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SPECIAL REPORT

Recommendation for a definition of acute symptomatic seizure

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Summary

Purpose: To consider the definition of acute symptomatic seizures for epidemiological studies, and to refine the criteria used to distinguish these seizures from unprovoked seizures for specific etiologies.

Methods: Systematic review of the literature and of epidemiologic studies.

Results: An acute symptomatic seizure is defined as a clinical seizure occurring at the time of a systemic insult or in close temporal association with a documented brain insult. Suggestions are made to define acute symptomatic seizures as those events occurring within 1 week of stroke, traumatic brain injury, anoxic encephalopathy, or intracranial surgery; at first identification of subdural hematoma; at the presence of an active central nervous system (CNS) infection; or during an active phase of multiple sclerosis or other autoimmune diseases. In addition, a diagnosis of acute symptomatic seizure should be made in the presence of severe metabolic derangements (documented within 24 h by specific biochemical or hematologic abnormalities), drug or alcohol intoxication and withdrawal, or exposure to well-defined epileptogenic drugs.

Discussion: Acute symptomatic seizures must be distinguished from unprovoked seizures and separately categorized for epidemiologic purposes. These recommendations are based upon the best available data at the time of this report. Systematic studies should be undertaken to better define the associations in question, with special reference to metabolic and toxic insults, for which the time window for the occurrence of an acute symptomatic seizure and the absolute values for toxic and metabolic dysfunction still require a clear identification.

KEY WORDS: Epidemiology, Definition, Acute symptomatic seizure.

Acute symptomatic seizure (also known as reactive seizures, provoked seizures, and situation-related seizures) occur at the time of a systemic insult or in close temporal association with a documented brain insult (Commission on Classification Terminology of the International League Against Epilepsy, 1989; Hauser et al., 1991; Commission on Epidemiology and Prognosis, International League Against Epilepsy, 1993). This definition was created for use in epidemiologic studies. Acute symptomatic seizures are classified as ''situation related seizures'' in the Revised Classification of Epilepsies and Epileptic Syndromes (Commission on Classification and Terminology of the International League Against Epilepsy, 1989), a category also encompassing seizures for which there is no apparent obvious cause. Recently, the International League Against Epilepsy (ILAE) has defined epilepsy as ''a disorder characterized by *an enduring predisposition* to generate epileptic seizures and by neurobiologic, cognitive, psychological and social consequences of this condition. This definition requires the occurrence of *at least one epileptic seizure*'' (Fisher et al., 2005). ''Enduring'' is yet to be defined, but if it includes people with structural brain lesions, the concept would include most seizures traditionally considered acute symptomatic. Because of difficulties in adapting this ILAE definition to epidemiologic studies, the Commission on Epidemiology and Prognosis decided to retain the use of the term acute symptomatic seizures as separate from the unprovoked seizures that define epilepsy. Recent evidence suggests that the prognosis of acute symptomatic seizures differs from that of unprovoked seizures (Hesdorffer et al.,

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2009), further supporting the definition. We aim to provide guidelines for determining the circumstances in which a seizure should be classified as acute symptomatic for epidemiologic studies. Not all potential etiologies are discussed, because some potential causes of acute symptomatic seizures are rare and unlikely to have a major impact upon epidemiologic studies. In addition, we do not address prescribed drugs, although some have known association with acute symptomatic seizures (Ruffmann et al., 2006).

This article results from a meeting held in November 2004 and subsequent teleconferences over the next two and a half years. The commission developed definitions for each category of acute symptomatic seizure to establish guidelines for epidemiologic research. Literature was reviewed by the group and the results of those discussions are reflected herein. The report has been endorsed by the ILAE Executive Committee.

Acute symptomatic seizures differ from epilepsy in several important aspects. First, unlike epilepsy, the proximate cause of these seizures is clearly identifiable to the extent one can ever be certain of a causal association. The close temporal sequence makes causality likely for acute symptomatic seizures in association with conditions such as head injury or stroke, when they immediately precede or are concurrent with the seizure. Biologic plausibility also supports causality, as illustrated by the acute disruption of brain integrity or of metabolic homeostasis in association with the insult. Often a dose effect exists, with more severe injury leading to a higher risk of seizures. Although risk ratios have not been calculated, they are likely enormous. Second, unlike epilepsy, acute symptomatic seizures are not necessarily characterized by a tendency for recurrence, exempting them from the new definition's criteria of enduring predisposition to seize. Although individuals experiencing such insults are sometimes at an increased risk for developing epilepsy in the future, acute symptomatic seizures are unlikely to recur unless the underlying acute causal condition recurs (Hesdorffer et al., 1998). As a corollary, most individuals need not be treated on a long-term basis with antiseizure medication, although such treatment may be warranted on a short-term basis until the acute condition is resolved.

