Seizures and Epilepsy After Ischemic Stroke

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Background—Although a long-recognized clinical phenomenon, there remain many questions regarding the epidemiology of seizures and epilepsy after ischemic stroke, their effect on outcome, and their treatment.

Summary of Review—Interpretation of the various studies that have been conducted of postischemic stroke seizures and epilepsy are complicated by their heterogeneous designs, inconsistent uses of terminology, small sample sizes, different periods of follow-up, and ambiguities in seizure identification and classification. Estimates of the rate of early postischemic stroke seizures range from 2% to 33%. The rates of late seizures vary from 3% to 67%. The rate of postischemic stroke epilepsy is ≈2% to 4% and is higher in those who have a late seizure. Data reflecting seizure subtypes are limited. Aside from cortical location and, possibly, stroke severity, no other risk factors for postischemic stroke seizures have been consistently demonstrated. Results regarding the impact of postischemic stroke seizures on outcome are inconsistent.

Conclusions—Much additional work is needed to better understand the epidemiology and social impact of postischemic stroke seizures and epilepsy, their prevention, and optimal management. **(*Stroke*. 2004;35:1769-1775.)**

Key Words: epilepsy ■ ischemia ■ seizures ■ stroke

Despite being first described more than a century ago,[1] many questions regarding poststroke seizures and epilepsy remain. The numerous studies that have been conducted often provide differing results because of their heterogeneous designs, inconsistent uses of terminology, small sample sizes, different periods of follow-up, and ambiguities in seizure identification and classification.

Studies included in this review were identified through a MEDLINE search incorporating the terms SEIZURES, or EPILEPSY and STROKE. Any English-language study published from November 1971 to September 2003 with an identifiable group or subgroup of patients providing data relevant to the epidemiology and predictors of postischemic stroke seizures, their effect on outcome, and their treatment were considered. The bibliographies of selected articles were also examined, and the results of any additional relevant studies were incorporated into the present review.

Pathophysiology

Poststroke seizures can occur soon after the onset of ischemia or can be delayed. Many clinical studies make a distinction between early and late seizures based on differences in their presumed pathophysiology. Early poststroke seizures are thought to result from cellular biochemical dysfunction leading to electrically irritable tissue.[2,3] Acute ischemia leads to increased extracellular concentrations of glutamate, an excitatory neurotransmitter that has been associated with secondary neuronal injury.[2,4] Recurrent epileptiform-type neuronal discharges can occur in neural networks of surviving neurons exposed to glutamate.[5] In addition, transient peri-infarct depolarizations have been observed in the penumbra after experimental occlusion of the middle cerebral artery.[6,7] Other investigators failed to confirm this phenomenon in humans.[8] There is a correlation between the number and the total duration of depolarizing events and infarct volume in the setting of ischemia,[9] perhaps due to reductions in capillary perfusion leading to more profound ischemia in penumbral tissue.[10] Experimental data also suggest that epileptogenesis is enhanced by hyperglycemia at the time of ischemia.[11]

In contrast to early-onset seizures, late-onset seizures are thought to be caused by gliosis and the development of a meningocerebral cicatrix.[12] Changes in membrane properties, deafferentation, selective neuronal loss, and collateral sprouting may result in hyperexcitability and neuronal synchrony sufficient to cause seizures.[13,14] Pronounced neocortical neuronal hyperexcitability was found in primary somatosensory neurons of rats 10 to 17 months after transient forebrain ischemia.[13,15,16]

Experimental studies in laboratory animals suggest that repeated seizure-like activity in the setting of cerebral ischemia significantly increases infarct size and can impair functional recovery, an effect that can be ameliorated with the administration of certain neuroprotective agents.[17–19] Although frequent repeated seizures are undoubtedly harmful, it is not entirely clear that infrequent seizures worsen the outcome after experimental brain injury.[20] In fact, isolated

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TABLE 1. Frequency of Seizures After Ischemic Stroke

