Value of random urinary calcium to creatinine ratio in diagnosing hypercalciuria in children with nocturnal enuresis

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ABSTRACT

Background: Nocturnal Enuresis is a common problem affecting 20% of five years old children and up to 2% of adolescent and young adult. Although it is a self limiting benign condition, it has social and psychological impact on the child and his family. Many pathophysiological theories had been suggested, but none is confirmed. Hypercalciuria has been suggested to be associated with higher incidence of nocturnal enuresis.

Objectives: The aim of our study to test the value of Ca/Cr ratio, on random urine sample, in diagnosing hypercalciuria in enuretic children.

Type of study: Cross sectional study.

Methods: Forty four enuretic children were enrolled in this study and forty five children without nocturnal enuresis were taken as control group.

Results: The prevalence of abnormal Ca/Cr ratio was higher among enuretic children when compared with control group; the result was statistically significant (P. value0.002). Among the enuretic children, higher Ca/ Cr ratio was statisticallyassociated with urinary symptoms, abnormal general urine examination, and positive family history. No such association was found with the gender or frequency of bed wetting per week.

Conclusions:the results of this study suggest that hypercalciuria has a significant association with NE, rendering routine screening of hypercalciuria by Ca/Cr ratio on a random urine sample, is reasonable. Furthermore, a large scale studies are needed to confirm the role of low calcium diet, and other measures in treatment of idiopathic hypercalciuria, in the management of enuretic children with abnormal Ca/Cr ratio.

Key Words: Ca/Cr ration, hypercalciuria, nocturnal.

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Nocturnal enuresis (NE) is defined as repeated, spontaneous voiding of urine during sleep in a child aged five years or older [1]. It is a common problem in childhood and early adolescent, affecting 20% of five years old children and up to 2% of adolescent and young adult [2]. Nocturnal enuresis is more common in boys than girls with a prevalence of 9% in boys and 6% in girls among seven years old children [3, 4]. In our country, there is no reliable population based estimate of the problem, but studiesfrom different governorate show different figures. A cross sectional study among primary health care attendance in Mosul report a prevalence of 6% while a study from Nassiriyah governorate shows a prevalence of 40.6 % among children aged 5-6 years and 5.4% among adolescent aged 13-15 yearswith an overall prevalence rate of 24.7%[5,6]. Although nocturnal enuresis in itself is a benign condition and has a high rate of spontaneous remission, the emotional impact on a child and family can be considerable, in which some children with enuresis report feelings of embarrassment and anxiety, loss of self-esteem, and effects on self-perception, and school performance[7]. Additionally, in our country, it is regarded as a social stigma. All these associated psychological and social problems necessitate the need for medical intervention. Studies on NE suggest different etiological theories including genetics, sleep and high arousal threshold, reduced functional bladder capacity, endocrinological (lack of increment in plasma vasopressin at night) and neurological disorders [8, 9]. Yet, no theory provided a conclusive evidence of the pathophysiology of the problem.

Hypercalciuria might be associated with different urinary tract symptoms in clinical practice including dysuria,urgency,frequency, abdominal and flank pain and gross or microscopic hematuria [10]. Hypercalciuria has been suggested by Pace et al in 1999, as an important pathogenic factor in NE [11], because he noted that a proportion of enuretic children had absorptive hypercalciuria. Since that time, many studies were done to confirm the association and some strategies were made to measure the urinary calcium excretion in the evaluation of nocturnal enuresis [12]. On the other hand, Nevéus et al [8] andKamperis et al [13] studies failed to demonstrate any significant difference in calcium excretion in children with or without NE.

The aim of our study wasto confirmthe association between nocturnal enuresis and hypercalciuria using a simple method by measuring calcium to creatinine ratio on a random urine sample of enuretic children and to compare it with a control group.

