COMMENT

The Pseudotumor Cerebri Syndrome: A Unifying Pathophysiological Concept for Patients with Isolated Intracranial Hypertension with Neither Mass Lesion Nor Ventriculomegaly

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ABSTRACT

In 1991 we proposed that while the syndrome of isolated intracranial hypertension might have many definite and probable causes, it has nonetheless a single unifying pathophysiological mechanism: namely, impairment of cerebrospinal fluid (CSF) reabsorption. For that reason, we also proposed then that it is best described by a single, unifying, inclusive term, namely, *pseudotumor cerebri syndrome*. Although it appears that there is, as far as nomenclature is concerned, now international agreement, there is as yet no agreement on pathophysiology and classification. Herein we outline our views on these matters and give our reasons.

Keywords: Benign intracranial hypertension, idiopathic intracranial hypertension, otitic hydrocephalus, pseudotumor cerebri

In 1991¹ we proposed that while the syndrome of isolated intracranial hypertension, that is, intracranial hypertension with papilloedema (usually) but without ventriculomegaly, brain tumour, or brain dysfunction, might have many definite and probable causes (Table 1), it has nonetheless a single unifying pathophysiological mechanism, namely, impairment of cerebrospinal fluid (CSF) reabsorption. For that reason, we also proposed then¹ and again more recently² that it is best described by a single, unifying, inclusive term, namely, *pseudotumor cerebri syndrome*. It appears that there is now, at least as far as nomenclature is concerned, international agreement.^{3,4}

A rose is a rose
“Pseudotumor cerebri”
Has too many names

バラはバラ以外の何者でもない。

「偽脳腫瘍 (pseudotumor cerebri)

には、あまりに多くの名前がある。

—Haiku by Deborah Friedman

In our opinion the data published in the last 20 years support the core of our hypothesis: that impairment of CSF reabsorption—mainly at the level of the arachnoid villi in the superior sagittal sinus and other dural sinuses, is the common factor leading to the development of the pseudotumor cerebri syndrome. The rate of CSF absorption depends on the difference between CSF pressure and superior sagittal sinus pressure, and on resistance to CSF reabsorption. Impaired CSF reabsorption is due either to high cerebral venous sinus pressure or to high arachnoid villous resistance. Normally, about 500 mL of CSF is

TABLE 1 Selected causes of pseudotumor cerebri syndrome according to mechanism, with selected references.

Cerebral venous sinus hypertension
Venous sinus stenosis ¹²⁻¹⁷
Venous sinus thrombosis ²⁰ : Behçet, systemic lupus erythematosus
Venous sinus thrombosis from middle ear infection (<i>otitic hydrocephalus</i>) ^{7,8,26}
Venous sinus compression by tumour; jugular foramen mass, metastasis, skull fracture, extradural haematoma ¹²
Dural arteriovenous fistula ¹⁵
Jugular vein occlusion
Pachymeningitis: neoplastic ^{29,30}
Autoimmune: Vogt-Koyanagi-Harada, POEMS
Changes in CSF composition
Chronic infectious leptomeningitis: cryptococcal ²⁷ ; tuberculous, ²⁸ syphilitic; brucella, cysticercosis
Acute infections leptomeningitis: lyme, typhus, varicella
High CSF protein: poliomyelitis, GBS, ³⁵ CIDP, vestibular schwannoma ³²
Spinal cord tumour ²²
Presumed increase in villous resistance
Hypercapnic respiratory failure
Vitamin A excess from diet or drugs (all- <i>trans</i> retinoic acid)
Other drugs, e.g. corticosteroids, tetracyclines, ²³ lithium
Anaemia ²¹
Endocrine: Graves disease and thyroid hormone, Cushing disease and corticosteroids
Renal failure and transplantation

formed and reabsorbed each day, about 3 times the total CSF volume. Total CSF volume should therefore be increased in pseudotumor cerebri syndrome² and recent data suggest that this is the case.⁵

