Seven Questions About Stroke and Epilepsy

Seizures and stroke are both common neurologic conditions, but when they occur in close temporal proximity they produce much more concern than either does alone. The stroke specialist (and the family) fear that convulsions will worsen the stroke because of acute hypertension and airway compromise, and the epileptologist is concerned that these acute seizures are the harbingers of later epilepsy. Other less commonly recognized but important aspects of this relationship are that subclinical seizures worsen some forms of stroke, and some anticonvulsants may have more adverse effects on stroke patients than they do in other groups. In surveying the connections between these two conditions, I have attempted to address seven questions. For some questions, there are data to help provide an answer; for others, there is only opinion; and for a maddening few, newer research is making older suggestions less certain.

1. How Often Do the Various Types of Strokes Present with Seizures?

Most studies of seizure incidence in stroke are handicapped by the lack of continuous EEG monitoring to detect subclinical seizures. Therefore, the bulk of the available information concerns convulsive activity, usually generalized. In addition, very few reports discuss population-based studies, so that the estimates of incidence are dependent on local practices and referral patterns.

The best data come from the Oxfordshire and Greater Cincinnati population-based studies. In the former, 14 of 675 patients suffered a seizure at stroke onset, including 10 of 545 (2%) with ischemic stroke, 2 of 66 (3%) with intracerebral hemorrhage, and 2 of 33 (6%) with subarachnoid hemorrhage (1). Among the ischemic stroke patients, 17 (3%) had a single seizure following the stroke, while 18 (3%) had recurrent seizures during 5 years of follow-up.

In the Cincinnati study, 190 of 6044 (3.1%) had a seizure within 24 hours of stroke onset, including 2.9% of ischemic stroke patients, 7.9% of intracerebral hemorrhage patients, and 10.1% of subarachnoid hemorrhage patients (but, see below) (2). Among ischemic stroke patients, seizures were almost twice as likely in those with a suspected cardioembolic etiology (3.0%) as in those suspected to be of either large- or small-vessel thrombosis (1.7% each). Experiencing a seizure was associated with a 2.65-fold increase in mortality (95% confidence interval [CI], 1.85–3.74), second only to the increase associated with hemorrhage (6.58-fold, 5.35–8.09).

Twenty-two percent of a group of 60 children with acute ischemic stroke presented with seizures (3).

A consortium of Italian investigators recently presented data on acute seizure incidence during the first 7 days after stroke (4). They excluded patients with subarachnoid hemorrhage but divided ischemic stroke patients into those with and without hemorrhagic transformation. Of their 714 patients, 45 (6.3%) had acute seizures. Patients with bland infarcts were the most common, but the least likely to have seizures (4.2%), while 12.5% of those with hemorrhagic transformation had seizures, compared with 16.2% of those with primary intracerebral hemorrhage. As might be expected, cortical involvement increased the risk of seizures in both intracerebral hemorrhage (odds ratio [OR] 6.0; 95% CI, 1.8–20.8) and ischemic stroke (OR 3.1; 95% CI, 1.3–7.8).

A recent review of intracerebral hemorrhage concluded that approximately 8% of patients suffered clinically recognized seizures; 60% occurred in the first 24 hours, and 90% within the first 3 days (5). When EEG monitoring is performed, the incidence of electrographic seizures may be as high as 28% even in patients with deep hemorrhages, however, and each such seizure is accompanied by more edema formation and worsening midline shift (6).

Some types of intracerebral hemorrhage, such as that which accompanies cerebral venous thromboses, seem to cause a higher incidence of seizures than the more typical hypertensive basal ganglionic hemorrhage, likely because the venous lesion predominantly affects the cortex. Among cerebral venous thrombosis patients, 37% of adults, 48% of children, and 71% of infants have acute seizures (7, 8). The reported incidence of seizures at the onset of subarachnoid hemorrhage varies between 4 and 26% (9). However, the higher estimates most likely result from the
misdiagnosis of decerebrate posturing (abnormal extension) as seizure activity. Since generalized seizures often cause an abrupt increase in mean arterial pressure, which may prompt rebleeding of an aneurysm, many neurointensivists attempt to prevent convulsions by empirically starting patients on antiepileptic drugs; however, the utility of this practice is unknown. Seizures, or posturing, may also occur as a consequence of rebleeding.

