Intracerebral microdialysis and CSF hydrodynamics in idiopathic adult hydrocephalus syndrome

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Objective: To investigate whether CSF hydrodynamic manipulation has an impact on biochemical markers related to ischaemia, brain tissue oxygen tension (PtiO2), and intracranial pressure.

Methods: A microdialysis catheter, a PtiO2 probe, and an intracerebral pressure catheter were inserted into the periventricular white matter 0–7 mm from the right frontal horn in 10 patients with IAHS. A subcutaneous microdialysis probe was used as reference. Intracranial pressure and intracerebral PtiO2 were recorded continuously. Samples were collected for analysis between 2 and 4 pm on day 1 (baseline) and at the same time on day 2, two to four hours after a lumbar CSF hydraulic manipulation.

Results: After CSF drainage, there was a significant rise in the intracerebral concentration of lactate and pyruvate. The lactate to pyruvate ratio was increased and remained unchanged after drainage. There was a trend towards a lowering of glucose and glutamate. Mean intracerebral PtiO2 was higher on day 2 than on day 1 in six of eight patients.

Conclusions: There is increased glucose metabolism after CSF drainage, as expected in a situation of postischaemic recovery. These new invasive techniques are promising tools in the future study of the pathophysiological processes in IAHS.
visit three to six months postoperatively, neuroradiology (computed tomography (CT) or MRI), mini-mental state examination, hydrodynamic investigations, and video recordings of the gait were repeated.

On day 1, surgery for implantation of catheters was done under general anaesthesia induced by a barbiturate (thiopentone (thiopental)) and maintained by inhalation of either isoflurane or sevoflurane. Insertion of the different catheters was guided from preoperative MRI imaging.

The intracranial pressure transducer (Codman Microsensor, Johnson and Johnson Professional, Raynham, Massachusetts, USA) was inserted into deep white matter close to the frontal horn of the right ventricle, at a depth of 20 to 35 mm from the cortical surface. The tip was radiologically verified to be located 0–7 mm from the ventricular wall (fig 1). A CMA/70 microdialysis catheter (10 mm semipermeable membrane with a cut off of 20 kDa; CMA Microdialysis, Solna, Sweden) was inserted into the same canal and to the same depth. In no case did the catheter penetrate into the ventricle. The microdialysis system was perfused with Perfusion Fluid CNS (CMA Microdialysis) at a flow rate of $2 \mu\text{l/min}$. In patients 3 to 10 a brain tissue oxygen tension catheter CMA/60 (CMA Microdialysis) was inserted in the abdominal wall as reference. This catheter was perfused with Ringer solution at a rate of $0.3 \mu\text{l/min}$. Samples were collected every 60 minutes throughout the observation time. The microdialysis samples were initially frozen at $-80^\circ\text{C}$. All dialysate samples from all the patients were analysed simultaneously for glucose, pyruvate, lactate, and glutamate, using a colorimetric enzymatic method in a CMA/600 microdialysate analyser (CMA Microdialysis). In 55 of the 388 samples analysed (14.2%), the concentration of the metabolite was not detectable by the CMA/600. In these cases, the lowest detectable level in the CMA/600 was used. There was no difference in the proportion of undetectable concentrations between days 1 and 2 (14.8% and 13.5%, respectively).

The CSF hydrodynamic procedure was undertaken on day 2 at 8:00 am. This pressure controlled infusion test, which is routinely performed in our department, has been described elsewhere. In brief, two needles are inserted into the L3–L4 interspace. Resting pressure is recorded with the patient in the supine position. Artificial CSF is infused to predetermined

![Figure 1](image1.png)  
**Figure 1** Sagittal (A) and coronal (B) computed tomography showing the locations of the probes. The brain tissue oxygen tension (PtiO2) probe was located anterior to the intracerebral pressure (ICP) probe. The non-radiolucent microdialysis catheter was located close to the ICP probe and at the same depth.

![Figure 2](image2.png)  
**Figure 2** Time chart for the study. In all cases, the brain microdialysis samples analysed were those taken between 2:00 and 4:00 pm on the two days.

