Poor-grade aneurysmal subarachnoid hemorrhage: relationship of cerebral metabolic to outcome

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Object. The majority of patients with poor-grade subarachnoid hemorrhage (SAH), that is, World Federation of Neurosurgical Societies (WFNS) Grades IV and V, have high morbidity and mortality rates. The objective of this study was to investigate cerebral metabolism in patients with low- compared with high-grade SAH by using bedside microdialysis and to evaluate whether microdialysis parameters are of prognostic value for outcome in SAH.

Methods. A prospective investigation was conducted in 149 patients with SAH (mean age 50.9 ± 12.9 years); these patients were studied for 162 ± 84 hours (mean ± standard deviation). Lesions were classified as low-grade SAH (WFNS Grades I–III, 89 patients) and high-grade SAH (WFNS Grade IV or V, 60 patients). After approval by the local ethics committee and consent from the patient or next of kin, a microdialysis catheter was inserted into the vascular territory of the aneurysm after clip placement. The microdialysates were analyzed hourly for extracellular glucose, lactate, lactate/pyruvate (L/P) ratio, glutamate, and glycerol. The 6- and 12-month outcomes according to the Glasgow Outcome Scale and functional disability according to the modified Rankin Scale were assessed.

In patients with high-grade SAH, cerebral metabolism was severely deranged compared with those who suffered low-grade SAH, with high levels (p < 0.05) of lactate, a high L/P ratio, high levels of glycerol, and, although not significant, of glutamate. Univariate analysis revealed a relationship among hyperglycemia on admission, Fisher grade, and 12-month outcome (p < 0.005). In a multivariate regression analysis performed in 131 patients, the authors identified four independent predictors of poor outcome at 12 months, in the following order of significance: WFNS grade, patient age, L/P ratio, and glutamate (p < 0.03).

Conclusions. Microdialysis parameters reflected the severity of SAH. The L/P ratio was the best metabolic independent prognostic marker of 12-month outcome. A better understanding of the causes of deranged cerebral metabolism may allow the discovery of therapeutic options to improve the prognosis, especially in patients with high-grade SAH, in the future.

Key Words • subarachnoid hemorrhage • cerebral metabolism • microdialysis • outcome

Traditionally, the outcome is poor for patients with high-grade aneurysmal SAH (WFNS Grade IV or V) [inability to obey commands] and V) and the majority of these patients are treated conservatively. Many factors contribute to this poor outcome, such as intracranial hypertension due to acute hydrocephalus, increase in cerebral spinal fluid outflow resistance, intracranial hemorrhage, cerebral edema, or a combination of these factors. Nevertheless, in the last decade a trend toward active management of disease in patients with poor-grade SAH has been ongoing, with treatments including immediate ventriculostomy, early surgery, and aggressive postoperative hypervolemic, hypertensive, and hemodilutional therapy. Although this strategy apparently reduced the mortality rate in some subgroups of patients with poor-grade SAH, the reduction appeared to occur at the expense of increasing numbers of severely disabled survivors. The first management recommendations for patients with poor-grade SAH were developed to select a patient subgroup that might benefit from surgery. This subgroup includes patients younger than 65 years who have no evidence on neuroimaging of irreversible brain destruction, who underwent early therapy for their hydrocephalus, and who responded with flexion to stimulation after a 24-hour period of withdrawal of sedating and paralyzing medications. With increased diagnostic and monitoring activities (for example, control of ICP) better overall outcome in SAH could be achieved. Cerebral microdialysis, an advanced neurointensive care monitoring modality that has recently become available, adds new information about the metabolic state of the injured brain. Because this subgroup of patients with SAH has the worst neurological outcome, an improved analysis of cerebral metabolic changes may lead to therapeutic options and a better outcome. Experimentally induced vasocostriction after SAH occurred independently of changes in ICP and cerebral perfusion pressure, but was associated with persistent elevations of extracellular glutamate and poor outcome. A clinical study conducted in patients with poor-grade SAH measured an almost 30-fold increase in extracellular levels of glutamate and a 10-fold increase in lactate levels compared with their levels in dialysates obtained in patients with favorable outcomes. Microdialysis may help the physician select patients with poor-grade SAH in whom the prognosis after surgery is more favorable.
Cerebral metabolism and outcome in patients with poor-grade SAH

The objectives of this study were as follows: 1) to evaluate whether cerebral metabolism measured by microdialysis differs in patients with high- and low-grade SAH; and 2) to determine if the microdialysis parameters are of prognostic value for the outcome in patients with SAH.

