Fluids and Barriers of the CNS

REVIEW

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Review of the lumbar infusion test use in pediatric populations: state-of-the-art and future perspectives

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Abstract

Background The lumbar infusion test (LIT) is a routine part of the diagnostic process of various CSF dynamics disorders in adults. However, it is rarely used in the paediatric population due to a lack of evidence substantiating its efficacy and overall indications.

Methods Articles utilizing the LIT in a paediatric cohort (≤ 18 years) were included according to the PRISMA guidelines with the Newcastle-Ottawa Scale to assess the risk of bias. This review was registered at PROSPERO database under number: CRD42024625857.

Results A total of 15 studies, yielding 441 patients, were included in the review. The most common indications for LIT were to predict shunt responsiveness in hydrocephalus and idiopathic intracranial hypertension (IIH). In IIH, the interaction between cerebrospinal fluid pressure (CSFp) and sagittal sinus pressure (SSp) may offer valuable diagnostic insights and present a novel assessment approach. The LIT is a validated tool, especially effective for predicting shunt responsiveness and detecting malfunctions in both IIH and hydrocephalus.

Conclusions Data surrounding LIT usage in children is lacking and most studies are outdated. Caution is needed when interpreting resistance to outflow (*Rout*) due to potential overestimation, with more attention directed to CSFp and the pressure within the venous system coupling in IIH. Future studies should focus on standardizing LIT protocols across age groups with focusing more on signal characteristics rather than individual parameters and fostering interdisciplinary collaboration to optimize diagnostic accuracy.

Keywords Lumbar infusion test, Infusion testing, Intracranial hypertension, Hydrocephalus, Pediatric, Children, Pediatric neurosurgery

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Introduction

Hydrocephalus, the most common disorder affecting cerebrospinal fluid (CSF) dynamics, is primarily associated with an imbalance in CSF production, resorption, or obstruction of CSF pathways [1]. Additionally, conditions such as idiopathic intracranial hypertension (IIH) and intracranial hypotension represent less thoroughly investigated disorders with complex underlying pathophysiological mechanisms. A unifying characteristic of these conditions is their multifactorial nature, influenced by the interplay of various determinants, as outlined by the Monro-Kellie doctrine [2]. Consequently, these conditions are intricately linked to fluctuations in cerebral blood flow (CBF), intracranial pressure (ICP), brain compliance, and other physiological parameters, complicating both diagnosis and treatment selection [3].

One diagnostic tool used in the evaluation of CSF dynamics is the lumbar infusion test (LIT), first described by Katzman and Hussey in 1970 [4]. The LIT was introduced as an advancement over the traditional lumbar puncture (LP), which was considered insufficient for diagnostic purposes in certain patient populations. LIT provides more comprehensive insights into CSF dynamics and can inform clinical decision-making, particularly in predicting shunt response [5, 6]. The procedure for LIT, akin to LP, involves the insertion of a needle into the lumbar subarachnoid space. CSF pressure is then continuously monitored while a CSF substitute, typically Ringer's solution, is infused. Analysis of the resulting pressure-volume curve and its characteristics enables the assessment of parameters related to CSF circulation dynamics [7]. This approach allows for monitoring ICP in response to controlled volume changes within the intracranial compartment, offering a more accurate understanding of the system's overall state and thereby facilitating more precise diagnostic conclusions compared to LP alone [8].

Currently, well-defined criteria for LIT exist in adults, particularly in the diagnosis of normal pressure hydrocephalus (NPH) [9], secondary or chronic hydrocephalus [10], IIH [11], and intracranial hypotension [12]. However, the application of LIT in the pediatric population remains poorly delineated, with a significant paucity of literature addressing its indications, especially in patients with IIH [13]. This lack of standardization poses challenges to the implementation of safe and effective clinical practices in children, despite an evident need for criteria tailored to pediatric CSF physiology. In children, CSF dynamics differ significantly from those in adults, with ICP thresholds varying across developmental stages due to factors such as skull growth, BMI, and suture closure, as well as a potential need for sedation during the procedure [14].

Thus, the present review aims to provide an overview of the current state-of-the-art use of LIT in pediatric clinical practice. It summarizes historical developments and incorporates institutional experiences to highlight the current indications for LIT in children, with the goal of contributing to the ongoing effort toward standardizing this diagnostic tool in the pediatric population.

Methods

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and its criteria [15] when creating this review. This review was registered at PROSPERO database under number: CRD42024625857.

Literature search and eligibility criteria

The following databases were searched for relevant studies: PubMed, ScienceDirect, Scopus, Medline Plus and the Cochrane Library. Several combinations of keywords were used during the search: (1)""lumbar infusion test" OR "LIT" in children", (2) ""lumbar infusion test" OR "LIT" in pediatrics", (3) "pediatric intracranial idiopathic hypertension", (4) "pediatric "IIH" OR "idiopathic intracranial hypertension"", (5) """LIT" OR "lumbar infusion test"" AND ""IIH" OR "idiopathic intracranial hypertension"""". The search yielded 622 unique articles. Titles and abstracts were screened for relevance and ultimately 37 full-text manuscripts met the screening criteria with 15 determined to be relevant to this topic. The references of these articles and excluded review articles were manually searched to obtain additional relevant articles. These articles formed the evidence base for the review. Articles published after September 24, 2024, were not included.

All studies regarding a lumbar infusion test in patients < 18 years were included and analysed, regardless of the specific etiology, due to the limited number of studies published on this topic. Review articles, case reports and meta-analyses and articles concerning the use of LIT in any other condition except CSF disorder were excluded. Only studies written in English were included. Each analyzed study consisted of unique subjects who were not included in other series.

Assessment of risk of Bias in included studies

Two reviewers (VN and AB) independently excluded titles and abstracts which did not meet the eligibility criteria. The Newcastle-Ottawa Scale (NOS) [16] was used to assess the risk of bias. Any discrepancies regarding the inclusion or exclusion of specific studies were resolved at consensus meetings.

Data extraction

Data were extracted on the following parameters: patient demographics (total number of patients, age, sex),

method of ICP measurement, method of LIT measurement, indication criteria, reported LIT parameters, efficacy in predicting outcomes (e.g., shunt response), type of treatment performed, and follow-up periods.