Nomenclature is important. The term *pseudotumor cerebri* was first used by Nonne in 1904.⁶ In 1931 the term *otitic hydrocephalus* was introduced by Sir Charles Symonds⁷ who later appreciated this to be a misnomer, as it was not associated with ventriculomegaly and later still he recognised it to be associated with transverse sinus thrombosis.⁸ In the 1950s benign intracranial hypertension⁹ was coined followed in 1969 by idiopathic intracranial hypertension¹⁰—a term that was immediately condemned as inappropriate.¹¹ These four different terms each describe different aspects of this disorder; in contrast, *pseudotumor cerebri syndrome* includes all of them. So we agree that cases in whom even rigorous investigation reveals no possible cause could, for the time being, be called “idiopathic”. However, many cases that were supposed to be idiopathic, are, we know now, caused by, or at least mediated by, cerebral venous hypertension.¹²⁻¹⁷ In humans,¹⁵ as in dogs,¹⁸ there is a positive feedback cycle: intracranial hypertension causes venous sinus compression that impairs CSF reabsorption, which then causes more intracranial hypertension. We now also know that venous sinus stenting lowers intracranial pressure and often improves the symptoms of intracranial hypertension. Although there might be disagreement about whether the venous stenosis is primary or secondary, there is

agreement that stenting is beneficial in most cases that have a venous pressure gradient.^{13,14,17} Although we would prefer the term *idiopathic pseudotumor cerebri* in cases where there is no plausible cause and no venous sinus stenosis, *idiopathic intracranial hypertension* is an acceptable alternative. In fact, the only disagreement now between “them”⁴ and “us”² is that whereas we consider idiopathic cases to be the exception, they consider them to be the rule. This disagreement could in part be due to the fact that patients with pseudotumor cerebri syndrome can be seen by at least six different medical specialists, all of whom tend to consider the patient from their own particular point of view. For the ophthalmologist the problem is papilloedema; for the neurologist it is headache; for the otologist it is pulsatile tinnitus; for the neurosurgeon it is intracranial hypertension; for the neuro-interventionalist it is venous sinus stenosis; and for the paediatrician it is the added responsibility of dealing with worried parents¹⁹ (Figure 1).

Classification is also important. Diseases causing pseudotumor cerebri syndrome can be classified as (a) those that cause cerebral venous hypertension, (b) those that cause changes in CSF composition, and (c) those that are assumed to cause high arachnoid villous resistance. An intriguing question is why patients with all these different diseases (Table 1) do not always develop pseudotumor cerebri syndrome. So for example, although we know that patients with sagittal sinus thrombosis²⁰ will often develop pseudotumor cerebri syndrome, because they have venous hypertension, we do not yet know why patients with anaemia²¹ or spinal tumour²² or those having tetracyclines²³ only rarely do so. There must be a second factor at work in these cases. Could this second factor be craniospinal compliance?²⁴ We also have no idea why pseudotumor cerebri is so much a disease of obese young women.³

Hydrocephalus in contrast to pseudotumor cerebri syndrome should be obvious on imaging, even if its clinical significance is not always appreciated.²⁵ The block of CSF circulation in hydrocephalus can occur inside or outside the ventricular system. If the block occurs inside the ventricular system, say, due to aqueduct stenosis or a 4th ventricular tumour blocking the outlet foramina—the result is *obstructive* hydrocephalus; if the block occurs at the level of the basal or hemispheric meninges, the result is *communicating* hydrocephalus—communicating, because there is still communication between the ventricles and the basal cisterns. In patients with communicating hydrocephalus all the ventricles enlarge, whereas in obstructive hydrocephalus only the lateral and 3rd ventricles do, but not the 4th. Previous subarachnoid haemorrhage or meningitis are two common causes of communicating hydrocephalus. Patients with communicating hydrocephalus rarely develop papilloedema, perhaps because the block of CSF circulation is

FIGURE 1 Six blind men examine the elephant. From Himmelfarb J, Stenvinkel P, Ikizler TA, Hakim RM. The elephant in uremia: oxidant stress as a unifying concept of cardiovascular disease in uremia. *Kidney Int* 2002;62:1524–1538. Reproduced with the authors' permission.

at the level of the basal meninges, “upstream” from the optic nerve sheaths; when they do, it might be after their shunt blocks, but in the absence of headache or obvious cognitive deterioration they might fail to notice deteriorating vision due to the papilloedema—until it is too late.²⁵ In “compensated” and in “normal pressure” hydrocephalus the intracranial pressure is not high, so not surprisingly, there is no papilloedema. Brain imaging can of course only show ventricular volume, CSF flow, and arterial and venous flow but cannot show CSF or venous pressure.

