LESS COMMON ETIOLOGIES OF STATUS EPILEPTICUS

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Status epilepticus is treated as a neurologic emergency and only later are the potential etiologies assessed. While sometimes the cause for status epilepticus is apparent (e.g., antiepileptic drug withdrawal), all too often it is not identified, even after extensive diagnostic testing has been performed. With emphasis on the less-common etiologies, this review will cover various probable and known causes of status epilepticus among adults, children, and those patients with refractory epilepsy.

The treatment of status epilepticus is unusual among neurologic disorders in that initial therapy usually precedes attempts to establish an etiologic diagnosis. In other neurologic emergencies, such as stroke, the physician first performs diagnostic testing to classify the type of cerebrovascular disease before beginning therapy. Treatment for status epilepticus is more akin to resuscitation after cardiac arrest or to the initial management of shock: stabilization takes precedence over diagnosis. Only after achieving adequate control of basic life support issues (i.e., airway, respiration, and circulation) and attempting to terminate status epilepticus with first-line therapeutic agents, is there time to ponder the cause of the patient's episode. Often, the etiology is apparent, such as alcohol withdrawal or abrupt cessation of anticonvulsant drug, in a patient with known epilepsy. Epileptologists, intensivists, and other clinicians who treat epilepsy are familiar with the more commonly encountered reasons for status epilepticus from the classic studies, such as that of Simon and Aminoff, published 3 decades ago (1), and of Lowenstein and Alldredge, who provided data from the same hospital over a 10-year period (2). Several other studies have produced data that are, in general, similar to these two investigations.

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Etiologies for Status Epilepticus

Table 1 reviews frequently diagnosed etiologies in adults. Children have a different distribution of etiologies, including some (e.g., febrile status epilepticus) that do not appear in adult studies. Table 2 presents data from a number of pediatric studies, stressing the work of the American Academy of Neurology guidelines committee in this area (3). In addition, Watemberg and Segal recently presented a useful approach to the less-common etiologies prompting childhood status epilepticus (4). Table 3 summarizes data from several published investigations for the etiologies of status epilepticus that were considered refractory to standard therapies. However, the different studies have greatly divergent rates for each of these etiologic categories. For example, the recent publication by Legriel and colleagues reported a much larger percentage of patients with acute stroke as the etiology than did the other papers (5).

Many intensivists and epileptologists are somewhat puzzled by this etiologic distribution, because, in their practice, they seem to encounter a much larger percentage of patients for whom the cause of status epilepticus is uncertain. Sometimes, clinicians have no idea what triggered the seizures of an individual patient, particularly with previously normal patients who present with refractory status epilepticus. In such patients, a large number of diagnostic tests frequently are ordered. Sometimes they reveal an etiology, or at least guide the clinician toward a class of diagnoses. However, often the clinician is left without anything useful to report to the patient's family or to their colleagues.

TABLE 1. *Common Etiologies of Status Epilepticus in Adults*

Anticonvulsant noncompliance	29%
Alcohol related (predominantly withdrawal)	26%
CNS infection	8%
Refractory epilepsy	6%
Trauma	6%
Tumor related	6%
Acute stroke	6%
Metabolic disorders	4%
Acute hypoxic–ischemic encephalopathy	4%
Miscellaneous and undetermined	6%

References: Aminoff & Simon (1); Lowenstein & Alldredge (2).

TABLE 2. *Etiologies of Status Epilepticus in Children*

Remote symptomatic epilepsy	27%
Acute symptomatic seizures	22%
Febrile	17%
Cryptogenic	14%
CNS infection	11%
Acute metabolic disorders	5%
Miscellaneous diagnosed causes	4%

References: Riviello, et al. (3).

Uncommon Etiologies for Status Epilepticus

The most troublesome diagnostic category is CNS "infection"; in most reports, what occurs is that a patient, who was febrile at some earlier time in their disease, and then has a lumbar puncture that reveals a pleocytosis (usually lymphocytic). In some countries, such as China, this event appears to be the leading cause of status epilepticus (6). In a minority of such cases, bacterial infection or a proven viral etiology (such as herpes simplex encephalitis) emerges. In the early days of MRI, a focus on an increased T_2 signal often led to suspicion of a focal encephalitis, but with time, diagnosticians learned to be more perspicacious about attributing etiologic significance to the transient finding of such increased signal.