Results and discussion

Theoretical background and technique

Physiological insights and related LIT parameters

In the supine position, CSF pressure (CSFp) and pulse amplitude at the lumbar region correspond to ICP and ICP pulse amplitude (ICPamp) [17]. Thus, LP can serve as an indirect method to evaluate ICP dynamics, which are modulated by the biophysical characteristics of the craniospinal system (spinal axis, vascular structures, and CSF). As per evaluated LIT parameters, resistance to outflow (*Rout*) is the most commonly used and is regarded as a key parameter in evaluating the efficiency of CSF absorption [17]. *Rout* is commonly calculated by determining the pressure at which ICP stops rising significantly and reaches a relatively stable value, as the speed of infusion will be equal to the speed of CSF absorption (plateau pressure, *Pp* in mmHg), minus the pressure measured before commencing the infusion of the CSF substitute (opening pressure, *Po* in mmHg), divided by the infusion rate (ml/min) [18]. In adults, the most commonly used cutoff value for *Rout* is 12 mmHg/ml/min [18]. *Rout* has been found to increase only slightly as we age, so cutoff values of either 10 mmHg/ml/min, 12 mmHg/ml/min or 13 mmHg/ml/min are most widely used in children [19].

$$Rout = \frac{Pp - Po}{infusion\ rate}$$

Various parameters have been proposed to assess the craniospinal system dynamics and its capacity to buffer pressure variations (Table 1). Compliance and its reciprocal elastance quantify craniospinal properties at specific ICP levels (Fig. 2). However, both compliance and elastance vary dynamically as ICP changes. To analyze this relationship comprehensively, the pressure-volume index (PVI) is employed, representing the exponential relationship between volume and pressure across the full physiological range of ICP. PVI denotes the volume (in mL) required to elevate ICP by a factor of 10.

$$Compliance = \frac{dV}{dP} \iff Elastance = \frac{dP}{dV}$$

The most commonly employed technique for assessing the PVI involves a single-bolus infusion of 3–5 mL at a rate of 1 mL per second, with several analytical models available for interpretation [20] (Fig. 1). A PVI value below 25 mL is recognized as a critical indicator of hydrocephalus [8]. When determined through continuous infusion, the threshold of concern is typically around 13 mL. A PVI between 20 and 25 mL is considered a "grey zone," where the clinical significance remains ambiguous. The methods for calculating PVI vary significantly; in some institutions, PVI is derived from the elasticity parameter obtained from LIT, often resulting in higher values compared to those obtained from bolus injection techniques. This variability highlights the importance

Table 1 Measured parameters during LIT and presented other relevant methods of assessing intracranial dynamics

Parameter	Units	Measurement and Description
Rout (resistance to outflow)	mmHg/ml/min	Measure of the resistance to CSF flow out of the craniospinal system.
Po (opening pressure)	mmHg	Initial measurement of CSF pressure (CSFp) obtained during LIT, taken when the CSF is first accessed
Pp (plateau pressure)	mmHg	The steady-state pressure reached during infusion once the infusion has been ongoing long enough for the pressure to stabilize.
RAP		Correlation coefficient between mean ICP and AMP (i.e., the correlation coefficient [R] between AMP amplitude [A] and mean pressure [1]. Indicator of compensatory reserve, accurate measure of intracranial compliance.
SSp (sagittal sinus pressure)	mmHg	Venous pressure within the sagittal sinus. Reflects the pressure in the dural venous sinus system, role in the overall dynamics of CSF and ICP.
PVI (pressure-volume index)	ml	Volume of a bolus injection required to achieve a tenfold increase in ICP. Indicator of CSF dynamics and intracranial elastance.
Compliance	ml/mmHg	The change in volume (ΔV) per unit change in pressure (ΔP), exactly the inverse of elastance. Ability of the intracranial compartment to accommodate an increase in volume without a large increase in ICP
Elasticity	mmHg/ml	Ability of an intracranial compartment to resume its normal shape after being compressed. Reflects the responsiveness of the craniospinal system to changes of ICP and CSF volume. It is the reciprocal value of compliance.

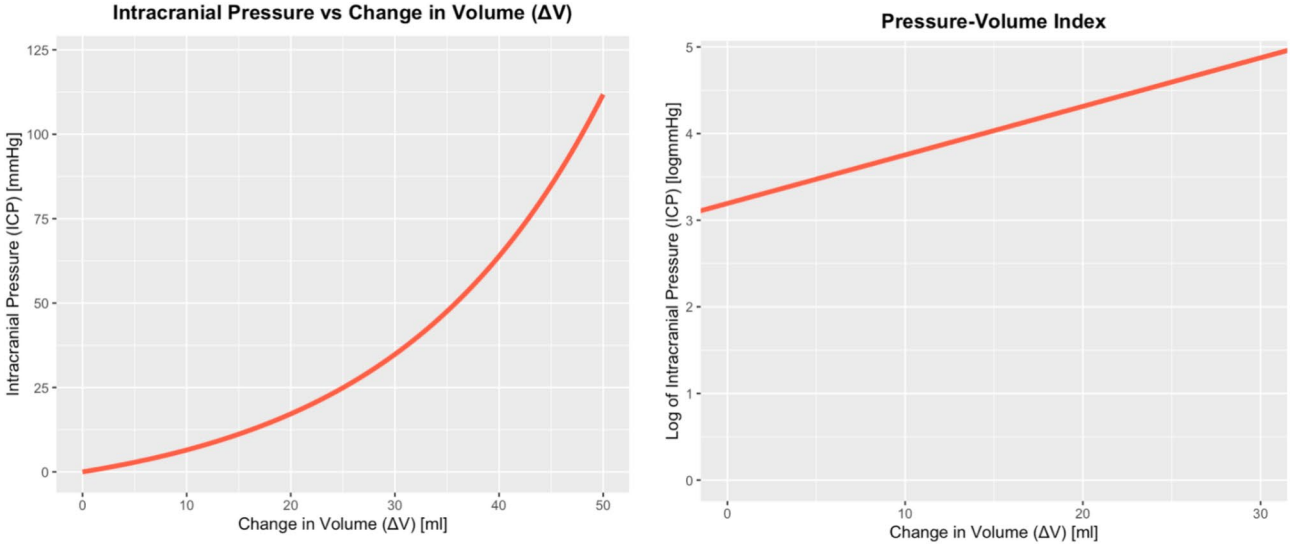

Fig. 1 The relationship between ICP and change of intracranial volume (ΔV) which reflects the brain compliance. The second graph depicted PVI as a relationship between log of ICP and change in intracranial volume

of method selection in interpreting PVI and its clinical implications.

Pressure-volume data from these assessments allow for the calculation of CSF dynamics variables, such as ICPamp and compensatory reserve. The latter is typically measured as the moving correlation coefficient between mean CSFp and pulse amplitude, represented by the RAP index (pressure-volume compensatory reserve), as well as the magnitude of slow waves in CSFp [21]. As intraluminal volume increases, ICP rises exponentially, eventually reaching a point where compensatory mechanisms become impaired. At this stage, compliance declines significantly, and the RAP index reaches a value of <1. Consequently, ICP pulse amplitude increases linearly in relation to mean ICP. Upon exceeding a critical ICP threshold, regulatory mechanisms fail, leading to the collaps of cerebral arterioles. This results in a rapid decline in ICP pulse amplitude, despite continued elevation of mean ICP, producing a RAP index of less than 1 (Fig. 2). Ultimately, ICP and mean arterial pressure (MAP) equilibrate, leading to reduced cerebral perfusion pressure.

Review of LIT indications and outcomes

A total of 15 studies have been published addressing this topic, with only 4 of them appearing since 2000. Summary of identified studies with their characteristics is presented in Table 2.

Idiopathic intracranial hypertension

When further restricted to studies examining the use of LIT in pediatric IIH cases, the data pool narrows to just 2 publications [10, 22]. This significant paucity of contemporary research highlights a critical gap in knowledge and underscores the need for further investigation into the diagnosis and management of pediatric IIH.

