PEDIATRICS INTERNATIONAL Official Journal of the Japan Pediatric Society

Pediatrics International (2022) **64**, e15089 doi: 10.1111/ped.15089

Original Article

First afebrile seizures: Clinical and radiological view with emergent testing

Tuğçe Aksu Uzunhan,[1] Alper Kaçar,[2] Ebru Mısırlı Özdemir[2] and Özge Yapıcı[3]

Departments of [1]Pediatric Neurology, [2]Pediatrics, [3]Pediatric Radiology, Cemil Taşcıoğlu City Hospital, University of Health Sciences, İstanbul, Turkey

Abstract

***Background*:** The first afebrile seizures in children are an important and common reason for emergency department admissions. We aim to examine the presentation, laboratory/neurodiagnostic investigation, and emergency management of children with first afebrile seizures.

***Methods*:** The retrospective study included 333 patients aged 1 month to 18 years admitted with a first afebrile seizure to the pediatric emergency department of Prof. Dr. Cemil Taşcıoğlu City Hospital between January 2017 and January 2020. Age, gender, seizure duration and type, treatments for seizures, laboratory, neurophysiological, and radiological investigations, ward or intensive care unit hospitalizations, and antiepileptic drugs on discharge were recorded.

***Results*:** The average age of the patients was 81.6 ± 62.9 months; 187 (56.2%) were male and 146 (43.8%) were female. Two hundred and sixty-one (78.4%) patients had only one seizure. In 45 (13.5%) of the patients, the seizure recurred in the emergency department. Hypoglycemia, hyponatremia, and hypocalcemia were detected in 13 (3.9%) patients. Patients with clinically significant cranial computed tomography results were at an increased risk for seizures lasting longer than 5 min. Patients with focal seizures had more recurrences, were given more antiepileptic drugs during the emergency, had better known etiology, more intensive care unit hospitalization, and greater post-discharge antiepileptic drug prescription.

***Conclusions*:** Biochemical abnormalities remain in the background in the etiology of afebrile seizures. Patients with abnormal neuroimaging on cranial tomography tended to have longer seizures. Patients with focal seizures followed a more complicated course as they had more recurrences and more hospitalization in the intensive care unit.

Key words child, cranial computed tomography, first afebrile seizure, intensive care unit, status epilepticus.

First afebrile seizures are a common cause of admission to pediatric emergency departments. When clinically indicated, the experts advise that laboratory and radiological investigations should be performed. The clinical signs can be subtle and it may sometimes be difficult to examine infants and children neurologically and the guidelines on the subject are ambiguous; biochemical tests and neuroradiological investigations have therefore become part of almost every seizure assessment in clinical practice.[1] Nevertheless, for most children, the diagnostic value of these tests is low.[2,3] Saz *et al*.[4] evaluated pediatric seizures in the emergency department and found that the frequency of metabolic abnormalities was significantly higher under 2 years of age. Maytal *et al*.[5] reported on new-onset pediatric afebrile seizures excluding simple febrile seizures and found that the imaging findings were of immediate therapeutic significance in 6% of patients. It is crucial to determine which patients will benefit most from laboratory and radiological examinations to guide clinicians in evaluating patients with afebrile seizures.[6]

The use of emergent treatment of pediatric seizures is an important issue in their management. A benzodiazepine antiepileptic is the first choice when a child arrives in the emergency department with a seizure. Nevertheless, about 30%–43% of all patients with status epilepticus do not respond to the first-line treatments.[7] In the study by Cohen *et al*. 26% of patients required four or more doses of antiseizure medications to abort seizures.[8] Determining the factors that affect seizure duration and antiepileptic requirements may help protect patients from the long-term consequences of status epilepticus and recurrent seizures.

Pediatric afebrile seizures were generally evaluated separately in the literature in terms of biochemical, radiological investigations, and treatment. There are also very few reports that include information on post-discharge antiepileptics and hospitalizations from emergency to ward or intensive care unit for pediatric afebrile seizures without febrile seizures. In our

Correspondence: Tuğçe Aksu Uzunhan, MD, Department of Pediatric Neurology, Prof. Dr. Cemil Taşcıoğlu City Hospital, University of Health Sciences, Darülaceze cad. No:27 Şişli, İstanbul, Turkey. Email: tugceuzunhan@yahoo.com

Received 23 April 2021; revised 4 November 2021; accepted 3 December 2021.

study, we aimed to present all aspects of treatment, including clinical features, laboratory, radiological investigations, hospitalizations, and treatment approaches, of patients who were admitted to a single pediatric emergency center with a first afebrile seizure. From this, we aim to provide relevant information to guide the management of such patients.

Methods

Study design and setting

Patients aged 1 month to 18 years who were admitted with a first afebrile seizure to the pediatric emergency department of Prof. Dr. Cemil Taşcıoğlu City Hospital between January 2017 and January 2020 were included. The study was thus retrospective, single centered, descriptive, and cross-sectional. Study approval was obtained from the local ethics committee (19.03.2019-1200). We included first-ever afebrile seizures occurring in the previous 24 h, recurrences of that first seizure (new episodes after the first), seizures that were still ongoing at the time of admission, and those that had already resolved before arrival in the emergency department. The emergency department had an admittance of 232 242, 227 471, and 246 997 patients yearly over the previous 3 years, respectively, and it serves as a leading emergency center and center of referral. The pediatric emergency department does not take care of children with trauma or accident. The hospital covers the pediatric patient population below the age of 18 years of four main counties – Şişli (45 173 children), Kağıthane (102 897), Eyüp (99 627), and Beyoğlu 48 916 – making a total of 296 613 children.

