Editorial

Subarachnoid hemorrhage and microdialysis

R. Loch Macdonald, M.D., Ph.D.

St. Michael’s Hospital, University of Toronto, Ontario, Canada

Aneurysmal subarachnoid hemorrhage (SAH) affects 10 per 100,000 people each year, and the outcome is poor. Many patients die immediately, and among those who reach the hospital alive, 25% die and ~ 50% of the survivors remain disabled. Death and disability are usually attributed to brain damage from the initial effects of the hemorrhage and delayed complications such as delayed cerebral ischemia usually due to vasospasm. Given the major impact of the initial hemorrhage, a better understanding of it would be important for improving the overall outcome, although little has been achieved in that regard. Rebleeding as a cause of poor outcome has been declining in importance with the advent of routine early aneurysm obliteration and perhaps short courses of anti-fibrinolytic drugs if early obliteration cannot be done.

Thus, we tend to focus on preventing secondary brain injury and treating delayed cerebral ischemia. In their prior analysis, Samuelsson et al. identified 13 episodes of “energy crisis” indicated by an L/P ratio > 40 in the 33 patients. The hemodynamics during these episodes must be analyzed.

The key point the authors make is that lowering the ICP to maintain adequate or high levels of pyruvate and Gln may be beneficial, and that these biochemical effects may occur with lower ICPs (that is, < 15–20 mm Hg) than are sometimes recommended. This provocative recommendation contrasts with some management schemes. For example, one method of managing increased ICP is CPP-guided: one tries to keep the CPP > 60 or 70 mm Hg without specifically addressing the increased ICP. Another example is when after SAH, I sometimes do not use ventricular drainage in patients with good clinical grades who undergo surgery when the brain is slack and brain retraction is not needed.
vascular treatment of a ruptured aneurysm, ventricular drainage is usually used only in patients with poor clinical grades. This finding is based in part on the unproven assumption that forcing normal intracranial circulation of CSF out of the ventricles and through the subarachnoid space promotes clot clearance and decreases the delayed detrimental effects of SAH on the brain. The ICP can be high in these patients. But there is emerging evidence to support the contention of Samuelsson and colleagues that this may not create the best milieu for the brain. For example, Dunham, et al.2 found evidence of cerebral hypoxia at some times in patients with head injuries even when CPP was > 70 mm Hg.

Some assumptions and limitations still must be addressed with further research before we fully understand these data and adopt the recommendations. Microdialysis samples only a small area of the brain. The findings in this study are only correlations of biochemical measurements and CPP. Their statistical methods also could have been conducted another way. The authors assumed that each measurement (3617 hours or measurements in 33 patients or ~ 109 measurements per patient) was independent, whereas they had multiple measurements (~109) in 33 patients. This approach is different and is usually handled differently statistically. The authors report a trend in which Gln and pyruvate tend to increase over time; this trend should be taken into account when analyzing the data.

In summary, the authors have a substantial database of microdialysis monitoring in patients with SAH from which they will be able to generate some interesting hypotheses. The current analysis suggests that increased ICP, perhaps independent of reduced CPP, impairs brain metabolism. If this hypothesis can be confirmed in larger numbers of patients and treatment can be undertaken with improved outcome, then a major advance will have been made.

References


Response

CAROLINA SAMUELSSON, M.D., PH.D., TIMOTHY HOWELLS, PH.D., EVA KUMLrien, M.D., PH.D., PER ENBLAD, M.D., PH.D., Lars Hillered, M.D., Ph.D., AND ELISABETH RONNE-ENGSTRÖM, M.D., PH.D.

Uppsala University Hospital, Uppsala, Sweden

We appreciate the editorial comments. Maintaining an adequate cerebral energy metabolic capacity is of major importance in neurointensive care. Events resulting in failing substrate delivery or increasing metabolic demands are known as secondary insults and can lead to energy failure and a worse outcome. Patients with aneurysmal SAH appear to be sensitive to such secondary disturbances, probably because most of these patients experienced transient global brain ischemia at the time of aneurysm rupture.

From animal studies, it is known that a major part of the brain’s energy consumption is connected to the Glt-Gln cycle. Therefore, an interesting question arose: was there a possible relationship between signs of disturbed cerebral energy metabolism and the interstitial levels of Glt and Gln as measured with intracerebral microdialysis in patients with SAH?

