Review Article

Status Epilepticus in Pediatric Patients in Saudi Arabia: A Systematic Review

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Abstract

Children frequently experience status epilepticus (SE), a neurologic emergency. Based on current findings in the medical literature, this systematic review aimed to review the published literature of the updates in epidemiology of Status epilepticus in pediatric patients in Saudi Arabia. Because they are reliable sources, PubMed and EBSCO Information Services will be used as the search databases for the publications used in the study. Status epilepticus (SE), seizures, mental health issues, and GABA receptor were among the topics that should have been covered in the project, so those papers were chosen based on their applicability. A total of 105 studies were found after searching the aforementioned databases, which were then used for title screening. 32 of them were excluded after 63 of them were included for abstract screening. The full texts of the remaining 31 publications were examined. Seven studies were enrolled for final data extraction, which includes 23 papers that were excluded as a result of the full-text revision. SE is a complex neurological condition that is primarily seen in children and older individuals, two separate age groups. As the second most prevalent neurological disorder to result in death, it has a high mortality and morbidity rate. Concerning the cause of SE an electrolyte imbalance and febrile seizures were the two most frequent causes of convulsive status epilepticus, respectively. The diagnosis is based mainly on ECG, where children who have SE show abnormalities in their imaging. Management of the condition mainly using antiseizure medications such as Midazolam, lorazepam, and diazepam with almost similar efficacy.

Keywords: Epilepsy, Status epilepticus, Pediatrics, Saudi Arabia

Introduction

Status epilepticus (SE), a neurologic emergency, frequently affects kids. It is defined as the occurrence of recurring epileptic seizures with insufficiently long interepisode intervals (at least 30 minutes) to produce a stable and durable epileptic condition. SE may result from any acute insult to the central nervous system, or it may be an undiagnosed form of epilepsy. In some cases, SE is a child's first unannounced seizure who had previously been healthy [1-3]. According to the recently updated definition, T1 and T2 are the two time-point markers for SE. T1 is the moment in time at which the therapy should start. For the convulsive kind of SE, T1 lasts for 5 min; however, there is a strong likelihood that the seizures will last longer than 5 min. T2, which continues to last for 30 min, is the time point after which seizures may have long-term effects. The ILAE model leads to the conclusion that the type of SE largely determines the urgency of management time or intervention time. In order to apply this term, one must be aware of the significance of time variability [4-6].

Epilepsy occurs in infants aged 1 to 12 months at a prevalence of 144 per 100,000 person-years worldwide, and in children aged 0 to 5, it occurs at a rate of 58 per 100,000 (1–10). Saudi Arabia has few studies on the subject, and the majority of available data was provided by hospitals, which may not accurately reflect the true prevalence of the condition. In one community-based investigation, it was found that Saudi Arabia's prevalence of epilepsy was comparable to that of Western nations (6.24 per 1000 people) [7-9].

According to additional research, the prevalence rate of active epilepsy in Saudi Arabia is 6.54/1,000 (95% CI 5.48–7.60), with a generalized onset accounting for the majority of cases. Major neurological disorders are the most

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prevalent chronic pediatric illnesses in Saudi Arabia, where the incidence rate of epilepsy is 8.8 per 10000, with men being more afflicted. The quality of life (QOL) of many epilepsy patients is impacted by concurrent physical or mental health conditions [10, 11].

In terms of socioeconomic factors, it has been found that developing nations have a higher prevalence of SE than developed nations. Due to inadequate health care infrastructure, sustainable management practices, reduced hygienic conditions, and limited resources, SE is more common, which is also reflected in developing countries' higher mortality indices. According to the information that is currently accessible, 80 percent of SE patients live in poor nations and number close to 50 million [12-14].

The key factor preventing seizures from ending is an imbalance between the excitatory glutamate-mediated system and the inhibitory GABA (gamma-aminobutyric acid) route. During SE, the inhibitory systems are either temporarily impaired, permanently destroyed, or both, causing an extended period of epileptic bursting [15].

