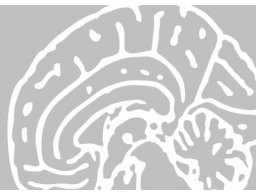
What is status epilepticus? Clinical natures updated



송파멜라
인제대학교 의과대학 일산백병원 신경과

Pamela Song, MD
Department of Neurology, Inje University Ilsan-Paik Hospital

Status epilepticus (SE) is one of the most commonly neurologic emergencies, with high mortality and morbidity. Understanding the pathophysiology are now focused on the neuroinflammatory and systemic inflammatory changes involved in the status epilepticus.

Key Words: Status epilepticus, Inflammation

Introduction

Status epilepticus (SE) is one of the most commonly neurologic emergencies, with high mortality and morbidity. The practical definition of status epilepticus is a 5 minutes of continuous seizures or discrete seizures with incomplete recovery of consciousness. Status epilepticus is result from failure of normal mechanisms that terminate an isolated seizure. I will review the definition, incidence, etiology, physiologic changes, and pathophysiology of status epilepticus. Further on, clinical natures in terms of immune and inflammation of status epilepticus, and updates will be discussed.

Definition

The definition of status epilepticus is a neurological emergency which requires immediate evaluation and timely treatment. The basic concept of status epilepticus is persisting seizure, however definition have been variably used in research and in clinical practice. The 1981 International League Against Epilepsy's definition of status epilepticus defined it as whenever a seizure persists for a sufficient length of time or repeated frequently enough that recovery between attacks does not occur.[1] Following reports have suggested specific duration of seizure for definition. The Epilepsy Foundation of America working group defined status epilepticus as 30 minutes from which the patient did not regain consciousness.[2] A widely accepted duration of status epilepticus as practical definition is 5 minutes following 2010 European Federation of Neurological Societies Guidelines, and 2012 Neurocritical care Society Guidelines.[3,4]

Incidence and etiology

The incidence of status epilepticus in the general population was reported to be between 18.3 to 41 per 100,000 in the United States, and 9.9 to 17.1 per 100,000 in Europe, with a first peak before 1 year of age and a second peak after 60 years of age.[5-8] In about half of the cases, there is history of epilepsy; it is most common in partial-onset epilepsy. About 15 % of epilepsy patients will experience an episode of status epilepticus in their lifetime and it presents as initial manifestation in 12 % of cases.[5,9] Etiology is the most important prognostic indicator, differs according to age group. In children, etiology of status epilepticus is usually infection with fever (50%), and other common causes of are remote symptomatic events (38%)

Pamela Song, MD
Department of Neurology, Inje University Ilsan-Paik Hospital, 2240 Daehwa-dong, IlsanSeo-gu, Goyang, Korea
TEL:+82-31-910-7013
E-mail: songpama@gmail.com

and low antiepileptic drug level (21%). The major cause of status epilepticus in adults are cerebrovascular disease (acute and remote hemorrhagic and ischemic strokes, 40%), followed by low antiepileptic drug level (35%), remote symptomatic brain injury (20%), and alcohol withdrawal (15%).[6] Aside from these common causes of status epilepticus, uncommon causes; Autoimmune disorders, Mitochondiral disease, and genetic disease, (typically occurring at a frequency 〈%) have been reported.[10,11]

