Idiopathic intracranial hypertension: any light on the mechanism of the raised pressure?

Everyone knows that no one knows the mechanism of the increase of intracranial pressure in idiopathic intracranial hypertension (IIH; also called pseudotumour cerebri; see table 1 for diagnostic criteria). Does it much matter? After all, for most affected people IIH is a benign, self limiting condition. However, sometimes it is not, and current therapies are unsatisfactory. Medical treatment is poor and of unproved benefit. Surgical interventions (optic nerve sheath fenestration, lumboperitoneal shunting) have appreciable hazards and failure rates. Moreover, the mechanism of increase in intracranial pressure in IIH might have relevance to raised intracranial pressure and its management in other situations such as meningitis and hydrocephalus.

Normal intracranial pressure
In normal circumstances intracranial pressure is maintained by cerebral arterial pressure which itself is subject to cerebral autoregulation such that, other things being equal, intracranial pressure remains constant over a wide range of systemic arterial blood pressure. Intracranial pressure is also greatly influenced by cerebral venous pressure. Furthermore, intracranial pressure is determined by CSF formation and absorption, but whether there are any physiological regulatory mechanisms operating at the choroid plexus or arachnoid villi and granulations is unclear. Pressure in CSF varies enormously in the lumbar region and at the vertex depending on posture (reviewed in Fishman).

Increased intracranial pressure
At a simple level, various perturbations could lead to an increase in intracranial pressure without the development of hydrocephalus or florid visible abnormality on structural imaging. These are summarised in table 2. For any of these mechanisms to be operative, it is necessary that any compensatory processes are no longer functioning. Thus an increase in cerebral volume with an equivalent reduction in CSF volume will obviously not change the status quo. Over the years investigational techniques of every imaginable degree of complexity and invasiveness have been used to explore these possibilities in IIH. Many of the relevant indices such as CSF formation rate, CSF outflow resistance, CSF outflow rate, and sagittal sinus pressure can be measured or calculated, but some of the techniques used require certain assumptions and are therefore possibly fallible. Particular difficulties exist in knowing to what extent the brain is compressible in response to increasing CSF pressure, and to what extent the CSF space is expandable. These factors influence CSF outflow resistance calculations in infusion or perfusion studies.

Increased cerebral volume
Computed tomography offered a way of assessing cerebral volume in IIH, albeit somewhat crudely. A reduction in the size of the ventricular system, indicating an increase in cerebral volume, was reported in some studies, but not in others, and it remains controversial as to whether cerebral volume is significantly increased in IIH. The disagreement perhaps reflects heterogeneity of pathogenesis. The hope has been expressed that MRI will provide a great deal more information about what is going on in IIH, but thus far there has not been an abundance of reported studies of cerebral and CSF volumes in IIH, nor of the composition of cerebral tissue. Moser et al reported an increase in white matter water signal, suggesting diffuse mild oedema, and Gideon et al detected increased water mobility in subcortical white matter. Both studies required the use of special MRI sequences, routine sequences showing no abnormality. The brain in IIH has also been studied by positron emission tomography. Notably, no change in

Table 1 Modified Dandy criteria for IIH

<table>
<thead>
<tr>
<th>Symptom/Sign</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased ICP</td>
<td>Headache, papilloedema</td>
</tr>
<tr>
<td>No localising signs</td>
<td>Normal neurological examination (except sixth cranial nerve lesion(s) or rarely other false localising signs)</td>
</tr>
<tr>
<td>Normal neuromaging</td>
<td>No evidence of venous obstructive disease</td>
</tr>
<tr>
<td>Increased ICP</td>
<td>Measured by lumbar puncture (&gt;25 cm CSF)</td>
</tr>
<tr>
<td>Normal CSF constituents</td>
<td>Awake and alert patient</td>
</tr>
<tr>
<td>No other cause of increased ICP present</td>
<td>Benign clinical course apart from visual deterioration</td>
</tr>
</tbody>
</table>

ICP=Intracranial pressure.