Patient selection and data collection

Neonates, patients with febrile seizures, syncope, breath-holding spells, pseudoseizures, a diagnosis of epilepsy, or prior febrile seizures, and those using antiepileptics, those already in the hospital in other wards, including the intensive care unit, with new-onset seizures were excluded. Syncope, breath-holding spells, and pseudoseizures were excluded as they are non-epileptic paroxysmal disorders. We also excluded patients in other wards with new-onset seizures as we aimed to evaluate patients admitted to the emergency department. Finally, neonatal seizures were excluded as they differ from other children's seizures in terms of etiology. Three hundred and forty-seven children were analyzed, but with exclusions 333 children met the inclusion criteria. Written informed consent was obtained from the patient(s) for their anonymized information to be published in this article.

We abstracted the data retrospectively from written and computerized emergency medical files, pediatric neurology consultation notes, inpatient admission notes, and discharge patient reports. The records of patients were then reviewed for eligibility for the study and according to seizure classification and etiology. Age, gender, date of admittance, complaints, seizure type, features of seizures before admittance, seizures in the emergency department, medical history, family history, acute or chronic drug treatments of patients, treatments for seizures in the emergency department, findings from physical examination, laboratory, neurophysiological, and radiological investigations, the post-seizure status of the patient, ward or intensive care hospitalizations from the emergency department and drugs on discharge were all abstracted from the patients' files. Findings were considered not available if they were not found on the computer registry or in the documentation from the treating physician.

Study protocol

The number and duration of seizures before arrival in the emergency department were recorded according to the patients' and parents' narration. The number of seizures in the emergency department was also recorded. Each seizure's duration, whether inside or outside of the hospital, was classified as either <5 min, 5–30 min, or >30 mins. The seizure type was classified according to the ILAE 2017 seizure classification as either focal, generalized, or of unknown onset.[9] Furthermore, each seizure type was subclassified further according to the same classification system. If patients had a further seizure in the emergency department, in addition any that they had outside the hospital, the seizure type would be determined according to the medical records of the attending physician. If not, the seizure features as reported by the patient and parents were used to specify the seizure type.

Biochemical testing was performed for each patient involving blood glucose, renal function tests (urea, creatinine), sodium, calcium, liver function tests (SGOT, SGPT), and a complete blood count. Other biochemical tests were performed according to the patients' status, such as a blood gas analysis, coagulation, and/or infection markers. Hyponatremia associated with seizures was defined as a sodium concentration of less than 130 mmol/L; levels between 125–130 mmol/L were considered moderate, and levels below 125 mmol/L were defined as profound. Hypocalcemia was defined as a calcium concentration of less than 7.0 mg/dL, and hypoglycemia reflected a serum glucose level lower than 45 mg/dL.

Emergent neuroradiological investigations, such as cranial computed tomography (CT) and diffusion-weighted magnetic resonance imaging (MRI), were performed mostly in the first 24–48 h where necessary, and later, cranial MRI was performed electively, although some patients underwent an urgent full-scale cranial MRI directly from the emergency department. Intravenous contrast was given where indicated. Neuroradiological investigations were classified as normal, clinically significantly abnormal, not significantly abnormal, or not performed. Clinically significant abnormalities were defined as those that could potentially result in a change in management, that would indicate etiology, or that gave prognostic information.[3,10] Clinically insignificant findings were those incidental to the patient's seizure (e.g., mega cisterna manga, extra-axial subarachnoid enlargement). Patients underwent emergent routine electroencephalogram (EEG) according to the 10–20 system, including hyperventilation for 3 min and intermittent

photic stimulation at 1–20 Hz with the eyes open and closed at each frequency. Patients who could not adapt to routine EEG performed sleep EEG. Seizure etiology was classified as structural, genetic, infectious, metabolic, immune, or unknown, according to the ILAE 2017 classification.[9] Unprovoked seizures were described as seizures occurring in the absence of precipitating factors, or no more than 7 days after an acute injury or insult such as stroke or brain hemorrhage, and they may be caused by a static injury (remote symptomatic seizures) or a progressing injury (progressive symptomatic seizures).[11] Antiepileptic drugs applied in the emergency department, or before arrival, were specified with dosages and methods of administration. Antiepileptic drug prescribing indications were 2 ≤seizures, status epilepticus, one seizure with a high risk of recurrence indicated by EEG and MRI findings. Ward hospitalization criteria were an etiology with a higher risk of seizure recurrences, patients with a need of any intravenous treatment, and also according to the treating physician's judgment. Intensive care unit administration indications were respiratory compromise, intubation, and need for mechanical ventilation, administration of third-line anesthetics such as midazolam, propofol, and barbiturates, and patients with super-refractory status epilepticus.