People with epilepsy can also experience an acute symptomatic seizure. Whether they are more likely to have such an episode in association with a specific insult is a point for future study. In our opinion, provoked seizures and situation-related seizures are synonyms for acute symptomatic seizures. Reflex epilepsy and photosensitive epilepsy are distinct entities defined by the response to precipitants. Sleep deprivation has been insufficiently studied as a seizure precipitant in individuals without epilepsy or as a risk factor for seizures in people with epilepsy. Although the criteria for acute symptomatic seizures are somewhat arbitrary, this is a first attempt to codify the levels of risk associated with a broad spectrum of insults.

Few epidemiologic studies report the frequency of acute symptomatic seizures, but when reported, these seizures account for 34% of all afebrile seizures (Hauser et al., 1996). Adding febrile seizures increases this percentage to roughly 55% of all seizures (Hauser et al., 1996). Differences in the proportion of people with acute symptomatic seizures across studies may result from difficulties in their definition. Such seizures are seldom indexed as a diagnosis—rather a diagnosis of the underlying condition is likely to be coded, making studies relying on seizure ICD codes inefficient, with probable gross under enumeration. Furthermore, these individuals are seldom referred for long-term follow-up to neurologists and, given the acute nature of the underlying insult, an electroencephalographic evaluation may not be warranted or appropriate, thus eliminating these sources of case identification. In studies relying on field surveys, a moderate amount of sophistication is necessary to distinguish acute symptomatic seizures from unprovoked seizures. Therefore, although the causation and prognosis of acute symptomatic seizures differ from epilepsy, some epidemiologic studies have included such seizures as ''epilepsy'' (Placencia et al., 1992), or failed to distinguish these from unprovoked seizures (Luhdorf et al., 1986).

Distinction between Unprovoked Seizures and Acute Symptomatic Seizures

This report develops definitions to differentiate acute symptomatic seizures from unprovoked seizures in order to systematically classify cases and determine prognosis.

Definition of acute symptomatic seizures

Acute symptomatic seizures are events, occurring in close temporal relationship with an acute CNS insult, which may be metabolic, toxic, structural, infectious, or due to inflammation. The interval between the insult and the seizure may vary according to the underlying clinical condition (see subsequent text). The term acute symptomatic seizure should be used instead of provoked seizure, reactive seizure, or situation-related seizure.

Definition of unprovoked seizures/epilepsy

Unprovoked seizures are defined as seizures occurring in the absence of a potentially responsible clinical condition or beyond the interval estimated for the occurrence of acute symptomatic seizures. Unprovoked seizures differ from acute symptomatic seizures in risk of seizure recurrence and mortality for several etiologies.

Misclassification of acute symptomatic seizures

Misclassification of acute symptomatic seizures as unprovoked seizures can occur, because the age distribution of incident seizures is similar and acute symptomatic

seizures are almost as frequent as epilepsy (Loiseau et al., 1990; Hauser et al., 1991; Annegers et al., 1995). The challenge is to identify the acute symptomatic seizures and separately define unprovoked seizures, particularly problematic in resource-poor settings, but also difficult elsewhere.

Factors excluded from consideration in this document

We do not consider factors that may induce seizures in people with documented epilepsy, such as sleep deprivation and photic stimulation.

General rules

Seizure in the setting of two causes where one cause would classify the seizure as acute symptomatic

Seizures occurring in the setting of an acute insult associated with events where there is also a remote symptomatic etiology should be classified as acute symptomatic seizure, because it is the more proximate cause. For example, a seizure occurring in association with an acute stroke where there is also an old traumatic brain injury (TBI) should be classified as acute symptomatic due to the acute stroke. If a person has preexisting epilepsy, a seizure that meets criteria for acute symptomatic will still be so classified.

Specific Causes of Acute Symptomatic Seizures

Ideally acute symptomatic seizures related to structural or metabolic changes associated with an acute CNS insult (i.e., stroke or traumatic brain injury) are categorized separately from unprovoked seizures occurring after stabilization. This definition is biologically plausible because acute symptomatic seizures and unprovoked seizures have different prognoses (Hesdorffer et al., 2009). Seizures are considered acute symptomatic if they occur within the first 7 days of cerebrovascular disease (Jennett et al., 1973; Camilo & Goldstein, 2004); TBI, including intracranial surgery (Jennett et al., 1973; Annegers et al., 1998); and CNS infections (Annegers et al., 1988). For TBI, longer intervals are acceptable for subdural hematoma without known trauma when the hematoma is identified. Similarly, seizures in association with arteriovenous malformations are acute symptomatic during the acute hemorrhage. For CNS infections, acute symptomatic seizures can occur beyond 7 days, with persistent clinical or laboratory findings. Acute symptomatic seizures occur in the setting of several infectious diseases: when imaging identifies at least one parasite in the transitional or degenerative phase for neurocysticercosis, when malaria is accompanied by fever, during treatment of cerebral tuberculoma and brain abscess, and during acute infection or severe metabolic disturbance in HIV infection. In multiple sclerosis, acute symptomatic seizures occur as the first presenting symptom or within 7 days of relapse. Such seizures also occur in autoimmune diseases when signs or symptoms of activation are noted. All seizures occurring with congenital toxoplasmosis and with Creutzfeldt-Jacob disease are remote symptomatic, and those occurring in degenerative diseases of the elderly are progressive symptomatic.

