Interleukin-6 and Stroke: Cerebral Ischemia Versus Nonspecific Factors Influencing Interleukin-6

To the Editor:

We have read with great interest the article of Acalovschi and colleagues.1 Highly appreciating the scientific value of this article, we would like to address several important issues not discussed by the authors.

Albeit about 8 independent studies have demonstrated interleukin-6 (IL-6) increase in serum/plasma of acute stroke patients, the virtual magnitude of this phenomenon is still difficult to assess. Many factors can confound the results of human studies. Some of these factors, such as psychological stress that could increase IL-6 level in blood,2 are difficult to control and quantify. The important group of factors significantly elevating IL-6 level constitutes vascular risk factors: hypertension, diabetes mellitus, obesity, and cigarette smoking.3,4 Coronary artery disease (even stable angina), a condition not rare in stroke patients, is also associated with increased serum IL-6 level.5 When a stroke patient group is compared with healthy subjects, it is not possible to separate serum IL-6 increase due to vascular risk factors from that triggered by cerebral ischemia. Serial measurement of IL-6 during stroke is helpful to determine kinetics of this cytokine (relative increase or decrease), but it does not allow to determine in which degree brain ischemia by itself elevates IL-6 level. Therefore it seems rational to use in future studies not only one control group consisting of healthy individuals, but also another control group matched not only for age and sex, but also for cardiovascular risk factors profile.

Several drugs often used in stroke patients (aspirin, statins, and probably beta-blockers and ACE-inhibitors) could significantly reduce serum IL-6 level.5–7 In the study of Acalovschi and colleagues, a significant number of patients was treated with antiplatelet drugs and statins during hospitalization (but it is not clear how the patients were treated after discharge during the follow-up period). These drugs, by inhibiting effects on the inflammatory reaction, could lessen the differences of IL-6 between studied groups. Therefore, in future studies the control group should include, if possible, subjects treated similarly as stroke patients (for example, patients with stable angina treated with aspirin and statins).

The choice of control group could explain why, in contrast to some previous studies including subjects with cardiovascular risk factors as controls,4,8 in the study of Acalovschi and colleagues, IL-6 level measured after 90 days of stroke onset was still higher in stroke patients than in controls.

All above considerations can be also applied to C-reactive protein (CRP), the molecule induced by IL-6.

And a last point: the authors have written that “the ischemic brain appears to be a major source of IL-6 in stroke . . . .” In our opinion the alternative hypothesis stating that blood cells (monocytes) are the major source of blood IL-6 in stroke patients merits consideration. First, in an experimental model of cerebral ischemia, mRNA for IL-6 increases first in serum, and then in the brain.9 Second, the brain can tightly control IL-6 production by blood cells. Interleukin-1 increase in brain tissue (seen in animal models of stroke) can trigger IL-6 release into blood.10 Third, monocytes isolated from the blood of stroke patients release significantly more IL-6 in vitro than cells from controls.11 To summarize: the source of IL-6 in human stroke still remains unknown.

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Response

We have read the comments of Dr Dziedzic et al with great interest. They are right that the elevation of interleukin-6 (IL-6) in acute stroke patients compared with healthy controls could be due to the cerebral ischemia or to the preexisting vascular pathology. However, Beamer and colleagues have already shown that IL-6 serum concentrations decline over 1 year after the event.1 This strongly argues for an elevation of IL-6 levels by the acute stroke as we cannot assume the underlying atherosclerosis to regress. Nevertheless, vascular risk factors are likely to contribute also to the observed elevation of IL-6 levels in acute stroke patients.

The source of IL-6 in serum after stroke is another important issue. As IL-6 is ubiquitously expressed, we fully agree with Dziedzic et al that a nonneural source of IL-6 after stroke is conceivable. Unfortunately, there are no means to determine the origin of IL-6 in human stroke. The suggestion that serum IL-6 reflects, at least partly, IL-6 production of the ischemic brain is based on the following evidence: (1) Several studies have reported a tight correlation between stroke volume and IL-6 serum levels.2–4 (2) In animal models of stroke there is a profound increase of IL-6 expression in neural cells.5,6 (3) Tarkowski and colleagues have found a higher rise of IL-6 in cerebrospinal fluid than in serum after stroke.5 It is no contradiction that in the experimental study of Clark et al, serum levels of IL-6 had a marked increase by 3 hours, whereas IL-6 mRNA accumulation in the mouse brain (assessed by a single measurement of pooled samples) was not elevated until 12 hours.8 The fact that Clark et al missed an earlier induction of IL-6 in the brain is due to the lack of statistical analysis since other studies have shown that IL-6 in the brain is significantly upregulated after only 2 hours of focal cerebral ischemia.6,8 With refined analytic techniques or genetic approaches,
it is hoped that future studies will elucidate the tissue source of the IL-6 rise in stroke. Definite evidence for a neural source of IL-6 in stroke would provide a tool to study neuroinflammatory processes in the human brain.

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