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Original Article

Prevalence of Idiopathic Hypercalciuria in Children with Urinary System Related Symptoms Attending our University Hospital in 2019.

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Abstract

Introduction: Idiopathic hypercalciuria is a group of diseases which can be manifested with urinary symptoms. Its importance is due to high prevalence, recurrent infections, and stone formations which are often asymptomatic.

Aim of the study: The objective of this study was to determine the prevalence of idiopathic hypercalciuria in children with urinary system related symptoms attending Pediatric Nephrology Clinic & General Pediatric Clinic at Fayoum University Hospital from June to December 2019.

Methods: This descriptive cross-sectional study was done in2019 at Fayoum University Hospital on 206 children who were between 2 to 12 years old. Random morning urine samples was collected from all patients for measurement of Calcium/Creatinine levels**.** UCa/Cr ≥0.20 mg/mg has been used as an accepted cutoff value for screening children of 3 yr or more with hypercalciuria.

Results: We studied 206 children. IH was found in 32 out of 206 studied children (15.5%). The prevalence of idiopathic hypercalciuria was 46.9% in children with urinary tract infection, 12.5% and 6.3% in children with microscopic and macroscopic hematuria respectively. In children with dysuria, there were 90.6%, and34.4%, in children with kidney stone which was confirmed with sonography, 0% in children with urinary incontinence.

Conclusion: Hypercalciuria can be presented with different symptoms associated with urinary symptoms. Therefore, it is recommended to check the urinary calcium level in children with urinary symptoms with no definite etiology.

Keywords: idiopathic hypercalciuria, Urinary symptoms, Children

Running Title: Prevalence of Idiopathic Hypercalciuria in Children with Urinary System Related Symptoms Attending our University Hospital in 2019.

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INTRODUCTION

Hypercalciuria is generally considered to be the most common identifiable metabolic risk factor for calcium nephrolithiasis. It also contributes to osteopenia and osteoporosis [1]. The first description of idiopathic hypercalciuria (IH) was made from Albright et al., 1953 [2], who described normocalcemic patients with renal stones and increased urinary Ca excretion. Since then, IH is diagnosed with increasing frequency, affecting approximately 2.2-6.4% of the pediatric population [3, 4]. Hypercalciuria is defined as a 24-hour urinary calcium excretion more than 4 mg/kg/d in a child who weighs less than 60 kg. In infants younger than 3 months, 5 mg/kg/d is considered the upper limit of normal for calcium excretion [5, 6] .

The calcium-creatinine (Ca/Cr) concentration ratio (mg/mg), determined from a randomly collected urine sample, can be used to initially screen pediatric patients for hypercalciuria. The Urinary Ca/Cr greater than 0.2 in children and greater than 0.8 in infants is considered as hypercalciuria [7, 8]. Although many children with this problem are asymptomatic, (IH) has been identified in 20% to 30% of children with hematuria, dysuria, frequency-urgency syndrome, and voiding dysfunction [5, 9].

Idiopathic hypercalciuria is the most common cause of isolated tract stones [10, 11]. Also, idiopathic hypercalciuria is a risk factor for recurrent urinary tract infection which can be prevented via suitable diagnosis and treatment [12]. Suitable treatment prevents stone formation and decrease of bone density in both children and adults [13].

Hematuria is the major non-calculi manifestation of IH in children. The presence of hematuria in a child with IH also appears to be a strong predictor for the subsequent development of calcium oxalate nephrolithiasis. Microscopic hematuria due to IH is asymptomatic; whereas some discomfort such as dysuria or suprapubic pain is often seen with gross hematuria. The gross hematuria is often transient, although a few children have been reported to have gross hematuria lasting for several days [9, 14]. Prevalence of idiopathic hypercalciuria is variable in different countries. Idiopathic hypercalciuria is associated with higher risk of renal stones among affected children [15]. Hypercalciuria is one of the most frequent risk factors for nephrocalcinosis and urolithiasis [16, 17].