Convulsive status epilepticus (CSE) and non-convulsive status epilepticus are the two forms of status epilepticus that are recognized clinically (NCSE). Pediatric emergencies typically involve CSE1, but in recent years, as EEG monitoring has become more widely used, NCSE has been increasingly discovered. NCSE could signal a worse prognosis 8. Only a few studies from Saudi Arabia have been recorded. Mah *et al*. discovered that 28% of hospitalized pediatric seizure episodes were caused by SE in research conducted in Saudi Arabia 9. In addition, there are other SE etiologic classifications. The Maytal *et al*. categorization of idiopathic, acute symptomatic, remote symptomatic, febrile, and progressive encephalopathy is the most widely used one [16-19].

Evaluation and treatment of epilepsy in pediatric children is done mainly by the neurologist. The key to evaluating epilepsy, as with many other medical conditions, is collecting a thorough medical history. The history data includes the history of the seizures, any medications used, comorbidities, and the usage of alcohol or any illicit substance. It's also crucial to consider any past malignancies or immunosuppression. The biomarker electroencephalography (EEG) is used to diagnose epilepsy. Additionally, electrolytes should be taken, and lumbar puncture should be addressed in patients who have a fever. Imaging is recommended if a patient has a history of severe head trauma, malignancy, fever, recurrent headaches, and anticoagulation, is over 40 years old, or has focal seizures, and there is a suspicion of an acute intracranial phase [20, 21].

As primary or supplementary treatments, a wide variety of substances may be useful in the treatment of epilepsy. The decision may be made in consultation with a neurologist and may be influenced by potential side effects. According to how they work, medications for epilepsy can be divided into GABA receptor agonists and sodium channel blockers (carbamazepine, oxcarbazepine, phenytoin, lamotrigine, and lacosamide) or benzodiazepine and barbiturates. Other medications with similar mechanisms include glutamate antagonists like topiramate, felbamate, and perampanel, GABA reuptake inhibitors like tiagabine, inhibitors of GABA-transaminase like vigabatrin, and medications with other mechanisms including gabapentin, pregabalin, and valproic acid. The most common category of management medications includes benzodiazepines including lorazepam, midazolam, and diazepam. Second-class epileptic medications include phenytoin and phenobarbital [22, 23].

Study Objectives

Based on current findings in the medical literature, this systematic review aimed to review the published literature of the updates in epidemiology of Status epilepticus in pediatric patients in Saudi Arabia.

Materials and Methods

Study Design

Simple Review Article.

Study Duration

Data will be collected during the period from 1– 31 April, 2022.

Data Collection

Because they are reliable sources, PubMed and EBSCO Information Services will be used as the search databases for the publications used in the study. The National Center for Biotechnology Information (NCBI), a division of the United States National Library of Medicine, created PubMed, one of the biggest digital libraries on the Internet. The creation of the essay drew on material on neurological illnesses, status epilepticus, and other subjects. Titles and an examination of the abstracts were used to filter the fundamental papers.

Inclusion Criteria

Status epilepticus (SE), seizures, mental health issues, and GABA receptors were among the project's required themes, and these publications were chosen based on their applicability to the research.

Exclusion Criteria

All other publications without one of these subjects as their main goal, as well as any reruns of research and reviews of studies, were disregarded.

Statistical Analysis

The data will not be analyzed by any program. The information was taken from a certain form that includes the

publication's title, author's name, objective, summary, results, and outcomes. To verify validity and reduce errors, each member's results underwent a second revision.

In order to ensure that the studies we enroll are relevant to the goal of our study and to prevent or reduce errors in the results, studies were double-reviewed and their results were examined during the article selection process.

Results and Discussion

A total of 105 studies were found after searching the aforementioned databases, which were then used for title screening. 32 of them were excluded after 63 of them were included for abstract screening. The full texts of the remaining 31 publications were examined. Seven studies were enrolled for final data extraction, which includes 23 papers that were excluded as a result of the full-text revision **(Table 1)**.