Statistical analysis

Data were evaluated statistically using IBM SPSS Statistics for Windows, version 21.0 (IBM Corp., Armonk, N.Y., USA). While evaluating the study data, frequency distribution (number, percentage) for categorical variables, and descriptive statistics (mean, standard deviation) for numerical variables were described. To see whether there was a difference between the two groups, an independent sample *t*-test was used, and to see whether there was a difference between more than two groups, a one-way analysis of variance (one-way ANOVA) was examined. The one-way ANOVA made it possible to check with the Levene test for variance homogeneity, and then a multiple comparison test (either Bonferroni or Tamhane's T2) indicated from which group or groups the difference originated. Bonferroni was used to examine the difference between groups in variables that provided variance homogeneity, and Tamhane's T2 test was used to examine for differences between groups in variables that did not provide variance homogeneity. The Pearson correlation test was used to examine a relationship between two numerical variables. The χ^2 test was used to evaluate the relationship between two categorical variables. Logistic regression analysis was used to study the association between a categorical dependent variable and a set of independent variables. Statistical significance was accepted as $P < 0.05$.

Results

The mean age of the 333 patients included in the study was 81.6 ± 62.9 months, with a median of 77 months. There were 187 males (56.2% of the patients) and 146 females (43.8% of the patients). The number of patients with one seizure before admittance was 261 (78.4%). Seizures were generalized in 293 (88%) of patients, and they lasted for less than 5 min in 239 (72%). Seizures recurred in 45 (13.5%) patients while in the emergency department. Thirty patients (9%) had ongoing seizures upon arrival. Twenty-four of the patients with ongoing seizures were treated with midazolam (19 intravenous, six intranasal), three with diazepam outside our facility, and the others with phenytoin and levetiracetam. Five (16.7%) of the patients had been given antiepileptics in facilities other than our emergency department. Seventy-two (21.6%) patients had pre-existing neurological conditions, and 61 patients (18%) had a relative with epilepsy, 30 (9%) of them having a first-degree relative. Detailed data of patients and their seizures are presented in Table 1.

While searching for an etiology, abnormal biochemical results indicating hypoglycemia, hyponatremia, and hypocalcemia were determined in 13 (3.9%) patients. The mean age of the patients with biochemical abnormalities was 60.2 ± 65.8 months, with a median of 26 months. Only one of these had an ongoing seizure during admittance; the other 12 were conscious during admittance. Acidosis and alkalosis were present in 42 (13%). Electroencephalogram was normal in 56 patients (16.8%) and showed epileptiform discharges in 48 (14%) patients, 29 of them generalized, and focal discharges in 19 patients. Two patients had a disorganized background. Six (1.8%) patients had been diagnosed with acute injuries (two patients with skull fracture, two encephalitis, one posterior reversible encephalopathy syndrome, and one stroke) and the rest of the 327 patients (98.1%) had unprovoked seizures. The neuroradiological results of patients were evaluated, and 23 patients out of 293 had a clinically significant abnormality that was identified by a CT and/or MRI. A clinically significant abnormality was detected through cranial CT (15/293), and/or diffusion-weighted MRI (6/167), and/or cranial MRI (16/122). Pre-existing conditions were as follows: four patients with hydrocephalus and a VP shunt, three patients with cerebral palsy, and one patient with post-traumatic cerebral injury. The CT result was normal in six patients where cranial MRI revealed a clinically significant abnormality. Cranial tomography was compatible with a clinically non-significant abnormality in one patient where the MRI showed a clinically significant abnormality. In 8 (2.7%) patients whose cranial CT results showed a clinically significant abnormality, the cranial MRI results showed the same. Fifteen (5%) patients out of 293 patients were detected with a new clinically significant abnormality that was not known before admission. Immediate neurosurgery was not performed on any patient. The results of each imaging are described in Table 2. The first antiepileptic drug treatment was performed in the emergency department in 156 (47%) patients, whereas 14 (14%) patients had received antiepileptics in another facility, which was either an ambulance or another hospital. Intravenous levetiracetam was the most common drug used, and 171 (51%) patients had been given at least one antiepileptic. Ward hospitalization was necessary for 100 (30%) patients, and 18 (5.4%) patients were admitted to the intensive care unit. One hundred and sixty-four (49.2%) patients were prescribed

Table 1 Patient characteristics and seizure descriptors

Median age/month (Range/month)	77 (1–288)
Age group	***n* (%)**
1 month-2 years	98 (29)
2–4 years	32 (10)
4–12 years	129 (39)
>12 years	74 (22)
Gender	
Male	187 (56.2)
Female	146 (43.8)
Seizures before admittance	
1 seizure	261 (78.4)
2 seizures	55 (16.5)
3 seizures	10 (3)
>3 seizures	7 (2.1)
Seizure type	
Focal onset	40 (12)
Generalized onset	293 (88)
First seizure duration	
<5 min	239 (72)
5–30 min	77 (23)
>30 min	17 (5)
Status of the patient during admittance	
Ongoing seizure	30 (9)
Postictal	25 (7.5)
Conscious	278 (83.5)
Seizures during sleep or not	
During sleep	176 (53)
Not sleeping	157 (47)
Seizure recurrence in emergency	
Yes	45 (13.5)
No	288 (86.5)
Pre-existing conditions	
Global developmental delay	15 (4.5)
Traumatic head injury	9 (2.7)
Cerebral palsy	8 (2.4)
ADHD	5 (1.5)
Autism spectrum disorders	5 (1.5)
Hydrocephalus, VP shunting	4 (1.2)
Genetic syndrome	2 (0.6)
Remote cerebral injury	1 (0.3)
Inborn errors of metabolism	1 (0.3)
Cerebral AVM	1 (0.3)
Congenital infection	1 (0.3)
Others	20 (6)
Total	72 (21.6)
None	261 (78.4)
Family history	
Epilepsy	61 (18.3)
1-degree relative	30 (9)
2-degree relative	26 (8)
3-degree relative	5 (1.5)
Febrile seizure	10 (3)
1-degree relative	5 (1.5)
2-degree relative	5 (1.5)
Others	10 (3)
None	252 (76)

ADHD, attention deficit hyperactivity disorder; AVM, arteriovenous malformation; min, minutes; VP, ventriculoperitoneal.

medication for post-discharge. Investigations and treatment, in general, are detailed in Table 3.

