Poststroke Seizures and Epilepsy: Clinical Studies and Animal Models

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Poststroke seizures and epilepsy have been described in numerous clinical studies for many years. Most studies are retrospective in design, include relatively small numbers of patients, have limited periods of follow-up, and report a diversity of findings. Well-designed clinical trials and population studies in the recent past addressed several critical clinical issues and generated important findings regarding the occurrence of poststroke seizures and epilepsy. In contrast, the pathophysiologic events of injured brain that establish poststroke epileptogenesis are not well understood, and animal modeling has had limited development. Reviews of several important clinical studies and animal models that hold promise for a better understanding of poststroke epileptogenesis are presented.

Introduction

Detailed review articles have examined the epidemiology, risk factors, pathophysiology, clinical manifestations, and associated management issues of poststroke seizures and epilepsy (1–3) and the special circumstances of their occurrence in the elderly (4–6). These reviews are challenged with analyzing diverse sets of clinical data that include differences in terminology and definitions; variable inclusion of stroke occurring in cerebrum, cerebellum, and brainstem; ischemic and hemorrhagic strokes; subarachnoid hemorrhage; transient ischemic attacks; patients with a history of seizures or epilepsy; and different periods of patient follow-up. Most studies have been retrospective, include small numbers of patients, and have limited periods of follow-up. In contrast, relatively few studies have had a prospective design to include large numbers of patients with extended follow-up. Results from well-designed clinical trials and population studies have advanced our understanding of poststroke seizures and epilepsy by resolving many of the inconsistent or ambiguous findings reported from numerous studies in the past. Findings of several important studies are highlighted.

Terminology and Definitions

Seizures associated with stroke have been described and studied according to their temporal relation with the onset of stroke. Seizures have been classified as occurring immediately before, immediately after (within 24 h), or of early or late onset. Early-onset seizures are considered to be provoked seizures (i.e., occurring shortly after the stroke and caused by the acute metabolic and physiologic derangements associated with acute infarction). Early-onset seizures have been defined in most studies as occurring within 1 week (7–10) or 2 weeks after stroke (11–13). Use of the 1- or 2-week interval is determined somewhat arbitrarily because the acute phase of infarction cannot be defined by a specific time course or set of pathophysiologic events during which seizures are clearly provoked. The 2-week interval is a conservative estimate and comparable to paradigms used to study posttraumatic seizures (14). Late-onset seizures are considered to be unprovoked seizures that occur after the acute phase of infarction from areas of partially injured brain where neuronal networks have undergone anatomic and physiologic alterations predisposing to hyperexcitability and synchronization. Late seizures occur 1 or 2 weeks after stroke, depending on the study, and are considered epileptic seizures when they recur. After stroke, there is no defined limit to the amount of time during which recurrent unprovoked seizures define the poststroke epileptic state. When long periods (years) of follow-up elapse before an apparent second unprovoked seizure occurred, it is sometimes indeterminate whether the seizure clearly was due to the previously identified stroke. Aging, intercurrrent illness, trauma, and subclinical cerebrovascular events unrelated to the previous stroke can cause unprovoked seizures independently, thereby affecting and possibly distorting the identification of epilepsy arising from a specific stroke.

Clinical and Population Studies

A recent large prospective international multicenter study was conducted by the Seizures After Stroke Study Group to deter-

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mine the incidence, outcome, and risk factors for seizures after cerebral stroke (13). The study followed 1,897 patients with acute stroke for an average duration of 9 months (97% of patients). Overall, seizures occurred in 8.9% of patients (8.6% with ischemic stroke and 10.6% with hemorrhagic stroke), and epilepsy occurred in 2.5% of patients (2.1% ischemic; 2.6% hemorrhagic). Seizures occurring within 24 h of stroke occurred in 40% of ischemic strokes and in 57% of hemorrhagic strokes. Of the patients who experienced at least one seizure, epilepsy developed in 28%. Partial seizures (including simple partial and secondarily generalized seizures) accounted for 53% of seizures in ischemic stroke patients and for 50% in hemorrhagic stroke patients. Multivariate analysis indicated that (a) compared with ischemic stroke, there was a nearly twofold risk of seizures with hemorrhagic stroke; (b) cortical location and stroke disability were risk factors for seizures after ischemic stroke; (c) the only risk factor for seizures after hemorrhagic stroke was cortical location; and (d) late onset (>2 weeks) of the first seizure was an independent risk factor for epilepsy after ischemic stroke but not after hemorrhagic stroke. This study did not report the incidence of status epilepticus (SE) nor was it more specific about the occurrence of different seizure types than that described earlier. For these reasons, it is unclear what impact SE may have had on the development of epilepsy, and what other seizure types would account for nearly 50% of all seizures. However, by clearly differentiating and analyzing ischemic and hemorrhagic stroke, this study provided important findings on both risk factors and the incidence of seizures and epilepsy within a reasonable period of follow-up.