Two of the four hospital-based studies were carried out in Jeddah and the other two in Riyadh. Only 37% of SE episodes had a correct initial diagnosis, and only 31% of SE episodes as a whole received the appropriate AED medication, according to a study from Jeddah by Mah *et al*. [24], while 70% of non-SE episodes received the appropriate AED treatment. The results demonstrated that inadequate AED treatment was caused by the use of multiple doses of benzodiazepines, the lack of second- or third-line medicines, or the delayed delivery of second- and third-line pharmaceuticals. While Alyoubi, Reem *et al*. [25] also in Jeddah reported that a febrile seizure was the most frequent cause of convulsive status epilepticus, followed by electrolyte imbalance and hydrocephalus.

Alotaibi, Badriyah *et al*. [26] also reported that in comparison to patients who followed the BNF guideline, the group who followed the standard practice was shown to have a higher rate of reported adverse effects. According to this study's findings, titrating antiepileptic medications are harmful to children. Hommady, Raid Harb *et al*. [27] showed that Mah conducted the final Saudi Arabian study to look into pediatric SE in 1999. In comparison to this analysis, Mah's study revealed a comparable demographic distribution by sex and history of epilepsy. The distribution of etiology varied, nevertheless. Instead of only 5% in Mah's study, this study discovered that 40% of patients had a remote clinical etiology. The acute symptomatic and febrile etiologies of SE were previously determined to be the most common causes of SE, but in this analysis, they only accounted for 8.6% and 14.7%, respectively.

Jafarpour, Saba *et al*. [28] Using the questionnaire reported that Pediatric SE has a comparatively low mortality rate, but morbidity is more problematic. It has been shown that the underlying cause of SE is a highly important predictor of the outcome after SE; hence, there is a need for high-quality long-term data looking at QoL, neuroimaging, the use of continuous infusions, and the cognitive and behavioral outcomes of children who suffer SE. Similar findings were found in a second questionnaire by Horaib, Wesal, and colleagues [29]. More frequent seizures, the number of fears, concerns, and worries that patients and caregivers had, and prolonged treatment duration all had a negative impact on quality of life, while better family states and being male had a positive impact. Another questionnaire targeting the children and their mothers was also conducted by Bahkali MA, Choudry *et al*. [30] which showed that 40% of mothers believed that their epileptic kid could hurt themselves during an epileptic attack, and 58% said that their children need constant supervision out of concern for harm or injury. 71% of the families had been to Raqi (those who utilize the Quran to heal epileptics), and 4% had been to Sorcerer (persons who use magic for treatment). Due to their busy schedules with child health care, 36% of moms reported that they always struggled to find time for their own needs. 59% said they were generally happy, and 50% of moms said they would like to know what to do in the event of an epileptic seizure.

