Letters to the Editor

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C-Reactive Protein in Ischemic Stroke

To the Editor:

I read with interest the article by Di Napoli et al, who reported the first-ever ischemic stroke to further analyze the relationship between C-reactive protein (CRP) values measured immediately and at different times after stroke, and the 1-year outcome. The important message of this article is that the relationship between CRP and prognosis after cerebral ischemia could be of greater utility for risk stratification and may predict future cardiovascular events or death.

Ischemic cerebrovascular disease accounts for a substantial proportion of all strokes. Although the proximate cause of most brain infarcts is thrombus formation, atherosclerosis is the chief underlying cause.2 CRP, one of the acute-phase reactants, is an indicator of underlying systemic inflammation and a novel plasma marker of atherothrombotic disease.3 Furthermore, elevated plasma levels of CRP are not disease specific but are sensitive markers produced in response to tissue injury, infectious agents, immunologic stimuli, and inflammation.4,5

Plasma CRP levels are known to be higher in smokers, obese individuals, individuals with abnormal fibrinolytic activity (plasmin-antiplasmin complex), and individuals with subclinical atherosclerosis.

We believed that the use of plasma CRP levels may aid in identifying a potentially large number of men and women who are at risk for cerebrovascular events, as described by Rost et al.6

Our clinical prospective data7 from a large community-based cohort of men and women of stroke and transient ischemic attack demonstrate a strong association between CRP and fibrinogen in both sexes. In our cases, 25.3% of patients have normal levels of CRP after stroke, and our data indicate that 21.6% of patients with ischemic stroke who have CRP levels ≥1.5 mg/dL have died, as Di Napoli et al described. We have also detected that some of the ischemic stroke patients have history of the trauma.6

As a result, the detection of especially CRP and fibrinogen is very important in patients with ischemic stroke and transient ischemic attack in determination of possible risk factors, subsequent vascular events or death, and severe neurological deficit and disability, and stratify poststroke patients into relatively high-risk groups.

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Response

We thank Dr İyigün for his interest in our report. Ischemic stroke is a multifactorial disease. It would not be reasonable to consider inflammation as the precipitating cause in all patients, nor to search for a common cause of inflammation in all patients with ischemic stroke. The consistency of data concerning CRP in primary prevention does not imply that screening for CRP among ischemic stroke patients will have clinical utility, thus, rather than generalizing results from primary prevention,1 carefully controlled studies in ischemic stroke patients that include information on stroke severity and other important prognostic factors are needed to determine whether CRP evaluation has utility in secondary prevention. Actually, recent available data suggest that ischemic stroke triggers an acute phase response resulting in a rise of circulating CRP level.2-4

Although infarct size and stroke severity are major determinants for short-term prognosis after ischemic stroke, CRP predicts prognosis, in particular mortality or new vascular events during the first 1-year, independent of infarct size and stroke severity.3,4 However, the degree of the inflammatory response to ischemic stroke is variable: about 25% of patients with first-ever ischemic stroke have normal levels of CRP after stroke, implying that ischemic stroke itself does not induce a full-blown acute phase response.3,4 CRP elevation can result from a variable intensity of the individual acute phase response to cerebral ischemia such that determining an individual’s underlying basal level is difficult. However, the patients in whom the inflammation system reacts most intensely showed a greater 1-year risk of death and a worse functional status with a relevant disability at 1 year.5 CRP levels can increase a thousand-fold, and there is evidence that in some patients constitutional hyperresponsiveness might lead to very high CRP levels even following mild stimuli. Of course, in the presence of overt inflammatory and infectious disease, the data should be interpreted cautiously. Furthermore, distribution of CRP is rightward skewed such that clinical application will likely require recasting measured levels into an ordinal system. A useful approach is to divide CRP values into quartiles. In the Villa Pini Stroke Data Bank, the risk estimate based on such an analysis is shown in the Figure. The relative risk of death

6. Bakirci Y. Fibrinogen and C-reactive protein levels determination in ischemic stroke patients. PhD thesis, Department of Neurology, Faculty of Medicine, Atatürk University, Erzurum, Turkey; 2001.
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Predictive value of C-reactive protein (CRP) and fibrinogen among patients with first-ever ischemic stroke. Data from the Villa Pini Stroke Data Bank.3,4,8
or new nonfatal vascular events was 7.38 (95% CI, 4.19 to 13.00) in individuals with a fibrinogen level in the highest quartile compared with those with a level in the lowest quartile and 8.68 (95% CI, 5.17 to 14.55) for CRP. There is a clearly increased risk of death or suffering of a future vascular event only for patients above a threshold of CRP: there is no evidence of moderate elevation (middle quartile) conferring greater risk of a combined end point. The strong correlation between levels of fibrinogen and CRP \((r=0.45; P<0.001)\) indicates a possible common mechanism, making both fibrinogen and CRP prognostic risk factors. However, the increased risk associated with elevated CRP levels is independent of the prognostic influence of fibrinogen, which indicates that a separate mechanism also contributes.

