Letters to the Editor

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Proinflammatory Cytokines and Glutamate in Acute Stroke

To the Editor:

I have with great interest read the article, “Proinflammatory Cytokines and Early Neurological Worsening in Ischemic Stroke,” by Vila et al.1 Bearing in mind the complexities of interleukin (IL)-6 effects, I would like to ask the authors the following questions:

Are the patients included in this study the same patients as in the earlier published studies2 from the same research group concerning glutamate?

If so, is there a relationship between IL-6 and glutamate that can be identified in the material?

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Glutamate, Interleukin-6, and Early Clinical Worsening in Patients With Acute Stroke

To the Editor:

We appreciate Dr Christensen’s interest in our work, recently published in Stroke.1 As we stated in the Subjects and Methods section of that article, the 231 patients analyzed in our study were selected from a larger cohort of 249 patients admitted consecutively between October 1992 and December 1996. Shrewdly, Christensen correctly guesses that this larger cohort includes the 128 patients that supported our report on glutamate excitotoxicity in acute ischemic stroke.2 Therefore, this larger series gives additional ground and further credit to the role of glutamate and IL-6 on neurological deterioration in patients with ischemic stroke.

The concentrations of glutamate in plasma (309.6 ± 64.8 versus 106.3 ± 49.3 μmol/L; P < 0.0001) and CSF (13.3 ± 3.8 versus 6.4 ± 4.2 μmol/L; P < 0.0001) were significantly higher in patients with clinical deterioration than in patients who remained stable or improved during the first 48 hours. Glutamate and IL-6 levels were positively correlated in samples of both plasma (Spearman coefficient 0.66, P < 0.001) and cerebrospinal fluid (CSF) (Spearman coefficient 0.49, P < 0.001). As shown in the Table, variables that remained independently associated with early clinical deterioration on multivariate analysis included IL-6 > 21.5 pg/mL in plasma or > 6.3 pg/mL in CSF, glutamate > 200 μmol/L in plasma or > 8.2 μmol/L in CSF, admission Canadian Stroke Scale score, and serum glucose.

As pointed out by Dr Christensen, IL-6 has complex mechanisms of action that at present are not clearly understood. While we and others3 suggest proinflammatory properties in acute stroke, a recent article reported in this journal4 disputed these conclusions and found deleterious properties of IL-6. In this study, infarct size and neurological function at 24 hours were not different in animals deficient in IL-6 after transient cerebral ischemia.5 Moreover, other animal models6 have shown that the local infusion of IL-6 attenuated the neurotoxic effects of NMDA in striatal cholinergic neurons, thus suggesting neuroprotective rather than proinflammatory actions.

Glutamate and IL-6-disclosed related effects in our patients, in agreement with the overlap observed between inflammatory and excitotoxic pathways in experimental models. The increased expression of cytokine genes after injection of NMDA suggested that overactivation of NMDA receptor is one of the main stimuli to cytokine gene transcription in the ischemic brain.6 IL-1 may interact with AMPA and NMDA receptors in the striatum to stimulate cortical pathways that lead to neuronal death, probably through glutamate release.7 In contrast, IL-1 receptor antagonist blocks cerebral damage caused by both NMDA and AMPA receptor activation.8 Finally, IL-10 prevents apoptotic changes induced in response to glutamate release. Cortical cultures obtained in IL-10 knockout mice are more vulnerable to NMDA injury in vitro, whereas the administration of IL-10 to this culture prevents neuronal death induced by excitotoxic stimuli.9,9

In summary, our results suggest that glutamate and IL-6 are important and independent contributors to neurological deterioration in patients with acute stroke. However, additional studies will be needed to clarify the mechanisms underlying neurological worsening, including the interaction between IL-6 and glutamate. Hopefully, this deeper understanding will result in more effective therapeutic strategies for this devastating condition.