In the International Subarachnoid Aneurysm trial, seizures occurred in about 2% of patients between aneurysm obliteration and discharge; approximately twice as many patients who underwent clipping had seizures as those who were coiled (10).

2. Is This a Stroke or a Todd's Paresis?
When a patient presents with a hemiparesis, or another focal neurologic disorder, following a seizure, the clinician is confronted with a dilemma: is this a postictal paresis that will resolve, or is this a stroke with a seizure at onset? Todd's description in 1849 captures the condition: "A paralytic state remains sometimes after the epileptic convulsion. This is more particularly the case when the convulsion has affected only one side or one limb: that limb or limbs will remain paralyzed for some hours, or even days, after the cessation of the paroxysm, but it will ultimately perfectly recover" (11). Before there were therapies for acute stroke, the question was interesting but not therapeutically important.

In a study of 328 patients with partial epilepsy undergoing video-EEG for presurgical evaluation, 44 (13.4%) had a postictal paresis (12). The median duration of weakness was about 3 minutes but extended out to 22 minutes. Weakness in this highly selected population would thus have resolved before consideration of acute stroke intervention in most cases. Another registry of 648 patients reported that 20 of their 42 patients with stroke mimics had seizures, although the duration of Todd's paresis was not reported (13). However, these authors also reported that among 13 of these patients with seizures who had generalized convulsions, 10 of them suffered convulsions at stroke onset, while only three had convulsions followed by focal neurologic abnormalities as stroke mimics, underscoring the need to recognize that seizures, especially of new onset, may be the presentation of a stroke.

Of course, longer durations of postictal paresis are known, and although the question does not commonly arise, stroke centers are occasionally confronted by it. In a study of 539 patients who underwent thrombolysis for stroke, 11 were subsequently determined to have postictal parases rather than a stroke (14).

Initially, brain diffusion and perfusion imaging held promise for resolution of this question, hoping that certain patterns could be detected that would distinguish stroke from postictal parases. However, both conditions produce similar findings (15, 16). One potential discriminator is that the area of hypoperfusion soon after a seizure is often quite extensive, resembling that seen with large arterial occlusion, but flow in the relevant arteries is normal. However, further research is needed before using this observation diagnostically.

3. Should This Patient with Postictal Paresis Receive Thrombolytics?
In the initial studies of intravenous thrombolysis for stroke, patients presenting with seizures who then showed signs suggesting an acute stroke were excluded, so that any improvement from resolution of a postictal paresis would not be mistaken for a drug effect. However, this prohibition was only introduced for clinical trials and should not be carried forward into clinical practice.

Within the time frame of relevance for intravenous thrombolysis (up to 4.5 hours from the last time the patient was observed to be at his or her neurologic baseline) or intra-arterial treatment (up to 8 hours, depending on the modalities of treatment being considered), diffusion-weighted imaging does not clearly distinguish between the two conditions. Angiographic studies are very useful when they detect an appropriate intracranial arterial lesion, suggesting that thrombolytic treatment may be beneficial (17). However, thrombolytic treatment is also efficacious after small-vessel occlusions below the resolutions of these techniques, so denying patients intravenous thrombolytic treatment based on an angiogram is not appropriate (intra-arterial treatment does require a visible occlusion in an appropriate artery). If perfusion studies suggest a large area of postictal hypoperfusion without a corresponding arterial lesion, one might reasonably conclude that this patient probably has a postictal paresis and therefore withhold thrombolysis. Because each additional study consumes potentially valuable time, delay in the pursuit of greater diagnostic certainty may not be in the patient's best interest. The clinician must also recognize that intravenous recombinant tissue plasminogen activator (rt-PA) very rarely produces complications in patients without an acute stroke.

4. What Diseases Can Manifest As Both Stroke and Epilepsy?
Aside from the common cerebrovascular conditions noted above, in which acute stroke may cause acute seizures and later epilepsy, there are some less frequent conditions that can manifest as both stroke and epilepsy. The most common ones are arteriovenous and cavernous malformations. Both of these may come to medical attention because of seizures that precede symptomatic intracerebral hemorrhage, although the mechanisms of seizure production in such patients are often inferred to include small hemorrhages resulting in cortical irritation. This argument is particularly problematic with cavernous malformations, which are often at some distance from gray matter structures.

