



Relation of Symptomatic Idiopathic Hypercalciuria with Urinary Tract Infection in Patients Attending to Children Hospital

Kambiz Ghassemi^{1*}, Maryam Esteghamati¹, Mohammad Bagher Rahmati¹, Yaghoob Hamed², Abdolmajid Nazemi¹, Mohamad Ali Molavi¹, Seyed Ali Alavi³

¹Department of Pediatric, Hormozgan University of Medical Sciences, Children Clinical Research Developments Center, Bandar Abbas, Iran

²Hormozgan University of Medical Sciences, Bandar Abbas, Iran

³Student Research Committee, Hormozgan University of Medical Sciences, Bandar Abbas, Iran

* Corresponding author's Email:kambizghassemi@yahoo.com

ABSTRACT: Urinary tract infection (UTI) is known as one of the most frequent disease in pediatric medicine. A new additional risk factor to predisposing patients to UTI is mentioned as Idiopathic Hypercalciuria (IHC). IHC is defined as a hypercalciuric status with normal level of calcium in serum and absence of any secondary cause of Hypercalciuria. In this study our aim was to evaluate relation of symptomatic idiopathic hypercalciuria with UTI in children. This prospective case-control study includes 251 patients who were presented to outpatient clinic of Children hospital of Bandar Abbas. Patients divided in two groups. Case group contains 182 patients with proven UTI and control group contains 69 patients without any signs or symptoms of UTI. Mid-stream urine sample to determine Ca/Cr ratio collected from all patients. 24 hours urine collection was ordered for patients with Ca/Cr ratio more than 0.21mg/mg. diagnosis of IHC was based on Ca/Cr ratio more than 4 mg/mg/kg in 24 hours with no secondary cause of IHC. We evaluated association between idiopathic hypercalciuria and UTI in 251 patients. In case group after collecting 24 hours urine, 66 (36.3%) patients and in control group 3 (4.3%) patients detected as idiopathic hypercalciuria. We discovered that frequency of hypercalciuria is higher in female (66.6%) than male (34.4%) and idiopathic hypercalciuria was found significantly more in patients with UTI ($P=0.001$); but we did not find any evidence to prove relation between recurrent UTI and idiopathic hypercalciuria ($P=0.64$). Our findings show, the most common manifestations of idiopathic hypercalciuria were dysuria, frequency and hematuria. On the basis of these results, we confirmed the hypothesis that idiopathic hypercalciuria is an important risk factor of UTI ($P=0.001$) but there was no significant association between recurrent UTI and idiopathic hypercalciuria.

Key words: Idiopathic hypercalciuria, Urinary tract infection, Children

ORIGINAL ARTICLE

INTRODUCTION

Urinary tract infection (UTI) is the most common urogenital disease and the second most common bacterial infectious disease. About 2% of children and 5% of girls acquire it and 25% of them will have recurrences in the first year of life. After two episodes of UTI the risk of recurrence increases to 50%. The importance of recurrent UTI is a rise in the risk of renal scars, hypertension and decreased renal function (Jackson, 2005; Yousefi et al., 2012). A new risk factor of recurrent UTI is idiopathic hypercalciuria (IHC). UTI, as a clinical manifestation of hypercalciuria, was first mentioned by Heliczer in 1987 (Sadeghi-Bojd and Hashemi, 2008). Idiopathic hypercalciuria is an autosomal dominant disorder which is observed in 39% of asymptomatic children and 20% of children who visited in nephrology clinic (Scheinman, 1999; Esfahani, 2007). Patients with idiopathic hypercalciuria have elevated levels of urinary calcium excretion and normal serum calcium concentration with no

proven underlying cause. It seems that accumulation of calcium oxalate microcrystals and epithelial damage to renal tubules might lead to an increased rate of infection in these patients (Vachvanichsanong et al., 1994). Epithelial damage prepares a bacterial colonization site, and also leads to voiding dysfunction. These factors foster propagation of UTI in these patients (Yousefi et al., 2012). Idiopathic hypercalciuria is believed to be the cause of a variety of urinary tract complaints in clinical pediatrics, including urinary frequency, urgency, and/or dysuria, often associated with gross or microscopic hematuria, renal colic, or obstructive uropathy (Kalia et al., 1981; Perrone et al., 1996; Esfahani, 2007; Sadeghi-Bojd and Hashemi, 2008). In some studies, increased water intake, limitation of sodium intake, and consumption of potassium citrate have been recommended in these patients to prevent recurrent UTIs. Dietary limitations, forcing water intake, and potassium citrate are not suitable treatment in

