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Original Article

Discrimination of culture negative pyelonephritis in children with suspected febrile urinary tract infection and negative urine culture results

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Proteinuria;
Urine sodium-potassium ratio

Abstract *Background:* We investigated whether the C-reactive protein (CRP) level, urine electrolytes, and urine sodium-potassium ratio (uNa/K) could be useful markers for discriminating children with culture negative pyelonephritis (CNP) from children with suspected febrile urinary tract infection (fUTI) and negative urine culture results.
Methods: We examined 264 children experiencing their first fUTI consecutively admitted to our hospital between January 2011 and October 2014. Blood tests (CRP, white blood cell count [WBC], erythrocyte sedimentation rate [ESR], electrolytes) and urine tests (urine protein to creatinine ratio [uProt/Cr], electrolytes, uNa/K) were performed upon admission. All children with fUTI underwent 99m-dimercaptosuccinic acid (DMSA) scanning at admission. Data were compared between children with acute pyelonephritis (APN), CNP, lower UTI and controls. Using multiple logistic regression analysis (MLRA), the ability of these parameters to predict a cortical defect on DMSA scan (APN and CNP) was analyzed.
Results: The laboratory findings of CNP children were similar with those of APN children except uProt/cr. The CRP level, WBC count, and ESR were higher in children with CNP, while uNa and uNa/K were lower than in children with lower UTI and control. By MLRA, CRP levels and uNa/K were the most relevant factors for predicting a cortical defect on DMSA scan ($P = 0.002$, <0.001, respectively).
Conclusion: We conclude that the combination of CRP or WBC and uNa/K are useful for discriminating children with CNP from children with suspected fUTI and negative urine culture results.

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Introduction

Culture negative pyelonephritis (CNP) is often identified after acute pyelonephritis (APN) is confirmed by a 99m-Tc-dimercaptosuccinic acid (DMSA) renal scan or computed tomography among patients clinically diagnosed with febrile urinary tract infection (fUTI) because of abnormal urinalysis and the absence of other causes of fever at visit but a negative urine culture. The number of children with CNP is not too small to be neglected. Tsao et al. reported that among children with UTI with a cortical defect on DMSA scanning, 31% had negative results on urine culture with samples obtained by suprapubic aspiration.[1] CNP is a important disease leading to acquired renal scars in young children. However, patients with CNP can be neglected from appropriate treatment of APN due to negative urine culture result. It is challenging to find markers able to predict cortical defect lesions on DMSA scans in fUTI children, and it is an unacceptable strategy to perform DMSA in all patients with a negative urine culture.

In the present study, we aimed to investigate whether the C-reactive protein (CRP) level, urine electrolyte values, and urine sodium to potassium ratio (uNa/K) could be useful tools in discriminating CNP children in children with a clinical suspicion of fUTI at admission and negative urine cultures.

