NONCONVULSIVE AND UNUSUAL FORMS OF STATUS EPILEPTICUS

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The recognition, diagnosis, management, and outcome of status epilepticus (SE) can only be described clearly once it is specified exactly what type of SE the patient has. Depending on the type of SE being evaluated, definitions vary; they are usually based on clinical features, often with EEG correlation. SE, like seizures, can be organized into those with a focal onset and those with a generalized onset -- although many generalized cases cannot be separated easily into those of a primarily generalized nature vs. those with a focal onset and secondary generalization. Seizures and SE can also be convulsive or nonconvulsive (Table 1).

Table 1. Different Forms of Status Epilepticus

Convulsive	
Generalized	**Focal**
Generalized convulsive SE (GCSE) Primary generalized GTC Secondarily generalized GCSE (focal onset) Myoclonic [see Table 2.] Tonic (may actually start as focal) Clonic (") Atonic (very rare for SE)	Focal motor SE *Epilepsia partialis continua* (EPC)
Nonconvulsive	
"Classic" absence SE Other primary generalized NCSE [See Table 3.] "Atypical" absence SE "Non-classic" generalized NCSE (often secondarily generalized) ('Electrographic SE," "SE in coma")	Complex partial SE, with prolonged or repeated CP seizures. Other focal SE with non-motor features: e.g. aphasic, sensory

It is important to understand the different clinical syndromes of SE because some SE is associated with morbidity and even mortality, while others types are more benign. Status epilepticus must be recognized and treated quickly, in part for concern that refractory SE may develop and become particularly difficult to treat; there is also concern about long-term sequelae. Nevertheless, "not all status is created equal," and not all forms of SE are equally threatening. The best example is the difference between generalized convulsive status epilepticus (GCSE) and nonconvulsive status epilepticus (NCSE). GCSE warrants aggressive treatment; concern for over-treatment exists, but this is not the first priority. On the other hand, there is very little evidence of lasting harm due to most types of NCSE, and thus the treatment imperative is less, while still not negligible. NCSE has been referred to as "underdiagnosed and overtreated" [1]. In many cases, failure to recognize the NCSE is the greatest clinical problem.

Generalized convulsive status is the best described syndrome and has the greatest morbidity, mortality, and clinical urgency for treatment. Most GCSE, however, has some evidence of a focal onset or focal lesion [2,3]. The simplest example is “acute symptomatic” SE in the setting of a new stroke. **Myoclonic seizures** are often generalized. They occur in benign forms, and in others with a terrible prognosis. Some **NCSE**, such as absence status, is generalized, but some cases of presumed “absence SE” may be secondarily generalized. **Focal SE** has many varied clinical manifestations, depending largely on localization. Focal motor SE is the most readily recognized. Non-motor (i.e. nonconvulsive) forms of focal SE include aphasic, sensory, and autonomic SE. The persistence or recurrence of **complex partial seizures** is probably the most common form of NCSE in adults – at least among those who are not critically ill.

Gastaut defined SE as "an epileptic seizure that is so frequently repeated or so prolonged as to create a fixed and lasting epileptic condition [4].” No precise duration was specified. The International League Against Epilepsy specified "a single epileptic seizure of >30-min duration or a series of epileptic seizures during which function is not regained between ictal events in a 30-minute period” [5]. Although without a definite scientific basis, this 30 minute criterion was the standard in most clinical studies [3]. More recently, most neurologists have followed the proposal by Lowenstein, Bleck, and Macdonald [6] to use an "operational" definition, **at least for GCSE**, of five minutes, i.e. the time by which SE should be interrupted to avoid morbidity, mortality, or refractory SE. This point may also be considered the onset of “impending SE” or a time of urgency to interrupt **GCSE** before dangerous consequences ensue [7]. For other, likely less dangerous, forms of SE, this chapter will retain the 30 minute definition.

I. Myoclonic Status Epilepticus

Myoclonic status epilepticus (MSE) presents with a remarkable variety of causes and in many epilepsy syndromes, although clinical presentations may be very similar from one to the next (Table 2). MSE provides a microcosm of the variety within types of SE.