![Figure 3](image3.png)  
**Figure 3** Mean values and standard deviations of intracerebral microdialysis samples for all 10 patients. Black bars, day 1; grey bars, day 2. The changes for lactate and pyruvate were significant (Wilcoxon sign rank test, $p < 0.01$).
pressure levels of 35 and 45 mm Hg, and these are maintained for at least 10 minutes each, followed by drainage to a lumbar CSF pressure of zero (which means drainage of approximately 40 ml of CSF).

In this study we chose to analyse and compare samples collected between 2:00 and 4:00 pm on day 1 with the corresponding samples collected at the same time on day 2. The same time intervals were chosen on both days in order to avoid any diurnal variation (fig 2). Every sample reflects the mean concentration of extracellular metabolites during the previous 30 minutes, delayed by two minutes, which is the dead volume time needed for the dialysate to reach the microvial. The samples collected between 2:00 and 4:00 pm thus reflect brain metabolism between 1:28 and 3:58 pm. Intracranial pressure and \( \text{PtiO}_2 \) were recorded continuously throughout the observation time. The technical procedure for collecting data is described in detail elsewhere.

Before removing the catheters, computed tomography was done to confirm the position of the catheters and to rule out any complications. We compared the mean intracranial pressure and the mean \( \text{PtiO}_2 \) between 1:28 and 3:58 pm on days 1 and 2 to determine whether they had any correlation with the metabolic changes.

The ethics committee of Umeå University approved the study and each patient gave informed consent.

### Statistics

Statistical analyses were carried out with JMP® statistical software for the Macintosh computer. Spearman’s \( R \) was used to test for correlations between continuous variables. Differences between two means were assessed with the Wilcoxon sign rank test for paired observations.

### RESULTS

#### Microdialysis

The mean concentrations of the metabolites on days 1 and 2 for the 10 patients are presented in fig 3. After the CSF hydrodynamic investigation, there were significant increases in lactate \( (p < 0.01) \) and pyruvate \( (p < 0.01) \) (Wilcoxon signed rank test). The lactate to pyruvate ratio was unchanged. There was a trend towards a reduction in glucose and glutamate but this was not significant. The subcutaneous microdialysis samples on day 2 did not deviate from those on day 1 for any of the metabolites studied (table 2).

The results of the microdialysis analysis on each patient are shown in fig 4. Overall, the same pattern as described above was seen in the individual patients. A rise in lactate was seen in all patients. The concentration of pyruvate increased in all except patient 3, in whom no sample reached detectable values for this metabolite. Glutamate was lower on day 2 in eight of the 10 patients. A lowering of glucose was seen in seven patients.

| Table 2 | Analyses of subcutaneous microdialysis samples from 1:28 to 3:58 pm, corresponding to the intracerebral samples |
|---|---|---|---|
| Day 1 (µmol/l) | Day 2 (µmol/l) | Wilcoxon sign rank |
| Glucose | 3.5 (1.6) | 4.7 (1.2) | NS |
| Lactate | 1395 (950) | 1280 (420) | NS |
| Pyruvate | 84.3 (29.8) | 94.1 (40.8) | NS |
| Glutamate | 13.8 (12.7) | 15.7 (11.8) | NS |
| Ratio of lactate to pyruvate | 16 (8.0) | 16 (8.3) | NS |

Values are means (SD).

Figure 4  Mean values of intracerebral microdialysis samples for each patient [individual patient numbers under the bars]. There was a rise in lactate in each case, and in pyruvate in nine of the 10 cases.
Brain tissue oxygen tension microdialysis samples. age and changes in any of the various metabolites in the between the changes in intracranial pressure after CSF drain-

white matter lesions are seen with increased frequency in hydrodynamic investigation, PtiO2 increased in five of the eight patients after CSF drainage.

The microdialysis technique provides information on regional disturbance and the cognitive dysfunction are considered to be of subcortical origin. The frontal horns are pathologically widened, and surrounding parts of the brain have an anatomical relation to nerve tissue, which may explain these symptoms. Biopsy studies on IAHS patients support the anatomical relation to nerve tissue, which may explain these symptoms.

Outcome
Follow up was at three to six months after shunt surgery. Gait ability had improved in nine of the 10 patients (patients 2 to 10), as judged by differences in the preoperative and postoperative video recordings. No improvement was seen in patient 1. No clinical or radiological complications were noted following the experimental procedure or the shunt surgery.