Methods

Patients

Initially, this study included 329 children who were consecutively admitted to our hospital with their first fUTI between January 2011 and October 2014. Forty children who had missing data for the required parameters, or had results of urine electrolytes from samples collected 24 h after hydration were excluded. Furthermore, 25 children who did not undergo a DMSA scan at the acute stage were excluded. Finally, a total of 264 children were included in this study. All male patients included in this study were uncircumcised. fUTI at admission was defined as follows: high fever $\geq$38 °C, abnormal urinalysis (pyuria, >5 WBC/high-power field [HPF] and positive leukocyte esterase, and one or more positive findings of protein, nitrite, or red blood cells on urinalysis), positive CRP results (>0.3 mg/dL), and the lack of any other cause of fever. Significant bacteriuria was defined as the presence of more than 1×10^5 colony-forming units/HPF for a single-strain isolate. Urine was sampled by collecting a midstream urine specimen in toddlers or in older children and using the clean catch bag method in young children under 2 years old. The mean duration of admission was 4.2 days. All children enrolled underwent a DMSA renal scan upon admission. In addition, blood (CRP, WBC, ESR, electrolytes, creatinine [Cr], and serum osmolarity [Osm]) and spot urine tests (electrolytes, urine Cr, protein and urine Osm) were performed. Spot urine samples obtained for electrolyte analysis on presentation, if they were collected 24 h after hydration, were excluded from this study because renal compensation for increasing plasma volume could alter the value of urine electrolytes. CRP levels were measured by turbidimetry. Urine proteins were analyzed using pyrogallol red dye (7600 DP; Hitachi Ltd, Tokyo, Japan). DMSA scanning was performed using the planar technique, and findings were interpreted by both a nuclear medicine consultant and a pediatric nephrologist. Positive DMSA result was defined as the presence of a cortical defect on a DMSA scan with reduced or absent localization of the tracer and indistinct margins that did not deform the renal contour. There was no patient with congenital hypoplastic kidney among patients enrolled in this study. Study population was grouped by following definitions. APN was defined as cases with significant bacteriuria and positive DMSA results. CNP was defined as cases with negative urine culture results and positive DMSA results. Lower UTI was defined as cases with significant bacteriuria and negative DMSA results. Controls included the cases with negative urine culture results and negative DMSA results. VCUG was performed only when DMSA scanning revealed cortical defects at the first fUTI episode. Written informed consent was obtained from parents of all children with fUTI prior to performing DMSA scanning and VCUG.

All blood and urine data were collected prospectively. uProt/cr, uNa/K, fractional excretion of sodium (FENa), and transtubular potassium gradient (TTKG) were calculated. All data were compared between the groups.

Statistical analysis

All variables are presented as the mean $\pm$ standard deviation, and continuous variables were analyzed using the Student's *t*-test, and analysis of variance (ANOVA) and post hoc analysis with Turkey HSD test were used for analyzing the differences among three group means. Qualitative variables and correlations were analyzed using the Pearson chi-squared test and Pearson correlation coefficient (two-tailed probability), respectively. To investigate the ability of relevant parameters to predict a cortical defect on DMSA scan in children with fUTI, multiple logistic regression analysis (MLRA) was used. Statistical analysis was performed using SPSS statistics 20 (SPSS Inc, Chicago, IL). Statistical significance was defined as $P \leq 0.05$.

Ethics statement. The CHA University Institutional Review Board approved this study including the consent procedure (CHA IRB No. BD2015-057). The doctors in charge read the informed consent form in front of their parents of all subjects at admission, and the parents signed the consent form together with the doctors in charge and responsible researchers. Our study was conducted according to the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Results

Demographic findings of study population

The demographic characteristics of children with APN, CNP, lower UTI, and controls are shown in Table 1. Voiding cystourethrography (VCUG) was performed in 35 patients (16 kidney units, grade 1–3; 8 kidney units, grade 4–5 [classification of the International Reflux Study Committee]).

Parents of 75 children with positive DMSA results did not provide consent to perform VCUG.

Comparison parameters between APN, CNP, lower UTI, and control (Table 1)

One hundred ten children (41.7%) of study population had positive DMSA results, and of these, 39 children (35.5%) were CNP. Even though CNP children were older than APN children (17.1 ± 29.3 vs. 6.9 ± 6.3 months), CNP children had similar values of all laboratory parameters with the exception of lower uProt/cr ($P = <0.001$), compared with APN children. CNP children had a lower uNa, FENa, and serum sodium (sNa), while CRP level and ESR were higher than those in control. uProt/cr in CNP children was similar with that of control, while lower than that of lower UTI ($P < 0.0001$). Comparing between CNP and lower UTI, CRP, WBC and ESR were higher in CNP ($P = <0.001$, $P = <0.001$ and $P = <0.001$, respectively), while uNa and uNa/K were lower in CNP than in lower UTI ($P = 0.010$ and $P = 0.034$, respectively).