children (Lopez et al., 1999). The findings of a recent study by Michel M. Lopez and colleagues showed that idiopathic hypercalciuria is a major predisposing factor for UTI (Lopez et al., 1999). The prevalence of idiopathic hypercalciuria in cases of Vesico-ureteral reflux and UTI was studied by Mahmoodzadeh and colleagues. They reported an increase (1.54-fold) in idiopathic hypercalciuria compared with control group, although this was not statistically significant (Mahmoodzadeh et al., 2010). Because of many controversies about the relation between idiopathic hypercalciuria and UTI, and the importance of UTI in children, we decided to evaluate this relation in Bandar Abbas-Iran.

MATERIALS AND METHODS

Prospective case control study was carried out between May 2009 to August 2011 in children hospital of Bandar Abbas-Iran. This study was designed to survey the relation between idiopathic hypercalciuria in children with recurrent UTI. 251 children aged 2-14 years old were enrolled to this study. The study population consisted of patients who did not suffer from endocrinopathies, malnutrition, nephropathy or other urinary tract metabolic disorders that could predispose them to hypercalcemia and secondary hypercalciuria. The diagnosis of hypercalciuria in patients and control group was made if random urinary calcium/creatinine (Ca/Cr) ratio was greater than 0.21 mg/mg in urine sample. In all patients with pathological value of urine Ca/Cr ratio (≥ 0.21), the diagnosis was confirmed by a 24h urinary calcium excretion over 4 mg/kg per day. UTI was defined as the presence of more than 105 colony forming bacteria per ml on urine sample

obtained by midstream collection of voided urine. Recurrent UTI was defined as two or more episodes of UTI. Age at presentation, gender, presenting complaints, random urine Ca/Cr ratio, serum calcium, phosphorous, creatinine, and parathyroid hormone were assessed for all participants. Children with nephrolithiasis and secondary hypercalciuria excluded from study. After collecting these information, statistical analysis were performed by using SPSS version 19.

RESULTS

Of 251 children were enrolled to this study, 190 children were female (75.6%) and 61 were male (24.3%). The case group contained 182 children with proven UTI and mean age of 2.6 ± 5 years. There was no other underlying disease or complications in this group. The control group contained 69 children with no clinical signs and symptoms of UTI and mean age of 2.8 ± 5 years. In both groups we had no case to loss follow up. In patients group 66 (36.3%) of children had ICH while in control group just 3 (4.3%) children had idiopathic hypercalciuria (Table 1). This difference was absolutely significant ($P=0.001$) and shows that urinary tract infection is related to idiopathic hypercalciuria. Of all patients with UTI, 40.1% (73/182) had recurrent UTI and 59.9% (109/182) had UTI for the first time. In the group of patients with recurrent UTI 37.9% (25.73) had idiopathic hypercalciuria but, only 62.1% (41.109) were reported in group with first time UTI ($P>0.05$) (Table 2). In patients group (182 children), 39 patients were boy and 144 patients were girl. Prevalence of idiopathic hypercalciuria in boys was 56.4% (22.39) and in girls were 36.5% (44.144). P values was <0.05 .

Table 1: Relation between UTI and Idiopathic Hypercalciuria

	Without IHC	With IHC	Total
Case group	116(63.7%)	66(36.3%)	182
Control group	66(95.7%)	3(4.3%)	69
Total	182	96	251

Table 2: Relation between Recurrent UTI and Idiopathic Hypercalciuria

	Without IHC	With IHC	Total
Without IHC	68(58.8%)	48(41.8%)	116
With IHC	41(62.1%)	25(37.9%)	66
Total	109	73	182

DISCUSSION

The relation between idiopathic hypercalciuria with UTI has been pointed out by several studies. Vesna D. and colleagues noticed the association between idiopathic hypercalciuria and UTI. Their report shows idiopathic hypercalciuria diagnosed in 10% of patients with first time UTI but in the present study, 36% of patients with UTI, diagnosed as idiopathic hypercalciuria and found a significant relation between idiopathic hypercalciuria and UTI (Stojanović et al., 2007). Sadeghi and colleagues

conducted a study to investigate this relation and found a strong relation between UTI and idiopathic hypercalciuria (Sadeghi-Bojd and Hashemi, 2008). This relation can be due to formation of Calcium oxalate monohydrate microcrystals (COM) and renal stone, which can protect bacteria from urine fluid excretion. In other way, accumulation of microcrystals, damage epithelial cells while epithelial cells have an important role in the protection of urinary tract from bacteria infiltration

