Disputes & Debates: Editors' Choice

Steven Galetta, MD, FAAN, Section Editor

Editors' note: Idiopathic intracranial hypertension: The veno glymphatic connections

In the article "Idiopathic intracranial hypertension: The veno glymphatic connections," Lenck et al. hypothesized that idiopathic intracranial hypertension (IIH) may be triggered by an initial impairment in interstitial fluid (ISF) transport from the glymphatic system to the dural venous sinuses, speculating that a specific subtype of aquaporin is involved in this transport. In response, Drs. De Simone and Ranieri argue that the proposed asymptomatic primary impairment of ISF/CSF outflow via "aquaporin-4" dysfunction is unlikely. They cite literature questioning the existence of the glymphatic system as an ISF/CSF outflow route; they also note that intraventricular tracer drainage occurs through nasal lymphatics and not venous sinuses in rat models, that vascular arachnoid granulations (AGs) can be seen without IIH, that sinus walls should withstand CSF pressures higher than those associated with asymptomatic outflow dysfunction, and that intracranial pressure (ICP) returns to fully physiologic values in patients with IIH responding to sinus stenting. In their reply, the authors clarify that their hypothesis relates to some unknown aquaporin, not aquaporin-4, and note that although direct discharge of glymphatic fluid into venous blood has not been documented, venous CSF outflow has also been questioned by other studies. They caution against extrapolating CSF physiology findings from animals to humans. Although conceding that AGs may be incidentally found, they explain that their term "vascular" AGs refers to a specific type of AG mostly seen in the transverse sinus, which may permit a connection between perivascular spaces of large cortical veins and dural venous sinuses, thereby mediating glymphatic-to-venous ISF/CSF flow. Furthermore, they present arguments in favor of sinus stenoses in IIH being due to compression by congested brain and CSF, with stent placement reestablishing direct reabsorption of CSF into the sinuses, thereby normalizing ICP and relieving symptoms. Drs. Kronenberg and Kunte write in support of the hypothesis. With respect to the authors' speculation that chronic CSF overflow in the olfactory bulb sheaths may cause CSF rhinorrhea by eroding the cribriform plate, they note that olfactory dysfunction is an underrecognized presentation of IIH and that dysfunction of the extensive lymphatic network around the olfactory nerves was postulated to be causally linked to IIH in a previous article. In response, the authors present arguments in favor of most patients with idiopathic CSF leaks having underlying IIH, suggesting that the leaks—such as CSF rhinorrhea—represent overflow from the overburdened lymphatic CSF outflow pathway, with the consequent CSF diversion relieving IIH symptoms. They argue that surgical repair of such leaks can potentially reactivate this cycle unless the patient is concurrently treated for underlying IIH.

Aravind Ganesh, MD, and Steven Galetta, MD

Reader response: Idiopathic intracranial hypertension: The veno glymphatic connections

Roberto De Simone (Naples) and Angelo Ranieri (Naples)

We read the interesting idiopathic intracranial hypertension (IIH) pathogenetic Medical Hypothesis by Lenck et al.[1] We agree that the lymphatic interstitial fluid (ISF)/CSF outflow is increased by intracranial hypertension and may explain part of IIH symptoms. However, the asymptomatic primary impairment of ISF/CSF outflow proposed by the authors—mediated by a putative aquaporin 4 (AQP4) dysfunction at the vascular arachnoid granulation (VAG) interface with the dural sinuses, followed by the secondary sinus stenosis with symptomatic shift—is exceedingly weak and possibly misleading. In fact, the AQP4 glymphatic existence as a convective vs diffusive ISF/CSF outflow route has been very recently questioned.[2] ISF/CSF containing intraventricular administered tracers do not drain through venous sinus, as proposed, but through the nasal lymphatics.[3] The VAGs are very common in subjects without intracranial vascular pathology,[4] whereas IIH is rare. The sinus wall should bear CSF pressure much higher than that possibly associated with an asymptomatic stage of lymphatic dysfunction.[5] Finally, after sinus stenting, the intracranial pressure returns to fully physiologic values in responders.[6] Therefore, the hypothesis of an asymptomatic primary CSF hypertension by glymphatic impairment leading to a secondary symptomatic sinus stenosis is highly unlikely.

