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LEADING TOPIC

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Overlapping challenges of treating cerebrospinal fluid dynamic disorders

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In my role as the guest editor of the current issue of Leading Topics published in the Polish Journal of Neurology and Neurosurgery, I am delighted to introduce a collection of articles on disrupted cerebrospinal fluid (CSF) dynamics (Tab. 1).

The parameters of CSF dynamics include intracranial pressure, volume, resistance to CSF outflow, cerebrospinal compliance, compensatory reserve, and waveform components [1, 2]. Imbalances in these parameters can lead to a variety of disorders of CSF dynamics, primarily encompassing the conditions of hydrocephalus, pseudotumour cerebri syndrome (PTCS), spontaneous intracranial hypotension, Chiari malformation, and syringomyelia. Although each condition typically occurs independently, there can be a striking continuum of abnormalities and 'never right' dynamics when these conditions intersect. This results in considerable challenges in diagnosis, and consequently many treatment dilemmas.

PTCS is nearly always associated with papilloedema [3] which in and of itself confirms pathologically sustained intracranial hypertension. Published criteria for the more rare PTCS without papilloedema exist, relying heavily on a constellation of radiographic stigmata of sustained intracranial hypertension [4]. These diagnostic criteria do not account for the patients who have 'self-decompressed' their pressure through a cranial or spinal CSF leak preventing papilloedema, or preventing the full expected radiographic picture, as we will see in this issue's work by Macedo et al. Such a case is presented and illustrated in Figure 1.

Macedo et al. present a narrative review of the association between PTCS and spontaneous CSF rhinorrhea [5]. Their extensive literature review, encompassing a total of 943 patients, focuses on the commonly identified patient characteristics, clinical presentation, imaging findings and management of spontaneous skull-based CSF leaks caused by intracranial hypertension. Many diagnostic and treatment challenges were

Table 1. Leading Topic articles: disorders of cerebrospinal fluid dynamics; PJNNS 1/2024

Title	Authors
INVITED REVIEW ARTICLES	
Spontaneous rhinorrhea and idiopathic intracranial hypertension: a complex and challenging association	Leonardo Jose Monteiro de Macedo Filho, Carolina Carmona Pinheiro Machado, Gabrielle Brito Bezerra Mendes, Luma Maria Figueiredo Santana, Mauro Emiliano Ruella, Sanjeet Grewal, Kaisorn Chaichana, Alfredo Quinones-Hinojosa, Olga Fermo, Joao Paulo Almeida
Headache associated with intracranial hypotension: diagnostic challenges and difficulties in everyday neurological practice	Magdalena Boczarska-Jedynak, Daniel Stompel
Normal pressure hydrocephalus, or Hakim syndrome: review and update	Philip W. Tipton, Benjamin D. Elder, Petrice M. Cogswell, Neill Graff-Radford
INVITED RESEARCH PAPERS	
Neuronal pentraxin 2 correlates with neurodegeneration but not cognition in idiopathic normal pressure hydrocephalus (iNPH)	Megha Patel, Yifan Zhang, Mei-Fang Xiao, Paul Worley, Abhay Mogheka
Recurrence of cerebrospinal fluid-venous fistulas at different spinal levels following transvenous embolisation or blood/fibrin glue patching	Roaa Zayat, Olga P. Fermo, Thien J. Huynh