In the comprehensive population-based study of the incidence of epilepsy and unprovoked seizures in Rochester, Minnesota, from 1935 through 1984 (15), for persons with an identified etiology, cerebrovascular disease accounted for 35% of cases in adults (aged 35–64 years) and for 67% of cases in the elderly (older than 65 years). A subsequent study in Rochester was the first population-based analysis of the association of an initial ischemic stroke and subsequent seizure disorders (9). This study followed 535 patients until death or migration from Rochester. The mean duration of follow-up was 5.5 ± 7.1 years; for those patients surviving longer than 1 week after stroke, there were 2,930 person-years of follow-up. The investigators found that in 6% of patients, early-onset (<1 week) seizures developed, 78% of which occurred within 24 h after infarction. Of the 436 patients who survived >1 week after stroke, 6% had an initial late seizure, and in 4%, epilepsy developed. Univariate analysis indicated that early seizure occurrence was the only factor with a significantly higher risk of developing an initial late seizure and epilepsy. Risks for developing an initial late seizure and epilepsy were 3.0% by 1 year, 4.7% by 2 years, 7.4% by 5 years, and 8.9% by 10 years. Multivariate analysis indicated that the only factor predictive of early-onset seizure was an anterior hemisphere location of the infarct.

Recognizing the differences in study design and patient mix in the studies described earlier, the findings nonetheless provide sound, evidence-based support to several concepts. An important risk factor for development of epilepsy after stroke is the involvement of the cerebral cortex (11,16); solitary lacunar, subcortical, or posterior circulation infarcts are infrequently associated with the development of epilepsy. Hemorrhagic strokes result in seizures more frequently than do ischemic seizures. In general, poststroke seizures are focal in onset, likely arising from areas in close proximity to the area of infarcted tissue (5). Most early-onset seizures are likely to occur within 24 h of stroke. Early seizure occurrence predisposed epilepsy to develop in those with initial late seizures. The risks of developing late seizures and epilepsy are highest in the first year after stroke and decline in subsequent years.

The association of stroke and SE has been evaluated in several studies in the recent past (10,17–19). In the large, population-based study of SE in Richmond, Virginia, acute stroke accounted for 22% of all cases (17). In the prospectively identified, population-based study of incident stroke cases in the Northern Manhattan Stroke Study, SE occurred in 1.1% of all patients, representing 27% of patients with early onset (<1 week) seizures (10) [reviewed in *Epilepsy Currents* (20)]. This study also found that lesion location and stroke subtype were strong determinants of the risk of early-onset seizures, which did not predict 30-day mortality. In a recent hospital-based study of 1,174 patients with first-time stroke, in 1.4% of patients, SE developed; early-onset SE (<1 week) was associated with a higher risk for SE recurrence and a higher mortality than was late-onset SE [reviewed in *Epilepsy Currents* (21)]. Taken together, the findings of these studies indicate that stroke is responsible for a substantial number of cases of SE, but that the overall incidence of SE after stroke is very low (∼1%). Additionally, SE as the presenting sign of acute stroke did not necessarily predict subsequent epilepsy (18).

It has been long recognized that patients with acute stroke and periodic lateralizing epileptiform discharges (PLEDs) are predisposed to the development of seizures (22). The specific relation of acute stroke, PLEDs, and the subsequent development of epilepsy has been estimated in small retrospective studies but remains to be described thoroughly. With regard to therapy after stroke, treatment with an antiepileptic drug (AED) is an option after the first poststroke seizure but has no influence on the development of recurrent seizures after discontinuing medication (23), corroborating the general understanding that AEDs can control seizures but are not antiepileptogenic.

The few studies reviewed here, as well as many others,

have steadily advanced our knowledge of the clinical characteristics and epidemiology of poststroke seizures and epilepsy. They also highlight the need for an improved understanding of the progressive biochemical, anatomic, and physiologic changes of poststroke epileptogenesis, and for shifting the focus of therapeutic strategies from control of symptoms to prevention and cure (24).