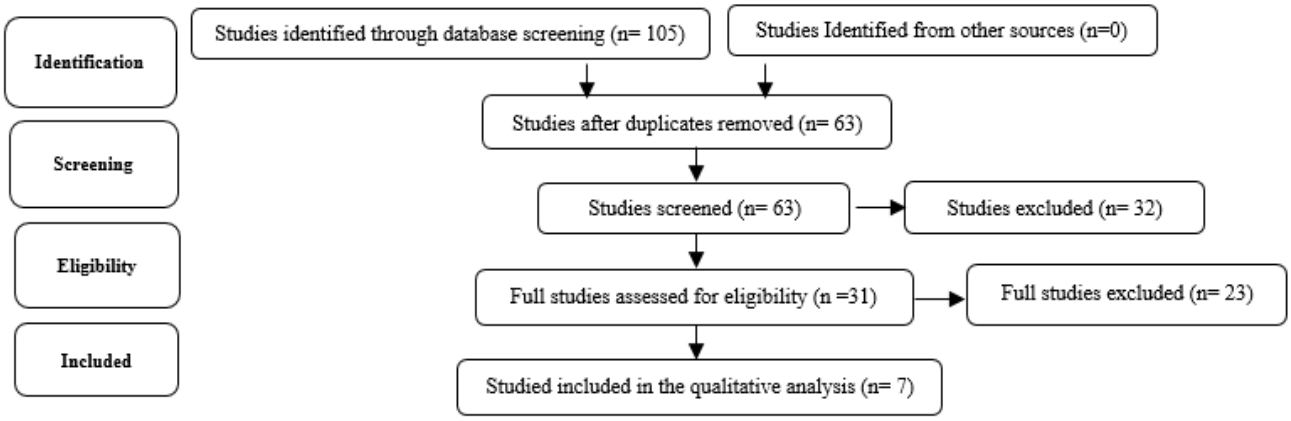

Figure 1. Flow chart representing the data extraction process and the included studies

Table 1. Author, country, year of publication, methodology and results

Author, Country, Publishing Year	Objective and Methodology	Results and Conclusion
Mah, J K, and M W Mah *et al.* (1999) [24]	A convenience sample of all pediatric admissions (12 years of age or under) from January 1992 to June 1997 was found using the medical records database of the community hospital in the Saudi Arabian city of Jeddah. By using ICD-9 diagnosis codes, all hospitalizations for seizures were identified. Seizure evidence, demographic data, and seizure risk factors were then reviewed in the medical records of these admissions.	In the first five years of life, almost 80% of the patients first presented. The majority (58%) of patients were male; 43% had no prior history of seizures; and 17% had been transferred from another institution. 47 (24%) of the 200 patients had SE. The 59 seizures that these 47 kids suffered were all categorized as SE. Only 41 (27%) of the 153 non-SE events required AED treatment for seizures lasting less than 30 minutes, and 29 (70%) of these 41 episodes were treated with the appropriate AEDs. The use of benzodiazepines in excessive dosages, by themselves or with the postponed use of second- and third-line medications, were all linked to ineffective AED treatment.
Alyoubi, Reem A *et al.* (2021) [25]	This research was carried out in **Jeddah, Saudi Arabia** to determine what causes status epilepticus (SE) in pediatric patients. Medical records from the years 2006 to 2017 were used to gather the data. All the patients aged between 28 days to 14 years old were included and SE was defined as 5 minutes seizure duration. The continuous variables were reported using means and standard deviations (SD), and the distribution of epilepsy was compared with gender and nationality using the Pearson's chi-square test.	Generalized epilepsy (91.8%) was the most common form of seizure among the cases, and that protracted febrile seizures (30.5%) were the primary cause, and electrolyte imbalance is the second reason (11.9%). Additionally, the study's findings showed that men (67.2%) and non-Saudi participants (64.3%) had greater rates of epilepsy than Saudi participants (35.7%), and that it is important to educate families and patients about antiepileptic medications.
Alotaibi, Badriyah S *et al.* (2021). [26]	In order to evaluate the effects of dose titration for several oral antiepileptic medications in epileptic children, this prospective cohort study was carried out in a military hospital in Riyadh, Saudi Arabia. 48 epileptic patients were included in this study after being vetted out of a total of 76 over a 3-month period. In the titration processes, 31 of the 48 patients adhered to standard procedure, and 17 patients followed the British National Formulary (BNF) guideline.	The physician followed the normal practice guideline. 15 of the 31 patients were children receiving levetiracetam as a monotherapy where they had trouble controlling their seizures. The patient was experiencing some behavioral issues and sedative effects from the combination medication of phenytoin and levetiracetam. The physician adhered to the BNF recommendation, and 17 participants Were gathered. When compared to patients who followed the standard of care, the total incidence of seizures in BNF-following patients was considerably lower. The most frequently prescribed medications in this group were topiramate (n = 12), levetiracetam (n = 7), carbamazepine (n = 7), and valproic acid (n = 6). Patients who took levetiracetam and adhered to the BNF recommendation documented the frequency of seizures. After a 6-month period of observation, patients on levetiracetam had fewer side effects and no behavioral abnormalities compared to those receiving regular practice.
Hommady, Raid Harb *et al.* (2017) [27]	In order to conduct this study, the records of every SE patient admitted to the pediatric department of King Abdulaziz Medical City in Riyadh, Saudi Arabia, between January 2005 and December 2015 were examined. Aiming to describe the predictors of SE outcome. The primary treatment protocol is intravenous administration of benzodiazepines for 1-2 doses, along with phenytoin and phenobarbital as a second line. IV thiopental drip, IV midazolam drip, or other antiepileptic medications were used as third-line therapy.	The majority of occurrences lasted between 30 and 60 minutes, and lasting longer than 24 hours was rare. The majority of SE cases had remote symptoms, and increasing encephalopathy was the least frequent etiology. The observed reason that appeared in the majority of the cases under study was unknown, most likely a hereditary element. Hypoxic ischemic encephalopathy was the second most common cause, followed by traumatic brain damage and periventricular leukomalacia. The short-term outcome of status epilepticus was not significantly impacted by the type of treatment in this study.
Jafarpour, Saba *et al.* (2019) [28]	Only studies that looked at mortality, recurrence of seizure and status epilepticus, neurological, cognitive, or behavioral impairment, and health-related quality of life following status epilepticus in pediatric populations were included in the search. The search term "status epilepticus" was combined with "outcome", "mortality", "morbidity," "recurrence," and "quality of life."	The short-term death rate was higher in less developed countries. Acute symptomatic reasons, such as infections of the central nervous system, trauma, metabolic disorders, and hypoxia, frequently had worse prognoses than individuals with unclear underlying causes or febrile seizures. Depending on the length of follow-up, long-term mortality ranged from 2.3% to 11%. Studies conducted after 2000s showed a lower percentage of mortality, 2.1% to 6%. However, this percentage increased to 2.7% to 11.5% in studies conducted before 2000. In patients under one year old, acute symptomatic etiology is also more prevalent, which explains why infants under one year old have a greater fatality rate.