(Stojanović et al., 2007). To activate antibacterial response, a close contact between bacteria and the epithelial cell surface is necessary (Mannhardt, Becker et al., 1996). Calcium oxalate monohydrate crystals adherence on uroepithelial cells may influence the mechanisms of cellular defense. Within the uroepithelial cell, COM may activate the process of proliferation, and interaction between the cell and crystal leads to retention of the crystals in the kidney and promotion of interstitial fibrosis (Lieske, Leonard et al., 1996). The association of idiopathic hypercalciuria and recurrent UTI is also considered as an important variant in this study. In patient group 40.1% of cases had recurrent UTI criteria and in 37.9% of these patients idiopathic hypercalciuria was detected while in the rest of patients who had just one episode of UTI, the idiopathic hypercalciuria was detected in 62.1%. Our findings show there is no relation between recurrent UTI and idiopathic Hypercalciuria. This irrelevant relation is contrary to Lopez and colleagues (Lopez et al., 1999) who noticed the association between idiopathic hypercalciuria and recurrent UTIs. Another controversy was presented by Nikibakhsh and colleagues in 2007. They found hypercalciuria in 34.8% children with recurrent UTI and in 8.6% of control group ($P < 0.05$) (Nikibakhsh et al., 2007). Although in our study ICH was found in girls, more than boys but chance to develop to UTI due to idiopathic hypercalciuria was greater in boys. This result was not evaluated in previous studies and it can be a new concept that shows impact of gender. ICH is a metabolic and genetic related disorder that has many uncertain aspects, so more studies to find the answer of this difference is needed.

REFERENCES

- Esfahani, S. T. M., Abbas Siadati, Ali Ashraf Nabavi, Mohammad (2007). "Prevalence and symptoms of idiopathic hypercalciuria in primary school children of Tehran." *Iranian Journal of Pediatrics* 17(4).
- Jackson EK. *Diuretics*, B. L., Lazo JS, Parker KL (2005). Goodman & Gilman's the pharmacological basis of therapeutics. 11th Ed, New York, McGraw_Hill; 753-789.
- Kalia, A., L. B. Travis, et al. (1981). "The association of idiopathic hypercalciuria and asymptomatic gross hematuria in children." *J Pediatr* 99(5): 716-719.
- Lieske, J. C., R. Leonard, et al. (1996). "Adhesion of calcium oxalate monohydrate crystals to anionic sites on the surface of renal epithelial cells." *Am J Physiol* 270(1 Pt 2): 192-199.
- Lopez, M. M., L. A. Castillo, et al. (1999). "Hypercalciuria and recurrent urinary tract infection in Venezuelan children." *Pediatr Nephrol* 13(5): 433-437.
- Mahmoodzadeh, H., A. Nikibakhsh, et al. (2010). "Idiopathic hypercalciuria in children with vesico ureteral reflux and recurrent urinary tract infection." *Urol J* 7(2): 95-98.
- Mannhardt, W., A. Becker, et al. (1996). "Host defense within the urinary tract. I. Bacterial adhesion initiates an uroepithelial defense mechanism." *Pediatr Nephrol* 10(5): 568-572.
- Nikibakhsh, A., H. MAHMOUDZADEH, et al. (2007). "Hypercalciuria associated with recurrent urinary tract infections in children." *MEDICAL JOURNAL OF TABRIZ UNIVERSITY OF MEDICAL SCIENCES*.
- Perrone, H. C., J. Toporovski, et al. (1996). "Urinary inhibitors of crystallization in hypercalciuric children with hematuria and nephrolithiasis." *Pediatr Nephrol* 10(4): 435-437.
- Sadeghi-Bojd, S. and M. Hashemi (2008). "Hypercalciuria and recurrent urinary tract infections among children in Zahedan, Iran." *JPM* 58(624).
- Scheinman, S. (1999). "Nephrolithiasis." *Semin Nephrol* 19(4).
- Stojanović, V., B. Milošević, et al. (2007). "Idiopathic hypercalciuria associated with urinary tract infection in children." *Pediatric Nephrology* 22(9): 1291-1295.
- Vachvanichsanong, P., M. Malagon, et al. (1994). "Urinary incontinence due to idiopathic hypercalciuria in children." *J Urol* 152(4): 1226-1228.
- Yousefi, P., M. Firouzifar, et al. (2012). "Does hydrochlorothiazide prevent recurrent urinary tract infection in children with idiopathic hypercalciuria?" *Journal of pediatric urology*.