

# Intracerebral microdialysis and CSF hydrodynamics in idiopathic adult hydrocephalus syndrome

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**Background:** In idiopathic adult hydrocephalus syndrome (IAHS), a pathophysiological model of "chronic ischaemia" caused by an arteriosclerotic process in association with a CSF hydrodynamic disturbance has been proposed.

**Objective:** To investigate whether CSF hydrodynamic manipulation has an impact on biochemical markers related to ischaemia, brain tissue oxygen tension (PtiO<sub>2</sub>), and intracranial pressure.

**Methods:** A microdialysis catheter, a PtiO<sub>2</sub> 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 PtiO<sub>2</sub> 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 hydrodynamic manipulation. The concentrations of glucose, lactate, pyruvate, and glutamate on day 1 and 2 were compared.

**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 PtiO<sub>2</sub> 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.

The pathophysiology of idiopathic adult hydrocephalus syndrome (IAHS) remains unknown. This syndrome is characterised by a CSF disturbance with a low CSF outflow conductance, a normal or slightly increased intracranial pressure, and improvement after shunt surgery.<sup>1,2</sup> Clinically, the patients present with symptoms of gait disturbance, urinary incontinence, and dementia of subcortical origin. There are clinical and radiological similarities with subcortical arteriosclerotic encephalopathy,<sup>3</sup> and both entities usually show risk factors for arteriosclerosis, such as hypertension.<sup>4,5</sup>

A model of chronic ischaemia or benign oligoemia in deep white matter, caused by an arteriosclerotic process in association with a CSF hydrodynamic disturbance, has been proposed.<sup>6</sup> This theory is supported by studies on cerebral blood flow, which have revealed a decrease in blood flow in patients with IAHS.<sup>7</sup> Thus an attractive way of studying the pathophysiological process in IAHS would be to analyse markers for ischaemia and cellular damage in the target area and simultaneously manipulate the intracranial pressure by a CSF hydrodynamic investigation.

Intracerebral microdialysis and measurement of brain tissue oxygen tension (PtiO<sub>2</sub>) are new techniques, which, together with measurement of intracranial pressure, are now becoming routine methods in a neurointensive care setting. The method of microdialysis enables endogenous substances to be extracted from the extracellular fluid, and thus allows in vivo studies of biochemical events in the region of interest.<sup>8</sup> It has been shown that PtiO<sub>2</sub> is correlated with the availability of oxygen for cellular energy metabolism,<sup>9</sup> so assessment of PtiO<sub>2</sub> can contribute to the investigation of ischaemic processes in brain tissue.

This is the first study to use intracerebral microdialysis and PtiO<sub>2</sub> measurements in patients with IAHS. Our aims were to investigate PtiO<sub>2</sub> and biochemical markers related to ischaemia in the periventricular white matter, and, by CSF manipulation,

to determine whether a change in CSF hydrodynamics has an impact on these variables.

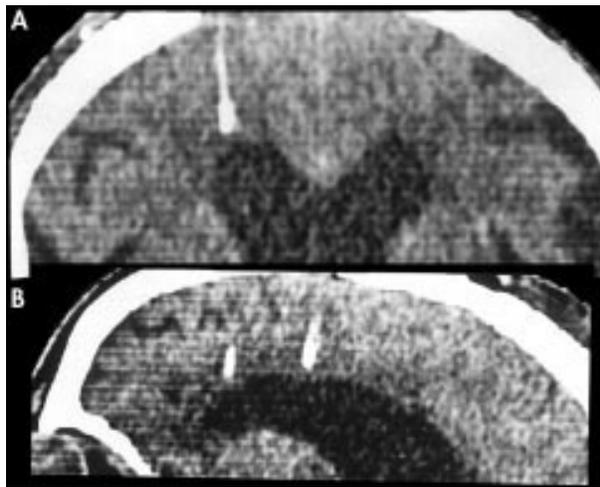
## METHODS

We studied 10 patients with IAHS—eight men and two women. Their mean age was 69 years (range 55 to 78). The presence of a gait disturbance was considered to be the cardinal clinical feature of IAHS, preceding the development of cognitive decline and urinary symptoms (table 1). Gait ability was video recorded. In all cases magnetic resonance imaging (MRI) of the brain showed communicating hydrocephalus—that is, dilated ventricles, narrow sulci, and an open aqueduct. Major ischaemic lesions and severe cortical atrophy were ruled out, as were major white matter changes.<sup>7,10</sup> The patients were monitored before and after a lumbar CSF infusion test, microdialysis, and brain tissue Po<sub>2</sub>. All patients subsequently received an adjustable shunt device after a time delay of one to two months in order to avoid contamination. At a follow up

