

CYTOKINES AND STROKES OF ILL FORTUNE

Incidence of Seizures in the Acute Phase of Stroke: A Population-based Study. Szaflarski JP, Rackley AY, Kleindorfer DO, Khoury J, Woo D, Miller R, Alwell K, Broderick JP, Kissela BM. *Epilepsia* 2008;49(6):974–981. **PURPOSE:** The incidence of seizures within 24 h of acute stroke has not been studied extensively. We aimed to establish the incidence of acute poststroke seizures in a biracial cohort and to determine whether acute seizure occurrence differs by race/ethnicity, stroke subtype, and/or stroke localization. **METHODS:** We identified all stroke cases between July 1993 and June 1994 and in 1999 within the population of the Greater Cincinnati metropolitan region. Patients with a prior history of seizures/epilepsy were excluded from analysis. **RESULTS:** A total of 6044 strokes without a history of seizure(s) were identified; 190 (3.1%) had seizures within the first 24 h of stroke onset. Of ICH/SAH patients, 8.4% had a seizure within the first 24 h of stroke onset ($p \leq 0.0001$ vs all other stroke subtype). Of the patients with ischemic stroke, we observed higher incidence of seizures in cardioembolic versus small or large vessel ischemic ($p = 0.02$) strokes. Patients with seizures experienced higher mortality than patients without seizures ($p < 0.001$) but seizures were not an independent risk factor of mortality at 30 days after stroke. Independent risk factors for seizure development included hemorrhagic stroke, younger age, and prestroke Rankin score of ≥ 1 . Race/ethnicity or localization of the ischemic stroke did not influence the risk for seizure development in the studied population. **DISCUSSION:** The overall incidence of acute seizures after stroke was 3.1%, with a higher incidence seen in hemorrhagic stroke, younger patients, and those presenting with higher prestroke Rankin scores. Acute seizures were associated with a higher mortality at 30 days after stroke.

COMMENTARY

As the authors state, cerebrovascular disease is the most common identifiable cause of new-onset symptomatic epilepsy in studies of various elderly populations (1,2). This study by Szaflarski et al. encompassed a geographic area that is possibly more representative of the United States population, in terms of median age, percentage of black race, income, education, and proportion of patients living below the poverty level, than some earlier reports on cerebrovascular disease and epilepsy. Providing greater relevance to acute stroke care, the investigators defined early seizures as those occurring within 24 hours of stroke onset, in contrast to definitions of 7 to 14 days poststroke found in several other studies. Although strokes in their patient population occurred in an era before tissue-type plasminogen activator (tPA) was available, the data are currently applicable and meaningful, as a majority of eligible stroke patients do not receive this therapy (3).

As a retrospective study that depended upon annotated seizure data, it was not possible to categorize seizure type, and nonmotor seizures were likely missed. Nonconvulsive status epilepticus, *epilepsia partialis continua* (if manifestations are limited), and pure aphasic seizures are examples of acute stroke seizure types (4). Any of these acute stroke seizure types may be overlooked without an EEG in the acute phase. Epileptiform discharges, including periodic lateralized epileptiform discharges (PLEDs), correlate highly with clinical seizures occurring within the first weeks after stroke (5); EEG would be

particularly helpful in situations in which poststroke seizures are likely to occur. In this study, hemorrhagic stroke emerged as an independent risk factor for seizure development. Experimental cortical injection of blood or iron produces neuronal loss and gliosis, along with recurrent seizures (6,7); glial glutamate transport becomes impaired in this model (8). A prestroke Rankin score ≥ 1 also independently predicted poststroke acute seizure. Such seizure development likely reflects a preexisting cortical lesion. The association between the prestroke Rankin score and acute seizure has a parallel in seizures arising from experimental cortical foci: a second lesion augments spike quantity of a first lesion, and seizure severity increases more than proportionately to number of foci (9).

Acute stroke induces a massive glutamate release, causing an elevated intracellular free calcium increase and neuronal depolarization. This sequence may contribute to acute seizures and neurotoxicity (10,11). Microglial activation also occurs in acute stroke, followed by an influx of lymphocytes and macrophages into the brain, which is triggered by the production of proinflammatory cytokines (12,13). Experimental seizures may elicit prototypic inflammatory cytokine release, such as interleukin (IL)-1 β , IL-6, and tumor necrosis factor, from rodent astrocytes and microglia (14). These experimental findings have been corroborated by demonstration of microglia and astrocytic activation of the IL-1 β system in human temporal lobe tissue, resected at surgery (15). Because glia-derived cytokines can promote neuronal death, a poststroke seizure may increase the extent of an ischemic lesion. Moreover, IL-1 β may enhance extracellular glutamate concentrations, increase function of NMDA receptors, and inhibit glial reuptake of glutamate. A consequent increase in calcium influx into neurons would further augment epileptogenesis and neurotoxicity.

Reported risk factors for chronic stroke-related epilepsy differ little from those of early seizures reported here: early seizures themselves; hemorrhagic stroke; cortical involvement; and strokes involving more than one-half of a hemisphere (16–20). Thus, the likelihood of chronic seizure development can be assessed from data obtained in the acute period of stroke. Given the deleterious effect of seizures on an already compromised brain, seizure detection by careful and repeated neurological assessment and even intermittent or continuous EEG monitoring in the acute period (although this was not expressly demonstrated) can now be considered essential for patients harboring risk factors for poststroke epilepsy.

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References

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