One major limitation in IIH diagnosis and treatment lies in the poorly understood mechanisms underlying the disease's etiology. Pediatric IIH can be categorized into two groups: (1) prepubertal IIH, which lacks a clear correlation with gender or BMI, and (2) postpubertal IIH, which predominantly affects obese females, similar to adult cases [35]. In 2019, Krishnakumar and Parker [22] conducted a study on 15 children aged 3 to 15 years (median age 12 years) with suspected IIH. Of these, 10 exhibited elevated CSFp or borderline CSFp with elevated, leading to a diagnosis of IIH in 6 children and secondary intracranial hypertension in the remaining 4. All children diagnosed with IIH underwent steady-state CSFp assessment, and 4 proceeded to LIT. The 2 remaining IIH patients, who had ICP levels exceeding 40 mmHg, were excluded from LIT.

During infusion, even with elevated ICP, *Rout* frequently remains within normal limits, suggesting, as observed in adult patients, that dynamic interactions between ICP and sagittal sinus pressure (SSp) may exacerbate intracranial hypertension [36]. Discrepancies between steady-state measurements and infusion tests can occur, as each assesses different aspects of CSFp dynamics. For instance, patients with confirmed papilledema but normal opening pressure may present such discordance. Additional diagnostic parameters, including the infusion plateau, clinical and radiological findings including MRI and MRV parameters and ophthalmologic findings, are critical in confirming IIH diagnosis [37]. Traditionally, SSp was considered independent of CSF pressure; however, the discovery of venous sinus stenoses and the implementation of venous sinus stenting in

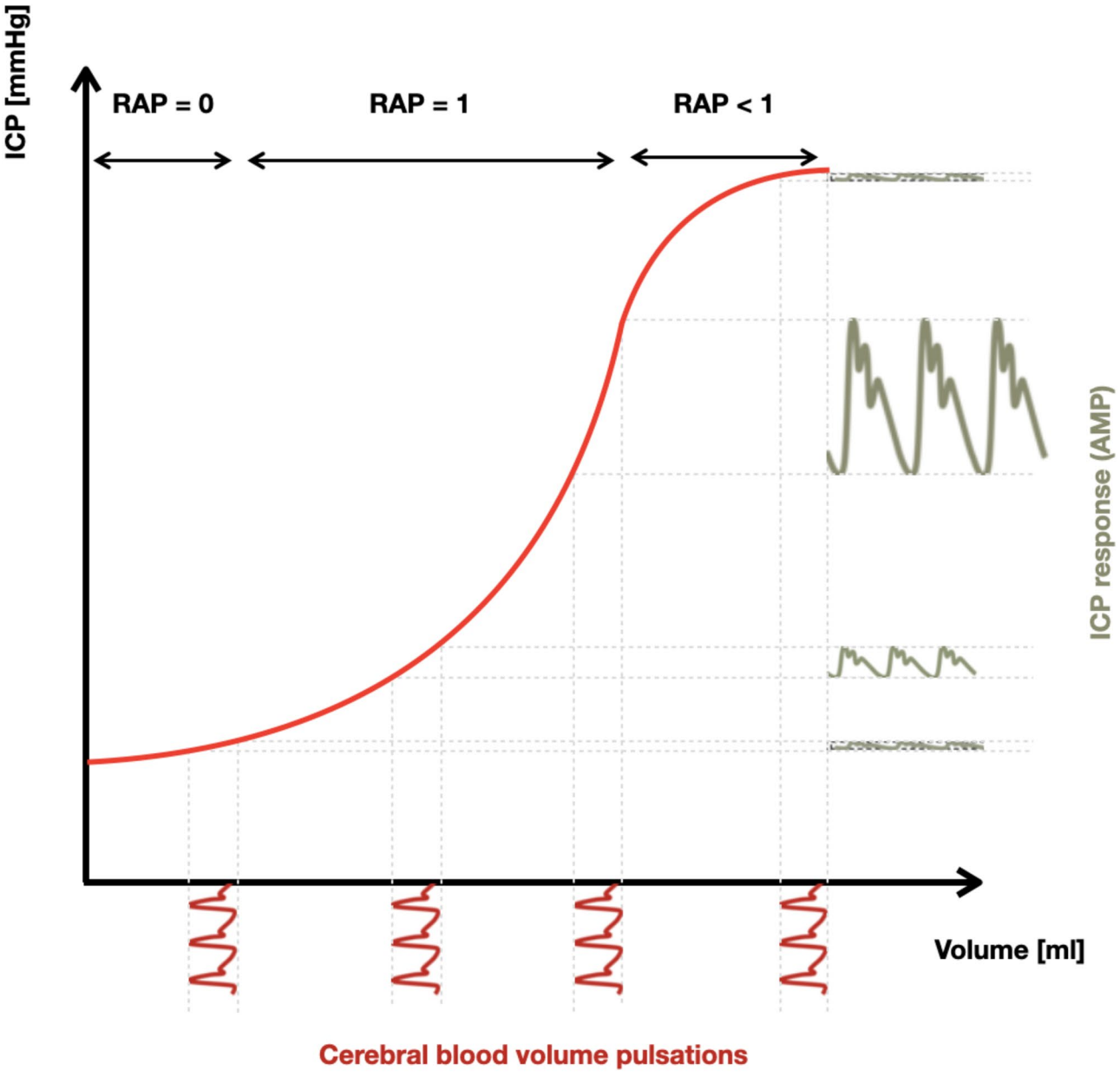

Fig. 2 Intracranial pressure-volume diagram. RAP: correlation coefficient between the change in pulse amplitude and the mean ICP value. The pulsations of CBV are shown in red, and the pulsatile response of ICP is in grey. System elastance is proportional to the dp/dV. RAP = 0 → Good Compensatory Reserve: At RAP = 0, the body has sufficient compensatory mechanisms in place, such as vasoconstriction and increased cardiac output, to maintain adequate tissue perfusion. The system is in a linear phase, meaning small changes in RAP do not lead to dramatic changes in venous return or cardiac output. RAP < 1 → Start of Depletion of Compensatory Reserve. As RAP decreases below 1 (but remains linear), the body begins to deplete its compensatory mechanisms. Although still linear, the system's reserve capacity is gradually being exhausted. Transition at RAP = 1: This appears to represent a critical point where compensatory reserve is nearly or fully exhausted. Beyond this point, small changes in RAP lead to steep declines in venous return and cardiac output, signaling the onset of physiological decompensation

IIH have emphasized the role of venous drainage in its pathophysiology [38]. Studies demonstrate that CSFp and SSp, including their amplitudes, show significant correlations both at baseline ($p = 0.001$) and during infusion ($p = 0.003$) in adult cohorts [36]. A similar trend is anticipated in pediatric populations. During drainage, this correlation persists until SSp stabilizes, while CSFp continues to decline.