When analyzing our material we used 3 different approaches. First, we used microdialysis criteria to define ischemia as periods in which the L/P ratio reached above 40.4 We found that periods with an L/P ratio > 40 and low pyruvate levels were associated with decreased interstitial Gln levels, suggesting a disturbed energy producing capacity leading to failing astrocytic Glu uptake and low Gln synthesis. Conversely, periods with an L/P ratio > 40 with normal or high pyruvate levels were associated with increased interstitial Gln levels, which may represent a more favorable metabolic situation with maintained astrocytic Glu uptake and intense Gln synthesis. Thus, it seems that moderately elevated L/P ratios cannot always be interpreted as failing energy metabolism. In cases of high L/P ratio, pyruvate and/or Gln levels may determine whether or not there is sufficient energy for Glu-Gln cycling. We found this notion particularly interesting in the context of the emerging concept of relative glucose deficiency due to competition among the energy-consuming pathways recently observed in brain-injured patients.1

Intracranial pressure and CPP levels are carefully

Editorial
monitored in neurointensive care patients since deviant ICP and CPP readings can indicate impending ischemia. Our second approach, and the aim of our paper, was to study microdialysis data in relation to cerebral hemodynamics. When exploring potential relationships among ICP, CPP, and microdialysis patterns, correlation analyses were done using all monitoring hours from all patients. As pointed out, there are problems with this practice since the values represent series of repeated measurements and are not independent. One must also remember that the hemodynamic parameters to some extent were controlled variables because intervention (for example, intermittent CSF drainage) commonly occurred once they exceeded certain limits. Most of the patients experienced periods with ICP readings in the 15–20–mm Hg range during some part of their neurointensive care unit stay. Severe ICP insults were rare. In only 3 cases was a sharp decrease in ICP induced by opening the ventricular drain at 10 mm Hg; however, those 3 cases allowed us to observe instantaneous metabolic improvements associated with the ICP reduction. The consciousness level improved in 1 patient (Fig. 3A) as soon as ICP was lowered. A second patient’s (Fig. 3B) condition improved gradually during the following 72 hours. A third patient (Fig. 3C) remained in a poor clinical condition until the end of monitoring. The CPP levels in these 3 patients fluctuated but remained above 60 mm Hg throughout. Analysis of the data further suggested that the Gln increase is associated with the ICP reduction and not a CPP elevation. Although our material contains only 3 examples and clinical improvement did not always appear, the consistent instantaneous surge in Gln and pyruvate assured us of an improved cerebral metabolism when the ICP was lowered. Consequently, we wondered whether patients with SAH and moderately elevated ICP (15–20 mm Hg) on the whole would benefit from CSF drainage at pressure levels lower than those usually indicated in current clinical management protocols.

In a third approach, described in a recently published paper, ischemia is defined as the development of delayed ischemic neurologic deficits (DINDs) and/or CT-verified infarctions. Such ischemic events were related to metabolic patterns including Gln levels. In short, we found that in patients admitted in a poor clinical condition, the initial interstitial Gln levels were low. Surges in Gln were further frequent in the material and occurred during DIND without ischemic CT signs and without ischemic microdialysis patterns and also appeared in the recovery phase following DINDs.

In conclusion, our observations have lead us to hypothesize that increasing interstitial Gln and pyruvate levels may be a sign of augmented astrocytic energy metabolism with accelerated Glt uptake and Gln synthesis. This process could occur either in response to an energy metabolic challenge, such as evolving ischemia, or in the recovery phase following an acute energy crisis or a constraint.

The findings and conclusions in our paper may be “provocative” considering that existing protocols mainly target CPP in patients with SAH; however, with future clinical studies, SAH management may well undergo development similar to that for the NICU treatment of traumatic brain injury (TBI) in which the former rigid recommendations of keeping CPP high have gradually changed. Today it is apparent that the treatment of TBI ought to be either ICP- or CPP-guided depending on whether or not the individual patient’s autoregulation is intact.

Our observations must be confirmed in larger sets of patients for whom prospectively collected data ensure that all information about, for example, clinical status, ICP, CPP, and CT scans are collected at the same time points and intervals in all the patients. Despite the limitations of our study we believe that our observations—where a low ICP relates to improved metabolic patterns—are intriguing. We welcome further debate and investigation in this field.

References

Please include this information when citing this paper: published online May 8, 2009; DOI: 10.3171/2009.3.JNS09275.