Neuroradiology (2022) 64:2097–2099
https://doi.org/10.1007/s00234-022-03051-3

EDITORIAL

Commentary: predictor of shunt response in idiopathic normal pressure hydrocephalus

Àlex Rovira[1] · Jérôme Hodel[2]

Published online: 15 September 2022

Normal pressure hydrocephalus (NPH) is a surgically treatable reversible neurological disorder initially identified in 1957 by a Colombian neurosurgeon, Solomon Hakim [1]. At that time, the cause of this chronic form of communicating hydrocephalus, in which there is not objective obstruction of cerebrospinal (CSF) circulation and absorption, was not known, and this disease was considered "idiopathic" (iNPH). Since then, patients with known causes of NPH such as subarachnoid hemorrhage and meningitis (secondary NPH) have been identified, which are usually younger and tend to respond better to shunting than the idiopathic variety, likely because of poor historical selection criteria for the idiopathic form.

iNPH is characterized clinically by a triad of gait and balance impairment, cognitive deterioration, and urinary incontinence, and radiologically by a communicating ventricular enlargement (Evans index > 0.3), in the context of a CSF opening pressure of < 24 cm of H_2O (in recumbent position) [2, 3]. The primary differential includes neurodegenerative conditions such as Alzheimer disease (AD), and studies have shown that there is some overlap between these two conditions with many patients having a component of both [4, 5].

The term "normal pressure" hydrocephalus was based on the observation that the lumbar puncture opening pressures were not elevated in these patients but transient episodes of increased CSF pressure can occur, particularly when the intracranial pressure is monitored overnight during sleep, and hence NPH is also termed "intermittent pressure hydrocephalus."

The basic pathophysiological processes underlying the development of iNPH still remain unclear. The classical concept that iNPH is simply a form of CSF circulation disorder, involving an imbalance between CSF production and reabsorption, is probably not valid. In fact, unlike other forms of hydrocephalus, the CSF pressure is not abnormal, which implies that such a simplistic hydrodynamic theory would be insufficient to explain the pathophysiology of this condition. Other factors might contribute in the development of iNPH. Chronic arterial hypertension and white matter disease may lead to periventricular ischemia that increases the compliance of the ventricular wall and causes gradual ventricular enlargement. Alternatively, periventricular ischemia may also lead to locally increased venous resistance that may lead to decreased CSF absorption and ventricular enlargement. Finally, diminished vascular (arterial) compliance that frequently occurs in the aging brain might produce a redistribution of systolic vascular pulsations, which are then transmitted directly into the ventricular system, progressively increasing its size [6, 7].

Diversion of CSF through ventriculoperitoneal shunts is the standard of surgical care for iNPH. The objective of this treatment is to normalize or at least reduce the intermittent increase of the intraventricular pressure, and to improve or stabilize the clinical symptoms [3]. The diagnosis of iNPH and the decision whether or not to treat a patient is typically a multistage and challenging process, because not all patients with a diagnosis of iNPH will benefit from to shunt surgery, a surgical procedure with a small but not negligible complication rate [8]. Therefore, the objective of clinical and paraclinical tests in iNPH goes beyond the diagnosis of this condition, and is essential for the identification of those patients who will have a favorable response to shunting.

Different morphological imaging features have been proposed for predicting shunt response. The callosal angle, defined as the angle between the medial superior borders

This article is an editorial comment to article https://doi.org/10.1007/s00234-022-03021-9.

✉ Àlex Rovira
alex.rovira.idi@gencat.cat

[1] Section of Neuroradiology, Department of Radiology, Hospital Universitari Vall d'Hebron, Universitat Autònoma de Barcelona, Barcelona, Spain

[2] Department of Radiology, Groupe Hospitalier Paris-Saint Joseph, Paris, France

of the left and right lateral ventricle [9, 10], which is significantly smaller in patients with iNPH than those with AD or healthy controls, has been proposed to predict shunt responders, as these patients have a significantly smaller mean preoperative angle compared with non-responders, using 63° as the cut-off value to achieve the best prognostic accuracy [11].

Another imaging feature that has shown diagnostic value as well as in predicting shunt response is the presence of a "disproportionately enlarged subarachnoid space hydrocephalus" (DESH), which refers to the combination of three components: 1, ventriculomegaly (Evans index > 0.3); 2, narrow high-convexity and medial subarachnoid spaces; and 3, enlarged Sylvian fissures (disproportionate distribution of the CSF between the inferior and superior subarachnoid spaces) [12, 13]. Due to the ambiguity of defining each DESH component, Shinoda et al. [14] have proposed a DESH scale (0–10) that incorporates two additional radiological features (callosal angle and focal sulcal dilation). In their study, it was shown that high DESH scores (> 6) have a high positive predictive value for neurological improvement after surgery, supporting its prognostic value. In fact, the DESH score is used in some neurosurgical centers, mainly in Japan, for both iNPH diagnosis and predicting shunt response, without the need of a CSF tap test or other invasive neurosurgical procedures.

