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An observational epidemiological study of febrile convulsion due to urinary tract infection

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ABSTRACT

Background: Febrile convulsion (FC) is the most common seizure disorder in childhood. Few studies focused on epidemiologic characteristics of urinary tract infections accompanied by FC.

Objectives: To evaluate prevalence and incidence rates of FC among children with urinary tract infection.

Patients and Methods: An observational study in epidemiology was performed in nephrology clinic of a tertiary children hospital from June 2002 to 2016. Totally 1242 cases were followed and those aged 6-60 months enrolled in the study. Demographic characteristics were compared between patients with and without FC.

Results: 784 cases including 704 girls (89.8%) and 80 boys (10.2%) enrolled. Twenty-five patients (3.18%) presented with FC. FC occurred in 25 of 503 cases (5%) with febrile urinary tract infection. Twenty girls and 5 boys were in FC and 684 girls and 75 boys were in non-FC groups ($P=0.1$). The average age in FC and non-FC groups were 15.52 ± 8.4 and 25.16 ± 16 months respectively ($P=0.004$). Patients were divided into 2 age sub-groups: 6-24 and 26-60 months. A significantly higher number of cases in FC compared with non-FC group were in age subgroup of 6-24 months ($P=0.028$).

Conclusions: Our study revealed a prevalence rate of 3.18% and an incidence rate of 5% for FC among children with urinary tract infection. Also FC subjects had a significantly younger age at presentation than non-FC cases. We found that FC as presentation of urinary tract infection occurred up to 3 years old, and there is no significant gender difference between FC and non-FC cases.

Implication for health policy/practice/research/medical education:

FC is not a common presentation of UTI, but seems it exclusively occurs following febrile UTI in the first 3 years of life with majority of cases in 6-12 months. In children 3 up to 5 years, rarely urinary tract infection presents as FC.

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1. Background

Urinary tract infection (UTI), with the prevalence rate of 5% in febrile children, is a common cause for visits in pediatric emergency departments. Also febrile convulsion (FC) is a common reason for admissions in emergency sections of children hospitals (1,2). FC, the most common types of seizure in children, affects 2-5% of pediatric population (3), however the incidence rate of 14% had been reported by some old studies (4). The source

of infection in FC patients is different including upper respiratory tract infections, pneumonia, otitis media, gastroenteritis and UTI (5,6-8).

Over the past decades, several studies have investigated the prevalence of UTI among children with FC. It has been reported between 0.75% and 11.1% (5,9-11). Few studies focused on prevalence and incidence rates of FC among children with UTI, but not in a large population (12,13).

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2. Objectives

To offer new insight, the present epidemiologic study was carried out to evaluate the prevalence and incidence rates of FC in a large population of children with UTI as well as description the epidemiological characteristics of this population.

3. Patients and Methods

An observational study in epidemiology was performed in nephrology clinic at a tertiary hospital (Dr. Sheikh children hospital) from June 2002 to June 2016.

1242 patients with the first episodes of either symptomatic or asymptomatic UTI referred. They were including 178 (14.33%), 784 (63.12%) and 243(19.57%) cases aged <6 months, 6-60 months and >60 months respectively (Figure 1). Clinical manifestations in enrolled cases (784 patients) are presented in Table 1. The age at presentation in 37 cases (2.98%) were not registered. Because of demographic characteristics comparison, patients were classified as FC and non-FC groups (NFC). Also NFC patients were classified as febrile and non-febrile groups. In NFC group (759 patients), 478 cases (63%) presented by febrile UTI and 257 cases (33.85%) had not fever at presentation (suggestive of lower UTI or cystitis) (Figure 1). Parents of 24 children were not sure about presence or absence of fever at presentation. Regarding the age of patients, they were classified as 6-24 months and 24-60 months.

