

Research Article

J Ped. Nephrology 2015;3(3):104-108
http://journals.sbm.ac.ir/jpn

The Association Between Hyponatremia and Reflux-Related Renal Injury in Acute Pyelonephritis

How to Cite This Article: Yousefichaijan P, Taherahmadi H, Rafiei Mohammad. et al. The Association Between Hyponatremia and Reflux-Related Renal Injury in Acute Pyelonephritis. J Ped. Nephrology 2015;3(3):104-108.

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Received: Apr-2015

Revised: June-2015

Accepted: June-2015

Introduction

Reflux-related renal injury is a global public health problem, its incidence is steadily increasing amongst children [1]. Iran is a country populated with a high percentage of children; children aged 1-14 years represent 28.2% of the population. Iran is similar to other developing countries regarding no current national epidemiologic data on pediatric reflux nephropathy and its risks.

Detection and management of renal problems in children are of major importance for CKD (chronic kidney disease) prevention; this in turn would decrease the burden of CKD in the pediatric population. Sodium is the dominant cation of the ECF (Extracellular fluid) and it is the principal determinant of extracellular osmolality. Thus,

Introduction: The kidney regulates sodium balance and is the principal site of sodium excretion. Sodium is unique among electrolytes because water balance, not sodium balance, usually determines its concentration. Although water balance is usually regulated by osmolality, volume depletion stimulates thirst, renal protection of water and ADH secretion. Volume reduction has priority over osmolality; volume depletion stimulates ADH secretion, even if a patient has hyponatremia. The aim of this study was to consider scar nephropathy in children with UTI and hyponatremia and compare it with children without hyponatremia.

Material and Methods: 200 children with pyelonephritis were included in this case-control study as case and control groups, respectively. Subjects were selected from children referred to the pediatric clinic of our hospital in Arak, Iran. Case group included children with hyponatremia and UTI (with VUR) and control group included children with UTI (With VUR) and normal serum sodium. Data was analyzed using SPSS ver.18

Results: Among 200 (100%) children in both groups, 5 children (5%) had normal sodium and reflux nephropathy and 23 children had hyponatremia and reflux nephropathy.

Conclusions: Hyponatremia in children with reflux nephropathy was significantly more common than children without reflux nephropathy. The observed correlation between reflux-related injury and hyponatremia necessitates evaluation of electrolytes in children with pyelonephritis.

Keywords: Pyelonephritis; Child; Hyponatremia; Vesico-Ureteral Reflux.

Running Title: Association Between Hyponatremia and Reflux Nephropathy

sodium is necessary for survival of intravascular volume [2].

Less than 3% of sodium is intracellular. More than 40% of total body sodium is in bone; the remainder is in interstitial and intravascular spaces. A child's diet determines the amount of sodium ingested, a predominantly cultural determination in older children [3]. An occasional child has salt craving because of an underlying salt-wasting renal disease or adrenal insufficiency. Vesicoureteral reflux refers to the retrograde flow of urine from the bladder to the ureter and kidney. The ureteral attachment to the bladder is normally diagonal, between detrusor muscle and bladder mucosa, creating a flap-valve mechanism preventing reflux [4]. Reflux occurs when the sub-mucosal tunnel between the mucosa and detrusor muscle is short or absent. Reflux is usually congenital, occurs in families and affects approximately 1% of children. Reflux predisposes to infection of the kidney (pyelonephritis) by facilitating the transport of bacteria from the bladder to the upper urinary tract [5]. The inflammatory reaction caused by a pyelonephritic infection can result in renal injury or scarring, also called reflux-related renal injury or reflux nephropathy. In children with a febrile urinary tract infection (UTI), those with reflux are three times more likely to develop renal injury compared to those without reflux [6]. Extensive renal scarring impairs renal function and can result in renin-mediated hypertension, renal insufficiency or end-stage renal disease, impaired somatic growth and morbidity during pregnancy [7]. Reflux nephropathy once accounted for as much as 15-20% of end-stage renal disease in children and young adults. Reflux nephropathy remains one of the most common causes of hypertension in children [8]. Hyponatremia is the most common electrolyte abnormality in clinical practice, but little is known about the association between febrile urinary tract infection (UTI) and hyponatremia or its significance to clinical outcomes [9]. Hyponatremia may be a substantial inflammatory marker and is significantly and independently associated with the degree of inflammation in children with febrile UTI. Secondary pseudohypoaldosteronism type 1 develops due to transient aldosterone resistance in renal tubules and characterized by hyponatremia, hyperkalemia, high plasma aldosterone levels and renal sodium loss. However, many reasons described, urinary tract infections and/or urinary tract anomalies are the most common reasons. Although the reason of

