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A Suggested Approach to the Etiologic Evaluation of Status Epilepticus in Children: What to Seek After the Usual Causes Have Been Ruled Out

Nathan Watemberg, MD, and Gil Segal, MD

Status epilepticus represents a true neurologic emergency that requires immediate treatment to stop seizure activity and prompt diagnostic evaluation to recognize potentially treatable causes. Although an etiology may be detected in many cases, in a significant number of patients the cause is not established by the usual laboratory or neuroimaging studies. We performed an extensive literature review of all unusual and often overlooked causes of status epilepticus in children, in an attempt to provide physicians with practical information on the diagnostic approach to patients, particularly those with refractory status epilepticus, for whom an etiology can not be detected by routine diagnostic protocols.

Keywords: status epilepticus; etiology; seizures; EEG

Methods

A search of the PubMed database (www.ncbi.nlm.nih.gov/PubMed) was performed using the key words status epilepticus, pediatric, etiology, symptomatic, and convulsive in different combinations. The search included all published papers with no limitation of time or language. Special care was taken to choose those articles reporting on unusual or unsuspected etiologies of status epilepticus, as most available literature on the diagnostic...
work-up of these patients usually addresses the subject in a general fashion (etiologic groups rather than single causes). The specific etiologies reported were classified according to their nature (ie, infectious, metabolic, etc) and to whether they are potentially treatable or not. Finally, a diagnostic flowchart was designed to provide a practical, real-time approach to seeking the etiology of status epilepticus after the usual, better recognized etiologies have been ruled out.

**Etiology of Pediatric Status Epilepticus: Causes That Can Be Determined With Routine Diagnostic Work-Up**

Determining the etiology of status epilepticus in a specific patient is of essence, particularly in cases where treatment aimed at correcting the cause can be administered. Moreover, etiology plays a significant role in the prognosis of convulsive status epilepticus. In 1993, the International League Against Epilepsy (ILAE) Commission on Epi-emiology and Prognosis proposed an etiologic classification based on the status epilepticus presentation in regard to the presence or absence and the timing of a central nervous system insult, and on whether the patient has pre-existing epilepsy after the usual, better recognized etiologies have been ruled out.

<table>
<thead>
<tr>
<th>Type (Frequency)</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Acute symptomatic (26%)</td>
<td>SE due to an acute central nervous system illness or insult</td>
</tr>
<tr>
<td>Remote symptomatic (33%)</td>
<td>SE occurring without an acute provocation in a patient with a previous central nervous system insult</td>
</tr>
<tr>
<td>Remote symptomatic with an acute precipitant (1%)</td>
<td>SE occurring with an acute provocation in the presence of chronic encephalopathy</td>
</tr>
<tr>
<td>Progressive encephalopathy (3%)</td>
<td>SE developing in a patient with an underlying, progressive central nervous system disorder</td>
</tr>
<tr>
<td>Febrile (22%)</td>
<td>Fever-related SE, after ruling out a direct central nervous system infection</td>
</tr>
<tr>
<td>Cryptogenic (15%)</td>
<td>SE without an apparent cause</td>
</tr>
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</table>

Note: SE, status epilepticus.

The Practice Parameter suggested by the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society summarized the published findings on 2093 children with status epilepticus (Table 1). Work-up recommendations by the Practice Parameter can be summarized as follows:

- There are insufficient data to support or refute obtaining blood cultures and performing a spinal tap when there is no suspicion of infection.
- Antiepileptic drug levels should be considered in treated children with status epilepticus.
- Toxicology testing may be considered when no apparent etiology is identified. Given the multitude of potential toxic agents, the yield of a general toxic screening is low.
- There is insufficient evidence to support or refute the need for the routine use of metabolic studies and genetic testing.
- Although it usually does not provide etiologic clues, an electroencephalogram may be considered to help establish whether seizures may be focal or generalized in origin, and whether there are abnormal findings that may influence diagnostic and treatment decisions. Furthermore, the EEG may help rule out pseudostatus epilepticus. Concerning nonconvulsive status, the evidence supporting the routine use of the EEG is insufficient.
- Neuroimaging may be considered according to clinical findings or if the etiology is unknown. Nevertheless, there is not enough evidence to support or refute routine neuroimaging.

The importance of reviewing the scientific basis for recommending specific diagnostic studies is enormous. However, this approach is too broad and does not make the bedside evaluation of the child with status epilepticus any easier.

