Review

A Narrative Review of Non-Convulsive Status Epilepticus in Adults in Intensive Care

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ABSTRACT

Background

Seizures are common in the Neurocritical Intensive Care Unit. Early identification and treatment of clinical and sub-clinical seizures remain important in managing the neurologically critically ill patient.

Aim

The aim of this narrative review is to provide an overview of the different types of sub-clinical seizures, diagnosis and detection, correlative physiology, and the importance of prompt treatment.

Methods

A group of physicians, advanced practice providers, and pharmacists performed a literature search based on their area of expertise and provided the most relevant evidence for the narrative review.

Findings

There are many types of subclinical seizures and pharmaceutical interventions. Seizures can be complex and early treatment is crucial to good outcomes.

Conclusions

This review is a narrative overview of sub-clinical seizures seen in the Neurocritical care unit. It is written for all practicing providers to describe the physiology, identification, and treatment of sub-clinical seizures to facilitate improved patient outcomes.

Keywords: Nonconvulsive status epilepticus, sub-clinical seizures, electroencephalogram, epilepsy, ketogenic diet, medications

INTRODUCTION

Seizures can be life-threatening. They are frequently a cause of admission into the Neurocritical Care Unit and may be a sequalae to many different neurological conditions. The most well-known and easily recognized type of seizure is status epilepticus (SE). Status epilepticus is defined as a clinical seizure that persists for greater than 5 minutes or is a series of seizures that repeats so rapidly that recovery between attacks

isn't possible (Assis, et al, 2012). Status epilepticus is further broken down into sub-types. Refractory status epilepticus (RSE) is a subset of SE in which seizure activity continues after initial pharmacological treatment. Suprefractory status epilepticus (SRSE) is seizure activity persisting for more than 24 hours after the onset of intravenous (IV) antiepileptic therapy (Lu et al., 2020). All of these forms of SE can be easily recognized and treated in the clinical setting since there are obvious observable manifestations.

Subclinical seizures, on the other hand, are defined as abnormal or ictal electrographic discharges in the brain without clinical seizure activity, behavioral alteration, or subjective symptoms (Fernandez-Torre et al., 2014). Non-Convulsive Status Epilepticus (NCSE) is also difficult to recognize, as there are few obvious clinical findings. NCSE is defined as prolonged or repetitive electrographic seizures without any motor manifestations lasting for more than 5 minutes (Kubota et al., 2016). Subclinical seizures require epileptiform electroencephalography (EEG) activity for diagnosis. NCSE is a neurological emergency and must be recognized and treated as early as possible.

NCSE is the main focus of this review as it is most often encountered in Neurocritical care settings and can be easily missed by healthcare providers. Advances in technology, such as continuous EEG (cEEG), have enabled providers to better diagnose NCSE. Prior to the availability of cEEG, NCSE was often undiagnosed leading to high morbidity and mortality in the neurocritically ill patient (Kubota et al., 2016). NCSE is often seen in patients with both neurological and non-neurological conditions and is most often a treatable condition with the use of parenteral and enteral medications; however, treatment is more successful when the condition is detected early.

This comprehensive narrative review of NCSE discusses epidemiology and mortality, clinical settings where NCSE is commonly seen, associated pathogenesis and pathology, monitoring devices and utility, clinical findings and symptoms, as well as pharmacological treatment.

Epidemiology

In general, the elderly have the greatest risk of cerebrovascular diseases and degenerative and metabolic disorders that contribute to seizure occurrence. In a large epidemiological study from Richmond Virginia, USA, the annual incidence rate for SE was 86 per 100,000 in the 60 years and older age population. This rate was found to be almost twice that of the general population, with the highest incidence found in those patients that are 70 years or older (Assis et al., 2012). In elderly patients over age 60, SE is associated with 38% mortality, while mortality is as high as 50% in those ages 80 or older (Assis et al., 2012). The research on SE has failed to demonstrate a significant difference in the incidence of SE based on sex and no differences have been found between low-resourced and higher-

resourced countries (Marawar et al., 2018).