**Clinical Material and Methods**

This study was approved by the local Research Ethics Committee at Charité Virchow Medical Clinic in accordance with the Declaration of Helsinki, as revised in Edinburgh in October 2000. Written informed consent was obtained from the patients or their nearest relatives.

**Patient Characteristics and Disease Management**

This study forms part of an ongoing prospective investigation of cerebral metabolism monitored by bedside microdialysis in patients with aneurysmal SAH. During the period between June 1996 and February 2003, 149 patients with SAH were enrolled. The inclusion criteria were: 1) SAH confirmed on cranial CT scans; 2) cerebral angiogram demonstrating intracranial aneurysm(s); and 3) previous surgical therapy. Clinical presentation was graded according to the WFNS scale (Table 1). The aneurysm location was assessed using four-vessel angiography on the day of admission. The distribution pattern of the hemorrhage was graded as proposed by Fisher, et al. Global handicap (“functional disability”) was assessed using a seven-point version of the mRS with ratings ranging from death to symptom-free full recovery, and by using the GOS assessments made at 6 and 12 months.

For comparisons of metabolic parameters, patients were classified in two groups, high-grade SAH (WFNS Grades IV [inability to obey commands] and V) and low-grade SAH (WFNS Grades I–III). Demographic data are summarized in Table 2. All patients considered surgical candidates were treated according to a uniform protocol. After preparative resuscitation, patients were treated with early ventricular drainage if hydrocephalus was present clinically and on CT scans, and with aneurysm surgery if patients responded with flexion to stimulation after a 24-hour period of discontinuation of sedation and paralysis. Patients with evidence of irreversible brain destruction on neuroimaging were excluded from the study.

**Bedside Microdialysis**

A 10-mm-long microdialysis catheter (model 70; CMA Microdialysis, Stockholm, Sweden; molecular weight limit 20,000) was inserted into the brain parenchyma of the vascular territory of the aneurysm immediately after clip occlusion of the lesion, for example, in the right frontal lobe in patients with an anterior communicating artery aneurysm. Care was taken to avoid insertion of the catheter into brain tissue that contained macroscopically detected lesions or into an intracerebral hemorrhage. Catheters were perfused with sterile Ringer solution at a flow rate of 0.3 μl/min- ute. Per fusates were collected in microvials attached to the outlet tube; these vials were exchanged hourly, and the contents were immediately analyzed at bedside in a mobile photometric, enzyme-kinetic analyzer (model 600; CMA Microdialysis). The estimated recovery for the system is 0.65 to 0.72. Microdialysis data are presented as microdialysate concentrations.

**Data Analysis**

Between-group comparisons were performed using the 24-hour median values for each microdialysis variable and for blood glucose recorded with nonparametric methods (Mann–Whitney U-test) for each patient during the first 7 days after SAH. In a second set of analyses we used the GOS to identify independent predictors of death and unfavorable outcome at 12 months by using a gradual linear regression. Outcome was dichotomized into favorable outcome (good recovery, moderate disability) and unfavorable outcome (severe disability, vegetative state, or death) and survivors were compared with nonsurvivors and used as the dependent variable. The following covariates were included in the model: patient age, WFNS grade, Fisher grade, blood glucose levels on admission (presence of hyperglycemia), and the mean of the 24-hour values of the microdialysis parameters (glucose, lactate, pyruvate, L/P ratio, glutamate, and glycerol over 3 and 7 days). Differences were considered to be statistically significant at probability values of less than 0.05 (version 11.0; SPSS, Inc., Chicago, IL).