Table 2 Perturbations which could lead to raised ICP

<table>
<thead>
<tr>
<th>Perturbation</th>
<th>Effect on CSF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased cerebral volume</td>
<td>Increased ISF volume</td>
</tr>
<tr>
<td>Increased CSF production rate</td>
<td>Increased blood volume</td>
</tr>
<tr>
<td>Increased CSF outflow resistance</td>
<td>Increased tissue volume</td>
</tr>
<tr>
<td>Increased cerebral arterial pressure transmitted to capillaries (loss of autoregulation)</td>
<td>Reduced CSF outflow</td>
</tr>
<tr>
<td>Increased cerebral venous pressure</td>
<td>Leading to increased venous blood volume and increased ISF volume</td>
</tr>
</tbody>
</table>

ISF=Interstitial fluid.
regional cerebral blood volume was found.29 The most invasive studies of cerebral tissue in IIH were cerebral biopsies, which were reported by Sahs and Joyn17 to show evidence of interstitial cerebral oedema, but necropsies19 have not confirmed those findings, nor did a review of some of the original biopsy material of Sahs and Joyn.20

**Increased CSF production**

Increased CSF production rate has been proposed as a mechanism of IIH. The production rate of CSF can be measured in patients, but the procedures (infusion or perfusion techniques) are invasive.21 In one study increased CSF production rate was reported in IIH.22 However, most investigators have not found CSF hypersecretion in IIH. An attempt at measuring CSF production rate non-invasively by recording CSF flow through the cerebral aqueduct using MRI gave highly variable results, but again did not support the view that CSF hypersecretion is important in IIH.23 The only condition in which the CSF production rate is known definitely to be increased is choroid plexus papilloma, a fairly rare paediatric tumour. With this tumour the situation can be complicated by obstructive hydrocephalus and hydrocephalus related to intraventricular haemorrhage. However, CSF overproduction has been proved in patients including one with a small non-obstructing tumour,24,25 and it is presumably part of the cause of the hydrocephalus. An IIH-like syndrome has not been reported in choroid plexus papilloma. Kollar and Johnson26 used embolisation to treat an arteriovenous malformation which involved the great vein of Galen in a 5 year old child. After the successful occlusion, which was not complicated by venous thrombosis, the patient developed a pseudotumour syndrome, and the proposal was that a result of the procedure might have been an increase in CSF production by the choroid plexuses of the lateral ventricles as a result of change in venous pressure in the choroid plexuses. The CSF production rate, however, was not measured. There has been speculation that the benign intracranial hypertension associated with hypervitaminosis A might be due to CSF hypersecretion, but evidence is lacking.27

Idiopathic intracranial hypertension would require a generalised increase in intracranial pressure without a significant pressure gradient across the cortical mantle, and without any capacity for the brain to be compressed. Mathematical modelling of ventricular size in the circumstance of increased CSF production predicts hydrocephalus, not IIH.28 Experimental infusion of artificial CSF into the lateral ventricles of dogs leads to modest ventricular enlargement, not an IIH-like syndrome.29

**CSF outflow reduction**

Much more important and relevant is the likelihood that impaired outflow of CSF into the venous system is a cause of IIH. However, herein lies a conundrum, as exactly the same mechanism is invoked to explain communicating hydrocephalus. In some studies the two groups of patients have even been analysed together, despite their striking clinical differences (for example, Borgesen and Gierriss30). An increase in CSF pressure, either due to CSF overproduction or due to impaired absorption, would be expected to lead to an increase in CSF volume, if the CSF space had the capacity for any expansion. Within a non-expansile skull and relatively non-expansile spinal canal, CSF could only easily accumulate at the expense of cerebral blood volume. In IIH there is neither a reduction in cerebral blood volume, nor an increase in CSF volume. In hydrocephalus, the main mechanism of ventricular dilatation is evidently a pressure difference between the ventricular CSF and the convexity CSF, but pressure atrophy is also thought to play a part in the ventricular dilatation (see Fishman31). However, pressure atrophy does not seem to be operative in patients with chronic IIH, except possibly for two patients reported by Malm et al32 who developed hydrocephalus after years of IIH. If the proposition is that the impairment of outflow of CSF is a lesion at the arachnoid villi and granulations level, then there is no reason to expect any transmantle pressure gradient, and it is easier to envisage this as a mechanism for IIH than NPH. Infants might represent a special case, as a non-acute increase in intracranial pressure may be expected to cause expansion of the skull vault, allowing the accumulation of CSF, either inside the ventricles or outside (external hydrocephalus). However, in the mathematical model of Rekate et al,33 an increase in CSF outflow resistance alone leads to hydrocephalus, and to generate the conditions found in IIH a reduction in brain compressibility is required as well.