In the intensive care unit (ICU), NCSE has been reported in 8% of those that were comatose or had an unexplained change in mental, cognitive, or behavioral conditions. The mortality rate in these patients has been shown to approach 36% (Assis et al. 2012). In another study conducted on 25 critically ill older patients with NCSE, a mortality rate of 52% was reported while death was associated with an increased number of co-morbid conditions and acute life-threatening medical problems at the time of diagnosis (Assis et al. 2012). NCSE portends high rates of morbidity and mortality in many disease states, and most severely impacts the elderly due to a complex interplay of etiologies, complex treatments, coexistent conditions, and the side effects and drug interactions of antiepileptic drugs (Cheng, 2014).

Associated Disease and NCSE

NCSE occurs most frequently in patients with acute and remote neurovascular disease and head trauma. In cases of stroke, patients with cortical ischemia and lacunar infarction have a higher risk of developing NCSE (Kubota et al., 2016). As discussed earlier, increasing age is an important determinant of seizure occurrence. In a retrospective study of 102 patients with SE who suffered their first seizure after the age of 60 years of age, 35% of seizures were in patients with neurovascular disease followed by 21% in head trauma patients (Assis et al., 2012). Patients with intracranial hemorrhage (ICH) occasionally develop seizures, however, the location of the bleeding determines incidence. Compared with deep ICH, such as in thalamic or putamen patients with cortical hemorrhage tend to develop NCSE more frequently (Kubota et al., 216). Nevertheless, all patients with stroke, regardless of the type and location, can have EEG patterns that put them at risk for developing seizures and should be monitored if seizures are suspected. Awareness of EEG abnormalities can lead to treatment that can improve outcomes in these patients.

Traumatic brain injury (TBI) is associated with a high risk of NCSE. Claassen et al. found that 18% of TBI patients experience subclinical seizures during cEEG monitoring (Kubota et al., 2016). Some ICU studies have shown an incidence as high as 18-30% of early seizures within 7 days after TBI, and most were non-convulsive (Tubi et al., 2019). Seizures in this population have been shown to increase intracranial pressure (ICP), worsen brain edema, metabolic crisis, and hippocampal atrophy (Tubi et al., 2019). Consequently, early detection and early treatment are paramount for improved overall outcomes in this patient population.

Numerous other conditions and disease states can lead to NCSE. The incidence of NCSE in patients with subarachnoid hemorrhage can range from 3% to 31% (Kubota et al., 2016). Other etiologies include hypoxia, metabolic

derangements, alcohol withdrawal, tumor, systemic and central nervous system infections, and hemorrhage (Assis et al., 2012). The International League Against Epilepsy (ILAE) has a broad list of etiologies that include neurodegenerative diseases, cortical dysplasia's, withdrawal of or low levels of antiepileptic drugs (AEDs), cerebral hypoxia or anoxia, autoimmune disorders, and mitochondrial diseases (Marawar et al., 2018). Autoimmune encephalitis usually presents with nonconvulsive seizures in 78% of patients whereas the most common involved antibodies are NMDA and VGKC receptors (Schmitt et al., 2012). In one study, anoxic brain injury was the cause of SE in 50% of cases, while another study showed encephalitis as a statistically common etiology. Hashimoto encephalopathy and Rasmussen encephalitis are more distinct syndromes and often present with RSE and should be considered in patients with abnormal endocrine-related conditions (Marawar et al., 2018).

One possible iatrogenic occurrence of NCSE can be during the postoperative period following craniotomy. Some anesthetic agents can lower the seizure threshold and lead to various types of seizure activity in post-surgical patients without a history of epilepsy (Kubota et al., 2016). Additionally, surgery for all supratentorial tumors, such as meningiomas, gliomas, and metastatic tumors, may have the possibility of causing NCSE. Therefore, neurosurgeons and ICU providers should always consider that NCSE is more common than reported, and it should be considered early in the differential diagnosis of any patient with unexplained impairment of consciousness after intracranial surgery (Kubota et al., 2016).

Timing in Diagnosis

Timing in diagnosis, as well as treatment, is very important in the discussion of NCSE. Expeditious cessation of clinical and electrographic seizure should be initiated without delay. In the suspicion of subclinical seizures, cEEG is required for evaluation to implement treatment and cessation. Pharmacologic treatment should be initiated early and will be discussed later, however in the elderly population, additional issues such as lower protein binding, decreased renal elimination, decreased hepatic metabolism, decreased enzyme inducibility, and increased use of pharmacology should be considered (Assis et al., 2012). Mortality of NCSE has been found to increase when the time to detection is increased, and seizures are undetected. It is recommended that non-comatose patients with altered mental status have at least 24 hours of cEEG monitoring, and in comatose patients, at least 48 hours of monitoring should be considered and will be discussed in greater detail later (Cheng, 2014).

