PAPER

Brain energy metabolism and intracranial pressure in idiopathic adult hydrocephalus syndrome

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Background: The symptoms in idiopathic adult hydrocephalus syndrome (IAHS) are consistent with pathology involving the periventricular white matter, presumably reflecting ischaemia and CSF hydrodynamic disturbance.
Objective: To investigate whether a change in intracranial pressure (ICP) can affect energy metabolism in deep white matter.
Methods: A microdialysis catheter, a brain tissue oxygen tension probe, and an ICP transducer were inserted into the periventricular white matter 0–7 mm from the right frontal horn in 10 patients with IAHS. ICP and intracerebral $PtiO_2$ were recorded continuously during lumbar CSF constant pressure infusion test. ICP was raised to pressure levels of 35 and 45 mm Hg for 10 minutes each, after which CSF drainage was undertaken. Microdialysis samples were collected every three minutes and analysed for glucose, lactate, pyruvate, and glutamate.
Results: When raising the ICP, a reversible drop in the extracellular concentrations of glucose, lactate, and pyruvate was found. Comparing the values during baseline to values at the highest pressure level, the fall in glucose, lactate, and pyruvate was significant ($p<0.05$, Wilcoxon sign rank). There was no change in glutamate or the lactate to pyruvate ratio during ICP elevation. $PtiO_2$ did not decrease during ICP elevation, but was significantly increased following CSF drainage.
Conclusions: Raising intracranial pressure induces an immediate and reversible change in energy metabolism in periventricular white matter, without any sign of ischaemia. Theoretically, frequent ICP peaks (B waves) over a long period could eventually cause persisting axonal disturbance and subsequently the symptoms noted in IAHS.

The pathophysiology of idiopathic adult hydrocephalus syndrome (IAHS) is still a puzzle after more than 40 years of research. It is considered to be a disorder of CSF circulation, as analysis of CSF pressure recordings and infusion studies show an increased resistance to CSF absorption[1 2] and an increased frequency of pathological pressure waves (B waves).[3] There is also evidence that changes in the cerebral circulation may play an important role in the pathogenesis, and a situation of chronic ischaemia has been proposed.[4 5] Risk factors for arteriosclerosis, such as hypertension are overrepresented.[6 7]

We have shown in a previous microdialysis study that CSF drainage can induce a decrease in the extracellular concentration of glucose and increased lactate and pyruvate concentrations, suggesting an increased metabolic rate in periventricular white matter.[8] The same pattern has been shown in patients with subarachnoid haemorrhage and a favourable outcome, suggesting hyperglycolysis.[9]

Our aim in this study was to investigate whether energy metabolism in deep white matter can be affected by temporary changes in ICP. This was measured by the techniques of intracerebral microdialysis and brain tissue oxygen tension ($PtiO_2$).

METHODS

Patients

Ten patients with clinical, radiological, and CSF hydrodynamic evidence of IAHS were included. Their mean age was 69 years (range 55 to 78), and there were eight men and two women. They all presented with gait disturbance as the first and major problem, followed by development of mild cognitive decline with or without urinary incontinence. Magnetic resonance imaging was carried out in all patients. This showed communicating hydrocephalus (that is, dilated ventricles, narrow sulci, and an open aqueduct). No significant ischaemic lesions or extensive leukoaraiosis in deep white matter were seen in any case. Apart from MRI, diagnostic workup included clinical characteristics, routine laboratory tests, mini-mental state examination (MMSE), and videotaping of the gait. All patients received an adjustable shunt device (Codman Medos™, Johnson & Johnson Professional Inc, Raynham, Massachusetts, USA), one to two months after CSF hydrodynamic investigation. At a follow up visit three to six months postoperatively, neuroradiology (computed tomography (CT) or MRI), MMSE, hydrodynamic investigations, and video recording of the gait were repeated. Nine of the 10 patients (Nos 2 to 10) were found to have improved from shunt surgery.

The ethics committee of Umeå University approved the study, and all patients gave their informed consent. This study is part of a larger project; two studies from the project have been published before.[8 10]

Probes

Surgery for implantation of catheters was carried out under general anaesthesia. Insertion depth of the different catheters was decided from the preoperative MRI imaging.