Primary idiopathic hypercalciuria is the most common cause of calcium-containing stones. It has traditionally been divided into a renal and an absorptive subtype, distinguished by an elevated fasting urinary calcium excretion in the renal subtype. Many pediatric patients, however, cannot easily be classified[18] . Balestracci et al., 2014 [19] have reported the prevalence of 20% for idiopathic hypercalciuria among children with urinary tract infection. Also, the association of idiopathic hypercalciuria and reduced bone mineral density is suggested by some researchers [20, 21]. It is shown that dietary interventions may reduce the complications of idiopathic hypercalciuria [20].

Aim of the study The objective of this study was to determine the prevalence of idiopathic hypercalciuria in children with urinary system related symptoms attending Pediatric Nephrology Clinic & General Pediatric Clinic at Fayoum

University Hospital from June to December 2019.

METHODS

This Cross-sectional descriptive study was conducted on all children attending Pediatric Nephrology Clinic & General Pediatric Clinic, who had urinary symptoms using convenience sampling during a 6- months -period. We enrolled 206 children who fulfill our inclusion & exclusion criteria from June to December 2019 that achieved study power 83%. **Inclusion criteria:** Children between 2 years -12 years old, with urinary symptoms including dysuria, frequency, urinary tract infection, macroscopic and microscopic hematuria, nocturnal and daily urinary incontinence and kidney stones confirmed with sonography. **Exclusion criteria:** Patients who are using nephrotoxic drugs, corticosteroids, vitamin D for causes other than urinary symptoms will be excluded from the study. Random morning urine samples were collected from all the patients for measurement of Calcium/Creatinine ratio. **Statements:** The study was carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) and after the approval of the local ethics committee. Informed consent was obtained from all study subjects after the nature of the study was explained. **All children were subjected to the following:**

* Full history with special regards to: Place of residence, Urinary symptoms such as dysuria, frequency, hematuria, nocturnal and daily urinary incontinence and family history of any urinary problems.
* Full clinical examination: Especially abdominal examination for tenderness, renal fullness and abdominal distension.
* Laboratory investigations: Kidney functions & Electrolytes, Urine analysis, Urinary Ca / Creat ratio and Pelviabdominal U/S for patients with high Ca/Cr ratio.

RESULTS

We studied 206 children, their mean age was (6.13±2.9) years and ranged between 2 and 12 years; 51% (105) were males. A positive history of renal stones was found in 13.6% of them. Main complaints, clinical manifestations & high calcium creatinine ratios are shown in **Tables 1, 2, 3** respectively. While **Table 4** shows that there was highly statistically significant percentage of high calcium./ creatinine ratio (p-value <0.05) among patients who had dysuria, and had enuresis but not renal stones.

Table 1: Frequency of the main Complaints among the Study Group.

Variables	Number (n=206)	%
Dysuria	89	43.2%
Abdominal pain	57	27.7%
Enuresis	35	17%
Hematuria	25	12.1%

Table 2: Frequency of Different Clinical Manifestation among the Study Group.

Variables (n=206)	Clinical manifestation	
	Number	%
Dysuria		
No	71	34.5%
Yes	135	65.5%
Hematuria		
No	156	75.7%
Gross	31	15%
Microscopic	19	9.2%
Enuresis		
No	176	85.4%
Yes	35	17%
Recurrent UTI		
No	131	63.6%
Yes	75	36.4%
Renal Stones		
No	178	86.4%
Yes	28	13.6%

Table 3: Frequency of High Calcium Creatinine Ratio among the Study Group.

Variables (n=206)	Ca / Creat ratio	
	Number	%
Normal	174	84.5%
High	32	15.5%

Table 4: Comparison of Ca/Creat ratio Categories in Different Clinical Manifestation among the Study Group.

Variables (n=206)	Ca /creat ratio		p-value
	Normal	High	
Dysuria			
No	68(39.1%)	3(9.4%)	**0.001***
Yes	106(60.9%)	**29(90.6%)**	
Hematuria			
No	130(74.7%)	26(81.3%)	0.3
Gross	29(16.7%)	2(6.3%)	
Microscopic	15(8.6%)	4(12.5%)	
Enuresis			
No	144(82.8%)	**32(100%)**	**<0.006***
Yes	30(17.2%)	0(0%)	
Recurrent UTI			
No	114(65.5%)	17(53.1%)	0.2
Yes	60(34.5%)	15(46.9%)	
Renal Stones			
No	157(90.2%)	21(65.6%)	**0.001***
Yes	17(9.8%)	**11(34.4%)**	

Table 5: Ultrasound and Urine Analysis Findings Among Patients.

