**ABSTRACT**

**Objective:** Hypoxia occurs following convulsions, and hypoxia is one of the most common causes of acute renal damage. The aim of this study was to investigate urinary levels of kidney injury molecules, including neutrophil gelatinase-associated lipocalin (NGAL), N-acetyl-β-D-glucosaminidase (NAG), and liver-type fatty acid-binding protein (L-FABP) in children with febrile seizures (FS) for the first time.

**Methods:** The study included 28 children with FS and 34 age and gender matched healthy children. Serum biochemistry and blood gases were measured in the serum samples. Estimated glomerular filtration rate (eGFR) was calculated. NGAL, NAG, L-FABP, and creatinine (Cr) were measured in the urine samples. The ratios of kidney injury markers to urinary Cr were used for comparisons.

**Results:** There were no significant differences in eGFR and serum chemistry values between the FS and the control group (p > 0.05). Hypoxia was detected in 67.9% of the FS patients. The FS group had significantly higher urinary kidney injury molecules to Cr ratios compared to the controls, including NGAL/Cr (17.9 ± 9.8; 6.7 ± 4.0, respectively; p < 0.001), NAG/Cr (0.55 ± 0.29; 0.21 ± 0.16, p < 0.001), and L-FABP/Cr (4.85 ± 2.93; 1.74 ± 1.16, p < 0.001).

**Conclusion:** Increased urinary NGAL/Cr, NAG/Cr, and L-FABP/Cr values, in patients with FS compared to healthy controls, suggest a possible subclinical renal damage in these patients.

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**Introduction**

Febrile seizure (FS) is a generalized convulsion, usually seen in children between the ages of 3 months and 6 years, with duration of less than 15 min, and nonrecurring within 24 h. To make a diagnosis of febrile convulsion, no history of any central nervous system disease, metabolic disorder, or afebrile convulsion should be present. The incidence of FS is around 2–5%. FS can usually be generalized as tonic-clonic jerks without focal neurological findings. The neurological prognosis of FS has been reported to be good in studies, and it has been reported not to cause impairment in the IQ level and academic performance, and does not lead to neuropsychological impairment and behavioral disorders. However, severe hypoxia has been reported to develop in FS patients especially during and after generalized tonic-clonic seizures.

Hypoxia is one of the most common causes of renal damage. Increased serum urea and creatinine are considered to demonstrate clinical renal damage. However, since the serum creatinine level is affected by gender and muscle mass, and increases only after the renal functional disorder is marked, it has the disadvantage of being used as a reliable marker. Therefore, the search for new molecules that can be biomarkers to detect renal damage during the early phase in which clinical renal damage is not prominent is ongoing. Neutrophil gelatinase-associated lipocalin (NGAL), N-acetyl-β-D-glucosaminidase (NAG), and liver-type fatty acid-binding protein (L-FABP) have been used as early biomarkers of renal damage in many studies, and urinary concentrations of these markers have been shown to increase, especially after hypoxia.

We found no studies in the literature that investigated renal damage in FS using urinary kidney injury biomarkers. Therefore, this preliminary study was planned to evaluate whether simple FS causes any renal damage detected by early kidney injury molecules, for the first time.
Materials and methods
Subjects and demographics
A total of 28 pediatric patients admitted to the Pediatric Emergency Ward of Dicle University Hospital and diagnosed as FS were included into the study. The control group consisted of 34 healthy children who applied to this hospital for routine checkup or for preoperative evaluation of elective minor surgical interventions (circumcision, hernia repair, etc.). Control subjects had no cardiac or lung problems, anemia that could cause hypoxia, no history of renal disease, or drug use that might affect renal functions.

FS was defined as convulsions due to fever in children who had no history of epilepsy, central nervous system infection, intracranial bleeding, central nervous system abnormalities, or metabolic disorders. Simple FS was defined as generalized tonic-clonic convulsions, which were nonrecurrent within 24 h (no more than once), without focal findings or a family history of epilepsy, and lasting shorter than 15 min, in patients with an age between 3 and 72 months.