Status Myoclonicus:

Before describing forms of *definitely epileptic* myoclonic status, it is fair to note that many clinical reports describe continuing myoclonus that *may or may not be epileptic* in origin. This is typically (and probably best) labeled *status myoclonicus,* or sometimes to as *myoclonus status.* It is defined clinically and includes prolonged, continuous, but frequently non-rhythmic, myoclonic jerking, usually of large amplitude, often involving the face, trunk and limbs, but sometimes multifocal or asynchronous. The cause is usually an acute, severe encephalopathy, often anoxia, or metabolic disturbances, particularly renal failure. Most patients are comatose, but not all [8]. The EEG may show widespread slowing indicative of an encephalopathy and have no spikes or sharp waves correlating with the myoclonic jerks. In more severe encephalopathies, there may be a burst suppression pattern or periodic discharges. [EEGs with persistent rapid, rhythmic epileptiform discharges are persuasive for an epileptic origin, in which case the diagnosis is better termed *Myoclonic Status Epilepticus*.] The prognosis in *status myoclonicus* follows the etiology. It is particularly ominous after anoxia but also poor (if somewhat more likely to be reversible) in metabolic encephalopathies and infection [8,9]. After anoxia, it is nearly uniformly fatal, although modest ameliorations of this prognosis have been made with hypothermia [10].

Myoclonic Status Epilepticus:

When myoclonus is epileptic in origin, it also has a variety of causes. They may be divided into epilepsy syndrome-related and symptomatic causes (Table 2). Many symptomatic cases have the same causes as *status myoclonicus*, but in MSE there is more evidence of an epileptic physiology [11]. In MSE, myoclonus may assume a more rhythmic and symmetric pattern of movement, but this is not uniform, even with generalized discharges on the EEG. When the EEG shows evidence of epilepsy, the prognosis still depends on the etiology [11].

Put simply, there are two major (very different) groups of MSE patients: those with MSE related to an epilepsy syndrome, and those with severe encephalopathies (and particularly, anoxic). The first tend to occur in people with epilepsy with a genetic basis, have characteristic EEG findings, are easier to diagnose, and are more likely to respond to anti-seizure drugs (ASDs). The second group’s course usually depends on that of the underlying

illness (and is often dismal); has more varied EEG findings (often more reflective of the severe encephalopathy); and often responds poorly to treatment – especially in the setting of anoxia, where MSE carries an extremely high risk of mortality.

Table 2: Myoclonic Status Epilepticus

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1. Myoclonic SE in Epilepsy Syndromes:

a) -- *"Primary"*(within, often '**benign,' epilepsy syndromes**): in generalized epilepsy syndromes such as absence epilepsy, juvenile myoclonic epilepsy and other myoclonic epilepsies, in which interictal myoclonus is common and MSE infrequent.

b) -- *"Secondary"* in **other epilepsy syndromes**, in which myoclonus is not so prominent an interictal feature, but there is often a severe or progressive encephalopathy:
Severe myoclonic epilepsy of infancy (Dravet's syndrome).
MSE in myoclonic astatic epilepsy, Lennox-Gastaut syndrome.
Epilepsy with myoclonic absences.
Status with negative myoclonus, and brief atonic episodes.

2. "Symptomatic" MSE:

-- i.e, "Symptomatic" of an acute (**non epilepsy syndrome**) neurologic illness, e.g. anoxia, injuries, metabolic and other encephalopathies.

{Summarized by Ohtahara [12]}

When MSE occurs in the setting of prior epilepsy syndromes, the individual syndrome predicts the frequency of SE [13]. There are many forms. Ohtahara describes "primary" and "secondary" epilepsy syndromes that lead to MSE [12] (Table 2). Primary forms are those in which myoclonus is characteristic interictally, such as in childhood and juvenile absence epilepsy, grand mal seizures upon awakening, and juvenile myoclonic epilepsy [14,15]. Often, the myoclonus is correlated with generalized spike and polyspike discharges on the EEG. Occasionally, myoclonus complicates absence SE. Patients with generalized myoclonic epilepsies (such as JME and other, usually genetic-based, 'idiopathic,' epilepsies) may go into MSE after sleep deprivation, when medications are changed [11], or when inappropriate ASDs are used, e.g. carbamazepine (or phenytoin, or oxcarbazepine) in these generalized myoclonic epilepsy syndromes [16,17]. Occasionally, MSE will lead to a generalized convulsion.

MSE may occur in JME upon awakening and, in these cases, may begin with irregular and isolated myoclonus with an accelerating or crescendo pattern ending in MSE. The myoclonus may be localized to one muscle group but is often bilateral, particularly in arm flexor muscles. Consciousness may be (surprisingly) preserved, even with frequent 3 - 6 Hz epileptiform discharges on the EEG and with frequent myoclonic jerks, up to 5/second. There may be prominent eyelid myoclonia. Benzodiazepines are often effective (and rapid) treatment [11], and valproic acid is also valuable [18]. In these primary genetic ('idiopathic') generalized epilepsy syndromes, the EEG is frequently definitive and may show a normal background with frequent generalized spikes and polyspikes interictally. Overall, these epilepsy syndromes lead to MSE relatively seldom, and the episodes of MSE are usually relatively easy to treat.