Variables (n=206)	Results of US/ urine analysis	
	Number	%
Abd. Ultrasound (n=53)		
No stone	25	47.2%
Stone	28	52.8%
Urine analysis (206)		
Pus	127	61.7%
RBCs (>10)	40	19.4%
Crystals	95	46.1%
Type of crystals in urine (n=95)		
Ca oxalate	42	44.2%
Urates	50	52.6%
Triple phosphate	3	3.2%

DISCUSSION

Idiopathic hypercalciuria (IH) is defined as hypercalciuria with normocalcemia in the absence of diseases known to cause increased urine calcium excretion [22]. The pathogenesis of IH is very complex and many potential factors can be involved, such as polymorphisms of the gene coding for proteins regulating tubular phosphate and calcium reabsorption and those responsible for proteins preventing calcium salt precipitation or gene coding for a water channel in the proximal tubule [23].

Furthermore, in families with an autosomal dominant mode of IH, inheritance connection between IH and loci on chromosome 1q23.3-q24, which contains the human soluble adenyl cyclase gene, chromosome 12q12-q14, which contains the vitamin D receptor gene and chromosome 9q33.2-q34.2, were established. [24] The gene responsible for familial IH has not been identified, but appears to be transmitted in an autosomal dominant manner [28]. Environmental factors may also significantly affect renal stone formation. Nutrient intake may change urine composition, but may also influence gene expression by epigenetic mechanisms [1].

Hypercalciuria is the most common cause of stones in children, representing up to 50% of metabolic risk factors identified, followed by hypocitraturia. In children with nephrolithiasis or nephrocalcinosis, hypercalciuria is found in 28–79% of cases. Most causes of hypercalciuria are idiopathic, both sporadic and familial [25]. Hypercalciuria with nephrolithiasis is associated with a wide variety of symptoms. The most common symptoms are abdominal pain (53–75%), gross hematuria (14–33%), and dysuria (15%), although 15% of cases present as an asymptomatic, incidental radiologic finding [26].

Urinary tract infection (UTI) is also a common associated symptom, affecting 8–45% children with nephrolithiasis [27]. Idiopathic hypercalciuria (IH) is a common metabolic abnormality in children [28].

Hypercalciuria is considered idiopathic if the serum calcium level is normal and known possible causes of normocalemic hypercalciuria can be excluded. Some differentials of normocalcemic hypercalciuria are

idiopathic hypercalciuria, hyperparathyroidism, furosemide or corticosteroid therapy, immobilization, Bartter syndrome, early vitamin D toxicity, limb fracture, thyrotoxicosis, and distal renal tubular acidosis (RTA) [9].

The normal upper limit for calcium excretion in children is generally considered to be 4 mg/kg/day and is best measured from 24-hour urine collection, which is recommended to exclude diurnal fluctuations related to intake of food and beverages [29]. The urinary calcium-to-creatinine ratio can be used as a screening test if 24-hour urine collection cannot be done. A ratio exceeding 0.21 in random voided urine can be defined as hypercalciuria [29].

In the current study, we assessed the frequency of idiopathic hypercalciuria in children between 2 to 12 years old with various urinary symptoms. Some studies have selected their samples from children with confirmed idiopathic hypercalciuria, and have reported the prevalence of different symptoms related to the urinary system in these patients. Both study designs are able to show the importance of urinary system related symptoms in children with idiopathic hypercalciuria. Assessment of 24-hour urine calcium level is difficult in children and we have used urine Ca/Cr level in random morning sample in study participants, which is shown to be accurate enough, and has specificity and sensitivity of more than 90%.