tubular resistance is not known truly, renal scar development because of obstruction and reduced sensitivity of mineralocorticoid receptors due to cytokines such as transforming growth factor (TGF)-beta are the feasible mechanisms. It is seen mainly during the first three months of life and the frequency decreases with age [10-11-12]. The aim of the current study was to determine the association between hyponatremia and reflux nephropathy among children, as early detection could aid in preventing the progression of renal diseases.

Materials and Methods

This case-control study was conducted on inpatients in the pediatric ward of Amir Kabir hospital in Iran. Participants included 1-5 year-old girls who had developed a form of acute pyelonephritis or UTI, for the first time and had indications of hospitalization due to UTI. Children with dehydration or vomiting, those unable to drink fluids or possibility of urosepsis should be admitted to hospital for IV rehydration and IV antibiotic therapy. According to the clinical conditions, these symptoms defined as mild to moderate dehydration requiring rehydration and IV antibiotic therapy. Girls with frequent vomiting and severe UTI due to dehydration or bacteremia were not included in the study. Girls and their parents were interviewed and underwent laboratory examinations to assess the inclusion criteria. These examinations included medical history of UTI symptoms, urinalysis and culture, level of BUN, Cr, Na, K, VBG (Hco3-), ultrasonography of the kidney, voiding cystourethrogram (VCUG) and Technetium (Tc)-99m dimercaptosuccinic acid scintigraphy (DMSA scan). The midstream catch method was used for urine culture. Girls' genital area was washed from front to back with soap and water three times and intermediate urine samples were collected in sterile bags and transferred to the hospital laboratory. To perform the urine culture and confirm the result, urine samples with infected medium were excluded from the study and urine samples prepared using the sterile method underwent analysis and culture for the second time. Since *E. Coli* is the most common cause of urinary tract infection (UTI) and for easier cloning of the subjects for UTI causative organism, only patients with UTI resulted by *E. Coli* were included in the study. Since this study aimed at analyzing urine samples with *E. coli* sensitive to Ceftriaxone and Cefixime, *E. coli* isolated from urine cultures

underwent sensitivity test for evaluating their resistance or sensitivity to Ceftriaxone and Cefixime antibiotics. Since Technetium (Tc)-99m dimercaptosuccinic acid scintigraphy is the gold standard method for the diagnosis and localization of acute pediatric pyelonephritis, all girls qualified for the study underwent this scan for evaluation of acute pyelonephritis. Girls with diagnosed renal scarring after DMSA scan were not included in the study. Acute scintigraphy pyelonephritis was defined as focal or diffuse areas of decreased DMSA uptake without evidence of cortical loss and renal scar was defined as areas of negative DMSA uptake. Inclusion criteria included: 1) 1-5 year-old girls, 2) Girls with medical history and symptoms of UTI and girls diagnosed with acute pyelonephritis based on fever (without any source other than UTI) and evidence of renal inflammation in DMSA scan and VUR in VCUG, 3) Culture results and positive urinalysis for only one type of UTI-causing organism, i.e. *E. coli*, 4) Isolated *E. coli* sensitive to Ceftriaxone and Cefixime antibiotics based on the disk diffusion method, 5) Obtaining informed consent from girls' parents for participating in the study and their proper compliance for cooperation and administration of prescribed drugs after their girl was discharged from hospital. Exclusion criteria were: 1) Diagnosis of renal scarring based on the results of DMSA scan 2) History of any form of UTI with any count, 3) Neurogenic bladder 4) History of voiding dysfunctions 5) Severe sepsis and bacteremia 6) Severe dehydration 7) Lack of hospitalization indications defined for the study. After assessment of girls and their parents, they were included in two groups (hyponatremia and normal sodium) and matched for gender, age, urinalysis, sodium level and culture results and DMSA scan results. Medications were administered for 14 days in a way that all girls received routine UTI treatment. The treatment included 50-75 mg/kg/day IV Ceftriaxone in two divided doses during hospitalization and 8 mg/kg/day of oral Cefixime in two divided doses after discharge. Considering the prevalence of UTI, sample size was determined 200. Girls were divided into two groups, 100 in each including case group with hyponatremia (Na <135 meq/liter) and control group with normal sodium level (135-145 meq/liter). As long as girls were hospitalized, drugs distributed by rendering physician and ward's personnel. After the girls were discharged, parents were provided with necessary training for administering medicine to girls. They were also

