Why now? Moving from stroke risk factors to stroke triggers

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Purpose of review

While chronic risk factors for stroke are reasonably well understood, the acute precipitants, or triggers, of stroke, remain relatively understudied.

Recent findings

Several converging lines of evidence indicate that transient perturbations in systemic metabolism may provoke the onset of cardiovascular events, including stroke. Epidemiologic data, including studies utilizing novel designs that consider intraindividual differences across different time periods, have been used to clarify triggers for myocardial ischemia, and these methods are beginning to be employed in stroke research. Acute infections, particularly upper respiratory infections, and other inflammatory stimuli have emerged as important triggers of acute ischemic stroke. The mechanisms involved include immunologically mediated activation of platelets and endothelial dysfunction. There also appears to be a period of time, or 'stroke-prone state', characterized by diffuse activation of the vasculature during which patients may be at increased risk of initial and recurrent ischemic events.

Summary

Confirmation of these findings in further studies may help elucidate the mechanisms behind this short-term increase in stroke risk. Improved methods of assessment of this period of heightened susceptibility could lead to more temporally focused preventive interventions.

Keywords

cerebral infarction, epidemiology, inflammation, stroke precipitants

Curr Opin Neurol 20:51–57. © 2007 Lippincott Williams & Wilkins.

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Sponsorship: Dr Elkind receives research support and honoraria for lecturing from BMS-Sanofi Pharmaceutical Partnership; honoraria for lecturing from Boehringer-Ingelheim, Inc.; research support from diaDexus, Inc; and serves as an expert witness for Merck.

Current Opinion in Neurology 2007, 20:51–57

Abbreviation

TIA transient ischemic attack

1350-7540

Introduction

Chronic risk markers and risk factors for stroke are now fairly well understood. Age is the most important non-modifiable risk marker for stroke. Men are at increased relative risk for stroke, although the absolute numbers of stroke are greater in women than men because, on average, women live to older ages than men [1]. In the US, the incidence of stroke is greater in African Americans and Hispanics than in non-Hispanic whites [2]. Well established medical and behavioral risk factors for stroke are also recognized, including hypertension, diabetes mellitus, cardiac diseases, cigarette smoking, hyperlipidemia and others. With this knowledge, determining those patients at increased long-term risk of stroke has become increasingly practical. Risk prediction models for stroke, like heart disease, can be accessed on-line and used in an office-based setting to calculate the individual patient's risk of stroke over several years [3]; risk factor modification or other therapy can then be instituted.

With all that is known about stroke epidemiology, however, it remains extremely difficult, if not impossible, to predict when a stroke will occur, even among those with a heavy burden of risk factors. Our knowledge of stroke precipitants, or triggers, to be contrasted with risk factors, remains relatively primitive. Nonetheless, recent evidence suggests that predicting not just who is at risk of stroke, but when stroke is most likely to occur, may be increasingly possible. This review will address the following questions: Why does a given patient, perhaps one with a history of hypertension and diabetes mellitus for decades, have a stroke today? Is this short-term risk of stroke a predictable or stochastic event? Can the stroke-prone state be measured in some way? If this state can be measured, and is therefore potentially predictable, is there something that can be done to prevent the consequent stroke?

Stroke triggers

Stroke is a heterogeneous condition, and thus studies of stroke precipitants are likely to depend on the specific stroke subtype and mechanism involved. The main stroke triggers may be summarized as follows: infections, including respiratory infections (influenza, others), urinary tract infections, and varicella (children); surgery (general and cardiac); cervical trauma and manipulation; pregnancy and the postpartum state; recreational drugs (cocaine, intravenous heroin); medications; diurnal fluctuations; winter season; air pollution; mental stress; anger and negative emotions and sudden changes in posture [1]. Precipitants of intracerebral hemorrhage

are likely to differ from those of ischemic infarction, for example, and immediate causes of lacunar stroke may similarly differ from causes of cardioembolic stroke. Case–control studies provide some evidence that chiropractic neck manipulation may provoke cervical artery dissection [4] and consequent stroke, for example. Similarly, the transient hypercoagulable state associated with the postpartum state increases the risk of ischemic stroke and venous sinus thrombosis [5]. There is also evidence that intracerebral hemorrhage is increased during pregnancy and, in particular, the postpartum state [6•]. Several drugs, including both recreational drugs (cocaine, intravenous heroin) and medications (over-the-counter propylphenylalamine and ephedra) have also been postulated to be stroke triggers, particularly for hemorrhagic stroke, although much of the data remain based on case–control studies subject to several methodological limitations, including selection and recall bias [7,8]. Nearly 5% of ischemic stroke in some populations, however, may be related to illicit drug use [9].