Horaib, Wesal *et al.* (2021) [29]	A cross sectional study conducted with Children (aged two to nine) and teenagers (aged 10 to 19) who had been diagnosed with epilepsy and were being monitored in epilepsy clinics were given an online questionnaire. The questionnaires were made to collect data on the following important topics: demographic data, seizure incidence, seizure medication, and length of treatment.	Patients in this study who had higher family income and socioeconomic status (64), as well as those who lived in Al Jubail (67), had higher mean QOL percentages (71). The frequency of seizures, the quantity of worries, issues, and fears, and the length of treatment were all negatively correlated with QOL. The two things that worry epileptic kids and teenagers the most are starting a relationship with someone else and what their peers would think if they had a seizure. Focusing difficulties and feeling agitated or upset were the most prevalent problems. The biggest concern for the future was continuing education.
Bahkali MA, Choudry AJ *et al.* (2019). [30]	A cross sectional study as an online questionnaire, the target here was the mothers of the children having SE, Study was conducted in 2 hospitals. First was Neurology Department of Children's hospital and Second was Pediatric Neurology Department, Riyadh. the study included mainly questions regarding the psychological state of the children and their families, and the effect of SE on the children ability to do activities especially in school	The average age of the kids was 7.5. The percentage of children who received a diagnosis in their first year is 26%, 46% between 2 and 6 years, and 28% between 8 and 12 years. Epilepsy was reported to have a significant impact on the general health of the child by 35% of the mothers, a moderate impact by 50%, and no impact by 15% of the mothers. In terms of self-harm, 40% of parents reported that their kids might hurt themselves during an epileptic attack, while 12% said their kids might hurt other people.

Children who have SE require prompt medical attention because it is a life-threatening condition. In order to treat them, epidemiological studies are needed to determine their prevalence and etiologies. Infants and young children have a significantly greater morbidity risk for SE than do adults, while adults have a higher fatality rate than the latter group [31]. Several characteristics, including the etiology, age, the length of the SE, and neurological and other non-neurological co-morbidities, have been identified as being related to mortality in SE. In a population-based study carried out in London, febrile status epilepticus (FSE) had a very good short- and long-term prognosis, and all fatalities in children with previously neurologically healthy conditions happened in patients with this disease. A different national cohort found that individuals with unprovoked or febrile CSE had lower death rates than those with acute symptomatic bouts [32].