told to refer 7-10 days and 4-6 months after the treatment for repeated urine culture and DMSA scan, respectively. The forms included their demographic information, VCUG results and DMSA scan findings 4-6 months after the treatment. The results of urine culture and DMSA were recorded in patients' clinical information forms at specific times and 4-6 months after the treatment, respectively. The collected data were analyzed using the SPSS software (version 18).

Results

The prevalence of reflux nephropathy was 5% in control group and 23% in case group. Distribution of reflux nephropathy was not homogenous in the two groups based on chi-square test ($p=0.001$). Mean grades of VUR were 2 ± 3 and 3 ± 4 for control and case groups, respectively and no significant difference was observed between the two groups ($p=0.976$). Based on logistic regression test, there was a significant association between both case and control groups and the occurrence of reflux nephropathy was 2.6 times more in case group than the control group (Odds ratio= 2.58 and $p>0.001$). The mean age, birth weight of all children and mother's age at birth were 8.12 ± 1.69 year, 2866.10 ± 617.77 grams and 25.32 ± 5.64 years, respectively. Mother's age at birth ($p=0.017$), maternal education ($p=0.001$), type of delivery ($p=0.001$) and household incomes ($p=0.004$) were significantly different between the case and control groups. The average age of children with hyponatremia and control group were 2.8 ± 1.81 and 3.37 ± 1.59 years, respectively, which the difference was not statistically significant ($p>0.05$). The results showed a significant association between birth weight ($p = 0.001$), gestational age ($p = 0.001$), marital status ($p = 0.001$) and type of delivery ($p = 0.001$) and reflux nephropathy. In the two groups, potassium (P-Value =0.1), Hco³⁻ (P-Value=0.4) and GFR (P-Value=0.5) were not significantly different. VUR grading in the two groups was similar.

Discussion

In developing countries, national epidemiologic data on reflux nephropathy and chronic kidney disease in the pediatric population is currently limited. In our study, Hyponatremia was a predictive factor in diagnosis of reflux nephropathy. Our study showed a higher incidence of hyponatremia in children with reflux nephropathy. Thus, if these disorders diagnosed