An ICP transducer (Codman MicroSensor™, Johnson & Johnson Professional Inc, Raynham, MA, 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.

Abbreviations: IAHS, idiopathic adult hydrocephalus syndrome; ICP, intracranial pressure; MMSE, mini-mental state examination; $PtiO_2$, brain tissue oxygen tension; SAE, subcortical arteriosclerotic encephalopathy

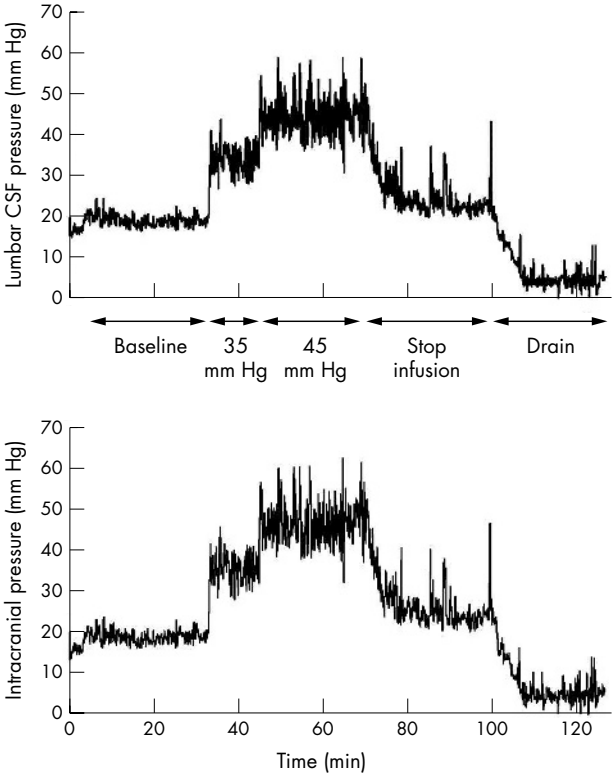

Figure 1 Simultaneous recordings of intracranial and lumbar pressure. Baseline period starts when the patient position is changed from sitting to supine. Pressure levels of 35 and 45 mm Hg are maintained by computer guided infusion of artificial CSF. The postinfusion period denotes spontaneous equilibration when infusion is stopped. Finally, approximately 40 ml of CSF is actively drained to a pressure level close to zero. Note the identical curve shapes.

At the end of the observation period, a CT scan was done to verify the location of the catheters radiologically.

A CMA/70 microdialysis catheter with a 10 mm semipermeable membrane (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, Solna, Sweden) at a flow rate of 2 µl/min.

In patients 3 to 10, a brain tissue oxygen tension catheter (LICOX Po_2 probe, GMS, Kiel, Germany) was used. As the $Ptio_2$ probe required a special bolt for fixation, it was inserted into a separate burr hole, located frontal to the two other probes. Additionally, in patients 3–10, a subcutaneous microdialysis catheter CMA/60 (CMA Microdialysis, Solna, Sweden) was inserted in the abdominal wall as reference. This catheter was perfused with Ringer solution at a rate of 0.3 µl/min. Samples were collected every 60 minutes throughout the observation period.

Monitoring

The patients were monitored by means of intracranial pressure, microdialysis and brain tissue Po_2, and standard neurointensive care monitoring over 30–32 hours. A lumbar CSF hydrodynamic investigation (infusion test) was carried out in the morning on the day after probe implantation. This hydrodynamic procedure is described elsewhere.[11–13] In brief, two needles are inserted into the L3-L4 interspace; baseline pressure is recorded with the patient in supine position; artificial CSF is infused using a computerised system to predetermined pressure levels of 35 and 45 mm Hg; these pressure levels are then kept stable for at least 10 minutes each, followed by drainage to a lumbar CSF pressure of zero, which usually means drainage of approximately 40 ml CSF (fig 1).