Comparison parameters between CNP and febrile non-UTI controls (Table 2)

Data of febrile non-UTI control were cited from author's previously published article (reference number 5). Those data were expressed as the mean and standard deviation. Febrile non-UTI controls who admitted to our hospital from January 2010 to December 2012 had high fever, no pyuria on urinalysis, negative urine culture results and other fever focus: bronchiolitis (8), bronchitis (4), croup (2), pharyngitis (16), acute suppurative otitis media (5), tonsillitis (4), herpangina (7), exanthema subitum (5), an unspecified fever (10), acute gastroenteritis (27), unspecified sepsis (8), and pneumonia (3).

CNP had significantly higher CRP, WBC, ESR and uProt/Cr, and lower sNa, sOsm, uNa, uNa/K, and FENa than febrile non-UTI controls.

Correlated factors with positive DMSA results (APN and CNP)

Positive DMSA results were strongly positively correlated with the CRP level, WBC count, and ESR, whereas it was negatively correlated with uNa/K (CRP: $r = 0.37387$, $P = 0.000$; WBC: $r = 0.32908$, $P = 0.000$; ESR: $r = 0.462548$, $P = 0.000$; uNa/K: $r = -0.12958$, $P = 0.041$).

Prediction of a cortical defect on DMSA renal scan (APN and CNP) (Table 3)

By MLRA including CRP, WBC, ESR, uNa/K, and uProt/cr, we observed that the CRP level, WBC count, ESR, and uNa/K were relevant factors for predicting a cortical defect on DMSA scan in children with fUTI. However, the odds ratio of WBC and ESR values was 1.01 and 1.02, respectively, which meant those parameters did not affect the odds of predicting a cortical defect on DMSA scan. Furthermore, the area under the curve of WBC (receiver operating

Table 1 Comparison of following four group means of laboratory data: acute pyelonephritis (APN), culture negative pyelonephritis (CNP), lower urinary tract infection (UTI), and controls.

	1.APN	2. CNP	3. Lower UTI	4. Control	*P* value
N	71	39	110	44	**ANOVA**[post-hoc test]
Age (months)	6.9 ± 6.3	17.1 ± 29.3	5.9 ± 6.2	13.1 ± 16	<0.001[1−2,2−3,2−4]
M: F	48: 23	25: 14	72: 38	18: 26	
Urine					
Protein/Cr	1.87 ± 2.06	0.58 ± 0.35	2.09 ± 2.88	0.33 ± 0.42	<0.001[1−2,1−4,2−3,3−4]
uNa (mEq/L)	16.8 ± 10.4	15.1 ± 11.9	27.6 ± 20.7	42.6 ± 34.1	0.001[1−4,2−4]
uK (mEq/L)	33.5 ± 21.6	25.2 ± 22.8	27.9 ± 19.9	19.9 ± 17.8	0.011[1−4]
uCr (mg/dL)	27.9 ± 15.1	27.2 ± 24.2	27.4 ± 25.2	21.9 ± 17.9	0.177
uOsm (mOsm/L)	262.7 ± 138.9	224.1 ± 162.3	234.7 ± 148.2	237.9 ± 153.9	0.127
uNa/K	0.67 ± 0.51	0.96 ± 0.86	1.53 ± 1.88	3.79 ± 4.04	<0.001[1−3,2−4,3−4]
Blood					
CRP (mg/dL)	8.5 ± 6.2	8.6 ± 5.5	3.19 ± 3.09	2.79 ± 2.36	<0.001[1−3,1−4,2−3,2−4]
WBC (/mm^3)	19165 ± 6356	18081 ± 6319	13743 ± 5558	14934 ± 7250	<0.001[1−3,2−3]
ESR (mm/hr)	59.6 ± 27.7	62.3 ± 33.6	30.4 ± 22.3	28.2 ± 21.9	<0.001[1−3,1−4,2−3,2−4]
Na (mEq/L)	136.1 ± 3.3	136.7 ± 3.1	137.6 ± 2	138.6 ± 2.6	0.001[1−4,2−4]
K (mEq/L)	4.8 ± 0.6	4.6 ± 0.5	4.8 ± 0.5	4.6 ± 0.5	0.118
Cr (mg/dL)	0.4 ± 0.1	0.44 ± 0.1	0.38 ± 0.05	0.39 ± 0.06	<0.001[2−3,2−4]
Osm (mOsm/L)	285.5 ± 17.9	280.3 ± 24.6	285.9 ± 7.9	284.3 ± 6.8	0.839
FENa	0.23 ± 0.22	0.27 ± 0.23	0.44 ± 0.62	0.81 ± 0.66	<0.001[1−4,2−4,3−4]
TTKG	8.3 ± 5.1	6.6 ± 3.2	7.1 ± 2.7	4.6 ± 2.7	0.047[1−4]