These findings suggest that patients with an enhanced acute-phase response after an ischemic stroke may differ from other patients and may have a higher risk because of an exaggerated response to some stimuli. This line of evidence may also help to explain why healthy subjects with borderline increased CRP are at higher risk for stroke or transient ischemic attack up to 12 years after the baseline sampling. Individual susceptibility in immune response is based at least in part on genetic background. Variations in baseline plasma CRP of individuals may reflect differences in CRP responses caused, for example, by genetic differences in the CRP gene yielding high and low responders, the former being at risk for cardiovascular disease. However, the search for a candidate gene per se is unlikely to be successful because of the multifactorial pathogenesis of ischemic stroke. An enhanced inflammatory response might depend also on the failure to turn off inflammation when it is not more useful to the organism. Thus it is possible that the search for the prognostic factors in ischemic stroke should be moved from the conventional prognostic factors to the individual predisposing causes. Careful clinical identification of very homogeneous subgroups of patients according to their history, risk factors, and inflammatory markers will be the first step of this search. From this standpoint, CRP measurements should be included according to the standardized protocols and reported on appropriate registries together with patient outcome. These registries will provide the presently lacking information and will gradually improve the prognostic information obtainable from CRP measurements according to age, sex population, clinical variables, and selected clinical endpoints. This is the objective of the ongoing C-reactive protein worldwide study in ischemic stroke (CRPWSIS): an international, multicenter, long-term, prospective, observational study to evaluate the prognostic impact of inflammation markers in ischemic stroke (available at mariodinapoli@katamail.com). Once these data are available, the profile of patients will be drawn; the causes, genetic or acquired, of the hyper-responsiveness can be sought; and new insights will be provided in ischemic stroke medicine.

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Alzheimer Disease as a Vascular Disorder:
Nosophological Evidence

To the Editor:
The recent review by de la Torre on the apparent overlap between Alzheimer’s disease (AD) and vascular dementia (VaD) neglects a fundamental difference between these disorders. AD pathology progresses in a well-described and hierarchically arranged spatial sequence, which begins in the mesiotemporal cortex and moves out, over decades, to affect the frontal, temporal, and parietal lobes. Any attempt to explain AD on the basis of vascular disorder must be capable of explaining its consistent onset in very select regions of interest and both its temporal and spatial progression afterward.

Growing literature suggests that the dementia syndrome associated with AD is merely its final stages. Six progressively widespread pathological stages have been described by Braak and Braak. The age-specific prevalence of stages V and VI almost exactly matches the expected prevalence of clinical AD. Thus, the entire familiar clinical course of mild, moderate, and severe AD may represent only its terminal stages. Many more elderly persons have lesser levels of AD pathology. There is essentially complete penetrance of low-grade AD pathology after 70 years of age, and as many as 40% of 40 year olds may be affected.

Moreover, the mere presence of AD pathology is not indicative of either dementia or imminent risk of conversion to dementia. AD lesions must reach the frontal lobes before clinicians recognize the disorder. Yet most elderly persons do not express that level of pathology. Such individuals’ risk of future progression to clinical AD is unknown. Even very elderly persons with AD pathology at autopsy can escape dementia.

I believe that the apparent overlap in these disorders arises from the failure of clinicians to critically document a pattern of clinical features consistent with the Braak and Braak progression. For example, AD must involve the hippocampus, whereas VaD may not. The memory impairments associated with hippocampal disease can be psychometrically distinguished from those related to frontal systems lesions (which may dominate VaD), yet this distinction is seldom used in AD case definitions. The Braak and Braak sequence also indicates that olfaction should be affected before memory. In fact, anosmia is specifically associated with a hippocampal pattern of memory impairments and faster progression of cognitive impairments, yet this too is seldom documented.

It seems more likely that frontal system VaD converts nonmented persons with early AD pathology to “dementia” by affecting frontal system function. This has been observed in the Nun Study and elsewhere. Because VaD-related executive impairments are likely to be superimposed on common but unrelated mesiotemporal AD pathology, a cross-sectional examination might fail to distinguish such cases from clinical AD (eg, Braak and Braak stage V or higher). However, it is essential to appreciate that dementia in these patients would reflect VaD only, because hippocampal AD pathology does not contribute significantly to clinicians’ impressions of dementia independently of frontal systems disease either in AD or when comorbidly associated with frontal system vasculopathy.
nal follow-up is needed to discriminate an AD-related dementia syndrome from VaD superimposed on subclinical AD pathology.

