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RESEARCH

A novel prognostic role of proton MR spectroscopy in shunted idiopathic normal pressure hydrocephalus

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Abstract

Objective To assess the prognostic potential of preoperative proton MRS in predicting postoperative outcomes for patients with INPH undergoing VPS.

Methods Preoperative MRS data were obtained and analyzed from 15 patients with INPH who underwent VPS. The concentrations of key metabolites—Cho, Cr, NAA, and Lac—were quantified in the Tha, BG, PV, and MF regions. Metabolite ratios were calculated, and clinical response to shunting was assessed using the Hellström INPH scale. Prognostic accuracy was determined via ROC analysis.

Results • *Cho:* Elevated levels in the left MF region were associated with favorable neuropsychological outcomes. Conversely, lower levels in the left Tha correlated with improved gait, cognitive, continence, and overall outcomes. • *Cr:* Decreased levels in the right Tha and BG were predictive of improved continence. • *NAA*: Higher levels in the right MF region and lower levels in bilateral frontal PV areas were linked to better neuropsychological response. • *Lac*: Elevated levels in the left BG were associated with improved balance. Threshold values predictive of a favorable total shunt response included left and average Tha Cho ≤ 6 and ≤ 5.4, respectively, and average Tha and BG NAA ≤ 9 and ≤ 7.35, respectively.

Conclusion Proton MRS demonstrates promising utility as a non-invasive tool for predicting postoperative outcomes in INPH patients. In particular, regional levels of Cho, Cr, and NAA provide critical insights for optimizing patient selection and surgical planning. These findings could also deepen our understanding of the intricate pathophysiological mechanisms underlying INPH.

Keywords Idiopathic normal pressure hydrocephalus (INPH) · Proton magnetic resonance spectroscopy (MRS) · Ventriculoperitoneal shunt (VPS) · Choline · Creatine · N-acetylaspartate · Lactate

Abbreviations

%	Percentage
AUC	Area Under the Curve
Avg.	Average
BG	Basal Ganglia
Cho	Choline
CI	Confidence interval
Cr	Creatine
CSF	Cerebrospinal fluid
INPH	Idiopathic Normal Pressure Hydrocephalus
Lac	Lactate
MF	Medial Frontal
MR	Magnetic Resonance
MRI	Magnetic Resonanca Imaging
MRS	Magnetic Resonance Spectroscopy

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n	Number
NAA	N-asetylaspartate
NPV	Negative Predictive Value
p-value	Probability Value
PPV	Positive Predictive Value
PV	Periventricular
ROC	Receiver operating characteristic
SD	Standart Deviation
Sen	Sensitivity
Spe	Specificity
SPSS	Statistical Package for the Social Sciences
Tha	Thalamus
VPS	Ventriculoperitoneal Shunt

Introduction

Background

INPH is a neurodegenerative disorder characterized by radiologically evident ventriculomegaly and a classic clinical triad comprising gait ataxia, cognitive impairment (dementia), and bladder dysfunction. Diagnosis is often difficult, and definitive diagnosis is possible with partial or complete resolution of symptoms after VPS surgery. However, the modest and highly variable clinical response to VPS (30–80%) and the current inability to accurately predict prognosis for optimal patient selection present significant challenges for clinicians [1–3].

While characteristic features of INPH are well-described, its precise pathophysiology remains incompletely understood. Mechanisms such as disorders in CSF dynamics, ischemia in the brain parenchyma, and neuronal damage are emphasized. These complex pathological processes increase the need for noninvasive or minimally invasive diagnostic and prognostic tools. MRS is a radiological technique that can noninvasively evaluate neuronal and metabolic changes and is increasingly being used in neurodegenerative diseases [4–6].

Although INPH has long been regarded as a mechanical disorder of CSF circulation, accumulating evidence indicates that its pathophysiology also encompasses neurodegenerative mechanisms, including PV axonal injury, chronic ischemia, and metabolic dysregulation. These changes are thought to contribute to the clinical triad of gait disturbance, cognitive decline, and urinary incontinence. Proton MRS allows for the non-invasive evaluation of brain metabolism by quantifying neurochemical markers such as NAA, Cho, Cr, and Lac, which reflect neuronal viability, membrane turnover, and energy metabolism. The detection of metabolic alterations in these metabolites offers valuable insight into the underlying cerebral dysfunction in INPH. Therefore, the use of MRS is justified not only for investigating disease mechanisms but also for exploring its potential prognostic value in predicting response to shunt surgery [7–9].

Objectives

The aim of this study was to evaluate the potential of preoperative MRS parameters in predicting surgical prognosis in patients undergoing VPS due to INPH. Using a systematic approach, we investigated (1) region-specific MRS metabolite patterns in relation to comprehensive clinical outcomes (overall and domain-specific: gait, neuropsychology, balance, continence), and (2) their potential as prognostic predictor of surgical response.

