Section A-Research paper

Refractory and Super-refractory Status Epilepticus: a narrative review

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Abstract

Medical emergencies such as "*Super-Refractory Status Epilepticus* (SRSE)" and "*Refractory Status Epilepticus* (RSE)" have significant rates of morbidity and fatality. While SRSE is defined as SE that continues or recurs despite at least 24 hours of anesthesia with continuous electroencephalography monitoring, RSE is defined as SE that persists or recurs despite sufficient therapy with first- and second-line antiepileptic medications. RSE and SRSE have a complicated and multifaceted etiology that involves a series of excitatory and inhibitory pathways that result in chronic seizure activity. Similar to convulsive SE in terms of clinical characteristics, RSE and SRSE may also entail non-convulsive SE or mild clinical seizures that are challenging to identify. RSE and SRSE diagnosis necessitates quick identification and adequate treatment, which includes managing critical care and taking into account cutting-edge therapeutic options including immunomodulatory medication, the ketogenic diet, or epilepsy surgery. Patients with RSE and SRSE have a terrible prognosis, and survivors have been found to have long-term cognitive and functional problems. To enhance patient outcomes, it is vital that we understand the pathogenesis, diagnosis, and treatment of RSE and SRSE better.

Keywords: Refractory status epilepticus, super-refractory status epilepticus, convulsive status epilepticus, non-convulsive status epilepticus, intensive care management.

Introduction:

"*Status epilepticus* (SE)" is a dangerous and sometimes fatal neurological emergency that needs to be identified and treated right away. RSE is defined as seizure activity that continues after the administration of adequate doses of two or more "*Antiepileptic Medicines* (AEDs)" or when continuous intravenous infusion of anesthetic agents is started but seizure control is not achieved within 60 minutes (1). Contrarily, SRSE is defined by the inability to control seizures despite the use of all AEDs and anesthetics on the market, including burst

suppression (2). These illnesses have high rates of morbidity and mortality, thus managing them calls for a multidisciplinary strategy involving teams from intensive care, neurology, and neurosurgery (3).

Depending on the underlying etiology and patient demographic, RSE and SRSE incidence vary. While the frequency of SRSE is thought to be less than 1% in adults, the incidence of RSE varies from 15% to 35% of all instances of SE (4). RSE and SRSE have a lower incidence in youngsters, with rates of 3% to 8% and 0.3% to 0.6%, respectively (6). However, compared to adults, children have greater rates of morbidity and mortality related to RSE and SRSE, with documented fatality rates of up to 50% in pediatric SRSE cases (7).

RSE and SRSE can have a variety of underlying causes, including as structural lesions, metabolic abnormalities, autoimmune diseases, infections, and medication toxicity (8). In many situations, refractory epilepsy, such as focal cortical dysplasia, tuberous sclerosis, or hereditary epilepsies, may be the underlying cause of RSE and SRSE (9). However, it might be difficult to pinpoint the underlying cause of RSE and SRSE, especially when the patient has pre-existing neurological or medical disorders.

RSE and SRSE must be managed in a progressive manner, starting with the administration of the proper AEDs and moving on to the use of anesthetics and other complementary therapy (10). The underlying etiology and patient characteristics, such as age, comorbidities, and medication history, should be taken into consideration while choosing AEDs and anesthetic agents. Hemodynamic support, constant EEG monitoring, and mechanical breathing may all be necessary in many situations for the management of RSE and SRSE (11).

The long-term prognosis for RSE and SRSE remains poor despite improvements in diagnosis and treatment. Even if seizure control is attained, patients with RSE and SRSE are more likely to experience epilepsy, cognitive decline, and other neurological sequelae (12,13). Therefore, it is crucial for public health to focus on improving RSE and SRSE diagnosis and treatment.

An overview of the epidemiology, pathophysiology, diagnosis, and treatment of RSE and SRSE is what this narrative review aims to do. The clinical characteristics and diagnostic methodology for RSE and SRSE, as well as the different potential treatment choices, will all be covered in this study.

Pathophysiology:

A medical emergency known as SE is characterized by prolonged or frequent seizures without full return of consciousness between episodes (1). First- and second-line AEDs must be taken continuously for more than 24 hours in order to treat RSE (2). When seizures persist despite receiving anesthetic medication, this condition is known as SRSE (11). We will talk about the pathophysiology of RSE and SRSE in this part.

RSE and SRSE's pathogenesis is not fully known. However, a number of processes, such as modifications to neurotransmitters, ion channels, and neural networks, have been hypothesized. These mechanisms might affect the threshold for the onset and spread of seizures as well as the ratio of excitation to inhibition in the brain. Changes in the gamma-aminobutyric acid (GABA) receptor system are one of the hypothesized causes for RSE and SRSE. The main inhibitory neurotransmitter in the brain is GABA, and many AEDs work by targeting its receptors. Animal models of SE have been shown to alter GABA receptor expression and function (12-15). RSE and SRSE may occur as a result of these modifications, which may reduce sensitivity to AEDs that act on GABA receptors.