	Type	Early Seizures	Late Seizures	Epilepsy
Lamy et al (2003)	P*	≤1 wk; 2.4% (14/550)	>1 wk; 3.4% (20/550)	2% (11/ 550) 55% (11/20) for patients with late seizures only
Arboix et al (2003)	P	≤48 h; 2.2% (18/452)	—	—
Labovitz et al (2001)	P†	≤1 wk; 3.1% (22/704)	—	—
Bladin et al (2000)	P†	≤2 wk; 4.8% (78/1632)	>2wk; 3.8% (62/1632)	2% (34/1632) 55% (34/62) for patients with late seizures
Burn et al (1997)	P†	≤24 h; 2% (10/545)	>24 h; 3% (17/545)	3% (18/545)
So et al (1996)	R	≤1 wk; 6% (33/535)	>1 wk; 5% (27/436)	4% (18/436)
Giroud (1994)	P†	≤15 d; ‡4.4% (36/814) §16.6% (21/126)	—	—
Lancman et al (1993)	P†	≤30 d; 3.8% (7/183)	>30 d; 3.2% (6/183)	—
Kilpatrick et al (1990)	P†	≤2 wk; 6.5% (24/370)	—	—
Gupta et al (1988)	R	≤2 wk; 33% (30/90)	>2 wk; 67% (60/90)	>2 wk; 39% (35/90)

*Early seizures were studied retrospectively and recurrent seizures prospectively, and included only cryptogenic infarction in young patients.
†Study included ischemic and hemorrhagic strokes, and ischemic stroke analyzed separately.
‡Atherothrombotic.
§Embolic.
P indicates prospective; R, retrospective; —, not analyzed.

seizures after experimental cortical contusion were found to accelerate behavioral recovery in rats.[21]

Other laboratory animal studies indicate that some antiepileptic drugs may impair recovery after stroke or other forms of focal brain injury.[22] Phenytoin, when given alone or in combination with an intracortical infusion of γ-aminobutyric acid (GABA), delays recovery of motor function after focal brain injury.[23] Phenobarbital and benzodiazepines may also retard the recovery process.[24,25] In contrast, there has been no demonstrable affect of carbamazepine on postbrain injury recovery.[26] Whether or not similar detrimental effects seen with certain anticonvulsants in laboratory animals also occur in humans recovering from stroke is discussed below.

Epidemiology

Studies of the epidemiology of postischemic stroke seizures and epilepsy have had somewhat varied results (Table 1). In general, these studies separate early from late seizures based on their differing presumed pathophysiologies. In a large epidemiological project, cerebrovascular diseases represented the most commonly identified etiology of secondary epilepsy (11%).[27] Stroke accounts for 30% of newly diagnosed seizures in patients >60 years old.[28,29] There was a 2% rate of poststroke epilepsy over a median of 9 months in one study[30] and a 4% rate over a median of 2 years in another.[31] In the Oxfordshire Community Stroke Project, the cumulative actuarial risk of having a seizure after ischemic stroke was 4.2% (95% CI, 2.2 to 6.2) at 1 year and 9.7% at 5 years (95% CI, 3.7 to 15.7).[31] The true rates of early and late-developing seizures are uncertain because of a lack of uniform definitions (Table 1). Early seizures have been defined as those first occurring within 24 to 48 hours,[31–33] 1 week,[34–36] 2 weeks,[30,37–42] or 1 month.[43] Late seizures have most commonly been described as occurring at least 2 weeks after stroke.[30,38,40,41,44,45] Depending on these definitions, the frequency of early postischemic seizures in the largest studies range from 2% to 33%,[30–32,34–36,40,41,44] with 50% to 78% occurring within the first 24 hours after stroke.[30,31,34] The frequency of late postischemic stroke seizures varies from 3% to 67%.[30–32,34–36,40,44]