Microdialysis samples from the brain were collected every 30 minutes from the end of surgery until the cerebrospinal hydrodynamic procedure was undertaken the next morning, after which sampling continued for another five to seven hours. Results from microdialysis sampling before and after this hydrodynamic procedure have been published.[8] During the CSF hydrodynamic procedure, brain microdialysis samples were collected every three minutes. The samples were frozen at −80°C pending analysis.

Analysis

Samples for all patients were analysed for glucose, pyruvate, lactate, glutamate, urea, and glycerol as one batch, using the enzymatic colorimetric method of CMA/600 microdialysate analyser (CMA Microdialysis, Solna, Sweden). Data are presented as mean values of samples collected during baseline. During raising and lowering of the intracranial pressure the last sample from each pressure level was analysed, and finally one sample 15–30 minutes after completing the hydrodynamic procedure. Dead-volume time from catheter tip to sample vial is calculated to 2.5 minutes. As each pressure level lasts 10 minutes or more, and samples were collected every three minutes, the samples analysed are considered to be representative of the pressure level in question. ICP and $Ptio_2$ were recorded continuously throughout the observation period. The technical procedure on collecting data is described in detail elsewhere.[10]

Statistical analyses were carried out with SPSS® 10.0 for Macintosh (SPSS Inc, Chicago, Illinois, USA). The nonparametric Friedman test for related samples was used to check for difference within series, and Wilcoxon sign rank for paired comparisons between individual sample pairs. Results were considered significant at $p<0.05$. No corrections for multiple analyses were carried out.

RESULTS

All patients underwent the procedure without complications. The CT scan carried out at the end of the observation time showed that all catheters were located with the tip within 7 mm of the ventricular wall. On the follow up visit after shunt surgery, a slight reduction in the ventricle size was seen in two of the 10 patients; in eight patients ventricle size was unchanged.

Microdialysis

Results from microdialysis during the CSF hydrodynamic investigation are shown in figs 2 and 3. When raising the intracranial pressure through infusion of artificial CSF, we found a fall in the extracellular concentration of glucose, lactate, and pyruvate. The ensuing CSF drainage resulted in a rise in the same analytes, and there was a tendency to overshoot, with values after drainage being slightly higher than during baseline. Comparing the values during baseline with those at the highest pressure level, the fall in glucose, lactate, and pyruvate was significant ($p<0.05$). Concentrations after drainage were significantly higher than corresponding values at the highest pressure level for all three glucose related analytes ($p<0.01$). The lactate to pyruvate ratio did not change significantly during the increase in ICP, but was lower ($p<0.05$) when comparing the value at drain with that at baseline. The concentrations of glutamate, urea, and glycerol (data for urea and glycerol not shown) did not alter during any phase of ICP change.

Subcutaneous microdialysis samples were collected every 60 minutes in patients 3 to 10. Results from samples