and treated, reflux nephropathy in children can be prevented or more easily treated. Stajić N, found that infants with urinary tract malformations (UTM) presenting with urinary tract infection (UTI) are prone to develop transient type 1 pseudohypoaldosteronism (THPA1). Male infants with hyponatremia, hyperkalemia and metabolic acidosis should undergo urine examination and renal ultrasound has to be performed to avoid underdiagnosis of THPA1 and inappropriate medication [10]. Park SJ concluded that hyponatremia is the most common electrolyte abnormality in clinical symptoms, but little is known about the relation between febrile urinary tract infection (UTI) and hyponatremia or its significance to clinical outcomes. This study indicated that hyponatremia may be a substantial inflammatory marker and is significantly and independently associated with the degree of inflammation in children with febrile UTI [11]. Park SJ concluded that timely diagnosis of hyponatremia is important for preventing potential morbidity and mortality, because it is often an indicator of basic disease. The most common reason of euvoletic hyponatremia is the syndrome of inappropriate antidiuretic hormone (SIADH) secretion. Recent studies showed that proinflammatory cytokines such as interleukin (IL) 1 β and IL-6 are involved in the development of hyponatremia, a condition associated with intense inflammation and related to antidiuretic hormone (ADH) secretion. Serum sodium levels in hyponatremia are inversely correlated with the percentage of neutrophils, C-reactive protein and N-terminal-pro brain type natriuretic peptide. In addition, elevated levels of serum IL-6 and IL-1 β are found in inflammatory diseases and their levels are higher in patients with hyponatremia. Hyponatremia could be used as a diagnostic marker of pediatric inflammatory diseases, because it is significantly correlated with the degree of inflammation in children. According to available evidence, we suppose that hyponatremia may be associated with inflammatory diseases in general. Knowing the mechanisms responsible for augmented ADH secretion during inflammation, monitoring patient sodium levels and selecting proper intravenous fluid treatment are important components that may lower morbidity and mortality of patients in a critical condition [12]. Lim GW concluded that the pathogenesis of hyponatremia (serum sodium <135 mEq/L) in Kawasaki disease (KD) remains unclear. In another study we showed the clinical significance of hyponatremia and the role of interleukin (IL)-6

and IL-1 β in the development of hyponatremia and syndrome of inappropriate antidiuretic hormone secretion (SIADH) in KD. Hyponatremia occurs in KD patients with severe inflammation, by increasing IL-6 and IL-1 β may activate ADH secretion, leading to SIADH and hyponatremia in KD [13]. Mori J concluded that the pathogenesis of hyponatremia in acute Kawasaki disease (KD) remains unknown. A recent case report of KD involved by syndrome of inappropriate antidiuretic hormone (SIADH) led us to determine the prevalence of SIADH in acute KD patients. This is the first report to show that SIADH is common as a cause of hyponatremia in acute KD and hence careful management of water and sodium is warranted [14]. Radha Nandagopal reported four infants presented with profound hyponatremia accompanied by urinary tract infection, finally leading to the diagnosis of impermanent pseudohypoaldosteronism. The cases suggest that renal tubular resistance to aldosterone is due to urinary tract infection itself rather than to underlying urinary tract anomalies typically found in these infants. Knowing this condition is important so that urine sodium, serum aldosterone and urine cultures may be obtained immediately in any infant presenting with hyponatremia and hyperkalemia in whom a diagnosis of congenital adrenal hyperplasia was not found. Appropriate substitution with intravenous saline and antibiotic therapy is sufficient to correct sodium levels over 24-48 hours [15]. Melzi ML indicated that a salt-losing syndrome with tubular resistance to aldosterone can occur during pyelonephritis in young infants with congenital UT deformity and the risk reduces considerably or disappears after three months of age, also in the absence of UT malformation pyelonephritis does not cause acute sodium loss of clinical relevance [16]. Meral Torun-Bayram concluded that secondary pseudohypoaldosteronism type 1 develops due to transient aldosterone resistance in renal tubules and is characterized by hyperkalemia renal sodium loss, hyponatremia and high plasma aldosterone levels. Although many reasons are explained, urinary tract infections and/or urinary tract anomalies are the most common causes. Although the cause of tubular resistance is not known exactly, renal scar development due to obstruction and reduced sensitivity of mineralocorticoid receptors due to cytokines such as transforming growth factor (TGF)- β are the possible mechanisms. It is seen especially within the first three months of life and the frequency

decreases with age. The treatment is usually elimination of the underlying cause. In this article, we presented four patients with several urinary tract anomalies and concomitant urinary tract infection who developed transient secondary pseudohypoaldosteronism [2].

Conclusion

In our study, there was a definite association between hyponatremia and reflux nephropathy. Hyponatremia in children with reflux nephropathy was significantly more common than children without reflux nephropathy. The observed correlation between reflux-related injury and hyponatremia necessitates evaluation of electrolytes in children with pyelonephritis. It is recommended to perform further studies with larger sample size.

Acknowledgement

The research team wishes to thank the vice chancellor of research for their financial support and children and their parents who contributed in this research.

Conflict of Interest

Authors have no conflict of interest to declare.

Financial Support

Authors have no financial support.

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