1. Lenck S, Radovanovic I, Nicholson P, et al. Idiopathic intracranial hypertension: the veno glymphatic connections. Neurology 2018;91:515–522.
2. Abbott NJ, Pizzo ME, Preston JE, et al. The role of brain barriers in fluid movement in the CNS: is there a "glymphatic" system? Acta Neuropathol 2018;135:387–407.
3. Murtha LA, Yang Q, Parsons MW, et al. Cerebrospinal fluid is drained primarily via the spinal canal and olfactory route in young and aged spontaneously hypertensive rats. Fluids Barriers CNS 2014;11:12.
4. Gailloud P, Muster M, Khaw N, et al. Anatomic relationship between arachnoid granulations in the transverse sinus and the termination of the vein of Labbe: an angiographic study. Neuroradiology 2001;43:139–143.
5. Martins AN, Kobrine AI, Larsen DF. Pressure in the sagittal sinus during intracranial hypertension in man. J Neurosurg 1974;40:603–608.
6. Patsalides A, Oliveira C, Wilcox J, et al. Venous sinus stenting lowers the intracranial pressure in patients with idiopathic intracranial hypertension. J Neurointerv Surg 2019;11:175–178.

Reader response: Idiopathic intracranial hypertension: The veno glymphatic connections

Golo Kronenberg (Leicester, UK) and Hagen Kunte (Berlin)

The Medical Hypothesis article by Lenck et al.[1] provided an exciting new angle on recent findings concerning CSF circulation in the brain. The authors succinctly summarized clinical and radiologic evidence supporting their hypothesis that dysfunction of veno glymphatic connections lies at the heart of idiopathic intracranial hypertension (IIH). In particular, the authors speculated that chronic overflow of CSF in the sheaths of the olfactory bulbs may result in CSF rhinorrhea by eroding the cribriform plate.[1] Olfactory dysfunction, especially a marked impairment in olfactory threshold levels, is an even more common yet underrecognized presentation of IIH.[2,3] Indeed, as early as 2008, Dr. Kapoor[4] speculated that dysfunction of the extensive lymphatic network around the olfactory nerves might be causally linked to IIH, making hyposmia a more sensitive predictor of IIH than other clinical features.

1. Lenck S, Radovanovic I, Nicholson P, et al. Idiopathic intracranial hypertension: the veno glymphatic connections. Neurology 2018;91: 515–522.
2. Kunte H, Schmidt F, Kronenberg G, et al. Olfactory dysfunction in patients with idiopathic intracranial hypertension. Neurology 2013; 81:379–382.
3. Bershad EM, Urfy MZ, Calvillo E, et al. Marked olfactory impairment in idiopathic intracranial hypertension. J Neurol Neurosurg Psychiatry 2014;85:959–964.
4. Kapoor KG. Do patients with idiopathic intracranial hypertension suffer from hyposmia? Med Hypotheses 2008;71:816–817.

Author response: Idiopathic intracranial hypertension: The veno glymphatic connections

Stéphanie Lenck (Paris) and Patrick Nicholson (Toronto)

We thank Drs. De Simone and Ranieri for their comments and interest in our article.[1] Our hypothesis does not support a dysfunction of aquaporin (AQP) 4 in idiopathic intracranial hypertension (IIH); rather, an unknown type of AQP (e.g., aquaglyceroporin) may be involved at the venodural junction and may trigger the hydrodynamic cascade of IIH. We agree that a direct discharge of glymphatic fluid into the venous blood has not been documented in studies of CSF hydrodynamics[2]; however, the techniques used to demonstrate the existence of the glymphatic and lymphatic systems of the brain were not able to detect any venous CSF outflow, leading some to question even the existence of a venous CSF outflow pathway in the brain.[3] Based on our clinical experience (i.e., cerebral venous thrombosis) and on previous experimental studies, we feel that a direct discharge of glymphatic fluid into venous blood seems highly likely.[4]