Animal Models of Poststroke Seizures and Epilepsy

In contrast to our clinical knowledge of poststroke seizures and epilepsy, less information exists on the pathophysiologic mechanisms of the brain that result in seizures or epilepsy after stroke. This is due in large part to animal models of stroke having had limited extension to the study of epileptogenesis and epilepsy. In vivo rodent models of cerebral ischemia fall into three main classes: global ischemia, focal ischemia, and hypoxia/ischemia; the latter is used in most studies with neonatal or juvenile animals (25). These models variably involve frank infarction of the brain, and relatively few studies have been designed to study the relation between ischemic injury and seizures in adult rats. For example, hyperglycemic rats developed fatal postischemic seizures in vascular occlusion models (26,27), and in other models, transient global ischemia produced by cardiac arrest or tamponade resulted in chronic susceptibility to sound-induced generalized tonic–clonic seizures (28,29). It is important to note that these models of ischemic brain injury resulted in provoked seizures, not in epilepsy.

Middle cerebral artery occlusion (MCAO) is the standard in vivo technique used to model cerebral infarction. MCAO typically produces a large cortical and subcortical infarct ipsilateral to the occlusion, characterized by an infarct core and a surrounding volume of partial cellular injury and death, often referred to as the "ischemic penumbra." In rodents, the hippocampus is likely to lie within the region of ischemic injury because it is perfused by the posterior cerebral artery, which can be blocked by MCAO (30). In humans, the hippocampus is typically unaffected by occlusion of the MCA because it is supplied by the anterior choroidal and posterior cerebral arteries. In recent well-performed EEG studies using adult rats, MCAO resulted in large cerebral infarcts and rhythmic spike–wave discharges in cortex ipsilateral to the occlusion during both ischemic and reperfusion periods (31–34). Although these findings clearly reflected the acute phase of injury after arterial occlusion, they suggested the potential for the development of epileptogenicity in the periinfarct area. Because these studies were terminated 1–7 days after lesioning, no conclusions can be drawn regarding whether the animals would have become epileptic. Despite its widespread use in stroke-related studies, there are several drawbacks to MCAO: the procedure is invasive and technically demanding; the size and distribution of the lesions are variable; and animal morbidity and mortality can be high. These considerations make arterial occlusion models less than ideal for many applications, especially when extended survival of animals is required; however, rigorous testing of this model in the study of epileptogenesis has yet to be reported.

An alternative to an arterial occlusion model is the technique of cortical photothrombosis and brain infarction using the photosensitive dye rose bengal (35). Rose bengal is injected into the animal and activated in brain vasculature by an external light beam that is focused on and penetrates the translucent skull and underlying cerebral cortex. The activated dye generates singlet oxygen, which causes peroxidation of endothelial cell membranes and occlusive platelet aggregation. Subsequent thrombus formation, vascular stasis, and vasogenic edema lead to focal cortical infarction and necrosis. This method is well characterized, relatively noninvasive, produces cortical infarcts that extend to the subcortical interface, and allows their selective placement with reproducible area, depth, and location. Compared with MCAO, photothrombosis results in much smaller infarct volumes ($\sim$20 mm^3 vs. $\sim$200–300 mm^3), an important consideration when trying to preserve as much cortical tissue as possible for epileptogenesis and to ensure an adequate surface area of viable neocortex from which to obtain EEG recordings. Initial studies in adult rats have shown that large photothrombotic brain infarcts can result in brief recurrent electrical seizures arising in the perilesional cortex associated with behavioral arrest of the animal occurring 1–2 months after lesioning (36). Animals otherwise demonstrated normal functioning and longevity. Although there are several advantages of the photothrombotic model, it has certain theoretical limitations. Photothrombosis preferentially occludes small-diameter pial cortical vessels, an end-arterial mechanism different than most cases of thrombotic stroke in humans. The thrombus formed as a result of endothelial damage by singlet oxygen contains virtually no fibrin. Endothelial discontinuities such as luminal surface microrupture caused by singlet oxygen peroxidation lead to early blood–brain barrier opening and severe vasogenic edema. Because the tissue bordering the lesion is consumed by the rapid development of severe edema, the penumbral area is very small compared with that of arterial occlusion models, extending only $\sim$500 μm from the infarct core (37,38). Despite its theoretic and practical shortcomings as an alternative model for studies focused primarily on penumbral tissue injury after stroke, photothrombosis may be a viable model for study of cortical infarction and mechanisms of secondary epileptogenesis.