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Response

I want to thank Dr Royall for his comments. I agree with most of the issues he raises. In my judgment, what is most interesting about vascular dementia (VaD) and Alzheimer’s disease (AD), which I outline in my review, is both their confluence and contrasting clinico-pathological features. In the recent Kyoto conference Vascular Factors in Alzheimer’s Disease1 (Kyoto, Japan, April 7–10, 2002), it was reported that mixed dementia (AD plus VaD) now appears as the most common of all dementias, surpassing either AD or VaD.2 What that finding implies is that a common pathological mechanism may be responsible for the origin of both conditions. This concept is supported by reports showing the many risk factors shared by both dementias,3 as well as identical pathological changes observed in the brains of AD/VaD patients such as the formation of senile plaques, neurofibrillary tangles, and vasculopathic lesions.4

For these reasons, it is important to open the door to the possibility that AD has been and continues to be erroneously classified. If this is true, the implications for patient treatment and management are vast. Dr. Royall’s letter of concern is a good step in airing and questioning this and other paradoxes involving AD.


Recurrent Cerebral Venous Thrombosis in a 24-Year-Old Puerperal Woman

To the Editor:

We read with interest the recent short communication by John Fink and colleagues1 on mastoid changes in patients with lateral venous sinus thrombosis (LST). Their observations are very interesting. Twenty-three LST were identified in 20 patients. Mastoid abnormalities were detected ipsilateral to 9 of the 23 thrombosed lateral sinuses. Only one patient showed evidence of infection, but a diagnosis of mastoiditis seemed unlikely.

This study is the first to suggest a new etiopathogenetic hypothesis for mastoid abnormalities in patients with LST.

We support the authors’ view that in absence of clinical evidence of infection, treatment should be directed at the underlying cerebral venous sinus thrombosis.

With reference to the above-mentioned study, we would like to report the case of a 24-year-old puerperal woman hospitalized and diagnosed with epileptic seizure. Prior to hospitalization, she experienced diffuse headache, right earache, nausea, vomiting, and mild left hemiparesis. At least 2 other members in her family were reported to have an antithrombin III deficiency or suffer from deep venous thrombosis.

She underwent cerebral MRI and MR venography, which showed not only a right transverse sinus, an ipsilateral jugular vein, and a partial superior longitudinal sinus thrombosis but also ipsilateral mastoid abnormality. She then received anticoagulants and empiric antibiotic treatment for 3 months. Follow-up MRI 1 month later showed both a partial resolution of the mastoid abnormality and a recanalization of the venous sinuses.

Two months later, the patient was again admitted for headache, vomiting, nausea, and dizziness. Indeed, it was then discovered that the control of anticoagulant treatment had not been adequate (international normalized ratio <1.5). Cerebral MRI and MR venography were performed and this time showed a left transverse sinus, an ipsilateral jugular vein, straight sinus, and a partial superior longitudinal sinus thrombosis but, again, ipsilateral mastoid abnormality was observed, whereas no mastoid abnormalities were observed on the other side.

The unusual finding of mastoid abnormalities ipsilateral to recurrent venous thrombosis without signs of infection in the same patient supports the hypothesis of Fink and colleagues.1 Mastoid changes are more likely the result, especially in adult life, of altered drainage of mastoid air sinuses rather than of infective mastoiditis, making long-term antibiotic treatment useless. Whereas mastoiditis is the most common risk factor in children,3 in adults there are many other risk factors4–7 that must be screened.

Treatment should be directed at underlying etiologic risk factors such as, in our case, the presence of a moderate decrease in the antithrombin III levels as well as a methylenetetrahydrofolate reductase mutation and a G20210A transition of the
Letters to the Editor

Re: Clinical and Imaging Findings in Cryptogenic Stroke Patients With and Without Patent Foramen Ovale

To the Editor:

We read with interest the article by Lamy et al1 in which they felt that their data did not support paradoxical embolism as the mechanism of stroke in patients with a patent foramen ovale (PFO). Their study excluded patients with a thrombophilia, which is the group most at risk for venous thromboembolism and hence paradoxical embolism. They therefore excluded the stroke patients most likely to have suffered paradoxical embolism. How many such patients were excluded?

They also argued that as deep vein thrombosis (DVT) was rarely detected in their stroke patients, it was unlikely that paradoxical embolism had occurred. However, in patients with a confirmed pulmonary embolism, which must have arisen from a DVT, the causative DVT usually cannot be detected despite extensive investigation.2,3 Considering that the origin of a paradoxical embolus may be a very small DVT, even a valve cusp thrombus, failure to document a DVT after a stroke does not exclude paradoxical embolism any more than it would exclude the diagnosis of pulmonary embolism.

We were interested to see that migraine was again found to be more common in cryptogenic stroke patients with a PFO than in those without a PFO. This association has been reported previously.4 It is biologically plausible that showers of microemboli crossing a PFO may cause cerebral vasospasm and migraine. Szotajel et al4 demonstrated that surgical closure or anticoagulant treatment in stroke patients with a PFO may cure migraine symptoms. Lamy et al do not seem to have considered the possibility that paradoxical embolism may cause migraine in some individuals.