It may seem hazardous to extrapolate the physiology of CSF excretion from animals to humans because the venous physiology and anatomy of quadrupedal animals are very different from those of bipedal humans.[5] We agree that the discovery of an arachnoid granulation (AG) may be incidental and that the prevalence of AG in the lumen of the sinuses increases with age; however, pathologic and radiologic studies have described a specific type of AG, mostly observed in the transverse sinus and particularly at the junction between the vein of Labbé and the transverse sinus (e.g., lateral sinus stenoses in IIH). These granulations are centered on a vein and associated with the point of entry of a cortical vein into the dural sinus. We named them "vascular AGs" to differentiate from avascular granulations, which allow the pressure-dependent transport of CSF from the subarachnoid space to the venous blood of the dural sinuses. These vascular AGs may allow a connection between the perivascular spaces of large cortical veins to the venous blood of the dural sinuses and may be involved in the discharge of interstitial fluid (CSF) from the glymphatic system to the venous blood of the dural vessels.[6]

Several arguments support the hypothesis that extrinsic stenoses are caused by the compression of the lateral sinus by the congested brain and CSF (and not by the increased intracranial pressure [ICP]), including the radiologic aspect of such stenoses on MRI, the propensity of such stenoses to reoccur outside the stented portion of the sinus, the fact that the radial force of the stent is usually enough to reopen the sinus with no need for balloon angioplasty, and their disappearance after CSF removal.[7,8] We agree that the venous sinus stenosis is the main precipitating factor in IIH symptoms because it makes the venous outflow pathway ineffective for the glymphatic reabsorption and the direct reabsorption, which aims to balance the ICP. Stent placement allows reestablishment of the direct reabsorption of the CSF from the subarachnoid space to the venous blood of the dural sinuses, thus regulating the ICP and resolving IIH symptoms.

We also thank Drs. Kronenberg and Kunte for their comments and interest in our Medical Hypothesis.[1] Several authors have suggested that most patients with idiopathic CSF leaks have underlying IIH.[9,10] Several clinical and radiologic arguments support this. First, there is the common clinical pattern in which the disease occurs (young obese women), then the high prevalence of radiologic signs of IIH in patients with idiopathic CSF leaks,[11] the development of IIH symptoms following CSF leak repair, and the high rate of recurrence after surgery.[12] We, therefore, suggest that the leaks are directly caused by overflow from the overburdened lymphatic CSF outflow pathway in these cases. The chronic excess of increased CSF pressure in the sheaths of the cranial nerves, and especially the olfactory bulbs, would lead to the progressive erosion of the bone and the dura matter at the level of the skull base (e.g., the cribriform plate), eventually resulting in CSF leaks. The leak will immediately relieve the headache and the IIH symptoms experienced by the patient because it is a "natural" CSF diversion procedure. However, its surgical repair may result either in the development of IIH symptoms or in a recurrence of a leak. This recognition of this entity is important in clinical practice, when facing a patient with a CSF leak caused by IIH, because the treatment of the leak should be performed in conjunction with treatment of IIH, which is the often the underlying cause of the leak.