Urine samples were taken by urine bags or midstream method in non-toilet-trained and toilet-trained patients respectively. The diagnosis of UTI was confirmed by positive urine culture (U/C), a growth of $\geq 10^4$ colony forming unit (CFU) of a single uropathogen in samples obtained by midstream method in symptomatic and

$>10^5$ in asymptomatic patients. In samples obtained by urine bags growth of a single pathogen with $CFU \geq 10^5$ on culture media was defined as positive if there was leukocyturia (white blood cells ≥ 5 cells in high powered filed on urinary sediment).

Asymptomatic bacteriuria (ABU) was defined as two consecutive positive cultures in the absence of symptoms of UTI (14, 15). "A seizure accompanied with fever and without central nervous system (CNS) infection, which occurs in infants and children of age 6 through 60 months" was defined as FC (16). Lumbar puncture (LP) was done in infants aged ≤ 18 months with fever and convulsion to exclude CNS infection. In children aged > 18 months LP was done if there was any sign or symptom of meningeal involvement.

3.1. Sample size

A sample size study population of 784 patients was considered appropriate between 2002 and 2016 according to enumeration method.

3.2. Ethical issues

The research followed the tenets of the Declaration of Helsinki. The study protocol was approved by the ethics committee of Mashhad University of Medical Sciences (# IR.MUMS.REC.1393.762).

3.3. Statistical analysis

SPSS Windows program version 16 (SPSS Institute, Inc., Chicago, IL, USA) was used for data analysis. All experimental values are presented as $\text{mean} \pm \text{standard deviation (SD)}$. All variables showed a normal distribution by using one sample Kolmogorov-Smirnov test. Chi-squared test was used to screen associations of variables.

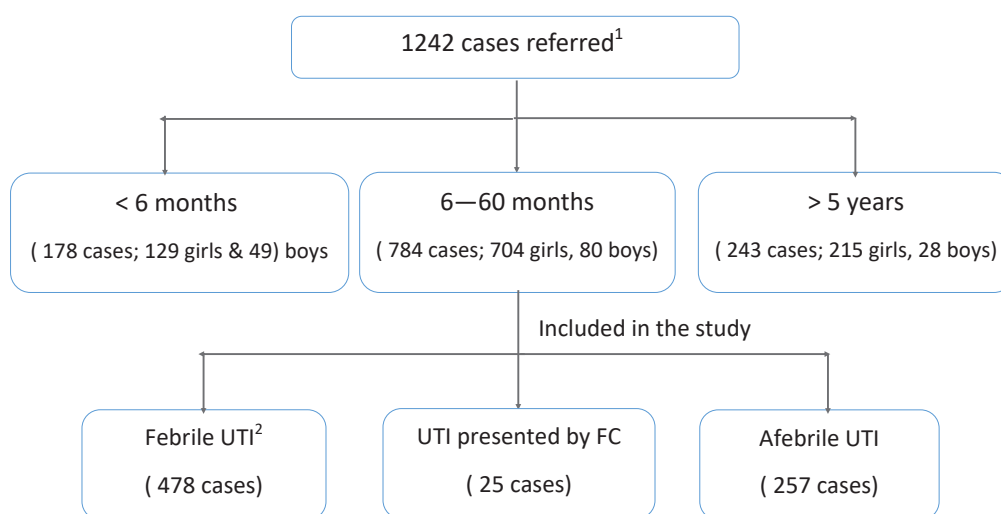


Figure 1. Characteristics of cases referred to nephrology clinic.

¹ Age at presentation was not clear in 37 patients; ²The type of UTI (Febrile or afebrile) was not defined in 24 cases.

T test was used for comparison between two groups. *P* values <0.05 was considered significant.