Other less easily predicted, but potentially identifiable, triggers of stroke could include perturbations in systemic metabolism, acute increases in blood pressure, or changes in coagulation and endothelial function. There is evidence that all stroke subtypes are more likely to occur in the morning hours (between 6 a.m. and noon), when diurnal fluctuations in blood pressure, coagulation parameters, and other factors, are most prominent [10]. Strokes are also more likely during the winter months [11•,12,13•]; the mechanisms of this difference may reflect an increased susceptibility to stroke in the setting of respiratory infections, as discussed below, although the mechanisms remain speculative. Other noninfectious causes of respiratory inflammation, such as air pollution, may also precipitate ischemic stroke [14•]. Using a combination of administrative databases, investigators were able to show that several potential causes of alveolar inflammation, including respiratory infections, air temperature, dry air, grass pollen, sulfur dioxide, and particulate matter in the air were independently associated with risk of stroke [15•].

Mental stress is increasingly recognized as a potential trigger of myocardial ischemia and sudden death [16••]. Acute cardiomyopathy appears to be associated with catecholamine release, and may occur in patients without any evidence of coronary disease, particularly among women. This may be the mechanism behind being 'scared to death', or dying of a 'broken heart' [17]. Less well established is whether mental stress or anguish is a risk factor for stroke [18].

The epidemiology of stroke triggers requires a different methodology

Studies of acute precipitants of stroke lend themselves to a different methodology than more conventional case–control or prospective cohort studies of chronic risk factors. In conventional epidemiological study designs, cases with the disease are compared to disease-free controls on a host of risk factors and markers, and these between-group differences lead to the conclusions regarding which factors are associated with disease and which are not. In determining acute precipitants of stroke, however, between group differences are less important than intraindividual differences. The factor of interest is not what characteristics make one person more likely to have a stroke than another person, but rather what makes one individual more likely to have a stroke at a particular point in time rather than at another point in time. The case–crossover design is particularly relevant to answering this type of question [19]. In this type of study, information about activities or events occurring during prespecified intervals of time leading up to an event are recorded. Analyses are then based on within-individual comparisons of these activities at different times. Activities or behaviors that occur more frequently just prior to stroke than at other times (i.e. either the prior day or during other periods, for example) are more likely to be precipitants of the stroke. An advantage of this methodology is that it allows each participant to serve as his or her own control, and therefore automatically accounts for interindividual differences in risk factors, responses on a questionnaire, or other factors.

Using this methodology, Mittleman and others [20,21] were able to show that certain events, such as episodes of anger and sexual activity, were potential triggers of myocardial infarction, although their absolute contribution to risk of an event remains small. The identification and significance of triggers of myocardial infarction was reviewed recently [22••]. The case–crossover design has thus far been used only sparingly in stroke research, but it was used in an analysis of stroke patients hospitalized in Israel to determine triggers [23]. Patients were interviewed between 1 and 4 days after stroke. Potential triggers evaluated included negative and positive emotions, anger, postural changes in response to a startling event, heavy physical exertion, heavy eating, and sudden temperature changes in the 2 h before stroke onset. Of 200 patients interviewed, 76 (38%) reported exposure to at least one trigger. Independent triggers included negative emotions, anger, and sudden changes in posture. Further studies are needed to confirm these findings and identify other triggers.

Infections as a stroke trigger

Acute or recent infections have been particularly well studied as causes of stroke. Several case–control studies have found recent (i.e., within 1 week) infection to be associated with acute stroke [24–28]. Dissection, in particular, appears to be particularly commonly preceded

by infection [29]. Perhaps even more convincingly, in a large prospective study conducted among British patients in general practices, both recent upper respiratory infections and urinary tract infections were associated with an increased risk of stroke [30]. Among more than 50 000 stroke patients in the United Kingdom General Practice Research Database, the investigators found that patients were more likely to have experienced a first and recurrent stroke during the 90 days after these infections. Using the case–series method, which also controls for interindividual variability, the risk of stroke in the 3 days after infection was approximately three times as high as during infection-free periods, and gradually diminished during the following 3 months.