The overall rate of postischemic stroke epilepsy is approximately 2% to 4% (Table 1). Early postischemic stroke seizures can be an independent risk factor for the subsequent development of late and recurrent seizures (Table 2).[34,36] One population-based study found that patients with early postischemic seizures were nearly 8 times (95% CI, 2.8 to 21.7) more likely to develop late postischemic seizures, and approximately 16 times (95% CI, 5.5 to 49.2) more likely to develop epilepsy as compared with patients without early seizures.[34] The cumulative probability of late postischemic stroke seizures increased from 3.0% during the first year to 7.4% by 5 years after an early postischemic seizure.[34] Among the 5% of patients with initial late seizures available for follow-up, 66% (3.3% of the initial cohort) developed epilepsy by 4.5 years.[34] Other studies have also suggested that late seizures are an independent risk factor for the development of postischemic stroke epilepsy (Table 2). A prospective study found seizure recurrences in 55% (34 of 62) of patients with late postischemic seizures,[30] similar to that observed in other studies with longer follow up periods[31,34] and higher than that reported for the general population experiencing a first unprovoked seizure.[46] Multivariate analysis has also shown that late-onset (>2 weeks) postischemic seizures are an independent risk factor for epilepsy (hazard ratio [HR] 12.37; 95% CI, 4.74 to 32.32; $P<0.001$).[30] These types of epidemiological studies can be confounded by the use (or lack of use) of anticonvulsant drugs.[27,38,39,44] One retrospective study found that 86% of patients having recurrent seizures were either not taking their seizure medications or had subtherapeutic blood levels.[44]

Data regarding seizure subtype (ie, simple partial, partial complex, partial with secondary generalization, or general-

TABLE 2. Independent Predictors of Early Seizures, Late Seizures, and Epilepsy After Ischemic Stroke

			Independent Predictors*		
	Type	N	Early Seizures	Late Seizures	Epilepsy
Lamy et al (2003)	P†	581	Cortical location, stroke severity	Large infarct, cortical signs, early seizures	Late seizures
Labovitz et al (2001)	P‡	704§	Lobar location	—	—
Bladin et al (2000)	P‡	1632§	Cortical location, stroke severity¶		Late seizures
Reith et al (1997)	P‡	900§	Stroke severity	—	—
Arboix et al (1997)	P‡	1012§	Cortical location	—	—
Burn et al (1997)	P‡	545§	Cortical location	NS	NS
So et al (1996)	P	535	Cortical location	Early seizures, stroke recurrence	Early seizures, stroke recurrence
Lo et al (1994)	R	696§	Cortical location	—	—
Giroud et al (1994)	P‡	1213§	Loss of consciousness	—	—
Gupta et al (1988)	R	90	Lesion size	NS	Cortical–subcortical location

*Independent predictors based on multivariable analysis for ischemic stroke.

†Early seizures were studied retrospectively and recurrent seizures prospectively, and included only cryptogenic infarction in young patients.

‡Study included ischemic and hemorrhagic strokes, and ischemic stroke analyzed separately.

§Data (N) reflects ischemic stroke only.

¶Early and late seizures were not analyzed separately.

P indicates prospective; R, Retrospective; —, not analyzed; NS, no significant association found.

ized) in studies of postischemic stroke seizures are limited by the retrospective design of the majority of the studies and are potentially confounded by interviewer and recall bias related to obtaining seizure descriptions from patients or observers. Up to 63% of seizures may not be recognized by patients.[47] Therefore, it is not surprising that different studies find different frequencies of seizure subtypes after stroke. Approximately 50% to 90% of early onset seizures appear to be simple partial seizures.[30,36,40,48] In contrast, 1 study reported a higher frequency (50%) of generalized tonic-clonic seizures without focal onset in patients with early-onset seizures.[49] Partial complex seizures are likely under-represented in these studies, as only 15% of those with partial seizures are aware of their spells.[47]

Generalized status epilepticus can be a life-threatening complication of acute ischemic stroke. Stroke may account for 25% of cases of status epilepticus in some series.[50] A single institution study found that 17 of 1174 patients with ischemic or hemorrhagic strokes (0.14%) developed status epilepticus, but the study did not provide data to permit calculation of subtype-specific rates.[51] A second single institution study reported that 22 of 2742 patients with ischemic stroke (0.8%) had status epilepticus (0.1% within the first 14 days).[52] This compares with a 0.9% rate from a population-based study.[35] Therefore, it appears that <1% of patients with ischemic stroke develop status epilepticus.