Materials and methods

Study design

This prospective observational study enrolled 15 patients diagnosed with INPH who underwent VPS placement. Preoperative proton MRS was performed to quantify metabolite concentrations (Cho, Cr, NAA, and Lac) in four predefined brain regions: Tha, BG, PV white matter, and MF cortex. The rationale for selecting these regions was based on prior studies, as also discussed in the Discussion section, which—despite being limited in number—have consistently focused on these areas due to their known involvement in the pathophysiology of INPH. These regions are closely associated with the key clinical manifestations of INPH, such as gait disturbance, cognitive dysfunction, and urinary incontinence, likely due to their proximity to the lateral ventricles and vulnerability to PV metabolic disruption. Metabolite ratios were calculated, and clinical outcomes were assessed postoperatively using the standardized Hellström INPH scale. ROC curve analysis was employed to determine prognostic thresholds for metabolite levels predictive of shunt responsiveness.

Patient selection and study cohort

This prospective cohort study initially screened 44 adult patients who underwent shunt surgery for suspected INPH at our single-center institution. The diagnosis of INPH was based on international guidelines proposed by the INPH Consensus Group and the Japanese Society of Normal Pressure Hydrocephalus [10]. Inclusion criteria

were: age ≥ 60 years, presence of at least one clinical triad symptom (gait disturbance, cognitive impairment, and/or urinary incontinence), ventriculomegaly defined by an Evans index > 0.3 on brain MRI, and normal cerebrospinal fluid opening pressure (≤ 200 mmH2O) on lumbar puncture. Supportive findings such as disproportionately enlarged subarachnoid-space hydrocephalus and improvement after a CSF tap test were considered but not required for inclusion.

Patients were excluded if they had obstructive or secondary hydrocephalus, comorbid neurodegenerative disorders (e.g., dementia, Parkinson's disease), a history of significant intracranial pathology (e.g., hemorrhage, mass lesions, prior surgery, Chiari malformation type 1, stroke, or major head trauma with parenchymal sequelae). Based on these criteria, 22 patients were diagnosed with INPH and treated with VPS. Of these, 7 were excluded due to postoperative complications (e.g., shunt infection, subdural hematoma, shunt dysfunction) or insufficient follow-up. The final study cohort consisted of 15 patients (10 males, 5 females; mean age 67.3 ± 6.7 years).

Proton MRS protocol

All patients underwent preoperative proton MRS using a 3 Tesla MRI scanner (Magnetom Skyra, Siemens, Germany). A multivoxel acquisition technique (TE/TR: 135/1700 ms; voxel size: $10 \times 10 \times 15$ mm^3; matrix: 16×16) was employed (Fig. 1). Spectral data were processed using syngo.via software (Siemens Healthineers), with visual quality control implemented to exclude voxels exhibiting poor spectral quality (Fig. 2). In this example (Fig. 3), four voxels were placed for the Tha, two for the BG, three for the PV area, and two for the MF cortex, with bilateral sampling for each region. Depending on individual anatomical variation (e.g., enlarged lateral or third ventricles), the exact number of voxels representing a region may differ (e.g., three voxels for the Tha or two for the PV area). For each brain region, the voxel with the highest representative value was selected for analysis. Voxels with distorted line shapes or excessive noise were excluded from analysis. Although quantitative spectral quality metrics such as signal-to-noise ratio (SNR) and full width at half maximum (FWHM) were not routinely measured, visual assessment of spectral quality was performed for all cases.

Metabolite measurements comprised both absolute peak intensities and metabolite ratios (e.g., Cho/Cr, NAA/Cr). It should be noted that absolute metabolite concentrations were not quantified in conventional units (e.g., millimolar), and values represent relative signal intensities derived from spectral peaks, as commonly observed in clinical MRS protocols. Partial volume effect correction was not applied; however, care was taken to select voxels minimizing contamination from cerebrospinal fluid or adjacent tissues.

Clinical assessment

The clinical status of the patients was evaluated preoperatively and at postoperative 3 months using the Hellström INBH scale [5]. Clinical outcomes were systematically assessed across four functional domains: gait, neuropsychological performance, balance and urinary continence. A composite score (%) was derived through weighted summation using the following formula: [(2 × gait(%) + neuropsychological(%) + balance(%) + continence(%))/5]. Patients demonstrating a postoperative improvement exceeding 5% relative to preoperative baseline values were classified as shunt responders, whereas those failing to meet this threshold were designated as non-responders. For each functional domain, patients demonstrating > 12.5% improvement in gait or > 25% improvement in other components were

