

Electroencephalography in the Pediatric Emergency Department: When Is It Most Useful?

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Abstract

This study aimed to identify the indications in which electroencephalography in the pediatric emergency department is most useful. We retrospectively reviewed the influence that the results of the emergent electroencephalogram had on the eventual disposition of patients at our pediatric emergency department. Sixty-eight children (mean age, 7.3 years; 32 males) underwent 70 emergent electroencephalograms. Fifty-seven emergent electroencephalograms were performed for the suspicion of ongoing seizures or status epilepticus. Thirteen of the 22 children (59.1%) discharged from the emergency department were sent home mainly based on the results of the emergent electroencephalogram, which prevented an admission. In particular, 11 of 38 children with frequent and recurrent paroxysmal events concerning for seizures and 2 of 19 children with suspected ongoing status epilepticus were discharged after excluding an epileptic disturbance. The emergent electroencephalogram provided meaningful clinical information that influenced disposition, especially in patients with ongoing events in which the clinical picture was clarified by a rapidly acquired electroencephalogram.

Keywords

diagnostic algorithms, paroxysmal events, seizures, status epilepticus

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The proportion of patients with seizures who visit the emergency department is larger during childhood than at any other age.^{1,2} The number of visits to the emergency department is higher in patients with epilepsy than in patients with febrile seizures or other provoked seizures, although both groups visit the emergency department more often than patients without seizures.³ Overall, in emergency department-based series, approximately 20% of patients with seizures present with seizure recurrence, and approximately 7% have status epilepticus in the emergency department.^{4,5} In addition to seizure recurrence, first-time unprovoked seizures have an incidence of 56.8 per 100,000 person-years⁶ and are among the most common causes of visits to the emergency department.^{7,8}

Despite the high frequency of seizures in the pediatric emergency department, the usefulness of an emergent electroencephalogram is not clear. There is enough evidence to recommend an electroencephalogram in all cases following a first unprovoked seizure,⁹ but the timing of this electroencephalogram is controversial, and there is not enough evidence to support the completion of an electroencephalogram before discharge from the emergency department after a first seizure.⁹ Among other scenarios in which an emergent electroencephalogram can be useful are

those in which patients present with persistently depressed consciousness after a prolonged seizure, those in whom nonconvulsive seizures are suspected, or those in which children present to the emergency department with ongoing motor activity of uncertain significance. It thus appears reasonable that an electroencephalogram obtained in the emergency department can be useful for these cases, but data as to the actual utility of this test

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Table 1. Studies That Have Evaluated the Value of the Electroencephalogram in the Emergency Department.

| Author (year) | No. of patients | Age, y | Study type | Inclusion criteria | Main findings |
|--|-----------------|--|---------------------------------|---|---|
| Study population consisting mainly of adults | | | | | |
| Yigit et al ²² (2012) | 449 | 36 children (<16 y), mean \pm SD: 45.5 \pm 21.8 | Retrospective descriptive study | All patients with a clinical presentation suggestive of a seizure in the emergency department | An abnormal EEG result was found in 71% of the hospitalized patients and in 59.5% of those discharged ($P = .019$). |
| Praline et al ¹² (2007) | 111 | 16 children, mean \pm SD: 3.4 \pm 4.5; 95 adults, mean \pm SD: 53 \pm 17.2 | Prospective descriptive study | All emergent EEG studies | The emergent EEG was considered to contribute to the diagnosis in 77.5% of cases. It helped confirm a clinically suspected diagnosis in 36% of cases and to rule it out in the remaining 64%. The results of the emergent EEG led to a modification in treatment in 37.8% of cases. |
| King et al ²⁰ (1998) | 300 | 59 children (<16 y), mean (range): 31.2 (5-83) | Prospective descriptive study | All patients aged \geq 5 y with first-time unprovoked seizures and initial EEG in different departments of the hospital | The EEG within 24 h of the episode detected more abnormalities than the EEG performed later. The proportion of first EEGs with abnormalities was higher in children. |
| Study population consisting mainly of children | | | | | |
| Kothare et al ¹⁰ (2005) | 32 | Mean (range): 4.5 (0.014-17) | Retrospective descriptive study | All EEGs performed during nonbusiness hours | Emergent EEGs were useful in decision making in 94% of cases. |
| Alehan et al ¹¹ (2001) | 56 | Range: 0.0056-25 | Retrospective descriptive study | All EEG studies performed in the emergency department | In the group of patients with new-onset nonfebrile seizures, the risk of seizure recurrence was much higher in children with abnormal EEG results (80% vs 31%; $P < .01$). Retrospectively, among all patients who received the diagnosis of epilepsy, 76% had had an abnormal EEG result in the emergency department. The EEG directly contributed to the diagnosis in 84% of patients. |
| Present study | 68 | Mean (range): 7.3 (0.096-21) | Retrospective descriptive study | All EEGs performed in the emergency department | From all the discharges from the emergency department, 59.1% were based on the results of the EEG. In the group of children with frequent paroxysmal events concerning for seizures, 29% of the patients were discharged based on the results of the emergent EEG. |