4. Results

Of the 784 included children, 89.8% (n=704) of cases were girls and 10.2% (n=80) were boys with an average age of 24.85 ± 16.69 months. Febrile UTI was the main presentation in 503 of 784 cases (64.15%) (Table 1). The occurrence of FC in a UTI context was confirmed in 25 of 784 enrolled cases (3.18%), and 25 of 503 patients with febrile UTI (5%). It indicates a prevalence rate of 3.18% and an incidence rate of 0.05(5%) of FC among children with UTI. In NFC group (759 patients), 478/759 (63%) cases presented by febrile UTI and 257/759 (33.85%) cases had not fever at presentation (suggestive of lower UTI or cystitis) (Figure 1). In 24/759 cases (3.15%) the type of UTI (febrile or without fever) was not clear.

Gender distribution was compared between FC and NFC groups. Among enrolled cases 684 girls and 75 boys were in NFC and 20 girls and 5 boys in FC groups (*P*=0.1). Patients with FC were significantly younger at presentation compared with NFC cases (15.52±8.4 months in FC versus 25.16±16 months in NFC, *P*=0.004). Patients were categorized and compared in age groups of 6-24 months and 24-60 months (3-5 years). The frequency of FC and NFC cases in this 2 age sub-groups were 20/25(80%) and 440/759(58%), 5/25(20%) and 319/759 (24%) respectively (*P*=0.028; Figure 2).

All patients with FC presented in the first 3-year of the life (6-36 months) with the peak at ages of 6-12 months (13 of 25 cases; 52%). Seven patients (28%) and 5 patients (20%) presented in the second and third years of the life respectively. Trend line for FC group showed a

Table 1. Clinical presentations of urinary tract infection in enrolled cases

Clinical manifestations	Number (%)
Fever	478 (61)
Dysuria	156 (19.9)
Irritability	66 (8.4)
Vomiting	66 (8.4)
Increased urinary frequency	65 (8.3)
Abdominal pain	48 (6.1)
Diarrhea	34 (4.3)
Urinary incontinence	28 (3.6)
FC	25 (3.2)
Gross hematuria	22 (2.8)
Flank pain	20 (2.5)
ABU	20 (2.5)
Bad urine Smell	7 (0.9)
Chill	7 (0.9)
FTT	6 (0.75)
Dribbling	4 (0.5)
Genital discomfort	3 (0.4)
Low urine caliber	2 (0.25)
Straining	1 (0.13)
Respiratory distress	1 (0.13)
Sepsis	1 (0.13)
Total patients	784 (100)

Abbreviations: FC, Febrile convulsion; ABU, asymptomatic bacteriuria; FTT, Failure to thrive.

sharp decrease between the first and second years of life. According to trend line 52% of cases presented in ages 6-12 months, which reached 28% in the second year.

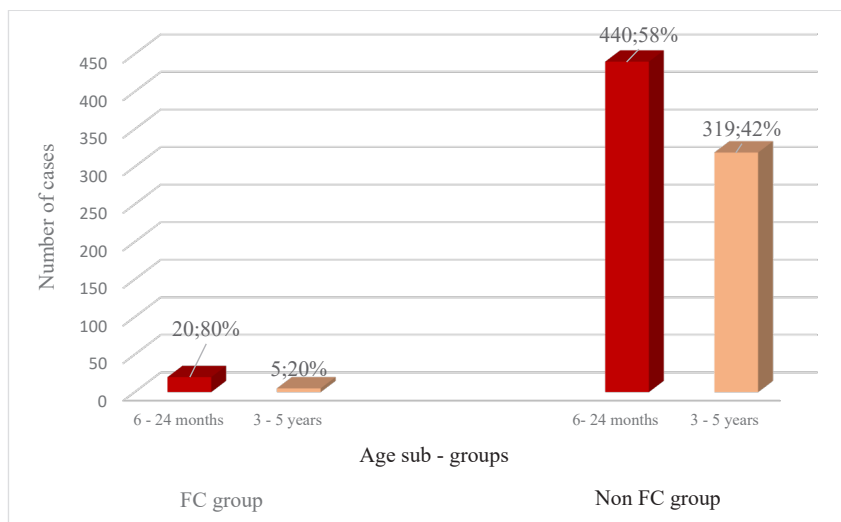
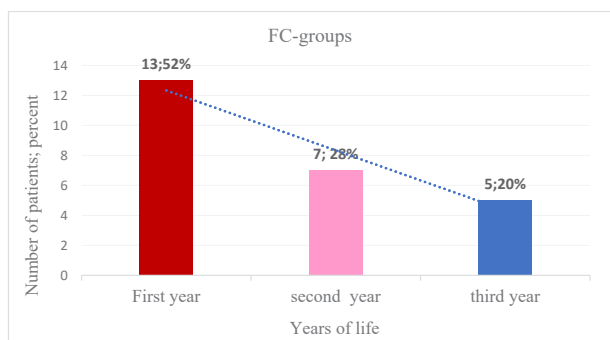
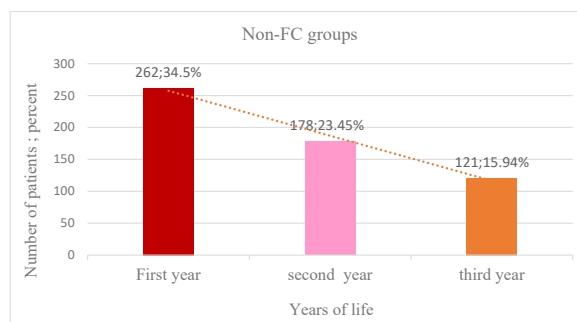