Attempts to determine the etiology of encephalitis, with or without status epilepticus, have been unrevealing, with less than half of all cases being identified. The most thorough investigation into these etiologies came from the California Encephalitis Project, which recently published results from a study of patients with suspected encephalitis (7). The authors divided patients into three groups: group 1 (43 patients) had refractory status epilepticus; group 2 (459 patients) included individuals with seizures or status epilepticus that was not refractory to initial therapy; and group 3 (649 patients) was without seizures. Patients in group 1 tended to be younger, more likely to present with seizures, have prodromal respiratory and gastrointestinal symptoms, and have had a rash. Interestingly, however, they were less likely to have had an initially abnormal neuroimaging study or a CSF pleocytosis. Unfortunately, an infectious diagnosis (including enteroviruses, rotavirus, Epstein–Barr virus, *Mycoplasma pneumoniae*, adenoviruses, and human herpesvirus 6) was obtained from only 26% of the group 1 patients. The authors rated many of the associations between viral infection and the status epilepticus as only possible or probable.

TABLE 3. *Etiologies of Refractory Status Epilepticus*

Infection	19%
Pre-existing epilepsy	18%
Metabolic	13%
Acute stroke	11%
Tumor related	10%
Alcohol or other drug withdrawal	9%
Drug intoxication	6%
Acute hypoxic–ischemic encephalopathy	6%
Acute trauma	6%
Miscellaneous or undetermined	2%

TABLE 4. *Autoimmune Diseases Associated with Status Epilepticus*

- Anti-NMDA receptor limbic encephalitis
- Antiglutamate receptor limbic encephalitides
- Antineuronal antibody syndromes with limbic encephalitis
- Paraneoplastic limbic encephalitis, without a demonstrable antibody
- Limbic encephalitis following various systemic viral infections
- Limbic encephalitis following various vaccines
- Limbic encephalitis associated with drug hypersensitivity reactions
- Hashimoto's encephalopathy (autoimmune thyroid encephalopathy)
- Systemic lupus erythematosus
- Antiglycolipid autoantibody syndrome

Recently, several investigators have reported that CNS or systemic autoimmune disorders may cause status epilepticus; in some cases, the diseases are paraneoplastic, but in others, they are cryptogenic. Since patients with these etiologies usually are described in case reports or small series, the contribution of the disorders to the epidemiology of status epilepticus is difficult to assess, but they appear to represent a substantial portion of cases previously diagnosed as infectious (since the patients often have a syndrome qualifying as an encephalitis) or cryptogenic. Table 4 lists some of the proven or probable associations between the CNS or systemic autoimmune disorders and status epilepticus. However, for many of the etiologies listed, the connection is only suspected, based on neuroimaging studies, spinal fluid analysis, or response to immunosuppressive treatments—without demonstrating a specific disease (8). This list will undoubtedly become much longer in the next few years, as research in this area continues to expand.

Conclusions

The recognition of associations between various disorders and incidences of status epilepticus, as well as the apparently beneficial response by some patients to various immunosuppressive treatments, suggests that diagnostic studies of patients with status epilepticus need to include consideration of viral and autoimmune conditions. How extensive such workups should be is not clear at this time. Immunosuppressive treatments, including corticosteroids, intravenous immunoglobulin or plasma

exchange, cyclophosphamide, and calcineurin antagonists, or other drugs usually employed to prevent transplant rejection can be considered for patients identified with such comorbidities. These treatments are rarely specific for any particular autoimmune syndrome, however, and the risks they pose regarding systemic infection must be considered.

Nevertheless, recognition of the broad range of potential etiologies for status epilepticus is an antidote for the frustration that commonly afflicts the physician caring for patients experiencing status epilepticus. As a larger percentage of these patients reach etiologic diagnoses, treatments will be more specific and hopefully more effective, not only for the underlying conditions themselves but also, perhaps, for refractory status epilepticus.

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