**Table 1** Patient characteristics

Patient No	Age (years)	Sex	Duration of gait disturbance (years)	MMSE (points)	Postoperative gait improvement
1	72	M	4	24/30	No
2	76	M	2	30/30	Yes
3	71	M	2	25/30	Yes
4	78	M	5	25/30	Yes
5	76	M	2	25/30	Yes
6	78	M	1.5	29/30	Yes
7	77	F	1	26/30	Yes
8	65	F	2	15/30	Yes
9	76	M	2	29/30	Yes
10	55	M	2	30/30	Yes

MMSE, mini-mental state examination.

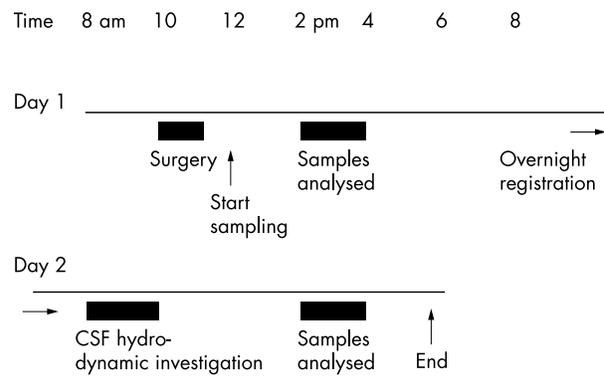


**Figure 1** Sagittal (A) and coronal (B) computed tomography showing the locations of the probes. The brain tissue oxygen tension ( $P_{\text{tO}_2}$ ) probe was located anterior to the intracerebral pressure (ICP) probe. The non-radiolucent microdialysis catheter was located close to the ICP probe and at the same depth.

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  $\mu\text{l}/\text{min}$ . In patients 3 to 10 a brain tissue oxygen tension catheter (LICOX  $\text{Po}_2$  probe, GMS, Kiel, Germany) was used. For technical reasons, this was inserted through a separate burr hole, located anterior to the two other probes (fig 1).

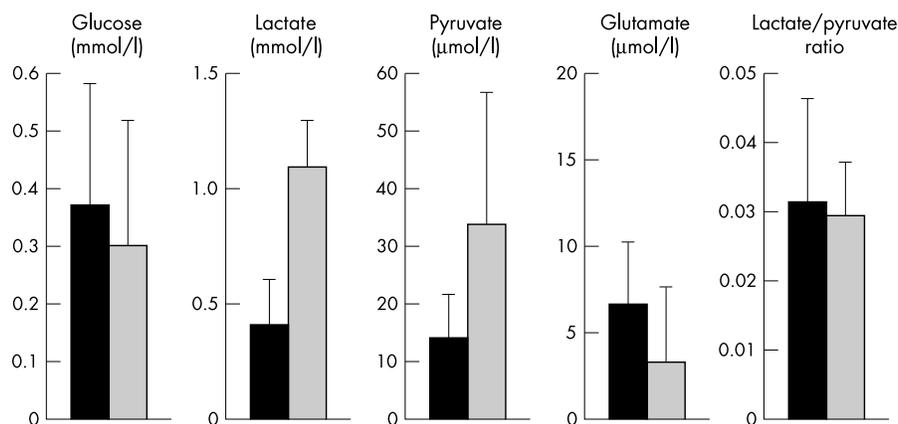


**Figure 2** Time chart for the study. In all cases, the brain microdialysis samples analysed were those taken between 2:00 and 4:00 pm on the two days.

Implantation of the probes was completed before 11:00 am for nine of the patients; one was completed at 1:00 pm. Microdialysis samples from the brain were collected every 30 minutes from the end of surgery until the time of the cerebrospinal hydrodynamic procedure next morning, after which sampling continued for another five to seven hours. The patients were monitored in the neurointensive care unit, where they were kept supine in bed, given an intravenous solution of buffered 2.5% glucose, and not allowed to eat or drink. External oxygen supplies were avoided if possible.

In patients 3 to 10, a subcutaneous microdialysis 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  $\mu\text{l}/\text{min}$ . 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.<sup>11–13</sup> 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 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,  $p < 0.01$ ).

**Table 2** Analyses of subcutaneous microdialysis samples from 1:28 to 3:58 pm, corresponding to the intracerebral samples

	Day 1 ( $\mu\text{mol/l}$ )	Day 2 ( $\mu\text{mol/l}$ )	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).