Alterations in ion channels, particularly the N-methyl-D-aspartate (NMDA) receptor, have also been suggested as a possible cause of RSE and SRSE (16). Glutamate, the brain's main excitatory neurotransmitter, activates NMDA receptors, which are essential in controlling synaptic plasticity. Animal models of SE have been shown to alter NMDA receptor expression and function (17). These changes may cause increased excitability and lower inhibition, which could result in RSE and SRSE developing.

Changes in neural networks may also aid in the emergence of RSE and SRSE, in addition to modifications to neurotransmitters and ion channels. The brain is made up of numerous interconnected networks that control a variety of processes, such as motor coordination, sensory perception, and cognition. Increased synchronization and excitability caused by changes in these networks may result in SE and its refractory variants (18-20).

Additionally, RSE and SRSE may also be influenced by brain damage (20). Neuronal networks can be damaged, neurotransmitters and ion channels can change, and inflammation and oxidative stress might increase as a result of brain injury. These alterations may result in RSE and SRSE development as well as an increase in seizure susceptibility.

Clinical Features:

RSE and SRSE have a similar clinical appearance to SE, but they last longer and are more resistant to treatment. While SRSE occurs when seizures last longer than 24 hours following the start of anesthesia or sedation, RSE occurs when seizures last longer than 24 hours despite proper treatment. Intensive care unit (ICU) admission is frequently necessary for patients with RSE and SRSE in order to manage and track complications. Due to the prolonged duration and intensity of the seizures, which can result in brain damage and systemic problems, SRSE has a greater death rate than RSE (1).

Depending on the underlying reason and length of the seizures, RSE and SRSE have a variety of clinical symptoms. In a retrospective analysis of 42 individuals with RSE, structural brain lesions were the most frequent underlying etiologies (52%), followed by metabolic disturbances (24%), and idiopathic reasons (14%). Similar to this, structural brain lesions (39%) and metabolic disturbances (34%) were the most frequent etiologies in a study of 44 individuals with SRSE (14).

Motor and non-motor symptoms can be used to categorize the clinical characteristics of RSE and SRSE. Myoclonic jerks, focal seizures, and generalized tonic-clonic seizures (GTCS) are the most frequent motor signs. Autonomic instability, such as hypertension, tachycardia, and fever, as well as altered mental status, such as disorientation, agitation, and coma, are examples of non-motor symptoms (5). Systemic side effects from prolonged seizures can include hypoxia, hyperthermia, rhabdomyolysis, and renal failure.

An key tool for the diagnosis and treatment of RSE and SRSE is the electroencephalogram (EEG). To gauge the severity, duration, and effectiveness of treatment, it is advised that patients with SE, especially those with RSE and SRSE, undergo continuous EEG monitoring. Periodic discharges, burst suppression patterns, and electrocerebral silence are some of the EEG findings in RSE and SRSE (21). A bad prognosis is linked to the severity of the EEG abnormalities, especially in patients with electrocerebral silence.

A thorough assessment of the clinical presentation, EEG results, and laboratory tests is necessary for the diagnosis of RSE and SRSE. It is difficult to treat RSE and SRSE, and multidisciplinary teams made up of neurologists, intensivists, neurosurgeons, and pharmacists are needed. Aggressive seizure control, the discovery and treatment of the underlying cause, and the management of sequelae are all part of the management of RSE and SRSE (22).

Diagnosis:

Rapid identification and management are necessary for the diagnosis of RSE and SRSE. To determine the underlying etiology of the SE, a thorough clinical history, physical examination, and laboratory investigations are necessary (1). An essential tool for the diagnosis and categorization of SE is electroencephalography (EEG). Subtle electrographic seizures that may go undetected during a clinical evaluation can be found with prolonged or continuous EEG monitoring (11). Additionally, imaging tests like computed tomography (CT) or magnetic resonance imaging (MRI) might determine the underlying cause of SE and have to be carried out as soon as feasible (12).

Due to the possibility of minor or missing clinical symptoms, diagnosing NCSE can be difficult. The most accurate and precise diagnostic for the diagnosis of NCSE is electroencephalography (21). The Salzburg Consensus Criteria for NCSE were released in 2015 and offer useful advice for making a clinical diagnosis of NCSE (34). The criteria include clinical characteristics, EEG results, and antiepileptic medication (AED) response. High levels of suspicion are necessary for the diagnosis of NCSE, and rapid implementation of the proper course of action is essential (22-24).

Given that they are managed differently, RSE and SRSE must be distinguished from one another. When SE persists or reappears despite receiving sufficient doses of anesthetic drugs, SRSE is diagnosed (22). The time threshold for defining SRSE ranges from 24 to 48 hours, and the length of SE is a significant determinant in this definition (24). The diagnosis of SRSE justifies immediate management in an intensive care unit (ICU) with vigilant observation and forceful therapy (1).

