Prevalence and Symptoms of Idiopathic Hypercalciuria in Primary School Children of Tehran

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Abstract

Objective: Determining prevalence of idiopathic hypercalciuria (IH) in primary school children of Tehran.

Material & Methods: We evaluated 778 primary school children (age 6-11, mean 9.1 years) in two steps: first (Screening test), we measured urine calcium to urine creatinine ratio (UCa/UCr) and in the second step (Definitive test), for those children who had UCa/UCr ratio more than 0.21 mg/mg we measured 24 hours urine calcium excretion. Children with secondary forms of hypercalciuria were excluded from the study. Children with idiopathic hypercalciuria were evaluated for manifestations of IH.

Findings: Among 778 children, 195 (25.1%) had UCa/UCr ratio more than 0.21 mg/mg, but from these 195 children only 128 children delivered 24 hours urine samples. Among these 128 children for whom 24 hours urine calcium measurements were done 28 children excreted more than 4mg/kg/day calcium without hypercalcemia or any other known causes of hypercalciuria and we defined them as having idiopathic hypercalciuria. If all 195 suspicious cases of IH had delivered 24-hrs urine samples we would have 42 cases of IH.

Conclusion: Prevalence of IH in our children was 5.4% and its manifestations were: hematuria, dysuria, recurrent abdominal pain, urinary incontinence, urgency, urinary tract infections and urolithiasis.

Key Words: Idiopathic hypercalciuria, Children, Urolithiasis, Hematuria, Dysuria, Urgency

Introduction

Idiopathic hypercalciuria (IH) is one of the most common human metabolic abnormalities and is present in approximately 60% of individuals with nephrolithiasis.¹ Anecdotal and uncontrolled data point to association between IH and signs and symptoms like hematuria, development of calcium oxalate nephrolithiasis, dysuria, urinary...
frequency, enuresis, abdominal and back pain, and urinary tract infection.\cite{2-4} There is a worldwide variation in prevalence of IH in children from 0.6\% in Japan\cite{5} to 26\% in France\cite{6}. Because there is not a report regarding prevalence of IH in Iranian children, we studied the prevalence and symptoms of IH in a large group of healthy primary school children living in Tehran.

**Material & Methods**

This is a descriptive and cross-sectional study. From October 1999 to February 2000, we went to some of primary schools in Tehran and with informed consent of parents, school directors and teachers we collected non-fasting random urine specimens from children. At this stage only healthy children were included into the study. After determining urine concentration of calcium and creatinine, children whose urine calcium to urine creatinine (UCa/UCr) ratio was more than 0.21 mg/mg, were defined as suspicious cases of hypercalciuria. 24 hours urine specimens were collected from these children and urine calcium excretions were measured. Children whose 24 hours urine calcium excretion exceeded 4 mg/kg body weight were defined as hypercalciuric children. In hypercalciuric children we performed physical examinations and laboratory tests (serum calcium, phosphorus, alkaline phosphates, PTH, urinalysis, urine culture, and 24 hours urinary protein). Children with secondary forms of hypercalciuria were excluded from the study.

Urine calcium was measured by colorimetric method with methylthymol blue. The 8-hydroxyquinolon was used to prevent Mg\textsuperscript{2+} ions interfering. Urine creatinine was measured by kinetic Jaffe reaction. All measurements were done by Automatic Analyzer, HITACHI 704 Boehringer Manheim.

Descriptive statistics included mean and standard deviation (SD) used for UCa/UCr ratios and 24 hour urine calcium excretion parameters. This study was approved by the Research and Ethics Committee of Tehran University of Medical Sciences.

**Findings**

Seven hundred and seventy eight primary school children aged 6-11 years (mean 9.1 years) were recruited into the study. Four-hundred seventy one of children (60.5\%) were boys and 307 (39.5\%) were girls. At this stage 195 children (25.1\%) had UCa/UCr more than 0.21 mg/mg, 143 (73.3\%) of them were boys and 52 (26.7\%) girls. Of 195 children who had hypercalciuria, only 128 children delivered 24 hours urine samples.

Among these 128 children of whom 24 hours urine calcium measurements were available, 28 children (21.9\%) excreted more than 4mg/kg/day calcium without hypercalcemia or any other known causes of hypercalciuria and we defined them as having idiopathic hypercalciuria. So if all 195 suspicious cases of IH had delivered 24-hrs urine samples we would have 42 cases of IH. Thus, prevalence of IH in our children is 5.4\%.

Seven of these 28 children had familial history of urolithiasis and 13 of them had signs or symptoms which could be due to IH (Table 2).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Girls</th>
<th>Boys</th>
<th>All children</th>
</tr>
</thead>
<tbody>
<tr>
<td>UCa/UCr ratio</td>
<td>0.38 ± 0.09</td>
<td>0.29 ± 0.04</td>
<td>0.33 ± 0.07</td>
</tr>
<tr>
<td>24 hr UCa</td>
<td>4.57 ± 0.40</td>
<td>4.60 ± 0.80</td>
<td>4.62 ± 0.45</td>
</tr>
</tbody>
</table>
Table 2- Signs and symptoms in hypercalciuric children*

<table>
<thead>
<tr>
<th>Signs and symptoms</th>
<th>Girls</th>
<th>Boys</th>
<th>All children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urolithiasis</td>
<td>-</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Hematuria</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Recurrent abdominal pain</td>
<td>2</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Dysuria</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Urgency</td>
<td>-</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Bedtime enuresis</td>
<td>2</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Daytime enuresis</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Bedtime+daytime enuresis</td>
<td>-</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>History of UTI</td>
<td>1</td>
<td>12</td>
<td>21</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>9</td>
<td>12</td>
<td>21*</td>
</tr>
</tbody>
</table>

* Some of 13 hypercalciuric children had more than one sign or symptom.