A follow-up study by the same research group [13] divided the patient cohort into three subgroups: (1) definite IIH, (2) probable IIH, and (3) definite non-IIH according to Friedman's criteria [39]. The primary objective was to identify a single parameter to aid in

Table 2 The summary and characteristics of included studies

Authors and year	Number of patients	Patients' age	Study description	Conclusions
Di Rocco et al. 1977 [23]	18	1 to 10 years	LIT used to reappraise children with apparently arrested hydrocephalus, followed by monitoring of patients' health	LIT produced results that differed from those obtained by lumbar puncture (LP) and was considered more effective in selecting patients requiring treatment than angiography
Caldarelli, **Di Rocco**, **Rossi 1979** [24]	59	1 month to 15 years	Patients with suspected CSF disorders underwent diagnostic LIT to guide treatment decisions, followed by monitoring of patients' health	Limited follow-up period, but LIT helped select patients requiring shunt surgery, especially in children with suspected hydrocephalus, suspected shunt malfunction and in cerebral atrophy
Shapiro, **Marmarou**, **Shulman 1980** [25]	23 children + 7 adults	children 3 months to 14 years + adults	LIT measurements were conducted to observe age-related changes in Rout, PVI and CSF formation rate (If)	Rout and If values were similar in both children and adults, while PVI increased with age
Sklar et al. 1980 [26]	11	6 months to 9 years	Patients with previously diagnosed arrested hydrocephalus were reappraised using LIT	In 8/11 children, the LIT disagreed with traditional diagnostic tests, demonstrating its potential in this area
Di Rocco, **Caldarelli**, **Di Trapani 1981** [27]	8	> 8 years	Children with obstructive hydrocephalus due to posterior fossa cysts were all treated based on their LIT results, followed by monitoring of their health	6/8 children had pathological LIT values that improved after surgery
Blomquist, **Sundin**, **Ekstedt 1986** [28]	232 patients, 70 infusion tests	2 days to 15 years	LITs were conducted in children undergoing diagnostic processes in an effort to present physiological LIT values in "healthy" children and in specific syndromes	The study did not report patients' treatment or subsequent development, making it difficult to judge the methods' efficacy
Di Rocco et al. 1988 [29]	75	> 1 year	Patients with suspected CSF disorders underwent a diagnostic LIT to help inform further treatment, followed by monitoring of patients' health	No follow-up and often provided ambiguous results, but did differentiate between progressive and arrested hydrocephalus
M. Czosnyka et al. 1988 [30]	24	1 to 14 years	Children with suspected CSF disorders underwent LIT to aid clinical decision making, while RAP was analysed as a potentially key diagnostic parameter	LIT aided in selecting patients requiring shunt treatment and RAP appeared to be validated as a useful indicator of the cerebrospinal systems' compensatory capacity
M. Czosnyka et al. 1993 [31]	115	mean age of 3.5 years	Patients with ventricular enlargement were separated into 4 distinct cohorts based on CSFP and Rout with additional parameters analysed to help define future decision-making	LIT distinguished between arrested hydrocephalus, normal pressure hydrocephalus, obstructive hydrocephalus and acute malresorptive hydrocephalus; however, no follow-up on patients' health was reported
Lundar 1994 [32]	14	3 to 19 years	Children with suspected shunt failure underwent LIT both with a shunt clamped and open to base further treatment on, followed by monitoring of patients' health	Study reported postoperative improvement in patients, thereby supporting the use of the method in this population
Bech et al. 1999 [6]	3	> 2 years	LIT used to aid diagnostic decision-making, followed by monitoring of patients' health	Small sample size, but all 3 children improved post treatment based off LIT results
Eide et al. 2001 [33]	28	5 to 91 months	Comparison of results between invasive ICP monitoring and LIT in children with suspected hydrocephalus or craniosynostosis	The two tests yielded discrepant results, which could be explained by large time period between the two tests
Munch et al. 2007 [34]	40	2 weeks to 13 years	Comparison of results between a ventricular and lumbar infusion test in children	The expected results were not observed, raising doubts about the efficacy of the methods in children
Krishnakumar et al. 2014 [22]	15	3–15 years	The value of the LIT in children with IIH was assessed within the context of a comprehensive diagnostic procedure	The study recommended the use of a LIT over the use of LP, particularly in borderline cases
Lalou et al. 2020 [10]	31	> 16 years	31 children with pseudotumor cerebri syndrome (PTCS) underwent LITs to identify markers characteristic of the disorder	Patients with definite PTCS were reported to have increased CSFP, amplitude, SSP and elasticity, with SSP and elasticity potentially serving as key markers in equivocal cases

Table 3 The summary of individual patient data from the the study by Lalou et al. [13] evaluating the diagnosis and treatment outcomes in a probable IIH cohort, including data on functional testing and parameters that assist in clinical decision-making

	Definite IIH	Probable IIH	Non-IIH	*p*-value (IIH vs. probable IIH)	*p*-value (IIH vs. non-IIH)
CSFp [mmHg]	29.18 ± 7.72	15.31 ± 3.47	17.51 ± 5.87	< 0.001	0.014
AMP [mmHg]	2.18 ± 2.06	0.68 ± 0.37	0.89 ± 1.03	0.014	0.143
RAP	0.58 ± 0.3	0.46 ± 0.18	0.37 ± 0.12	0.281	0.208
Elasticity [1/ml]	0.36 ± 0.19	0.39 ± 0.26	0.15 ± 0.06	0.951	0.003
SSp [mmHg]	18.99 ± 4.08	9.55 ± 11.9	8.65 ± 1.17	0.001	0.008
CSFpp [mmHg]	32.89 ± 2.92	25.42 ± 4.47	25.25 ± 6.1	< 0.001	0.040

differentiating between these groups. In the definite IIH group, CSFp, AMP, SSp, elasticity, and RAP were all elevated, with statistically significant differences between the definite and probable IIH groups (see Table 3 for details). In the definite non-IIH group, these parameters remained within physiological ranges. In the probable IIH group, only elasticity was elevated, while other parameters stayed within normal limits.

Of note is that there needs to be higher attention when interpreting *Rout*; venous sinus pressure can potentially rise in parallel with CSF pressure resulting in *Rout* overestimation. Implications of coupling between CSFp and SSp for the calculation of CSF outflow resistance are of great importance. Davson's equation, which refers to the steady state and assumes that SSp is independent of CSFp [40], is relevant in this context:

$$CSFp = Rout \times If + SSp$$

where If is the CSF formation rate derived from [40] which can be further evaluated by expressing SSp as a function of CSFp (SSp = a × CSFp + b):

$$CSFp = Rout \times If + a \times CSFp + b$$

$$CSFp = \frac{(Rout \times If + b)}{(1 - a)}$$

Davson's equation is based on the premise that modifying *Rout* according to its formulation provides a more precise estimation, with an average value of < 7 mmHg/min/mL [41]. In individuals with IIH, CSFp at plateau is typically only slightly elevated relative to baseline, closely mimicking normal CSF circulation, unlike in patients with hydrocephalus. In rare cases where a higher-than-expected CSF plateau is observed, understanding the role of SSp can provide crucial insights for differential diagnosis.

Malm et al. [42] demonstrated that there may be two groups of IIH patients using a constant pressure infusion technique—one group with genuinely reduced conductance (increased *Rout*) and a second group with increased SSp as the cause of their impaired CSF absorption. They also showed that changes in CSF conductance occur over time after the onset of IIH. These interpretations, however, do not account for the spatially distributed nature of CSF absorption. In most cases, CSF absorption is predominantly intracranial, and the pressure gradient between the sagittal sinus and jugular foramen is minimal, justifying the use of a single SSp value. In IIH, however, there may be two distinct CSF absorption pressure gradients—one above and one below the site of sinus stenosis. This would necessitate the application of two separate Davson's equations: one to describe CSF absorption upstream of the stenosis and another for downstream absorption [41].