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.<sup>14</sup> 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

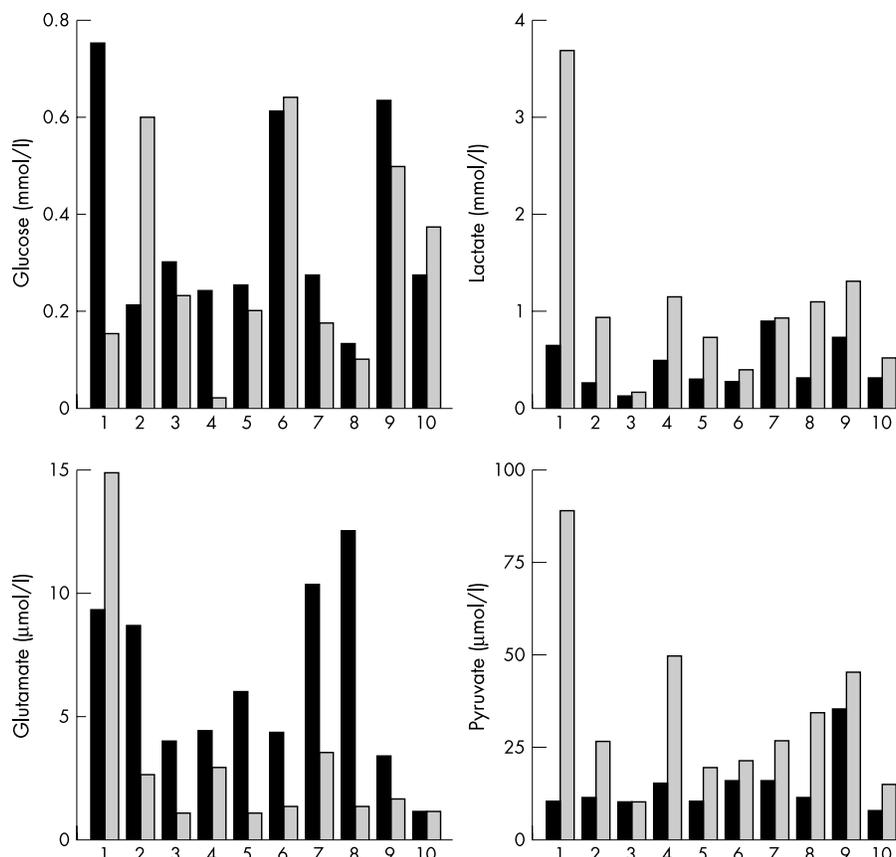
Statistical analyses were carried out with JMP® statistical software for the Macintosh computer. Spearman's  $R$  was used to test for correlations between continuous variables. Differences between two means were assessed with the Wilcoxon sign rank test for paired observations.

## RESULTS

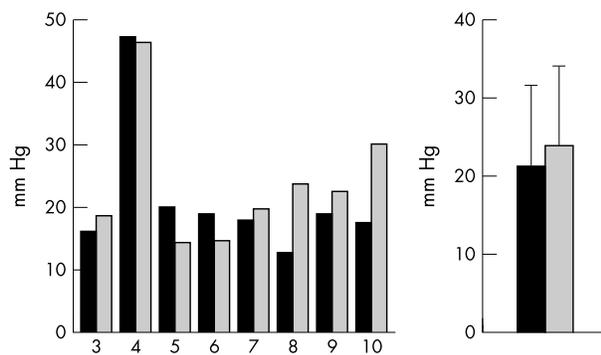
### Microdialysis

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.



**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.



**Figure 5** Changes in brain tissue oxygen tension ( $P_{tiO_2}$ ) for each patient, with the means and standard deviations alongside. Black bars, day 1; grey bars, day 2. Values below 20 mm Hg in this area of the brain are considered low.<sup>20</sup>  $P_{tiO_2}$  increased in five of the eight patients after CSF drainage.

### Intracranial pressure

The mean intracranial pressure during the sampling procedure was not significantly different between day 2 and day 1 (9.6 (5.0) v 7.7 (5.2) mm Hg). There were no correlations between the changes in intracranial pressure after CSF drainage and changes in any of the various metabolites in the microdialysis samples.