Pathogenesis and pathophysiology of NCSE

Regardless of the classification of SE in convulsive status epilepticus (CSE) and NCSE with coma (subtle) or without coma (focal and generalized), it is

important to highlight that SE is an evolving disorder with highly dynamic changes affecting both clinical and EEG features that share similar physiopathology (Baker et al., 2019). Also, most forms of generalized convulsive status epilepticus (GCSE) will develop into NCSE if not terminated early in the course. However, the diagnosis of NCSE is likely to be delayed or missed because of the persistent altered level of consciousness that can mimic postictal transient encephalopathy or delirium (Meierkord and Holtkamp, 2007).

Despite that NCSE shares many of the same physiopathology as GCSE, there are two important considerations to keep in mind. First, the pathophysiology of the primary underlying etiology (sepsis, tumor, autoimmune encephalitis, stroke, hypoxic brain injury, history of epilepsy, drugs, etc.) is frequently as significant as the NCSE itself. Second, the majority of the morbidity and mortality in GCSE is due to systemic complications of prolonged seizures (respiratory failure, rhabdomyolysis, lactic acidosis, etc.), which is generally not relevant in NCSE (Ruegg, 2017). However, the controversial data in animal and human studies support the hypothesis that prolonged excitation may result in neuronal cell death if NCSE is not aborted on time (Meierkord and Holtkamp, 2007).

NCSE is not a single illness, but a symptom with multiple potential etiologies with disruption of neuronal networks. Therefore, it should be assumed that in the development of SE, it is significant whether cell groups with important switching/linkage functions are involved in the generation and propagation of SE, since these lead to changes in the often distantly connected excitation and inhibitory networks (Meierkord and Holtkamp, 2007).

In focal partial status epilepticus with or without impairment of consciousness, the neuronal networks in the hippocampus and adjacent limbic and neocortical structures (including parietoccipital regions) experience the same cellular and molecular derangements that lead to self-perpetuating excitation in GCSE (Meierkord and Holtkamp, 2007). These changes are characterized by increased energy consumption leading to ATP-dependent sodium-potassium pump failure, and increased extra-cellular potassium levels, resulting in hyper-excitability as well as pronounced acidosis (Naylor and Liu, 2005). As a result, gamma-amino-butyric acid (GABA) receptors, type A (GABA-A) are down-regulated and endocytosed in the synaptic cleft, so the remaining membrane receptors are conformationally altered in their pentameric structure making them less reactive to inhibitory influences including their response to benzodiazepines (Goodkin et al., 2008).

Simultaneously, sustained epileptic activity results in an endoplasmic synthesis and upregulation of glutamatergic N-methyl-D-aspartate (NMDA) as well as α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA) receptors, which potentiate neuronal hyperexcitability (Hunt and Castillo, 2012). As a result,

neurons and glial cells are flooded by glutamate, which increases the cellular inflow of calcium, activating neuronal death cascade. These events also activate inflammatory processes (ammasomes), leading to the opening of the blood-brain barrier (BBB), the invasion of defense cells, and the production of cytokines and chemokines. The production of interleukins 1β,2, and 6 as well as tumor necrosis factor α greatly reduces the seizure threshold (Vezzani et al., 2015).

Regarding typical absence status epilepticus (ASE), there is an inhibitory state via GABA transmission in thalamocortical networks (Kinney et al., 2017). The thalamocortical relay cells excite GABAergic neurons of the nucleus reticularis thalami leading to recurrent inhibitory postsynaptic potentials (IPSPs) onto relay neurons (Huguenard and Prince, 1994). These IPSPs have both GABA-A and GABA-B receptor-mediated components that hyperpolarize the postsynaptic neurons and deinactivate a transient calcium current, which underlies the generation of low-threshold calcium spikes and bursts of sodium action potentials. The bursts generated by relay neurons, in turn, feedback onto nucleus reticularis neurons to re-excite them, beginning another cycle (Huguenard and Prince, 1994). In NCSE with coma (subtle), there are cell groups in the substantia nigra and subthalamic nucleus that can block the motor pathways like a gate function during SE without the SE ceasing, which leads to a virtually non-responsive burst-suppression pattern with a clinically non-convulsive appearance on EEG (Ruegg, 2017).