Davson's equation assumes that all infused CSF is absorbed through a single pathway that can be characterized by a single parameter. However, when CSF absorption is divided between upstream and downstream channels, the equation becomes inadequate, as the relative proportion of CSF absorbed by each pathway is unknown. The pressure in the transverse sinus or jugular venous pressure below the stenosis is significantly lower than the SSp measured above the stenosis. Recent research by Lublinsky et al. [43] has shown the presence of arachnoid granulations in the transverse sinuses in both healthy individuals and patients with IIH, further complicating the pressure dynamics in these regions. The scenario becomes even more intricate when the stenosis is reversible upon CSF removal and behaves like a Starling resistor [44]. In such cases, if a segment of the transverse sinus is compressible, any increase in CSFp may lead to a reduction in the sinus lumen, thereby elevating the hydrodynamic resistance to blood flow in the sinus. This elevation of resistance consequently raises SSp, assuming cerebral blood flow remains constant, which further escalates CSFp. This feedback loop functions as a 'vicious cycle,' driving both CSFp and SSp to reach a new, elevated equilibrium. This phenomenon has been previously simulated numerically with an advanced mathematical model, which predicted that a system featuring a collapsible transverse sinus, modeled as a Starling resistor, could exhibit two distinct steady states: one at low CSFp and the other at high CSFp.

As previously noted in reference [41], the model's predictive value diminishes in the absence of precise estimates for SSp and CSF production rates, and its

oversimplified linear relationship does not account for the multifactorial nature of ICP regulation. Emerging evidence increasingly supports the contribution of alternative CSF clearance mechanisms, notably the glymphatic system and meningeal lymphatic pathways, which offer parallel routes for interstitial and cerebrospinal fluid exchange and resorption. Studies such as those by Eide et al. (2021) [45] and Proulx (2021) [46] suggest that these pathways are especially relevant in conditions involving altered CSF homeostasis, including IIH, where impaired glymphatic clearance or lymphatic dysfunction may contribute to elevated ICP independent of classic Rout measurements. Therefore, while Davson's equation remains a useful theoretical model, its application should be contextualized within a broader, more integrated understanding of craniospinal fluid dynamics. Future studies incorporating advanced imaging and biomarker assessments of glymphatic and lymphatic function may help refine diagnostic and therapeutic approaches beyond the traditional resorptive paradigm.

The possible answer to the problem of IIH lies in disrupting the pathophysiological coupling between ICP and SSp. Such an approach could offer a novel therapeutic avenue for managing IIH, potentially improving patient outcomes by addressing the underlying pressure dynamics that contribute to the condition's progression.

Hydrocephalus

Several studies examining the use of the LIT in hydrocephalus cases have determined it to be an efficacious diagnostic tool primarily regarding the need for shunt placement in pediatric patients (Table 2) [6, 23, 24, 26, 27, 29, 33]. Moreover, there has been a trend toward using LIT for differentiation between individual hydrocephalus subgroups based on various underlying CSF dynamic mechanisms. In a study conducted by Czosnyka et al. [31], LIT was administered to 115 individuals with ventriculomegaly, who were then divided into four categories based primarily on CSFp, *Rout*, PVI, cerebrospinal compliance, pulse wave amplitude, and *Pp*. The outcomes of this study demonstrated that LIT is effective in differentiating between cerebral atrophy, non-communicating hydrocephalus, acute malresorptive hydrocephalus and NPH. Significant disparities were identified among the parameters characterizing compensatory capacity within these cohorts. Subjects with cerebral atrophy did not exhibit a noticeable deficit in compensatory reserve. The sole pathological manifestation was ventricular enlargement. This group exhibited the highest cerebrospinal compliance, whereas patients with acute hydrocephalus displayed the lowest cerebrospinal compliance.

The clinical presentation across the studied groups was relatively uniform, illustrating that the precise differentiation of arrested hydrocephalus in patients showing varying states of cerebrospinal compensation cannot be accomplished without pressure-volume assessment. The study's findings reveal that, in addition to CSFp and CSF outflow resistance as referred to RCSF, other cerebrospinal compensatory variables can elucidate differences among hydrocephalus types. This was later corroborated by multiple studies that emphasized the necessity of not solely depending on LIT for clinical decision-making, especially in scenarios with borderline ICP and *Rout* values, where the test did not yield conclusive results [13, 22, 29]. These findings thus indicate that the primary strength of the LIT in patients with hydrocephalus lies in identifying patients who would most likely benefit from a shunt or alternative CSF diversion procedure, rather than for differentiation of individual hydrocephalus subgroups.

The findings discussed above highlight the essential role of the LIT in confirming shunt dysfunction extending beyond hydrocephalus patients to include those with IIH. LIT is instrumental in distinguishing between functional shunts and those experiencing complete or partial failure, such as underdrainage, overdrainage, or obstruction [32]. It also aids in adjusting programmable shunt valves, optimizing shunt revision procedures, and proving cost-effective by reducing unnecessary hospital admissions and surgical interventions. Objective evaluation of implanted shunts through infusion studies is a well-established technique, grounded in both in vitro and in vivo analyses of the hydrodynamic properties of various commercially available shunts, particularly their critical pressure and resistance parameters. Recent validation of this methodology, in correlation with clinical outcomes and intraoperative findings during shunt revision, has been conducted in a large pediatric cohort across two European centers [17]. The negative predictive value of LIT referring to the accuracy with which a shunt infusion test can exclude a shunt obstruction has been reported as high as 95% in a recent study in mixed pediatric and adult cohorts with hydrocephalus [11]. This underscores the clinical utility of infusion testing in assessing shunt functionality and guiding surgical interventions. Avoiding unwarranted shunt revisions not only enhances patient outcomes but also delivers significant financial benefits to healthcare systems.

LIT alternatives and ICP measurements

One of the seminal studies in this domain was conducted by Eide et al. in 2001 [33], which compared LIT with continuous ICP monitoring in 28 children, aged between 5 and 91 months (mean age 21.5 months). The study found no significant correlation between opening pressure and mean ICP during sleep, with a mean difference of 2.7 mmHg. Furthermore, there was no significant correlation between *Rout* and mean ICP during sleep, nor between

Rout and elevated ICP (greater than 20 mmHg for at least 5 min) during sleep. The study concluded that both *Po* and *Rout* are unreliable predictors of ICP increase in children, highlighting the need for the establishment of pathological thresholds for both ICP and *Rout* in pediatric populations. However, a limitation of this research was the considerable time interval between tests, with 10 patients undergoing testing more than a month apart.

These findings were further explored in a study by Borgensen and Gjerris [47], which involved 230 patients with a mean age of 53 years. In contrast to Eide et al.'s results, Borgensen and Gjerris demonstrated a correlation between *Rout* and continuous ICP monitoring. This suggests that *Rout* may have a more relevant association with ICP in older pediatric patients, while LIT may still offer valuable insights into cerebrospinal fluid dynamics.