The laboratory examination results are expressed as mean ± standard deviation.
N, number of patients; ANOVA, one-way analysis of variance; post-hoc test, Tukey HSD test between each group (1−2, 1−3, 2−3); M, male; F, female; uNa, urine sodium; uK, urine potassium; uCr, urine creatinine; uOsm, urine osmolality; uNa/K, uNa to uK ratio; CRP, C-reactive protein; WBC, white blood cell count; ESR, erythrocyte sedimentation rate; FENa, fractional excretion of sodium; TTKG, transtubular potassium gradient; statistical significance, $P < 0.05$.

Table 2 Comparison of laboratory data: between culture negative pyelonephritis (CNP) and febrile non-UTI controls.[5]

	CNP	Febrile non-UTI Controls[5]	*P* value
N	39	100	
Age (months)	17.1 ± 29.3	6.7 ± 3.5	<0.001
M: F	25: 14	56: 44	
Urine			
Protein/Cr	0.58 ± 0.35	0.28 ± 0.35	<0.001
uNa (mEq/L)	15.1 ± 11.9	37.5 ± 32	<0.001
uK (mEq/L)	25.2 ± 22.8	23 ± 20.3	0.590
uCr (mg/dL)	27.2 ± 24.2	20.9 ± 19.7	0.120
uOsm (mOsm/L)	224.1 ± 162.3	264.2 ± 204.3	0.290
uNa/K	0.96 ± 0.86	3.53 ± 4.62	<0.001
Blood			
CRP (mg/dL)	8.6 ± 5.5	1.8 ± 2.7	<0.001
WBC (/mm^3)	18081 ± 6319	11660 ± 6224	<0.001
ESR (mm/hr)	62.3 ± 33.6	21.9 ± 24.6	<0.001
Na (mEq/L)	136.7 ± 3.1	138.3 ± 3.4	0.009
K (mEq/L)	4.6 ± 0.5	4.7 ± 0.4	0.270
Cr (mg/dL)	0.44 ± 0.1	0.4 ± 0.15	0.320
Osm (mOsm/L)	280.3 ± 24.6	290.2 ± 13.6	0.024
FENa	0.27 ± 0.23	0.69 ± 0.66	<0.001
TTKG	6.6 ± 3.2	5.9 ± 2.9	0.340

The laboratory examination results are expressed as mean ± standard deviation.
UTI, urinary tract infection; Controls,[5] data cited from reference number 5; N, number of patients; M, male; F, female; uNa, urine sodium; uK, urine potassium; uCr, urine creatinine; uOsm, urine osmolality; uNa/K, uNa to uK ratio; CRP, C-reactive protein; WBC, white blood cell count; ESR, erythrocyte sedimentation rate; FENa, fractional excretion of sodium; TTKG, transtubular potassium gradient; statistical significance, $P < 0.05$.

Table 3 Multiple logistic regression analysis (MLRA) of relevant variables to predict a cortical defect on 99m-Dimercaptosuccinic acid renal scan in children with febrile urinary tract infection.