There is ample evidence from infusion and perfusion studies that IIH is associated with an impairment of outflow of CSF.34-38 There is no direct evidence of dysfunction of arachnoid villi and granulations in IIH. Abnormalities of arachnoid villi have, however, been noted in certain conditions which involve raised intracranial pressure. Microscopy after subarachnoid haemorrhage has disclosed apparent obstruction of villi by cells and morphological changes in arachnoid villi and granulations.39 The outflow resistance of CSF is known to be increased in experimental subarachnoid haemorrhage.40,41 But the disturbance of CSF dynamics associated with subarachnoid haemorrhage is hydrocephalus, and the relevant site of CSF flow disturbance might be proximal to arachnoid villi and granulations. The same considerations apply to meningitis and experimental meningitis.42 However, a pseudotumour syndrome is sometimes seen in the context of meningitis (see for instance Cremer et al).43 Very high CSF protein concentration (spinal tumour, Guillain-Barré syndrome) is sometimes a cause of raised intracranial pressure with papilloedema,44,45 and the suggestion has been made that the protein leads directly to impaired CSF outflow, and there is experimental evidence to support this.46 Interestingly, some patients with raised intracranial pressure attributed to high CSF protein concentration from a spinal tumour develop hydrocephalus, and some have papilloedema without ventricular dilatation.44 Agenesis, deficiency, or dysplasia of arachnoid villi and granulations leads to hydrocephalus in infancy.44,45 (As indicated above, the capacity of the infant skull to expand may explain why hydrocephalus rather than a pseudotumour syndrome develops in this situation.) Vitamin A deficiency can cause a pseudotumour syndrome. Morphological abnormalities of arachnoid villi and granulations in experimental vitamin A deficiency have been described, and are presumably the cause of the increased CSF outflow resistance and the raised intracranial pressure.47 Regrettably arachnoid villi and granulations were not available for histological examination in the two patients with IIH who came to necropsy and were reported by Wall et al.40

An apparent difficulty with the idea that IIH is caused by any sort of impairment of CSF outflow is the normal or even low CSF protein concentration in IIH.40,41 The fluid which is made by the choroid plexuses is principally water and salt, with a low protein concentration. Protein gets into CSF diffusely throughout the system either from the brain and spinal cord parenchyma (mainly getting there across the blood-brain barrier) or directly across the blood-CSF barrier. Protein is absorbed into the venous system along with CSF. The gradient of CSF protein concentration (low in ventricular fluid and higher in lumbar fluid) is thus eas-
ily understood. In addition, the permeability of the blood-
CSF barrier may be greater in the lumbar region. An
increase in CSF outflow resistance might be expected to
involve an increase in CSF protein concentration, even if
once a steady state is re-established the overall CSF tur-
ner is unchanged. The low CSF protein concentrations
sometimes found in IIH are measured in lumbar CSF, and
a possible way of accounting for this would be an increase
in CSF absorption at a spinal level in the face of an impair-
ment of CSF absorption into the superior sagittal sinus (a
proportion of CSF is absorbed by arachnoid villi and
granulations which are in veins around spinal nerve roots).
Low lumbar spinal fluid protein concentration would be
compatible with a lesion affecting cerebral arachnoid villi
and granulations selectively or preferentially. It would also
be compatible with an increase in cerebral venous sinus
pressure, but presumably not a global systemic increase in
venous pressure which would affect spinal as well as cranial
CSF absorption. Furthermore it would be compatible with
an inverse relation between CSF protein concentration and
intracranial hypertension. Such a relation was reported by
Chandra et al., but not confirmed by Johnston et al. in a
larger study with more robust data.

Intracranial venous hypertension
The final candidate mechanism for IIH is the obvious one
of an increase in venous sinus pressure—obvious because
lesions which increase venous sinus pressure (for example,
dural arteriovenous malformations) can impede venous
drainage (for example, venous sinus thrombosis, malignant
obstruction of venous sinuses or jugular veins) are known
to give rise to the same syndrome as IIH. Clearly supe-
rior sagittal sinus thrombosis will secondarily have an ef-
effect on CSF absorption, but any disorder causing a rise in venous
pressure will secondarily have an effect on CSF absorption.

In the CT era it is in fact quite likely that cases of
cerebral venous sinus thrombosis were misdiagnosed as
having IIH, as the diagnosis was often made on the basis of
the clinical picture, an unremarkable scan and a lumbar
puncture. Magnetic resonance imaging and magnetic reso-
nance venography have improved the reliability of
non-invasive detection of cerebral venous sinus thrombo-
sis, but still some cases may be missed without catheter
angiography or venography. Recurrent thrombotic abnor-
malities of coagulation in IIH may be construed as indicat-
ing undetected cerebral venous sinus thrombosis remains a mechanism of
IIH, although other interpretations are possible.