In summary, the difference between typical absence and focal SE in terms of propensity to cause neuropathological changes is due to the activation of different networks. In the typical absence SE an inhibitory state occurs via thalamocortical networks via GABA in the nucleus reticularis thalami, whereas in focal SE there is hippocampal, limbic, and neocortical network activation via excitotoxic mediators such as NMDA and glutamate. Lastly, in NCSE with coma, there is blockage of the motor pathways in the substancia nigra and subthalmic nucleus.

Neuroimaging

During seizures, the cellular energy status is generally maintained due to an increase in cerebral blood flow (CBF), which is coupled with increased metabolic demand. If ictal activity persists, as occurs in SE, reversible or irreversible tissue changes can develop. To meet the increased glucose and oxygen demand of the epileptogenic cortex (network), ictal hyperperfusion first appears, and secondarily vasogenic and cytotoxic edema follow, resulting from uncoupling between metabolism and circulation (Meletti et al., 2018). These changes are reflected in different neuroimaging modalities, which could be theoretically useful either to diagnose status epilepticus or to localize the brain regions involved by ictal activity when EEG presents with patterns of undetermined ictal significance, or it is not available in the acute setting (Kinney et al., 2017).

Perfusion studies are more commonly used in the emergency setting for faster assessment in the diagnosis of NCSE than PET/SPECT. Computed tomography perfusion (CTP) and magnetic resonance perfusion (MRP) sequences can localize ictal hyperperfusion represented by high relative cerebral blood volume and relative CBF (Siclari et al., 2013). The logistically complex SPECT provides the same information as a CT perfusion and is therefore hardly used anymore in the diagnostic evaluation of NCSE. The more elaborate PET provides information similar to SPECT and CTP, but does not measure blood flow, but rather the metabolism of the brain regions (Meletti et al., 2018). While hypometabolism occurs in a stroke, hypermetabolism is evident during NCSE. However, these modalities can occasionally be limited by equivocal assessment of hypometabolism as an expression of a postictal condition vs. ischemia (Masterson et al., 2009).

It is noteworthy that periictal MRI abnormalities observed in NCSE are characterized by areas of restricted diffusion, suggesting cytotoxic edema represented by high signals in diffusion-weighted imaging (DWI) sequences and corresponding low values of apparent diffusion coefficient (ADC) (Meletti et al., 2018). In some cases, the high DWI signal is accompanied by high signal in the ADC map and corresponding hyperintensities in T2-weighted and fluid-attenuated inversion recovery (FLAIR) sequences representing vasogenic instead of cytotoxic edema (Yu and Tan, 2008). The areas more commonly involved with these changes are the cortical region involved in the SE, hippocampus, putamen, and nucleus caudate (Meletti et al., 2008). Most of the time, these changes are transitory, and they completely or partially disappear within a few days after resolution of NCSE on the follow-up MRI scans (Cartagena et al., 2014). However, in some cases of prolonged SE, these changes can be present for a long time and generate permanent structural damage such as cortical laminar necrosis, mesial temporal sclerosis, and focal brain atrophy, with consequent permanent functional damage and chronic epilepsy development (Cartagena et al, 2014).

Monitoring of Subclinical Status

Electroencephalogram (EEG) is a non-invasive tool that allows for the monitoring of brain electrical activity, and therefore the detection of seizures. Clinical seizures are seizures that have physical manifestations such as abnormal movements, jerking, stiffening, forced gaze, and abnormal facial movements to name a few. It's important to note that non-classical manifestations of seizures, such as sudden changes in hemodynamics or behavior (i.e. agitation) may also occur. Patients who have subclinical seizures exhibit little or no physical manifestations but still have abnormal electrical brain activity. Continuous EEG (cEEG) is imperative for the detection and treatment of subclinical seizures and non-convulsive status epilepticus (NCSE). Even after the resolution of clinical

seizures, 20-48% of patients continue to have subclinical seizures; of these patients, 14% are found to be in NCSE. Therefore, it is reasonable to place patients with persistently impaired mental status after a clinical seizure on cEEG (Gilmore and Claasen, 2008).