Abbreviations: EEG, electroencephalogram; SD, standard deviation.

are scarce. A study of 32 pediatric emergent electroencephalograms obtained for a variety of reasons showed that the electroencephalogram results influenced the decision-making process in 94% of cases (Table 1).¹⁰ In a series of 56 children who presented to the emergency department with a first-time nonfebrile seizure, there was a much higher risk of seizure recurrence within a mean follow-up of 19.5 months when the emergent electroencephalogram result was abnormal.¹¹ In the same study, 76% of the children who were eventually diagnosed with epilepsy had an abnormal initial emergent electroencephalogram (Table 1).¹¹

These studies are limited in number and warrant replication. In addition, the indications for the performance of an emergent electroencephalogram have not been identified in the available literature. Such evidence-based indications can lead to a more efficient use of this resource in the pediatric emergency department.

As a step toward addressing this need, the authors analyzed electroencephalograms completed in the emergency department and performed a retrospective review of the medical records (1) to evaluate the influence that the results of an emergent electroencephalogram had on the disposition of children in the

emergency department and (2) to identify indications in which the emergent electroencephalogram was particularly useful.

Methods

Protocol Approval

This study was approved by the institutional review board of Boston Children's Hospital.

Study Design

The authors performed a retrospective descriptive study.

Patients

The authors reviewed data on children in whom an electroencephalogram was performed in the emergency department at Boston Children's Hospital over a period of 29 consecutive months, in an estimated study base of 120,000 children who visited the emergency department in that time frame. All electroencephalograms were ordered during the course of a neurology consultation in the emergency department. Only the electroencephalograms completed in the emergency department on an emergent basis were included in the study, while those electroencephalograms ordered in the emergency department but completed at a later time in other departments of the hospital were excluded.

Emergent Electroencephalograms

All electroencephalograms had a minimum duration of 20 minutes. Scalp electrodes were placed according to the 10-20 international system of electrode placement. Video monitoring was concomitantly recorded at the bedside. Each electroencephalogram included standard activation procedures when the child's clinical state permitted. The data were interpreted in the clinical neurophysiology laboratory during the child's stay in the emergency department.

Analysis of Data From the Electroencephalogram

For the purposes of this study, all available data from the electroencephalograms were retrieved and re-reviewed. The authors extracted relevant information from the associated emergency department notes, the neurology consultation notes, the electroencephalogram request form, the electroencephalogram technologist's notes, and the formal electroencephalogram reading by a board-certified clinical neurophysiologist. They collected information on the duration of each electroencephalogram, on whether natural sleep was obtained, and on the abnormalities detected, if any.

