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EDITORIAL

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,[1] and current therapies are unsatisfactory. Medical treatment is poor and of unproved benefit.[2 3] Surgical interventions (optic nerve sheath fenestration, lumboperitoneal shunting) have appreciable hazards and failure rates.[4–10] 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[11]).

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,[12–14] but not in others,[15] 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*[16] reported an increase in white matter water signal, suggesting diffuse mild oedema, and Gideon *et al*[17] 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[3 79]

Symptoms and signs of increased ICP (headache, papilloedema)
No localising findings on neurological examination (except sixth cranial nerve lesion(s) or rarely other false localising signs)
Normal neuroimaging with no evidence of venous obstructive disease
Increased ICP as measured by lumbar puncture (>25 cm CSF)
Normal CSF constituents
Awake and alert patient
No other cause of increased ICP present
Benign clinical course apart from visual deterioration

ICP=Intracranial pressure.

Table 2 Perturbations which could lead to raised ICP

Increased cerebral volume	-increased ISF volume
	-increased blood volume
	-increased tissue volume
Increased CSF production rate	
Increased CSF outflow resistance	
Increased cerebral arterial pressure transmitted to capillaries (loss of autoregulation)	
Increased cerebral venous pressure	-leading to increased venous blood volume and increased ISF volume
	-leading to reduced CSF outflow

ISF=Interstitial fluid.

regional cerebral blood volume was found.[18] The most invasive studies of cerebral tissue in IIH were cerebral biopsies, which were reported by Sahs and Joynt[19] to show evidence of interstitial cerebral oedema, but necropsies[20] have not confirmed those findings, nor did a review of some of the original biopsy material of Sahs and Joynt.[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 presumptively part of the cause of the hydrocephalus. An IIH-like syndrome has not been reported in choroid plexus papilloma. Kollar and Johnson[26] 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, including so called normal pressure hydrocephalus. In some studies the two groups of patients have even been analysed together, despite their striking clinical differences (for example, Borgesen and Gjerris[30]). 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 Fishman[11]). However, pressure atrophy does not seem to be operative in patients with chronic IIH, except possibly for two patients reported by Malm *et al*[31] 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*,[28] 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.[31–36] 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.[37] The outflow resistance of CSF is known to be increased in experimental subarachnoid haemorrhage.[38] 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.[39] However, a pseudotumour syndrome is sometimes seen in the context of meningitis (see for instance Cremer *et al*[40]). Very high CSF protein concentration (spinal tumour, Guillain-Barré syndrome) is sometimes a cause of raised intracranial pressure with papilloedema,[41 42] and the suggestion has been made that the protein leads directly to impaired CSF outflow, and there is experimental evidence to support this.[43] 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.[45 46] (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*.[20]

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.[48 49] 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.[11] 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 turnover 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 impairment 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*,[49] but not confirmed by Johnston *et al*[48]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) or 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.[50–53] Clearly superior sagittal sinus thrombosis will affect cerebral venous pressure and drainage and will also directly affect 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 resonance venography have improved the reliability of non-invasive detection of cerebral venous sinus thrombosis, but still some cases may be missed without catheter angiography or venography.[54 55] Recent reports of potentially prothrombotic abnormalities of coagulation in IIH[56–58] may be construed as indicating that undetected cerebral venous sinus thrombosis remains a mechanism of IIH, although other interpretations are possible.

Different groups have proposed that increased intracranial venous pressure is the major mechanism of raised intracranial pressure in IIH.[31 54 59 60] Malm*et al*[31] 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*,[54] 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. Venography 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. Subsequently King *et al*[61] reported briefly on a larger patient series. Fifteen out of 17 patients with IIH had raised superior 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 manometry 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*[59] speculated that "most if not all aetiologies (of IIH) result in an increase in intracranial 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. Karahalios *et al*[59] 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*,[60 62 63] who contend that at least in morbidly obese persons pseudotumour cerebri is a direct result of obesity which leads to increased central venous and intracranial pressures (see below). Indeed they maintain that intracranial hypertension 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 intracranial 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 pressure has been shown to accompany the rise of venous pressure which occurs in right heart failure.[64]

Obesity and IIH

The relation between IIH and obesity has long been recognised.[65–67] Pressure in the CSF is higher in obese but otherwise normal people than in people of normal weight.[68] An association between recent weight gain and the development of IIH has been established.[65 66] Weight reduction has long been part of the treatment strategy. There is some evidence that weight reduction is therapeutic. In two retrospective studies, Kupersmith *et al*[69] and Johnson *et al*[2] independently found that weight reduction was associated with improvement in[69] or resolution of[2] papilloedema in their patients. Rowe and Sarkies[70] on the other hand found no correlation between weight change and visual improvement in their series. Sugarman *et al*[60] 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 reduction of CSF pressure to normal.