What a shame that the authors chose to investigate subjects up to the age of 55 years in whom atherosclerosis is clearly the predominant cause of stroke.5 Do their data show a greater frequency of PFO in their stroke patients aged under 40? It is not clear whether aortic arch atheroma was assessed during the transesophageal echocardiography investigation.6

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2. Hall DH, Hirsh J, Carter CJ, Jay RM, Dodd PE, Ockelford PA, Coates G, Gill GI, Turpie AG, Doyle DJ, Butler HR, Raskob GE. Pulmonary prothrombin gene, probably aggravated by puerperium.8 In this case, the detection not only of LST but also of jugular vein thrombosis, without clinical evidence of infection, supports the hypothesis of vascular congestion, interstitial edema, and transudation of fluid into the mastoid air spaces. Therefore, we decided to administer to the patient oral anticoagulants without additional antibiotic treatment.

Follow-up MRI 3 months later demonstrated both a reversal of mastoid changes and a complete recanalization of cerebral sinuses and jugular vein thrombosis.

The results reported by John N. Fink and colleagues are exciting, and we agree that other studies are necessary before confirming this interesting new hypothesis.

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Response

We are grateful to Dr Rizzato et al for their interest in our study and for Dr. Rizzato’s contribution to this field. They present a patient with recurrent lateral sinus thrombosis and associated mastoid abnormality. The patient was initially treated with a 3-month course of antibiotics in addition to anticoagulation when there are no clinical signs of infection. We read with interest the article by Lamy et al1 in which they felt that their data did not support paradoxical embolism as the mechanism of stroke in patients with a patent foramen ovale (PFO). Their study excluded patients with a thrombophilia, which is the group most at risk for venous thromboembolism and hence paradoxical embolism. They therefore excluded the stroke patients most likely to have suffered paradoxical embolism. How many such patients were excluded?

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2. Hall DH, Hirsh J, Carter CJ, Jay RM, Dodd PE, Ockelford PA, Coates G, Gill GI, Turpie AG, Doyle DJ, Butler HR, Raskob GE. Pulmonary


**Response**

We agree with Dr Khiani et al that a coagulation disorder may theoretically predispose to paradoxical embolism in patients with a PFO.1 although this remains to be proven. Patients with a definite cause of stroke (including coagulation disorders) were not included in the PFO-ASA study, but we kept a register of all consecutive patients (<55 years) with ischemic stroke who were screened for possible inclusion in the study.2 Of the patients who were not included because of the presence of a definite cause of stroke (whether or not associated with PFO), <5% had a coagulation or hematological disorder. Therefore, the vast majority of patients with PFO-associated stroke have no (currently identifiable) coagulation disorder.

As regards the prevalence of DVT, we only concluded that the low rate of search for DVT in our study suggests that many investigators either are not convinced that paradoxical embolism is a prevalent mechanism of PFO-associated stroke or are concerned about the low yield and pitfalls of a systematic search for DVT.3 We agree that DVT may remain undetected because of its location or the size of the thrombus, but it would be “paradoxical” to use the low yield of a systematic search for DVT as an argument for paradoxical embolism.

The relationship between PFO and migraine is unclear. Assuming cause-effect is a matter of speculation. Statistical association as determined by case-control studies does not necessarily imply causality, because it may result from bias, chance, or confounding.4 Given that the pathophysiology of migraine is poorly known, biological plausibility cannot be put forward to influence this situation. In our clinical experiences, the hemorrhagic complications of migraine (or stroke) will be confirmed when randomized controlled trials will demonstrate that “removal” of this septal disorder, by means of endovascular or surgical techniques, substantially reduces the risk of subsequent migraine attacks (or stroke), in the same way, the relevance of carotid stenosis has been confirmed by the finding that carotid endarterectomy substantially reduces the risk of ipsilateral ischemic stroke.

We selected patients who were <55 years of age because the association of PFO with cryptogenic stroke has been consistently reported in this age group.5 One of the conclusions of our study is precisely that stroke patients with PFO are significantly younger and less likely to have traditional risk factors for stroke than patients without PFO. These differences suggest different stroke mechanisms in patients with and without PFO but do not imply that the mechanism of stroke is paradoxical embolism. Aortic arch atheroma was systematically assessed during transesophageal investigation, and patients with complex atheroma of the aortic arch were not included in the PFO-ASA study.

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ized ratio (INR) range of 2.0 to 3.0, whereas an INR range of 1.6 to 2.5 appears to be associated with incomplete efficacy, estimated at ≈80% of that achieved with higher-intensity OAC.\textsuperscript{3,7,8} For patients with nonvalvular AF, an INR of 1.6 to 3.0 is efficacious and relatively safe. For primary prevention in most AF patients <75 years of age and for secondary prevention, an INR of 2.5 (target range, 2.0 to 3.0) seems reasonable. A target INR of 2.0 (target range, 1.6 to 2.5) is recommended for primary prevention in patients >75 years of age.\textsuperscript{3,9} In our clinics, advancing age generally increases the risk of major hemorrhage in patients given OAC for stroke prevention. Therefore, those patients should be treated with dose-adjusted OAC (INR, 1.6 to 2.5).