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2. Bener A, Almalki A, Dávalos A. Glutamate and interleukin-6 effects, I would like to ask the authors the following questions:


Coagulopathies in Ischemic Stroke

To the Editor:

In their progress review, Bushnell and Goldstein 1 have meta-analyzed the current literature (mostly retrospective case-control studies) about coagulopathies in ischemic stroke. Based on their calculated pretest probabilities and recommendations of coagulation experts, they propose a testing strategy that might help to reduce and interpret coagulation tests in unselected patients with ischemic stroke.

However, in their carefully combined analysis, we miss an interpretation and estimation of the impact of coagulopathies in ischemic stroke, especially in the young. This can be achieved by calculating the attributable risk, which combines the pretest probability (reflecting the prevalence of the risk factor in the population) with the relative risk. 2 Assuming the data given in the paper, the population-attributable risks for the reported coagulopathies can be calculated (Table 1; assuming that the odds ratios are an estimate for the relative risk). These data indicate, especially for younger patients, that although the pretest probability is low, due to high odds ratios the attributable risk is high. For all patients, the estimated attributable risk of coagulopathies is only 2% to 8.7%, which is low compared with other risk factors such as hypertension (which had an attributable risk of 26% in the Rochester Project 3).

As long as definitive guidelines and prospective population-based studies are lacking, coagulopathies have to be regarded as dominant ill-defining factors for many patients. We conclude that in younger patients, in whom common arteriosclerotic risk factors are often absent, it can be estimated that a considerable proportion of ischemic strokes are caused by genetic or acquired coagulopathies or other yet-to-be-defined coagulation defects.

Estimated Attributable Risk for FVL/APCR, Prothrombin Mutation, ACL, and LA

<table>
<thead>
<tr>
<th>Coagulopathy</th>
<th>Age ≤50 y (95% CI)</th>
<th>All Ages (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACL</td>
<td>19.4% (7.4–36.9)</td>
<td>7% (5.2–9.1)</td>
</tr>
<tr>
<td>FVL/APCR</td>
<td>9.5% (6.1–13.4)</td>
<td>2.9% (1.5–4.3)</td>
</tr>
<tr>
<td>LA</td>
<td>5.2% (0–24)</td>
<td>8.7% (1.5–22.8)</td>
</tr>
<tr>
<td>Prothrombin mutation</td>
<td>4.3% (1.5–9.1)</td>
<td>2% (0.1–4.3)</td>
</tr>
</tbody>
</table>

ACL indicates anticardiolipin antibodies; FVL/APCR, factor V Leiden/APC-resistance; and LA, lupus anticoagulant.

Response

Drs Weih and Villringer estimated attributable risk for ACL, LA, APCR, and the prothrombin mutation in ischemic stroke. We would first like to clarify that our analysis 4 was based on a systematic literature review and not a meta-analysis. Attributable risk estimates need to be calculated with multiple regression techniques so that each risk factor is adjusted for the others that may contribute to the outcome under consideration. 2 However, the majority of the odds ratios used by Drs Weih and Villringer to calculate these estimates were not adjusted for traditional stroke risk factors. This can lead to an overestimation of attributable risk. Whisnant 3 highlighted this problem during his 1997 Willis Lecture. He found that the unadjusted attributable risk for stroke for hypertension was 37% but decreased to 26% after adjustment for other risk factors and interactions in multiple regression modeling. In addition, O’Fallon and Sicks 3 have shown that all stroke risk factors have a higher attributable risk in younger patients. This could lead to a further overestimation of the attributable risk associated with coagulopathies. Because of these concerns, we felt that we could not calculate the attributable risk associated with specific coagulopathies.

Our review focused on the prevalence of coagulopathies in ischemic stroke patients from case-control studies of highly selected patients. Population-based estimates of the prevalence of these coagulation disorders in the general population and in ischemic stroke patients, as well as the number of ischemic stroke patients without these coagulation disorders, are needed to provide the most valid assessment of population-attributable risk. Because of the low yield of specialized testing for coagulopathies, an assessment of traditional risk factors and etiologies is necessary before the diagnosis is pursued.