**Results**

The demographic and clinical characteristics of the 149 patients are reported in Table 2. Eighty-nine patients were included in the group with low-grade SAH and there were 60 in the group with high-grade SAH; patient groups were comparable for age and sex, whereas the Fisher score was significantly elevated in patients with high-grade SAH. Eighty-seven percent of the 130 patients underwent early surgery (within 72 hours of the initial bleeding). Nineteen patients underwent clip placement after 72 hours; in 15 with low-grade SAH this procedure was performed late because symptomatic/angiographically confirmed vasospasm was present, and in four with high-grade SAH because of intracranial hypertension (ICP > 20 mm Hg) caused by cerebral edema.

**Cerebral Metabolism in High- and Low-Grade SAH**

The 24-hour median values of the microdialysate concentrations measured hourly on Days 1 through 7 after surgery in patients with high- and low-grade SAH are given in Fig. 1 (only patients with early surgery were included; interval to SAH surgery 23.7 ± 13.5 hours). The microdial-
ysate concentrations in patients with high-grade SAH were significantly increased compared with those found in patients with low-grade SAH (p < 0.05). The differences were most pronounced in the lactate levels and the L/P ratio, whereas glutamate, even at highly pathological levels, did not reach significance because of interindividual variability (Fig. 2). Interestingly, glycerol was elevated (two-fold that of normal values) during the first 2 days after surgery in patients with high-grade SAH (p < 0.01). The EAA glutamate correlated highly with the L/P ratio, a marker of anaerobic metabolism (Pearson r = 0.899, p < 0.01).

Blood Glucose Levels

Hyperglycemia (>120 mg/dl) on admission and elevated glucose levels during the 1st week after SAH are known predictors of poor outcome. These high glucose levels might influence microdialysis concentrations of glucose and the metabolites lactate and pyruvate. We determined blood glucose levels on admission and the morning blood glucose concentrations for the 7 days thereafter. The presence of hyperglycemia on admission (p = 0.012) and the blood glucose levels on the day of admission up to Day 5 were significantly elevated in patients with high-grade SAH compared with those with low-grade SAH (p < 0.01; Fig. 3). Univariate analysis revealed a significant relationship between hyperglycemia and 12-month dependency according to the mRS (p = 0.021) and 12-month outcome according to the GOS (p = 0.004).

Overall Dependency Outcome and Group Differences

The 6-month dependency according to the mRS was available in 142 patients (85 with low-grade and 57 with high-grade SAH) and the 12-month dependency according to the mRS was calculated in 134 patients (82 with low-grade and 52 with high-grade SAH; Table 3). Functional disability (mRS scores at 6 and 12 months) of the patients with high-grade SAH was significantly worse compared with the low-grade group (p < 0.001).

The 6-month outcome according to the GOS was available in 144 patients (86 with low-grade and 58 with high-grade SAH) and the 12-month outcome according to the GOS was assessed in 132 patients (80 with low-grade and 52 with high-grade SAH; Fig. 4). At 12 months, 95 patients (72%) had a favorable outcome (GOS Score 5 or 4 at 12 months) and 37 patients (28%) had an unfavorable outcome (GOS Score 1–3 at 12 months); of the latter group, 17 patients were dead (GOS Score 1 at 12 months). Of those who died, eight patients were considered to have succumbed to