In high-risk patients or when a series of procedures requires interruption of OAC therapy for a period >1 week, unfractionated or low-molecular-weight heparin may be administered intravenously or subcutaneously, respectively.\textsuperscript{3} Anticoagulants appeared to be more effective than aspirin.\textsuperscript{10} However, for low-risk individuals, aspirin is a reasonable alternative to anticoagulants.

In conclusion, OACs are indicated for patients with recent transient ischemic attack or ischemic stroke who are in AF. However, especially in use of OAC over much longer periods, one should be careful because of increased risk of the major hemorrhage in patients given OAC for stroke prevention. Also, in clinical practice, the need for antithrombotic therapy in patients with AF typically extends over much longer periods.

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Response
In his contribution, Dr. Lyigün addresses important questions regarding oral anticoagulant (OAC) therapy; the role of nonsteroid anti-inflammatory drugs (NSADs); international normalized ratio (INR) target range; and the importance of number, kind, and degree of risk factors for stroke or embolism in patients with atrial fibrillation (AF).

In patients with chronic AF who are on OAC, sufficient and adequate pain control without the use of NSADs or pain killers, which interact with OAC, is an important prerequisite. If patients are not informed and educated and are poorly followed up, the intake of NSADs may result in mucosal damage with gastrointestinal bleeding. Additionally, drug interactions between NSADs and OAC therapy may lead to increased propensity of bleeding from gastrointestinal, vesical, and respiratory mucosa and the integument.\textsuperscript{1} Furthermore, not only NSADs but a variety of other drugs interact with OAC.\textsuperscript{3} Additionally, it is not only the type of medication but also the absolute number of substances a patient is taking that leads to increasing bleeding risk.\textsuperscript{3}

Dr. Lyigün recommends a lower INR target range in older than for younger patients on the basis of the findings of Yasaka et al.\textsuperscript{4} In that study, however, only a small number of patients was investigated, the follow-up period was short, the distribution between sexes was uneven, and the prevalence of additional risk factors was not mentioned. Furthermore, Yasaka et al did not mention whether the prevalence of minor and major bleeding events differed between patients <75 and ≥75 years of age. On the contrary, a large case-control study showed that the risk of ischemic stroke in patients with OAC increases with decreasing INR values.\textsuperscript{11} In that study, >50% of the patients were >75 years of age. Furthermore, several studies that looked for the preventive effect of low-dose OAC had to be stopped prematurely because of an increased rate of stroke or embolism.\textsuperscript{5}

It is well known that with an increasing number of risk factors, the number of thromboembolic and bleeding events increases, even if the INR target range is 2.0 to 3.0.\textsuperscript{1} Whether a higher INR target range reduces the risk of thromboembolism without leading to more bleeding complications is unknown. Because there are indications that at an INR value of >4.0 the bleeding rate increases significantly, the target range should not be elevated depending of the number of risk factors.\textsuperscript{1}

The recommendation that OAC be given to patients with AF and transient ischemic attacks is not justified at the moment because there are no studies supporting this assumption. It is particularly difficult to investigate patients with transient ischemic attacks because of the heterogeneous causes and the episodic, short-lasting characteristics of these events.

Dr. Lyigün recommends heparin in high-risk patients or when procedures require interruption of OAC for >1 week. To the best of our knowledge, this recommendation is not based on data from the literature. In our institution, we follow the recommendation to give heparin before or after surgery only to AF patients with recent (<3 months) stroke or embolism.\textsuperscript{6}

In conclusion, we propose that OAC be administered to patients in whom AF is accompanied by at least 1 risk factor for thromboembolism (arterial hypertension, diabetes, previous stroke, age >75 years). The INR target range should be 2.0 to 3.0, regardless of the patient’s age. The presence of multiple additional risk factors does not necessitate an increase in OAC dosage in patients >75 years of age. Patients >75 years of age do not require lower INR values than patients <75 years of age. Care should be taken that medication interacting with OAC be avoided.