Age, gender, body weight, height, complaints at the time of presentation, and physical examination findings were recorded in all patients. They were questioned as to whether they had any renal disease or any disease affecting the kidneys, such as hypertension, systemic lupus erythematosus, or other disorders. Patients who had any disease affecting the kidneys, had chronic liver disease, chronic respiratory system disorders, or cyanotic cardiac disease and had been using drugs with potential effect on kidneys (nonsteroidal antiinflammatory drugs, amikacin, etc.) were excluded. The patients younger than 3 months or older than 72 months, and patients who had a history of epilepsy or febrile convulsion, were not included into the study.

Oxygen saturation (SO₂) of the patients was measured from the finger by a pulse oximeter device at the time of the presentation or through blood gas sample measurements. Patients who had SO₂ measurements below 95% on pulse oximeter or blood gas sample were accepted as hypoxic.

Biochemical analyses
After obtaining informed consent from the patients and/or caregivers, urine samples and venous and arterial blood samples were taken at the time of presentation. From the venous blood samples, complete blood count including white blood cell count (WBC), neutrophil and platelet (PLT) count and biochemical parameters including serum urea, creatinine (Cr), electrolytes [sodium (Na), potassium (K), calcium (Ca)], aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), and C-reactive protein (CRP) were measured. Oxygen saturation, partial carbon dioxide pressure, bicarbonate, and pH were determined in the arterial blood samples. Biochemical parameters were analyzed using an Abbott ARCHITECT C16000 (Abbott Park, IL) device using the enzymatic colorimetric method.

A urine sample of 10 mL was obtained from the patients and the control group. Urine samples were centrifuged at 3000 rpm for 3 min. Urine staying at the top of the tube was passed to five separate Eppendorf tubes and stored at −80°C until performing measurements. Subsequently, Cr and early markers of kidney injury including NGAL, NAG, and L-FABP were analyzed in the urine samples. Early markers of renal damage were analyzed as per the instructions of the manufacturer using the enzyme-linked immunosorbent assay (ELISA) method (SunRed Biotechnology Company, Shanghai, China). All urine markers were normalized obtained ratios by dividing their values with the urine creatinine value.

Serum glomerular filtration rate (eGFR) was measured using a modified Schwartz formula (eGFR (mL/min/1.73 m²) = height (cm) × 0.45/serum creatinine (mg/dL)). eGFR value higher than 90 mL/min/1.73 m² was accepted as normal. eGFR value of <90 mL/min/1.73 m² was accepted as decreased renal function. To consider whether the serum creatinine values of the patients were normal or not, age and gender of the patients were taken into consideration. Ethical approval was obtained from the Clinical Research Ethics Board of the Medical School of Dicle University.

Statistical analysis
SPSS (Statistical Package for Social Sciences) version 18.0 for Windows (SPSS Inc., Chicago, IL) program was used for statistical analyses. Quantitative values were expressed as mean ± standard deviation or median (range), whereas categorical data were expressed as number and percentage. The Kolmogorov–Smirnov or Shapiro–Wilk tests were applied to determine whether the data were normally distributed or not. The Student’s t-test or the Mann–Whitney U test was used for comparison between independent groups. The chi-square test was used to compare the categorical data. Relationships between numerical data were investigated by using Pearson’s or Spearman’s correlation analyses, based on the distribution pattern. A p value below 0.05 was considered statistically significant.
Results
Among the 28 patients diagnosed with FS, 15 (53.6%) were males and 13 (46.4%) females. In the control group, there were 34 children: 18 (52.9%) males and 16 (47.1%) females. The median ages of the patient and control groups were 22 months (range: 4–63) and 15 months (range: 2–63), respectively. No statistically significant differences were found in the age and gender between the patient and control groups (p > 0.05).