So what then about the borderlands of pseudotumor cerebri syndrome and hydrocephalus? There is of course a major functional difference between hydrocephalus and pseudotumor cerebri syndrome: hydrocephalus can produce progressive brain impairment especially of cognition and gait, whereas pseudotumor cerebri syndrome does not. Consider, however, the patient who has intracranial hypertension with papilloedema, without tumour, in whom it's hard to decide whether the ventricles are of normal size (the patient has pseudotumor cerebri syndrome) or large (the patient has hydrocephalus). And in the end does it really matter what we call it? Maybe otitic *hydrocephalus* wasn't such a bad term after all for what we would now call pseudotumor cerebri syndrome.²⁶ Furthermore, there are several disease states (in adults) producing intracranial hypertension with papilloedema and either large or normal-size ventricles. For example, the ventricles are usually normal in cryptococcal meningitis²⁷ but large in tuberculous meningitis.²⁸ In malignant meningitis,^{29,30} sagittal sinus thrombosis,^{20,31} vestibular schwannoma,^{32,33} spinal cord tumour,^{22,34} and

Guillain-Barré syndrome^{35,36} they can be either. Furthermore, in infants, with open fontanelles and unfused sutures, venous obstruction producing intracranial hypertension invariably results in large ventricles, i.e., hydrocephalus and not pseudotumor cerebri syndrome,^{37,38} whereas in older children with fused sutures or children with craniostenosis³⁹ the ventricles do not enlarge—i.e., they have pseudotumor cerebri and not hydrocephalus. Also in both hydrocephalus as well as pseudotumor cerebri syndrome there is increased collateral venous return, suggesting reduced venous return via the sagittal and transverse sinuses.²⁴

So then why don't the ventricles enlarge in pseudotumor cerebri syndrome? Is it because the block to CSF absorption is at the level of the arachnoid villi in the sagittal sinus so that the pressure is equally high on both sides of the cortical mantle or because the ventricles are non-compliant and cannot expand as occurs in the slit-ventricle syndrome of shunted hydrocephalus?⁴⁰ On the basis of their magnetic resonance imaging (MRI) venous flow studies, Bateman et al.²⁴ has proposed that in both pseudotumor cerebri syndrome and hydrocephalus the constant is venous hypertension and the variable is craniospinal compliance. We don't yet know for sure whether this is true, but it does look like idiopathic intracranial hypertension is actually just one part of a much bigger picture that should emerge through more physiological research. The term *hydrocephalus* is a unifying one, which includes many causes of ventriculomegaly, as well as also no known cause—idiopathic hydrocephalus. In parallel with the term hydrocephalus we suggest that the term pseudotumor

cerebri should be considered as a syndrome, and be used similarly: a unifying term to describe all patients with intracranial hypertension without tumour or ventriculomegaly. The term *idiopathic* intracranial hypertension should be used—as it would in other branches of medicine, only after all possible causes of intracranial hypertension have been conscientiously excluded, at least until the time we have final proof of the exact mechanism by which intracranial pressure can rise without enlarging the ventricles or impairing brain function.

The Blind Men and the Elephant

by John Godfrey Saxe (1816–1887)

It was six men of Indostan
To learning much inclined,
Who went to see the Elephant
(Though all of them were blind),
That each by observation
Might satisfy his mind.
The *First* approached the Elephant,
And happening to fall
Against his broad and sturdy side,
At once began to bawl:
“God bless me! but the Elephant
Is very like a WALL!”
The *Second*, feeling of the tusk,
Cried, “Ho, what have we here,
So very round and smooth and sharp?
To me ‘tis mighty clear
This wonder of an Elephant
Is very like a SPEAR!”
The *Third* approached the animal,
And happening to take
The squirming trunk within his hands,
Thus boldly up and spake:
“I see,” quoth he, “the Elephant
Is very like a SNAKE!”
The *Fourth* reached out an eager hand,
And felt about the knee
“What most this wondrous beast is like
Is mighty plain,” quoth he:
“‘Tis clear enough the Elephant
Is very like a TREE!”
The *Fifth*, who chanced to touch the ear,
Said: “E’en the blindest man
Can tell what this resembles most;
Deny the fact who can,
This marvel of an Elephant
Is very like a FAN!”
The *Sixth* no sooner had begun
About the beast to grope,
Than seizing on the swinging tail
That fell within his scope,
“I see,” quoth he, “the Elephant
Is very like a ROPE!”
And so these men of Indostan

Disputed loud and long,
Each in his own opinion
Exceeding stiff and strong,
Though each was partly in the right,
And all were in the wrong!

