the prevalence of proteinuria was 41% [16]. In another study on children with kavasaki, it was reported that the prevalence of proteinuria was 53.9% [17].

In present study among 168 febrile patients, 21 cases have transient proteinuria in grade of trace to 3+. These patients did not had any proteinuric renal disorder. According to present study the febrile convulsion and gastroenteritis were the most common causes responsible for transient proteinuria. Proteinuria is a common finding in pediatric practice, often detected incidentally.

A CRP test may be used to find or monitor conditions that cause inflammation including bacterial infections, fungal infection and inflammatory bowel disease. In our study there was significant relationship between proteinuria and positive CRP which may be due to bacterial infection. Also in present study ESR was significantly higher in children with proteinuria compared with children without proteinuria which confirmed the probability of infection presence in children with proteinuria.

Conclusion

Prevalence of proteinuria in febrile children in absence of renal diseases was 11.4%. Gastroenteritis and febrile convulsion were the most common diseases in febrile children with proteinuria. More studies with larger sample size were suggested to confirm the result of present study.

Limitations

There is no quantification assessment of proteinuria. Also there are no data if the proteinuria is tubular or glomerular.

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Conflict of interest statement. None declared.

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