Several studies have reported significant age-related variations in U Ca/Cr. Esbjörner and Jones.,1995 [30] found a weak but significant negative correlation between postprandial U Ca/Cr and age in a group of children aged 2-18 yr (N=153). Sargent et al.,1993 [31] found an age-related decrease in U Ca/Cr in children<6 yrs. of age but did not specify the age at which U Ca/Cr values became stable. Safarinejad.,2003 [32] reported that the 95th percentile for U Ca/Cr decreased progressively after 7 yrs. of age. Since creatinine is derived from creatine in muscle, its urinary excretion is dependent on the muscle mass of the subject [33]. Mori et al., 2006 [34] reported that urinary creatinine excretion depended on the sex and BSA in children. In our study, U Ca/Cr showed no relation to sex.

There is a wide variation in the prevalence of idiopathic hypercalciuria between countries. For example, in Eastern Europe countries, IH prevalence ranges between 3% and 7%; while in other countries it is as follows: Spain: 3.8%, Germany: 8.6%, Italy: 9.1%; United States of America: 10%, Japan: 0.6%, and Brazil:3.2% [35-40]. The prevalence of hypercalciuria in India according to a study by Rath et al., 1994 [41] was reported to 6.5%.

There is high difference in the prevalence of idiopathic hypercalciuria in different regions of Iran: Ahwaz (3%), Tehran (5.4%) and Bandar Abbas (47.7%), can be due to difference in climate, study designs and data collections [9, 42, 43].

It was found that the difference in prevalence of idiopathic hypercalciuria according to gender was not statistically significant Moore et al.,1978 [3] and Ahmadzadeh et al.,2008 [42] have reported higher prevalence of idiopathic hypercalciuria among males, but higher prevalence of idiopathic hypercalciuria is reported among females (42.9% versus 17.1%) in the study by Sadeghi et al.,2008 [43]. Also, there were studies that showed a male preponderance of idiopathic

hypercalciuri [9, 41, 45] . However, according to a study done by Safaei et al.,2013 [5] in Rasht, Iran, the prevalence of idiopathic hypercalciuria in males and females was the same, which came in agreement with our study.

In a study done by Safaei et al., 2013 [5] a family history of urinary calculi in first-degree relatives was found in 63.2% of patients with hypercalciuria. In Vijayakumar et al.,2014 [46] study, 37 out 91 children had a positive family history of either stone disease or hypercalciuria, indicating that idiopathic hypercalciuria may be a complex condition resulting from inheritance in association with various risk factors like diet, environment, high salt intake, and reduced fluid intake.

In this study, a history of renal stones was found in 13.6% of patients with hypercalciuria which had no statistically significant difference with p-value >0.05. Also, recurrent urinary tract infection was confirmed in 75 children, among which, 15(46.9%) had idiopathic hypercalciuria. That had no statistically significant difference with p-value >0.05. Mortazavi F et al., 2014 [47] found that hypercalciuria was detected in 47.5% of the patients with recurrent UTI that was significantly higher than the control group. Similar to them, studies by Lopez et al., 1999 [12] in Venezuela and Biyikli et al.,2005 [38]in Turkey showed that 32% and 43% of the patients with recurrent UTI had hypercalciuria, respectively.

In a study by Vachvanichsanong et al., 2001 [48] recurrent UTI was accompanied by hypercalciuria in 31.4%of the patients. In a study by Stojanociv et al., 2007 [39] 44% of the patients with recurrent UTI, 10% of the patients with the first episode of UTI, and 7 of the participants in the control group had hypercalciuria (P<0.05). In another study in Zahedan, Iran, 30% of the patients with recurrent UTI and 11.4% of the controls had hypercalciuria (P<0.05) [44]. In contrast to other researches mentioned above & in agreement to the current study, Nacaroglu et al.,2013 [49] found idiopathic hypercalciuria in 16.7% of the children who were diagnosed with UTI. They did not find any associations between idiopathic hypercalciuria and the recurrence of UTI and renal scar formation.

According to Fallahzadeh et al.,2010 [50] the incidence of hypercalciuria in the patients with dysuria and day-time frequency were 32.2% and 32.6% respectively, while in a similar study by Parekh et al.,2000 [51] , the incidence of hypercalciuria was 22% in patients with pure dysuria, 21% in those with pure childhood daytime frequency, and 28% in individuals with frequency, urgency and dysuria simultaneously. Esteghamati et al., 2017 [43] found the prevalence of idiopathic hypercalciuria was 52.1% in children with dysuria.