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Risk Factors for Aneurysmal Subarachnoid Hemorrhage

To the Editor:
I read with interest a recent article concerning risk factors for subarachnoid hemorrhage (SAH).1 The results of this study confirm the results of previous studies that showed for the first time that cigarette smoking is an independent risk factor for SAH irrespective of alcohol consumption, hypertension, or use of nonsteroidal anti-inflammatory drugs or narcotics.2,3 Cigarette smoking seems even today to be the most important risk factor with a similar attributable risk for SAH despite a well-known decreased prevalence in smoking in Western countries during the past 10 to 15 years. In addition, cigarette smoking increases the risk for SAH in a dose-response manner. Particularly, those smoking more than 20 cigarettes per day have an increased risk.2,3 The mechanism behind this increased risk is likely that cigarette smoking increases risk for rupture of an existing aneurysm by increasing its growth rate and, to a lesser degree, by causing aneurysm formation.4

Alcohol consumption seems to have a relatively short-term risk for SAH given that recent alcohol intake during the few days before SAH is a more important risk factor than long-term heavy consumption, likely because of alcohol-induced transient changes in blood pressure or other mechanisms, and because alcohol consumption seems not to cause aneurysm formation or to increase the growth rate of an existing aneurysm.2,3

Recently, family history of intracranial aneurysms has been offered as evidence for genetic causality of cerebral aneurysms.6,7 In the present study, cigarette smoking was for the first time analyzed as a confounding factor for this association. This is important because correlation of smoking habits between family members is higher than in the general population.7,8 Furthermore, 38% to 48% of SAHs can be attributed to current smoking.2,3 whereas risk attributable to affected first-degree relatives accounts for only 5%.7

In the present study, there may be 2 important sources of bias, which may overestimate the significance of family history as a risk factor. Firstly, familial aneurysm cases do not necessarily mean evidence of hereditary risk for aneurysm formation independent of environmental factors. Smoking behavior (number of cigarettes smoked per day or smoking intensity) seems also to be influenced by genetic factors.8 Previously, the number of cigarettes smoked per day was a more significant risk factor than current smoking, and <10 cigarettes smoked per day seems not to increase risk.2,3 This same seems to hold true for aneurysm growth.7 Thus, family history in the present study may be partly a proxy of smoking intensity or heavy smoking as a risk factor independent of current smoking.

Secondly, family history association with SAH was based only on interview data without confirmation of familial aneurysm cases. This confirmation may be a formidable task but it is necessary because even one third of cases giving a positive family history of SAH or cerebral aneurysm either in the interview or in review of medical records may be false-positive cases.6,7 A high number of family history cases in the present study was comparable to that obtained in eastern Finland, where the incidence of SAH is the highest in the Western countries.6,9 This also suggests that there may be a significant number of false-positive family history cases in the present study.

Our purpose was also to test family history as a risk factor for SAH in our previous study of 278 patients with a verified aneurysmal SAH (30% of whom died of SAH) and 314 controls.3 However, I gave up from coding this variable because there were several cases with spontaneous intracerebral hemorrhage, acute brain infarction, or even myocardial infarction or brain tumor who were considered as intracranial aneurysm cases during the interview of only first-degree relatives. This possibility is likely higher among SAH cases than among controls. So, reliability of coding family history of intracranial aneurysms without its verification may be even more difficult than coding alcohol consumption or hypertension.

It is recommended to use smoking intensity and verification of family history cases in future analyses to obtain valid estimates of relative risk of family history of SAH. Only these methods can show true hereditary proportion of risk. All we know is that there are families with a significant history of SAH cases. Fortunately, these cases are very rare in clinical practice, and SAH seems to a great degree to be a modifiable disease.

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References

Response
We appreciate Dr Juvela’s relevant concerns regarding the potential for bias or error in our retrospective case-control study.1 He points out that family history of subarachnoid hemorrhage (SAH) may be unreliable and that family history of smoking may be a confounder in our SAH cases. It is highly likely that SAH due to intracranial aneurysm rupture is a complex trait with important environmental and genetic risk factors. While the purpose of our study was to demonstrate the impact of risk factors on the incidence of SAH, Dr Juvela raises important concerns about such retrospective family histories.
With regard to a bias resulting from false-positive family history, it is true that we did not verify the family history by review of family members’ medical records or imaging studies. In a retrospective case-control study, the most commonly encountered bias regarding family history would be recall bias, in which affected families are more likely to be aware of their family history of SAH. As a measure of the degree of recall bias, we did ask both cases and controls about a family history of dementia and Alzheimer’s disease. We found no difference of positive responses among cases and controls, nor did we find a difference in reported family history of other stroke subtypes such as ischemic stroke or intracranial hemorrhage. Nevertheless, we agree that verification of the subtype of a family history of stroke is the next step in this analysis.

While family histories of SAH may be unreliable, it is not known if they are any more or less reliable in cases as compared with controls. Dr Juvela is correct that data about reliability of family history must be collected in future studies, but in a retrospective study such as ours, validation would be a formidable task requiring much time and expense. Such data will be collected systematically in a future study that will soon be starting (the Familial Intracranial Aneurysm or FIA Study). Our results are consistent with other published results in which odds ratios for family history ranged between 1.8 and 6.6.2–4

It is possible that family history of smoking may be a confounder for family history of aneurysmal SAH. We would first point out that many of our SAH cases with a family history of SAH did not smoke. It may be helpful to consider a pedigree from the FIA study in which 3 of 6 siblings had SAH as a result of ruptured intracranial aneurysm by age 40. While 2 of the 3 were smokers, the risk for SAH at this young age is extremely low (a cumulative absolute risk of <1% for smokers up to age 40). Given that 50% of siblings were affected by this age, it is unlikely that SAH was due solely to smoking. Rather, it is more likely that smoking increases the penetrance of a genetic predisposition to aneurysmal rupture.