**Discussion**

Hypercalciuria is named idiopathic if serum calcium level is normal and known causes of normocalcemic hypercalciuria (table 3) can be excluded.[7] IH is a common metabolic abnormality in children. The precise definition of idiopathic hypercalciuria has not been yet established, but in current clinical practice, the upper limit of normal for calcium excretion in children is generally considered to be 4 mg/kg/day.[8] Urinary calcium is best measured in 24-h collection. However such collections are difficult to obtain in children and many investigators have used the urinary calcium/creatinine ratio (UCa/UCr) as alternate measurement.[7-12] As in our study, some authors have used UCa/UCr ratio as a screening test and 24-h urine calcium as definitive test of diagnosing hypercalciuria.[7,13] Hypercalciuria is likely present when a randomly voided urine sample shows a calcium to creatinine ratio (both values in milligrams) exceeding 0.21.[7,8]

There is a wide variation in prevalence of IH in different countries. The lowest prevalence is reported from Japan: 0.6%.[5] Reported prevalence in other countries has been Germany 8.6%[14], Italy 9.1%[15], USA 12-13%[16,17], Turkey: 2.9%[18], Argentina 12.7%[19], and France 26%.[6] In our study it was 5.4%.

Most cases of IH are asymptomatic. The prevalence of symptoms and signs in children is different in reported surveys. In our study 46.4% children were symptomatic. Because the number of children is low, determining prevalence of each symptom is not possible.

IH is a complex disease resulting from an inheritance and is compatible with autosomal dominant transmission.[20-22] Many candidate genes have been studied to determine their role in the pathogenesis of hypercalciuria, but most of the candidate genes have produced negative to only marginal results[20, 23-27]. It seems that we are still on the way to discovering genes with a role in IH[26]. It is probably the most commonly diagnosed metabolic disorder in adults with renal calculi.[1,7,22,28,29] Between 30-50% of calcium stone formers have idiopathic hypercalciuria.[30] In a reported from UK, IH was defended in 25% of children with calculi.[31] The risk of nephrolithiasis increases progressively with the greater levels of IH.[29] In 85% of children with IH, renal calyceal microolithiasis has been reported in follow up sonographies.[32]

Children with IH have been noted with increasing frequency to manifest an array of predominantly lower urinary tract signs and symptoms, these symptoms and signs are probably due to micro crystallization with injury to the urinary tract epithelia.[33] Microscopic hematuria, urinary frequency-urgency syndrome, daytime incontinence, colicky abdominal pain, recurrent urinary tract infections and episodic gross hematuria are the most
Table 3- Causes of normocalcemic hypercalciuria

<table>
<thead>
<tr>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic hypercalciuria</td>
</tr>
<tr>
<td>Furosemide therapy</td>
</tr>
<tr>
<td>Corticosteroid therapy</td>
</tr>
<tr>
<td>Sarcoidosis</td>
</tr>
<tr>
<td>Immobilization</td>
</tr>
<tr>
<td>Hereditary hypercalciuria with hypophosphatemic rickets</td>
</tr>
<tr>
<td>CLCNS Cloride – Channel mutation</td>
</tr>
<tr>
<td>Bartter's syndrome</td>
</tr>
<tr>
<td>Seyberth syndrome</td>
</tr>
<tr>
<td>Vitamin D toxicity (early)</td>
</tr>
<tr>
<td>Limb fracture</td>
</tr>
<tr>
<td>Thyrotoxicosis</td>
</tr>
<tr>
<td>Distal renal tubular acidosis</td>
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</tbody>
</table>

common clinical symptoms in children with IH.\cite{7,33,34}. Hematuria is the major noncalculi manifestation of IH in children.\cite{28,35-37} The presence of hematuria in a child with IH also appears to be a strong predictor for the subsequent development of calcium oxalate nephrolithiasis.\cite{37} 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.\cite{36,37}

IH can produce dysuria-urinary frequency in children\cite{2,32} and irritability in infants.\cite{3} Also in a study of 124 children with idiopathic hypercalciuria 28 (23%) had urinary incontinence.\cite{38} IH may have a significant role in cases of functional voiding disorders.\cite{39} IH also has been implicated in producing nocturia in some children.\cite{7} Uncontrolled data also point to a possible association between IH and some cases of enuresis.\cite{7}

Recurrent abdominal and flank pain is also reported in children with IH.\cite{40,41} IH may be a contributing factor to recurrent UTI in children.\cite{42}

In recent years a great deal of attention has been directed towards the potential effect of IH on bone mineral density. Reduction of bone mineral density has been reported in both children\cite{43-46} and adults\cite{47-50} with IH.

IH had been traditionally divided into absorptive and renal types. This classification has been debated intensely in the literature. The current view is that both types are continuum and can occur in a child with IH\cite{51,52}. So in our study we did not try to characterize type of IH in children.

Conclusion

Prevalence of IH in our children was 5.4% and its manifestations were: hematuria, dysuria, recurrent abdominal pain, incontinence, urgency, urinary tract infections and urolithiasis.

References


Prevalence of Idiopathic Hypercalciuria in Primary School Children. ST Esfahani, et al