Furthermore, there is a question of whether the coupling of CSFp and SSp also applies to other intracranial pathologies, including acute intracranial hypertension, such as those associated with brain edema due to traumatic brain injury, stroke, or meningitis [48]. Preliminary evidence from earlier research suggests that up to 70% of ICP may be attributable to vascular mechanisms rather than CSF [33, 49].

LIT setting and future directions

Further research is crucial to elucidate how LIT parameters reflect the unique intracranial dynamics across different CSF disorders. The primary goal should be the individualization of LIT protocols tailored to each condition, reducing the likelihood of false-negative and false-positive outcomes and improving diagnostic precision.

While traditional interpretations of the LIT have focused on static parameters such as Rout and pressure amplitude, there is increasing recognition that analyzing the full dynamics of the LIT curve could offer deeper clinical value. Advanced computational approaches, including artificial intelligence (AI), machine learning (ML), and deep learning, enable more sophisticated, time-series-based assessments of these curves. Our previous work has shown that ML models can improve the accuracy of predicting shunt responsiveness by identifying complex, multivariate patterns that are not evident through conventional analysis [50]. Crucially, these models can provide feature importance rankings, highlighting which variables—such as CSF pressures, Rout, cranial compliance, age, or imaging findings—are most influential in determining patient outcomes. This not only aids clinical interpretation but also informs future research directions by pinpointing the most critical physiological markers.

One of important aspects of LIT settings is supported by findings reported by Eide et al. who provide important insights into the dynamic nature of CSF homeostasis and its modulation by physiological states, particularly sleep. Their work demonstrates that ICP exhibits state-dependent variability and that glymphatic activity—responsible for clearance of interstitial solutes—increases significantly during sleep, contributing to fluctuations in CSF dynamics not captured by short-duration tests such as the LIT. This is a critical consideration when interpreting LIT results, as the test is typically performed in awake patients over a brief time frame, without accounting for sleep-related changes in CSF flow and clearance. These observations emphasize that CSFp and *Rout*, as measured by LIT, represent only a subset of the broader, more complex regulation of intracranial dynamics. Incorporating this understanding into clinical interpretation may help refine the role of LIT in diagnosing disorders like IIH, where glymphatic or lymphatic dysfunction may contribute to pathophysiology beyond conventional resorptive pathways. Unfortunately, similar research in this area is lacking in pediatric population.

To translate these innovations into everyday clinical practice, ML tools must be developed with transparency and ease of integration in mind. Embedding predictive models within electronic health records or LIT analysis software could provide clinicians with real-time, individualized risk assessments and treatment recommendations, enhancing clinical decision-making without replacing physician judgment. For instance, after a LIT, an AI-powered system could automatically evaluate the infusion curve alongside patient-specific data and generate a probability score for shunt responsiveness, accompanied by a breakdown of the top contributing features. Such decision-support systems would make LIT interpretation more consistent, personalized, and data-driven, ultimately improving diagnostic precision and patient outcomes in pediatric hydrocephalus care.

A key challenge remains the scarcity of comprehensive, large-scale studies that explore these complex mechanisms, particularly considering the need to adapt LIT protocols to specific age groups, as intracranial dynamics evolve with age. Identifying normative physiological values of Rout, baseline CSFp and plateau CSFp across different age groups is essential. Additionally, characterizing the pressure-volume index and RAP relationships in these cohorts would greatly increase the accuracy of LIT. Given that the skull is not a completely rigid structure in very young children, these curves may not only shift along the x-axis but could exhibit fundamentally different characteristics compared to those observed in adult patients.

A promising approach would involve a multicenter strategy, promoting interdisciplinary collaboration among clinicians, neurologists, and biomedical engineers to integrate biological insights with physical principles

for optimizing diagnostic techniques. Some of the following could be used to tailor this collaboration:

1. **Age-Stratified Data Collection:** Initiate multicenter, longitudinal studies that stratify pediatric populations by developmental stage (e.g., neonates, infants, toddlers, school-age children, and adolescents). These studies should aim to define age-specific normative values for key parameters such as resistance to *Rout*, baseline CSFp, and plateau CSFp.
2. **Dynamic Modeling of Intracranial Compliance:** Given that the cranial structure in infants and very young children is not fully ossified, it is crucial to analyze how their PVI and RAP differ from those in older children and adults. This may involve creating distinct pressure-volume response models for each developmental stage to account for varying compliance and elasticity of the cranial vault.
3. **Customized Infusion Protocols:** Develop tailored infusion protocols with adjusted infusion rates based on patient age and skull rigidity. Infants may require lower infusion rates and extended monitoring times due to their more compliant cranial structures and slower equilibration of pressures.
4. **Sedation Guidelines:** Establish age-appropriate sedation protocols in collaboration with pediatric anesthesiologists to ensure patient safety and reduce variability in test outcomes. Sedation agents and dosages should be standardized for each age group to minimize their effect on intracranial pressure.
5. **Measurement and Monitoring Standardization:** Define uniform measurement techniques and thresholds for interpreting LIT results in each age group. This includes standardizing the duration of monitoring post-infusion and specifying acceptable ranges for physiological parameters.
6. **Interdisciplinary Collaboration and Logitudinal Study Establishment:** Form interdisciplinary teams of pediatric neurologists, neurosurgeons, radiologists, and biomedical engineers to translate developmental physiology into optimized test protocols. Integration of computational modeling and non-invasive imaging may also enhance interpretation and safety.

Conclusion

The pathophysiological mechanisms of the two most frequently cited conditions in pediatric populations—hydrocephalus and IIH—are fundamentally distinct and should be evaluated separately. In the case of IIH, the dynamic interaction between CSFp and SSp may hold substantial diagnostic value and could represent a novel approach to its assessment. However, caution should be exercised when interpreting *Rout* in IIH, as there is a tendency for its overestimation. The LIT has been validated as a reliable tool, particularly for predicting shunt responsiveness and identifying shunt malfunctions in both IIH and hydrocephalus. Future studies should more rigorously evaluate the efficacy of LIT, with particular emphasis on standardizing its use as part of the diagnostic assessment for CSF disorders in children in various age categories. Standardization will improve the reliability and comparability of results, enhancing its role in clinical decision-making. AI models could enhance the predictive accuracy of shunt responsiveness by analyzing the full dynamics of the LIT curve and identifying key contributing features through feature importance rankings. Incorporating extrapolated measures such as SSSp can further refine interpretation by offering insight into cerebral venous outflow, despite not being directly measurable. Finally, fostering interdisciplinary collaboration between clinicians, neurologists, and biomedical engineers to integrate both biological insights and physical principles is of great importance to optimize diagnostic methods.

Supplementary Information

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Supplementary Material 1

Author contributions

All authors contributed to the study's conception and design. Material preparation, data collection and analysis were performed by Vojtěch Novák, Adéla Bubeníková, Petr Skalický. The first draft of the manuscript was written by Vojtěch Novák and Adéla Bubeníková and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Human ethics and consent to participate

Not applicable.

Consent to participate

Not applicable since no human participants were involved.

Competing interests

The authors declare no competing interests.

