Evaluation of 0-2 Month Old Infants Brought to the Pediatric Outpatient Clinic for Restlessness

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Abstract: Restlessness is one of the most frequent causes to bring a baby to a medical facility by parents. Most of the restless infants are diagnosed with infantile colic. We aimed to evaluate hypercalciuria and urinary system in 0-2 month old infants who were brought to the pediatric outpatient clinic due to restlessness**.** Only the 0-2 month old infants who were evaluated only for restlessness between January 1 and December 31, 2018 were included in the study. The data were obtained as retrospective evaluation of medical records. Complete urine analysis, urine culture, abdominal ultrasonography, calcium to creatinine ratio in spot urine and blood calcium examination was performed. The 95th percentile of the urinary calcium/creatinine ratio was accepted as the upper limit of normal. Blood calcium level above 10.8 mg/dl was considered as hypercalcemia. Of the 240 infants included in the study. The number of infants receiving breast milk alone was 146 (73.3%). Leukocyturia was detected in 24 infants. Urine culture was evaluated as positive for 59 infants. Spot urine calcium/creatinine ratio was evaluated in 201 infants. Of these, 10 patients had a high calcium/creatinine ratio. In infants receiving breast milk alone had a lower calcium/creatinine ratio. Urinary calcium/creatinine ratio was found to be significantly higher in infants with urinary tract stones and hypercalcemia**.** Not all infants brought to a medical facility due to restlessness should be considered to have infantile colic. Urine analysis should be performed and urinary tract infection and hypercalcuria should be investigated. Positive urine cultures obtained using a bladder bag should be considered hesitantly and should always be repeated. © 2020 NTMS.
Keywords: Baby, Restlessness, Hypercalciuria, Urinary Tract Infection.

1. Introduction

Crying is a way for babies to communicate with the environment. In most babies, crying and restlessness begin spontaneously during the first weeks of birth and spontaneously diminish towards the 3rd to 4th months (1). Babies cry to express their physiological needs such as hunger, sweating, chills and irritation from fecal soiling.

If their needs are met, they stop crying and calm down in a short time. Although crying is a physiological event in infants, excessive crying and restlessness may also occur in pathological conditions such as infantile colic, otitis and urinary tract infection (UTI). Crying and restlessness are among the most common reasons to bring a healthy baby to a doctor's office in the first four

months of life. Infantile colic is the most common condition for those infants who present to hospitals with crying (2). Infantile colic is episodes of crying lasting more than three hours a day and more than three days a week and that lasts at least three weeks (3). It has been reported to occur in 5-30% of babies during infancy (4).

There may be an underlying organic cause in 10% of infants brought to a medical facility due to crying. Organic causes include cow and/or soy milk protein allergy, gastroesophageal reflux or lactose intolerance. All etiological causes should be evaluated in infants who present with crying. Medical reasons can often be ruled out by careful history taking and physical examination (1).

In this study, we aimed to evaluate hypercalciuria and urinary system in children with 0-2 months admitted to outpatient clinics with restlessness.

2. Material and Methods

Only the 0-2 month old babies admitted to our outpatient clinic between January 1, 2018 and December 31, 2018 due to restlessness were included in the study. Data were obtained retrospectively from patient files. Physical examinations were recorded in detail. Infants who were diagnosed with otitis media, upper respiratory tract infection, lower respiratory tract infection or infantile colic were excluded from the study. The age, gender, weight, type of feeding and the use of formula of the infants were recorded. The data of complete urine analysis, urine culture (using a sterile urinary bag), abdominal ultrasonography (USG), calcium to creatinine ratio in spot urine (Ca/Cr) and blood calcium levels were also recorded.

