Case Report

Neurochemical Monitoring of Fatal Middle Cerebral Artery Infarction

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Background—Microdialysis is a method for neurochemical monitoring that has been applied more frequently over the past few years in patients suffering from subarachnoid hemorrhage, acute brain injury, and stroke. It is used to study the course of extracellular molecules of low molecular weight, such as excitatory amino acids or metabolic end products.

Case Description—We report the case of a 43-year-old patient suffering from left hemispheric stroke with a space-occupying postischemic edema leading to a considerable mass effect on the contralateral side. For treatment of severe edema, hypothermia was initiated. The microdialysis and intracranial pressure probe were placed into the noninfarcted hemisphere. A massive increase in levels of glutamate, glycerine, and the lactate-pyruvate ratio was measured 24 hours before intracranial pressure elevation was observed and brain death occurred.

Conclusions—Monitoring excitatory amino acids, glycerine as a membrane component, and lactate-pyruvate ratio as an energy marker by microdialysis is a useful tool to increase our understanding of biochemical events in secondary brain damage. For future prevention of secondary ischemia in patients with massive stroke, close neurochemical monitoring might be valuable to improve therapy, particularly in the critically ill. (Stroke. 1999;30:460-463.)

Key Words: cerebral infarction ■ cerebral ischemia ■ glutamates ■ microdialysis ■ middle cerebral artery

Brain ischemia is associated with an excessive release of excitatory amino acids, such as glutamate or aspartate, and with a shift of energy-related metabolites from the intracellular to the extracellular fluid. Intracerebral microdialysis1 is a method by which these endogenous substances can be extracted from the extracellular fluid into a dialysate in which relative changes in concentration of these substances can be measured. Several animal studies applying microdialysis in neuronal injury models have been conducted.2-4 More recently, microdialysis found its way into neurological intensive care units as a tool for monitoring metabolism and neuronal injury in subarachnoid hemorrhage5 and severe head injury.6 Only very limited data are present on microdialysis in ischemic stroke.

In this case report, we demonstrate a massive increase in extracellular glutamate, glycerine, and the lactate-pyruvate ratio as a consequence of secondary brain damage in a patient with a fatal middle cerebral artery (MCA) infarction.

Subjects and Methods

This study was approved by the local Ethics Committee (approval number 34/97).

A 10-mm flexible microdialysis probe with an external diameter of 0.5 mm (CMA/70 custom probe, CMA/Microdialysis), and an intracranial pressure (ICP) measuring device (Spiegelberg AG) were inserted into the parietal parenchyma of the healthy hemisphere. A thermistor attached to the ICP device allowed continuous recording of brain temperature.7 A second microdialysis probe (CMA/60) placed into the abdominal subcutaneous tissue served as a reference.

In the neurological critical care unit, continuous ICP monitoring was performed and documented. The microdialysis probes were perfused at 0.3 mL/min with a sterile isotonic solution containing Na+ 147 mmol/L, K+ 4.0 mmol/L, Ca2+ 2.3 mmol/L, and Cl− 156 mmol/L, and the dialysates were sampled in microwells. Each microvial was replaced after 60 to 120 minutes. We measured the concentrations of glutamate, glycerine, pyruvate, and lactate on-line with the CMA 600 Microdialysis Analyser. This is a self-calibrating autoanalyzer designed for microdialysis samples that measures glutamate, glycerine, pyruvate, and lactate enzymatically. All microdialysis results are presented as dialysate concentrations without correction for probe recovery, as there is no suitable method available for continuous or repeated determination of in vivo probe recovery. In vitro recovery was not determined for reasons of sterility.

Physiological variables, such as blood gas analysis and blood pressure, and clinical events were documented regularly and added into the database of the mainframe computer, serving also for analysis of the microdialysis results.

Case Report

A 43-year-old patient was admitted to the Department of Neurology with a sudden onset of right-sided hemiplegia, global aphasia, and drowsiness. A CT scan performed 6 hours after the onset of symptoms revealed a large, early hypodensity covering two thirds of the MCA territory. During the first 24 hours after admission, the patient’s condition deteriorated rapidly. Her level of consciousness declined continuously,
and she developed forced head and eye deviations and an increased muscle tone in the contralateral extremities. A CT scan performed 24 hours after admission (Figure 1) revealed severe space-occupying postischemic edema with a mass effect and a 15 mm midline shift.