In the MSE within the "secondary" epilepsy syndromes, myoclonus is not a prominent feature of the baseline epilepsy, and there is often underlying brain dysfunction even interictally. These epilepsies include such (usually infant and pediatric) conditions as Lennox-Gastaut syndrome, where it may be mixed with other forms of SE such as "myoclonic astatic" seizures, and epilepsy with myoclonic absences. The classic case is that of Dravet's syndrome, or severe myoclonic epilepsy in infancy (SMEI), usually due to a *de novo* mutation in the SCN1A (sodium channel) gene. MSE also occurs in some of the progressive myoclonus epilepsies, often involving storage diseases [19]. Clinically, the myoclonic jerks are more often asymmetric and asynchronous and may be of

smaller amplitude than in the 'primary' epilepsy syndromes. Consciousness is more often impaired, but many episodes of MSE occur in children with severe baseline encephalopathies and early life structural or genetic deficits. MSE is relatively rare in these syndromes SE is not rare in the Lennox-Gastaut syndrome, but myoclonus is usually not the dominant feature. In these forms of MSE, the EEG may not show clear spike wave discharges but may show somewhat arrhythmic spikes on a slow background. This MSE is more frequently refractory to ASDs.

Among the 'symptomatic' forms of MSE, anoxia is a common cause [8,11,20], but MSE can be due to metabolic encephalopathies, including renal failure [11]. This MSE may be refractory, but it is the devastation from the underlying severe encephalopathy that is the most worrisome part of the illness.

The outcome of MSE is determined almost entirely by the etiology. In patients with myoclonic epilepsies of childhood, the episodes can remit and the patient return to baseline – but some baselines are normal and others are not. The same applies to patients with storage diseases and progressive illness; the SE may stop, but the underlying disease progresses. Patients with the (genetic) idiopathic generalized myoclonic epilepsies tend to respond to ASDs well and do better than all the others.

The prognosis is worst for patients with MSE due to an acute new illness, and is particularly poor following anoxia [21]. One summary of several papers covering 134 cases of post-anoxic MSE found that 89% died, 8% remained in a vegetative conditions and 3% survived; only two had a good recovery [22]. Anoxic MSE is nearly always fatal -- determined by the anoxia, rather than by the seizures [9]. Benzodiazepines and valproic acid are among medications that can diminish the myoclonic jerking, but they usually do not alter the ultimate outcome. Therapeutic hypothermia appears to improve the outcome for some patients [10].

Often, an EEG can distinguish among different causes of MSE. The genetic, idiopathic, generalized childhood myoclonic epilepsy syndromes often show generalized, frontally predominant, rapid (~ 4 Hz) polyspikes on a normal background; sometimes spikes precede a myoclonic jerk. In the "secondary" epilepsy forms, the spike and wave discharges are often slower (often 2 - 2.5 Hz). Here, and in the symptomatic types, there may be a background encephalopathy on EEG and more prolonged and rhythmic or periodic epileptiform discharges. After anoxia, the EEG background may be nearly flat, also auguring poorly for prognosis.

II. Nonconvulsive Status Epilepticus

Long ago (i.e., in the 1990s), descriptions and classification of nonconvulsive status epilepticus (NCSE) generally divided NCSE into two types: "absence SE" and complex partial SE. The former included all NCSE with generalized spike and slow wave discharges on the EEG. Complex partial status (CPSE) could have focal discharges on the EEG or a clear focal onset clinically and was considered the equivalent of prolonged or repetitive complex partial seizures [23]. This oversimplification is no longer tenable.

It is still reasonable to divide NCSE into those forms resembling CPSE on the one hand, and NCSE with generalized discharges and non-focal clinical manifestations on the other. The latter, however, should be divided further into generalized NCSE occurring in patients with genetic ('idiopathic') primary generalized epilepsies (some of whom really do have absence SE), and the remainder with generalized discharges that are presumably secondarily generalized from a focus. Clinical manifestations of different NCSE syndromes might be very similar to one another, but it is important to differentiate these syndromes because their appropriate treatments and prognoses are usually quite different [24].