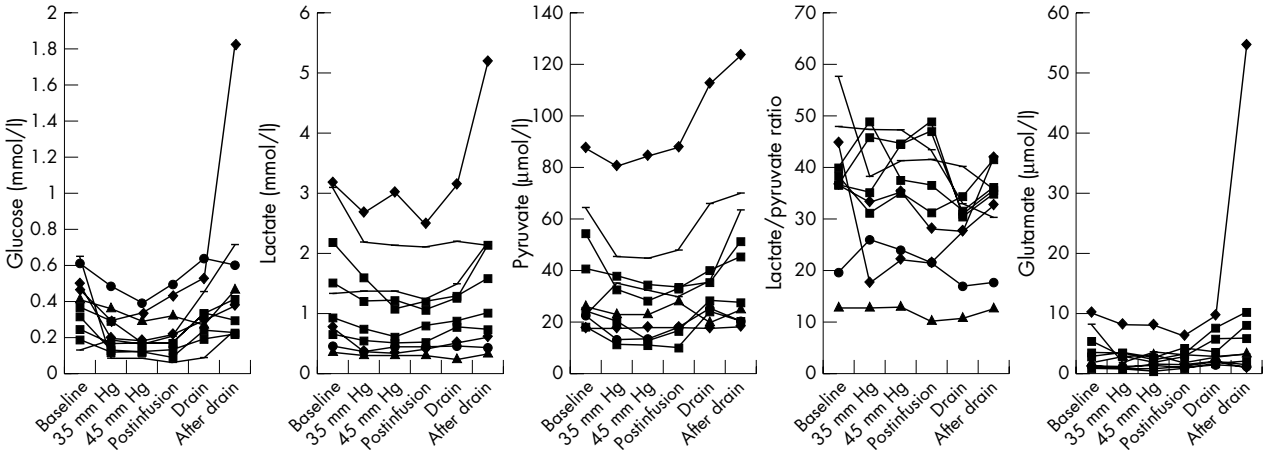

Figure 2 Microdialysis values during raising and lowering of intracranial pressure in the constant pressure infusion test. Each line represents one individual patient. Note the hammock shape in the glucose related analytes.

corresponding to the 60 minute periods before, during, and after the CSF hydrodynamic procedure are shown in table 1. Running the Friedman test, we found no differences except for pyruvate. During ICP elevation, there was one extremely low value in one patient, which was responsible for the significance. When leaving this extreme value out, the difference was no longer significant.

Brain tissue oxygen tension

In eight of the 10 patients, $Ptio_2$ was recorded (data shown in fig 4). There was no significant decrease in oxygen tension during ICP elevation. After drainage, there was a rise in $Ptio_2$ compared with both the highest pressure level and baseline ($p<0.05$ for both).

DISCUSSION

The symptoms in IAHS—gait disturbance, incontinence, and cognitive deficit—are all considered to be of subcortical origin, and from an anatomical point of view can be explained by lesioned nerve fibres in the periventricular white matter.[14 15] There are two main hypotheses on the cause of this compromised axonal function: a mechanical cause, from compression and axotomy from the distended ventricular walls or transependymal CSF diffusion[15 16]; and