Figure 2. Distribution of cases with and without febrile convulsion (FC and non-FC groups respectively) in age sub-groups of 6-24 and 24-60 months (3-5 years).



Figures 3. Trend lines for cases with febrile convulsion (FC) in the first 3-year of the life.



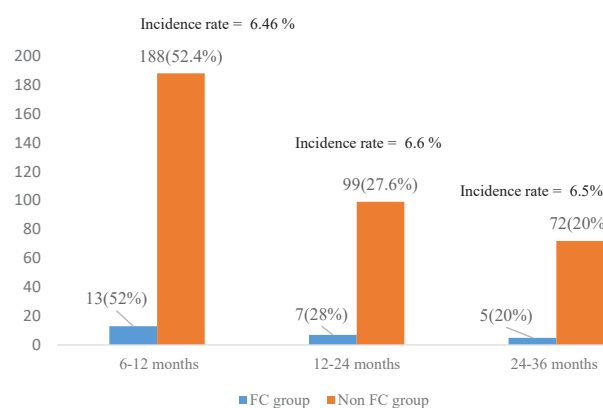
Figures 4. Trend lines for cases without febrile convulsion (FC) in the first 3-year of the life.

In FC population decrement continued with a slower slope in the third year of life and reached 20% of total cases (8% decrease in FC population in the third year of life). The line reached to zero in the fourth year of the life (Figure 3). Trend line in the first 3-year of the life in NFC group showed a slower slope. The population in the first year of the life composed 34.5% of total cases which reached to 23.45% in the second year (11.05% decrease in population), and continued in the third year of the life with a slower slope (7.51% decrease in population) (Figure 4).

Of 759 cases in NFC group, 561 patients (73.9%) presented in the first 3-year of the life (6-36 months) (Figure 4), the age-range that our cases with FC presented. Of these cases, 359 subjects (64%) presented with febrile infections. They included 188 (52.37%), 99(27.58%), and 72(20.05%) patients in ages 6-12, 12-24 and 24-36 months respectively. Presentation of FC in patients with febrile UTI was reported in 13 of 201 cases (6.46%) in ages 6-12 months, 7 of 106 subjects (6.6%) in ages 12-24 months, and 5 of 77 patients (6.5%) in ages 24-36 months (Figure 5).

Age and gender were compared in FC and NFC groups presented by febrile UTI. The gender in NFC and FC cases showed a pattern of female domination (428/478 cases; 89.5%; female/male ratio: 8.56 and 20/25 cases; 80%, female/male ratio of 4 respectively). Distribution of girls in NFC group was twice than FC group. No significant difference in gender was found ($P=0.136$).