TABLE 2
Demographic characteristics of 149 patients with SAH*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Patients</th>
<th>Low-Grade SAH</th>
<th>High-Grade SAH</th>
<th>p Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>no. of patients</td>
<td>149</td>
<td>89</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>age (yrs)</td>
<td>50.9 ± 12.9</td>
<td>49.6 ± 13.3</td>
<td>52.6 ± 12.1</td>
<td>0.148 (NS)</td>
</tr>
<tr>
<td>M/F ratio</td>
<td>42:107</td>
<td>25:64</td>
<td>17:43</td>
<td>0.974 (NS)</td>
</tr>
<tr>
<td>admission WFNS grade (%)</td>
<td>2.7 ± 1.6</td>
<td>1.5 ± 0.8</td>
<td>4.5 ± 0.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>0</td>
<td>3 (2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>53 (36)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>16 (11)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>17 (11)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>33 (22)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>V</td>
<td>27 (18)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hrs from SAH to op</td>
<td>49 ± 78</td>
<td>53.4 ± 83.5</td>
<td>42.6 ± 71.2</td>
<td>0.131 (NS)</td>
</tr>
<tr>
<td>Fisher grade</td>
<td>3 ± 1</td>
<td>2.5 ± 0.9</td>
<td>3.7 ± 0.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>location of ruptured aneurysm (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICA</td>
<td>36 (24)</td>
<td>19 (21)</td>
<td>17 (28)</td>
<td></td>
</tr>
<tr>
<td>MCA</td>
<td>45 (30)</td>
<td>26 (29)</td>
<td>19 (32)</td>
<td></td>
</tr>
<tr>
<td>ACA</td>
<td>61 (44)</td>
<td>42 (47)</td>
<td>19 (32)</td>
<td></td>
</tr>
<tr>
<td>PCA or other</td>
<td>7 (5)</td>
<td>2 (2)</td>
<td>5 (8)</td>
<td></td>
</tr>
<tr>
<td>duration of microdialysis (hrs)</td>
<td>161.8 ± 84.4</td>
<td>147.2 ± 79.1</td>
<td>183.5 ± 87.9</td>
<td>0.021</td>
</tr>
<tr>
<td>ventricular drainage (%)</td>
<td>63 (42)</td>
<td>21 (24)</td>
<td>42 (70)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>% with hyperglycemia on admission</td>
<td>75</td>
<td>58</td>
<td>80</td>
<td>0.003</td>
</tr>
<tr>
<td>% mortality at 6/12 mos</td>
<td>9/10</td>
<td>2/2</td>
<td>18/25</td>
<td></td>
</tr>
</tbody>
</table>

* Data are expressed as the mean ± standard deviation or the absolute number and percentage. Abbreviations: ACA = anterior cerebral artery; ICA = internal carotid artery; MCA = middle cerebral artery; NS = not significant; PCA = posterior cerebral artery.
† Patients with high-grade SAH were compared with those with low-grade SAH.

TABLE 3
Values according to the mRS in 134 patients with low- or high-grade SAH at 12-month follow up*

<table>
<thead>
<tr>
<th>mRS Score &amp; Definition</th>
<th>Low-Grade SAH (%)</th>
<th>High-Grade SAH (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0, no symptoms</td>
<td>39 (47.6)</td>
<td>9 (17.3)</td>
</tr>
<tr>
<td>1, minor symptoms</td>
<td>14 (17.1)</td>
<td>5 (9.6)</td>
</tr>
<tr>
<td>2, some restriction in lifestyle</td>
<td>11 (13.4)</td>
<td>3 (5.8)</td>
</tr>
<tr>
<td>0–2 inclusive</td>
<td>64 (78)</td>
<td>10 (19.2)</td>
</tr>
<tr>
<td>3, significant restriction in lifestyle</td>
<td>6 (7.3)</td>
<td>8 (9.8)</td>
</tr>
<tr>
<td>4, partially dependent</td>
<td>8 (9.8)</td>
<td>6 (11.5)</td>
</tr>
<tr>
<td>5, fully dependent</td>
<td>1 (1.2)</td>
<td>5 (9.6)</td>
</tr>
<tr>
<td>6, dead</td>
<td>3 (3.7)</td>
<td>14 (26.9)</td>
</tr>
<tr>
<td>3–6 inclusive</td>
<td>18 (22)</td>
<td>35 (67.3)</td>
</tr>
<tr>
<td>total</td>
<td>82</td>
<td>52</td>
</tr>
</tbody>
</table>

* Low-grade SAH was defined as WFNS scores of I to III, and high-grade SAH as WFNS scores of IV or V. An mRS score of 3 to 6 indicates functional dependency.
the severity of the initial hemorrhage with untreated intracranial hypertension and nine were believed to have died of extracranial causes (pneumonia in seven, cardiac failure in one, and complications after an abdominal surgery in one). The GOS score at 6 and that at 12 months in the patients with high-grade SAH were significantly worse compared with the low-grade group (p = 0.001; Fig. 4). Univariate analysis revealed a significant relationship between the Fisher score and 12-month dependency according to the mRS and 12-month outcome according to the GOS (p = 0.001).