There is also evidence from observational studies that vaccination against common infections, particularly viral influenza, can prevent stroke. In a case–control study among 370 consecutive stroke or transient ischemic attack (TIA) patients and an equal number of community controls, vaccination against influenza during the previous season was associated with just over a 50% reduction in risk of stroke, even after adjusting for other risk factors [31••]. The vaccination rate in patients was 19.2%, compared to a rate of 31.4% in control subjects ($P < 0.0001$). This protective effect did not, however, carryover to vaccinations against other organisms. Whether vaccinating stroke patients will lead to a reduction in risk of subsequent events has not been tested yet. A relatively small trial in cardiac patients, however, recently demonstrated that flu vaccination can reduce the risk of recurrent cardiac events and mortality. In the Flu Vaccination Acute Coronary Syndromes (FLUVACS) pilot trial [32], patients with acute myocardial infarction or stable patients undergoing percutaneous coronary intervention were randomly assigned to flu vaccine or control. At 6 months, cardiovascular death had occurred in 2% of vaccinated patients compared with 8% of the controls (relative risk reduction 75%, $P = 0.01$). The mechanism of this benefit from flu vaccination is uncertain but may reflect reduced immune activation of atherosclerotic plaque or coagulation [33]. For example, animal studies using the apolipoprotein E deficient mouse, which is prone to atherosclerosis, have shown that infection with influenza leads to increased inflammation, smooth muscle cell proliferation, and fibrin deposition in plaques [34]. Alternatively, fewer episodes of influenza may result in a reduction in less specific effects, such as illness-associated dehydration and respiratory impairment. Further studies, including in stroke patients, are warranted, but it may be difficult to perform such studies because of the emphasis in current annual flu vaccination guidelines on inclusion of several patient groups which overlap substantially with stroke patients, including those age 50 years and older and those with chronic medical conditions [35].

Whether other viruses can be similarly implicated in short-term stroke risk remains uncertain. In children, however, varicella infection appears to represent a period of increased stroke risk [36•].

Further indirect support for the notion that infection may precipitate stroke is available from studies that have examined the association of leukocyte count and stroke risk. In data from the prospective cohort Northern Manhattan Study, for example, baseline levels of leukocyte count were associated with an increased risk of subsequent ischemic infarction [37•], and leukocyte levels at the time of stroke were also associated with an increased risk of cardiovascular events in follow-up [38]. Even more convincingly, a secondary analysis of the large Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial showed that short-term changes in leukocyte counts result in an increased period of stroke risk [39]. Because individuals in this trial had frequent follow-up hematological tests performed to monitor for neutropenia, the investigators were able to assess whether changes in leukocyte count were associated with a short-term increased risk of stroke. Among 211 patients who had an ischemic stroke during follow-up, leukocyte levels in the prior week, but not earlier, were significantly increased above baseline levels (mean difference 0.5×10^9 cells/l). Whether this increase in leukocyte counts represented infection or some other pro-inflammatory phenomenon remains uncertain from the available data, but neutrophils appear to be the most closely associated with the increased risk of an event.

There are several reasonable biological explanations for the increased risk of ischemic stroke associated with infections. It is well known that severe and life-threatening infections are associated with hypercoagulability and platelet activation that contribute to tissue ischemia and necrosis of many organs during sepsis [40•,41]. There is also evidence, however, that even subseptic infections increase platelet reactivity and platelet–leukocyte interactions, leading to an increased risk of platelet aggregation, potentially precipitating stroke. Platelet activation assessed by P-selectin expression, and platelet–leukocyte aggregates, were both increased in stroke patients compared with controls among 58 stroke cases and an equal number of controls [42•]. Platelet activation and platelet–leukocyte aggregates were also increased among the 21 stroke patients with a history of infection within 1 week before the stroke compared to the 37 stroke patients without recent infection. Severity of stroke was also greater among those with recent infection. Group A streptococcal infections, the cause of necrotizing fasciitis, appear particularly capable of provoking dramatic platelet aggregation and tissue injury [43•]. The toxin streptolysin O induces platelet–neutrophil aggregation, mediated by platelet P-selectin. These

aggregates cause intravascular occlusion and reduced perfusion in animal models. Other organisms which have been implicated in causing atherosclerosis and ischemic events have also been associated with platelet aggregation, including *Chlamydia pneumoniae*, *Helicobacter pylori*, and periodontal infections [44,45,46•].