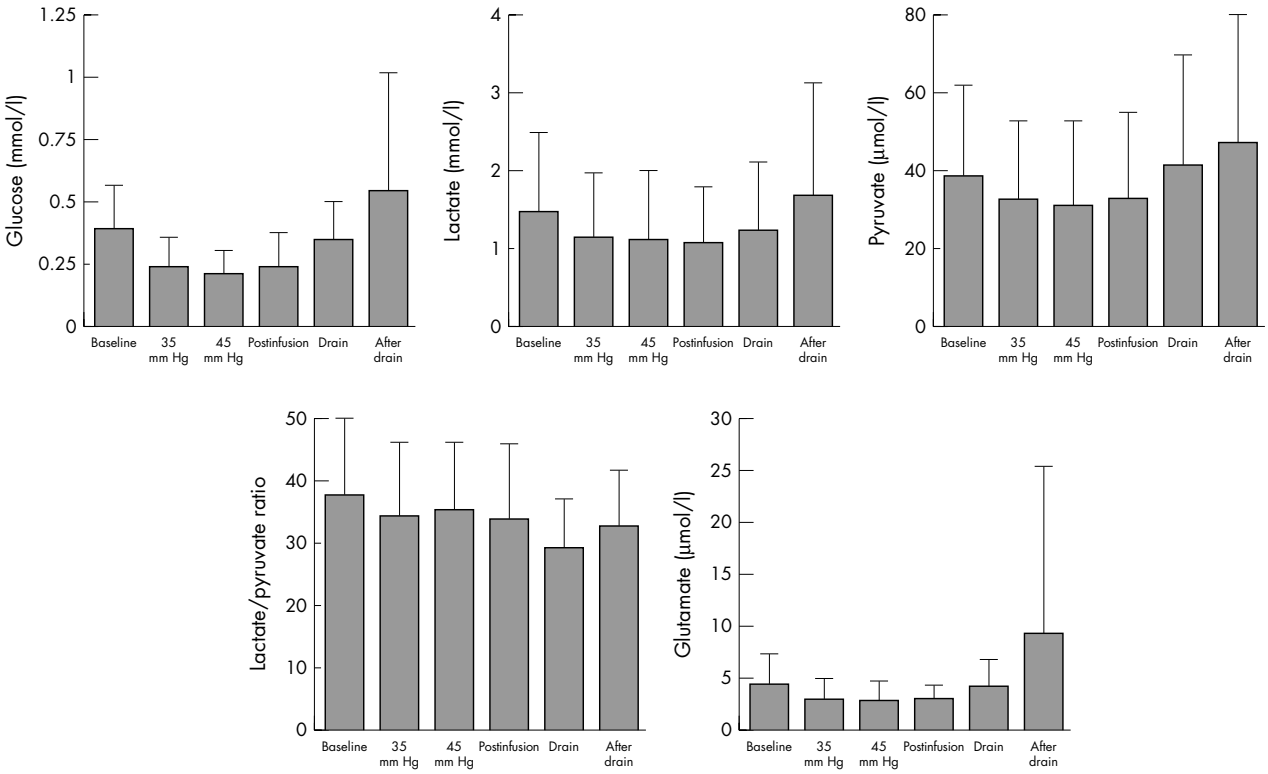

Figure 3 Means and standard deviations of each analyte, and the lactate to pyruvate ratio. The non-parametric Friedman test for related samples was significant ($p<0.05$) for all analytes except glutamate, where no difference was seen. Wilcoxon sign rank tests for baseline *v* highest pressure level were significant ($p<0.05$) for glucose, lactate, and pyruvate. The lactate to pyruvate ratio decreased during drainage compared with baseline ($p<0.05$).

Table 1 Analysis of subcutaneous microdialysis samples during 60 minutes before CSF hydrodynamic investigation, during intracranial pressure manipulation (infusion), and for the first 60 minutes after completed drain

Variable	Baseline (μmol/l)	Infusion (μmol/l)	Drain (μmol/l)	Friedman test
Glucose	4300	4100	3900	NS
Lactate	1682	1185	1403	NS
Pyruvate	105	76	89	$p<0.05$
Glutamate	16.4	12.9	16.6	NS
Lactate/pyruvate ratio	16.9	19.8	16.3	NS

The significant change in pyruvate is attributable to one single, very low sample in one patient during the infusion phase; this result might therefore be an artefact.

ischaemia from decreased blood flow in the area.[5] A combination of these causes is also proposed.[17] IAHS and subcortical arteriosclerotic encephalopathy (SAE) show similar clinical and radiological presentations, which explains why the clinical distinction is often difficult.[18] To make things even more complicated, we may have to accept that in many cases, there is a mix of both IAHS and SAE in some proportion. However, there is evidence that the pathophysiology of the two is different. In SAE, the underlying cause is considered to be hyalination of penetrating arterioles, causing lacunar infarcts and microinfarcts in the deep white matter. Necropsy studies have also shown demyelination and axonal loss.[19] In IAHS, on the other hand, there is evidence of primary compromised axonal function, leading to axonal damage with secondary demyelination and gliosis.[20 21]