Different groups have proposed that increased intracra-
nial venous pressure is the major mechanism of raised
intracranial pressure in IIH. Malm et al. reported a long
term study in which patients with IIH underwent
repeated assessments of CSF hydrodynamics by means of a
constant pressure infusion technique. In most of their
patients raised CSF pressure could be explained by
increased sagittal sinus pressure. Their hypothesis was that
the increase in pressure in the superior sagittal sinus was
secondary to cerebral swelling leading to a reduction of the
diameter of the superior sagittal sinus, but as has been
pointed out above brain swelling is not necessarily seen in
IIH. Their other patients had raised pressure on the basis of
reduced CSF outflow conductance, presumed to reflect
a lesion at the arachnoid villi and granulations level.

In nine patients studied by King et al., little abnormality
was visible in the venous phase of cerebral angiograms, but
manometry documented raised pressures in the superior
sagittal sinuses and proximal transverse sinuses, with a
drop in pressure in the distal transverse sinuses. Venogra-
phy showed narrowing of the transverse sinuses, with either
smooth tapering of uncertain cause, or intraluminal filling
defects suggestive of mural thrombus. Of note were two
patients whose intracranial hypertension was attributed to
minocycline, who did not have raised venous sinus
pressures, suggesting heterogeneity of pathogenesis. Subse-
sequently King et al. reported briefly on a larger patient
series. Fifteen out of 17 patients with IIH had raised supe-
rior sagittal sinus and proximal transverse sinus pressures
with a drop in pressure in the distal transverse sinus. In four
of these patients CSF was removed at the time of manom-
etry with a resultant lowering of intracranial pressure, and
that led to abolition of the apparent functional obstruction of
the distal transverse sinus, which suggested to the
authors that intracranial hypertension caused compression of
the transverse sinus in some patients. This study highlights the possibility that increases in CSF pressure
and venous pressure can interact so that each makes the
other worse. The authors imply that they do not consider
the increase in venous sinus pressure to be the primary
event in most of their patients.

By contrast, Karahalios et al. speculated that “most if
not all aetiologies (of IIH) result in an increase in intracra-
nial venous pressure as a final common pathway.” In their
series venous outflow obstruction was detected by
venography in five out of 10 patients studied. In the
remaining five there was no obstruction but venous
pressures were nevertheless increased, as were right atrial
pressures with transmission of the raised central venous
pressures back to the intracranial venous system. Karahal-
ios et al. discuss ways in which obesity might lead to raised
central venous pressures, but conclude that the mechanism
of increased central venous pressure in IIH remains
obscure.

No such doubts in the mind of Sugarman et al., who contended
that at least in morbidly obese persons pseudotu-
mour cerebri is a direct result of obesity which leads to
increased central venous and intracranial pressures (see
below). Indeed they maintain that intracranial hyper-
tension in this situation should no longer be considered
idiopathic. In their hands gastric bypass surgery had a high
success rate in resolution of symptoms of raised intracra-
nial pressure (as well as treating joint problems, gastro-
oesophageal reflux, high blood pressure, sleep apnoea,
hypoventilation, diabetes, and urinary incontinence!). It
might be speculated that increased venous pressure would
affect cerebral compressibility in such a way as to favour a
pseudotumour syndrome rather than hydrocephalus.
Unexplained by this hypothesis is the absence of
pseudotumour syndrome as a complication of right
ventricular cardiac failure, although increased CSF pres-
sure has been shown to accompany the rise of venous pres-
sure which occurs in right heart failure.

Obesity and IIH
The relation between IIH and obesity has long been
recognised. Pressure in the CSF is higher in obese but
otherwise normal people than in people of normal weight.
An association between recent weight gain and the
development of IIH has been established. Weight
reduction has long been part of the treatment strategy.
There is some evidence that weight reduction is therapeu-
tic. In two retrospective studies, Kupersmith et al. and
Johnson et al. independently found that weight reduction
was associated with improvement in papilloedema in their patients. Rowe and Sarkies on the
other hand found no correlation between weight change
and visual improvement in their series. Sugarman et al.
reported on a series of eight morbidly obese patients with
IIH, in all of whom gastric surgery for weight reduction was
successful in bringing about considerable weight reduction and also resolution of symptoms and signs of IIH including successful in bringing about considerable weight reduction 4 Walker al venous pressures, supporting a direct cause and express pressures, raised intrathoracic pressures, and raised central venous pressures, that their obese patients with IIH had raised intra-abdominal bidly obese people for a simpler mechanism. They showed only two out of eight morbidly obese patients of Sugarman patients without IIH. It would be easy to diagnose this cause of IIH, even though it may be the immediate cause in commoner in females than males, so obesity cannot be a sole aects males as well as females, whereas IIH is much particular, in many cases obesity may brain MR1 really should be able to provide definitive information about cerebral and CSF volumes in IIH, but as yet the tunnel has not shed much light, and intriguing enigmas remain. Laboratory animal research, if possible, into factors influencing function of the arachnoid villi might well be informative. More effective means of preventing or treating obesity would undoubtedly have an impact on the prevention and treatment of IIH.