A: Absence SE is the classic form of generalized NCSE. "True" absence SE occurs in patients with earlier absence seizures in the idiopathic epilepsy syndromes [13,25]. It may be considered as those cases similar to "status epilepticus in petit mal" described by Schwab in 1953 [26]. Typical absence SE has no features of a focal epilepsy and has rapid (~ 3 Hz), generalized, epileptiform discharges on the EEG. Typical clinical manifestations include confusion, with occasional minimal motor abnormalities such as blinking or myoclonus, with episodes lasting up to days. There may be just a relatively hard-to-diagnose change in responsiveness, with preserved alertness [13]. Medication withdrawal and other precipitants prompt some episodes. Physiologically, absence

seizures and SE may affect frontal cortex more than involving the entire brain, helping to explain the arrest of most motor activity, with maintenance of some limited awareness [27]. Some patients have episodes of absence SE as the primary manifestation of an epilepsy syndrome, with few other discrete, isolated seizures [27].

Most authors have found absolutely no long term morbidity from absence SE or any other idiopathic primary generalized SE [29]. Nevertheless, this conclusion usually rests on clinical impressions in moderate-sized series rather than on actual measurement (e.g. with neuropsychologic testing). Consequences depend on the etiology – in this case, the epilepsy syndrome, which is benign.

Some episodes of absence SE have been reported in older patients with no prior epilepsy ("*de novo* absence SE of late onset"), often in association with withdrawal of benzodiazepines, at times used for anxiety or sleep [30]. Some of the "*de novo*" patients may have had primary generalized epilepsies earlier in life without diagnosis, and others may have been misdiagnosed. It is unclear whether all of these cases are truly "*de novo*."

B: 'Absence' SE in other primary generalized epilepsies: There are several other idiopathic primary generalized epilepsy syndromes that can be manifested clinically as status epilepticus -- described superbly in one review [31] (Table 3). Absence-type SE with very rhythmic generalized EEG discharges occurs in other forms of idiopathic generalized epilepsies, even though those epilepsies are usually manifested by other types of seizures, e.g. myoclonus in juvenile myoclonic epilepsy. Fortunately, episodes of SE are relatively uncommon in these syndromes, and usually relatively easy to interrupt quickly.

Table 3: Status Epilepticus in the Genetic ('Idiopathic') Generalized Epilepsies.

Generalized convulsive tonic clonic SE, especially upon awakening
Myoclonic SE

Nonconvulsive forms:
Typical absence SE
Atypical absence SE
"*De novo*" absence SE
Autonomic SE (perhaps better characterized as regional).

{Adapted from Shorvon and Walker [31]}

C. Atypical absence status epilepticus (AASE) is relatively rare. It occurs primarily in children with cryptogenic and secondarily generalized epilepsy, with multiple seizure types (including tonic and myoclonic seizures), significant background encephalopathies, and substantial developmental delay [32]. Etiologies include LGS and several genetic syndromes associated with significant mental retardation [32].

The clinical manifestation is often a further slowing or reduction in cognitive activity -- from a poor baseline. AASE can go on for days, without any precise onset or ending, and can be very difficult to distinguish from the baseline encephalopathy. Intravenous benzodiazepines may interrupt the EEG discharges without changing behavior substantially.

During seizures and AASE, the EEG usually shows generalized spike or polyspike and slow-wave discharges with a frequency ranging from 1 to 2.5 Hz ("slow-spike-and-wave") with somewhat less rhythmicity and less perfect symmetry than seen in absence seizures [33].
Interictally, there may be generalized spike and sharp waves on a slow background.

AASE appears to involve deeper limbic circuits, correlating with the greater persistent memory and other cognitive problems clinically. In experimental models and in humans, there appears to be more involvement of hippocampal and other limbic structures beyond the primary involvement of thalamocortical circuitry in typical absence SE [34].

D: Complex partial status epilepticus (CPSE) may include an "epileptic twilight state" with a lack of responsiveness or confusion, and bizarre, and particularly fluctuating, behavior [35-39]. At times there are automatisms. Possibly because of the association with vascular disease and prior focal epilepsy, CPSE is often somewhat harder to treat than most primary generalized SE and is more likely to recur [39]. Some cases labeled as “atypical absence SE” may well be complex partial seizures with generalization and prolongation [23,40]. Many patients in NCSE cannot be placed easily into one of these categories.

Outcome of CPSE: Early reports on CPSE included very few patients. Most returned to normal or "baseline cognitive function" [29,37,41], but not all were studied thoroughly with subsequent neuropsychologic tests. In one CPSE series, none of 20 patients had cognitive deterioration, and five had meticulous neuropsychologic assessment [39]. Some reports have found prolonged memory deficits after NCSE [36,38,42]; it is uncertain whether they are permanent. In some cases, both clinical and scan abnormalities can resolve completely over a period as long as a year [41].