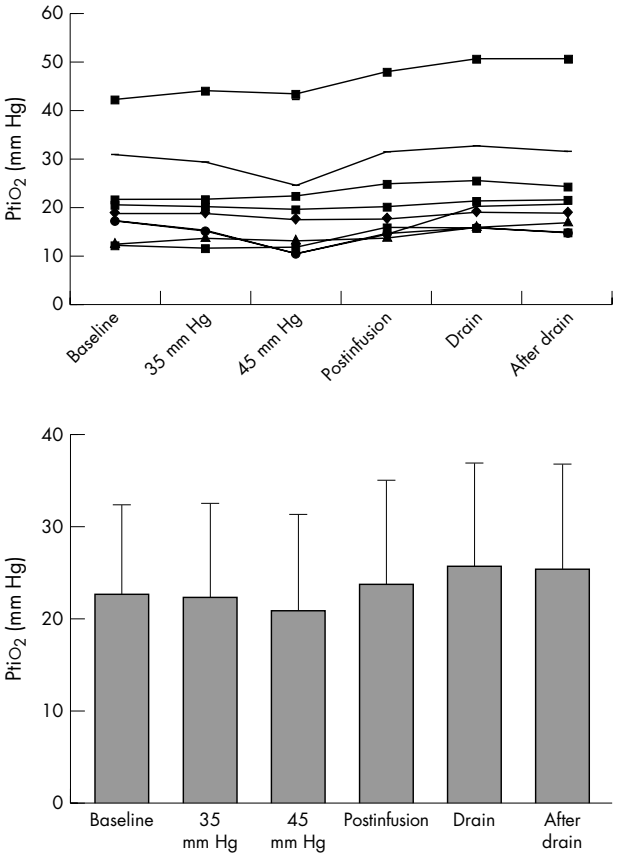

Figure 4 Brain tissue oxygen tension ($PtiO_2$) values throughout the hydrodynamic investigation; individual values (top) and means with SD (bottom). In two of the eight patients a decrease at the highest pressure level was seen. In the lower panel, the height of the columns represents mean $PtiO_2$ during the whole period at each pressure level. There was no change during pressure elevation compared with baseline. $PtiO_2$ during drainage was significantly higher than at baseline ($p<0.05$).

Glucose metabolism

Blood glucose is taken up by astrocyte endfeet linking to the intracerebral capillaries. In the astrocytes, glucose is subject to rapid dynamic turnover of glycogen formation and glycogenolysis/glycolysis. Energy supplies for neuronal use consist of glucose or lactate released to the extracellular space. Extracellular concentration of glucose is shown to decrease during neuronal activity but also in situations of low energy demand, such as anaesthesia, sleep, and hypoxia.[22 23] The concentration of extracellular glucose is considered to represent the balance between supply and utilisation.

Astrocytes serve several functions apart from fuel delivery. They are responsible for clearing glutamate and reactive oxygen species from the extracellular space and for buffering of extracellular K^+ and H^+. Other functions include influencing the blood–brain barrier, brain oedema, and the inflammatory response.[24] As white matter does not contain any synapses or neurone cell bodies, the main energy demand by axons should be the maintenance of ion balance at nodes of Ranvier and axonal transport.

Brain tissue oxygen tension

Our $PtiO_2$ values were constantly lower than previously reported from other human and experimental animal studies. However, these studies are all carried out during general anaesthesia, and, in humans, in situations of trauma or subarachnoid haemorrhage.[25 26] No $PtiO_2$ studies in non-sedated and non-traumatised human brains have been carried out before, to our knowledge. Investigation of regional cerebral perfusion was unfortunately not available during the CSF hydrodynamic procedure. If cerebral perfusion in deep white matter diminished because of a rise in ICP, the unchanged $PtiO_2$ can be explained as a higher oxygen extraction rate. When lowering ICP, brain tissue oxygenation increased, which may be interpreted as an amelioration of a chronic low grade ischaemia.

Microdialysis

The microdialysis results show a general decline in the extracellular concentration of glucose and its metabolites lactate and pyruvate during the period of raised ICP. This pattern is consistent with a situation of insufficient energy supply. There is no permanent damage to the neurones from this short period of raised ICP, as shown by the normalisation of energy metabolism when ICP is lowered. The rate of recovery is expected to be rather low, as a high perfusion rate was used, while the individual concentrations were lower than in previous studies.[27–29] There is a possibility that the recordings in this specific study were affected, as the semipermeable membrane may have been in close contact with the pressure monitoring probe. However, as the patients are followed longitudinally and no interindividual

comparisons were made, the absolute values are of minor importance.

There are several possible explanations for our results, all giving rise to further questions.

The fall in glucose during raised ICP could be secondary to diminished cerebral perfusion, resulting in low glucose and oxygen supply. Oxygen supply should not be the first limiting step even if there were periods of low perfusion, as these should be compensated by a greater arteriovenous oxygen difference.[30]

Another hypothesis is that the raised intracranial pressure leads to impaired axonal transport and subsequently to impaired neuronal activity. This results in low energy demand and decreased release of glucose and, possibly, lactate from astrocytes. As less glucose and lactate are oxidised, pyruvate decreases as well. This interpretation is supported by studies on experimental glaucoma, where compromised axonal transport in the optic nerve as a result of raised intraocular pressure has been shown. An additional supply of oxygen did not change these results.[31 32] To fully explain our results, there would have to be a net export of glucose from the extracellular space. This has not to our knowledge been shown.