Multivariate Analysis of Outcome

Using gradual multiple regression analysis in 131 patients, we identified four independent predictors of unfavorable outcome at 12 months: WFNS grade (p = 0.006, 95% CI); patient age (p = 0.01, 95% CI); glutamate (mean over 3 days of the 24-hour values; p = 0.027, 95% CI); and the L/P ratio (mean over 3 days of the 24-hour values; p = 0.024, 95% CI). Hyperglycemia on admission, the Fisher grade, and microdialysate concentrations of glucose, lactate, pyruvate, and glycerol failed to predict outcome in this multivariate model.

Because delayed vasospasm (not occurring within the first days after SAH) is a major factor contributing to outcome, we tested the model by using a longer period of microdialysis monitoring (mean of the 24-hour medians over 7 days) in a second regression analysis. The results were comparable: WFNS grade (p = 0.05, 95% CI); patient age (p = 0.023, 95% CI); glutamate (p = 0.02, 95% CI); and the L/P ratio (p = 0.019, 95% CI). These four variables were also identified as predictors of death by 12 months: WFNS grade (p = 0.006, 95% CI); patient age (p = 0.01, 95% CI); glutamate (mean of the 24-hour values over 3 days; p = 0.027, 95% CI); and the L/P ratio (mean of the 24-hour values over 3 days; p = 0.024, 95% CI).

Discussion

Patients with high-grade SAH (WFNS Grades IV and V) had a severely deranged cerebral metabolism compared with those suffering low-grade SAH; this was reflected in higher extracellular concentrations of lactate, a higher L/P ratio, and glycerol level, and, although it was not significant, a higher glutamate level. The outcome, which was determined using the GOS and functional disability classifi-
cations, was significantly worse in patients with high-grade SAH compared with individuals suffering low-grade SAH. To evaluate the prognostic value of microdialysis parameters for the outcome of patients with SAH, a multivariate regression analysis was performed in 131 patients. We identified four independent predictors of unfavorable outcome at 12 months, which were (in order of significance) the WFNS grade, patient age, and two microdialysis parameters (L/P ratio followed by glutamate level). Blood glucose levels on admission and as a 5-day mean of morning blood glucose, the Fisher grade, and microdialysis concentrations of glucose, lactate, pyruvate, and glycerol failed to predict the 12-month outcome in this model.

Outcome Assessment

The GOS for outcome assessment has the advantage of being widely known and used in many studies to grade patients with aneurysmal SAH.1 Several studies, however, have shown that SAH leads not only to clear neurological deficits but also to cognitive impairment. Therefore, many survivors are believed to have made a good recovery clinically or on global outcome measures such as the GOS, although they have severe cognitive deficits and a poor health-related quality of life.13,25 To improve outcome assessment, in this study both the GOS and the mRS (“functional disability” measure), based on the questionnaires we used to assess outcome, were applied. Both measures revealed a significantly worse outcome in patients with high-grade SAH compared with those with low-grade SAH. Our study lacks more sensitive instruments for outcome assessment, for example, the global mental status on the Telephone Interview for Cognitive Status.5 Nevertheless, with the exception of the aforementioned instrument, neuropsychological testing did not contribute an additional predictive value for concurrent mRS scores.26

A variety of prognostic factors were defined to predict outcome in patients with SAH, including the patient’s age, level of consciousness on admission, aneurysm size and location, the number of secondary insults (for example, a rehemorrhage), symptomatic vasospasm, characteristics of the hemorrhage on CT scans, initial systolic blood pressure, and the expertise available at the aneurysm center.21,27,29 In our study, the WFNS grade and patient age were important predictors of outcome, whereas the Fisher grade was significantly associated with outcome (GOS score) and functional disability (mRS score) only in the univariate analysis.