In clinical practice, the most common etiologies of acute symptomatic pediatric status epilepticus can be summarized as follows (Table 2):

- central nervous system infections—meningitis, encephalitis
- acute anoxic insult
- metabolic: hypoglycemia, inborn errors of metabolism
- electrolyte imbalance
Central nervous system infections—meningitis, encephalitis
Acute anoxic insult
Metabolic—hypoglycemia, IEM, Reye syndrome
Electrolyte imbalance
Central nervous system trauma/hemorrhage/tumors
Drugs, intoxications, poisoning
Hypoxic ischemic encephalopathy and IEM in newborn period
First unprovoked seizure presenting as SE—most commonly febrile status
SE in patients with epilepsies—epileptics on irregular treatment, sleep deprivation, intercurrent infections, and symptomatic epilepsies are more prone to developing SE
Cryptogenic

Hence, in clinical practice, certain basic diagnostic procedures are usually performed in the first stages of status. These are depicted in Table 3.

Identifiable Etiologies of Status Epilepticus

Among adult patients, some differences between community hospitals and urban medical centers regarding the causes of status epilepticus are recognized. Thus, although poor compliance with antiepileptic therapy is the most common precipitant for status epilepticus in both settings, alcohol- and drug-related seizures follow in frequency in urban centers while cerebrovascular disease is the second most common cause in the community. Interestingly, remote symptomatic and metabolic impairment–related causes are much more prevalent in the community. However, it appears that the percentage of adult cases in which no etiology is found is actually quite low.12

Data on the etiology of status epilepticus in children vary according to the origin of the reports and the classifications used. For example, febrile seizure, one of the most common pediatric etiologies, is at times stated as a separate entity and on other occasions as part of the acute symptomatic group. Among developing countries, in India13 acute symptomatic status epilepticus is most common, caused mainly by central nervous system infections, vascular etiologies, and acute metabolic derangement. Noncompliance with antiepileptic drug therapy is the second most common etiology. Febrile seizures were not described as a cause of status epilepticus. However, a study from Iran detected prolonged febrile seizures as the most frequent etiology, occurring in 51%. Discontinuation of antiepileptic drug was the second most common cause. An etiology could not be determined in almost 9% of cases.14 Moreover, in Tunisia and in Saudi Arabia, febrile and acute symptomatic cases accounted for over 80% of patients, and progressive encephalopathies and remote symptomatic cases were quite uncommon. Two to six percent of patients were considered as idiopathic cases.15,16 Finally, in Kenya, infection was the etiology of status epilepticus in 71% of 388 children. Malaria and febrile convulsions associated with this disease were extremely common, followed by bacterial meningitis. In 15% of confirmed convulsive status, encephalopathy of unknown cause was listed as the etiology of status epilepticus.17

Data from developed countries also vary among different regions. A retrospective study from Montreal on their 10-year experience with admissions for status epilepticus to the intensive care unit found epilepsy (32%), atypical febrile seizures (13.6%), meningitis (13%), and encephalitis (13%) to be the most common etiologies.18 The North London Status Epilepticus in Childhood Surveillance Study analyzed data on 226 children, including 176 with a first ever episode of status. Prolonged febrile convulsions were reported as the most frequent cause (32%), followed by acute and remote symptomatic cases (17%). About 10% were considered “idiopathic.”19 A large retrospective case note study from Liverpool, United Kingdom found prolonged febrile status epilepticus to be most common, affecting 34% of cases. Remote symptomatic etiologies, namely cerebral palsy and epilepsy (28%) and acute symptomatic seizures (18%) followed. The latter mainly included meningitis, encephalitis, trauma, and anoxia. In 5%, no cause could be discerned.20 A similar proportion of symptomatic and febrile seizures cases were reported from Finland.21 Conversely, a very recent retrospective US study on 154 children found febrile seizures in only 10.4% of cases. Remote symptomatic etiologies were most frequent, occurring in 35.7% of pediatric status

<table>
<thead>
<tr>
<th>Table 2. Principal Etiologies of Pediatric SE by Categories (Acute Situation-Related SE)</th>
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<tbody>
<tr>
<td>Etiology</td>
</tr>
<tr>
<td>Central nervous system infections—meningitis, encephalitis</td>
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<tr>
<td>Acute anoxic insult</td>
</tr>
<tr>
<td>Metabolic—hypoglycemia, IEM, Reye syndrome</td>
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<td>Drugs, intoxications, poisoning</td>
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<tr>
<td>Hypoxic ischemic encephalopathy and metabolic derangement in newborn period</td>
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<tr>
<td>Cryptogenic</td>
</tr>
</tbody>
</table>

Note: IEM, inborn errors of metabolism; SE, status epilepticus.