When patients were compared according to their status during admittance to the emergency department, children arriving with ongoing seizures or in a postictal state to the emergency department had been given more antiepileptics before admission to the facility than conscious patients. The patients with ongoing seizures had more focal seizures ($P < 0.05$), had received a greater number of antiepileptics, and had more seizures in the emergency department than the conscious patients ($P < 0.05$). Patients with ongoing seizures and those in the postictal state had more acidosis, a better-known etiology, were hospitalized in the intensive care unit, and were prescribed medications for post-discharge use to a greater extent than conscious patients ($P < 0.05$).

Patients with focal seizures were given more antiepileptic drugs in the emergency department than patients with generalized seizures, and their seizures recurred more in the emergency department ($P < 0.05$). Patients with focal seizures had a better known known etiology, more intensive care unit hospitalization, and more post-discharge antiepileptic drug prescriptions than patients who did not have focal seizures ($P < 0.05$; Table 4).

Patients whose first seizure was >30 min had more seizures in the emergency department, a higher rate of intensive care unit hospitalization, and were prescribed more anti-epileptic drugs for post-discharge use than patients with seizures lasting less than 30 min. Patients whose seizures lasted for longer than 30 min had already received antiepileptic drugs in other centers before arriving at our emergency department, and their total antiepileptic use was higher than that of patients whose seizures lasted less than 5 min. Acidosis was more prevalent in patients with seizures longer than 5 min compared with patients having seizures for less than 5 min. Children whose seizures were 5–30 min long or over 30 min received more antiepileptic drugs compared to those patients whose seizures lasted for less than 5 min ($P < 0.05$). Children with acidosis received more antiepileptic drugs and were more often hospitalized in the intensive care unit. Children with acidosis had a better known etiology than children without acidosis ($P < 0.05$; Table 4).

Logistic regression analysis revealed that patients with clinically significant cranial CT results had 7.532 times increased risk of having seizures lasting longer than 5 min compared with patients with normal and clinically non-significant results (OR: 7.53, 95% CI: 1.32–43.09). Patients with metabolic acidosis had 3.677 times increased risk of having seizures lasting longer than 5 min compared with patients without acidosis (OR: 1/0.272 95% CI: 0.12–0.623). Patients with focal seizures, compared those with generalized seizures, had a 3.077 times greater likelihood ($P = 0.051$; OR: 1/0.325, 95% CI: 0.11–1.01), and patients with acidosis had a 4.065 times greater likelihood (OR: 1/0.246, 95% CI: 0.09–0.68) of having used two or more antiepileptics in the emergency department ($P < 0.05$; Table 5).

Discussion

We evaluated comprehensively 333 children with a first pediatric afebrile seizure admitted to the major pediatric emergency

Table 2 Clinically significant neuroradiological investigations of patients

No	Age (months)/ Sex	Cranial CT	Diffusion-weighted MRI	Cranial MRI	Final diagnosis
1	102/M	Focal encephalomalacia	Not performed	Focal encephalomalacia and craniectomy defect	Post-traumatic cerebral injury
2	22/M	Skull fracture	Normal	Not performed	Skull fracture
3	13/F	Skull fracture	Not performed	Not performed	Skull fracture
4	168/M	Focal subcortical nodular hyperdense lesion	Right frontal nodular lesion without diffusion restriction	Right centrum semiovale nodular hemorrhage	Arteriovenous malformation
5	7/F	Hydrocephalus and VP shunt	Not performed	Not performed	Hydrocephalus and VP shunt
6	145/M	Hydrocephalus and VP shunt	Not performed	Not performed	Hydrocephalus and VP shunt
7	60/M	Hydrocephalus and VP shunt	Not performed	Hydrocephalus and VP shunt	Hydrocephalus and VP shunt
8	11/M	Left cerebellar hypodensity and bilateral parietooccipital hyperdensity	Diffusion restriction in cerebral and cerebellar areas	Left cerebellar and left thalamic hyperintensities	Acute ischemic posterior arterial infarction
9	10/M	Left frontotemporal cystic encephalomalacia	Not performed	Not performed	Encephalomalacia
10	11/M	Left parietooccipital encephalomalacia	Left parietooccipital encephalomalacia	Left parietooccipital encephalomalacia	Encephalomalacia
11	118/M	Left temporoparietal corticosubcortical hypodensity	Multiple areas of diffusion restriction	Left parietooccipital white matter hyperintensities	Encephalitis
12	6/F	Periventricular and deep gray matter hypodensity	Not performed	Not performed	Inborn errors of metabolism
13	90/M	Periventricular hypodensities	Not performed	Periventricular leukomalacia	Cerebral palsy
14	74/F	Periventricular volume loss	Not performed	Periventricular volume loss	Cerebral palsy
15	27/M	Temporal, periventricular cystic changes and periventricular calcifications	Not performed	Not performed	TORCH
16	90/M	Normal	Left parietooccipital white matter volume loss	Left parietooccipital white matter volume loss	Encephalomalacia
17	23/F	Normal	Multiple areas of diffusion restriction	Cortico-subcortical hyperintensities	Encephalitis
18	183/M	Not performed	Not performed	Hydrocephalus and VP shunt	Hydrocephalus and VP shunt
19	80/M	Not performed	Not performed	Left periventricular gliosis	Perinatal stroke
20	109/F	Normal	Normal	Biparietal and occipital cortical signal abnormalities	PRES
21	5/F	Normal	Not performed	Lissencephaly type I	Neuronal migration abnormality
22	35/M	Normal	Normal	Calcific subependimal nodule and tubers	Tuberosclerosis
23	89/M	Normal	Normal	Atrophic volume loss and multiple areas of hyperintense signals	Cerebral palsy