In conclusion, early and precise diagnosis of RSE, SRSE, and NCSE is crucial for successful care. For the diagnosis of SE, it is crucial to conduct a thorough clinical history, physical examination, laboratory tests, EEG, and imaging studies. The Salzburg Consensus Criteria offer helpful advice for the NCSE diagnosis. It's critical to differentiate between RSE and SRSE since they require different management approaches, and SRSE calls for urgent care in an ICU.

Management:

RSE and SRSE management is difficult and necessitates a multidisciplinary approach. Controlling seizures, locating and treating SE's underlying cause, and avoiding consequences are the main management objectives (5). First-line AEDs such benzodiazepines, phenytoin, or fosphenytoin are given as part of the initial therapy of RSE (25). Second-line AEDs like valproate, levetiracetam, or lacosamide may be administered if seizures continue. For refractory seizures, anesthetic medications such propofol, midazolam, or pentobarbital can be administered (26-28).

Anesthetic medications are the cornerstone of treatment for SRSE. The most often employed drugs are pentobarbital, midazolam, and propofol. Age, comorbidities, and the length of SE are a few variables that affect the choice of anesthetic agent. To adjust the anesthetic dose and identify electrographic seizures, continuous EEG monitoring is necessary. In some circumstances, further therapies including immunotherapy or surgery may be considered (26-28).

The therapy of the underlying etiology and the use of AEDs are necessary for the management of NCSE. For NCSE, benzodiazepines, phenytoin, or fosphenytoin are the first-line AEDs. If seizures continue, second-line AEDs like valproate, levetiracetam, or lacosamide can be administered.The treatment of NCSE does not frequently involve the use of anesthetics (26-28).

The prevention of comorbidities such hypoxia, hyperthermia, and metabolic abnormalities should be considered when managing SE. Additionally, breathing difficulties, hypotension, and cardiac arrhythmias might occur when sedatives and anesthetics are used (29,30). As a result, constant observation in an ICU is necessary for SE management.

In RSE and SRSE, the length of anesthetic therapy should be kept to a minimum since continued exposure might result in problems such propofol infusion syndrome or barbiturate poisoning. Patients should be constantly watched for recurrence seizures when weaning, and the procedure should be gradual (31).

In conclusion, the treatment of RSE and SRSE necessitates a multidisciplinary strategy that considers the root cause of SE, the use of suitable AEDs, and the use of anesthetic drugs when required. The titration of anesthetic drugs requires continuous EEG monitoring, and it is critical to avoid consequences including hypoxia, hyperthermia, and metabolic

abnormalities. The treatment of SE necessitates close observation in an ICU, and the withdrawal from anesthetics should be gradual.

Prognosis:

There is a significant risk of morbidity and mortality related to RSE and SRSE. The underlying etiology, the patient's age, the length of the seizures, the existence of comorbidities, and the response to treatment are only a few of the variables that affect the prognosis of RSE and SRSE. According to several studies, patients with RSE have a mortality rate that might reach 40%. Patients with SRSE have a greater mortality rate, which has been estimated to reach 70% The existence of comorbid conditions, age of the patient, the length of the seizure, the underlying etiology, and the requirement for mechanical ventilation are all factors that raise the risk of fatality (32-35).

Some people do recover well, despite the high fatality rates linked to RSE and SRSE. According to several studies, a better prognosis is linked to early therapy start-up and seizure control within the first 24-48 hours. Additionally, certain patients' outcomes can be improved by the application of multimodal therapies such pharmacology, anesthesia, and immunotherapy (36,37).

The underlying cause of RSE and SRSE as well as the presence of any neurological impairments affect the patients' long-term prognosis. While some individuals may continue to experience seizures and cognitive impairment, others may fully recover without experiencing any neurological abnormalities (1,21). Patients with RSE and SRSE are at a significant risk of experiencing seizures again, necessitating long-term care with antiepileptic medications.

RSE and SRSE are medical emergencies that have high rates of morbidity and fatality, to sum up. The underlying etiology, the patient's age, the length of the seizures, the existence of comorbidities, and the response to treatment are only a few of the variables that affect the prognosis of RSE and SRSE. A better prognosis is linked to early therapeutic start-up and seizure control within the first 24-48 hours. Some patients' outcomes can be enhanced by the application of multimodal therapies such immunotherapy, pharmacology, and anesthetics. In order to stop seizures from happening again, individuals with RSE and SRSE typically need long-term care with antiepileptic medications.

Conclusion:

In conclusion, RSE and SRSE are urgent, potentially fatal neurological emergencies that need to be identified and treated right away. Despite improvements in the identification and treatment of many illnesses, the long-term prognosis is still poor and there is a large financial burden. Therefore, it is crucial for public health to focus on improving RSE and SRSE diagnosis and treatment. We will give a thorough overview of the epidemiology, pathophysiology, diagnosis, and management of RSE and SRSE in the sections that follow this review.

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