Pathophysiology

The basic mechanisms of sustained seizure in status epilepticus involve failure of r-aminobutyric inhibition and enhanged excitotoxicity that mediated by glutamate. The receptor trafficking takes place at the beginning stage of status epilepticus which changes the number of inhibitory and excitatory receptors in the synaptic cleft.[12] The existing receptors mobilize from the synaptic membrane into the endosomes, or from storage sites to the synaptic membrane. Following this process is plastic changes in neuropeptide modulators, leading to a state of raised excitability. This is supported by immunocytochemical and confocal microscopy studies which have revealed a decrease in the number of GABA-A subunits present on the synaptic membrane and an increase inside the cell.[12] At the same time, a-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid and N-methyl D-aspartate (NMDA) receptor subunits move to the synaptic membrane where they form additional excitatory receptors. This change further increases excitability during uncontrolled seizures. Neuronal damage in SE result from sustained NMDA-mediated neuronal stimulation which leads to apoptosis.[13] During prolonged excitation, glutamate binds to neuronal NMDA receptors, causing depolarization and displacement of the magnesium ions that usually block ion flow into the neuron. Calcium enters the neuron, and this influx further prolongs depolarization, leading to excitotoxicity with neuronal injury and cell death.[14] When these neuronal cells are depolarized, the Mg 2+ ions blocking the channel diffuses outward, allowing sodium ions and Ca 2+ to flood the cell, resulting in a cascade of Ca +2 -mediated cytotoxic events, leading to neuronal injury, cell lysis, and cell death.

Physiologic changes

In the early stage of status epilepticus, there is massive release of catecholamines.[15] The catecholamine surge increases heart rate, blood pressure and temperature, along with other autonomic changes. Respiratory failure and lactic acidosis result in metabolic acidosis. Hyperglycemia is seen, but there may be hypoglycemia.[16] Renal failure may occur because of rhabdomyolysis and myoglobinuria.[17] At first, increased cerebral perfusion and decreased cerebrovascular resistance allow the increased metabolic demands of the brain to be met, thereby increasing the intracranial pressure. In the late stage, the compensatory cerebral autoregulation fails, and cerebral perfusion becomes dependent on systemic blood pressure.[18] Blood pressure declines 15 to 30 minutes after SE and may be markedly low after 2 hours of continuous seizure activity.

Clinical nature updated

The immune and inflammation have been emphasized for its role in seizure and sustain seizure activity.[19] The inflammation might be consequence as well as cause of epilepsy.[19] The inflammation activated inflammatory and anti-inflammatory molecules, to noxious stimuli or immune stimulation. The immune response can be evoked in within central nervous system (CNS), and systemic immune response can affect CNS. The blood brain barrier (BBB), by changing permeability, is key control in peripheral immunocompetent cells and molecules to enter into the brain. The brain injury resulting from infection, stroke, trauma, and prolonged seizures can alter the BBB.[20] Inflammation as a consequence of seizure are seen in studies that show proinflammatory cytokines (IL-1B, TNF and IL-6) are first expressed in activated microglia and astrocytes, and cytokine receptor expression in unregulated in microglia, astrocytes and neurons.[21] These initial events are followed by the induction of cyclooxygenase-2

(COX-2) and, hence, prostaglandins, and upregulation of compliment system in microglia, astrocytes and neurons.[19,22] And for status epilepticus, chemokines and their receptors are produced, especially in neurons and in activated astrocytes. Seizure as a consequence of inflammation is supported by studies that seizure activity leads to the induction of inflammatory molecules, in turn, affect seizure severity and recurrence. The elevation of cytokines, especially IL-B during fever has been found within hippocampus, cerebrospinal fluid studies in patients with febrile seizure. Further on, systemic injection of lipopolysaccharide, a prototypical inducer of inflammation both in the peripheral and in the brain, lowers seizure threshold. Brain inflammation following seizure and status epilepticus have been suggested to increase specific blood plasma cytokine levels, thus use as a biomarker for epilepsy, However, plasma cytokine changes of IL-6, CRP, IL-1B did not change following electrically induced status epilepticus in a rat model for temporal lobe epilepsy.

Conclusion

Based on the pathophysiology and newly discovered inflammatory changes involved in the status epilepticus should aid further understanding of mechanisms. And, thus developing the pathway to modify the epileptic process.