E: “Non-classic” and secondarily generalized NCSE: With the advent of continuous EEG monitoring, especially for critically ill patients, there has been a surge in the numbers of patients found with “non-classic” NCSE. The EEG in these patients often shows periodic epileptiform discharges – but not the simple or classic 3 Hz spike and wave discharges characteristic of the primarily generalized epilepsies. Many have secondarily generalized seizures, and many have major metabolic derangement or systemic illnesses or both as precipitants.

Most generalized NCSE in patients without genetic epilepsy syndromes is not truly absence SE. Often, these cases have been called absence SE, but most are presumed secondary from a focus even if generalized at the time of diagnosis and management. This non-classic NCSE may appear identical clinically, and on the EEG, to cases of primary generalized NCSE, and it may be impossible to tell the difference at the time of presentation. Secondarily generalized NCSE is the true diagnosis of most cases described earlier in the literature as “absence SE,” but they have little to do with absence epilepsy. Absence SE in the genetic generalized epilepsy syndromes is relatively uncommon, typically easy to treat, and has a superb prognosis. Non-classic SE and secondarily generalized SE usually has underlying (and often severe) lesions, is much harder to treat, and has the prognosis of the underlying illness.

This non-classic NCSE is sometimes called ‘Electrographic Status Epilepticus’ i.e., patients with ongoing electrographic seizure activity, often following earlier generalized convulsions or GCSE (usually with minimal or no motor convulsive activity) typically in the setting of severe medical illness such as anoxia, sepsis, or severe metabolic derangements, have received many different diagnostic labels. Those with minimal movement after GCSE have been called in “subtle” SE [43]; others are diagnosed as in electrographic status epilepticus (ESE) [44]. Others refer to “status epilepticus in coma,” but not all patients with ongoing electrographic seizures are comatose. [Some refer to these patients with severe medical illness as having "epileptic encephalopathies," indicating that the underlying disease causing the encephalopathy is the key diagnosis, and that the epileptic component is not primary and may not respond to ASDs. This term, however, is probably best reserved for childhood conditions such as Landau-Kleffner syndrome and electrographic status epilepticus in sleep (ESES).]

Such cases of very sick patients with SE on the EEG are not rare. Of 164 patients who had EEGs after apparent control of clinical SE in one series, 42% had continued seizure discharges, and 14% were considered in NCSE [45]. In the VA study of GCSE treatment, 20% of patients whose clinical SE appeared to stop had subsequent evidence of ongoing SE on the EEG [46]. Similarly, 8% of patients with coma of all causes and similar monitoring had NCSE, without clinical signs of seizures [47]. With continuous EEG monitoring for the question of seizures or for coma, another group found that 19% of patients monitored over a six year period had seizures detected by EEG alone; very few had clinical seizures [48]. Also, of 100 acutely ill children monitored prospectively with continuous EEG for at least 24 hours for altered mental status (half of whom had earlier clinical seizures), 46% were found to have seizures (mostly nonconvulsive), and 19% were in SE [49].

Coma, prior epilepsy, age < 18 years, and earlier convulsive seizures were risks for these nonconvulsive seizures, as iwa infection [50,51]. Many of these patients have serious cerebrovascular disease or toxic-metabolic encephalopathies, or both [44,51].

Electrographic status epilepticus (typical SE on the EEG, without obvious clinical manifestations) should generally be considered "true" status rather than “just an encephalopathy with some discharges” -- even if treatment is

unsuccessful in effecting a clinical improvement. The EEGs are very similar to those published in a wide variety of case reports of NCSE. Also, patients with such ESE upon emergence from pentobarbital or midazolam infusion treatment usually go on to have clinically evident seizures [52,53], indicating that ESE is not just an EEG aberration. Finally, some patients with this finding do respond well to ASDs [54].

Making a diagnosis of all types of NCSE traditionally involves the clinical picture of an abnormal mental status with diminished responsiveness, a supportive EEG, and often a response to anti-seizure medication. To diagnose NCSE, Tomson and colleagues required impaired consciousness for an hour and an EEG with continuous seizure activity [23] while Kaplan sought impaired consciousness for 30 to 60 minutes with some form of seizure activity on the EEG [55]. Recently, following the 'operational definition' of SE, 5 minutes has been the standard [although Lowenstein, Bleck and Macdoanld intended this operational definition to apply to GCSE only].
Outcome of other forms of NCSE: Long-term effects of NCSE may include a subsequently increased seizure frequency or worsened cognitive and neuropsychologic function. Most outcome studies are of GCSE, which correlates with worsened seizure control, but this may be attributed to the underlying illness rather than to the episode of SE itself [56].