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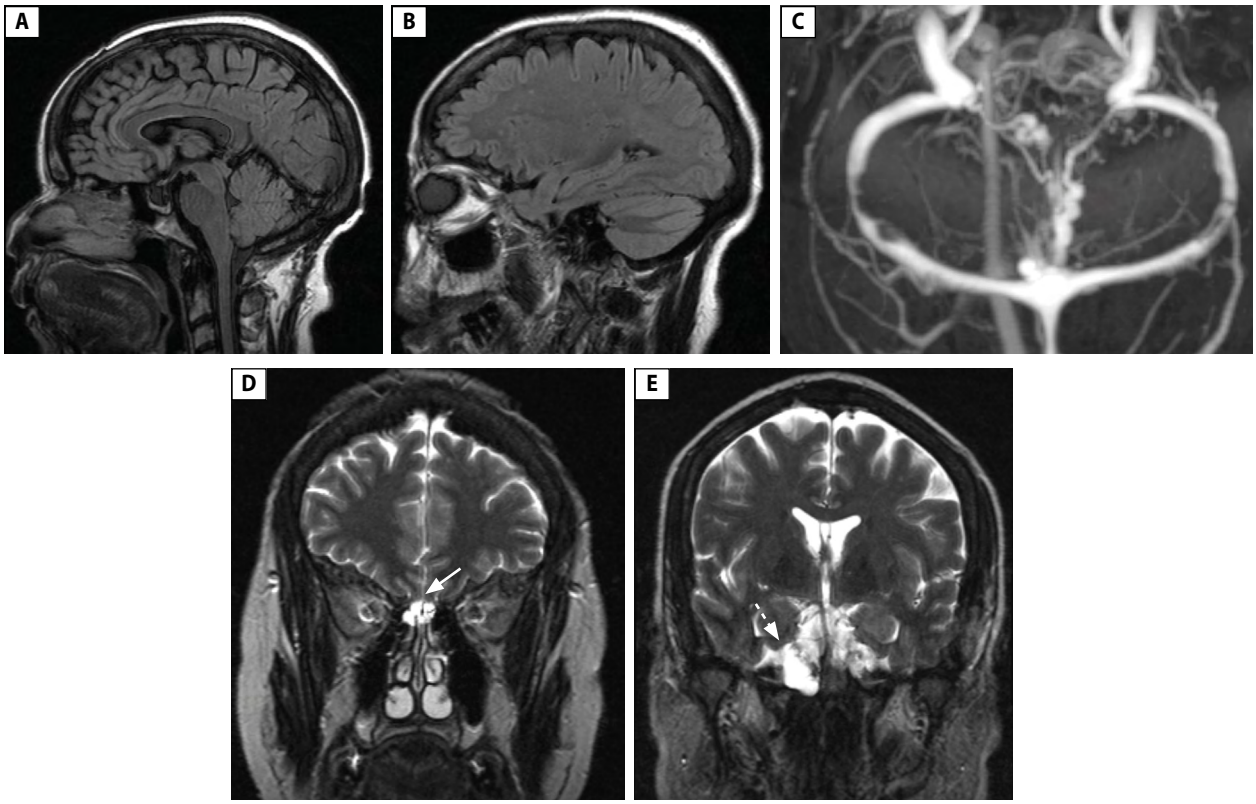

Figure 1. A patient with migraine was evaluated for daily left hemicranial headache after suffering a whiplash injury. History revealed intermittent clear rhinorrhea when bending over of 1–2 years' duration, unrelated to chief concern. Patient was suspected to have pseudotumour cerebri syndrome based on multiple radiographic stigmata of intracranial hypertension. However, lumbar puncture revealed an opening pressure of 8 cmH20 and there was no papilloedema. Image **A**: partially empty, expanded sella turcica; **B**: tortuosity of right optic nerve in vertical plane; **C**: bilateral transverse venous sinus stenosis; **D**: large right cribriform plate defect with meningocele and remodelling of ethmoid trabeculae (solid arrow); **E**: large right petrous apex and clivus osseous defect with meningocele (dashed arrow). Patient underwent endoscopic endonasal repair of right anterior cranial fossa for non-active CSF rhinorrhea one year after images were taken. Bolt intracranial pressure monitoring performed four months after surgery confirmed nocturnal intracranial hypertension (normal pressures while awake) with average overnight intracranial pressure of 26.6 cmH20 and maximum intracranial pressure of 31.38 cmH20. Intracranial pressure normalised after intravenous administration of acetazolamide 500 mg. The most likely aetiology of intracranial hypertension in this case was bilateral primary venous transverse sinus stenosis in combination with untreated sleep apnoea. Patient continued on oral acetazolamide to prevent papilloedema and development of recurrent or new skull-based CSF leak

identified, including difficulty in diagnosing PTCS according to the published criteria during an active leak, and the higher recurrence rate of skull-based CSF leak in the intracranial hypertension population compared to other types of cranial leaks. They identified several significant differences compared to PTCS without cranial leak. These differences included a relatively low incidence of headache as a presenting symptom (20.36% with cranial leak versus ≥ 84% without cranial leak [6]), the frequent absence of papilloedema before leak closure, a lower mean lumbar puncture opening pressure (25.52 cmH20 compared to c.34 cmH20 observed in the population studied in the Idiopathic Intracranial Hypertension Treatment Trial [7]), and a much lower prevalence of common imaging abnormalities. For instance, 42.3% of patients with cranial leak had a partially empty sella, compared to the previously reported 80% of patients with pseudotumour cerebri without papilloedema [3]. Additionally, 2.6% of patients with cranial leak had venous sinus stenosis, in contrast to 78% of patients with pseudotumour cerebri without papilloedema [3]. As highlighted by the authors, the distinct clinical variations between those individuals with intracranial hypertension who experience leaks and those who do not, create a challenge in terms of recognition.