1. Lenck S, Radovanovic I, Nicholson P, Hodaie M, Krings T, Mendes-Pereira V. Idiopathic intracranial hypertension: the veno glymphatic connections. Neurology 2018;91:515–522.
2. Iliff JJ, Wang M, Liao Y, et al. A paravascular pathway facilitates CSF flow through the brain parenchyma and the clearance of interstitial solutes, including amyloid β. Sci Transl Med 2012;4:147ra111.
3. Murtha LA, Yang Q, Parsons MW, et al. Cerebrospinal fluid is drained primarily via the spinal canal and olfactory route in young and aged spontaneously hypertensive rats. Fluids Barriers CNS 2014;11:12.
4. Boulton M, Young A, Hay J, et al. Drainage of CSF through lymphatic pathways and arachnoid villi in sheep: measurement of 125I-albumin clearance. Neuropathol Appl Neurobiol 1996;22:325–333.
5. Aurboonyawat T, Suthipongchai S, Pereira V, Ozanne A, Lasjaunias P. Patterns of cranial venous system from the comparative anatomy in vertebrates: part I, introduction and the dorsal venous system. Interv Neuroradiol 2007;13:335–344.
6. Trimble CR, Harnsberger HR, Castillo M, Brant-Zawadzki M, Osborn AG. "Giant" arachnoid granulations just like CSF?: NOT!!. AJNR Am J Neuroradiol 2010;31:1724–1728.
7. Baryshnik DB, Farb RI. Changes in the appearance of venous sinuses after treatment of disordered intracranial pressure. Neurology 2004;62:1445–1446.
8. Lenck S, Vallée F, Labeyrie MA, et al. Stenting of the lateral sinus in idiopathic intracranial hypertension according to the type of stenosis. Neurosurgery 2017;80:393–400.
9. Pérez MA, Bialer OY, Bruce BB, Newman NJ, Biousse V. Primary spontaneous cerebrospinal fluid leaks and idiopathic intracranial hypertension. J Neuroophthalmol 2013;33:330–337.
10. Bialer OY, Rueda MP, Bruce BB, Newman NJ, Biousse V, Saindane AM. Meningoceles in idiopathic intracranial hypertension. AJR Am J Roentgenol 2014;202:608–613.
11. Martínez-Capoccioni G, Serramito-García R, Martín-Bailón M, García-Allut A, Martín-Martín C. Spontaneous cerebrospinal fluid leaks in the anterior skull base secondary to idiopathic intracranial hypertension. Eur Arch Otorhinolaryngol 2017;274:2175–2181.
12. Teachey W, Grayson J, Cho DY, Riley KO, Woodworth BA. Intervention for elevated intracranial pressure improves success rate after repair of spontaneous cerebrospinal fluid leaks. Laryngoscope 2017;127:2011–2016.

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Distribution of cerebral microbleeds in the East and West

Individual participant meta-analysis

In the article "Distribution of cerebral microbleeds in the East and West: Individual participant meta-analysis" by Yakushiji et al.,[1] published ahead of print on February 1, 2019, Dr. Mok's degree should have been listed as MD. The degree appears correctly in the final print version of this article published on March 5, 2019. The authors regret the error.

Reference

1.   Yakushiji Y, Wilson D, Ambler G, et al. Distribution of cerebral microbleeds in the East and West: individual participant meta-analysis. Neurology 2019;92:e1086–e1097.

Imaging outcome measures of neuroprotection and repair in MS

A consensus statement from NAIMS

In the article "Imaging outcome measures of neuroprotection and repair in MS: A consensus statement from NAIMS" by Oh et al.,[1] first published online February 20, 2019, and in print March 12, 2019, Dr. Robert Zivadinov should have been listed as an author, appearing between Yunyan Zhang and Nancy Sicotte. The authors regret the error.

Dr. Zivadinov's disclosures should have been included as follows: Dr. Zivadinov has received personal compensation from Genzyme and Novartis for serving on scientific advisory boards; received speaker honoraria from EMD Serono, Inc., Novartis, Sanofi-Genzyme, and Celgene; received personal compensation from EMD Serono, Inc., Novartis, Sanofi-Genzyme for consulting fees; received personal compensation from EMD Serono, Inc., Novartis, and Sanofi-Genzyme for serving on speakers' bureaus; and financial support for research activities from EMD Serono, Inc., Novartis, Sanofi-Genzyme, Mapi Pharma, Celgene, and Protembis.

Dr. Zivadinov's full degrees and affiliation are as follows:

Robert Zivadinov, MD, PhD
Professor of Neurology
Director, Buffalo Neuroimaging Analysis Center, Department of Neurology
Director, Center for Biomedical Imaging at the Clinical Translational Science Institute
Jacobs School of Medicine & Biomedical Sciences
University at Buffalo, State University of New York

Finally, Dr. ZIvadinov's contributions to the paper should have been: Dr. Zivadinov contributed to the acquisition of data, analysis and interpretation, and critical revision of the manuscript for important intellectual content.

Reference

1.   Oh J, Ontaneda D, Azevedo C, et al. Imaging outcome measures of neuroprotection and repair in MS: a consensus statement from NAIMS. Neurology 2019;92:519--533.