Infections may also impair endothelial function. Leukocyte count measured at a single point in time is associated with reduced endothelial reactivity in cross-sectional studies [47•]. Infections may also transiently impair endothelium-dependent relaxation in clinical studies. In children, acute infections (predominantly upper respiratory infections) are associated with a temporary reduction in endothelial reactivity [48••]. Among 135 children with acute infection, brachial artery flow-mediated dilation was $6.3 \pm 2.7\%$, compared with $8.1 \pm 3.1\%$ among 166 children 2 weeks out from infection, and $9.7 \pm 2.5\%$ in a control group of 299 well children ($P < 0.001$ for both comparisons). The reduced brachial artery reactivity had returned to normal among the acutely infected children by 1 year later. In a randomized, experimental clinical study among 20 human volunteers, *Escherichia coli* endotoxin (lipopolysaccharide) reduced endothelium-dependent forearm vascular reactivity by 40–50% [49]. Four days of simvastatin reduced neutrophil oxidative burst and plasma tumor necrosis factor-α levels and completely abrogated the effect of endotoxin on vascular reactivity, however, indicating that a statin may protect against acute infection or inflammation-related endothelial dysfunction.

Vaccination may also transiently reduce endothelial reactivity. In a study of experimental *Salmonella typhi* vaccination in healthy volunteers, forearm vasoreactivity was impaired and leukocyte and pro-inflammatory cytokine levels were elevated 8 h after vaccination [50]. In a separate study among 100 healthy volunteers, *S. typhi* vaccination led to significant increases at 8 h in aortic pulse wave velocity, consistent with increased aortic stiffness, and reduced reflection waves, consistent with peripheral vasodilation [51••]. These changes were accompanied by increases in C-reactive protein and other inflammatory mediators. They were abolished, moreover, by pretreatment with aspirin.

The 'stroke-prone state'

In general the current enthusiasm for inflammatory markers as a measure of the risk of subsequent cardiovascular events, including stroke, does not address their potential role as markers of acute susceptibility. Most studies have focused on these markers, particularly high sensitivity C-reactive protein (hsCRP), as a marker of longstanding low-grade inflammation. These studies have generally emphasized the stability of the measurement in individuals over time, recognizing that there is likely to be some noise in repeated measurements. Considered in this way, however, these measures are assumed to represent a chronic condition of the patient, not unlike the way in which a single measurement of blood pressure would represent some insight into the presence of hypertension in a patient. They are less likely to tell us when a stroke will occur, however.

The concept of an imminently high-risk, or stroke-prone, state is perhaps better supported by other lines of evidence. For example, several studies demonstrate that patients with a recent TIA have a particularly increased risk of having stroke in the few days immediately after the event, with the risk decreasing thereafter. The risks are front-loaded, apparently, rather than being distributed evenly over the ensuing months or years. In the now classic analysis of emergency room diagnosed patients with TIA from Kaiser-Permanente in northern California, 50% of the TIA patients who went on to have stroke did so within the first 2 days after the presenting TIA, while the remaining 50% were spread over the ensuing 90 days [52]. Other recent studies have since confirmed this finding in other populations [53].

Repeated neuroimaging discloses that even in the absence of recurrent clinical stroke, there is evidence of subclinical recurrent infarction in many patients with initial stroke. Using diffusion-weighted MRI to assess recurrence, recurrent stroke occurred in a third of stroke patients by 1 week in one study [54]. In another, among 143 patients with stroke or TIA, approximately 10% developed evidence on imaging of recurrent infarction by 30 days, with just over half being asymptomatic [55•]. There is a period, it appears, during which the patient continues to experience ischemic events. This may be the mechanism behind the occurrence of multiple simultaneous infarcts in different vascular territories occurring in patients without known sources of cardiac emboli or pathologically-proven vasculitis [56]. The duration of the high-risk state is uncertain, and in some cases or conditions may last much longer than days or even weeks. In the North American Symptomatic Carotid Endarterectomy Trial (NASCET), for example, the highest risk of having an event was in the first year after stroke [57].

