Nonconvulsive Status Epilepticus

Morbidity and Consequences

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Nonconvulsive status epilepticus (NCSE) is protean in its clinical manifestations and often difficult to recognize. It is clearly underdiagnosed. It has a tremendous variety of precipitants or causes. The complexity in categorization or classification makes it difficult to determine its morbidity or consequences. NCSE comprises many different illnesses, such that diagnosis and management are different for the many types, and the prognosis varies accordingly. Neurologists generally agree that episodes of NCSE should be avoided or treated, but the consequences and long-term risks are varied, difficult to ascertain, and controversial.

There are many types of outcome to consider. Mortality from NCSE itself (as opposed to that from the underlying lesion or precipitating illness) is rare. “Brain damage” or neuronal injury is extremely difficult to be sure of. Consequences can be studied from the point of view of experimental animal studies, human pathologic studies, and, primarily, clinical reports. In addition to mortality and adverse structural consequences, morbidity can include physical injury during NCSE, treatment complications, recurrences of status epilepticus, longer-term cognitive deficits, and the likelihood of NCSE leading to or exacerbating epilepsy. Recurrence is probably the most common complication. Most other morbidity is assessed by clinical neurologic evaluation, particularly for memory, cognitive, and other neurologic deficits.

1. EXPERIMENTAL STUDIES IN ANIMALS

Many superb experimental models of generalized convulsive status epilepticus (GCSE) have aided immensely our understanding of the physiology, pathophysiologic mechanisms, and consequences of GCSE. Models of NCSE are far more difficult to design and to learn from.

The experiments of Meldrum and colleagues in the 1970s established that episodes of convulsive SE lasting up to several hours produce substantial neuronal damage in the neocortex, cerebellar Purkinje and basket cells, and hippocampal cells in baboons (1–3). The SE was initiated by systemically administered bicuculline and included major electrolyte and acid–base disturbances, hyperpyrexia, and cardiac
The hours of SE included rapid epileptiform discharges punctuated by flat periods on the electroencephalogram (EEG). Much of the ensuing cellular damage correlated with hyperpyrexia, hypotension, hypoxia, acidosis, and hypoglycemia. Controlling for these factors by paralysis and artificial ventilation reduced the damage in the neocortex, thalamus, and hippocampus, showing that systemic factors contributed to some of the injury (3). Maintenance of homeostasis, however, provided incomplete protection in the neocortex and hippocampus. Hippocampal neuronal loss was still substantial, suggesting strongly that the electrical activity of SE damages hippocampal neurons independent of systemic and metabolic factors. These experiments provided a model primarily for GCSE. Importantly, they indicated that the brain activity associated with GCSE (even without convulsions) was damaging by itself. The question of damage from NCSE was not addressed directly.

Lothman and colleagues demonstrated that excitotoxins, particularly kainic acid (whether applied systemically or locally in the hippocampus) affected limbic structures preferentially. Kainic acid produced seizures that were primarily nonconvulsive, providing more of a model of NCSE (4,5). To overcome concern that the neuronal injury following such seizures was due to a toxic effect of kainic acid directly on the neurons, they also used electrodes implanted in the rat hippocampus (6,7). Rapid repetitive electrical stimulation for 30 to 90 min produced seizures and eventually self-sustaining SE persisting for 12 to 24 h after the stimulation ceased. Stimulation included 10-s periods of 50 Hz, 1-ms pulses alternating with 3 s for EEG recording, with the entire episode lasting 90 min. It produced electrographic seizures with very rapid epileptiform discharges, often more than 10 Hz. Later seizures were nonconvulsive and described as “limbic,” with prominent hippocampal discharges rather than generalized convulsions. This model also led to neuronal loss in the hippocampal CA-1 region. Interestingly, however, rats with briefer or less-frequent seizures did not sustain the same injury (8). Some of the limbic changes were reversible, resolving after weeks (7). The experiments thus raised the possibility that damage from NCSE might be less substantial or less permanent than that from GCSE.

There is concern that the chemical and electrical methods of inducing SE may damage neurologic tissue themselves, independent of the electrical discharges of seizures or SE. To obviate these concerns, Sloviter showed that indirect electrical stimulation via the perforant pathway (the primary afferent excitatory pathway to the hippocampus) could lead to damage in rat hippocampal neurons (9). This avoided direct injection of potentially toxic chemicals or penetrating electrodes. Typical stimulations, however, were vigorous: 1-ms pulses of 20 V at a 2 Hz frequency maintained for 24 h, with additional 10-s runs of 20-Hz activity once a minute.

The typical stimulations used to provoke seizures and SE in these models have been intense. The intensity of the resulting epileptiform discharges appears to correlate with the likelihood of subsequent neuronal damage. Localized prepiriform bicuculline injection produced both heat shock protein (HSP; a sign of neurologic damage) and neuronal death in the thalamus, amygdala, and piriform cortex in