Functional MRI studies, such as cardiac-gated phase-contrast flow-sensitive MRI, which can measure an increase in the aqueductal CSF stroke volume in iNPH, have been used to predict shunt response [15]. However, there is insufficient evidence to utilize this metric to select iNPH for shunt surgery because its predictive value has not been confirmed [16].

In this issue of neuroradiology, Carlson et al. [17] performed a systematic literature review and meta-analysis aimed to identify radiological features that could be used to discriminate iNPH shunt responders from non-responders. Not unexpectedly, no single imaging parameter was repeatedly and consistently reported as different between responders and non-responders across the 27 articles included in the analysis. This negative result can be explained by different factors, such as differences in patient inclusion criteria and imaging analysis, and in the reference standard to define shunt response. However, the most likely factor that could explain the negative results is the neglection in most studies of non-radiological factors such as the duration of symptoms before shunt surgery; it has been demonstrated that the best short-term benefits of surgical intervention are achieved when shunt surgery is performed in patients with short disease duration or when surgery is performed within few months of decision to surgery [18, 19]. This finding can be explained by the fact that iNPH is a progressive disease, causing brain damage if not treated promptly, with long disease duration allowing the disease more time for developing irreversible progression.

Other factors that may diminish shunt response include more severe presurgical clinical symptoms, advanced age, and established cerebrovascular disease such as diabetes mellitus, hypertension, hyperlipidemia, and history of myocardial infarction [20]. The association of radiological appearances of iNPH with primary neurodegenerative disorders, such as AD and subcortical vascular dementia, can also explain the lack of response in some shunt-treated patients. In fact, shunt-responsive patients appear to have lower pathological burdens of neuritic plaques or intraventricular amyloid and tau [21].

The recently discovered glymphatic system also seems to play a role in the pathogenesis of iNPH. This system is fundamental for the clearance of waste metabolites, such as amyloid-b peptides (Aβ1-42) and tau protein from the brain interstitial space, and is proposed to be instrumental in normal aging and brain pathology such as AD and brain trauma [22–24]. In iNPH, impaired glymphatic circulation may lead to brain tissue damage and eventually dementia [25]. This system can be visualized by different non-invasively MRI techniques such as intrathecal injection of gadolinium-based contrast agent that analyzes the clearance time of this tracer from CSF and brain parenchyma, or with "diffusion tensor image analysis along the perivascular space (DTI-ALPS)" that quantifies the diffusivity of perivascular water flow in the periventricular area. With these techniques, some studies recently suggested that the glymphatic system could be impaired in iNPH patients (decreased clearance of the tracer from the subarachnoid space along with persisting enhancement in brain parenchyma, or decreased diffusivity along the x-axis in the projection fibers area), probably leading to neuronal damage or dysfunction [22, 24, 26]. Bae et al. have shown that glymphatic activity, measured by means of DTI-ALPS, is not only reduced in iNPH patients than in control subjects, but it is also lower in non-responders than in responders, reflecting higher disease severity and indicating that assessment of impairment severity of glymphatic activity may predict an unfavorable outcome following CSF shunting [26].

In conclusion, although imaging and in particular MRI play an essential role in establishing the diagnosis of iNPH, and in selecting (with or without invasive surgical procedures) shunt candidates, we cannot expect that any of the morphological features proposed accurately predict shunt responders, as other non-radiological factors contribute in this prediction, such as concomitant presence of a neurodegenerative and vascular disorders, age, and duration of the clinical symptoms. Analysis of the glymphatic circulation by means of non-invasive MRI is a promising technique that might help in the future for predicting shunt responders, by assessing the degree of impairment of this system, which in

turn determines the severity of the disease and the degree of irreversible tissue damage.