Appropriate Length of EEG monitoring

The appropriate length of EEG monitoring varies dependent on the clinical scenario. A "spot" or routine EEG typically lasts 20 minutes to 2 hours. A cEEG is longer but may vary in length depending on the findings. Indications of cEEG monitoring include patients who are comatose, have unexplained exam fluctuations, and/or have persistently impaired mental status following a seizure. Furthermore, cEEG monitoring typically should last at least 24 hours as most patients experience their first electrographic seizure within the first 24 hours of monitoring (Steinberg et al., 2017). In patients who are found to be in NCSE, cEEG is at least required until the resolution of NCSE and throughout the titration and weaning of continuous intravenous anesthetics, most often versed and ketamine.

Feedback and Limitations

It is also important to note the usefulness of nursing feedback during EEG monitoring. Many EEG monitoring systems have a method by which observations can be noted in the recording. These are events such as abnormal movements noted or administration of a new antiepileptic drug. This feedback aids in the diagnosis and treatment of NCSE. Feedback allows the EEG reader to correlate clinical findings with the electrographic recording. Many times, recurrent movements such as shivering, or tremors can be misinterpreted as seizure activity. Making a note of these occurrences on EEG can be helpful in distinguishing if they are truly manifestations of a seizure.

It is also helpful to note the time of administration or titration of AEDs as it helps the reader to assess the effectiveness of the treatment. It is also important to note that EEGs are very susceptible to artifact. Therefore, movements such as shivering can make obtaining a reliable EEG recording difficult. In these cases, additional medications such as paralytics may be required. It is important to communicate these types of occurrences to other members of the care team. It should be noted that communication between the bedside nurse, critical care team, and the EEG readers is essential to ensure effective management of NCSE.

Pharmacological Treatment

NCSE is a heterogeneous disease state where the responsiveness to treatment may be very low. For example, one of the large randomized, controlled trials of SE patients found that first-line drug therapy was unsuccessful in more than 85% of patients who had the presence of coma and seizure activity only on EEG, highlighting the challenge in treating these patients (Treiman et al, 1998). Additionally, the proper treatment algorithm for NCSE remains unclear due to a

paucity of evidence in this population, which is mostly limited to retrospective studies or case reports. Thus, treatment of NCSE is generally extrapolated from guideline-recommended treatment of GCSE or based upon expert opinion (Wasim and Husain, 2015).

The 2012 Neurocritical Care Society Guidelines for the Evaluation and Management of Status Epilepticus recommend benzodiazepines (BZD) as first-line emergent treatment for all forms of SE (Brophy et al., 2012). Despite this recommendation, the efficacy of BZDs in treating NCSE remains low according to available high-quality data. The randomized, controlled trial (RCT) known as the VA Cooperative Study found that intravenous (IV) lorazepam successfully terminated clinical and electrographic evidence of seizure activity in only 17.9% of patients who had seizure activity similar to the current definitions of NCSE (Treiman et al, 1998). In contrast, BZDs were shown to terminate seizures without the need for rescue therapy in convulsive SE in 64.9% in the same trial, with another RCT of BZDs showing termination in 63.4% to 73.4% of patients (Silbergleit, et al, 2012). Despite this lack of efficacy in NCSE, BZDs remain a cornerstone of treatment largely due to familiarity, ready access to the medication, and ease of rapid administration. However, treatment with BZDs is not always benign. A prospective, observational study that included an elderly, critically ill NCSE population suggests that IV BZDs may increase mortality (Cheng, 2014). Thus, the risk versus benefit of aggressive treatment with BZDs should be carefully weighed in each patient presenting with NCSE, and other treatment options may be considered as first-line therapy in this population.