### Brain tissue oxygen tension

$P_{tiO_2}$  was measured in patients 3 to 10 (fig 5). On day 1, the  $P_{tiO_2}$  was below 20 mm Hg in seven of these eight patients. Two patients with known pulmonary disease (patients 4 and 5) had a  $P_{tiO_2}$  close to the normal value or high. After the CSF hydrodynamic investigation,  $P_{tiO_2}$  increased in five of the eight patients compared with baseline.  $P_{tiO_2}$  was not correlated with transcutaneous  $P_{o_2}$ , and seemed to be correlated with periods of external oxygen supply only in patient 5, who suffered from chronic silicosis. Patient 4 had chronic obstructive lung disease and received aggressive treatment with bronchodilating agents throughout the observation time, which might explain the high oxygen levels. During the period of increased intracranial pressure in the hydrodynamic investigations,  $P_{tiO_2}$  showed a slight but non-significant decline, but there was no sign of procedure induced hypoxia.

### 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.<sup>2</sup> No improvement was seen in patient 1. No clinical or radiological complications were noted following the experimental procedure or the shunt surgery.

### DISCUSSION

The pathophysiology of IAHS is not known but various theories are based on the concept of white matter disease. The gait disturbance and the cognitive dysfunction are considered to be of subcortical origin.<sup>1</sup> 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 theory of engagement of white matter,<sup>15</sup> and MRI verified white matter lesions are seen with increased frequency in IAHS patients.<sup>16</sup> These white matter lesions are also related to other typical characteristics of IAHS, such as old age, hypertension, gait disturbance, and risk of falling.<sup>17</sup> White matter lesions are also seen in other forms of dementia, and this gives rise to important differential diagnoses for IAHS.<sup>18</sup> The microdialysis technique provides information on regional

biochemistry close to the dialysis probe. Consequently, we placed the probes in the white matter as close to the ventricular wall as possible.

### 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 juxtacortical 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.<sup>19</sup> Brain tissue  $P_{o_2}$ , which is an indirect measure of the microcirculation, showed a trend to increase after CSF drainage. Baseline  $P_{tiO_2}$  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.<sup>20</sup> 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.<sup>21</sup>

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 “hyper-metabolism” must be considered a possibility.<sup>22–23</sup>

A shortcoming of using an infusion test in our study is the need to increase the intracranial pressure in order to calculate the CSF outflow conductance. As the increased intracranial pressure is maintained for rather a short time, and as there was no change in  $P_{tiO_2}$  during the infusion, we assume that the changes in metabolism were secondary to the spinal tap.

Glutamate was also lowered after the CSF hydrodynamic procedure, which could reflect a decrease in ischaemic damage. However, white matter contains few or no synapses, so excitotoxic mechanisms are not considered important in the development of ischaemia.<sup>24–25</sup> The time for glutamate to reach baseline after surgery has been found to be four to six hours, which is longer than for any of the other metabolites studied in this series,<sup>19</sup> and may therefore not have reached true baseline levels at the time of the first sampling on day 1.

When interpreting microdialysis results, we must bear in mind that our knowledge of brain metabolism is based on *in vitro* studies of whole parenchyma specimens. Several factors may influence the extracellular concentrations of metabolites, such as transport mechanisms over cell membranes and mitochondria, the condition of the blood–brain barrier, and whether mild ischaemia affects enzymatic regulation. Our knowledge of these mechanisms is insufficient.

### White matter changes

The brain tissue in the area studied, where our probes were located, consists of myelinated axons, oligodendrocytes, and astrocytes.<sup>25</sup> The arterial supply is mainly provided by long medullary branches from the brain surface, and to a lesser

extent by perforating striatal arteries from the middle cerebral artery. The pathological changes in the medullary arteries in patients with subcortical arteriosclerotic encephalopathy and in those with hypertension are characterised by intimal fibrosis with or without atheroma.<sup>26</sup> Similar changes are described in IAHS, where hypertension is also an important risk factor.<sup>16</sup>

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.<sup>27</sup> 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 symptom triad and for the periventricular white matter lucencies that are common findings in IAHS.<sup>7</sup> Sleep disturbances, which are common in IAHS, might contribute through decreased oxygen saturation and periods of hypoxia during sleep.<sup>28</sup> 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.<sup>3</sup> 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 oligoemia, and the ischaemia is reversible because patients improve with tap tests and shunting. The markers of ischaemia showed good concordance between our patients (fig 4), and we consider the material sufficient to allow a cautious interpretation in spite of the small population. The results support our hypothesis that in IAHS characteristic CSF hydrodynamic disturbances, together with vascular changes in the periventricular white matter, provide the conditions for chronic ischaemia. Our study indicates that intracerebral microdialysis—an interesting technique with a low complication rate—can be used in the further study of the pathophysiology in IAHS, and also in other forms of dementia. So far, the technique is only suitable for experimental studies in patients with intact or slightly impaired cognition, as informed consent is crucial. Several issues need to be resolved before microdialysis can be introduced into clinical practice in the evaluation of IAHS.

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