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Re: Anticardiolipin Antibodies Are Not an Independent Risk Factor for Stroke

To the Editor:

The role of anticardiolipin antibodies (aCL) as risk factors for stroke was examined in an incident case-referent study nested within the MONICA and Västerbotten Cohort Project. 1 The authors conclude that while aCL were associated with future stroke, they did not constitute an independent risk factor. Their
data do not support a causative role for IgA-aCL and IgG-aCL but neither do the data justify dismissing IgM-aCL as an independent risk factor.

On multivariate adjustment for hypertension, diabetes mellitus, current cigarette smoking, and smokeless tobacco, the odds ratio for future stroke associated with IgM-aCL decreased from 1.34 to 1.24 and was no longer statistically significant. However, the 95% confidence interval was fairly narrow (0.98 to 1.56). It is highly likely that a type II error could explain this loss of statistical significance. The authors gave no indication of the power of the study to detect the independence of aCL as risk factors for stroke. The effective sample size would also have decreased because of missing values. Data from Table 1 of the article suggests that several patients and controls had no data on the covariates included in multivariate logistic regression model on which the authors based their conclusion. For example, 11 patients and 15 controls had no data on hypertensive status.

Smoking was not an independent risk factor in this study, either. However, it would be imprudent to suggest on the basis of this study that smoking is not a risk factor for stroke. As the authors indicate, this is the only prospective study to report an association between aCL and stroke. Furthermore, few studies have examined the role of IgM-aCL. In light of this, the consequences of a misleading conclusion are important.

Some of the risk associated with IgM-aCL was explained by the other classic risk factors included in the regression model, and the antibodies could be the result of endothelial cell damage induced by these factors. On the other hand, they may have a causal role, and this needs to be further investigated. IgM-aCL increased the risk of stroke by only 24% in this study. If this is a true indication of the strength of the association, then future studies will need larger sample sizes to be able to assess the independence of IgM-aCL as a stroke risk factor.

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Response

We examined antibodies against cardiolipin as predictive factor for future stroke in an incident case-referent study nested within the MONICA and Västerbotten cohort project. According to our results, IgM ACL are not an independent risk factor for stroke: an incident case-referent study nested within the MONICA and Västerbotten cohort project. Stroke. 2000;31:1289–1293.


Question

Visiting the Question, “Is the Acetazolamide Test Valid for Quantitative Assessment of Maximal Cerebral Autoregulatory Vasodilation?”

To the Editor:

The letter of Derdeyn 1 in response to the article by Demolis et al 2 discusses the evidence against the use of acetazolamide for maximal cerebrovascular dilation. This is important because (1) compared with CO2, acetazolamide is safer and more easily administered in assessing cerebrovascular reserve (CVR), and (2) CVR assessed by quantitative cerebral blood flow (CBF) with acetazolamide is predictive of increased stroke risk. If CVR proves to be equivalent in detecting Powers 3 stage II compromised CVR, it would be more readily available, more easily done, and done at lower cost than PET OEF. Demolis et al 2 studied “CBF” changes in rats subjected to changes in arterial blood pressure with and without acetazol-
amide treatment and by 7% CO₂ challenge. CO₂ caused further dilation above that induced by 42 mg/kg acetazolamide. That CO₂ causes further cerebrovascular dilation beyond that caused by acetazolamide is not surprising. Acetazolamide decreases tissue and extracellular fluid buffering capacity, thus enhancing the effectiveness of CO₂ in lowering extracellular fluid pH, which does not invalidate the use of acetazolamide in detecting stage II compromised CVR. There is more to cerebrovascular autoregulatory dilation than brain pH.

True to the title of their study, Demolis et al² studied the effect of acetazolamide on cerebrovascular autoregulation. However, it is not a model to assess the validity of acetazolamide in detecting compromised CVR. Thus, the extension of this work to the clinical realm may be questionable, but Derdeyn expressed concern about even suggesting a value of acetazolamide-based studies.

Citing Hauge et al.,³ Derdeyn states that the vasodilatory effects of acetazolamide are complex and very likely caused by mechanisms other than PCO₂-induced vasodilation. The basis for this suggestion is purely speculative. Hauge et al. noted a rapid effect of acetazolamide in causing cerebrovascular dilation, the magnitude of which they estimated would require an increase in brain PCO₂ of 2 kPa (15 mm Hg), which was thought highly unlikely since arterial PCO₂ was unchanged. Arterial PCO₂ has no bearing on whether brain PCO₂ may be elevated.