Methods. This case control study was conducted at a privatepediatrics clinic in AL-Sadar city, Baghdad, during the period from November 2012 to November 2013. Random

samples of children, aged 5-15 years, with NE consulting the clinic were enrolled in the study. An age and sex matched children without NE, consulting the clinic for different reasons, were taken as a control group. Pretested questionnaires were filled after interviewing with the parents of the target child, the questionnaire involved the important demographical variables (age, gender, family history of nocturnal enuresis, urinary symptoms, frequency of nocturnal enuresis).Urine samples sendfor general urine exam and calcium / creatinine ratio. General urine exam was regarded as abnormal when it reveals signs of infection like pus cell more than 5 per high power field and bacteruria. Urinary calcium levels were determined by the specific binding of cresolphthaleincomplex one (OCC) and metalchromic indicatorspecterophotometer method (Linear chemicals, Spain) , urinary creatinine levels were measured by enzymatic method(kinetic) with Jaffe's reaction.All the tests were done in one laboratory by one personal (author). Ca/Cr ratio exceeding 0.21 considered abnormal [14].

Statistical analysis

Data where introduced to PC and MINITAB version 16 statistical software were used in statistical analysis. Tables and graphs were used to describe results. Chi square and T test were used to find out significant association or differences between relevant variables. P. value of < 0.05 was considered as statistically significant.

Results. Forty four children with NE were enrolled in this study, and 45 continent children comprised the control group. There was no statistically significant difference between the two groups regarding the age and gender (p value > 0.05) Table 1. Hypercalciuria was found in 17(38.6%) of patients with NE and nine (20.4%) of the control group. The difference was statistically significant (P value 0.002, 95% CI, 0.0332-0.1398) Table 2.

Table1: Two samples t-test showing age distribution of cases and control group.

	Number	Means	St dev	95%CI	P. value
Cases	44	8.36	2.06	-0.631, -0.958	0.683
Control	45	8.20	1.69		

Table 2: Two-Sample t-test and CI: Ca/Cr ratio of cases and control groups.

Group	No.	Abnormal Ca/Cr ratio No (%)	Mean	SE mean	95%CI	P. value
Cases	44	17(38.6)	0.253	0.023	0.0332, 0.1398	0.002
Control	45	9(20.4)	0.167	0.014		

Table 3 shows the clinical characteristics of NE group with and without hypercalciuria. Other urinary symptoms, abnormal GUE and positive FH were significantly higher among those with NE and hypercalciuria than those without hypercalciuria while the gender, age and frequency of bedwetting per week found to be non-significant.

Table 3: Clinical characteristics of NE group with and without hypercalciuria.

Finding	Normal Ca/Cr ratio N 27	Abnormal Ca/Cr ratio N 17	P value
Gender Boy Girl	16 11	7 10	0.39
Age	Mean=8.33 SD=194	Mean=8.38 SD=1.88	0.936
Frequency of bedwetting per week	Mean= 5.37 SD= 1.94	Mean =5.24 SD= 1.95	0.824
Urinary symptoms	Yes = 10 No = 17	Yes = 12 No = 5	0.03
Abnormal GUE	Yes = 6 No = 21	Yes = 13 No = 4	0.001
Positive Family history	Yes = 11 No = 16	Yes = 16 No = 1	0.001

Figure 1 shows a statistically significant higher incidence of positive family history of NE among cases when compared with control group, P value 0.026.

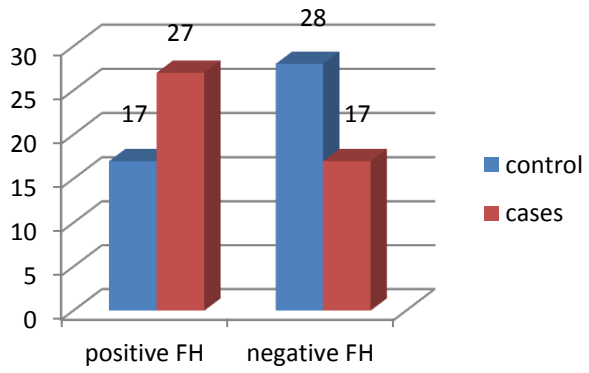

Figure 1: Association between NE and family history of NE. Chi-Sq. = 4.951 P-Value = 0.026

Discussion.NE is a common problem in children and adolescent causing social and psychological disturbances in implicated children and their families. Hypercalciuria in children has been reported to present with various noncalculus lower urinary tract symptoms, including dysuria, urgency, microscopic and macroscopic hematuria, urinary tract infection, supra pubic pain and enuresis. In practice, routine workup of a child with NE does not include detection of hypercalciuria. Conflicting data has been published about the role of hypercalciuria in NE. Recently hypercalciuria has been demonstrated as a main pathogenic factor in children with nocturnal enuresis with a correlation between hypercalciuria and nocturnal polyuria, low urinary osmolarity and increase sodium and osmolar excretion in the night time urine sample [15], which was first discovered by Pace et al, who found that children with nocturnal enuresis had increased urinary calcium excretion [11].On the other hand, some other studies failed to find such association between hypercalciuria andNE[13]. Because of the difficulty of 24 hours urine collection in children, we try to use a simple method for detection ofhypercalciuria in enuretic children that can be done on outpatient bases using a random urinary sample.