Analysis of Clinical Data and Influence of the Electroencephalogram on Disposition

The authors collected clinical variables including demographics, clinical presentation, and indication for performing an emergent electroencephalogram. They analyzed the disposition of the children in detail before and after the results of the emergent electroencephalogram became available. They also determined whether and how the results of the electroencephalogram affected the emergent disposition. In children who presented without a prior diagnosis of epilepsy, the authors determined whether they were diagnosed with epilepsy on follow-up and

correlated those data with the results of the initial emergent electroencephalogram.

Results

Patient Demographics

The authors reviewed data on 68 children (32 males) who underwent 70 emergent electroencephalograms (2 patients were evaluated with 2 electroencephalograms each). The mean age was 7.3 years (range, 0.096-21 years). In this population, 17 (25%) children were younger than 1 year of age, and 34 (50%) were younger than 5 years of age.

Baseline Medical Conditions

Thirty-four children previously sought medical attention for seizures on at least 1 occasion prior to the index emergency department visit. An episode of nonepileptic seizures had been diagnosed in 1 of them. Thirty children were taking at least 1 antiepileptic medication, and 2 had an implanted vagal nerve stimulator. Other associated medical conditions are presented in Table 2.

Characteristics of the Electroencephalograms

All electroencephalograms were successfully completed, and the data were of sufficient quality to obtain a reliable formal reading from a clinical neurophysiologist. In the entire series, 31 electroencephalogram results (44% of total) were normal. Spontaneous sleep was achieved during 26 (37%) electroencephalograms. Electroencephalogram duration was not reported in 2 cases, and these 2 reports were excluded from duration analysis. The mean duration of the 68 analyzed electroencephalograms was 29.9 minutes (range, 20-75 minutes). During the performance of the emergent electroencephalogram, 5 children were sedated for control of convulsive status epilepticus, and 2 of these were intubated and pharmacologically paralyzed.

Indications for an Emergent Electroencephalogram

The 2 main reasons for performing an emergent electroencephalogram were (1) evaluation of frequent paroxysmal events that raised suspicion for ongoing seizures or evaluation of suspected status epilepticus ($n = 57$ electroencephalograms in 56 children) or (2) evaluation of children without the suspicion of ongoing seizures who had recovered after a witnessed seizure ($n = 13$ electroencephalograms in 12 children). Details on the specific conditions are presented in Tables 3 and 4.

Influence of Electroencephalogram Results on Patient Disposition

Twenty-two children were discharged from the emergency department, and 13 of those discharges (59.1%) were directly based on the results of the emergent electroencephalogram as indicated in the consultation and discharge summary. Seven

Table 2. Concomitant Medical Diagnoses in the Patient Population.

| Primary neurological conditions | n | Other admitting diagnoses as stated in the emergency department | n |
|-------------------------------------|---|---|---|
| Shunted hydrocephalus | 2 | Fever | 6 |
| Autism | 1 | Chromosomal abnormalities | 4 |
| Brain stem glioma | 1 | Upper respiratory infection without fever | 2 |
| Chiari type II malformation | 1 | Congenital heart disease | 2 |
| Resected craniopharyngioma | 1 | Gastrointestinal hemorrhage | 1 |
| Lissencephaly | 1 | Hypotension | 1 |
| Periventricular heterotopia | 1 | Mild hyponatremia | 1 |
| Resected arteriovenous malformation | 1 | Sinusitis | 1 |
| Stroke | 1 | | |
| Tuberous sclerosis | 1 | | |
| Viral meningitis | 1 | | |

Table 3. Results of the Electroencephalograms and Disposition of Children in the Emergency Department.