Treatment of arteriovenous malformations typically involves endovascular embolization in place of, or prior to, surgical therapy, depending on the anatomy of the malformation, its arterial supply, the presence of aneurysms, stenosis, or varices, and its venous drainage. The commonly used embolic material, Onyx, may be associated with seizures during the days or months following the procedure (18).

Takayasu's arteritis typically presents with stroke (19) but may initially present with seizures in almost as many cases (20). Homocystinuria (hyperhomocysteinemia) has several forms. In infants with methylenetetrahydrofolate reductase deficiency, infantile spasms may be the presentation, with the
later evolution of other seizure types (21). Because of their tendency to thrombosis, many patients with homocystinuria will develop strokes at a young age. These may be typical arterial occlusions, but these patients are also prone to developing cortical vein and venous sinus thrombosis. In these conditions, venous infarction with secondary hemorrhage is common. Sagittal sinus thrombosis may produce bilateral convexity infarcts with seizures arising independently from each hemisphere, producing a confusing clinical picture until imaging studies are obtained.

Mitochondrial disorders may manifest with both stroke and seizures. The prototypic disorder is mitochondrial myopathy with lactic acidosis and stroke-like episodes (22), but almost any disorder of the mitochondrial respiratory chain can present with these problems (23, 24).

5. Which Stroke Types Are Associated with Chronic Epilepsy in What Percentage of Patients?

This question is deceptively difficult to answer; there are remarkably few population-based epidemiologic data addressing it. In the Stockholm Incidence Registry of Epilepsy, the OR for subsequent epilepsy was 9.4 (95% CI, 6.7–13.1) after cerebral infarction, 7.2 (95% CI, 3.9–13.6) after intracerebral hemorrhage, 7.2 (95% CI, 2.9–18.1) after subarachnoid hemorrhage, and 3.2 (95% CI, 1.9–5.5) after a transient ischemic attack (25). In this study, the risk of developing epilepsy was greatest in the first post-stroke year, but incident cases continued to present for at least a decade after the stroke.

Patients suffering from cerebral amyloid angiopathy frequently develop recurrent seizures, sometimes associated with cortical intracerebral hemorrhages (26). This is an inflammatory disorder that frequently requires immunosuppressive therapy.

In a series of 77 children with stroke, 21% had seizures at presentation, and 24% of the 66 survivors developed epilepsy (27). Six of the patients had status epilepticus during their initial hospitalization; five of them had nonconvulsive status epilepticus captured during EEG monitoring.

6. What treatments are optimal for epilepsy after a stroke?

There is no clearly superior anticonvulsant agent for the treatment of either acute post-stroke seizures or epilepsy. However, as many stroke patients are older, and since post-stroke epilepsy may develop a decade or more after the initial insult, consideration must be given to the tolerability of the medication chosen. For example, a large randomized trial in elderly patients (mean age, 72 years), in whom stroke was the most commonly identified etiology of epilepsy, showed that although seizure control was similar with the drugs tested, patients randomized to lamotrigine or gabapentin tolerated these agents better than they did carbamazepine (28). In a smaller study of post-stroke patients, lamotrigine was superior to carbamazepine with regard to seizure as well as tolerability (29). Experience with gabapentin has been published, but there was no comparison with other agents (30).

In subarachnoid hemorrhage, observational studies suggest that chronic phenytoin exposure is associated with poorer long-term neuropsychological outcome (31), leading many to choose another agent for patients who have had seizures, or to discontinue these drugs for those who have not seized. Similar problems have been reported with phenytoin after intracerebral hemorrhage (32).

7. Can Post-Stroke Epilepsy be Prevented?

Sadly, few data are available that directly address this question in humans (33). An attempt to test levetiracetam as a preventive agent was terminated, after several years of study, because the investigators had randomized only 16 of the over 500 stroke patients screened (34). A small placebo-controlled study of valproate, administered for 1 month after intracerebral hemorrhage, reduced early seizures but did not affect the incidence of later epilepsy (35).

References

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