CT, cranial tomography; F, female; M, male; MRI, magnetic resonance imaging; PRES, posterior reversible encephalopathy syndrome; TORCH, toxoplasma other agents rubella cytomegalovirus herpes simplex; VP, ventriculoperitoneal.

department in Prof. Dr. Cemil Taşcıoğlu City Hospital, emphasizing laboratory investigations, radiological tests, and emergent management with detailed data. Neuroradiological investigations – CT, diffusion-weighted, and cranial MRI – revealed a new clinically significant abnormality in 5% of patients in our study. We included all children presenting to the ED with new-onset seizures regardless of their neurological background. Thus, in our study, an additional 2.7% already had a pre-existing condition (e.g., hydrocephalus, cerebral palsy) that related to a neuroradiological abnormality. In the literature, clinically relevant abnormalities have been reported in up to 9% identified by CT,[12,13] but identifying an urgent finding was much lower, and Dayan *et al*. concluded that, in unprovoked seizures, urgent abnormalities occur in less than 1% of children as detected by CT or MRI.[14] Although we detected new clinically significant abnormalities through neuroimaging, no patient required immediate neurosurgery. Cranial tomography is typically preferred over MRI in the emergency department as it can be done without sedation, but overuse of CT scans is inadvisable due to the risks of radiation from the scans.[15] In our study, cranial CT gave false negative results in six patients, whereas cranial MRI was able to detect the

Table 3 Laboratory investigations of patients including neuroimaging, EEG, and antiepileptic treatments

	n (%)
Metabolic abnormality (*n* = 13)	
Hypocalcemia	6 (1.8)
Hypoglycemia	4 (1.2)
Moderate/severe hyponatremia	2 (0.6)/1 (0.3)
Blood gas abnormalities (*n* = 42)	
Respiratory acidosis	24 (7.2)
Metabolic acidosis	8 (2.4)
Metabolic and respiratory acidosis	5 (1.5)
Metabolic acidosis and respiratory alkalosis	5 (1.5)
No abnormality	159 (47.7)
Blood gas not obtained	132 (39.6)
Electroencephalography	
Normal	56 (16.8)
Generalized epileptiform discharges	29 (8.7)
Focal epileptiform discharges	19 (5.7)
Disorganized background	2 (0.6)
Not performed or could not retrieve	227 (68.2)
Cranial computed tomography	
Normal	263 (79)
Clinically significant abnormality	15 (4.5)
Clinically non-significant abnormality	15 (4.5)
Not performed	40 (12)
Diffusion-weighted cranial MRI	
Normal	155 (46.5)
Clinically significant abnormality	6 (1.8)
Clinically non-significant abnormality	6 (1.8)
Not performed	166 (49.8)
Cranial MRI	
Normal	85 (25.5)
Clinically significant abnormality	16 (4.8)
Clinically non-significant abnormality	21 (6.3)
Not performed	211 (63.4)
Where was the first AED executed	
Emergency department	156 (47)
Another hospital	14 (14)
Ambulance	1 (0.3)
No drugs	163 (48.9)
First AED	
Intravenous levetiracetam	100 (30)
Intravenous midazolam	32 (9.6)
Intravenous phenytoin	19 (5.7)
Intravenous diazepam	10 (3)
Others	10 (3)
None	162 (48.6)
Total antiepileptics executed	
1 AED	112 (33.6)
2 AED	30 (9)
3 AED	16 (4.8)
4 AED	9 (2.7)
5 AED	4 (1.2)
Etiology	
Structural	22 (6.6)
Metabolic	12 (3.6)
Infectious	3 (0.9)
Genetic	2 (0.6)
Unknown	294 (88.3)
Post-seizure status	
Discharge from the emergency department	210 (63.1)
Ward hospitalization	100 (30)
Hospitalization to an intensive care unit	18 (5.4)
Refusing hospitalization	5 (1.5)
Post-discharge drug prescription	
Yes	164 (49.2)
No	152 (45.6)
Unknown	17 (5.1)

AED, antiepileptic drug; CT, cranial tomography; MRI, magnetic resonance imaging.

abnormality. The results of our study, together with existing evidence,[14] indicate that the diagnostic utility of cranial CT should be balanced in the emergency department against the potential risks of radiation exposure and its relatively low sensitivity.