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References

1. Bothwell SW, Janigro D, Patabendige A. Cerebrospinal fluid dynamics and intracranial pressure elevation in neurological diseases. Fluids Barriers CNS. 2019;16:9. https://doi.org/10.1186/s12987-019-0129-6.
2. Wilson MH. Monro-Kellie 2.0: the dynamic vascular and venous pathophysiological components of intracranial pressure. J Cereb Blood Flow Metab. 2016;36:1338–50. https://doi.org/10.1177/0271678x16648711
3. Atchley TJ, Vukic B, Vukic M, Walters BC. Review of cerebrospinal fluid physiology and dynamics: A call for medical education reform. Neurosurgery. 2022;91:1–7. https://doi.org/10.1227/neu.0000000000002000.
4. Katzman R, Hussey F. A simple constant-infusion manometric test for measurement of CSF absorption. I. Rationale and method. Neurology. 1970;20:534–44. https://doi.org/10.1212/wnl.20.6.534.
5. Hasselbalch SG, Carlsen JF, Alaouie MM, Munch TN, Holst AV, Taudorf S, Rørvig-Løppentien C, Juhler M, Waldemar G. Prediction of shunt response in idiopathic normal pressure hydrocephalus by combined lumbar infusion test and preoperative imaging scoring. Eur J Neurol. 2023;30:3047–55. https://doi.org/10.1111/ene.15981.
6. Bech-Azeddine R, Gjerris F, Waldemar G, Czosnyka M, Juhler M. Intraventricular or lumbar infusion test in adult communicating hydrocephalus? Practical consequences and clinical outcome of shunt operation. Acta Neurochir (Wien). 2005;147:1027–35. https://doi.org/10.1007/s00701-005-0589-0. discussion 1035– 1026.
7. Skalicky P, Mladek A, Bubenikova A, Vlasak A, Whitley H, Bradac O. Lumbar infusion test. In: Bradac O, editor. Normal pressure hydrocephalus: pathophysiology, diagnosis, treatment and outcome. Volume 1, 1 ed. Springer Cham; 2023. https://doi.org/10.1007/978-3-031-36522-5.
8. Jannelli G, Calvanese F, Pirina A, Gergelé L, Vallet A, Palandri G, Czosnyka M, Czosnyka Z, Manet R. Assessment of CSF dynamics using infusion study: tips and tricks. World Neurosurg. 2024;189:33–41. https://doi.org/10.1016/j.wneu.2024.05.131.
9. Skalický P, Mládek A, Vlasák A, De Lacy P, Beneš V, Bradáč O. Normal pressure hydrocephalus-an overview of pathophysiological mechanisms and diagnostic procedures. Neurosurg Rev. 2020;43:1451–64. https://doi.org/10.1007/s10143-019-01201-5.
10. Lalou AD, Levrini V, Czosnyka M, Gergelé L, Garnett M, Kolias A, Hutchinson PJ, Czosnyka Z. Cerebrospinal fluid dynamics in non-acute post-traumatic ventriculomegaly. Fluids Barriers CNS. 2020;17:24. https://doi.org/10.1186/s12987-020-00184-6.
11. Lalou AD, Czosnyka M, Garnett MR, Nabbanja E, Petrella G, Hutchinson PJ, Pickard JD, Czosnyka Z. Shunt infusion studies: impact on patient outcome, including health economics. Acta Neurochir (Wien). 2020;162:1019–31. https://doi.org/10.1007/s00701-020-04212-0.
12. Häni L, Fung C, Jesse CM, Ulrich CT, Miesbach T, Cipriani DR, Dobrocky T, Z'Graggen WJ, Raabe A, Piechowiak EI, et al. Insights into the natural history of spontaneous intracranial hypotension from infusion testing. Neurology. 2020;95:e247–55. https://doi.org/10.1212/wnl.0000000000009812.
13. Lalou AD, McTaggart JS, Czosnyka ZH, Garnett MR, Krishnakumar D, Czosnyka M. Cerebrospinal fluid dynamics in pediatric pseudotumor cerebri syndrome. Childs Nerv Syst. 2020;36:73–86. https://doi.org/10.1007/s00381-019-04263-4.
14. Stroh JN, Albers DJ, Bennett TD. Personalization and pragmatism: pediatric intracranial pressure and cerebral perfusion pressure treatment thresholds. Pediatr Crit Care Med. 2021;22:213–6. https://doi.org/10.1097/pcc.0000000000002637.
15. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71. https://doi.org/10.1136/bmj.n71.
16. Wells G, Shea B, O'Connell D, Peterson j, Welch V, Losos M, Tugwell P. The Newcastle–Ottawa Scale (NOS) for Assessing the Quality of Non-Randomized Studies in Meta-Analysis. 2000.
17. Zhang C, Long SY, You WD, Xu XX, Gao GY, Yang XF. The value of the correlation coefficient between the ICP wave amplitude and the mean ICP level (RAP) combined with the resistance to CSF outflow (Rout) for early prediction of the outcome before shunting in posttraumatic hydrocephalus. Front Neurol. 2022;13:881568. https://doi.org/10.3389/fneur.2022.881568.
18. Kim DJ, Kim H, Kim YT, Yoon BC, Czosnyka Z, Park KW, Czosnyka M. Thresholds of resistance to CSF outflow in predicting shunt responsiveness. Neurol Res. 2015;37:332–40. https://doi.org/10.1179/1743132814y.0000000454.
19. Dias SF, Lalou AD, Spang R, Haas-Lude K, Garnett M, Fernandez H, Czosnyka M, Schuhmann MU, Czosnyka Z. Value of computerized shunt infusion study in assessment of pediatric hydrocephalus shunt function-a two center cross-sectional study. Childs Nerv Syst. 2020;36:59–71. https://doi.org/10.1007/s00381-019-04264-3.
20. Svedung Wettervik T, Howells T, Enblad P, Lewén A. Intracranial pressure variability: relation to clinical outcome, intracranial pressure-volume index, cerebrovascular reactivity and blood pressure variability. J Clin Monit Comput. 2020;34:733–41. https://doi.org/10.1007/s10877-019-00387-9.
21. Hall A, O'Kane R. The best marker for guiding the clinical management of patients with Raised intracranial pressure-the RAP index or the mean pulse amplitude? Acta Neurochir (Wien). 2016;158:1997–2009. https://doi.org/10.1007/s00701-016-2932-z.
22. Krishnakumar D, Pickard JD, Czosnyka Z, Allen L, Parker A. Idiopathic intracranial hypertension in childhood: pitfalls in diagnosis. Dev Med Child Neurol. 2014;56:749–55. https://doi.org/10.1111/dmcn.12475.
23. Di Rocco C, Caldarelli M, Maira G, Rossi GF. The study of cerebrospinal fluid dynamics in apparently 'arrested' hydrocephalus in children. Childs Brain. 1977;3:359–74. https://doi.org/10.1159/000119687.
24. Caldarelli M, Di Rocco C, Rossi GF. Lumbar subarachnoid infusion test in paediatric neurosurgery. Dev Med Child Neurol. 1979;21:71–82. https://doi.org/10.1111/j.1469-8749.1979.tb01582.x.
25. Shapiro K, Marmarou A, Shulman K. Characterization of clinical CSF dynamics and neural axis compliance using the pressure-volume index: I. The normal pressure-volume index. Ann Neurol. 1980;7:508–14. https://doi.org/10.1002/ana.410070603.
26. Sklar FH, Beyer CW Jr, Ramanathan M, Clark WK. Servo-controlled lumbar infusions in children. A quantitative approach to the problem of arrested hydrocephalus. J Neurosurg. 1980;52:87–98. https://doi.org/10.3171/jns.1980.52.1.0087.
27. di Rocco C, Caldarelli M, di Trapani G. Infratentorial arachnoid cysts in children. Childs Brain. 1981;8:119–33. https://doi.org/10.1159/000119973.
28. Blomquist HK, Sundin S, Ekstedt J. Cerebrospinal fluid hydrodynamic studies in children. J Neurol Neurosurg Psychiatry. 1986;49:536–48. https://doi.org/10.1136/jnnp.49.5.536.
29. Di Rocco C, Caldarelli M, Mangiola A, Milani A. The lumbar subarachnoid infusion test in infants. Childs Nerv Syst. 1988;4:16–21. https://doi.org/10.1007/BF00274075.
30. Czosnyka M, Wollk-Laniewski P, Batorski L, Zaworski W. Analysis of intracranial pressure waveform during infusion test. Acta Neurochir (Wien). 1988;93:140–5. https://doi.org/10.1007/BF01402897.
31. Czosnyka M, Batorski L, Roszkowski M, Tomaszewski J, Wocjan J, Walencik A, Zabolotny W. Cerebrospinal compensation in hydrocephalic children. Childs Nerv Syst. 1993;9:17–22. https://doi.org/10.1007/bf00301929.
32. Lundar T. Shunt removal or replacement based on intraventricular infusion tests. Childs Nerv Syst. 1994;10:337–9. https://doi.org/10.1007/BF00335174.
33. Eide PK, Due-Tønnessen B, Helseth E, Lundar T. Assessment of intracranial pressure volume relationships in childhood: the lumbar infusion test versus intracranial pressure monitoring. Childs Nerv Syst. 2001;17:382–90. https://doi.org/10.1007/s003810000437.
34. Munch TN, Bech-Azeddine R, Boegeskov L, Gjerris F, Juhler M. Evaluation of the lumbar and ventricular infusion test in the diagnostic strategy of pediatric hydrocephalus and the therapeutic implications. Childs Nerv Syst. 2007;23:67–71. https://doi.org/10.1007/s00381-006-0186-4.
35. Gaier ED, Heidary G. Pediatric idiopathic intracranial hypertension. Semin Neurol. 2019;39:704–10. https://doi.org/10.1055/s-0039-1698743.
36. Lalou AD, Czosnyka M, Czosnyka ZH, Krishnakumar D, Pickard JD, Higgins NJ. Coupling of CSF and sagittal sinus pressure in adult patients with pseudotumour cerebri. Acta Neurochir (Wien). 2020;162:1001–9. https://doi.org/10.1007/s00701-019-04095-w.
37. Amin S, Monaghan M, Forrest K, Harijan P, Mehta V, Moran M, Mukhtyar B, Muthusamy B, Parker A, Prabhakar P, et al. Consensus recommendations for the assessment and management of idiopathic intracranial hypertension in children and young people. Arch Dis Child. 2024;109:654. https://doi.org/10.1136/archdischild-2023-326545.
38. Zhao K, Gu W, Liu C, Kong D, Zheng C, Chen W, Li X, Liang Y, Zhou H. Advances in the Understanding of the complex role of venous sinus stenosis in idiopathic intracranial hypertension. J Magn Reson Imaging. 2022;56:645–54. https://doi.org/10.1002/jmri.28177.
39. Friedman DI, Jacobson DM. Diagnostic criteria for idiopathic intracranial hypertension. Neurology. 2002;59:1492–5. https://doi.org/10.1212/01.wnl.0000029570.69134.1b.
40. Davson H, Domer FR, Hollingsworth JR. The mechanism of drainage of the cerebrospinal fluid. Brain. 1973;96:329–36. https://doi.org/10.1093/brain/96.2.329.