Risk Factors

Ischemic stroke subtype, stroke location, and stroke severity have been considered as possible predictors of seizure development (Table 2).

Stroke Subtype

Results of clinical and autopsy studies have suggested that seizures are more common with cardioembolic infarction than other types of ischemic stroke.[34,38,48,53–57] The results of other studies cast doubt about such an association.[58–60] Early studies suggesting a relationship between embolism and seizures were observational, often included small samples of patients, and were performed before modern neuroimaging and echocardiographic techniques became available.[34,53–56] In the Seizures After Stroke Study (SASS), the largest prospective, multicenter study conducted to date, patients who had a probable cardioembolic stroke were not at elevated risk of a first seizure (HR, 1.00; 95% CI, 0.67 to 1.50; $P=0.99$) or recurrent seizures (HR, 0.68; 95% CI, 0.31 to 1.48; $P=0.33$).[30] None of the 137 patients with presumed embolism had seizures in the Lausanne Stroke Registry.[59] Similarly, there was no association between seizure at onset and the presence of a cardiac source of embolism in the National Institute of Neurological Disorders and Stroke (NINDS) Stroke Data Bank study.[60] Therefore, clinical data showing a clear relationship between cardiogenic embolism and seizures are lacking (Table 2).

Available studies report a low frequency (1.8% to 3.7%) of seizures associated with transient ischemic attack (TIA).[40,61] However, distinguishing a TIA from a focal seizure can sometimes be difficult. This is particularly true in cases of so-called limb-shaking TIAs. Described over a 1 decade ago,[62,63] numerous cases have since been recognized.[61,64–67] Limb-shaking TIAs are thought to result from focal cerebral hypoperfusion due to carotid artery occlusive disease.[61–67] Because of diagnostic uncertainty, the true frequency of seizures associated with TIA remains uncertain.

Stroke Location

Cortical location is the best-characterized risk factor for early seizures after ischemic stroke and is supported by studies with widely differing designs (Table 2); these results have been repeated in numerous studies.* It was a significant risk factor in the multivariate analysis of data from the SASS study (HR, 2.09; 95% CI, 1.19 to 3.68; $P<0.01$).[30] A

*References 30,31,34,36,38,40,41,43,48,51,52.

TABLE 3. Effect of Postischemic Seizures On Outcome

			Mortality		Functional Outcome	
	Type	Seizure Type	Univariate	Multivariate	Univariate	Multivariate
Arboix et al (2003)	P	ES	Increased (in-hospital)	Increased (in-hospital)	—	—
Vernino et al (2003)	R	†	Increased	Increased	—	—
Labovitz et al (2001)	P*	ES	Increased (48 h)	NS (48 h)‡¶	—	—
Bladin et al (2000)	P*	ES, LS, RS	Increased (30 d/y)	—	Worsened (30 d/y)	—
Bogousslavsky et al (1992)	R	LS	—	—	Worsened	—

*Study included ischemic and hemorrhagic strokes, and ischemic stroke analyzed separately.
†Seizures were not classified by time of onset.
‡After adjustment for stroke severity.
¶Multivariate analysis did include stroke subtype.
P indicates prospective; R, retrospective; —, not analyzed; NS, no significant association found; ES, early seizures; LS, late seizures; RS, recurrent seizures.

relationship between cortical involvement and postischemic seizures was not found in a community-based prospective study[42] or in one small retrospective study,[44] in which only a minority of patients had confirmatory neuroimaging studies.

Although seizures seem to be more common after strokes with cortical involvement, they may also occur in the setting of subcortical ischemic stroke, a possible consequence of a substantial release of glutamate from axonal terminals arising from injured thalamocortical neurons.[68] For example, 1 retrospective study reported seizures in 3.5% of patients with lacunar stroke.[69] In SASS, seizures were reported in 8 (2.6%) of 307 patients with a diagnosis of lacunar infarction.[30] However, CT scanning was normal in the majority of these patients, and brain MRI was not performed; therefore, the possibility of cortical involvement cannot be completely excluded.