According to our institutional protocol, the patient was intubated and sedated, and hypothermia of 33°C was initiated as antiedema therapy. Parenchymal ICP and microdialysis probes were placed after consent was obtained from the patient’s husband.

Over the next 3 days, there was further deterioration in the patient’s clinical condition, despite adequate hypothermic temperatures. At first, her left pupil became dilated and nonresponsive to light, a sign of local compression of the third cranial nerve. There was no clinical improvement on application of mannitol, although the ICP remained well below 20 mm Hg. One day later, her right pupil also dilated and became nonreactive to light. Her condition continued to deteriorate, and she developed transtentorial herniation and died 5 days after admission.

**Results**

A total of 64 microvials were collected over the sampling period of 3 days, and a total of 256 analyses were performed. Figure 2 demonstrates the ICP and the microdialysis results, respectively, including the concentrations of glutamate and glycerine, and the lactate-pyruvate ratio given as quotient of the lactate and pyruvate concentrations. Glutamate levels were <50 mmol/L at the beginning of the measurements, with <2 mmol/L considered normal for cerebral extracellular fluid. Once clinical signs of brain swelling of the noninfarcted hemisphere appeared, glutamate levels started to rise up to 400 mmol/L, ie, a 200-fold increase of normal values. A 10- to 12-fold increase was seen in glycerine concentrations, which rose from 100 mmol/L to approximately 1100 mmol/L. As a sign of metabolism under ischemic conditions, the lactate-pyruvate ratio increased from 0.1 to 0.6 during the same time interval, with lactate increasing from 2 to 3 mmol/L and pyruvate decreasing from approximately 60 to 6 mmol/L.

The ICP remained at <20 mm Hg except at the point of the last measurement, at which time it increased to 23 mm Hg. Temperature was kept at 33.3 ± 0.5°C during the entire time.

Concentration levels for glutamate measured in the subcutaneous reference microdialysis probe remained unremarkably stable, between 20 and 40 mmol/L throughout the monitoring period. The same holds true for glycerine concentrations, which were between 50 and 150 mmol/L. The lactate-pyruvate ratio remained comparably low at 0.05.

**Discussion**

Extensive brain infarction and subsequent brain edema formation are neurological disorders requiring specific neurological intensive care but still carrying a mortality rate of up to 80%. Various treatment measures, such as osmotic agents, craniotomy, and hypothermia, are currently under investigation to minimize brain edema, reduce mortality, and improve outcome. However, monitoring the efficacy of these treatment measures is often difficult. ICP monitoring or measurement of venous jugular bulb oxygen saturation offer some guidance for therapy, but these methods are not sensitive enough to detect early neuronal damage.
Microdialysis was developed for neurochemical monitoring and allows measurement of the extracellular concentrations of various endogenous substances, such as excitotoxic amino acids or metabolic end products. Enblad et al evaluated the results of microdialysis measurements with simultaneously performed PET scans in patients with subarachnoid hemorrhage. They demonstrated a significant correlation between ischemia and increase of excitatory amino acids. In another study comparing microdialysis with somatosensory evoked potentials and EEG in patients undergoing cerebrovascular surgery, glutamate monitoring by microdialysis was more sensitive than the routinely measured alterations in evoked potentials in the detection of ischemic events. To date, most studies have investigated microdialysis in patients with subarachnoid hemorrhage or acute brain injury or during brain tumor resection. The value of microdialysis after stroke is still not fully understood.

The patient described in this case report showed the clinical and neuroradiological features of a space-occupying left hemispheric stroke. The microdialysis and ICP probe were inserted into the noninfarcted hemisphere 24 hours after the patient developed further neurological deterioration with decrease of consciousness. CT scan at that time (Figure 1) demonstrated extensive brain infarction with severe mass effect. Brain edema was treated with hypothermia and osmotic agents. Hypothermia was considered experimental rescue therapy, although evidence is increasing that moderate hypothermia is a potent measure to treat brain edema.