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

Note: Figure 1 of this article is available in colour online at www.informahealthcare.com/oph

REFERENCES

- [1] Johnston I, Hawke S, Halmagyi GM, Teo C. The pseudotumor syndrome. Disorders of cerebrospinal fluid circulation causing intracranial hypertension without ventriculomegaly. *Arch Neurol* 1991;48:740–747.
- [2] Johnston I, Owler B, Pickard J. The Pseudotumor Cerebri Syndrome: Pseudotumor Cerebri, Idiopathic Intracranial Hypertension, Benign Intracranial Hypertension and Related Conditions. 1st ed. Cambridge, UK: Cambridge University Press; 2007.
- [3] Fraser C, Plant GT. The syndrome of pseudotumour cerebri and idiopathic intracranial hypertension. *Curr Opin Neurol* 2011;24:12–17.
- [4] Friedman DI, Liu GT, Digre KB. Revised diagnostic criteria for the pseudotumor cerebri syndrome in adults and children. *Neurology* 2013;81:1159–1165.
- [5] Alperin N, Ranganathan S, Bagci AM, Adams DJ, Ertl-Wagner B, Saraf-Lavi E, Sklar EM, Lam BL. MRI evidence of impaired CSF homeostasis in obesity-associated idiopathic intracranial hypertension. *AJNR Am J Neuroradiol* 2013;34:29–34.
- [6] Nonne M. Über Fälle vom Symptomenkomplex “Tumor cerebri” mit Ausgang in Heilung (Pseudotumor cerebri). Über letal verlaufene Fälle von “Pseudotumor cerebri” mit Sektionsbefund. *Dtsch Z Nervenheilkd* 1904;27:169–216.
- [7] Symonds CP. Otitic hydrocephalus. *Brain* 1931;54:55–71.
- [8] Symonds CP. Otitic hydrocephalus. *Neurology* 1956;6:681–685.
- [9] Foley J. Benign forms of intracranial hypertension; toxic and otitic hydrocephalus. *Brain* 1955;78:1–41.
- [10] Buchheit WA, Burton C, Shaw D. Papilledema and idiopathic intracranial hypertension: report of a familial occurrence. *N Eng J Med* 1969;280:938–942.
- [11] Rozear MP. Nomenclature of intracranial pressure. *N Eng J Med* 1969;281:46–47.
- [12] Owler BK, Parker G, Halmagyi GM, Johnston IH, Besser M, Pickard JD, Higgins JN. Cranial venous outflow obstruction and pseudotumor cerebri syndrome. *Adv Tech Stand Neurosurg* 2005;30:107–174.
- [13] Ahmed RM, Wilkinson M, Parker G, Thurtell MJ, Macdonald J, McCluskey PJ, Allan R, Dunne V, Hanlon M, Owler BK, Halmagyi GM. Transverse sinus stenting for idiopathic intracranial hypertension: a review of 52 patients and of model predictions. *AJNR Am J Neuroradiol* 2011;32:1408–1414.
- [14] Kumpe DA, Bennett JL, Seinfeld J, Pelak VS, Chawla A, Tierney M. Dural sinus stent placement for idiopathic intracranial hypertension. *J Neurosurg* 2012;116:538–548.
- [15] Ahmed RM, Khoury B, Wilkinson M, Parker GD, Halmagyi GM. Venous hypertension as the cause of intracranial hypertension in patients with transverse