In vitro modeling of ischemia has been performed on organotypic cultures (brain slices) and primary neuronal/glial cultures. Brain-slice preparations have become widely used models for studying anoxic and ischemic damage. In the

hippocampal slice preparation, anoxia is achieved typically by transient substitution of O_2/CO_2 with N_2/CO_2 in the bathing solution. When glucose is omitted from the bathing solution, the preparation is considered "ischemic." Thus tissue preparations deprived of both oxygen and glucose are considered to model anoxic (hypoxic)/ischemic injury; however, they do not truly model infarction. To overcome this limitation, a recent in vitro study was designed to model stroke-related excitotoxic phenomena by using primary hippocampal/glial cocultures exposed to glutamate (39) [reviewed in *Epilepsy Currents* (40)]. After exposure of the cultures to glutamate, surviving neurons manifested a persistent epileptiform phenotype characterized by paroxysmal depolarizing shifts and high-frequency spike firing. This model incorporated aspects of poststroke phenomena including increases in extracellular glutamate, reversible depolarization with loss of synaptic activity, acute neuronal swelling, and delayed neuronal death. Systematic development of this and other in vitro models that specifically model neocortical infarction and ischemia potentially can add considerable insight into the network, cellular, and molecular events of poststroke epileptogenesis. The long-range goal of both in vivo and in vitro models is to identify critical steps or pathways in poststroke epileptogenesis and to develop interventional strategies to prevent or limit the poststroke epileptic state.

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References

1. Pohlmann-Eden B, Cochius JI, Hoch DB, Hennerici MG. Stroke and epilepsy: critical review of the literature, Part I: Epidemiology and risk factors. Cerebrovasc Dis 1996;6:332–338.
2. Pohlmann-Eden B, Cochius JI, Hoch DB, Hennerici MG. Stroke and epilepsy: critical review of the literature, Part II: Risk factors, pathophysiology and overlap syndromes. Cerebrovasc Dis 1997;7:2–9.
3. Silverman IE, Restrepo L, Mathews GC. Poststroke seizures. Arch Neurol 2002;59:195–201.
4. Hauser WA. Epidemiology of seizures and epilepsy in the elderly. In: Rowan AJ, Ramsay RE, eds. Seizures and epilepsy in the elderly. Boston: Butterworth-Heinemann, 1997:7–18.
5. Loiseau P. Pathologic processes in the elderly and their association with seizures. In: Rowan AJ, Ramsay RE, eds. Seizures and epilepsy in the elderly. Boston: Butterworth-Heinemann, 1997:63–85.
6. Thomas RJ. Seizures and epilepsy in the elderly. Arch Intern Med 1997;157:605–617.
7. Hauser W, Kurland L. The epidemiology of epilepsy in Rochester, Minnesota, 1935–1967. Epilepsia 1975;16:1–16.
8. Hauser W, Annegers J, Kurland L. Prevalence of epilepsy in Rochester, Minnesota:1940–1980. Epilepsia 1991;32:429–445.
9. So EL, Annegers JF, Hauser WA, O'Brien PC, Whishnant JP. Population-based study of seizure disorders after cerebral infarction. Neurology 1996;46:350–355.
10. Labovitz DL, Hauser WA, Sacco RL. Prevalence and predictors of early seizure and status epilepticus after first stroke. Neurology 2001; 57:200–206.
11. Heuts-van Raak EP, Boellaard A, De Krom MC, Lodder J. Supratentorial brain infarcts in adult-onset seizures: the Maastricht epilepsy case register. Seizure 1993;2:221–227.
12. Reith J, Jorgensen HS, Nakayama H, Raaschou HO, Olsen TS. Seizures in acute stroke: predictors and prognostic significance: the Copenhagen Stroke Study. Stroke 1997;28:1585–1589.
13. Bladin CF, Alexandrov AV, Bellavance A, et al. Seizures after stroke. Arch Neurol 2000;57:1617–1622.
14. Jennett B. Posttraumatic epilepsy. Adv Neurol 1979;22:137–147.
15. Hauser WA, Annegers JF, Kurland LT. Incidence of epilepsy and unprovoked seizures in Rochester, Minnesota: 1935–1984. Epilepsia 1993;34:453–468.
16. Dhanuka AK, Misra UK, Kalita J. Seizures after stroke: a prospective clinical study. Neurol India 2001;49:33–36.
17. DeLorenzo RJ, Hauser WA, Towne AR, et al. A prospective, population-based epidemiologic study of status epilepticus in Richmond, Virginia. Neurology 1996;46:1029–1035.
18. Rumbach L, Sablot D, Berger E, Tatu L, Vuillier F, Moulin T. Status epilepticus in stroke: report on a hospital-based stroke cohort. Neurology 2000;54:350–354.
19. Velioglu SK, Ozmenoglu M, Boz C, Alioglu Z. Status epilepticus after stroke. Stroke 2001;32:1169–1172.
20. Westerhouse E. Predictors of early seizures after stroke. Epilepsy Curr 2002;2:75–76.
21. Westerhouse E. Status epilepticus in acute settings. Epilepsy Curr 2002;2:43–44.
22. Holmes G. The electroencephalogram as a predictor of seizure following cerebral infarction. Clin Electroencephalogr 1980;11:83–86.
23. Gilad R, Lampl Y, Eschel Y, Sadeh M. Antiepileptic treatment in patients with early postischemic stroke seizures: a retrospective study. Cerebrovasc Dis 2001;12:39–43.
24. Jacobs MP, Fischbach GD, Davis MR, et al. Future directions for epilepsy research. Neurology 2001;57:1536–1542.
25. Lipton P. Ischemic cell death in brain neurons. Physiol Rev 1999;79: 1431–1568.
26. Mourre C, Smith M-L, Siesjo BK, Lazdunski M. Brain ischemia alters the density of binding sites for glibenclamide, a specific blocker of ATP-sensitive K+ channels. Brain Res 1990;526:147–152.
27. Lundgren J, Smith M-L, Mans AM, Siesjo BK. Ischemic brain damage is not ameliorated by 1,3-butanediol in hyperglycemic rats. Stroke 1992;23:719–724.
28. Reid KH, Iyer V, Schurr A. Post-ischemic sound-induced seizures in rat: similarities and differences from the genetically epilepsy-prone rat. FASEB J 1994;8:A660.
29. Kawai K, Penix LP, Kawahara N, Ruetzler CA, Klatzo I. Development of susceptibility to audiogenic seizures following cardiac arrest ischemia in rats. J Cereb Blood Flow Metab 1995;15:248–258.
30. Del Zoppo GJ. tPA: a neuron buster, too? Nat Med 1998;4:148–150.
31. Tortella FC, Britton P, Williams A, Lu XCM, Newman AH. Neuroprotection (focal ischemia) and neurotoxicity (electroencephalographic) studies in rats with AHN649, a 3-amino analog of dextromethorphan and low-affinity *N*-methyl-D-aspartate antagonist. J Pharmacol Exp Ther 1999;291:399–408.
32. Lu XC, Williams AJ, Tortella FC. Quantitative electroencephalography spectral analysis and topographic mapping in a rat model of middle cerebral artery occlusion. Neuropathol Appl Neurobiol 2001; 27:481–495.