Although ICP values remained below critical levels, the patient’s clinical condition worsened. With the loss of light responsiveness of both pupils, a dramatic increase in glutamate, glycerine, and lactate-pyruvate ratio was measured. The 200-fold increase of glutamate following ischemia was also observed in a case report by Bullock et al. It is consistent with the findings of Persson and Hillered, who measured glutamate in ischemic brain areas in patients with grade IV subarachnoid hemorrhage. The role of glutamate as an excitotoxic agent in the deterioration of an acutely injured brain is widely recognized. Its release into the extracellular fluid can reflect a vesicular release from the transmitter pool due to depolarization, an inhibition of the cellular reuptake mechanism, or a leakage from dying cells undergoing autolysis or through a disturbed blood-brain barrier. In fact, glutamate itself may have caused further clinical deterioration by leading into a fatal neuronal death cascade.

Experimental studies in rats have demonstrated a beneficial effect of mild or moderate hypothermia on the release of excitatory amino acids after cerebral ischemia. This mechanism was hypothesized to contribute to the neuroprotection also seen in histopathologic analyses. Not measuring in the infarcted hemisphere, we obtained glutamate values that remained low during the first 24 hours after probe insertion. However, a sharp rise in glutamate indicated a subsequent clinical deterioration long before ICP increased. One might speculate whether mild hypothermia might have delayed but not prevented secondary neuronal injury in this case.

Taking the glycerine levels into account, the major mechanism by which glutamate was released in this patient appears to be autolysis of neuronal cells. Glycerine is one of the end products of membrane phospholipid degradation, which reflects the disruption of cellular membranes with loss of barrier and transport function leading to various deleterious events, such as edema formation and autolysis. The trigger for membrane degradation might be a loss of calcium homeostasis, energy failure, or a mechanism mediated by free radicals. Hillered et al recently studied interstitial glycerine concentrations through microdialysis in 4 patients with severe subarachnoid hemorrhage. Secondary ischemic events were associated with a pronounced increase of glycerine of up to 15-fold, which is consistent with our finding of a 10-to 12-fold increase. Although they pointed out that membrane phospholipid degradation can occur without structural brain damage, ie, in hypoglycemic coma, experimental studies demonstrated a good correlation between increases of interstitial glycerine levels and energy failure during experimental cerebral ischemia.

Another indicator of energy failure is an increasing lactate-pyruvate ratio, which occurred concomitantly with the glutamate and glycerine increase in our patient. The positive correlation between lactate-pyruvate ratio and glycerine has recently been reported. Under hypoxic conditions, the aerobic metabolic pathway of carbohydrates is shifted from pyruvate to lactate as the anaerobic end product. The values of the lactate-pyruvate ratio presented in this case report are relatively low compared with reviewed numbers given by Persson et al. This might be due to the lower absolute values for lactate concentration measured in our study. Absolute differences in concentrations can arise from different membrane lengths of the microdialysis probes used for measurement. However, the relative change is similar to that described previously.

It is a striking finding that neurochemical alterations in the noninfarcted hemisphere, in particular a sharp rise in glutamate and glycerine, commenced hours before pupillary disturbances occurred, evoked potentials became absent, and a marked increase in ICP was measured. Thus, microdialysis may be able to predict secondary deterioration more sensitively than routinely applied methods of ICP monitoring.

In summary, the increase of glutamate, glycerine, and lactate-pyruvate ratio in our patient indicated a fatal severe neuronal damage secondary to the contralateral MCA infarction. Surprisingly, ICP values remained within normal limits even when clinical signs of brain herniation occurred. We conclude that microdialysis may be a more sensitive method to detect secondary ischemia and neuronal damage. In the future, microdialysis studies could help to improve our understanding of metabolic alterations in patients who are in danger of secondary brain ischemia. Furthermore, microdialysis might become increasingly important as a monitoring tool in neurological critical care units and as a method for evaluating drugs to counteract the delayed deterioration in stroke patients by preventing secondary ischemia.

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References


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