This underlines the importance of a collaborative, multidisciplinary approach to the care of these patients, involving otolaryngologists, neurosurgeons, neurologists, and radiologists. Given that these patients often require multiple diagnostic interventions, such a comprehensive team strategy becomes essential. Moreover, the extended period preceding leak recurrence shown by our authors, c.20.5 ± 13 months, highlights the need for longitudinal team follow-up [5].

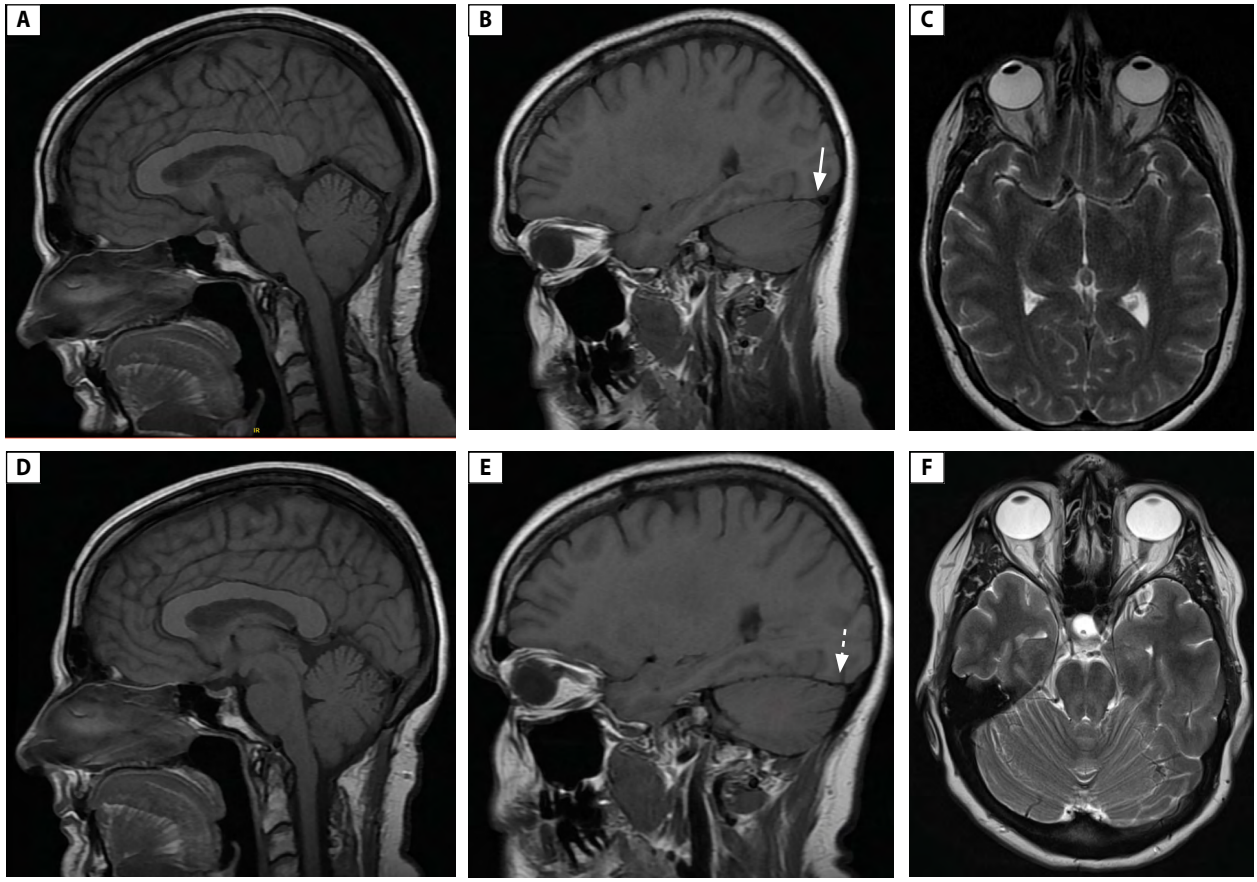

Figure 2. A patient with new daily persistent headache for 30 years was found to have spontaneous intracranial hypotension from a multilevel, ventral, upper thoracic spine, longitudinal epidural fluid collection. There was a history of posterior fossa decompression for a (questionable) Chiari 1 malformation diagnosis 18 years prior to leak discovery. Patient underwent CT-guided fibrin patching to ventral upper thoracic spine 10 months after pre-treatment images (**A, B, C**) were taken, which show classic stigmata of intracranial hypovolemia. **A:** engorged pituitary gland and mild brain sag; **B:** right optic nerve is straight in vertical plane (normal); right transverse venous sinus is engorged (solid arrow); **C:** optic nerves are straight in horizontal plane (normal). Patient developed a headache pattern change and papilloedema with peri--nerve haemorrhage within three weeks of patch. Post-treatment images (**D, E, F**) were taken six weeks after treatment, demonstrating new stigmata of intracranial hypertension. **D:** partially empty sella turcica; **E:** subtle tortuosity of right optic nerve in vertical plane (abnormal), and development of right transverse sinus stenosis (dashed arrow). **F:** bilateral horizontal optic nerve tortuosity (abnormal). Patient ultimately required ventriculoperitoneal shunting for persistent intracranial hypertension despite high-dose oral acetazolamide therapy

In contrast to the *relatively* few patients with cranial leaks experiencing headache, as shown by Macedo et al. [5], headache is overwhelmingly the most common presenting symptom of a spontaneous spinal CSF leak, present in 98.6% of patients [8]. Spontaneous intracranial hypotension from a spinal CSF leak can be misdiagnosed as a Chiari type 1 malformation when subtle imaging findings are overlooked, a problem that Boczarska-Jedynak and Stompel set out to rectify in this issue [9].

To further complicate matters, spontaneous intracranial hypotension from a spinal CSF leak may be caused by underlying intracranial hypertension [10] akin to the cranial leaks described in this issue by Macedo et al. [5], and the treatment of spontaneous intracranial hypotension can result in intracranial hypertension [11]. These problems are illustrated in the case in Figure 2. As pointed out by Boczarska-Jedynak and Stompel in this issue [9], many patients with actively leaking spinal leaks have normal opening pressure, and some even have intracranial hypertension during the leak [12]. Given the strong correlation between a normal opening pressure and a normal brain MRI in the presence of a spinal leak [12], the phenotypic criteria presented in this issue become crucial for maintaining a high level of suspicion for an inconspicuous disorder.