<table>
<thead>
<tr>
<th>Table 3. Commonly Performed Diagnostic Procedures in Pediatric Status Epilepticus</th>
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<tbody>
<tr>
<td>Initial Tests</td>
</tr>
<tr>
<td>Serum electrolytes</td>
</tr>
<tr>
<td>Blood gases</td>
</tr>
<tr>
<td>Blood urea</td>
</tr>
<tr>
<td>Complete blood count</td>
</tr>
<tr>
<td>Serum calcium and magnesium in neonates and young infants</td>
</tr>
<tr>
<td>Blood gases</td>
</tr>
<tr>
<td>Blood gases</td>
</tr>
</tbody>
</table>

Note: CT, computed tomography; EEG, electroencephalography; MRI, magnetic resonance imaging.
epileptic cases, followed by acute symptomatic causes in 26%. Among patients within the acute symptomatic etiology group, acute metabolic derangements, encephalitis, trauma, stroke, hypoxic ischemic encephalitis, and drug noncompliance accounted for all cases. In this series, idiopathic cases were quite common, representing almost 20% of patients, although the authors included children with idiopathic epilepsy within this group. Indeed, a little over one third of their idiopathic cases presented with status epilepticus without previous history of seizures.

Thus, the vast majority of pediatric status epilepticus events are the consequence of remote symptomatic or acute symptomatic etiologies. However, little has been published on the diagnostic work-up to perform when an etiology is not evident at the time of presentation. Indeed, laboratory, neurophysiologic, and neuroimaging studies to be obtained are usually suggested in an etiology-based manner. For instance, for white matter disease, obtain computed tomography (CT), magnetic resonance imaging (MRI) with diffuse-weighted imaging and diffuse-tensor imaging, and so on. Neuroimaging may be considered for the evaluation of the child with status epilepticus if there are clinical indications or if the etiology is unknown. This approach does not assist the reader in choosing the most effective studies to be performed in specific cases, particularly in those without previous neurological history.

**Uncommon, Potentially Treatable Etiologies**

Numerous reports have been published on rare causes of status epilepticus that are potentially treatable or at least reversible. The classification suggested here pertains to etiologies that cannot be detected with the routine and commonly used approach of obtaining a full blood count, serum chemistry, blood gases, renal and liver function tests, serum antiepileptic drug levels, and toxicology screening. As for head CT or brain MRI, we sought those rare etiologies that may be associated with nonspecific or diffuse findings. The main subgroups of potentially treatable/reversible etiologies are infectious, autoimmune, toxic, metabolic, epileptic, and (rarely) anatomic.

**Infectious**. Viral infection plays a significant role in acute symptomatic (afebrile and febrile) status epilepticus. Human herpes virus 6 appears to be quite common, followed by influenza A, adenovirus, human herpes virus 7, echovirus, mycoplasma, and rotavirus. Respiratory syncytial virus has also occasionally been reported as the cause of status epilepticus in infants with bronchiolitis. The incidence of neurological complications ranges between 1.2% and 1.8% of respiratory cases. However, most patients develop acute encephalopathy and only a minority sustains status epilepticus. Parvovirus B19, even in the absence of the classic skin rash, has also rarely been associated with status in immunocompetent patients. West Nile virus neuroinvasive disease is an uncommon complication in which convulsive seizures commonly occur. Status epilepticus, however, has rarely been reported among patients with active seizures. This complication seems to correlate with a high fatality rate. Mycoplasma pneumonia and Epstein-Barr virus rarely present as encephalitis with prolonged seizures in the absence of respiratory symptoms or the clinical symptomatology of infectious mononucleosis. A group of pediatric patients present with a particularly serious form of status epilepticus in the course of presumed encephalitis, that is, cases in which clinical evidence suggests a viral etiology but no virus is detected in the cerebrospinal fluid. This presentation is associated with a relatively high mortality and, especially, with serious neurological sequelae.

Effective treatment is still lacking for most of these infections. Ganciclovir has not proven efficacious for human herpes virus 6. However, there are anecdotal reports on methylprednisolone pulse therapy promoting resolution of symptoms. Pulse therapy, particularly when administered early in the disease, appears to be beneficial in some cases of influenza encephalopathy. In fact, Japanese specialists have devised a treatment protocol for this complication that includes antiviral agents (oseltamivir), intravenous immunoglobulins, methylprednisolone pulse therapy, antithrombin III, brain cooling, plasmapheresis, and cyclosporine A. Reportedly, the mortality rate of influenza encephalopathy in Japan has declined from 30% to 15% in recent years. Pulse therapy has also been advocated for the rare cases of parvovirus B19 encephalitis in healthy children.