Results of EEG and functional neuroimaging studies seem to support the concept that seizures in the setting of apparent lacunar stroke may be a reflection of concurrent cortical involvement. Early studies found abnormal EEGs in 22% to 38% of patients with lacunar infarction.[70,71] A population-based study also found lateralized EEG abnormalities in the subgroup of lacunar stroke patients with early seizures.[48] Consistent with this observation, a small study using quantitative EEG analysis also reported lateralized abnormalities in 83% of patients with lacunar infarctions.[72] The small subgroup of patients with lacunar infarcts in SASS showed evidence of cortical dysfunction on Single Photon Emission CT and had lateralized EEG abnormalities even when the routine CT scan was normal.[30]

Stroke Severity

Both a population-based[42] and a prospective multicenter study reported that stroke severity was independently associated with the development of seizures after ischemic stroke (HR, 10; 95% CI, 1.16 to 3.82; $P<0.02$).[30] Multivariable analysis in a subsequent study found that after adjusting for stroke location and subtype, stroke severity was no longer associated with early postischemic seizures.[35] Stroke extent, as measured by CT scan, was not independently associated with the development of seizures in the SAAS.[30] Therefore, the independent affect of stroke severity as measured either clinically, or based on radiographic studies remains uncertain (Table 2).

Impact of Poststroke Seizures on Outcome

Stroke severity is the most important determinant of outcome in stroke patients. Whether or not seizures per se worsen the outcome of ischemic stroke is uncertain (Table 3). It is plausible that early seizures in penumbral areas might be harmful because of the additional metabolic stress they may cause in already vulnerable tissue.[42] Clinical studies exploring the relationship between poststroke seizures and outcome often do not account for important covariates or do not use validated stroke outcome scales. At least 1 prospective cohort study found a higher mortality at 48 hours among patients with early seizures (30.8%) versus those without early seizures (7.4%; $P<0.01$).[33] The effects of stroke severity and location were not controlled. Further, the difference in mortality rates was no longer significant at hospital discharge or at follow-up after 27 months. In a large prospective study, univariate and multivariate analyses found that early postischemic seizures were associated with increased in-hospital mortality.[49] Nonetheless, after accounting for stroke severity, population-based studies have not found an association between early postischemic seizures and mortality.[35,42] In contrast, the SASS investigators found higher mortality rates among stroke patients with seizures after 30 days and 1 year.[30] Those with postischemic seizures also had a significantly poorer neurological score during the acute hospitalization and worse Rankin scores at follow-up (median 9 months). More recently, a large population-based study found that new onset postischemic seizures were independent predictors of mortality; unfortunately, the impact of early- and late-occurring seizures was not analyzed separately.[73] None of the available studies include a multivariable analysis of the effect of early or late seizures on functional outcome after ischemic stroke (Table 3).

The impact of late postischemic stroke seizures on outcome is similarly unclear. Worsening of stroke sequelae after delayed postischemic seizures was reported in a small cohort study.[74] In addition to other methodological limitations, functional status was tested immediately after the seizures and, therefore, could not account for postictal states or ongoing subclinical seizures. A large prospective observa-

tional study with a 1-year follow-up found no effect of late seizures on rehabilitation outcome as measured by the Barthel Index or the River–Mead Mobility Index.[75] Although epilepsy significantly affects health-related quality of life (QOL),[76] the additional impact of postischemic seizures on poststroke QOL has not been firmly established.

Although mortality rates in stroke patients with status epilepticus can be high,[52] data reflecting the independent affect of postischemic status epilepticus on outcome is limited because it is confounded by other factors related to the stroke, particularly stroke severity. The numbers of patients with generalized as compared with partial-status epilepticus is small and often not specifically analyzed. An epidemiological study had too few cases to draw any conclusions,[35] and another study found no independent relationship between the occurrence of status eplilepticus and mortality rate.[51] In contrast, a prospective study reported an almost 3-fold increase in mortality among patients with acute ischemic stroke and generalized convulsive status epilepticus as compared with patients with acute ischemic stroke alone (39% versus 14%, $P<0.001$).[77] Whether or not nonconvulsive status epilepticus affects outcome after ischemic stroke is largely unknown.