In their review of headache attributable to intracranial hypotension, the authors immediately point out the challenges in diagnosing this clinical syndrome beyond the hypotension dilemma. These challenges also encompass the fact that key symptoms such as headache, neck pain, and vestibulocochlear disturbance are relatively nonspecific. Patients may exhibit signs of meningeal irritation [13], such as photophobia, which can mimic migraine. Additionally, subtle positive diagnostic

imaging findings may be easily overlooked by those without specialised training [9]. They move on to expand on the International Classification of Headache Disorders, 3rd edition diagnostic criteria of Headache attributed to low CSF pressure, the three reviewed conditions being post-dural puncture headache, CSF fistula headache (not to be confused with CSF venous-fistula), and spontaneous intracranial hypotension [14]. Emphasising another aspect of this syndrome's complexity — the variability in clinical presentations—the authors lead us through three distinct scenarios. A sudden, possibly thunderclap-onset, headache when presented in a hospital setting may mimic subarachnoid haemorrhage, acute central nervous system infection, ischaemia, or thrombosis. This is juxtaposed against an indolent chronic headache disorder often misdiagnosed as migraine, tension headache, or cervicogenic headache which persists as medically refractory for years, and in some cases even decades. The authors finish with a description and prevalence of the head imaging abnormalities caused by intracranial hypotension, followed by a discussion of localising spinal imaging findings [9].

Even after overcoming the challenges of diagnosing spontaneous intracranial hypotension, further difficulties emerge. As demonstrated by Zayat et al. [15] in this issue, patients may experience a second leak even after successful treatment of the initial spinal CSF leak. In this original research submission, the authors describe the clinical and radiographic characteristics of 4/42 patients with myelography-proven CSF venous fistulas who developed leak symptoms after successful venous fistula embolisation. These four patients were discovered to have new CSF venous fistulas at spinal levels different from their initially identified fistulas. Notably, three of the four exhibited the persistence or recurrence of intracranial radiographic signs indicative of intracranial hypovolemia before the diagnosis of the recurrent leak. In the fourth patient, a recurrent fistula was discovered despite an improvement in brain imaging, although it remained abnormal. This underlines the importance of post-treatment surveillance brain imaging for assessing treatment response and establishing a new radiographic baseline. Additionally, the worsening Bern score serves as a valuable indicator in confirming the recurrence of a leak after treatment. However, as illustrated in the last case, improving imaging results may provide a false sense of reassurance. Therefore, a high level of suspicion for recurrent leaks should persist, especially when clinical symptoms are present. Regrettably, there is still a significant amount to discover within the realm of spontaneous intracranial hypotension. The precise triggers for spinal CSF leaks remain unclear, and the factors contributing to recurrence are not understood. In this issue's other editorial, Cutsforth-Gregory proposed several possible risk factors for fistula recurrence including regionally abnormal CSF and venous pressure or fluid dynamics or the development of rebound intracranial hypertension [16]. By examining recurrent leaks like Zayat et al., we may advance our understanding of leak origin.