Classical neuroradiological indications for cranial CT or MRI are unprovoked focal seizures and/or abnormal focal findings on physical examination, and according to history and physical examination.[16] In our study, patients with focal seizures had been given more antiepileptic drugs in the emergency department than patients with generalized seizures, and their seizures recurred more often in the emergency department ($P < 0.05$). However, we could not detect any relationship between focal seizures with neuroradiological abnormalities on CT or MRI. The latest studies reveal some additional risk factors for abnormal neuroimaging other than the established ones: children below two years of age, status epilepticus, and a high-risk medical history (e.g. coagulopathy, sickle cell disease, cardiac defect, or ventricular shunt).[2,13,14,17] A seizure duration of longer than 5 min, which could be interpreted as status epilepticus, was identified as a risk factor for clinically significant abnormality in CT in our study, as well. The majority type of seizures is generalized in our study. Although generalized epileptiform discharges were more than focal discharges in EEG recordings, the discrepancy was not so significant as in the seizure type. An EEG could only be performed in 106 (32%) patients in the emergency setting. We believe patients without an EEG might have contributed to the disagreement.

We detected 13 (3.9%) patients with a metabolic abnormality in the etiology of the afebrile seizures. Almost half of them were infants of less than 2 years. The first step in the laboratory investigations after admission to the pediatric emergency department is biochemical testing. Physicians request biochemical testing for each patient with an afebrile seizure because there are no clear clues that can guide them to metabolic abnormalities in the history or through physical examination.[18] Valencia and Saz *et al*. suggest that children aged less than 2 years are more likely to have a significant laboratory abnormality associated with their seizures.[4,19] Scarfone *et al*.,[20] while studying infants aged 1 day to 12 months, recommended laboratory testing not for all infants but for those infants who are actively seizing in the emergency department, have hypothermia, or who are only neonates. We were unable to reach any conclusions based on biochemical testing that would corroborate or contradict previous studies. Another recent study also examined emergent laboratory investigations

Table 4 Comparison of the patient's status during admittance with different variables

		Status during admission			*P*	Seizure type		Test/*P*	First seizure duration			*P*	Acidosis		*P*
		Ongoing seizure *n* (%)	Postictal *n* (%)	Conscious *n* (%)		Focal *n* (%)	Generalized *n* (%)		<5 min *n* (%)	5-30 min *n* (%)	>30 min *n* (%)		Yes *n* (%)	No *n* (%)	
First AED	ER	24 (82.8)	16 (80.0)	115 (95.0)	**0.019**	26 (89.7)	129 (91.5)	0.723	98 (96.1)	46 (88.5)	11 (68.8)	**0.001**	22 (84.6)	77 (92.8)	0.246
	Other	5 (17.2)	4 (20.0)	6 (5.0)		3 (10.3)	12 (8.5)		4 (3.9)	6 (11.5)	5 (31.3)		4 (15.4)	6 (7.2)	
Seizure type	Focal	11 (36.7)	3 (12.0)	26 (9.4)	**0.001**	-	-		23 (9.6)	12 (15.6)	5 (29.4)		9 (21.4)	17 (10.7)	0.065
	Generalized	19 (63.3)	22 (88.0)	252 (90.6)					216 (90.4)	65 (84.4)	12 (70.6)	**0.029**	33 (78.6)	142 (89.3)	
Total number of AED in ER		2.47 ± 1.25	1.44 ± 1.33	0.60 ± 0.85	**0.001**	1.58 ± 1.50	0.73 ± 0.98	**0.001**	0.62 ± 0.92	1.08 ± 1.11	2.59 ± 1.37	**<0.001**	1.43 ± 1.47	0.80 ± 1.07	**0.012**
Seizure recurrence in ER	Yes	11 (36.7)	7 (28.0)	27 (9.7)	**0.001**	10 (25)	35 (11.9)	**0.023**	28 (11.7)	11 (14.3)	6 (35.3)	**0.022**	11 (26.2)	22 (13.8)	0.055
	No	19 (63.3)	18 (72.0)	251 (90.3)		30 (75)	258 (88.1)		211 (88.3)	66 (85.7)	11 (64.7)		31 (73.8)	137 (86.2)	
Acidosis	Yes	8 (44.4)	9 (52.9)	25 (15.1)	**0.001**	9 (34.6)	33 (18.9)	0.065	21 (14.1)	14 (33.3)	7 (70.0)	**<0.001**	-	-	
	No	10 (55.6)	8 (47.1)	141 (84.9)		17 (65.4)	142 (81.1)		128 (85.9)	28 (66.7)	3 (30.0)				
Etiology	Known	9 (30.0)	4 (16.0)	26 (9.4)	**0.003**	10 (25)	29 (9.9)	**0.015**	22 (9.2)	11 (14.3)	6 (35.3)	**0.004**	12 (28.6)	16 (10.1)	**0.002**
	Unknown	21 (70.0)	21 (84.0)	252 (90.6)		30 (75)	264 (90.1)		217 (90.8)	66 (85.7)	11 (64.7)		30 (71.4)	143 (89.9)	
Post-seizure status	Discharge from ER	8 (27.6)	11 (44.0)	191 (69.7)	**0.001**	18 (47.4)	192 (66.2)	**0.022**	157 (66.5)	48 (64.0)	5 (29.4)	**<0.001**	19 (45.2)	94 (59.5)	**0.002**
	Hospitalization	13 (44.8)	10 (40.0)	77 (28.1)		15 (39.5)	85 (29.3)		73 (30.9)	21 (28.0)	6 (35.3)		15 (35.7)	58 (36.7)	
	ICU	8 (27.6)	4 (16.0)	6 (2.2)		5 (13.2)	13 (4.5)		6 (2.5)	6 (8.0)	6 (35.3)		8 (19.0)	6 (3.8)	
Post-discharge AED	Yes	21 (80.8)	15 (68.2)	128 (47.8)	**0.002**	28 (73.7)	136 (48.9)	**0.004**	106 (45.9)	46 (63)	12 (100)	**<0.001**	21 (55.3)	82 (53.6)	0.853
	No	5 (19.2)	7 (31.8)	140 (52.2)		10 (26.3)	142 (51.1)		125 (54.1)	27 (37)	0 (0)		17 (44.7)	71 (46.4)	