- sinus dural arteriovenous fistula. *J Neuroophthalmol* 2013; 33:102–105.
- [16] Dwyer CM, Prelog K, Owler BK. The role of venous sinus outflow obstruction in pediatric idiopathic intracranial hypertension. *J Neurosurg Pediatr* 2013;11:144–149.
 - [17] Radvany MG, Solomon D, Nijjar S, Subramanian PS, Miller NR, Rigamonti D, Blitz A, Gailloud P, Moghekar A. Visual and neurological outcomes following endovascular stenting for pseudotumor cerebri associated with transverse sinus stenosis. *J Neuroophthalmol* 2013;33:117–122.
 - [18] McCormick JM, Yamada K, Rekate HL, Miyake H. Time course of intraventricular pressure change in a canine model of hydrocephalus: its relationship to sagittal sinus elastance. *Pediatr Neurosurg* 1992;18:127–133.
 - [19] Tibussek D, Distelmaier F, von Kries R, Mayatepek E. Pseudotumor cerebri in childhood and adolescence—results of a Germany-wide ESPED survey. *Klin Paediatr* 2013;225:81–85.
 - [20] Biousse V, Ameri A, Bousser MG. Isolated intracranial hypertension as the only sign of cerebral venous thrombosis. *Neurology* 1999;53:1537–1542.
 - [21] Tugal O, Jacobson R, Berezin S, Foreman S, Berezin S, Brudnicki A, Godine L, Davidian MM, Jayabose S, Escobedo V. Recurrent benign intracranial hypertension due to iron deficiency anemia. Case report and review of the literature. *Am J Pediatr Hematol Oncol* 1994;16:266–270.
 - [22] Costello F, Kardon RH, Wall M, Kirby P, Ryken T, Lee AG. Papilledema as the presenting manifestation of spinal schwannoma. *J Neuroophthalmol* 2002;22:199–203.
 - [23] Kesler A, Goldhammer Y, Hadayer A, Pianka P. The outcome of pseudotumor cerebri induced by tetracycline therapy. *Acta Neurol Scand* 2004;110:408–411.
 - [24] Bateman GA, Smith RL, Siddique SH. Idiopathic hydrocephalus in children and idiopathic intracranial hypertension in adults: two manifestations of the same pathophysiological process? *J Neurosurg* 2007;107:439–444.
 - [25] Trobe JD. Papilledema: the vexing issues. *J Neuroophthalmol* 2011;31:175–186.
 - [26] Sadoghi M, Dabirmoghaddam P. Otitic hydrocephalus: case report and literature review. *Am J Otolaryngol* 2007;28: 187–190.
 - [27] Cremer PD, Johnston IH, Halmagyi GM. Pseudotumour cerebri syndrome due to cryptococcal meningitis. *J Neurol Neurosurg Psychiatr* 1997;62:96–98.
 - [28] Raut T, Garg RK, Jain A, Verma R, Singh MK, Malhotra HS, Kohli N, Parihar A. Hydrocephalus in tuberculous meningitis: incidence, its predictive factors and impact on the prognosis. *J Infect* 2013;66:330–337.
 - [29] Ahmed RM, Halmagyi GM. Malignant meningitis presenting as pseudotumor cerebri. *J Neurol Sci* 2013;329:62–65.
 - [30] Omuro AM, Lallana EC, Bilsky MH, DeAngelis LM. Ventriculoperitoneal shunt in patients with leptomeningeal metastasis. *Neurology* 2005;64:1625–1627.
 - [31] Weidauer S, Marquardt G, Seifert V, Zanella FE. Hydrocephalus due to superior sagittal sinus thrombosis. *Acta Neurochir (Wien)* 2005;147:427–430; discussion 430.
 - [32] Grainger J, Dias PS. Case report: optic disc edema without hydrocephalus in acoustic neuroma. *Skull Base* 2005;15: 83–86.
 - [33] Gerganov VM, Pirayesh A, Nouri M, Hore N, Luedemann WO, Oi S, Samii A, Samii M. Hydrocephalus associated with vestibular schwannomas: management options and factors predicting the outcome. *J Neurosurg* 2011;114: 1209–1215.
 - [34] Mirone G, Cinalli G, Spennato P, Ruggiero C, Aliberti F. Hydrocephalus and spinal cord tumors: a review. *Childs Nerv Syst* 2011;27:1741–1749.
 - [35] Ropper AH, Marmarou A. Mechanism of pseudotumor in Guillain-Barré syndrome. *Arch Neurol* 1984;41:259–261.
 - [36] Ozdemir O, Calisaneller T, Sonmez E, Caner H, Altinors N. Atypical presentation of Guillain-Barre syndrome with acute hydrocephalus. *Acta Neurochir (Wien)* 2008;150:87–88; discussion 88.
 - [37] Sainte-Rose C, LaCombe J, Pierre-Kahn A, Renier D, Hirsch JF. Intracranial venous sinus hypertension: cause or consequence of hydrocephalus in infants? *J Neurosurg* 1984;60:727–736.
 - [38] Rekate HL. Hydrocephalus and idiopathic intracranial hypertension. *J Neurosurg* 2007;107:435–438.
 - [39] Bonfield CM, Tamber MS, Losee JE. Blindness from late presenting undiagnosed pancraniosynostosis mimicking pseudotumor cerebri. *J Child Neurol* 2013 Jul 17. Epub ahead of print. doi: 10.1177/0883073813495307.
 - [40] Eymann R, Schmitt M, Antes S, Shamdeen MG, Kiefer M. Dynamics of cerebrospinal fluid flow in slit ventricle syndrome. *Acta Neurochir Suppl* 2012;113:181–186.