Patients had infectious diseases leading to high fever and FS including acute upper respiratory tract infection (pharyngitis, tonsillitis, and otitis media) in 24 (85.7%), bronchitis in 2 (7.1%), and gastroenteritis in 2 (7.1%) patients. The median duration of convulsions was 10 min, and 85% terminated in 5 min or less. Urine samples were obtained from the patients in 4.2 ± 2.3 h (range: 1–8). Serum ALT (U/L) 15.5 (8–35), AST: aspartate transaminase; ALT: alanine aminotransferase; LDH: lactate dehydrogenase; NS: not significant.

Hypoxia measured by SO2 on arterial blood gas sample was studied. Hypercarbia was present in 23.5% (23.5%) among those in whom arterial blood gases were studied. Acidosis was observed in 13 (76.5%) patients and respiratory alkalosis in four (76.5%) patients. Oxygen saturations were evaluated by obtaining arterial blood gas samples in all patients in the postictal period and by pulse oximeter in all patients who were still in the iactal period. Arterial blood gas samples were not obtained during the ictal period in any patients. Serum AST (U/L) 33.0 (16–104), ALT: alanine aminotransferase; LDH: lactate dehydrogenase; NS: not significant.

Patients with FS had significantly higher levels of NGAL/Cr (17.9 ± 9.8 vs. 6.7 ± 4.0, respectively; p < 0.001), NAG/Cr (0.55 ± 0.28 vs. 0.21 ± 0.16, respectively; p < 0.001), and L-FABP/Cr (4.85 ± 2.93 vs. 1.74 ± 1.16, respectively; p < 0.001) compared to the healthy control children (Table 3).

Discussion
The levels of urinary NGAL/Cr, NAG/Cr, and L-FABP/Cr, which are among the early markers of kidney injury that significantly higher in patients with FS compared to the controls (p < 0.001; p < 0.001; p = 0.006, respectively). No significant differences were found in PLT count and hemoglobin values between the two groups (p > 0.05) (Table 2).

Children with FS had significantly higher levels of NGAL/Cr (17.9 ± 9.8 vs. 6.7 ± 4.0, respectively; p < 0.001), NAG/Cr (0.55 ± 0.28 vs. 0.21 ± 0.16, respectively; p < 0.001), and L-FABP/Cr (4.85 ± 2.93 vs. 1.74 ± 1.16, respectively; p < 0.001) compared to the healthy control children (Table 3).

Table 2. Hematological characteristics and C-reactive protein values in children with febrile convulsions and the controls group [median(range)].

|                      | Febril convulsion (n = 28) | Control group (n = 34) | p    |
|----------------------|---------------------------|------------------------|------|
| WBC (/mm³)           | 15.0 (12.0–23.6)          | 7.1 (4.1–10.5)         | <0.001|
| Neutrophil (%)       | 63.7 (52.0–83.6)          | 46.4 (27.9–57.7)       | <0.001|
| Hemoglobin (g/100 mL)| 11.0 (8.0–13.5)           | 12.1 (8.3–13.9)        | NS   |
| PLT (/mm³)           | 321.0 (179–553)           | 315.5 (214–488)        | NS   |
| CRP (mg/dL)          | 14.1 (1.2–38.6)           | 0.30 (0.20–3.0)        | 0.006|

WBC: white blood cells; PLT: platelets; CRP: C-reactive protein; NS: not significant.

Table 1. Demographic and biochemical characteristics of children with febrile convulsions and the control group [median(range)].