Reports of NCSE not necessarily specifying generalized or CPSE are more numerous. They show little long-term sequelae [23,57,58], but most had limited follow up. That of Guberman and colleagues had 5 year follow up on eight patients and showed no intellectual, memory, or behavioral deterioration [59]. Scholtes and colleagues evaluated 65 patients and found good outcomes in all but one [60]. When NCSE occurs in the setting of severe medical or neurologic disease, however, morbidity and mortality can be substantial [61]. Little of this morbidity can be attributed to the NCSE itself, but complications of treatment can contribute to morbidity [62,63].
While risks of treatment exist, patients with NCSE should be treated quickly with ASDs for several reasons. They are clearly ill with ongoing seizures and have impaired consciousness and other neurologic deficits that are potentially reversible and certainly treatable. NCSE, like other forms of SE, entails the attendant morbidity of incidental trauma, aspiration pneumonia, etc. Also, many episodes of NCSE begin, and may end, with generalized convulsions, in turn potentially harmful. Finally, there is the possibility that some prolonged episodes might cause lasting damage. NCSE remains an under-diagnosed, treatable condition and one well worth both diagnosing and treating.

For the non-classic NCSE or ESE, the clinical outcome is determined primarily by the etiology. Many cases are caused by anoxia or sepsis with multiple medical problems. These patients are at least as sick as those with evident GCSE, in part because it takes time after the initial insult or deterioration to obtain the EEG. [Patients who improve from SE quickly usually do not need or have EEGs.] Patients with ESE in the setting of serious medical illness have a terrible prognosis, but it is not possible to dissect out that portion of the long-term harm done by epileptiform discharges or NCSE [44,54,64,65] from the damage caused by the underlying illness.

III. Focal Nonconvulsive Status Epilepticus

Types and Causes of Focal Status:

It is very difficult to know the incidence, duration, morbidity, and mortality of simple partial SE because its manifestations are so impressively varied. They range from readily-recognized focal motor seizures to focal sensory and aphasic seizures that are almost certainly markedly underdiagnosed. The ictal symptoms and signs of SPSE reflect the involvement of discrete regions of brain, such as motor, sensory, special sensory, psychic, or autonomic symptoms [66].

There are many causes of focal SE. Focal NCSE can occur after strokes or other acute brain injuries and should be suspected when patients do not recover as expected. Infections (e.g. encephalitis), vasculitis, mass lesions, trauma, multiple sclerosis, developmental abnormalities (such as heterotopias or other migration abnormalities), several autoimmune syndromes, and rarely mitochrondrial or degenerative disorders may also cause focal SE [67-69]. Occasionally, benign idiopathic focal epilepsies lead to SE of the same type [70].

Focal SE may be either simple partial status epilepticus (SPSE) without impairment of consciousness, or complex partial SE, with impaired consciousness. Non-motor (nonconvulsive) forms of focal SE are the topic of interest in this review. They include persistent sensory disturbances (e.g. visual hallucinations) and autonomic, and cognitive deficits, including affective, amnestic, and language disturbances such as aphasia [55].

Outcome: In a large epidemiologic study, SE with focal features had a greater mortality than SE with generalized features [71]. [Still, while generalized SE is usually considered more ominous than focal or complex partial SE, this large database included relatively benign absence and other forms of NCSE in the generalized group, while generalized SE cases included partial-onset seizures with secondary generalization.] Overall, the mortality associated with generalized or focal-onset SE appears similar -- 20-30% [72]. Of course, this depends heavily on exact diagnostic schemes used in determination of partial or generalized SE and whether generalized SE with a partial onset is classified as partial or generalized.

As elsewhere, the morbidity and mortality of focal SE are determined largely by etiology. Cases of SE in Rolandic epilepsy had no mortality or significant morbidity [73]. For simple partial SE *without* motor manifestations, there is no evidence of mortality or long-term morbidity. Four of 47 patients in one large series of simple partial SE died -- all due to strokes [74]. Persistent morbidity occurred in another 10 patients, almost always attributed to the underlying lesion, usually a stroke.

Nonconvulsive SE with focal or regional 'semiology' [signs / deficits] can be very difficult to diagnose, or even suspect – for several reasons. Many cases do not appear to resemble seizures, but rather, appear clinically identical to focal or regional, static (stroke-like) deficits.

