


Original Article

Severe Refractory Status Epilepticus Owing to Presumed Encephalitis

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ABSTRACT

The severe refractory type of status epilepticus is very rare in the pediatric population. Eight children with the severe refractory type of status epilepticus owing to presumed encephalitis are described. The age at the onset of status epilepticus of the eight study children ranged between 2.5 and 15 years. Seven of the eight children presented with fever several days prior to the onset of seizures. A comprehensive clinical and laboratory investigation failed to delineate a cause for their seizures. Burst suppression coma was induced by pentothal, midazolam, propofol, or ketamine in all of the children. The mean duration of anesthesia was 28 days (range 4-62 days), but the seizures persisted in spite of repeated burst suppression cycles in all of them. Two children died. Four of the surviving children continued to suffer from seizures, and cognitive sequelae were present throughout follow-up in four children. In summary, the severe refractory type of status epilepticus of the acute symptomatic type owing to relatively mild encephalitis carries a high mortality rate and poor morbidity in terms of seizures and cognition at follow-up. (J Child Neurol 2005;20:184-187).
Refractory status epilepticus is defined as the persistence of seizure activity despite appropriate medical and antiepileptic therapy. The relative incidence of refractory status epilepticus is estimated as being 9% of all status epilepticus in adults, whereas it is unknown in children. Severe refractory status epilepticus is defined as the reappearance of seizures following treatment with coma-inducing drugs, and its relative incidence is not known for any age group. Several studies reported on the duration of episodes of status epilepticus in children: it was longer than 1 hour in 26% to 45%, longer than 2 hours in 17% to 25%, and longer than 4 hours in 10%, with the longer duration of a status epilepticus occurring significantly more often in the acute symptomatic group.

The etiology of status epilepticus has been classified into idiopathic, remote symptomatic, febrile, acute symptomatic, and a type associated with a progressive encephalopathy. There is a small subgroup of pediatric patients with severe refractory status epilepticus that belongs to an acute symptomatic group; these children undergo normal neurodevelopment and present with the symptomatology of a mild infection prior to the status epilepticus. This small group comprises 36% of all children with severe refractory status epilepticus and carries a significantly higher mortality rate than that predicted in children with status epilepticus.

Severe refractory status epilepticus is very rare among children, and we found only one published series of eight such patients in our search of the literature. We describe the clinical symptomatology, treatment, and outcome of eight more pediatric patients with severe refractory status epilepticus.

**PATIENTS**

From January 1998 to March 2003, eight children with severe refractory status epilepticus of unknown etiology were hospitalized in five hospitals in Israel. During this period, an additional three children were treated in these hospitals for severe refractory status epilepticus owing to known etiologies (metabolic diseases in two, meningitis in one). Three of them had an apparently normal medical and neurologic status prior to the onset of seizures, one had mild cognitive delay, one had rare photosensitive seizures, one had two episodes of febrile convulsions, and two were diagnosed as having familial Mediterranean fever with no prior history of seizures.

Seven of the study children had a febrile disease during the 2 to 10 days prior to the presentation of severe refractory status epilepsy. Notably, fever was present ≤ 5 days before seizure onset in six of them. One child also presented with a concomitant erythematous rash.

Severe refractory status epilepticus developed within a few hours to 4 days from the first seizure episode and within 24 hours in five of them. All eight of our patients presented with partial seizures, including simple partial seizures, partial seizures secondarily generalized, and complex partial seizures.

Investigation

All eight patients underwent a thorough investigation during their hospitalization, including serologic tests for viruses including cytomegalovirus, Epstein-Barr virus, enteroviruses, and polymerase chain reaction in the cerebrospinal fluid for herpes simplex. In addition, most children also underwent serologic tests for Bartonella henselae (the agent for cat scratch disease), Mycoplasma pneumoniae, and Rickettsia sp. They underwent a full metabolic workup, as well as routine tests to rule out collagen-vascular diseases. All test results were negative.

Cerebrospinal fluid studies showed mild pleocytosis (> 5 white blood cells but < 100) in five patients; the white blood cell count in the cerebrospinal fluid was 19 to 27 WBC/mm³ in four patients. There was a predominance of monocytes (80–100%) in all cases. The glucose level in the cerebrospinal fluid ranged from 60 to 83 mg/dL, and protein levels were 20 to 60 mg/dL.