|                      | Febril convulsion (n = 28) | Control group (n = 34) | p    |
|----------------------|---------------------------|------------------------|------|
| Age (month)          | 15 (2–63)                 | 22 (4–63)              | NS   |
| eGFR (mL/min/1.73 m²)| 102.7 (91.6–116.8)        | 105.7 (93.4–122.5)     | NS   |
| Serum glucose (mg/dL)| 91.0 (76–106)             | 88.50 (84–120)         | NS   |
| Serum urea (mg/dL)   | 20.0 (9–37)               | 20.00 (4–38)           | NS   |
| Serum creatinine (mg/dL) | 0.39 (0.11–0.53) | 0.43 (0.24–0.59) | NS |
| Serum sodium (mEq/L) | 138.0 (133–144)           | 137.0 (131–140)        | NS   |
| Serum potassium (mEq/L)| 4.2 (3.6–4.9)             | 4.4 (3.6–5.2)          | NS   |
| Serum calcium (mg/dL)| 9.7 (8.6–10.4)            | 9.9 (8.7–10.0)         | NS   |
| Serum AST (U/L)      | 33.9 (16–61)              | 28.5 (21–45)           | NS   |
| Serum ALT (U/L)      | 15.5 (8–57)               | 17.5 (7–35)            | NS   |
| pH                   | 7.31 (7.13–7.50)          | –                      | –    |
| PaCO₂                | 40.7 (25.5–54.1)          | –                      | –    |
| SO₂ (%)              | 85.0 (60.0–97.0)          | –                      | –    |
| HCO₃                 | 19.3 (7.5–21.9)           | –                      | –    |

AST: aspartate transaminase; ALT: alanine aminotransferase; LDH: lactate dehydrogenase; NS: not significant.
Table 3. Urinary levels of kidney injury molecule in children with febrile convulsions and the controls group (mean ± standard deviation).

| biomarker        | Febril convulsion (n = 28) | Control group (n = 34) | p   |
|------------------|----------------------------|------------------------|-----|
| NGAL/Cr          | 17.95 ± 9.81               | 6.77 ± 4.03            | <0.001|
| NAG/Cr           | 0.55 ± 0.28                | 0.21 ± 0.16            | <0.001|
| L-FABP/Cr        | 4.85 ± 2.93                | 1.74 ± 1.16            | <0.001|

NGAL: neutrophil gelatinase-associated lipocalin; NAG: N-acetyl-L-glucosaminidase; L-FABP: liver-type fatty acid-binding protein; Cr: creatinine.

Demonstrate damage prior to any increase in the serum creatinine, were found to be increased in the present study. In addition, blood oxygen saturations were low in one-third of the patients during or after the seizure.

Hypoxia plays an important role in the pathogenesis of acute renal damage. Ischemia especially affects the proximal tubule and the Henle loop of kidney. Although, the clear mechanism of hypoxic renal damage has not been completely understood yet, some mediators effective in the regulation of vascular structures such as endothelin and nitric oxide (NO), and factors such as ATP depletion, changes in cytoskeleton and heat-shock proteins, initiation of inflammatory response, and production of reactive oxygen radicals, have all been suggested to play a role in the pathogenesis.

NO is a vasodilator produced by nitric oxide synthase (eNOS) and plays a role in the regulation of renal blood flow. eNOS functions are impaired following ischemic damage, and vasoconstriction occurs in the renal vessels. The activity of inducible nitric oxide synthase (iNOS) which plays a role in the production of oxygen radicals and nitrogen molecule also increases during hypoxia. Free oxygen radicals produced during ischemic reperfusion also plays a role in the production of acute renal damage. In addition, the level of endothelin-1 has also been demonstrated to increase during acute kidney injury (AKI). Possibly, alterations in the balance of vasoconstrictive and vasodilator effects are involved in the pathogenesis of hypoxic/ischemic AKI. Previous studies suggested that recovery from hypoxic/ischemic and nephrotoxic AKI was complete; however, recent studies have shown that recovery may be partial and returning to normal renal functions cannot be achieved. In addition, hypoxic/ischemic renal insults can result in physiological and morphological changing in the kidney, which can lead to chronic kidney disease in future.

Severe hypoxia has been demonstrated to occur during and after tonic-clonic convulsions by pulse oximeter. In another study, half of the children who had convulsions were found to have ictal hypoxia. In the same study, ictal hypoxemia (hypoxemia during convulsions) was observed in 59% of the patients with generalized tonic-clonic convulsions. The severity of hypoxia was found to be correlated with the duration and type of the convulsion, so that it was more severe in individuals who had generalized tonic-clonic convulsions.