While controversy exists on the role of BZDs in NCSE, there is also scarce evidence on which antiepileptic medications (AEM) should be used as alternative treatments or as urgent control treatment after BZDs are administered. In a recent trial that compared the efficacy and safety of levetiracetam, fosphenytoin, and valproate in BZD-refractory convulsive status epilepticus, there was no difference between any of the three agents (Kapur et al., 2019). Many clinicians may advocate that these agents may be used equally in a NCSE patient because of this, but true efficacy remains unknown. At this time, there is only one prospective, randomized trial that evaluated AEM safety and efficacy in NCSE. The TRENdS study compared lacosamide and fosphenytoin in achieving the primary outcome of termination of electrographic seizures per cEEG monitoring for 24 hours following drug administration. The primary endpoint was met in 19 of 30 (63%) patients in the lacosamide group and in 16 of 32 (50%) in the fosphenytoin group. The trial's primary conclusion was that the two agents were equally effective because the 13% difference favoring lacosamide did not meet the statistical threshold for superiority of one agent. Additionally, no significant differences in adverse events occurred in the study population; however, the study was not powered to assess safety outcomes, and there were numerically more adverse effects that occurred

in the fosphenytoin group (Husain et al, 2018).

When evaluating which agent to use in NCSE, administration limitations may become an important decision-making point for some clinicians. Recent data show that it is safe to administer lacosamide as an undiluted IV push at a rate of 80 mg/min (Daidson et al., 2018), whereas fosphenytoin has to be compounded and administered at a slower rate (150 mg/min) due to adverse effects associated with faster infusion rates (Brophy et al, 2012). Use of lacosamide may result in faster time to administration since undiluted IV vials may be stored in automated dispensing cabinets and quickly administered as an IV push.

While the TRENdS study provides the most robust data available that specifically assesses AEM efficacy and safety in NCSE, other agents have shown efficacy in this population. An observational study evaluating perampanel in 75 NCSE patients showed 41.3% resolution of seizures within 72 hours of initiation (Alsherbini et al, 2020). Additionally, retrospective trials and case studies have shown efficacy of levetiracetam in NCSE (Rupprecht et al., 2007). These agents, as well as phenobarbital, topiramate, and valproic acid are potential second and third-line treatment options. In general, administering an agent that can quickly reach therapeutic drug concentrations should guide selection of therapy during this treatment phase (Brophy et al., 2012).

When treatment with intermittent doses of AEMs fails to terminate seizures, the Neurocritical Care Society Guidelines recommend that continuous infusions of midazolam, propofol, or pentobarbital be initiated. Ketamine infusions are also a widely emerging treatment in refractory status epilepticus, with more evidence available since the most recent guidelines have been published. There is no preferred agent; thus, the selection of these infusions is typically directed by provider discretion and adverse effect profiles. During this stage of treatment, patients will almost always need to be mechanically ventilated, and many may require vasoactive infusions due to the hypotension induced by these AEMs (Brophy et al., 2012).

When seizure activity is terminated, patients will typically be weaned from continuous infusions and transitioned to maintenance regimens. There are no specific guidelines regarding how to make this transition, but patients are generally given intermittent AEMs to achieve adequate control of seizures while minimizing adverse effects (Brophy et al., 2012). Both loading doses and maintenance doses, as well as common adverse effects, are available for reference in Table 1.

Table 1.

Common Intermittent Anti-epileptic Drugs (AEDs) and Dosing

Drug	Initial Dose	Suggested Maintenance Dose	Common Adverse Effects
Levetiracetem	60 mg/kg IV Max: 4500 mg	500 – 1500 mg twice daily	Agitation
Phenytoin/ Fosphenytoin	20 mg/kg IV	4 – 6 mg/kg/day (divided 2 to 4 times daily)	Hypotension Cardiac arrhythmias Purple glove syndrome
Valproic acid	40 mg/kg IV Max: 3000 mg	10 – 60 mg/kg/day	Hepatotoxicity Hyperammonemia Thrombocytopenia Pancreatitis
Lacosamide	400 mg IV	200 mg twice daily	PR prolongation Hypotension
Phenobarbital	20 mg/kg IV	2 mg/kg/day (divided 2 to 3 times daily)	Hypotension Respiratory depression
Perampanel	12 mg NG/PO	2 – 12 mg daily	Neuropsychiatric events
Topiramate	200-400 mg NG/PO	300-1600 mg/day (divided 2 to 4 times daily)	Metabolic acidosis

Brophy et al., 2012; Kapur et al., 2019

Non-pharmacological Treatment

When NCSE evolves to refractory or super refractory SE alternative therapeutic strategies should be considered when pharmacological therapy has been maximized (IV anesthetics) in the critical care unit. Many therapies and treatments have been explored, including hypothermia, immunotherapy, epilepsy

surgery, vagus nerve stimulation, electroconvulsive therapy, and a ketogenic diet (KD), all with varying levels of success. However, limited information is available on the effectiveness, safety, or outcome of these therapeutic approaches (Park et al., 2019).