The cardiac literature provides evidence for the presence of a diffuse state of activation of inflammatory cells in the coronary vasculature in patients with unstable angina and acute coronary syndromes. In a study evaluating neutrophil activation based on measurement of myeloperoxidase activity, it was shown that myeloperoxidase activity in veins draining both culprit and nonculprit lesions were similar in patients with unstable angina [58]. Multiple complex coronary lesions (defined as having at least two characteristics of thrombus, ulceration, plaque irregularity, and impaired flow), not limited to the territory of

ischemia, were present in approximately 40% of patients with myocardial infarction [59]. Taken together, these data are consistent with the notion that in patients with acute events there exists a state of a diffusely activated vasculature, rather than the pathophysiological process being simply limited to one focus. This idea of a relatively short-term stroke-prone state is consistent with the new concept recently advocated in the cardiac literature of the 'vulnerable patient', as opposed to the former focus on the 'vulnerable plaque' alone [60].

Therapeutic implications

Identification of a short-term state of elevated stroke risk could have several therapeutic implications. Patients with a history of stroke, or with a significant burden of risk factors for stroke, might be targeted for more intensive stroke prevention therapy during the period of increased risk. For example, an increased dose of antiplatelet agents or statin therapy may be warranted during times of fever or infection, as alluded to above [49,51••]. Use of higher doses of these medications may not be routinely indicated because of the risk of dose-related side effects, but during times of increased stress the benefit may outweigh the risk. Similarly, during periods of inflammatory stress, such as surgery, changes in medication regimen may be instituted.

Alternatively, therapies directed at preventing the stressors in the first place could be targeted to stroke patients. Currently, guidelines for influenza vaccine [35] refer to the treatment of patients over age 55 years, and refer to debilitated stroke patients at increased risk of respiratory complications. They do not advocate treatment of all stroke patients, however. Recent evidence cited above [31••,32–34] suggests the hypothesis that prevention of influenza in patients with history of cerebrovascular disease, or at high risk of stroke, perhaps including those with carotid artery or intracranial stenosis, may prevent not only influenza but stroke as well.

Treatment of patients experiencing stroke despite use of aspirin could also change. Not infrequently one hears the term 'aspirin failure' used to describe the patient who was taking aspirin regularly and yet had an ischemic stroke. One of many explanations for this 'failure' may be invoked: noncompliance, insufficient dose, aspirin resistance, and so forth. Therapy may then be changed due to what is thought to be refractoriness to aspirin (or other drug). An alternative plausible explanation, however, is that the dose of aspirin being used is appropriate for the patient at most times, but that at a particular point in time, perhaps due to the transient presence of a stroke-prone state for the reasons given above, the same dose of aspirin is transiently no longer effective. The same idea of a 'breakthrough' of disease is commonly encountered in other neurological conditions such as seizures and migraine. Febrile seizures in children, moreover, may often be treated only at the time of the inciting fever [61]. Precipitants are also well recognized in migraine. In migraine therapy, moreover, breakthrough events are considered the norm; in fact, the standard definition of a successful migraine prophylactic agent is one that reduces the frequency of migraine by 50% [62]. While a 50% failure rate in stroke prevention therapy would (and should) be considered unacceptable, this line of reasoning does provide a rationale for an alternative understanding of failure of therapy. The threshold of disease may transiently change, and therapy may need to be altered accordingly.

Conclusion

While stroke would appear to be a stochastic event, there is increasing evidence that its occurrence may in fact be more predictable than formerly believed. Several converging lines of evidence provide evidence that transient perturbations in systemic metabolism may provoke the onset of cardiovascular events, including stroke. Infections and other inflammatory stimuli are thought to be foremost among these systemic challenges. Interactions among the immune system, platelets, and endothelium, in particular, likely contribute to the onset of ischemic events. Confirmation of these findings in further studies, particularly among stroke patients, should help elucidate the mechanisms behind this short-term increase in risk. Recognition of the 'stroke-prone state' may also enable improved and more temporally focused preventive interventions.

Acknowledgements

This work was supported by the Kathleen Scott Research Fellowship of the American Heart Association (AHA 0355596T) and grants from the National Institute of Neurological Disorders and Stroke (K23 42912, R01 NS 48134).

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 85–86).

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