1. "Aura continua"

Some simple partial sensory status epilepticus (SPSSE) may be manifested exclusively by sensory symptoms [75], making them very difficult to recognize. These include olfactory hallucinations or other sensations, without motor accompaniment. Some may consist of visceral sensations, or persistent abdominal distress, or nonspecific fear. Some cases may last hours or even days and still have no EEG manifestations [75]. Hallucinations may be of any sensation, including visual, auditory, olfactory, gustatory, somatosensory, or vertiginous perception [76]. Olfactory hallucinations from temporolimbic epilepsy may be the most common. Some SPSSE consists of auditory sensations alone, with epileptiform discharges confined to Heschl's gyrus [77]. Occasionally, benign rolandic epilepsy, which includes speech arrest, drooling, dysphagia, facial weakness, head deviation and mild confusion, may be prolonged enough to constitute NCSE [68,73].

Persistent sensory seizures (without motor accompaniment) have been called "aura continua" [77,78]. SPSSE is the same as a prolonged continuation of an isolated 'aura continua.' Local inhibitory function prevents these seizure from spreading more broadly – although some do so eventually. Pure sensory SPSE is thought to be rare, but this could reflect a detection bias. The EEG may show little during the seizure [66], and the sensation may be attributed to transient ischemia [79] or other nonepileptic causes.

2. "Psychic" status:

Unusually, isolated cognitive deficits such as acalculia, or agraphia, or apraxia may occur as manifestations of NCSE, as can panic attacks and prolonged mood changes, such as depression [80]. Intense emotional states can be epileptic in origin. For example, episodes of intense fear have been reported as the sole manifestation of focal nonconvulsive SE [81]. Sudden bizarre behavior or confusion may be due to prolonged seizures or 'psychic status" (an example will be shown), and a few cases of well-defined psychosis have been diagnosed as definitely due to ongoing seizures [82,83].

3. Dysmnestic status epilepticus:

Following complex partial seizures there may be persistent memory dysfunction, and even more if the episode is complex partial SE [36,38]. There are also (fairly rare) episodes of 'pure' amnesia (with preserved cognitive function in other realms) due to seizures and, if prolonged enough, NCSE [84,85]. This is typically labeled "transient epileptic amnesia (TEA)" [86]. TEA most often occurs in older patients with earlier epilepsy and is often

associated with additional persistent memory deficits. Seizures preferentially affecting memory appear to require involvement of medial temporal structures bilaterally -- as shown by depth electrode recording [87]. In older patients, TEA may be mistaken for (nonepileptic) transient global amnesia. If TEA is prolonged beyond 30 minutes, this constitutes NCSE with amnesia as the sole clinical manifestation [86].

4. Visual phenomena as SPSE:

Occipital seizures and status epilepticus can cause a variety of 'positive' visual sensations, or deficits including transient cortical blindness or visual field loss. This "status epilepticus amauroticus" can be a manifestation of occipital SPSE [88], but the simple and complex visual hallucinations, scotomata, and ictal blindness are usually shorter than 30 minutes in duration [89,90]. Occipital seizures can also include macropsia, micropsia, misperception of spatial orientation, hallucinations of faces or animals, or simple patterns of color and light [89], and seemingly migrainous phenomena [91].

These visual system seizures may produce minimal EEG changes at surface electrodes. Some can be demonstrated by evidence of ictal SPECT hypermetabolism at the time of symptoms [92]. Some similar seizures may be evident with invasive EEG only [93].

Why is focal non-motor NCSE difficult to diagnose?
Reason #1: "Inconvenient Location":
Seizures may be deeper and not evident on surface EEGs.

5. Aphasic status:

The term "aphasic status" should signify a relatively pure aphasia, with preserved responsiveness, without confusion or other cognitive deficits, i.e. a clinical deficit restricted to language dysfunction alone [94-97]. It is a focal or regional NCSE, while complex partial SE implies a disturbance in responsiveness. Careful language testing is necessary to ascertain that the deficit is truly an aphasia [95,98]. Speech arrest alone can result from seizures in many areas. A focal neurologic deficit in speech production may be mistaken for other syndromes such as transient ischemia or psychiatric illness.

The ongoing epileptiform discharges on EEG during aphasic SE may correspond to the cortical area associated with a particular aphasia, e.g. with a left posterior temporal epileptic focus in patients with a Wernicke's-type aphasia [96] and with more frontotemporal discharges during anterior aphasias, in which patients are unable to speak but may retain verbal memory and the ability to respond properly to verbal instructions, i.e. showing evidence of relatively preserved comprehension [80,94]. Nevertheless, there is not always a good correspondence between the classical (usually stroke-defined) region of aphasia and the location of the epileptiform discharges [98]. Aphasic SE may occur in patients with prior epilepsy, but it often occurs in patients with diabetes or old strokes, thus becoming confused with a new stroke or psychosis.