The first magnetic resonance imaging (MRI) performed during the acute phase was normal, whereas the second MRI performed several weeks after disease onset revealed mild atrophy in five patients. These five included two who were not treated with corticosteroids. One patient had bilateral hippocampal hyperintensity in T2, suggestive of focal edema, one had endyminal enhancement on MRI suggestive of encephalitis, and one had normal results. A follow-up MRI after discharge from the hospital was performed in three of five survivors who originally had abnormal findings, and their results were normal.

Electroencephalography (EEG) performed continuously or intermittently during the hospitalization revealed one (n = 4) or two (n = 4) epileptic foci in all patients during the non–burst suppression periods.

Treatment

All patients were treated part of the time with pentothal (pentobarbital is not available in Israel), mostly during the burst suppression trial, and part of the time with midazolam drips (n = 7), which seemed to enable a lower level of sedation while still controlling the seizures. In addition, the children were treated with propofol (n = 3), high-dose phenobarbital (n = 2), diazepam drip (n = 2), and ketamine (n = 1).

Burst-suppression coma was induced in all patients. A single burst suppression period lasted 15 to 96 hours (burst suppression cycle continued for 48 hours or more in all but two children). The total period of mechanical ventilation was 4 to 62 days (mean 27.76 days, SD 19.4 days). The child with only 4 days of burst suppression anesthesia continued with a midazolam drip with no need for further mechanical ventilation.

Concomitantly with anesthetics, the children were treated with different combinations of antiepileptic drugs: 5 to 10 antiepileptic drugs for each patient, intravenous immunoglobulin (n = 7), and corticosteroids (n = 5). Corticosteroids were given as a pulse of either dexamethasone (4–8 mg/d) or methylprednisolone (20–30 mg/kg/d) for a period of several days. The seizures gradually disappeared in all patients, with no clear correlation with either the repetitive trials of induced burst suppression coma or treatment with multiple antiepileptic drugs.

Follow-up

Two children died (25%). The first was an 8-year-old boy who died owing to sepsis and liver failure after 41 days of anesthesia, and the second was a 15-year-old boy who died owing to a tear in the esophagus and bleeding into the lungs following 28 days of anesthesia.

All six survivors needed rehabilitation following the cessation of the status epilepticus. The period from cessation of mechanical ventilation until steady state lasted between 1 and 6 months and was correlated to the duration of anesthesia. During that period, the children manifested cortical blindness (n = 2), autistic behavior (n = 2), loss of speech (n = 1), and ataxia and choreoathetosis (n = 1).
At follow-up, four of the six surviving children had seizures, whereas two had refractory complex partial seizures. One child has mild developmental retardation. Three children have severe attention-deficit hyperactivity disorder and learning disabilities. One child has normal development, and one has mild global delay. This child had mild developmental delay prior to hospitalization, and there is no clear evidence of cognitive deterioration.

**DISCUSSION**

The severe refractory type of status epilepticus is very rare in the pediatric population, and the available information on this condition is sparse. Our search of the literature turned up one article by Sahin et al, who retrospectively reviewed 22 cases of severe refractory status epilepticus treated at Children's Hospital, Boston, between 1992 and 2000, of whom eight apparently had severe refractory status epilepticus with a presumed encephalitic etiology.

We report the clinical presentation, investigation, and outcome of eight additional patients whose presumed etiology for severe refractory status epilepticus was encephalitis and in whom burst suppression coma was induced. Seven of the eight patients had febrile illness prior to or concomitant with seizure onset. All had negative bacterial and viral cultures, as well as a negative polymerase chain reaction for herpes simplex. We therefore postulated that the etiology for the acute disease might be encephalitis of an unidentified agent. Five of the children presented with mild pleocytosis in their cerebrospinal fluid. This finding, however, does not confirm the presence of encephalitis because pleocytosis was noted in a substantial number of patients with status epilepticus without encephalitis.

All of our patients had either continuous EEG monitoring or repeated EEG recordings. The recording showed that four patients had two seizure foci. The existence of more than one epileptic focus owing to encephalitis is not surprising and probably plays a part in the severity of the epileptic process.