Derdeyn cites the work of Inao et al⁵ and Kazumata et al⁶ as showing striking discordances in the comparison between acetazolamide and hypercapnia. Inao et al.⁵ studied 6 patients with unilateral “steno-occlusive lesion” and PET cerebral blood flow (CBF) measured during primary sensorimotor cortex activation (PSM) by bilateral hand clamping and after acetazolamide. The authors reported that with PSM activation, rCBF increased in both PSM regions. In contrast, their Figure 1 and Table 3 show that acetazolamide increased CBF markedly in the contralateral, unaffected hemisphere without increasing CBF in the ipsilateral hemisphere, suggesting that the lack of an increase with acetazolamide in the compromised region was probably due to interhemispheric steal. The comparison of PSM and acetazolamide in the compromised region was probably due to the basis for this suggestion is purely speculative. Hauge et al. noted a rapid effect of acetazolamide in causing cerebrovascular dilation, the magnitude of which they estimated would require an increase in brain PCO₂ of 2 kPa (15 mm Hg), which was thought highly unlikely since arterial PCO₂ was unchanged. Arterial PCO₂ has no bearing on whether brain PCO₂ may be elevated.

The study by Kazumata et al⁶ reported that acetazolamide identified patients with compromised CVR who had good responses to hypercapnia. However, the administration of CO₂ caused a significant increase in arterial blood pressure despite the authors’ statement that they could not find a correlation between change of blood pressure and CO₂ reactivity. Our regression analysis of their data shows that the change in blood pressure correlated linearly with the change in PacO₂ (P = 0.0128), and more importantly, that the change in blood pressure and the change in CBF was significant in the ipsilateral (P = 0.037) but not in the contralateral (P = 0.159) hemisphere. Thus, the discrepancy between hypercapnia and acetazolamide can be explained by the effect of hypercapnia on blood pressure. Furthermore, only 4 of the 11 patients would have been identified with compromised CVR by our previously published criteria.⁸

Derdeyn cited methodological flaws in the study by Yonas et al⁷ that we believe were not flaws. The use of a mixed patient population would be a flaw if one were to use the qualitative method of OEF estimation used by Grubb et al.⁹ It requires “normal” contralateral hemispheres and patients without bilateral carotid disease, but it is not a requirement in quantitative CBF measurement of CVR. Yonas et al retrospectively defined hemodynamic thresholds to identify normal and abnormal acetazolamide responses because it was a hypothesis building study. On the basis of this information, the study was subsequently extended in a publication by Webster et al.,¹⁰ which again identified a high-risk subgroup and should logically be followed by a larger multicenter study to validate or establish the CVR thresholds.

Although Derdeyn cited the study by Yokota et al¹¹ as also indicating the lack of utility of acetazolamide as a cerebrovascular challenge, this study was flawed. They used the ratio of the affected side to that of the “normal” side for an asymmetry index or (ΔAI) based on qualitative SPECT measurements. As shown by Yonas et al.,¹² a CBF ratio approach fails to identify 50% of the patients with compromised CVR. Use of an average ΔAI index from a normative curve for comparison is an inferior statistical design that eliminates the power of repeated measures analysis. Quantitative CBF assessment makes no assumptions and simply assesses compromised CVR for a given region in response to acidosis induced by acetazolamide.

Finally, the relationships between changes in CBF, OEF, CMRO₂, and cerebral blood volume, to which we would add CBF, as illustrated by Powers,³ is based on the normal brain, and even then partly on speculation. We know little about the changes in these variables in the hemodynamically stressed brain. Despite the belief of Derdeyn et al¹³ that only OEF provides a measure of stage II hemodynamic stress, the use of the interhemispheric relative OEF ratio provides a view of only a highly select subgroup of patients, which may not be generalizable to the greater universe of patients with symptomatic occlusive vascular disease.

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Coagulopathies in Ischemic Stroke
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