Bacteria can also provoke status epilepticus. Q fever, caused by Coxiella burnetii, usually presents as a flu-like illness and has been reported to cause pediatric status epilepticus as part of the rare complication of encephalitis. It should be suspected in endemic areas or in patients that have been in frequent contact with cattle. Chlamydia psittaci DNA was detected in the cerebrospinal fluid of an adult patient presenting with status. Full recovery followed treatment with doxycycline. Cat-scratch disease encephalopathy is an under-recognized cause in school-aged children and should be suspected in previously healthy individuals with sudden onset encephalopathy or status epilepticus. The outcome is excellent despite a usually stormy clinical course. Central nervous system tuberculosis also occasionally results in convulsive status epilepticus, particularly those with supratentorial tuberculomas.

**Parasites—fungi**. As previously mentioned, cerebral malaria is a major cause of convulsive status epilepticus in endemic areas and should be suspected in children returning from sub-Saharan Africa, tropical Central and
South America, and Asia. A rarely seen condition in the West is chronic cerebral paragonimiasis, caused by the genus *Paragonimus*. Although neuroimaging findings consisting of conglomerate, multiple, ring-shaped enhancements with surrounding edema are quite evident, an index of suspicion is necessary in nonendemic areas to diagnose this condition. Neurocysticercosis is one of the most common causes of epilepsy in older children and adults in tropical countries, often presenting as partial or secondarily generalized status epilepticus. The lesions are readily recognized by heat CT or brain MRI.

Systemic illnesses. This group of diseases mainly includes autoimmune and paraneoplastic illnesses. Status epilepticus as the presenting symptom in a previously undiagnosed patient, albeit uncommon, has mostly been reported in adults. However, several potentially treatable conditions which rarely present in childhood merit mention in this review. Hashimoto encephalopathy, an increasingly recognized complication of Hashimoto thyroiditis, can manifest as epilepsy, occasionally presenting as convulsive status epilepticus leading to its diagnosis. This encephalopathy appears to respond to steroid therapy, hence the importance of its prompt recognition. Systemic lupus erythematosus, though often associated with epilepsy, has occasionally been reported to present with status epilepticus in adults and quite rarely in children. Status epilepticus was the presenting symptom in a previously undiagnosed case of renal artery stenosis. Hemophagocytic lymphohistiocytosis (non-Langerhans cell histiocytosis) was diagnosed in 1 toddler and in a young girl who presented with encephalopathy and status epilepticus weeks to months before developing the classic systemic symptoms of the disease.

Drugs and toxins. As a group, drugs and toxins represent a significant cause of status epilepticus in children. Tricyclic antidepressant overdose was the most common cause of seizures among 25 children in whom poisoning was the proven cause. Status epilepticus was the presenting symptom in 6 cases: 2 due to carbon monoxide (CO) intoxication, and 1 case of each of amitriptyline, acepromazine, isoniazid, and organophosphates. A retrospective review of poison-related seizures from the California Poison Control System evaluated 386 cases of toxin- and drug-related seizures and found that in recent years bupropion, tramadol, and venlafaxine have become a leading cause of drug-related seizures, while amitriptyline, antihistamines, cocaine, and isoniazid continue to be common culprits. Status epilepticus occurred in less than 4% of cases, and no predilection for a specific substance was detected. Thus, although overdose of certain drugs is frequently associated with seizures, no specific substance seems to be more specifically associated with status epilepticus.