In NFC patients with febrile UTI of 478 cases, 305 (63.8%) and 173 patients (36.2%) presented in age ranges of 6-24 months and 24-60 months respectively. For FC group (25 patients) these values were 20 (80%) and 5 cases (20%) respectively ($P=0.123$). Mean \pm SD of age in FC patients was 15.52 ± 8.4 months, while it was 22.78 ± 16.01 months in NFC cases with febrile UTI ($P=0.025$, 95% CI: 0.927, 13.6).



Figures 5. Incidence rates of febrile convulsion among children presented by febrile urinary tract infection in the first 3-year of the life.

5. Discussion

In our series of 784 enrolled cases, 25 (3.18%) patients presented by FC. It indicates a prevalence rate of 3.18% for FC among patients presented by UTI. In patients with febrile UTI, 25 of 503 cases (5%) had seizure which indicates an incidence rate of 0.05(5%) for FC in this population. To our knowledge, the present study is the first epidemiologic report in a large population that focuses on prevalence and incidence rates of FC in childhood UTI. Based on the literature, the prevalence of FC ranges from 3.5/1000 to 17/1000 (17, 18). In a study by Delpisheh et al (8) UTI was the 5th common etiology of FC (3.2%) after upper respiratory tract infections (42.3%), gastroenteritis (21.5%), otitis media (15.2%) and pneumonia (8.7%). A study in African children (7) reported viral and bacterial upper respiratory infection including otitis media as the most common etiology (24%) and febrile UTI as the 4th etiology of FC (4.7 %).

A study in Turkey (6) with 10,742 enrolled cases reported the prevalence rate of FC among boys, girls and total population, 4.3%, 4.2% and 4.3% respectively. In

our enrolled cases who consisted of children presented with UTI, FC was occurred in 5 of 80 boys (6.25%), 20 of 704 girls (2.85 %) and 25 of 784 enrolled cases (3.2%). Comparing with Turkish study (6), the prevalence rates of FC in our subjects among girls and total population were lower (2.85% vs. 4.2% and 3.2% vs.4.3% respectively), whereas the prevalence rate of FC for boys was higher (6.25% vs.4.3%). The population studies by Canpolat et al (6) were completely different from our cases. They studied FC cases with different infectious etiologies as the source of FC arising from upper and lower respiratory systems, gastrointestinal and urinary tract. In our series prevalence rate of FC was evaluated just in patients presented by UTI. We found a higher prevalence rate of FC among boys with UTI compared with girls (6.25% vs.2.85 %).

Actually in our cases FC was 2.2 times more prevalent in boys rather than girls population. Forsgren et al (19) found that FC is more common among boys, with a male to female ratio of 1.72 to 1. They also reported a cumulative incidence rate of 4.1% for FC which is approximately similar to our results. However our study confirms higher prevalence rate of FC among boys population, gender distribution has not been supported by literature review (20).

Turkish study (6) used The international league against epilepsy (ILAE) criteria for diagnosis of FC. Based on ILAE criteria (21-23) FC defines for seizures occur in ages one month up to 7 years in the absence of electrolytes abnormalities and CNS infections. In Turkish study 11.6% and 9% of FC populations aged <6 months and 5-7 years respectively. The peak of FC was in the ages of 18-24(27.6%) followed by 24-60 months (27.1%) respectively, and just 16.4% of FC happened in ages 6-12 months. In contrast to Turkish study, in our series the peak age for FC was 6-12 (52%) followed by 12-18 months (28%). Based on definition for FC presented by subcommittee on febrile seizures, 2002–2010 (16) we did not enroll neither cases <6 months nor those 5-7 years with fever and seizure in the study (Figure 1). In our series of 178 cases <6 months, 3 cases (1.7%) presented by fever and seizure. Laboratory evaluations in these cases did not show any CNS infection or electrolyte abnormalities as the etiology of seizure. However in Turkish study 9% of Fc population were in ages 5-7 years (6), in our series no case of seizure associated with fever was reported in children >5 years who were not included in the study (Figure 1).