AED, antiepileptic drug; ER, emergency; ICU, intensive care unit. Bold values indicate $p<0.05$.

Table 5 (A) Logistic regression analysis of the patients with afebrile seizures regarding the risk of seizures lasting >5 mins. (B) Logistic regression analysis of the patients with afebrile seizures regarding the risk of requiring two and more antiepileptic drugs

	B	SE	Wald	df	Sig.	Exp(B)	95% CI for EXP(B)	
							Lower	Upper
(A)								
Clinically significant CT abnormality	2.019	0.890	5.148	1	**0.023**	7.532	1.316	43.092
Metabolic acidosis	−1.301	0.422	9.495	1	**0.002**	0.272	0.119	0.623
Constant	−0.267	0.356	0.562	1	0.454	0.766		
(B)								
Seizure type (focal seizures)	−1.125	0.577	3.802	1	0.051	0.325	0.105	1.006
Metabolic acidosis	−1.401	0.517	7.346	1	**0.007**	0.246	0.090	0.679
Constant	1.854	0.652	8.088	1	0.004	6.383		

CI, confidence interval; CT, computed tomography; sig., significance. Bold values indicate $p<0.05$.

and was unable to identify any significant predictors for laboratory abnormalities.[18] It seems, in general, that it is difficult to detect absolute risk factors for metabolic abnormalities as the etiologies that may cause biochemical abnormalities are so diverse and rare that they share very little in common, both epidemiologically and clinically.

The first seizure duration was <5 min in 72% and ≥5 min in 28% of the patients in our study, with 9% of patients having ongoing seizures during admittance. Sartori *et al*. reported that 76.8% of patients had seizures shorter than five minutes and that 6.5% had ongoing seizures on arrival.[21] Bergamo *et al*. stated that 5% of their patients were still seizing upon arrival in the emergency department.[22] Our rate for ongoing seizures was almost 1.5–2 times that reported in these other studies. However, the previously mentioned studies had included febrile seizures as well as afebrile seizures, and febrile seizures tend to be shorter, which could account for the lower rates of ongoing seizures in the studies mentioned. Bergamo *et al*. revealed that 19% of children had been administered drugs before admission to the emergency department. In the study by Sartori *et al*., only three patients had received pre-hospital treatment that resulted in seizure cessation. In our study, 16% of patients with ongoing seizures had been administered antiepileptics outside the facility, including those given by the medical services in the ambulance. Chin *et al*. demonstrated that inappropriate emergency management of status epilepticus in children contributes to the need for intensive care.[23] In our study, patients with ongoing seizures, as compared to patients who were conscious upon arrival were more often hospitalized in the intensive care unit, which can be associated with morbidity. Proper treatment, starting in the prehospital setting, is important to reduce the morbidity and mortality associated with seizures.

In our study, the ward hospitalization rate was 30%, as compared to the 15.7% reported by Sartori *et al*.[21] But when febrile seizures were excluded from their study, their hospitalization rate rose to 41.9%. Our intensive care unit hospitalization rate was 5.4%. The rate of intensive care administration was reported to be 0.9% by two different studies that included both febrile and afebrile cases.[21,22] Another study reported even higher rates of ward hospitalization and intensive care unit admission at 80% and 12%, respectively, although this study included both types of seizures.[24] The differences between studies can be related to the variable patient populations admitted to each center and the different socio-cultural and medical approaches adopted. In our study, the risk factors associated with intensive care unit hospitalization were ongoing seizures and postictal state upon admission, focal seizures, first seizure longer than 30 min, and acidosis.

One of the limitations of our study is its retrospective nature. Although all our physicians are familiar with status epilepticus management, there is no treatment protocol specifically assigned for such an emergency. Our study did not enable us to give prevalence rates for afebrile seizures in the district. However, we evaluated detailed information concerning first afebrile seizures from a large number of patients at a single center from a significant emergency center in İstanbul over 3 years. We deliberately excluded febrile seizures, which are a more common cause of admission than afebrile seizures, because they differ from afebrile seizures as a clinical entity.

Our work provides significant data about the epidemiology and clinical course of first afebrile seizures in children admitted to the emergency department. Being familiar with the possible natural history of children with epileptic seizures is very important in guiding the appropriate diagnostic and therapeutic approach. A study with a prospective design and a standardized protocol is necessary to provide additional evidence relating to children with afebrile seizures.

Disclosure

The authors declare no conflicts of interest.