Treatment

The dilemmas facing the clinician are whether to treat an isolated seizure and what antiepileptic drug (AED) to use in patients who have had single or recurrent seizures. Unfortunately, studies addressing these questions generally do not distinguish between the treatment of early and late seizures, do not include seizure recurrence or epilepsy as an end point, and do not provide data regarding dosages or patient compliance.[31,33,34,36,37,40] Observational studies with small numbers of patients suggest that an isolated early seizure after cerebral infarction does not require treatment or can be easily controlled with a single drug.[33,40,57] A prospective cohort study of gabapentin monotheraphy in patients with a first, late poststroke seizure (67% were patients with postcerebral infarction epilepsy) found that 81% had excellent seizure control with no seizure recurrence after 30 months.[78] Because there was no control group, whether this result is better than would have occurred without treatment, or with treatment with an alternative AED, cannot be assessed. One study reported at least 1 seizure relapse in 50% of patients who received antiepileptic treatment after a first seizure during a follow-up period of 47 months.[27] However, beginning treatment after the first early poststroke seizure has not been associated with a reduction of recurrent seizures after discontinuing the medication.[79]

Patients who develop recurrent early or late postischemic stroke seizures generally require pharmacological treatment. An observational hospital-based study and a prospective cohort study showed that 54% and 67% of patients with cerebral infarction and epilepsy were seizure-free for at least 1 year with the majority of patients being treated with a single drug.[80,81]

As demonstrated in laboratory animal studies of focal and global ischemia, antiepileptic drugs may also act as neuroprotectants.[82] For example, phenytoin,[83] benzodiazepines,[84] lamotrigine,[85–88] topiramate,[89–91] levetiracetam,[92] and zonisamide[93] have neuroprotective properties and might, therefore, have beneficial effects when used to treat seizures in the setting of hyperacute stroke. However, there remain no clinical data proving this to be true, and the comparative risks and benefits of the different antiepileptic drugs have not been well studied in stroke patients. There remain no data showing that administration of anticonvulsant drugs after stroke, or other acute brain injuries, prevents the later development of epilepsy.[94]

Based on experimental studies, there is some concern that the use of phenytoin, phenobarbital, and benzodiazepines may impair poststroke recovery. Relevant clinical data are limited. A retrospective cohort study compared the motor recoveries of stroke patients who received 1 or a combination of theoretically detrimental drugs, including benzodiazepines and phenytoin, with the recoveries of a similar group of patients who were not given any of these medications.[95] Those who received these drugs had poorer recoveries than controls. Multivariable analysis indicated that the effect remained even after controlling for the contributions of other factors, including the initial severity of the patients' stroke-related neurological deficits. The potential deleterious effect of this group of drugs on motor recovery was also found in a separate cohort of patients who were control subjects in a prospective acute interventional stroke trial.[96] Multivariable analysis again found that the drug group had a negative effect on outcome, independent of the degree of the initial motor impairment, comorbid conditions, and other patient characteristics. Because both studies involved retrospective analyses, it cannot be certain that the reason for the administration of a given drug rather than the drug itself influenced recovery. The impact of the individual drugs could not be determined because of sample size limitations, nor were analyses of dose or timing effects possible. However, these clinical studies are consistent with laboratory experiments and suggest that phenytoin, phenobarbital and benzodiazepines be avoided during the poststroke recovery period if possible.

Unanswered Questions

This review points to several important questions regarding seizures after ischemic stroke that need to be addressed in future research. Current understanding of the pathophysiology, epidemiology, risk factors, and treatment of poststroke seizures remains incomplete. Better definition of factors placing patients at very high risk for the development of postischemic stroke epilepsy might help identify a population that could benefit from therapies aimed at reducing epileptogenesis. Data regarding the relative effects of the various anticonvulsants on clinical outcome when given during the acute and recovery periods would help physicians make more rational drug treatment choices.

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