	ROC		MLRA		
	AUC	*P* value	OR	CI	*P* value
CRP	0.811	<0.001*	1.21	1.07–1.36	0.002*
WBC	0.522	0.559	1.01	1.00–1.02	0.008*
ESR	0.779	<0.001*	1.02	1.01–1.04	0.003*
uProt/cr	0.524	0.543	0.85	0.71–1.01	0.057
uNa/K	0.700	<0.001*	0.47	0.31–0.71	<0.001*

ROC, receiver operating characteristic; AUC, area under the curve; OR, odds ratio; CI, 95% confidence interval; CRP, C-reactive protein; WBC, white blood cell count; ESR, erythrocyte sedimentation rate; uProt/cr, urine protein to creatinine ratio; uNa/K, urine sodium to potassium ratio; *, $P < 0.05$.

characteristics) was not statistically significant. Therefore, CRP levels in blood samples and uNa/K in urine samples could be the most relevant factors for predicting a cortical defect on DMSA scan in children with fUTI.

Discussion

The literature reports that CNP is detected in 9–38% of UTI patients with positive DMSA results.[2–4] The results of urine culture in UTI children can be negative in the following situations: 1) antibiotics are prescribed before sampling for urine culture; 2) urinary frequency prevents bacterial growth in the bladder; 3) dilute urine, for example when the urine sample is collected after hydration, where the number of bacteria in the urine sample can be too small to grow in the culture media; 4) causative infectious agents being one of fungi, anaerobic agents, or unidentified organisms; 5) pretreatment of the genital area before urine is sampled, probably affecting bacterial growth in culture media; 6) possible technical errors in the management of sample storage or transporting samples in media or in the environment around culture media.

We have previously reported the usefulness of CRP, uProt/cr, and uNa/K as a subsidiary tool for predicting cortical defects on DMSA scan in infants with a first fUTI.[5] In our previous study, UTI infants with a higher CRP (>3 mg/dL) had a significantly higher probability of having a cortical defect on an acute DMSA scan than infants with a lower CRP. Proteinuria (uProt/cr > 0.4) present in infants with fUTI was associated with a significantly higher probability of having a significant bacteriuria compared to infants with negative proteinuria. uNa/K had a strongly negative correlation with CRP. CRP and uNa/K were significant factors in predicting cortical defects on DMSA scan in fUTI infants. This suggests that these parameters can be useful to discriminate CNP children from children with suspected fUTI but a negative urine culture. In order to demonstrate such a utility of these parameters, the present study was designed enrolling a larger population than in our previous study.

There have been many reports indicating that CRP has a role in discriminating upper UTI in fUTI children, while on the contrary there are many studies reporting that CRP was not a significant factor in predicting a cortical defect on DMSA scan in fUTI.[6–9] In this study, CRP was a significant factor in predicting cortical defects on acute DMSA scans in children with fUTI. This result suggests that febrile children with abnormal urinalysis, with no other cause of fever, and high CRP level should be treated and considered as children having APN or CNP even though the results of urine culture are negative.

According to previous reports, 63–83% of patients with culture-confirmed UTIs exhibit positive results for protein tests.[10–12] Its pathogenesis has not yet been fully elucidated. Recent studies revealed the association between the expression of Toll-like receptor (TLR)-4 in glomeruli, tubules, or monocytes and proteinuria in patients with type 2 diabetic nephropathy or IgA nephropathy.[13–15] The role of TLR-4 in APN is to recognize uropathogens breaching the physical barriers of the urothelium and then to mobilize the innate immune responses of the bladder and kidney epithelial cells.[16] However, proteinuria could not distinguish upper UTI from fUTI. In this study, proteinuria (uProt/cr > 0.4) was detected in 92.9% of APN children, while it was present in 79.6% of lower UTI children. Proteinuria could not predict APN in the fUTI, but the amount of

proteinuria in fUTI children with significant bacteriuria (APN or lower UTI) was significantly higher than that in children without bacteriuria like CNP children or control. This suggests that febrile children with abnormal urinalysis, no other cause of fever, and an elevated uProt/cr should be treated and considered as children having significant bacteriuria initially and as requiring blood sampling for CRP or additional tests in order to predict APN or CNP before the result of urine culture reveals.