Occasionally, commonly used drugs may provoke status epilepticus in therapeutic doses. In 2008, a case of convulsive status was reported in a 9-year-old girl with congenital hemiplegia who presented in convulsive status epilepticus shortly after beginning clonidine therapy for attention deficit hyperactivity disorder. Overdose of certain compounds may result in status epilepticus. Isoniazid is a well-recognized neurotoxic agent that has often been associated with status epilepticus. As this intoxication may be corrected with parenteral pyridoxine, it should be promptly suspected in children with otherwise unexplained status epilepticus. Dimenhydrinate (Dramamine), an over-the-counter medication can also cause convulsive status at high doses. Alcohol abuse is well recognized as a cause of seizures, particularly in adults, occurring in up to 10.8% of cases. Although the incidence of alcohol abuse in children is very low, this diagnostic possibility needs to be considered in teenagers presenting with unexplained status. Cocaine and NDMA (3,4-methylenedioxymethamphetamine, “ecstasy”) have occasionally been associated with status epilepticus in toddlers, especially in the presence of hyperpyrexia secondary to intoxication. Poisonous agents known to produce multiorgan symptoms that include neurological derangement may occasionally manifest as convulsive status epilepticus as the main symptom. These include the fungicide maneb (manganese ethylene-bis-dithiocarbamate), camfor (an antiflatulence substance), neem oil (margosa oil), a traditional component of traditional medications in India, and tetramine, a banned neurotoxic rodenticide from China that usually presents as status epilepticus and has been identified as a cause for this complication in the United States.

Epilepsy. Convulsive status epilepticus occurs frequently in patients with well-established epilepsy. However, status as the initial seizure leading to a diagnosis of epilepsy in an infant or a child with no previous neurological history is relatively rare. In fact, only 2 epilepsy syndromes may present as nonsymptomatic status epilepticus in an otherwise healthy patient: occipital epilepsy of the Panayiotopoulos type and severe myoclonic epilepsy of infancy. Both syndromes show a tendency for status epilepticus recurrence.

Metabolic causes. Pyridoxine-dependent epilepsy usually presents in the neonatal period or occasionally in utero. Seizures are generalized, either tonic-clonic or myoclonic. Nevertheless, pyridoxine-responsive focal status epilepticus has been described. Mitochondrial myopathy,
encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) may present as status epilepticus in patients without previous history of epilepsy. Most reported cases, though rare, belong to adult patients. Nevertheless, the recently described success of L-arginine infusion in shortening the duration of recurrent status epilepticus episodes in an 11-year-old girl merit considering MELAS in the differential diagnosis of potentially treatable causes of status epilepticus.

Status epilepticus was also the presenting symptom in a 16-year-old girl and a 17-year-old boy with Wilson disease. Although psychiatric complaints had been present for several months, the disease was only diagnosed following an episode of generalized convulsive status epilepticus. Among the leukodystrophies, adrenoleukodystrophy may rarely present as status epilepticus. The disease was diagnosed in a 20-month-old boy with status epilepticus followed by cortical blindness. Furthermore, about 9% of adrenoleukodystrophy cases present acutely, including 1% of cases in which status epilepticus is the presenting symptom.

Uncommon, Untreatable Etiologies

Metabolic. Although epilepsy occurs rarely as an isolated symptom in mutations of the mitochondrial polymerase $\gamma$ gene, convulsive status epilepticus can be presenting symptom. Pyrimidine degradation defects, particularly $\beta$-ureidopropionase deficiency, may manifest in infancy as febrile status epilepticus in the presence of developmental delay.

Genetic. Convulsive status epilepticus is a common feature of several chromosomal aberrations, especially the Wolf-Hirschhorn (4p-) syndrome, ring chromosome 14, ring chromosome 20, the monosomy 1p36, and inversion-duplication of chromosome 15. However, no reports on status epilepticus as the presenting symptom leading to diagnosis were found. Other well-recognized syndromes such as Down and Angelman are usually diagnosed before severe epilepsy ensues.

Systemic. Henoch-Schöenlein purpura was diagnosed in a 7-year-old boy admitted with status epilepticus following a 2-week history of headache and abdominal pain.

Conclusion

The aim of this review was to provide the physician with updated information and practical suggestions on the
diagnostic work-up of an otherwise healthy child presenting with cryptogenic status epilepticus. The data presented here pertain to status epilepticus for which the standard diagnostic approach fails to reveal an etiology, in the hope of assisting the physician in seeking rare but diagnosable causes, many of them potentially treatable.

Figures 1 and 2 provide diagnostic flowcharts for febrile and nonfebrile patients. As new reports on rare etiologies will undoubtedly be published in the future, the information provided here will need to be expanded accordingly.

**Figure 2.** Diagnostic flowchart for cryptogenic convulsive status epilepticus (first episode): nonfebrile patient. CO, carbon monoxide; LP, lumbar puncture; SMEI (severe myoclonic epilepsy of infancy).

### References


66. Dorn T, Schaller A, Gallat S, Krämer G. Postmortem diagnosis of POLG mutation in a sibling with fatal status epilepticus. 8th European Congress on Epileptology; September 2008; Berlin.


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