Our study demonstrated that hypercalciuria was significantly associated with nocturnal enuresis as it is found in 38.6% of enuretic children and 20.4% of non enuretic children with a P value of 0.002. This finding is consistent with Aceto et al study that found hypercalciuria was present in 39.8% of enuretic children and it has a pivotal role in nocturnal enuresis, as it is significantly associated with low ADH levels and nocturnal polyuria [16]. Ehsan V et al found that hypercalciuria present in 21.3% of patients with nocturnal enuresis [17], Another two studies found a lower rate of hypercalciuria among enuretic children 10% and 15% respectively [12,18]. These differences in the prevalence rate of hypercalciuria in enuretic children might be attributed to the cutoff point definition of hypercalciuria, in addition, to several factors that affect urinary calcium excretion like geographical area, dietary intake of calcium and the level of urinary sodium, phosphate and magnesium [19, 20].As we found hypercalciuria significantly higher in enuretic children when compared with the control, routine screening for hypercalciuria should be part of the initial evaluation of all children with NE. Diagnosis and treatment of idiopathic asymptomatic hypercalciuria by dietary manipulation with low calcium dietand high fluid intake might improve the symptoms of NE. This is in agreement with the conclusion of the study done by Giovanna Valenti et al [21].Further clinical study, with a trial of low calcium diet in enuretic children, with or without thiazide diuretics, is required to confirm this conclusion.

Among the group of enuretic children, we find no statistically significant differences regarding the gender or the frequency of wet night per week. This is comparable to Ehsan V study that didn't find a significant sex difference [17], and Rath et al study who found no statistically significant gender difference in hypercalciuria [19].

Previous reports have shown that children with hypercalciuria can present predominately with symptoms and findings involving the renal system including gross hematuria, microscopic hematuria, frequency, urgency, dysuria, urinary tract infection and suprapubic pain [10, 22]. Our study showed that there is a significant correlation between hypercalciuric children with nocturnal enuresis and urinary symptoms and findings in comparison withenuretic children without hypercalciuria. This finding is consistent with Fallahzadeh et al study who found urinary Ca/Cr ratio is significantly increased in children with all types of urinary symptoms [10]. Also, Vachvanichsanong et al who found 23% of children with idiopathic hypercalciuria had urinary incontinence of which 45% nocturnal [23].Urinary tract infection in children might present with various signs and symptoms including NE. Hypercalciuria might be associated with urinary tract infection as revealed by Stojanovic et al study who assume that renal calculi and crystals are predisposing factors for UTIS, because bacteria may present within damaged calcium crystals which offer a safety net to bacteria, protecting them from being washed away by urine [24].

There are publications demonstrating an important association between nocturnal enuresis and family history and genetics [25]. This study showed that there is a significant correlation between nocturnal enuresis and positive family history when compared cases with control , figure 1, this finding is comparable to a study done by Gulumser et al that found the presence of enuresis in family members, had a significant effect on the appearance of enuresis in the child [26]. Furthermore, this study shows a significant correlation between family history and hypercalciuria among enuretic group, table 3. One explanation might be the familial predisposition for hypercalciuria as some studies show that approximately half of patients with idiopathic hypercalciuria have a positive family history of renal stones [27] and other studies suggest autosomal dominant trait as a mode of inheritance for idiopathic hypercalciuria [28].

In conclusion, the results of this study suggest that hypercalciuria has a significant association with NE, rendering routine screening of hypercalciuria by Ca/Cr ratio on random urine sample, is reasonable. Furthermore, a large scale studies are needed to confirm the role of low calcium diet, and other measures in treatment of idiopathic hypercalciuria, in the management of enuretic children with abnormal Ca/Cr ratio.

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