A 24-hours urinary Ca excretion level above 4 mg/kg or 95th percentile values of urinary Ca/Cr ratio in children was accepted to be the upper limits of normal (5,6). The 5th, 10th, 25th, 50th, 75th and 95th percentile values were calculated for the Ca/Cr ratio. The 95th percentile value of the Ca/Cr ratio was accepted as the upper limit of normal. Blood calcium levels above 10.8 mg/dl were considered as hypercalcemia. (7)

The present study was approved by the clinical ethics committee of Erzincan University Faculty of Medicine (accession number: 604.01.02-E.43283)

2.1. Statistical Analysis

Data were interpreted using SPSS statistical package program (SPSS Inc, v22.0, USA). All results were expressed as Mean±Standard Deviation (SD). Using the Kolmogorov Smirnov test, the data was determined to have a non-normal distribution. For this reason, non-parametric tests were used. Spearman correlation test and Mann Whitney U test were applied to analyse the association between variables. $P < 0.05$ was considered statistically significant.

3. Results

Of the 240 babies included in the study, 114 were female (47.5%) and 126 were male (52.5%). The mean age of the infants was 29.9±15.4 days. When breast milk feeding was questioned, 180 (75%) infants were found to receive breast milk alone, 13 (5.5%) infants received formula alone and 47 (19.6%) infants received breast milk+formula. Demographic characteristics of the babies participating in the study were shown in Table 1.

Table 1: Demographic characteristics of infants.

Age	Male	31.4±15.2 days (Min-Max: 7-59)	
	Female	28.2±15.6 days (Min-Max: 6-59)	
	Total	29.9±15.4 days (Min-Max: 6-59)	
Gender	Male	126 (n)	52.5%
	Female	114	47.5%
Height		53.67±2.4 cm	Min-Max: 46-61
Weight		3917±695 g	Min-Max: 2800-6200
Head circumference		35.8±1.35 cm	Min-Max: 32-39
Nutritional status	Breast milk	180(n)	75%
	Formula	13	5.4
	Breast milk+Formula	47	19.6

Urinalysis and urine culture were requested in a total of 240 infants. Leukocyturia was detected in 24 (10%) infants. Urine microscopy was normal in 216 infants (90%). *E.coli* (76%) and *Klebsiella* (24%) was isolated in the urine of 59 infants with positive urine culture. Positive urine culture samples were repeated using a urinary catheter and 27 (45%) of them revealed to be positive for growth (Table 2).

Table 2: Results of urinalysis and incidences.

Finding	Number	Percentage
Normal	175	73
Leukocyturia	24	10
Hematuria	6	2.5
Crystals	35	14.5
Growing microorganism		
E.coli	45	76
Klebsiella spp	14	24

Spot urine calcium/creatinine (UCA/Cr) was analysed in 201 infants. Mean spot urine Ca/Cr was found to be 0.30±0.19. Hypercalciuria was found in 111 cases with an accepted cut-off of hypercalciuria as 0.21. Urinary hypercalciuria was found to be 0.77 in the 95th percentile and the UCa/Cr ratio was found to be high in 10 cases (Table 3).

Table 3: UCa/Cr value and percentile.

UCa/Cr	Number	Percentage
Over 0.21	111	55.2
Over 95 p	10	4.9

The mean spot UCa/Cr was compared between the genders. There was no significant difference in mean UCa/Cr between the males (0.29±0.17) and the females (0.31±0.21), (p=0.66). Spot UCa/Cr averages were compared between those who were breastfed alone and who received breastfeeding and formula or formula alone. Urine UCa/Cr averages were significantly lower in those who were breastfed alone (p=0.005).

No statistically significant difference was found between the mean UCa/Cr spot urine in infants with and without UTI (p=0.53). Urinary USG was performed in 108 of the infants in the study group. Vesicoureteral reflux (VUR), ureteropelvic stenosis, hydronephrosis, cystitis and calcium stones were observed in 2, 2, 1, 6 and 9 infants, respectively. Mean urine calcium to creatinine ratio was significantly higher in patients who had positive findings revealed by an imaging method compared to patients with negative findings by an imaging method (p=0.01).

Blood calcium and creatinine levels were measured in 70 of the infants. Creatinine level was normal in all infants. Blood calcium levels were elevated in 11 infants. Mean urinary UCa/Cr was found to be significantly higher in babies with hypercalcemia compared to babies with a normal blood calcium level (p<0.01). Correlation analysis showed a significant correlation between urinary calcium and blood calcium (r:0.38, p<0.001).