Cerebral energy metabolism and intracranial pressure
The concentration of extracellular molecules sampled is influenced by recovery—that is, the relation between the true extracellular concentration and the concentration found in the sample collected. Recovery depends on many factors, the most important being membrane length and perfusion rate. Two different membrane lengths and a wide range of perfusion rates have been used in previous studies. Additionally, the concentration of metabolites and amino acids differs between different areas of the brain. As most previous studies have been done in patients with different pathological conditions and with a juxta cortical placement of the microdialysis catheter, there is a lack of comparable normal values for human brain metabolism. The interpretation of our results must therefore be restricted to the patterns in metabolite concentrations and their alterations.

The pattern of baseline values on day 1 of our study—that is, before manipulation of the CSF system—were consistent with disrupted energy metabolism. The lactate to pyruvate ratio was increased, as it is in patients with subarachnoid haemorrhage and moderate ischaemia. Brain tissue P02, which is an indirect measure of the microcirculation, showed a trend to increase after CSF drainage. Baseline PtiO2, level was low in our patients compared with patients in a recently published report, where the same type of probe was used in the same position in the brain. These findings are supported by an animal study in hydrocephalic cats, where MRI was used to show an increased anaerobic utilisation of glucose in frontal white matter as an indirect sign of impending ischaemia.

After the CSF hydrodynamic investigation, the concentrations of the metabolites changed. Extracellular glucose decreased, while lactate and pyruvate both rose significantly. The lactate to pyruvate ratio remained increased. This pattern has been noted previously in cases of subarachnoid haemorrhage with good clinical outcome, and though the explanation is not clear, an increased glucose utilisation rate or “hypermetabolism” must be considered a possibility.

In our study, we have demonstrated that the concentration of extracellular molecules sampled is influenced by recovery—that is, the relation between the true extracellular concentration and the concentration found in the sample collected. Recovery depends on many factors, the most important being membrane length and perfusion rate. Two different membrane lengths and a wide range of perfusion rates have been used in previous studies. Additionally, the concentration of metabolites and amino acids differs between different areas of the brain. As most previous studies have been done in patients with different pathological conditions and with a juxta cortical placement of the microdialysis catheter, there is a lack of comparable normal values for human brain metabolism. The interpretation of our results must therefore be restricted to the patterns in metabolite concentrations and their alterations.

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extent by perforating striatal arteries from the middle cerebral artery. The pathological changes in the medullary arteries in patients with subclinical arteriosclerotic encephalopathy and in those with hypertension are characterized by intimal fibrosis with or without atheroma. Similar changes are described in IAHS, where hypertension is also an important risk factor.

Blood flow studies have shown that in arteriosclerosis, normal cerebral oxygen consumption is maintained through extraction of larger than normal proportions of the arterial blood oxygen. When blood flow is further reduced, cerebral vascular insufficiency and chronic relative hypoxia is produced. Our results support the hypothesis that the characteristic CSF hydrodynamic disturbances of IAHS combined with ischaemia in the periventricular watershed areas of the brain provide conditions for the typical IAHS syndrome and for the periventricular white matter lucencies that are common findings in IAHS. Sleep disturbances, which are common in IAHS, might contribute through decreased oxygen saturation and periods of hypoxia during sleep. In that case, the white matter changes could be secondary to ischaemia. It has recently been shown that the white matter changes in IAHS and in subcortical arteriosclerotic encephalopathy cannot be differentiated on MRI, and that they are sometimes reversible after shunting. Microdialysis might be a fruitful tool to investigate the nature of these changes in order to predict reversibility. Further studies are needed to answer this issue.

Future studies should aim at explaining the relation between these variables, the final common pathway for the genesis of ischaemia and hydrocephalus, and also why patients improve after shunt installation.

Conclusions

Our main findings point to compromised metabolism with anaerobic glycolysis in the periventricular white matter in patients with IAHS. Manipulating the cerebrospinal fluid system can influence this “chronic ischaemia” or oligemia, and the ischaemia is reversible because patients improve with tap saturation and periods of hypoxia during sleep. In that case, the white matter changes could be secondary to ischaemia. It has recently been shown that the white matter changes in IAHS and in subcortical arteriosclerotic encephalopathy cannot be differentiated on MRI, and that they are sometimes reversible after shunting. Microdialysis might be a fruitful tool to investigate the nature of these changes in order to predict reversibility. Further studies are needed to answer this issue.

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