The strategy of treating refractory status epilepticus involves the acquisition of burst suppression by means of agents such as pentobarbital, pentothal, midazolam, and propofol. Many studies had been designed to evaluate the relative efficacy of these different agents, as well as of the use of isoflurane or ketamine. The depth and duration of burst suppression can also play a role in determining the efficacy of the treatment. No conclusions regarding the efficacy of therapeutic strategies can be made from the present series owing to the small number of patients. In spite of several periods of burst suppression with different durations for each patient, this technique did not achieve persistent freedom from seizures in any of them. Our observation is, therefore, that there was no clear correlation between cessation of seizures and any of the agents we used. This observation is supported by data from animal studies. Refractory status epilepticus or self-sustaining status epilepticus occurs when seizures continue in a self-sustaining manner for many hours after the initial cause has been eliminated. This phenomenon demonstrates that status epilepticus differs from single seizures, which are terminated by powerful inhibitory feedback and are followed by postictal changes that make the brain refractory to further seizure activity. A model for self-sustaining status epilepticus was recently developed by intermittent electrical stimulation of the perforant path in free-running rats. This model demonstrated that resistance to standard anticonvulsants develops progressively during the course of self-sustaining status epilepticus: although diazepam and phenytoin were highly effective when given before or at the onset of self-sustaining status epilepticus, both lost their effectiveness when their administration was delayed beyond 70 minutes after the onset of stimulation.

A number of physiologic and biochemical changes have been described that can account for the refractoriness of the seizures, among them the failure of inhibitory mechanisms or the enhancement of excitatory mechanisms. Failure of inhibition can be associated with changes in γ-aminobutyric acid (GABA)A receptor function, thus explaining the failure of GABAergic drugs, such as diazepam, when given late in the course of self-sustaining status epilepticus. At the same time, however, diazepam-resistant self-sustaining status epilepticus can be interrupted by neuromodulators, which presynaptically modulate glutamate release or postsynaptically block N-methyl-D-aspartate (NMDA) receptors. Experiments in rats have shown that the maintenance phase of self-sustaining status epilepticus depends on activation of NMDA receptors and that NMDA receptor blockers (ie, MK-801 and ketamine) can abolish the status epilepticus.

These observations might suggest novel approaches to the treatment of refractory status epilepticus. Specifically, optimal pharmacotherapeutic strategies for status epilepticus might need to be matched to the molecular state of the seizing networks, either by the development of new agents with affinity for NMDA receptors, such as felbamate, or by the use of anesthesia involving the currently available NMDA channel blocker ketamine in refractory cases.

Owing to its rarity, there are no large-scale studies on the mortality or neurologic sequelae following severe refractory status epilepticus.
epilepticus. The mortality rate in children with status epilepticus reaches 3.6% to 7%. All seven deaths in the study of Maytal et al, as well as six of the eight deaths in Dunn's study, were attributed to either a severe acute insult or a progressive disease. The mortality rate of the specific subgroup of severe refractory status epilepticus as observed by the only relevant published study was considerably higher, reaching 25%. This rate is similar to the mortality in our group of patients.

In four of our six surviving children, seizure persisted following the refractory status epilepticus. This figure is in agreement with that of an 83% seizure persistence among the survivors in Sahin et al.'s severe refractory status epilepticus group. Seizure types in our follow-up included complex partial seizures and partial seizures secondarily generalized. Two of our study children had never had a seizure-free period following the severe refractory status epilepticus and currently present with refractory seizure disorder.

In one series on short-duration status epilepticus, the neurologic sequelae associated with etiologic subgroups included acute symptomatic or progressive encephalopathy. This is especially relevant to patients with encephalitis or presumed encephalitis. In addition, long durations of an induced coma, as well as repetitive seizures during the period of status epilepticus, can play a role in the long-term morbidity, and, indeed, both mortality and morbidity were correlated with the duration of treatment. There was also a low probability of returning to baseline following a treatment duration of longer than 30 days.

It is important to note that a specific diagnosis can be made later in some patients whose initial diagnosis was presumed to be encephalitis, for example one child with human herpesvirus 6 and one child with Alpers' disease diagnosed at autopsy in Sahin et al.'s study. Therefore, every effort to identify the specific diagnosis should continue in parallel with medical treatment.

Because two of the six surviving children in our present series had developed severe refractory epilepsy at follow-up, the end point of suppressive treatment is not clear. Moreover, because longer suppressive treatment can be associated with a higher probability of cognitive sequelae at follow-up, the timing for discontinuation of suppressive therapy and relying on conventional antiepileptic drugs or a low titration rate with midazolam should be considered.

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References