Dysuria is reported in 135 (65.5%) of the children in our study, among which 29 (90.6%) had idiopathic hypercalciuria with high statistically significant difference with p-value <0.05.

Vachvanichsanong et al., 1994 [52] demonstrated that hypercalciuria is frequently associated with urinary incontinence in children. Of 124 children who were evaluated for hypercalciuria, 23% had urinary incontinence. They concluded that random urinary Ca/Cr ratio, which was used to screen hypercalciuria, should be part of the initial evaluation for urinary incontinence in children. Fallahzadeh et al., 2010 [50]

found that 39.6% of patients with urinary incontinence were hypercalciuric. Recently, Esteghamati et al., 2017 [43] found the prevalence of idiopathic hypercalciuria is 28.6% and 37.5% in children with nocturnal and daily urinary incontinency respectively. This study came in contrast to these studies, 30 children (14.6%) had urinary incontinence among which 0 (0%) had idiopathic hypercalciuria, that there is statistically significantly higher percentage of high calcium/ creatinine ratio with p-value <0.05 among patients who do not have urinary incontinence.

In agreement with our results, Neveus et al., 2002 [53] in their study concluded that the urinary calcium excretion does not differ between enuretic and dry children. Kamperis et al., 2006 [54] in another study observed no significant difference among calcium excretion of children with or without nocturnal enuresis. Microscopic hematuria has been reported to be the most common non-calculous manifestation of hypercalciuria in children in previous studies [52, 55, 56]. Five children were evaluated for painless hematuria by Roy et al.,1981 [57]and they inferred that hypercalciuria was the probable cause of the unexplained painless hematuria in those children. In a study in 2001 Penido MG et al [39] reported the prevalence of 31% for hematuria, among the patients with idiopathic hypercalciuria. In Fallahzadeh et al.,2010 [50] study, 32.9% of the patients with microscopic hematuria had hypercalciuria. Esteghamati et al., 2017 [43] found the prevalence of idiopathic hypercalciuria was 54.9% and 53.6% in children with microscopic and macroscopic hematuria respectively. In the current study, 19 (9.2%) had microscopic hematuria and 31 (15%) had gross hematuria. Among them, 4 (12.5%) and 2 (6.3%) had idiopathic hypercalciuria respectively with no statistically significant difference with p-value >0.05.

About 30-50% of calcium stone formers have idiopathic hypercalciuria [58] In a reported from UK, IH was defended in 25% of children with calculi [59]. The risk of nephrolithiasis increases progressively with the greater levels of IH [60]. In 85% of children with IH, renal calyceal microlithiasis has been reported in follow up sonographies. [61]. Ultrasonography of the abdomen can be performed to document renal stone disease. Polito et al., 2000 [45] reported 42 children with microcalculi and 4 with calculi on ultrasonography. Also, the prevalence of kidney stones was 56% in the study by Penido MG et al.,2001 [36] and 49.1% in Esteghamati et al.,2017 [43] study. In our study, ultrasonography showed kidney stones in 28 (13.6%) including 11 (34.4%) children with idiopathic hypercalciuria with high statistically significant difference with p-value <0.05.

CONCLUSION AND RECOMMENDATIONS

Based on the results of our study, the prevalence of idiopathic hypercalciuria is high among children with urinary symptoms. The importance of our findings is that idiopathic hypercalciuria should be considered as an important cause of urinary symptoms in children even abdominal pain when other causes are less probable. It is important to

establish a reference value for urinary calcium excretion in each geographic area

LIMITATION OF THE STUDY

The present study had several limitations. The major limitation was the lack of a group of normal children for comparison. That means we need more comprehensive and multicenter studies.

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AUTHORS' CONTRIBUTIONS

The submitted manuscript is the work of the author & co-author.
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Conception and design of study: All authors.
Acquisition of data: 2nd, 3rd & 4th author.
Analysis and/or interpretation of data: All authors.
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STATEMENTS

Ethics approval and consent to participate
This study protocol and the consents were approved and deemed sufficient by the Ethical Committee of Fayoum University, Faculty of Medicine-and informed written consent was obtained in every case from their legal guardians.

Consent for publication
Done

Availability of data and material
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