| | Evaluation for suspicion of ongoing seizures/status epilepticus | N = 57 (56) | Evaluation without suspicion of ongoing seizures/status epilepticus | N = 13 (12) |
|--|--|----------------|--|----------------|
| Results of the EEG, n | <ul style="list-style-type: none"> Frequent paroxysmal events concerning for seizures | 38 (37) | <ul style="list-style-type: none"> Recovered after a first episode concerning for seizures without symptoms, suggestive of ongoing seizures | 13 (12) |
| | Paroxysmal event captured during the EEG | 24 | Normal EEG result | 10 |
| | Normal EEG finding during the event | 12 (11) | Focal slowing and multifocal epileptiform activity | 2 (1) |
| | EEG without correlate during the event | 6 | | |
| | EEG with correlate during the event | 6 | | |
| | <ul style="list-style-type: none"> Clinical suspicion of ongoing status epilepticus | 19 | <ul style="list-style-type: none"> Altered level of consciousness without symptoms, suggestive of ongoing seizures | 1 |
| | Nonconvulsive status epilepticus confirmed | 2 | Slowing without seizures | 1 |
| | Electrographic seizures but not status epilepticus | 2 | | |
| | Focal or multifocal epileptiform activity | 4 | | |
| | Frequent generalized spike wave but not status epilepticus | 2 | | |
| | Diffuse slowing | 4 | | |
| | Focal slowing | 3 | | |
| | Normal EEG result | 2 | | |
| Disposition in the emergency department, n | Discharged after exclusion of an ongoing seizure | 12 (11) | Discharged based on clinical and EEG data | 7 |
| | Discharged after status epilepticus was excluded | 2 | | |

Abbreviation: EEG, electroencephalogram. n, number of EEGs (when the number of EEGs is different than the number of patients, the number of patients is shown in parentheses).

Table 4. Type of frequent Paroxysmal Events Concerning for Seizures.

| Frequent paroxysmal events concerning for seizures | No. of patients |
|--|-----------------|
| Abnormal paroxysmal movements of limbs or torso | 25 |
| Abnormal paroxysmal movements of eyes, face, or head | 11 |
| Abnormal paroxysmal sensation | 1 |

discharges were based on clinical and electroencephalogram data, and 2 discharges were based mainly on clinical findings.

In particular, of the 19 children with suspected status epilepticus, 2 (10.5%) children were discharged after excluding nonconvulsive status epilepticus on electroencephalograms, and of the 38 children with frequent paroxysmal events, 11 (29%) were discharged after excluding that the event in question was epileptic (Table 3). Seven of 12 (58.3%) children evaluated after recovery from a first episode concerning for seizures without suspected ongoing seizures in the emergency department were discharged home, but the results of the electroencephalogram, together with other clinical factors, contributed to the immediate management and final disposition.

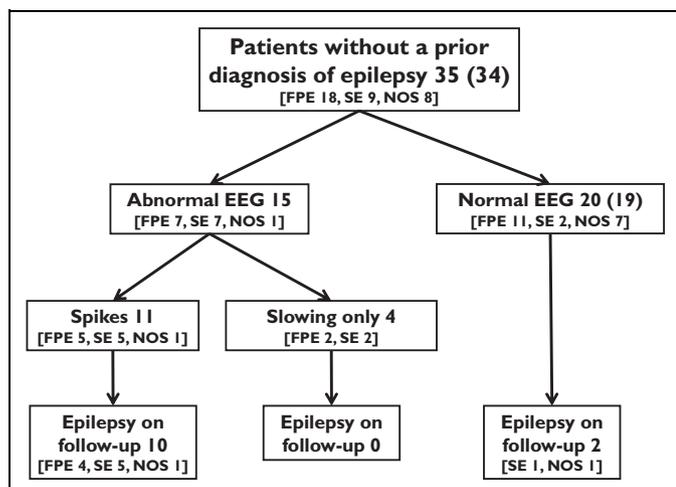


Figure 1. Relationship between the results of the emergent electroencephalogram and the eventual diagnosis of epilepsy. An emergent electroencephalogram with spikes was highly predictive of epilepsy, while an electroencephalogram with only slowing did not predict epilepsy. Numbers represent the number of electroencephalograms in each category. When the number of patients and the number of electroencephalograms do not coincide, the number of patients is provided in parentheses. EEG indicates electroencephalogram; FPE, frequent paroxysmal events; NOS, no ongoing seizures; SE, status epilepticus.