How does obesity lead to an increase in intracranial pressure? Hormonal mechanisms have been postulated,[70] but Sugarman *et al*[62] have provided persuasive evidence in morbidly obese people for a simpler mechanism. They showed that their obese patients with IIH had raised intra-abdominal pressures, raised intrathoracic pressures, and raised central venous pressures, supporting a direct cause and effect relation. However, they did not have a satisfactory, concurrent control group, and did not provide an explanation as to why the pulmonary artery pressures were higher in their obese patients with IIH than in equivalently obese patients without IIH. It would be easy to diagnose this patient group as just having a pickwickian syndrome, but only two out of eight morbidly obese patients of Sugarman *et al*[60] had evidence of alveolar hypoventilation with reduced blood oxygen and raised blood carbon dioxide concentrations. Obesity is common, whereas IIH is rare, and obesity affects males as well as females, whereas IIH is much commoner in females than males, so obesity cannot be a sole cause of IIH, even though it may be the immediate cause in a suitably predisposed person. The established relation between obesity and IIH raises further questions. Although IIH in obese persons may be rare, headache in people of all shapes and sizes is very common, and the question does arise as to whether a proportion of obese persons with headache but without papilloedema in fact do have IIH. In the classic IIH series, papilloedema was present in 100% cases and was a diagnostic sine qua non.[71–74] However, it is not necessary to modify the Dandy criteria much further to open up a whole new vista of cases of overweight patients with bad headache and with high CSF pressures. Indeed, only 12 out of 24 patients had papilloedema in the updated series of Sugarman *et al*.[63] Several centres have published on IIH without papilloedema.[75–77] Disappointingly, the response of the patients to medication aimed at lowering intracranial pressure was poor.

Conclusion

It seems inescapable that the condition currently called IIH is heterogeneous, and indeed Johnston *et al*[78] proposed using the term pseudotumour syndrome to encompass this heterogeneity. In some patients there may be just one aetiology 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.

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EDITORIAL COMMENTARIES

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.[1] Various pathological entities can affect structures in this circuit, resulting in amnestic syndromes. In this issue of the *Journal* (pp 13–28), two related papers by Colchester *et al*[2] and Kopelman *et al*[3] used volumetric MR to assess the differing patterns of atrophy in patients with amnesia caused by several neurological diseases, and to examine the relation of these MR volumes to cognitive performance.

A great deal of recent work has focused on detecting atrophy in patients with neurodegenerative dementias, in particular Alzheimer's disease. Recent papers have reported significant atrophy in structures within the medial temporal lobe in memory impaired subjects even before the clinical diagnosis of Alzheimer's disease.[4–6] Relatively few studies have examined volumes of medial temporal lobe and other memory subserving structures in non-degenerative amnestic syndromes.

The report of Colchester *et al*[2] suggests that atrophy among the components of the circuit of Papez can be reliably quantified using MR volumetric assessment, and that amnestic syndromes of varying aetiology show specific patterns of atrophy. Of particular interest was the consistent finding of thalamic atrophy in the patients with Korsakoff's syndrome.

Complementing this work, Kopelman *et al*[3] examined the correlations between MR volumes of multiple brain regions and performance on several cognitive tests in patients with amnestic and other cognitive syndromes. Of note, the strongest relations were seen between hippocampal volume and anterograde memory measures, particularly evident in a factor analysis of the neuropsychological tests, although the thalamic measures did correlate with several memory tests.

These studies provide additional evidence for the critical role of the hippocampus in memory, and support the contribution of additional structures within the circuit of Papez to memory function. This work suggests that volumetric MR may be useful in elucidating the pattern of injury to neuroanatomical networks in various cognitive impairment syndromes.

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