41. Lalou AD, Levrini V, Garnett M, Nabbanja E, Kim DJ, Gergele L, Bjornson A, Czosnyka Z, Czosnyka M. Validation of Davson's equation in patients suffering from idiopathic normal pressure hydrocephalus. Acta Neurochir (Wien). 2018;160:1097–103. https://doi.org/10.1007/s00701-018-3497-9.
42. Malm J, Kristensen B, Markgren P, Ekstedt J. CSF hydrodynamics in idiopathic intracranial hypertension: a long-term study. Neurology. 1992;42:851–8. https://doi.org/10.1212/wnl.42.4.851.
43. Lublinsky S, Kesler A, Friedman A, Horev A, Shelef I. Quantifying response to intracranial pressure normalization in idiopathic intracranial hypertension via dynamic neuroimaging. J Magn Reson Imaging. 2018;47:913–27. https://doi.org/10.1002/jmri.25857.
44. Piechnik SK, Czosnyka M, Richards HK, Whitfield PC, Pickard JD. Cerebral venous blood outflow: a theoretical model based on laboratory simulation. Neurosurgery. 2001;49:1214–22. https://doi.org/10.1097/00006123-200111000-00034.
45. Eide PK, Pripp AH, Ringstad G, Valnes LM. Impaired glymphatic function in idiopathic intracranial hypertension. Brain Commun. 2021;3(2):fcab043. https://doi.org/10.1093/braincomms/fcab043.
46. Proulx ST. Cerebrospinal fluid outflow: a review of the historical and contemporary evidence for arachnoid Villi, perineural routes, and dural lymphatics. Cell Mol Life Sci. 2021;78(6):2429–57. https://doi.org/10.1007/s00018-020-03706-5.
47. Børgesen SE, Gjerris F. The predictive value of conductance to outflow of CSF in normal pressure hydrocephalus. Brain. 1982;105:65–86. https://doi.org/10.1093/brain/105.1.65.
48. Marmarou A, Foda MA, Bandoh K, Yoshihara M, Yamamoto T, Tsuji O, Zasler N, Ward JD, Young HF. Posttraumatic ventriculomegaly: hydrocephalus or atrophy? A new approach for diagnosis using CSF dynamics. J Neurosurg. 1996;85:1026–35. https://doi.org/10.3171/jns.1996.85.6.1026.
49. Israelsson H, Carlberg B, Wikkelsö C, Laurell K, Kahlon B, Leijon G, Eklund A, Malm J. Vascular risk factors in INPH: A prospective case-control study (the INPH-CRasH study). Neurology. 2017;88:577–85. https://doi.org/10.1212/wnl.0000000000003583.
50. Mládek A, Gerla V, Skalický P, Vlasák A, Zazay A, Lhotská L, Beneš V, Sr., Beneš V Jr., Bradáč O. Prediction of shunt responsiveness in suspected patients with normal pressure hydrocephalus using the lumbar infusion test: A machine learning approach. Neurosurgery. 2022;90:407–18. https://doi.org/10.1227/neu.0000000000001838.

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