References

1. Adams RD, Fisher CM, Hakim S, Ojemann RG, Sweet WH (1965) Symptomatic occult hydrocephalus with normal cerebrospinal-fluid pressure. A treatable syndrome. N Engl J Med 273:117–126
2. Rovira A (2019) Communicating hydrocephalus. Normal pressure hydrocephalus. In Barkhof F et al. (eds) Clinical neuroradiology. Springer Nature Switzerland AG, pp 489–518
3. Mori E, Ishikawa M, Kato T et al (2012) Japanese Society of Normal Pressure Hydrocephalus. Guidelines for management of idiopathic normal pressure hydrocephalus: second edition. Neurol Med Chir (Tokyo) 52:775–809
4. Müller-Schmitz K, Krasavina-Loka N, Yardimci T et al (2020) Normal pressure hydrocephalus associated with Alzheimer's disease. Ann Neurol 88:703–711
5. Allali G, Laidet M, Armand S, Assal F (2018) Brain comorbidities in normal pressure hydrocephalus. Eur J Neurol 25:542–548
6. Wang Z, Zhang Y, Hu F, Ding J, Wang X (2020) Pathogenesis and pathophysiology of idiopathic normal pressure hydrocephalus. CNS Neurosci Ther 26:1230–1240
7. Israelsson H, Carlberg B, Wikkelsö C et al (2017) Vascular risk factors in INPH: a prospective case-control study (the INPH-CRasH study). Neurology 88:577–585
8. Schenker P, Stieglitz LH, Sick B, Stienen MN, Regli L, Sarnthein J (2018) Patients with a normal pressure hydrocephalus shunt have fewer complications than do patients with other shunts. World Neurosurg 110:e249–e257
9. Ishii K, Kanda T, Harada A et al (2008) Clinical impact of the callosal angle in the diagnosis of idiopathic normal pressure hydrocephalus. Eur Radiol 18:2678–2683
10. Miskin N, Patel H, Franceschi AM et al (2017) Diagnosis of normal-pressure hydrocephalus: use of traditional measures in the era of volumetric MR imaging. Radiology 285:197–205
11. Virhammar J, Laurell K, Cesarini KG, Larsson EM (2014) The callosal angle measured on MRI as a predictor of outcome in idiopathic normal-pressure hydrocephalus. J Neurosurg 120:178–184
12. Hashimoto M, Ishikawa M, Mori E, Kuwana N, Study of INPH on neurological improvement (SINPHONI) (2010) Diagnosis of idiopathic normal pressure hydrocephalus is supported by MRI-based scheme: a prospective cohort study. Cerebrospinal Fluid Res 7:18
13. Virhammar J, Laurell K, Cesarini KG, Larsson EM (2014) Preoperative prognostic value of MRI findings in 108 patients with idiopathic normal pressure hydrocephalus. AJNR Am J Neuroradiol 35:2311–2318
14. Shinoda N, Hirai O, Hori S et al (2017) Utility of MRI-based disproportionately enlarged subarachnoid space hydrocephalus scoring for predicting prognosis after surgery for idiopathic normal pressure hydrocephalus: clinical research. J Neurosurg 127:1436–1442
15. Baroncini M, Balédent O, Ardi CE et al (2018) Ventriculomegaly in the elderly: who needs a shunt? A MRI study on 90 patients. Acta Neurochir Suppl 126:221–228
16. Kahlon B, Annertz M, Ståhlberg F, Rehncrona S (2007) Is aqueductal stroke volume, measured with cine phase-contrast magnetic resonance imaging scans useful in predicting outcome of shunt surgery in suspected normal pressure hydrocephalus? Neurosurgery 60:124–129
17. Carlsen JF, Munch TN, Hansen AE et al (2022) Can preoperative brain imaging features predict shunt response in idiopathic normal pressure hydrocephalus? A PRISMA review. Neuroradiology. https://doi.org/10.1007/s00234-022-03021-9
18. Vakili S, Moran D, Hung A et al (2016) Timing of surgical treatment for idiopathic normal pressure hydrocephalus: association between treatment delay and reduced short-term benefit. Neurosurg Focus 41:E2
19. Chidiac C, Sundström N, Tullberg M, Arvidsson L, Olivecrona M (2022) Waiting time for surgery influences the outcome in idiopathic normal pressure hydrocephalus - a population-based study. Acta Neurochir (Wien) 164:469–478
20. Badagard H, Braun M, Nilsson D, Stridh L, Virhammar J (2020) Negative predictors of shunt surgery outcome in normal pressure hydrocephalus. Acta Neurol 141:219–225
21. Hamilton R, Patel S, Lee EB et al (2010) Lack of shunt response in suspected idiopathic normal pressure hydrocephalus with Alzheimer disease pathology. Ann Neurol 68:535–540
22. Ringstad G, Vatnehol SAS, Eide PK (2017) Glymphatic MRI in idiopathic normal pressure hydrocephalus. Brain 140:2691–2705
23. Carlstrom LP, Eltanahy A, Perry A et al (2022) A clinical primer for the glymphatic system. Brain 145:843–885
24. Soldozy S, Yağmurlu K, Kumar J et al (2022) Interplay between vascular hemodynamics and the glymphatic system in the pathogenesis of idiopathic normal pressure hydrocephalus, exploring novel neuroimaging diagnostics. Neurosurg Rev 45:1255–1261
25. Eide PK, Ringstad G (2019) Delayed clearance of cerebrospinal fluid tracer from entorhinal cortex in idiopathic normal pressure hydrocephalus: a glymphatic magnetic resonance imaging study. J Cereb Blood Flow Metab 39:1355–1368
26. Bae YJ, Choi BS, Kim JM, Choi JH, Cho SJ, Kim JH (2021) Altered glymphatic system in idiopathic normal pressure hydrocephalus. Parkinsonism Relat Disord 82:56–60