33. Williams AJ, Lu X.M, Slusher B, Tortella FC. Electroencephalogram analysis and neuroprotective profile of the N-acetylated-alpha-linked acidic dipeptidase inhibitor, GPI5232, in normal and brain-injured rats. J Pharmacol Exp Ther 2001;299:48–57.
34. Williams AJ, Tortella FC. Neuroprotective effects of the sodium channel blocker RS100642 and attenuation of ischemia-induced brain seizures in the rat. Brain Res 2002;932:45–55.
35. Watson BD, Dietrich WD, Busto R, Wachte MS, Ginsberg MD. Induction of reproducible brain infarction by photochemically initiated thrombosis. Ann Neurol 1985;17:497–504.
36. Kelly KM, Kharlamov A, Hentosz TM, Kharlamov EA, Williamson JM, Bertram EH, Kapur J, Armstrong DM. Photothrombotic brain infarction results in seizure activity in aging Fischer 344 and Sprague–Dawley rats. Epilepsy Res 2001;47:189–203.
37. Watson BD, Dietrich WD, Prado R, et al. Concepts and techniques of experimental stroke induced by cerebrovascular photothrombosis. In: Ohnishi ST, Ohnishi T, eds. Central nervous system: trauma research techniques. Boca Raton: CRC Press, 1995: 169–194.
38. Witte OW, Bidmon H-J, Schiene K, Redecker C, Hagemann G. Functional differentiation of multiple perilesional zones after focal cerebral ischemia. J Cereb Blood Flow Metab 2000;20:1149–1165.
39. Sun DA, Sombati S, DeLorenzo RJ. Glutamate injury-induced epileptogenesis in hippocampal neurons: an *in vitro* model of stroke-induced "epilepsy." Stroke 2001;32:2344–2350.
40. Bernardo LS. An in vitro model of stroke-induced epileptogenesis. Epilepsy Curr 2002;2:61–62.