Microdialysis and Outcome

Advanced neuromonitoring procedures, such as assessments of cerebral oxygenation conducted using brain tissue PO2 monitoring and jugular venous O2 saturation in combination with microdialysis, have been developed for the detection and treatment of secondary brain damage. These procedures were shown to identify critical episodes of hypoxia, ischemia, and a deranged metabolism measured by microdialysis, all of which are conditions associated with a poor outcome in severely head injured patients.11 In several studies of severe head injury, increased lactate and decreased glucose levels, indicating accelerated glycolysis, were observed in conjunction with cerebral ischemia or hypoxia,10,33 and increased anaerobic glycolysis with high L/P ratios and high glutamate levels were associated with a poor outcome.11,12,32 Others interpret high glutamate and lactate levels as glutamate-induced astrocytic glycolysis, with lactate not only as a marker of anaerobic glycolysis due to hypoxia/ischemia but also as a neuronal energy source.1,2

Microdialysis and Outcome in SAH

Only scarce data on microdialysis and outcome are available for SAH,21,29,36 and to our knowledge, this study presents the largest series of patients with SAH monitored with microdialysis so far. In a series of studies other investigators have proposed glutamate as an excellent marker of ischemia in patients with SAH.28,32,34,35 Concerning long-term effects, however, there was only a weak association between abnormal glutamate levels and unfavorable 3- and 6-month outcomes in 40 patients with SAH.21 Interestingly, in the latter study, episodes of glutamate levels higher than 10 mmol/L or of L/P ratios greater than 40 for more than 1 hour were associated with an unfavorable outcome. Nevertheless, the differences in glutamate levels in 18 patients

Fig. 3. Graph showing blood glucose levels in patients with high- and low-grade SAH. Blood glucose levels on admission (adm) and on Days 1 through 5 after surgery were significantly increased in patients with high-grade SAH.

Fig. 4. Bar graphs showing outcome in patients with high-grade compared with low-grade SAH. Outcome at 6 and 12 months in all patients presenting with aneurysmal SAH is shown; patients are categorized as those with low-grade (WFNS Grades 0–III) and high-grade (WFNS Grade IV or V) SAH. The GOS categories are as follows: death (GOS Score 1); vegetative state (VS, GOS Score 2); severe disability (SD, GOS Score 3); moderate disability (MD, GOS Score 4); and good recovery (GR, GOS Score 5).
Cerebral metabolism and outcome in patients with poor-grade SAH

with low-grade (mean glutamate level 3.5 μmol/L) compared with 22 with high-grade SAH (mean glutamate level 5.5 μmol/L) were only modest, and profound changes were seen only at a terminal stage. This contrasts with our results, even excluding six patients with extreme glutamate levels (in the range of 100–700 μmol/L), as done in the study by Kett-White, et al. Glutamate levels were a mean of 11.3 (range 6.8–17.7 μmol/L) higher in patients with poor-grade SAH, which correlates to three times the normal baseline values. The different insertion method used by Kett-White and coworkers (triple-lumen cranial access device) might be responsible for these observed differences. Staub, et al., reported unfavorable outcomes in four patients with SAH and high levels of EAAs (≤ 30-fold), lactate (≤ tenfold), and nitrite, compared with normal levels observed in six patients with favorable outcomes when peak levels of the means for a 12-hour period at maximal values were analyzed. These authors described a biphasic temporal profile for EAAs in patients with poor outcomes, with peak levels on Days 1 to 2 or Day 7, which is in agreement with results from another study and our own previous results, which demonstrated increased levels of glutamate in some patients only early (after initial bleeding), in others only later (Days 5–7), and in still others both early and late. In our view, the initial peak of glutamate is an insertion effect, but when it lasts longer (> 6–8 hours) it reflects local metabolic disturbances, for example, those caused by the SAH or a concomitant intracerebral hemorrhage. The secondary increase in EAAs (or lactate and the L/P ratio) at approximately Day 7 after the ictus might be attributable to secondary ischemia caused by vasospasm or brain edema. In the present study, the L/P ratio increased secondarily only in patients with poor-grade SAH. For prediction of outcome, however, a 3-day interval of microdialysis monitoring was sufficient to predict the 12-month outcome for the parameters L/P ratio and glutamate. The 7-day interval, including the secondary deterioration of the L/P ratio, was not superior for predicting the outcome or mortality rate, which might be explained by the overall highly pathological microdialysate levels in patients with poor-grade SAH.