Etiologies of FC in Canpolat's study (6) were respiratory tract infection (67.6%), acute gastroenteritis (14.4%), UTI (8.1%), acute otitis media (7.7%), post-vaccination fever (2.2%) and nonspecific infections (0.4%). Little data is available about prevalence and incidence rates of UTI

among children presented by FC, however frequency of UTI in children with FC have been evaluated in different studies(5,9-12). In infants aged < 2 years, 2.6% of UTIs manifest as FC (13), and UTI accounts for 7.4% of total cases of FC (12). In our series 460 of total cases (58.7%) aged 6-24 months. Of these patients 20 subjects presented as FC (4.35%).

A study reported the peak of FC presentation in the second year of life (6,7,9), with the occurrence of 50% of first attacks in ages of 6-24 months, 27.1% and 9% in the ages of 3-5 and 5-7 years respectively (6). These reports emphasize that majority of first FC attacks following febrile UTI happen before age 3 years. In the present study focusing on demographic characteristics of FC due to febrile UTI, 52%, 28% and 20% of cases presented in the first to the third year of life. The peak age of FC was 6-12 months and more than 50% of cases presented in the first year of life, 80% until 2 years old, and all case manifested before 3 years old. Abedi et al (10) reported the peak incidence of FC in the age of 12-18 months, of course their patients included cases presented by FC due to different sources of infection including febrile UTI. Bello et al (7) found febrile UTI as the etiology of FC in 10.3% of patients and suggested that UTI is more prevalent among children with FC rather than general pediatric population (10.3% versus 1-3%).

In the present study FC occurred in 20 of 448 girls (4.46%) and 5 of 55 boys (9.1%) with febrile UTI. It means that the incidence rate of FC due to febrile UTI in boys was about 2 times more than girls. This emphasizes the higher incidence of FC as presentation of UTI among boys compared to girls. Some other studies have been reported the male preponderance among children with febrile UTI presented by FC. They found that 58.8%-58.8-80% of FC due to febrile UTI have happened in boys (7,10,21). Similar to our finding Lee and Verrier Jones (11) and Momen et al (5) reported a girl preponderance (63% and 66.6% respectively) in FC cases with UTI. Trainor et al (24) evaluated children aged 6-60 months with the first episode of simple FC to define the risk of serious bacterial infections, meningitis, occult bacteremia, pneumonia and UTI. Main sources of FC in their patients were pneumonia (12%), UTI (5.9%) and occult bacteremia (1.3%). Finally they concluded that the frequency of UTI in patients with FC is similar to febrile children with no seizure.

6. Conclusions

Based on reviewing the literature it is the first report of the prevalence and incidence rates of FC among children with UTI. We observed that FC is an uncommon presentation of UTI with prevalence and incidence rates of 3.18% and

5% respectively. Our findings suggest that there is no significant gender difference between UTI cases presented with FC compared with those not presented by FC. We observed that the occurrence of FC in UTI context is 2 times more common in boys rather than girls. The peak of FC in UTI cases is in ages of 6-12 months and all cases present until age 3 years. In addition FC cases are significantly younger at presentation compared with those not experience seizure following UTI.

Limitations of the study

Because of retrospective design, there was no data about the types of seizures (generalized or focal, simple or complex), but according to parent's information, the types of seizures were simple generalized tonic clonic in most of patients.

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Authors' contribution

MN designed and conducted the study, made the primary draft and editing the final manuscript. EB participated in making the primary draft and did the data analysis. NT was involved in the acquisition of data. All authors read and sign the final paper.

Conflicts of interest

The authors have no conflicts of interest to declare for this study.

Ethical considerations

Ethical issues (including plagiarism, misconduct, data fabrication, falsification, double publication or submission, redundancy) have been completely observed by the authors.

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