Author contributions

T.A. conceived and designed the study, performed the analyses, and wrote the paper. A.K. collected data. E.M.Ö. collected data. Ö.Y. collected data and made substantial contributions to the analysis of the data. All the authors

revised the article critically for important intellectual content and they approved the final version to be published.

References

1 Hirtz D, Ashwal S, Berg A *et al*. Practice parameter: Evaluating a first nonfebrile seizure in children: Report of the Quality Standards Subcommittee of the American Academy of Neurology, the Child Neurology Society, and the American Epilepsy Society. *Neurology* 2000; **55**: 616–23.

2 Sharma S, Riviello JJ, Harper MB, Baskin MN. The role of emergent neuroimaging in children with new-onset afebrile seizures. *Pediatrics* 2003; **111** (1): 1–5.

3 Landau YE, Waisman Y, Shuper A. Management of children with nonfebrile seizures in the emergency department. *Eur. J. Paediatr. Neurol.* 2010; **14**: 439–44.

4 Saz UE, Polat TB, Gokben S. Are laboratory workup really needed on management of pediatric seizures at emergency rooms? *Int. J. Med. Adv. Discov.* 2012; **3**: 1–4.

5 Maytal J, Krauss JM, Novak G, Nagelberg J, Patel M. The role of brain computed tomography in evaluating children with new onset of seizures in the emergency department. *Epilepsia* 2000; **41**: 950–4.

6 Trinka E, Cock H, Hesdorffer D *et al*. A definition and classification of status epilepticus - Report of the ILAE Task Force on Classification of Status Epilepticus. *Epilepsia* 2015; **56** (10): 1515–23.

7 Mayer SA, Claassen J, Lokin J *et al*. Refractory status epilepticus: frequency, risk factors, and impact on outcome. *Arch. Neurol.* 2002; **59**: 205–10.

8 Nt C, Jm C, Wd G. Timing and selection of first antiseizure medication in patients with pediatric status epilepticus. *Epilepsy Res.* 2019; **149**: 21–5.

9 Scheffer IE, Berkovic S, Capovilla G *et al*. ILAE classification of the epilepsies: Position paper of the ILAE Commission for Classification and Terminology. *Epilepsia* 2017; **58**: 512–21.

10 Shinnar S, O'Dell C, Mitnick R, Berg AT, Moshe SL. Neuroimaging abnormalities in children with an apparent first unprovoked seizure. *Epilepsy Res.* 2001; **43**: 261–9.

11 Wa H, Beghi E. First seizure definitions and worldwide incidence and mortality. *Epilepsia* 2008; **49** (Suppl 1): 8–12.

12 Hsieh DT, Chang T, Tsuchida TN *et al*. New-onset afebrile seizures in infants: Role of neuroimaging. *Neurology* 2010; **74** (2): 150–6.

13 Harden CL, Huff JS, Schwartz TH *et al*. Reassessment: Neuroimaging in the emergency patient presenting with seizure (an evidence-based review): Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology* 2007; **69** (18): 1772–80.

14 Dayan PS, Lillis K, Bennett J *et al*. Prevalence of and risk factors for intracranial abnormalities in unprovoked seizures. *Pediatrics* 2015; **136**: e351–60.

15 Pearce MS, Salotti JA, Little MP *et al*. Radiation exposure from CT scans in childhood and subsequent risk of leukaemia and brain tumours: A retrospective cohort study. *Lancet* 2012; **380**: 499–505.

16 Garvey MA, Gaillard WD, Rusin JA *et al*. Emergency brain computed tomography in children with seizures: Who is most likely to benefit? *J. Pediatr.* 1998; **133**: 664–9.

17 Al-shami R, Khair AM, Elseid M *et al*. Neuro-imaging evaluation after the first afebrile seizure in children: A retrospective observational study. *Seizure* 2016; **43**: 26–31.

18 Strobel AM, Gill VS, Witting MD, Teshome G. Emergent diagnostic testing for pediatric nonfebrile seizures. *Am. J. Emerg. Med.* 2015; **33**: 1261–4.

19 Valencia I, Sklar E, Blanco F *et al*. The role of routine serum laboratory tests in children presenting to the emergency department with unprovoked seizures. *Clin. Pediatr. (Phila)* 2003; **42**: 511–7.

20 Scarfone RJ, Pond K, Thompson K, Fall I. Utility of laboratory testing for infants with seizures. *Pediatr. Emerg. Care* 2000; **16**: 309–12.

21 Sartori S, Nosadini M, Tessarin G *et al*. First-ever convulsive seizures in children presenting to the emergency department: Risk factors for seizure recurrence and diagnosis of epilepsy. *Dev. Med. Child Neurol.* 2019; **61**: 82–90.

22 Bergamo S, Parata F, Nosadini M *et al*. Children with convulsive epileptic seizures presenting to padua pediatric emergency department: The first retrospective population-based descriptive study in an Italian health district. *J. Child Neurol.* 2015; **30**: 289–95.

23 Chin RFM, Verhulst L, Neville BGR, Peters MJ, Scott RC. Inappropriate emergency management of status epilepticus in children contributes to need for intensive care. *J. Neurol. Neurosurg. Psychiatry* 2004; **75** (11): 1584–8.

24 Chen CY, Chang YJ, Wu HP. New-onset seizures in pediatric emergency. *Pediatr. Neonatol.* 2010; **51** (2): 103–11.