Of the 38 children with a suspicion of ongoing seizures, a paroxysmal event was captured in 24 during the electroencephalogram. Of the 19 children with suspicion of status epilepticus, nonconvulsive status epilepticus was confirmed in 2, and 2 others had electrographic seizures but not status epilepticus. In an additional 2 cases, status epilepticus was excluded, and these last 2 patients were discharged from the emergency department (Table 3).

Predictive Value of the Emergent Electroencephalogram in the Final Diagnosis of Epilepsy

After the emergent electroencephalogram, children were followed up for a mean ± standard deviation of 3.51 ± 3.29 years. There was a difference in the duration of follow-up in those with a diagnosis of epilepsy prior to the emergent electroencephalogram who were followed for 5.17 ± 3.09 years and in children without a prior diagnosis of epilepsy who were followed for 1.85 ± 2.61 years (independent-samples *t* test, *P* < .0001).

Thirty-five electroencephalograms came from 34 children without a prior diagnosis of epilepsy. Of those, 19 children (20 electroencephalograms) had a normal electroencephalogram, and 15 had an abnormal electroencephalogram (4 of them had slowing without epileptiform activity, and 11 had sharp waves or spikes with or without slowing). Of the 15 children with abnormal electroencephalogram results, 10 were found to have epilepsy on follow-up. Of the 19 children with normal electroencephalogram results, 17 did not have epilepsy

on follow-up, while 2 did (Figure 1). The results were broken down by the specific indication for performing the electroencephalogram and are illustrated in Figure 1.

Retrospectively, among the 34 children without a diagnosis of epilepsy prior to the electroencephalograms in the emergency department, 12 (35.3%) children were diagnosed with epilepsy on follow-up. In those 12 children, the electroencephalogram in the emergency department revealed sharp waves or spikes in 10 and was normal in 2 (in 1 of them, sleep was not captured during the recording). Therefore, in our sample, an emergent electroencephalogram with sharp waves or spikes had a sensitivity of 0.83, a specificity of 0.96, a positive predictive value of 0.91, and a negative predictive value of 0.91.

Discussion

We found that rapidly obtained electroencephalogram results influenced the disposition of children in the emergency department, particularly in instances in which patients presented with frequently recurrent or continuous symptoms that raised concern for ongoing seizures or for status epilepticus. In contrast, an emergent electroencephalogram after a first clinical seizure without suspicion of ongoing seizures upon arrival to the emergency department contributed little to the final disposition. Yet, in this group, most patients (6/7) with a normal electroencephalogram did not develop epilepsy, while the only patient with an abnormal electroencephalogram did. We note, however, that the differences between groups were not statistically significant, probably because of the low numbers.

Indications for an Emergent Electroencephalogram

The reasons for ordering an emergent electroencephalogram in children and adults are different.^{10,11} In accordance with previous pediatric studies, in this series, the most common reasons for ordering an emergent electroencephalogram were evaluation of frequent paroxysmal events, subclinical status epilepticus, and further investigation of a witnessed first episode concerning for seizures, while evaluation of altered mental status without other manifestations was uncommon. In contrast, the main reasons for ordering an emergent electroencephalogram in adults are suspected brain death, altered level of consciousness, nonconvulsive status epilepticus, subtle status epilepticus, and follow-up of convulsive status epilepticus, while evaluation of paroxysmal movements concerning for seizures is not so common as in children.^{12–15} The difference in indications for ordering an emergent electroencephalogram in children and adults suggests that decisions made based on findings from emergent electroencephalograms in adult studies may not be applicable to pediatric populations.