An issue focused on cerebrospinal fluid dynamic disorders would not be complete without a discussion of probably the most studied hydrodynamic anomaly, i.e. normal pressure hydrocephalus. In this issue, Tipton et al. [17] present a comprehensive review of contemporary normal pressure hydrocephalus management. The authors initiate their topic with the proposal that the term 'normal pressure hydrocephalus' is outdated, based on newer evidence that stretches our previous definition of 'normal' intracranial pressure. Considering a more comprehensive understanding of the diverse factors contributing to shunt-responsive hydrocephalus, including congenital, vascular, and absorptive derangements, the authors suggest adopting the term 'Hakim Syndrome' to refer to the combination of gait disorder with cognitive decline and/or urinary dysfunction. The authors emphasise the complexity for several reasons of reaching a diagnosis, including the variable and sometimes asymptomatic clinical presentation, the presence of commonly associated comorbidities, the absence of a consensus definition for a positive response to cerebrospinal fluid diversion, and the lack of proven cerebrospinal fluid biomarkers that could aid in the diagnostic process. With these limitations in mind, the authors recommend a thorough, cautious and systematic methodology to assessing suspected Hakim Syndrome. They conclude with a discussion of the latest approaches to minimising shunt-related complications.

In a further quest to better understand the pathophysiology of normal pressure hydrocephalus, Patel et al. [18] present their original research regarding the diagnostic and prognostic value of the synaptic protein neuronal pentraxin-2 (NPTX2). The authors found that CSF NPTX2 concentrations were not correlated with short-term improvement on the Timed Up and Go Test after temporary CSF removal or long-term improvement after shunt surgery, indicating that NPTX2 cannot be used as a diagnostic or prognostic biomarker for the condition. They also found no correlation between NPTX2 and baseline cognitive performance, implying that mechanisms other than synaptic degeneration are responsible for the cognitive decline seen in some patients with normal pressure hydrocephalus.

One wonders whether the extensive progress made in the understanding of normal pressure hydrocephalus is a precursor to reimagining the other disorders of CSF dynamics. As presented by Tipton et al. [17], normal pressure hydrocephalus is probably best considered a final common pathway for several different congenital or acquired pathologies. Could this same umbrella concept hold true for PTCS and spontaneous intracranial hypotension? Are these actually collections of different disorders with a final common symptomatology? Much work remains to be done.

At the current juncture, the work presented in this issue showcases the plethora of challenges faced when treating disorders of CSF dynamics. On the one hand, this may occur because subtle diagnostic features are overlooked or misinterpreted, such as misdiagnosing a spinal CSF leak as Chiari or failing to recognise that intracranial hypertension can cause tonsillar descent, mimicking Chiari. On the other hand, it may be because the patient genuinely has two competing conditions

that 'cancel each other out', as seen in cases of PTCS leading leak, or when a spinal CSF leak is complicated by post-treatment intracranial hypertension.

The key 'takeaway' from this issue is the importance of a thorough familiarity with all cerebral spinal fluid dynamic disorders. Consider the possibility of cranial leaks in patients with PTCS who do not present with papilloedema. This is not usually an immediate consideration because it is not part of the diagnostic criteria for PTCS. Think about spinal leaks, or postdural puncture headaches in the patients with PTCS who have changing headache patterns. It is suggested that clinicians should protect the patients with cranial CSF leaks from headaches, papilloedema, and leak recurrence by developing a system to check and monitor for intracranial hypertension postoperatively, as in Figure 1. Finally, consider the emergence of intracranial hypertension in the patient with a spinal CSF leak who fails to improve after successful treatment, as in Figure 2, or the patient who continues to develop new spinal leaks.

To gain a comprehensive understanding of each abnormality, it is essential to view them as part of a continuum.

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