In the present study, enrolling a larger population than our previous study, uNa/K was also significantly lower in APN and CNP children than in lower UTI children and controls ($P < 0.0001$). Therefore, febrile children with abnormal urinalysis, no other cause of fever, an elevated uProt/cr, and a low uNa/K (<1.15)[5] could be considered as APN or CNP children before blood sampling or other additional tests are performed. On the contrary, febrile children with abnormal urinalysis results, no other cause of fever, a normal uProt/cr, and a high uNa/K could be treated with oral antibiotics until the results of urine culture are obtained, even without any additional tests, because they will have a low probability of having positive DMSA results, even though the results of urine culture will likely be positive.

Its exact mechanism is unknown. However, in a previous report, the authors asserted the possibility that these phenomena might be related to the local renin-angiotensin-aldosterone system (RAAS). There has been no report on how the RAAS may bring about change in kidneys inflamed by bacteria. The authors set up the following hypothesis: if inflammation occurs in the renal cortex, which is composed of a profuse microvascular structure, the changes in renal plasma flow in the affected area, especially the perfusion of the juxtaglomerular apparatus, or the changes of diameters of microvessels, or release of catecholamines, could affect activation of the RAAS in the kidneys.[5] RAAS activation can result in the strong tubular reabsorption of uNa and secretion of urine potassium (uK).[17] If our hypothesis is correct in APN or CNP children, final uNa levels would be lower and uK levels would be higher than the values observed in lower UTI and controls. Furthermore, uNa/K is known to be a useful index of the renal response to aldosterone.[18]

Hyponatremia (<136 mEq/L) was found more frequently in APN children (28.6%) than in lower UTI children and control (9.6%). sNa concentration was negatively correlated with CRP, WBC, and ESR levels ($P < 0.001$, $P < 0.001$, and $P = 0.004$). Such results were similar with results reported by Park et al.[19] They insisted that hyponatremia in APN could be caused by vasopressin release through non-osmotic stimulation of interleukin-6 produced from monocytes and macrophages in the process of an inflammatory response in line with the report by Swart et al.[20] However, their reports did not provide clear evidence on the mechanism of vasopressin activity or the relationship between hyponatremia and APN. Furthermore, these studies did not check the changes of urine electrolytes that could not help being affected concomitantly by vasopressin release. If vasopressin release be a main cause of hyponatremia in APN children with normal renal function, as in patients with inappropriate secretion of antidiuretic hormone, they would have uNa >20 mEq/L and increased uOsm due to the secretion of atrial natriuretic peptide to compensate for transiently increased intravascular volume by vasopressin. However, in this study, the mean values of uNa and uOsm were 16.3 mEq/L and 245.8 mOsm/L, respectively. Furthermore, uNa and uNa/K were negatively correlated with CRP ($P = 0.041$ and $P = 0.025$, respectively). This study verified that vasopressin release is not a major cause of hyponatremia in APN children.

The present study also verified the usefulness of those parameters in discriminating CNP children from those with suspected fUTI and negative urine culture results. These parameters can contribute to reduce the total number of acute DMSA scans performed in order to differentiate APN or CNP in children with a suspicious fUTI. When the results of urinalysis are equivocal, these parameters can contribute to identifying children with a high probability of APN or CNP, and then assist in determining whether they should be admitted or wait while receiving oral antibiotic treatment until the results of urine culture can be obtained and in deciding when imaging studies should be performed.

A disadvantage of these parameters, when they are used in practice, is that if urine sampling is performed >24 h after hydration and intravenous antibiotic treatment is initiated, uProt/cr and urine electrolyte values tend to return to their normal levels.

The present study has the following limitations: 1) urine culture was collected using a sterile urine bag in children less than 2-year-old; 2) this method does not provide any information on the development of renal scarring in APN children; and 3) the effects of urinary tract anomalies on the changes of urine electrolyte levels could not be evaluated because VCUG was not performed in all children with fUTI.

In conclusion, the combination of serum CRP or WBC and uNa/K level are helpful in discriminating CNP children in those with suspected fUTI and negative urine culture results.

Conflict of interest

The authors have declared that no conflict of interest exists.

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