Increased extracellular glycerol concentrations have been observed in patients with SAH who suffered clinical vasospasm and ischemic events. These probably originate from phospholipid breakdown of disintegrating cell membranes, for example, caused by ischemia, leading to energy failure. Patients with high-grade SAH had significantly elevated (twofold) glycerol concentrations during the first 2 days of monitoring compared with those with low-grade SAH. A transient glycerol increase, therefore, might reflect reversible local tissue damage, a hypothesis that is supported by the unimportance of the glycerol level in predicting outcome in these patients.

Hyperglycemia and Outcome

Hyperglycemia (> 120 mg/dl or 6.66 mmol/L) on admission and elevated blood glucose levels during Days 3 and 7 were predictive of a poor outcome (at 3 months determined according to the GOS). This observation was confirmed by several studies and is also reflected in our results; 94% of patients with high-grade SAH had hyperglycemia on admission, and their blood glucose levels were significantly higher on Days 1 to 5 compared with patients who suffered low-grade SAH. Consequently, univariate analysis revealed a significant relationship between hyperglycemia and outcome. Nevertheless, gradual multivariate regression analysis excluded (in order of importance) both hyperglycemia (level in blood) and glucose levels according to extracellular microdialysis as predictors of outcome. On the other hand, because hyperglycemia is injurious in brain ischemic conditions, it should be a general strategy to normalize glucose levels in patients with SAH.

There are several pitfalls involved in microdialysis monitoring. The location of the microdialysis probe is crucial, and care should be taken to avoid inserting it directly into a clot. Even when inserting the microdialysis probe into the vascular territory that is at highest risk for occurrence of secondary pathophysiological events, such as regional ischemia, the affected brain region might be missed in some patients. The volume of brain tissue monitored by the microdialysis catheter is within a few millimeters of the membrane; studies with positron emission tomography in severely head injured patients used a region of interest of 20 mm to achieve optimal imaging results. Because of the reduced recovery, relative changes in microdialysis parameters might be more relevant than absolute extracellular concentrations. With these pitfalls in mind, microdialysis can indicate metabolic derangements in patients with SAH, with the glutamate level and the L/P ratio as the most relevant metabolic markers in terms of outcome prediction. Future studies may individualize the main causes of disturbed regional metabolism detected by microdialysis, especially in patients with high-grade SAH. In our view the real value of microdialysis monitoring can only be evaluated in future, ongoing studies, when treatment effects are reflected in changes of the microdialysis parameters and, finally, if therapeutic regimens designed to improve the metabolic status of the brain tissue can improve outcome despite a poor initial WFNS grade.

Conclusions

Cerebral metabolism was severely deranged in patients with high-grade compared with low-grade SAH who had higher levels of lactate, the L/P ratio, glycerol, and, although it was not significant, of glutamate. We identified four independent predictors of poor outcome at 12 months, which were (in order of significance) the WFNS grade, patient age, the L/P ratio, and glutamate. Microdialysis parameters reflected the severity of SAH; of these, the L/P ratio was the best independent prognostic marker of the 12-month outcome. A better understanding of the causes of disturbed cerebral metabolism may allow the discovery of therapeutic options to improve the prognosis, especially of patients with high-grade SAH, in the future.

Disclaimer

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