Several recent cases of aphasic status illustrate the difficulty of diagnosis of non-motor focal SE [99]. The manifestations of seizures on the EEG can be fleeting, and not always with good correlation to the clinical manifestations of the aphasia. Prolonged or continuous EEG monitoring may be necessary to make the diagnosis.

6. Parietal syndromes; severe hemispatial neglect:

Parietal NCSE appears to be rare, and very hard to diagnose. Many cases include ictal sensory symptoms of persistent paresthesias and numbness [100]. Some have an origin in the somatosensory area. The "positive" symptom of pain during SPSE appears to be rare, although shorter painful seizures have been reported [76,101]. Other unpleasant epileptic sensory seizures may include nausea, ictal fear, anorexia, poorly described visceral sensations, and the distress of "abdominal epilepsy," the latter more likely from mesial temporal seizures, especially those involving the amygdala [101,102]. There are other very unusual presentations with asomatognosia and an alien hand syndrome, although these appear to involve spread from frontotemporal foci [103].

Some unusual cases of severe hemispatial neglect (mimicking stroke syndromes nearly exactly) will be presented [104]. They also illustrate the point that the EEG may fluctuate even while the clinical deficits of focal NCSE persist -- similar to the cases of aphasic status, above. They help to show that the manifestations and clinical effects of SE may last longer than recordable seizures, and that the correlation between the clinical condition and the electrographic seizure activity is (very) imprecise. A 30 min EEG will diagnose some cases of aphasic SE and NCSE manifested as a severe neglect syndrome, but long-term EEG monitoring is necessary for diagnosis in many -- and for even more patients, for guiding treatment.

Why is focal non-motor NCSE difficult to diagnose?
Reason #2: Status epilepticus fluctuates, clinically and on EEG.
T**he clinical 'semiology' or deficit and the electrographic evidence of seizures may have very different time courses!**

<u>Where to look for new cases of NCSE:</u>

1 Prolonged "postictal state" after generalized convulsions.
2. Diminished alertness post-op or after a neurologic insult.
3. Acute onset of LOC, or fluctuating cognition (including some normal cognition).
4. Impaired mentation + myoclonus or nystagmus.
5. Episodic: staring, aphasia, automatisms, perseveration.
6. Aphasia without a structural lesion.
7. Acutely altered behavior, without other explanation, especially in the elderly. [105]

More:
8. After clinical seizures and SE, when the pt "stopped seizing but isn't waking up."
9. Elderly, with almost any altered mental status, but especially if on benzodiazepines.
10. Post operatively, especially in patients who have had seizures or epilepsy earlier.
11. Strokes: when the patient "looks worse" than the scan!
12. Any patient with fluctuating neurologic deficits.

Conclusions: Status epilepticus occurs in many forms. Just as it is inappropriate to speak of a cause, typical presentation, morbidity, prognosis, or single proper treatment for "epilepsy," so too is it important to consider the many different illnesses composing **"the status epileptici"** in formulating one's understanding of the clinical problem at hand, its implications, and the urgency and appropriate choice of treatment. The field includes many different illnesses, and the prognosis for each depends very heavily on the cause or condition leading to the SE and may also be influenced by age, concomitant medical illness, duration of SE, and almost certainly by the subsequent treatment. Some types of SE have an excellent prognosis, without good evidence of morbidity in any case, whereas others have a very high likelihood of mortality. No case is a trivial one, and almost all benefit from treatment. A more enriched understanding of the variety of status epilepticus should enhance the treatment and outcome for these widely different patients.

<u>Case: What kind of status epilepticus (and epilepsy) is this?</u>

The patient was a 35 yr old R handed man with a long history of seizures that were often difficult to characterize. He reported that they "started at birth" and were due to "anoxia." He had a learning disorder but finished college. He had several psychiatric problems and was abused by one partner. His maternal grandmother and 2 cousins had epilepsy, but he did not know what kind of seizures they had. He reported the following types of seizures:

- "Petit mal" (staring) starting at age 2 years.
- Generalized convulsions, sometimes occurring "every 5 years," sometimes "every day."
- Focal R arm and L leg (simultaneously).
- "Temporal lobe seizures" including kicking, decreased awareness, and progression to generalized convulsions.
- "Psycho" seizures with arm and head jerking, but no loss of consciousness.

He often did well on CBZ, VPA, and ACZ.
At age 28, EEG monitoring of episodes of 'petit mal, psycho" and grand mal seizures showed no EEG changes, but there were "brief generalized electrographic seizures" without clinical correlate.
At age 35, with 'lots of stress' there were staring spells, and reports of more generalized seizures, without loss of consciousness.

He was admitted for EEG monitoring, withdrawal of ASDs, and seizure characterization.

Diagnostic information will be displayed!

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