Children with SE exhibit MRI abnormalities, which are probably connected to the underlying cause of SE. But idiopathic SE patients can exhibit MRI abnormalities, indicating that the changes are caused by the SE itself. 22 of the 226 children with febrile SE in the FEBSTAT research (9.7%) exhibited an aberrant hippocampus signal on their initial MRI. After a year, follow-up MRIs were performed on 130 patients, and only one of the initial aberrant hippocampus signal changes persisted, indicating that this discovery is acute. However, in the follow-up MRI, 14 of the 22 people (71%) with signal abnormalities met the visual criteria for hippocampal sclerosis. These findings suggest that a chain of events leading to hippocampal sclerosis may have been initiated by the initial feverish SE episode [33, 34].

According to one study, acute characteristics only account for 8.6% and 14.7% of SE, respectively; another study found that fever causes only account for 14.7% of SE. On the other hand, Kroczka *et al*. [35] found that children who were sent to hospitals with convulsions had physical/metabolic epilepsy, which is brought on by brain disorders that result in developmental delay, neurological diseases, and aberrant EEG communal. With a proportion of 59%, high parental consanguinity rates in Saudi Arabia were also noted as a risk factor [36]. According to a study from Abha, 27% of epileptic patients had a family history of the condition (FHE), which is relatively close to the 22% of study participants who also had FHE. The different ways that people describe family history may be the cause of this discrepancy. Another study conducted in Jordan found that having first-degree relatives with epilepsy increases the probability of developing the condition by an OR of 9.8 (95% CI 3.3-38.9) [37].

Antiepileptic drug administration over an extended period of time is the foundation of conventional epilepsy treatment. Although the majority of patients who use these antiepileptic medicines experience long-term seizure remission, it was found in a European study that roughly 30% of patients do not completely recover from their seizure disorder as a result of their treatment with currently available AEDs [38]. Antiseizure medications (ASDs) are a cornerstone of SE treatment. ASDs alter the biological pathways in the CNS, which causes a pharmacological reaction. Most drugs for SE function by either enhancing the GABA-mediated route or by reducing glutamate and Na+/Ca++-mediated neuronal excitation [39]. Midazolam, lorazepam, and diazepam have all been utilized as first-line SE-aborting medications. A double-blind, randomized clinical trial comparing the effectiveness of lorazepam against diazepam in the treatment of pediatric SE found that SE ceased in 72% of patients treated with diazepam and 73% treated with lorazepam after 10 minutes, with no return of the condition within 30 minutes. Aided ventilation was required in 16% of diazepam-treated individuals and 18% of lorazepam-treated patients. Because it was also shown that lorazepam patients were more likely to be sedated than their peers, the experiment did not conclusively demonstrate that lorazepam has a preferential effect compared to diazepam in that group [40].

Since the introduction of benzodiazepines, phenytoin or fosphenytoin has been the most popular anti-seizure medication among pediatric emergency room physicians and neurologists. But historically, there hasn't been much proof that these medications are superior to alternative methods like levetiracetam, phenobarbital, or valproate. Recent meta-analytic methods have demonstrated that benzodiazepines are 50% less potent than phenobarbital, valproate, and levetiracetam (69 percent) [41].

Conclusion

SE is a complex neurological condition that is primarily seen in children and older individuals, two separate age groups. As the second most prevalent neurological disorder to result in death, it has a high mortality and morbidity rate. Concerning the cause of SE An electrolyte imbalance and febrile seizures were the two most frequent causes of convulsive status epilepticus, respectively. The diagnosis is based mainly on ECG, where children who have SE show abnormalities in their imaging. Management of the condition mainly uses antiseizure medications such as Midazolam, lorazepam, and diazepam with almost similar efficacy.

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