Acute symptomatic seizures in association with metabolic, toxic, and other systemic illness

Metabolic conditions that provoke seizures: Alterations of metabolic homeostasis are associated with seizures in many situations. Our approach to cutoffs for metabolic abnormalities has been to favor specificity over sensitivity, thus reducing the false positives (those whose seizures were really not due to the metabolic disturbance). The propensity of metabolic disturbances to cause seizures may depend on the rapidity with which the disturbance develops: the more rapid the more likely it is to induce seizures (Riggs, 2002). The blood sample upon which classification is based should reflect the time of the seizure, operationally within 24 h of the seizure, so that it is logical to assume that the findings are similar to those at the time of the seizure.

In a literature search of studies of metabolic disorders and seizures or status epilepticus, only case studies were found, and in these the biochemical abnormalities were mostly reported as group means with standard deviations. In the absence of clear data on cutoffs, we have provided cutoffs at the extreme end of abnormalities until future studies provide better information (Table 1). The cutoffs are arbitrary and are only supported to some extent by the literature (Riggs, 2002; Castilla-Guerra et al., 2006; Posner et al., 2007). When there is suspicion that the seizure may be acute symptomatic due to a metabolic derangement but the proposed cutoffs are not met, seizures should not be classified as acute symptomatic. This does not mean that they should be classified as unprovoked. Instead, they will likely be placed into an ''unknown'' category, but excluded as epilepsy. Better cutoffs will require specific studies in the future.

Cerebral hypoxia

Similar to cerebrovascular disease, seizures occurring within 1 week of anoxic encephalopathy should be classified as acute symptomatic, until further information is available.

Seizures associated with drugs and toxic substances

Alcohol

Alcohol and drug withdrawal and alcohol intoxication.
The following are considered appropriate indicators of acute symptomatic seizures associated with alcohol withdrawal: history of chronic alcohol abuse, history of current alcohol use with recent reduction in consumption, and generalized tonic–clonic seizure with other symptoms of withdrawal such as tremors, sweats, or tachycardia. The seizure must occur within 7–48 h of the last drink. If there is a history of

Table 1. Proposed cutoff values for acute symptomatic seizures in common metabolic disorders

Biochemical parameter	Value
Serum glucose	<36 mg/dl (2.0 mM) or >450 mg/dl (25 mM) associated with ketoacidosis (whether or not there is long-standing diabetes)
Serum sodium	<115 mg/dl (<5 mM)
Serum calcium	<5.0 mg/dl (<1.2 mM)
Serum magnesium	<0.8 mg/dl (<0.3 mM)
Urea nitrogen	<100 mg/dl (>35.7 mM)
Creatinine	>10.0 mg/dl (>884 μM)

recent alcohol abuse without a known history of chronic alcohol abuse, then clinical judgment should determine whether the seizure was due to alcohol withdrawal. Seizures in the setting of acute alcohol intoxication (Hillbom et al., 2003; Brathen et al., 2005) (due to extremely high quantities consumed) are likely associated with that exposure. Acute symptomatic seizures also occur with withdrawal of barbiturates and of benzodiazepines.

Illicit drugs

Seizures are considered acute symptomatic based upon the probability of seizure occurrence for specific drugs. There is high probability for cocaine and crack if metabolites are found in urine or blood; Normeperidine; meperidine; Methaqualone; Glutarimide; stimulants (e.g., methylenedioxymethamphetamine) taken in excess; and inhalants. There is fair probability for hallucinogens; angel dust (PCP, Phencyclidine) (phencyclidine and quatadine). There is low or no probability for heroin and for marijuana.

Seizures associated with febrile illness

Febrile seizures in children are well described, although the temperature for inclusion varies. We suggest that the minimum rectal temperature be 38.5°C (101.0°F) (Berg et al., 1992), which may be modified if fever reduction is attempted using antipyretic drugs or other measures. Although first febrile seizures are rare after the age of 5, epidemiologic data suggest that there should not be an upper age limit for the occurrence of febrile seizures in childhood.

Future Activities

The preceding criteria are guidelines for the classification of seizures as acute symptomatic. Each recommendation is based upon the best available data at the time of this report. It is suggested that systematic studies be undertaken to better define each of the associations in question. For neurologic insults, further definition of timing of seizures in relation to the acute event is necessary, and further refinement may be possible after taking into account clinical factors associated with neurologic insults (i.e., severity of trauma for head injury; area of the lesion for cerebrovascular disease). For metabolic and toxic insults, further work is needed to clarify the time window in which an acute symptomatic seizure can occur as well as the absolute values for metabolic and toxic dysfunction. Additional work is also needed to further understand the prognosis of this subgroup of seizures.

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The authors confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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