The cause of hypoxia during and after convulsion has been reported to be possibly secondary to mechanical airway obstruction, such as aspiration of excess secretions into the airways and obstruction of the airway by the tongue. In addition, central or mixed apnea accompanied by bradycardia has also been suggested to cause hypoxia in patients with seizures. Convulsions also have direct effects on autonomic, cardiovascular and respiratory functions. Cardiovascular dysfunction, pulmonary edema, and postictal depression of autonomic respiratory reflexes and cardiovascular function may contribute to hypoxia. Among the patients in the present study, hypoxia was detected in 63.6% of the patients during convulsions and in 69.6% during postictal period. Seven of our patients had elevated urine biomarkers despite having no hypoxia at admission; however, this may be related to time of admission that they were admitted after cessation of the convulsions and recovery of the hypoxia.

Urea and creatinine values have been used in clinics in the diagnosis and follow-up of renal damage. However, serum creatinine and urea measurements have been inadequate in demonstrating early kidney injury, since urea and creatinine elevation does not occur unless the loss of renal function reaches an important level, and since these parameters are affected by age, gender, muscle mass, dehydration, and drugs administered.

Therefore, a biomarker that demonstrates the kidney injury in an earlier stage has been sought, and NGAL, NAG, and L-FABP have been demonstrated to reflect the renal damage in the early period.

NGAL, one of the members of lipocalin family with a 25 kDa molecular weight, is a protein in the small glycoprotein structure. It is released from renal tubular cells, hepatocytes, and endothelial cells as a response to cellular stress in certain conditions, such as ischemia and inflammation. In addition to its use as a marker of acute kidney injury, it is mainly a bacteriostatic substance released from secondary granulocytes of neutrophils. In a study performed in rats, the amount of NGAL increased in the urine in the early period after ischemia. Another study demonstrated an increase in urine and serum as a response to ischemia from renal tubular cells in the early period following ischemic damage, independent of the glomerular filtration; it was also shown to be a sensitive marker. NAG is a...
lysosomal enzyme present in renal tubules. The urine concentration of this substance increases in tubular cell damage. Enzyme filtration is inhibited by the capillary wall, due to its high molecular weight. On the other hand, the amount of urinary NAG increases because it is released in greater quantities due to damage in active renal tubular disease.25

L-FABP is a protein mainly produced in the liver, filtered by glomerular filtration, and reabsorbed by proximal tubular cells.26,27 Its excretion from the proximal tubule increases in tubulointerstitial damage.28 The amount of urinary L-FABP has been found to increase in a short time after AKI in some conditions, such as acute tubular necrosis, sepsis, and cardiac surgery.8,9,26,29 In a study in Japan, L-FABP levels were found to be positively correlated with the severity of renal ischemia.30

In a study performed in patients following cardiac surgery, NAG and urinary L-FABP were shown to be highly specific and highly sensitive, respectively, in demonstrating AKI.31 In the present study, the reason for high levels of urinary NGAL/Cr, NAG/Cr, and L-FABP/Cr might be subclinical kidney injury secondary to hypoxia that occurred in the patients during and after convulsions.

This study had some limitations, including a limited number of patients with FS and only once measurement of urinary markers. Another limitation is the cross-sectional design of the study, which precludes long-term measurements of kidney injury molecules. The most important limitation of the study is the impossibility of knowing the exact time of occurrence of hypoxia, because it is important to detect elevated levels of urinary biomarkers as soon as possible, to detect AKI even before an increase in serum creatinine is noted.

In conclusion, in this preliminary study, increased urinary NGAL/Cr, NAG/Cr, and L-FABP/Cr levels of patients with FS support the presence of a subclinical renal injury due to hypoxia in these patients.

Ethical approval

“All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards”.

Disclosure statement

The authors of this paper have no conflicts of interest.

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