Smoking is consistently recognized as the most important risk factor for SAH and may aggregate in families due to environmental/behavioral reasons as stated by Dr Juvela or due to genetic causes (ie, a gene for smoking or addiction). It is thus possible that the familial aggregation of SAH may indeed be a genetic susceptibility to smoking, which leads to SAH.

Given that we did not ask about family history of smoking in our interviews, we cannot quantify this effect. Any such information obtained would also be subject to recall bias unless all first- and second-degree family members among cases and controls were interviewed directly. In our study,1 family history of subarachnoid hemorrhage was a risk factor for SAH independent of both current and former smoking (see Table 3, matched logistic regression). Our report was a preplanned midpoint analysis and there was insufficient power to consider interactions. In the final logistic regression analysis, an interaction between smoking and family history may lend further indirect evidence to the effect of smoking among families. Our upcoming Familial Intracranial Aneurysm study will examine the importance of a family history of smoking and the potential susceptibility to SAH.

Dr Juvela’s points are well taken. Future epidemiologic studies of SAH must take these factors into account as much as can be done practically.

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Global Cerebral Edema After Subarachnoid Hemorrhage

To the Editor:
We have read with great interest the article by Claassen et al on cerebral edema after subarachnoid hemorrhage (SAH).1 Their results are in agreement with those we presented in another recent article.2 When analyzing the factors associated with bad prognosis at hospital admission in 294 patients suffering SAH admitted to our center during a 10-year interval, global cerebral hypodensity was present in 7% of the patients, a figure similar to that presented by the authors. Global brain hypodensity stood as an independent factor for bad prognosis in both univariate and multivariate logistic regression analyses. In our series, as in this recent article, global brain hypodensity in the admission CT was clearly related to mortality, as more than 90% of patients with this factor died, sooner than patients without edema (median 2 versus 10, 2 versus 8 in the Claassen et al series) and more often as a direct result of the hemorrhage (84% in our series).

The analysis of which factors are related to global brain edema is a unique feature of the study by Claassen et al. We have performed the same analysis in our own data, as presented in the Table. The level of consciousness at admission was the main variable related to the presence of global brain hypodensity in our series, and loss of consciousness at stroke was also an associated factor in the univariate analysis. We agree with the mechanisms the authors propose as responsible for the presence of global brain hypodensity. Ictal circulatory arrest and insufficient cerebral perfusion caused by severe intracranial hypertension leads to diffuse ischemic encephalopathy after suffering severe SAH. Several studies using acute MR diffusion-weighted and positron-emission tomographic techniques3,4 have shown widespread ischemic areas in patients suffering poor-grade SAH, supporting that a widespread vascular dysfunction after severe SAH could exist and most probably be responsible for the poor clinical condition of the patients. However, we still do not know whether the presence of the hypodensity on CT is a consequence of this dysfunction or a treatable cause.

The genesis of delayed edema is also considered by the authors, and interestingly it seems that its presence could be partly due to the initial damage to the cerebral circulation caused by the bleeding and to the use of vasopressors. “Triple-H” therapy has not yet gained widespread acceptance, and recently its results have been questioned.5,6 Thus it would be desirable to know which patients could be in danger of developing such a complication, and most probably this will be the subject of further investigation.

Finally, one of the main drawbacks of using brain edema as a prognostic factor is the possible lack of interobserver reliability and/or CT definition when assessing this characteristic. The
Factors Related on Admission to Global Brain Hypodensity in the Initial CT Scan in 294 Patients Suffering Spontaneous Subarachnoid Hemorrhage

<table>
<thead>
<tr>
<th>Admission Global Hypodensity</th>
<th>With (n=21)</th>
<th>Without (n=273)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>47±15</td>
<td>55±14</td>
<td>0.02</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>11 (52)</td>
<td>167 (61)</td>
<td>0.427</td>
</tr>
<tr>
<td>Loss of consciousness, n (%)</td>
<td>21 (100)</td>
<td>180 (66)</td>
<td>0.001</td>
</tr>
<tr>
<td>Seizures, n (%)</td>
<td>0 (0)</td>
<td>31 (11)</td>
<td>0.1</td>
</tr>
<tr>
<td>WFNS poor grade, n (%)</td>
<td>18 (86)</td>
<td>67 (25)</td>
<td>0.001</td>
</tr>
<tr>
<td>Admission CT scan &lt;24 h after ictus, n (%)</td>
<td>20 (96)</td>
<td>223 (82)</td>
<td>0.1</td>
</tr>
</tbody>
</table>