The use of KD has been shown to be effective for intractable epilepsy, and recent reports suggest that the KD can also be useful as an acute treatment for refractory SE in adults and children (Alqahtani et al., 2020). These studies have shown adequate efficacy and safety in reducing seizure frequency and weaning from prolonged mechanical ventilation (Park et al., 2019). Seizure control in SE has been achieved in diets that consist of a ratio of ketone-producing fats to non-ketogenic proteins and carbohydrates from 3:1-4:1. Despite the efficacy of KD in controlling seizures, coexistent medical problems specific to critically ill patients in the ICU may act as obstacles in initiating or maintaining the KD. Such challenges include decreased gastrointestinal motility due to prolonged coma therapy, increased susceptibility to infection, hyperlipidemia, hypoglycemia, nephrolithiasis, and preexisting acidosis (McDonald et al., 2020).

Ketogenic diets are high-fat, low-carbohydrate, and adequate protein diets that are designed to mimic a fasting state and induce ketone body production through fat metabolism (Park et al., 2019). The brain uses various ketone bodies like acetoacetate and b-hydroxybutyrate as an alternative source of energy during ketotic states. The conversion of fatty acids by the liver is necessary as long-chain fatty acids are not able to cross the BBB. The brain contains specific enzymes like succinyl-CoA that convert ketone bodies into acetyl-CoA, a step mandatory for utilization of ketone bodies as a metabolic fuel across the mitochondrial membrane for b-oxidation (Mahmoud et al., 2019). This acetyl-CoA subsequently enters into the TCA cycle inside the mitochondria where oxidative phosphorylation of acetyl-CoA generates ATP and CO2 as by-products.

Ketones become an alternative source of energy for the brain and have been shown to exhibit antiepileptogenic, antinflammatory and neuroprotective properties (Park et al., 2019). While the mechanism of action of the KD antiepileptogenic effects is largely unknown, several mechanisms have been postulated including an increase in the synthesis of GABA due to the decrease availability of oxaloacetate to convert glutamate into aspartate, thus more glutamate is metabolized into GABA. Another antiepileptic mechanism is the activation of A1R (adenosine receptors) in the brain due to a surge of adenosine/ATP that inhibits the glutaminergic system and hyperpolarizes the neuronal membrane by the opening of ATP-sensitive potassium (KATP) channels reducing neuronal excitability. The KD also increases the number of mitochondria in brain cells reducing oxidative stress by increasing the production of reduced glutathione and the expression of mitochondrial uncoupling proteins decreasing

the production of free radicals. Additionally, the diet increases polyunsaturated fatty acids (PUFAS) affecting various ion channels, blocking sodium and calcium channels, and causing the opening of potassium channels, thus producing an antiepileptic effect. PUFAS also reduces seizures by affecting PPAR (peroxisome proliferator-activated receptor) that controls the transcription of numerous genes that affect metabolism and energy. Finally, KD with a restricted carbohydrate diet also gives a neuroprotective effect reducing cell death provoked by glutamate or ROS (McDonald et al., 2020).

SUMMARY

Healthcare providers in neurocritical care should be aware of the general populations that may be subject to developing NCSE and in what instances to look for the diagnosis. As stated, the older adult population is at greater risk and when a coma is observed, NCSE should be considered. As there are many broad etiologies and causes, NCSE is an emergency and should be investigated in a timely manner with cEEG and neuroimaging for swift diagnosis and treatment. Moreover, using a multitude of different combinations of medications, NCSE can be treated pharmacologically and with non-pharmacologic methods in the ICU setting. It is important to stay astute to the many facets of NCSE and to remain aware of the nature and seriousness of the diagnosis. Playing an active clinical role in the awareness, management, and treatment, NCSE can be reduced and terminated for better outcomes in the neurocritcally ill patient.

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