As glucose delivery from blood flow to neurones is an enzymatic multistep procedure, the most plausible explanation may be a primary astrocyte disturbance. Astrocytes are known to be vulnerable to reactive oxygen species, hypoxia, and acidosis. Water is taken up in astrocyte endfeet through aquaporins by osmosis. Therefore, in brain oedema the astrocyte pericapillary endfeet are the first cellular elements to swell. The raised ICP could theoretically lead to dysfunction in glucose uptake and release, with consequences for axonal function.[24] This hypothesis is supported by a newly published experimental study in a rat kaolin model.[33]

The possibility of a dilutional effect from increased fluid content in the extracellular space as a result of the change in ICP seems unlikely, as the reduction in microdialysis concentrations is seen only in glucose and its metabolites lactate and pyruvate, and not in glutamate, urea, or glycerol.

Although our study is small, we think it is sufficient for a cautious interpretation as the pattern is consistent. Also the clinical improvement after shunt surgery suggests that our findings may be valid for the pathological conditions studied. Our findings show that even short periods of raised ICP lead to disturbances of energy metabolism in the periventricular white matter. We hypothesise that, over years, frequent periods of impaired energy metabolism coupled with raised ICP could lead to axonal damage and eventually to demyelination. Early in the course of IAHS, CSF shunting could restore axonal function through neutralising spontaneous variations of the ICP (B waves). The degree of demyelination may limit the benefit from shunt surgery. A method of diagnosing the degree of demyelination with enough sensitivity and specificity would be helpful in the preoperative evaluation of IAHS.

Conclusions

When intracranial pressure increased, we found a prompt decrease in energy metabolism in the periventricular white matter, without any signs of ischaemia. There was no sign of permanent damage, as the changes were reversible when ICP was lowered. Theoretically, frequent ICP peaks (B waves) could over a long period eventually cause persisting axonal damage and secondary demyelination. This leads to the hypothesis that the benefits of shunt surgery result from neutralisation of spontaneous ICP variations, which subsequently interrupts the pathological process while it is still to some extent reversible.

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ECHO

IV cyclophosphamide bodes well for neuropsychiatric SLE

Please visit the *Journal of Neurology, Neurosurgery, and Psychiatry* website [www.jnnp.com] for a link to the full text of this article.

Doctors may have found an effective treatment for one of the worst complications of systemic lupus erythematosus (SLE), if findings from an initial trial are correct. Theirs is a larger and longer term comparative study than many others and one of the few controlled trials in SLE.

Intravenous (IV) cyclophosphamide (Cy) was more effective than IV methylprednisolone (MP) for patients with acute severe neuropsychiatric SLE expressing seizures, peripheral neuropathy, optic neuritis, and brainstem disease. Treatment with Cy failed in just one patient out of 19 compared with seven of 13 given MP.

Thirty two patients were studied out of 38 recruited from two tertiary referral centres in Mexico City. All were aged 18 years or over and had incident neuropsychiatric SLE of 15 days or less or refractory seizures. After randomisation all received induction treatment of MP 1 g daily for three days followed by either Cy (0.75 g/m^2 monthly for a year, then quarterly for another year) or MP (1 g daily for three days, monthly for four months, bimonthly for six months, then quarterly for a year). Patients were followed up each month. Improvement or deterioration was judged as a 20% difference compared with baseline measures at the fourth month after treatment started.

Neuropsychiatric complications, though the cause of much illness and death in SLE, are not well understood, nor is treatment well defined. In severe cases immunosuppressive high dose corticosteroids, IV pulse MP and Cy, and IV immunolglobulins have been used, with varying results.

▲ Barile-Fabris L, *et al*. *Annals of the Rheumatic Diseases* 2005;**64**:620–625.