Radiographic findings on admission

<table>
<thead>
<tr>
<th></th>
<th>With (n=21)</th>
<th>Without (n=273)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAH sum score</td>
<td>15±8</td>
<td>12±9</td>
<td>0.2</td>
</tr>
<tr>
<td>IVH</td>
<td>1.14</td>
<td>0.84</td>
<td>0.95</td>
</tr>
<tr>
<td>ICH, n (%)</td>
<td>5 (24)</td>
<td>61 (22)</td>
<td>0.8</td>
</tr>
<tr>
<td>Hydrocephalus, n (%)</td>
<td>4 (19)</td>
<td>70 (26)</td>
<td>0.5</td>
</tr>
<tr>
<td>Fisher 3 or 4, n (%)</td>
<td>21 (100)</td>
<td>222 (81)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

χ² statistics were used for discrete variables and Student's t test for continuous variables. Bold P value denotes significance maintained after multivariate logistic regression analysis. WFNS indicates World Federation of Neurological Surgeons; SAH, subarachnoid hemorrhage; IVH, intraventricular hemorrhage; ICH, intracerebral hemorrhage.

authors brilliantly solve this problem by accurately defining global and focal edema and achieving good interobserver reliability indexes.


Response

We thank Dr. Lagares et al for their interest in our study and appreciate their confirmatory findings regarding predictors of global edema after subarachnoid hemorrhage (SAH). We believe that this phenomenon has not received enough interest in the past. Data they have presented in their earlier article and additional data presented in their reanalysis of their original cohort confirm our findings in terms of the frequency of admission global edema, the earlier timing of death in these patients, and the overall negative impact on outcome.

In addition, their analysis of predictors of admission global edema corroborates the strong association of this entity with admission clinical and radiographic findings. Again, they confirm the key observation that loss of consciousness at onset, which presumably reflects intracranial circulatory arrest, is strongly related to the development of global edema. However, their overall frequency of loss of consciousness was higher than in our study (68% versus 37%). As in our study, none of the admission CT findings remained independent predictors in their multivariate analysis.

We agree that future studies will have to investigate the genesis of global edema and determine whether this is an unpreventable occurrence in a severely injured brain, or if treatment strategies can be developed to prevent its development. MR and CT perfusion imaging may more accurately demonstrate the development of global edema and determine the role of cerebral blood flow abnormalities, microdialysis may help to understand its pathophysiology on a cellular level, and animal studies might be helpful in developing treatment strategies. As it has become clear that most of the burden of morbidity and mortality after SAH is attributable to the direct effects of bleeding, it is our hope that early ICU-based resuscitation strategies may allow us to eventually improve the outlook for these extremely poor-grade patients.

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Body Temperature in Acute Stroke

To the Editor:

I read with great interest the recent article by Boysen and Christensen on body temperature. Their study is probably the first to have described the hourly changes in body temperature after onset of stroke and intracerebral hemorrhage. Although they used paracetamol for the patient with a body temperature >37°C, the pattern was very similar to that observed in an animal experiment. This suggests that the basic mechanisms underlying the temperature changes after cerebral stroke are the same in both animals (rats) and humans. However, I have one very serious question. The authors measured body temperature at the tympanic membrane but did not show the normal value of the body temperature measured by this method. They administered paracetamol to reduce body temperature when the temperature exceeded 37.0°C. However, several studies have documented that the normal body temperature measured at the tympanic membrane is 37.5°C. This means that, in fact, the initial body temperature after cerebrovascular disorders reported by them (36.5°C) may have been lower than normal (ie, hypothermic). Therefore, I think that the true explanation of their result is that
cerebral ischemia or intracerebral hemorrhage can lower body temperature, at least for the first few hours after onset.

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Response  
We thank Dr Takagi for his interest in our study on body temperature in acute stroke. In our study, temperature was measured by a tympanic thermometer, FirstTemp Genius 3000 A. Dr Takagi suggests that normal body temperature at the tympanic membrane is 37.5°C, and that our patients were hypothermic initially.

We recently compared rectal temperature measured by mercury thermometer and temperature measured by the tympanic device in 95 stroke patients. The mean temperature by rectal temperature measurements was 37.16°C (range, 36.2°C to 38.1°C). The mean temperature by the tympanic measurement was 37.12°C (range, 35.5°C to 38.3°C). We thus could not confirm that the investigated tympanic device results in higher temperatures than the rectal measurements. However, we found that tympanic temperatures varied more than the rectal temperatures.

We agree that in the cited article, initial temperature in our acute stroke patients was slightly below normal, especially in those with severe stroke. The rise in temperature over the first 10 to 12 hours was restricted to patients with severe strokes.

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C-Reactive Protein in Ischemic Stroke
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