REFERENCES

1. Proposal for revised clinical and electroencephalographic classification of epileptic seizures. From the Commission on Classification and Terminology of the International League Against Epilepsy. Epilepsia. 1981;22(4):489-501. Epub 1981/08/01.
2. Treatment of convulsive status epilepticus. Recommendations of the Epilepsy Foundation of America's Working Group on Status Epilepticus. Jama. 1993;270(7):854-9. Epub 1993/08/18.
3. Meierkord H, Boon P, Engelsen B, Gocke K, Shorvon S, Tinuper P, et al. EFNS guideline on the management of status epilepticus in adults. European journal of neurology : the official journal of the European Federation of Neurological Societies. 2010;17(3):348-55. Epub 2010/01/07.
4. Brophy GM, Bell R, Claassen J, Alldredge B, Bleck TP, Glauser T, et al. Guidelines for the evaluation and management of status epilepticus. Neurocritical care. 2012;17(1):3-23. Epub 2012/04/25.
5. Hesdorffer DC, Logroscino G, Cascino G, Annegers JF, Hauser WA. Incidence of status epilepticus in Rochester, Minnesota, 1965-1984. Neurology. 1998;50(3):735-41. Epub 1998/04/01.
6. DeLorenzo RJ, Hauser WA, Towne AR, Boggs JG, Pellock JM, Penberthy L, et al. A prospective, population-based epidemiologic study of status epilepticus in Richmond, Virginia. Neurology. 1996;46(4):1029-35. Epub 1996/04/01.
7. Knake S, Rosenow F, Vescovi M, Oertel WH, Mueller HH, Wirbatz A, et al. Incidence of status epilepticus in adults in Germany: a prospective, population-based study. Epilepsia. 2001;42(6):714-8. Epub 2001/06/26.
8. Coeytaux A, Jallon P, Galobardes B, Morabia A. Incidence of status epilepticus in French-speaking Switzerland: (EPISTAR). Neurology. 2000;55(5):693-7. Epub 2000/09/12.
9. Aminoff MJ, Simon RP. Status epilepticus. Causes, clinical features and consequences in 98 patients. The American journal of medicine. 1980;69(5):657-66. Epub 1980/11/01.
10. Tan RY, Neligan A, Shorvon SD. The uncommon causes of status epilepticus: a systematic review. Epilepsy research. 2010;91(2-3):111-22.
11. Trinka E, Höfler J, Zerbs A. Causes of status epilepticus. Epilepsia. 2012.
12. Naylor DE, Liu H, Wasterlain CG. Trafficking of GABA(A) receptors, loss of inhibition, and a mechanism for pharmacoresistance in status epilepticus. The Journal of neuroscience : the official journal of the Society for Neuroscience. 2005;25(34):7724-33.
13. Szczurowska E, Mareš P. NMDA and AMPA receptors: development and status epilepticus. Physiological research / Academia Scientiarum Bohemoslovaca. 2013;62 Suppl 1:38.
14. Meldrum BS. Concept of activity-induced cell death in epilepsy: historical and contemporary perspectives. Progress in brain research. 2002;135:3-11.
15. Benowitz NL, Simon RP, Copeland JR. Status epilepticus: divergence of sympathetic activity and cardiovascular response. Annals of neurology. 1986;19(2):197-9.
16. Meldrum BS, Horton RW. Physiology of status epilepticus in primates. Archives of neurology. 1973;28(1):1-9.
17. Grossman RA, Hamilton RW, Morse BM, Penn AS, Goldberg M. Nontraumatic rhabdomyolysis and acute renal failure. The New England journal of medicine. 1974;291(16):807-11.
18. Lothman E. The biochemical basis and pathophysiology of status epilepticus. Neurology. 1990;40(5 Suppl 2):13-23.
19. Vezzani A, French J, Bartfai T, Baram TZ. The role of inflammation in epilepsy. Nature Reviews Neurology. 2011.
20. Shlosberg D, Benifla M, Kaufer D, Friedman A. Blood-brain barrier breakdown as a therapeutic target in traumatic brain injury. Nature reviews Neurology. 2010;6(7):393-403. Epub 2010/06/17.

21. Vezzani A. Inflammation and epilepsy. Epilepsy currents / American Epilepsy Society. 2005;5(1):1-6. Epub 2005/08/02.
22. Vezzani A. Epilepsy and inflammation in the brain: overview and pathophysiology. Epilepsy currents / American Epilepsy Society. 2014;14(1 Suppl):3-7. Epub 2014/06/24.