4. Discussion

As restlessness and crying are common symptoms in infancy, obtaining a good anamnesis from the parents is the first and most important step in the diagnosis and approach to the infant. Another important step in diagnosis is a detailed physical examination of the infant and evaluation of his/her growth and development. In addition, laboratory and radiological examinations are needed in infants with a good weight gain and normal physical examination. There are studies suggesting that urine analysis might be the only useful laboratory test especially in a baby crying a lot with a normal history and physical examination. (8)

In our study, only infants with the complaint of restlessness were included in the study. Babies with any findings in their examinations or interpreted in favor of infantile colic were excluded from the study, and 240 asymptomatic babies were examined. As indicated by Freedman et al. (8), complete urine analysis and urine culture were requested from all infants. Although leukocyturia was observed in 24 babies, Urine culture of about 1 in 4 babies were positive. Positive urine culture samples were repeated using a urinary catheter and half of them were found to have a positive growth. The rate of false positivity of the urine culture obtained using a bag in the neonatal period was demonstrated to be high (9). In this present we also found this false positive rate to be high. This shows that the urine cultures obtained using a bag should be considered hesitantly and if necessary, urine cultures should be repeated with urinary catheters or suprapubic aspiration.

Urinary infection is more common in males in the newborn period compared to females (10, 11). In our study, 24.6% of the infants had a positive urine culture and urine culture positivity was found to be higher in males compared to females. The urine of the infants with positive urine cultures was positive mostly for *E.coli*. *E. coli* has been reported to be the most frequently isolated pathogen in UTI in many studies (12-14).

Hypercalciuria is one of the most important risk factors for stone disease in children and adults. Most patients, especially younger children, are asymptomatic (15). Young patients present with complaints of restlessness, UTI, vomiting or fever rather than abdominal and flank pain. In this present study, urinary stone and hypercalciuria were found in 8.3% and 4.9%, respectively of infants presenting with restlessness. In the study conducted by Melek et al., the most common reason for presentation in children less than 5 years of age with urinary system stones was reported as restlessness (16). Also, in a similar study by Baysal et

al. 29 patients diagnosed at the first two years of age were reported to be presenting with restlessness as the most common cause (17). In the study of Altincik (18), the mean UCa/Cr of the patients with complaints of restlessness was significantly higher compared to those without complaints.

In this present study, no difference was found between the mean urinary Ca/Cr between male and female infants. Similarly, in the studies of Sonmez et al. (19) and Donmez et al. (6), no association was found between gender and mean urinary Ca/Cr.

In the literature, there are some studies showing that feeding with formula has an effect on urinary stone and hypercalciuria formation (20, 21). Similar to our study, in the study of Erol et al. it was reported that the mean urine Ca/Cr was significantly lower in breastfed infants (22).

In our study, no statistically significant difference was found between the mean spot urine UCa/Cr in infants with and without UTI. It is stated that there is no significant relationship between UTI and urinary calcium excretion (18). Vachvanichsanong et al. reported that the quantitative urinary calcium excretion in children with UTI is not different from those without UTI (23).

In many studies (24-26), urinary calcium excretion was found to be higher in patients with urinary stone detected on USG. Similarly, in our study, it was found that infants with urinary stones had a significantly higher rate of hypercalciuria.

The amount of calcium filtered from the glomeruli varies directly with the concentration of calcium in the serum and glomerular filtrate. The serum concentration of calcium and filtered calcium increase, the amount of calcium excreted in the urine also increases (27). In this present study, it was observed that there was a significant increase in urinary calcium as the blood calcium level of infants increased.

5. Conclusions

As a result, although no definite cause could be found in most of the babies brought for restlessness or they are considered to have infantile colic, urine analysis should be performed and urolithiasis should be excluded in infants who have complaints of restlessness. In patients with hypercalciuria, imaging methods should be used for urinary system stone disease.

Conflict of interest statement
The authors declare that they have no conflicts of interest.

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