Timing of the Electroencephalogram in the Emergency Department

Based on the available evidence, an electroencephalogram has been recommended after all nonprovoked seizures in children.^{9,16–19}

However, there is insufficient evidence to recommend for or against the performance of an electroencephalogram before discharge from the emergency department, although an electroencephalogram obtained early after a seizure is more likely to detect abnormalities than an electroencephalogram performed later.^{9,20} For instance, unilateral slowing after a seizure can provide lateralizing evidence in patients with partial seizures.²¹ Yet, abnormalities such as postictal slowing can be transient and should be interpreted with caution in the context of presentation and time frame after a seizure.⁹

In adults, data suggest that an emergent electroencephalogram is often useful, although, as with pediatric emergent electroencephalograms, more prospective data will be needed to identify the true utility of this test. In one series of 111 adults, the emergent electroencephalogram contributed to the diagnosis in 77.5% of the cases and led to a modification in treatment in 37.8% (Table 1).¹² In another series of 449 adults who underwent an electroencephalogram within 16 hours of the initial paroxysmal event, an abnormal result was present in 71% of those admitted to the hospital and in 59.5% of those who were discharged from the emergency department ($P = .019$), but the clinical relevance of these numbers is uncertain.²²

In children, the published data are also limited but do suggest a utility for the emergent electroencephalogram. In a series of 32 children, the results of the emergent electroencephalogram were useful in the decision-making process in 94% of cases.¹⁰ However, similar to our findings, the approval of the electroencephalogram by a neurologist could have influenced this high rate.¹⁰ In a series of 56 children, within a mean follow-up period of 19.5 months, the risk of seizure recurrence was much higher in those with an abnormal emergent electroencephalogram, and it was estimated that the emergent electroencephalogram contributed to the diagnosis in 84%.¹¹ However, these studies did not evaluate the immediate usefulness of the emergent electroencephalogram within the emergency visit (Table 1).^{10,11} This case series is thus the largest to date and provides a new analysis of the value of pediatric emergent electroencephalograms.

Value of an Emergent Electroencephalogram for Different Indications

According to our data, an emergent electroencephalogram is most useful when the clinical picture is ambiguous and the epileptic nature of frequent paroxysmal events is questionable. In this series, frequent and recurrent paroxysmal events suspicious for seizures were captured in 24 of 38 cases, allowing for the evaluation of its epileptic nature. Under these circumstances, the emergency department staff is presented with a simple binary measure: the event is or is not epileptic. In contrast, the emergent electroencephalogram obtained after recovery from a witnessed seizure did not have much impact on the disposition of the child in the emergency department; the authors suspect it is largely because interictal electroencephalogram data are most relevant to the formulation of a long-term seizure treatment plan and can have less impact on hour-to-hour management in the emergency department.

Additionally, although an argument can be made for the value of capturing a postictal focal abnormality, such abnormalities (eg, unilateral slowing) can be prolonged and available for capture by electroencephalograms outside of an emergency department setting.²¹ In summary, an emergent electroencephalogram was most beneficial for ruling out ongoing seizures or ongoing status epilepticus. In contrast, the impact on immediate management and disposition was relatively low when the electroencephalogram was performed after recovery from a first episode concerning for seizures, without suspected ongoing seizures in the emergency department. The emergent electroencephalogram in this series excluded status epilepticus in 2 cases and confirmed its presence in another 2 cases. The inconclusive classification in most cases of suspected status epilepticus can reflect a delay from arrival in the emergency department to the time in which the electroencephalogram is acquired and can also reflect the prompt and effective treatment of clinically evident status epilepticus by the emergency department staff (Table 3).

In the group of 12 patients in whom the emergent electroencephalogram was performed after recovery from a witnessed seizure, without suspected ongoing seizures, 1 patient (2 electroencephalograms) had focal slowing and multifocal epileptiform activity, and 1 patient had slowing without seizures. Of these patients, only the latter had a clinical reduction in level of consciousness, while the other patient was conscious.