Conclusion It seems inescapable that the condition currently called IIH is heterogeneous, and indeed Johnson et al 6 proposed using the term pseudotumour syndrome to encompass this heterogeneity. In some patients there may be just one etiology operating, such as occult venous sinus thrombosis. Perhaps others have risk factors which combine to precipitate the condition. In particular, in many cases obesity may be a risk factor whereas in extreme cases it may be a sufficient cause. Brain MRI really should be able to provide definitive information about cerebral and CSF volumes in IIH, but as yet the tunnel has not shed much light, and intriguing enigmas remain. Laboratory animal research, if possible, into factors influencing function of the arachnoid villi might well be informative. More effective means of preventing or treating obesity would undoubtedly have an impact on the prevention and treatment of IIH.

R W H WALKER
Department of Neurology, Bart’s and the London NHS Trust, The Royal London Hospital, Whitechapel, London E1 1BB, UK

The volumes of memory

In 1937, Papez described a circuit for the processing of emotions, which has subsequently proved to be critical for memory function. Various pathological entities can affect structures in this circuit, resulting in amnestic syndromes. In 1937, Papez described a circuit for the processing of emotions, which has subsequently proved to be critical for memory function. Various pathological entities can affect structures in this circuit, resulting in amnestic syndromes.

The volumes of memory...
Cognitive function in the oldest old: women perform better than men

In the paper by van Exel et al in this issue (pp 29–32), the authors examine the influence of sex and formal education on cognitive functioning in a community based sample of subjects over the age of 85. Based on the cognitive reserve theory of dementia, the authors hypothesise that women would be expected to score more poorly than men on cognitive tests due to a lower level of formal education.

Previous studies provide support for the theory that a lower educational level is a risk factor for the development of dementia. This relation seems to be more pronounced.
in female subjects than males, although data regarding the influence of sex on cognitive functioning in non-demented persons were not available.

The results of the current study showed better cognitive performance in the female group, despite their lower level of formal education. One possible explanation raised by the authors was that medical risk factors (for example, atherosclerosis) may be greater in the male group. An alternative, or contributing factor, may be use of formal education as a measure of “cognitive reserve”. Although years of education have traditionally been used to estimate premorbid functioning, some authors have suggested that formal education may be less important than later life experiences, such as primary occupation. A follow up to the current study might examine the role of non-educational experiences on cognitive functioning between men and women.

This paper makes an important and timely contribution to the field of aging research, with the recent emphasis on early diagnosis of dementia. Understanding variables related to cognitive functioning in elderly people, such as the influence of sex, is essential for improving the ability to detect preclinical markers of dementia and identify “at risk” people who could benefit from clinical prevention trials.

N JOHNSON
Department of Psychiatry, Cognitive Neurology and Alzheimer’s Disease Center, Northwestern University Medical School, 320 EAST Superior Street, Suite 11–499, Chicago, IL 60611–3010, USA
johnson-n@northwestern.edu


---

1st Asia Pacific Forum on Quality Improvement in Health Care
Three day conference
Wednesday 19 to Friday 21 September 2001
Sydney, Australia

We are delighted to announce this forthcoming conference in Sydney. Authors are invited to submit papers (call for papers closes on Friday 6 April), and delegate enquiries are welcome. The themes of the Forum are:

- Improving patient safety
- Leadership for improvement
- Consumers driving change
- Building capacity for change: measurement, education and human resources
- The context: incentives and barriers for change
- Improving health systems
- The evidence and scientific basis for quality improvement.

Presented to you by the BMJ Publishing Group (London, UK) and Institute for Healthcare Improvement (Boston, USA), with the support of the the Commonwealth Department of Health and Aged Care (Australia), Safety and Quality Council (Australia), NSW Health (Australia) and Ministry of Health (New Zealand).

For more information contact: quality@bma.org.uk or fax +44 (0) 7383 6869