Emergent Electroencephalogram as a Predictor of the Development of Epilepsy

The data show that the sensitivity, specificity, and predictive values of an abnormal emergent electroencephalogram for the eventual diagnosis of epilepsy are very high. Retrospectively, among the children who received the diagnosis of epilepsy, 83.3% had an abnormal electroencephalogram result in the emergency department. These data are comparable to those from the series by Alehan et al,¹¹ who found that, retrospectively, among all children who eventually received the diagnosis of epilepsy, 76% had an abnormal electroencephalogram result in the emergency department. When the authors broke the usefulness of emergent electroencephalograms down by indication to predict the development of epilepsy, low numbers did not allow finding tendencies towards a difference between the indications to perform an electroencephalogram.

Potential Impact of the Data

We found that the electroencephalogram can be most useful in the pediatric emergency department for the management of children who present with frequent paroxysmal motor events concerning for seizures or a change in consciousness concerning for ongoing nonconvulsive seizures. For those indications, the emergent electroencephalogram can be a cost-effective means to expedite disposition and to reduce unnecessary hospital admissions.

Outlook

The data can fuel the performance of prospective studies to evaluate the usefulness of an emergent electroencephalogram for every indication by comparing the planned disposition before and after its performance. In addition, this series raises the question of whether the results of an emergent electroencephalogram actually reduce the use of emergent medications and the length of hospital stay. This question will be better answered with a subsequent prospective study design, potentially including cost-benefit analyses.

Limiting steps to a wider application of the electroencephalogram in the emergency department are the availability of equipment and personnel to acquire the data and the availability of clinical neurophysiologists to read the electroencephalogram within a reasonable time frame. Recent developments of automated methods for seizure detection can be a step forward in providing real-time interpretation of the electroencephalogram.^{23–27}

Strengths and Weaknesses

These results need to be interpreted in the clinical setting of data acquisition. The decision to obtain an emergent electroencephalogram remained at the discretion of the attending neurologist on call, and therefore, it was not completely independent of the initial disposition decisions based on clinical history and physical examination. However, in the children in whom the results of the emergent electroencephalogram strongly influenced the final disposition, the reasons were well documented in the clinical charts. Not all emergency departments have a child neurologist available at all times to screen patients and determine who will benefit most from an emergent electroencephalogram. Therefore, these results cannot be directly generalizable to settings where the decision to perform an emergent electroencephalogram is made without the direct input and approval of a neurologist. However, our results can be generalizable to a large number of pediatric emergency departments where a consultation with a child neurologist is readily available. The impact of the emergent electroencephalogram on dispositions to discharge was more clearly documented than the impact on dispositions to admit to the hospital. Apparently, the clinical evolution in the emergency department and other tests appeared to have contributed more to the eventual disposition to admit to the hospital.

The numbers from which sensitivity, specificity, and predictive values are calculated are quite small to be generalizable. However, the encouraging results warrant replication in larger prospective studies.

We thus present the largest series on the value of the electroencephalogram in clinical decision making in the pediatric emergency department. A major advantage of this study is that it compares the usefulness of the emergent electroencephalogram based on the specific indications, potentially modifying future guidelines.

Conclusion

These data support the use of an electroencephalogram in the pediatric emergency department, especially for those children with suspicion of ongoing seizures or status epilepticus.

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Author Contributions

ISF participated in the study design, collected clinical data, participated in the statistical analysis, revised the article for important intellectual content, and participated in the preparation of the figure. TL participated in the study design, participated in the statistical analysis, and revised the article for important intellectual content. AD edited the first version of the article and revised the article for important intellectual content. SVK participated in the study design and revised the article for important intellectual content. JJR participated in the study design, collected clinical data, drafted the first version of the article, participated in the statistical analysis, and revised the article for important intellectual content. AR conceived the study, participated in the study design, collected clinical data, drafted the first version of the article, participated in the statistical analysis, and revised the article for important intellectual content.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical Approval

This study was approved by the institutional review board of Boston Children's Hospital.

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