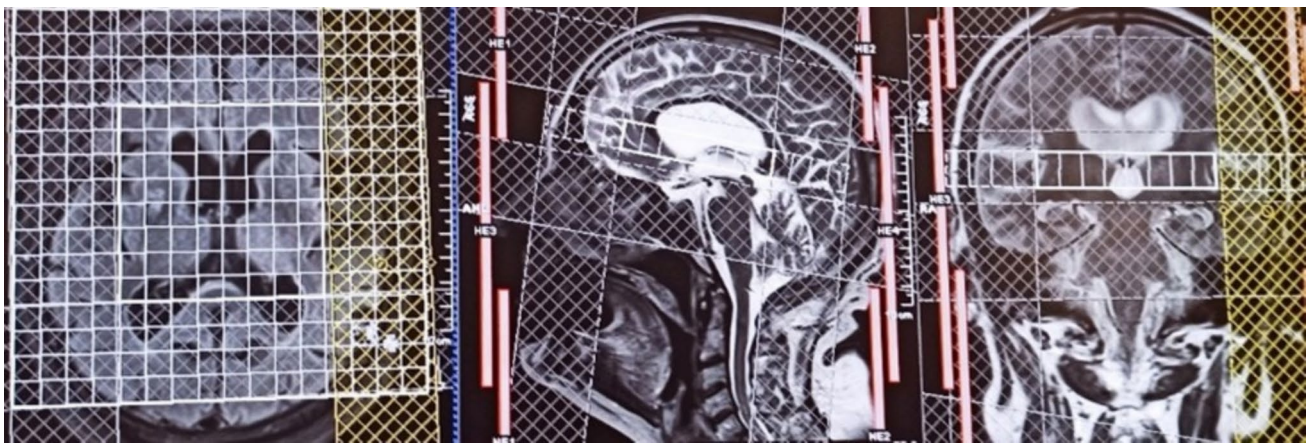


Fig. 1 An example of multi-voxel magnetic resonance spectroscopy

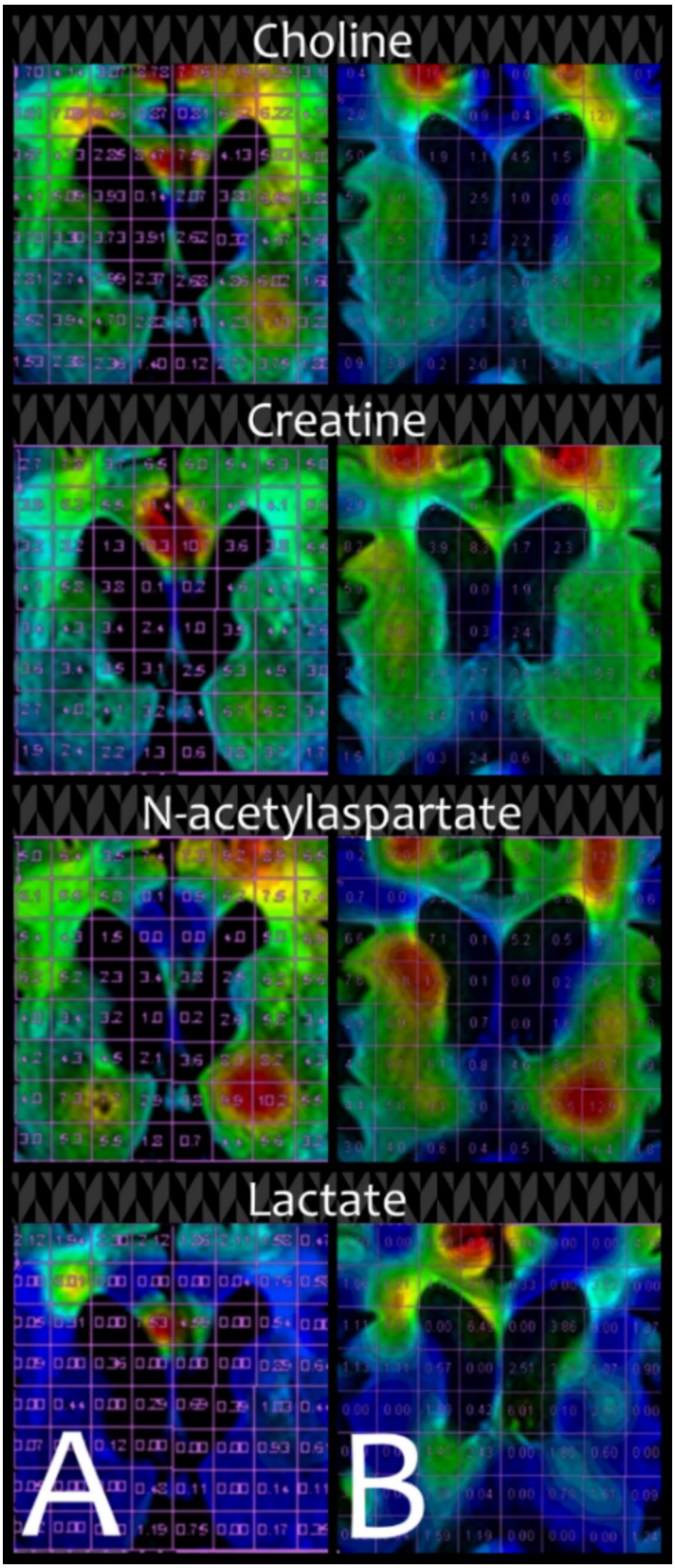


Fig. 2 Illustration of preoperative values of multi-voxel magnetic resonance spectroscopy with two case examples. Cho, Cr, NAA and Lac values of a shunt responder (**A**), a shunt non-responder (**B**)

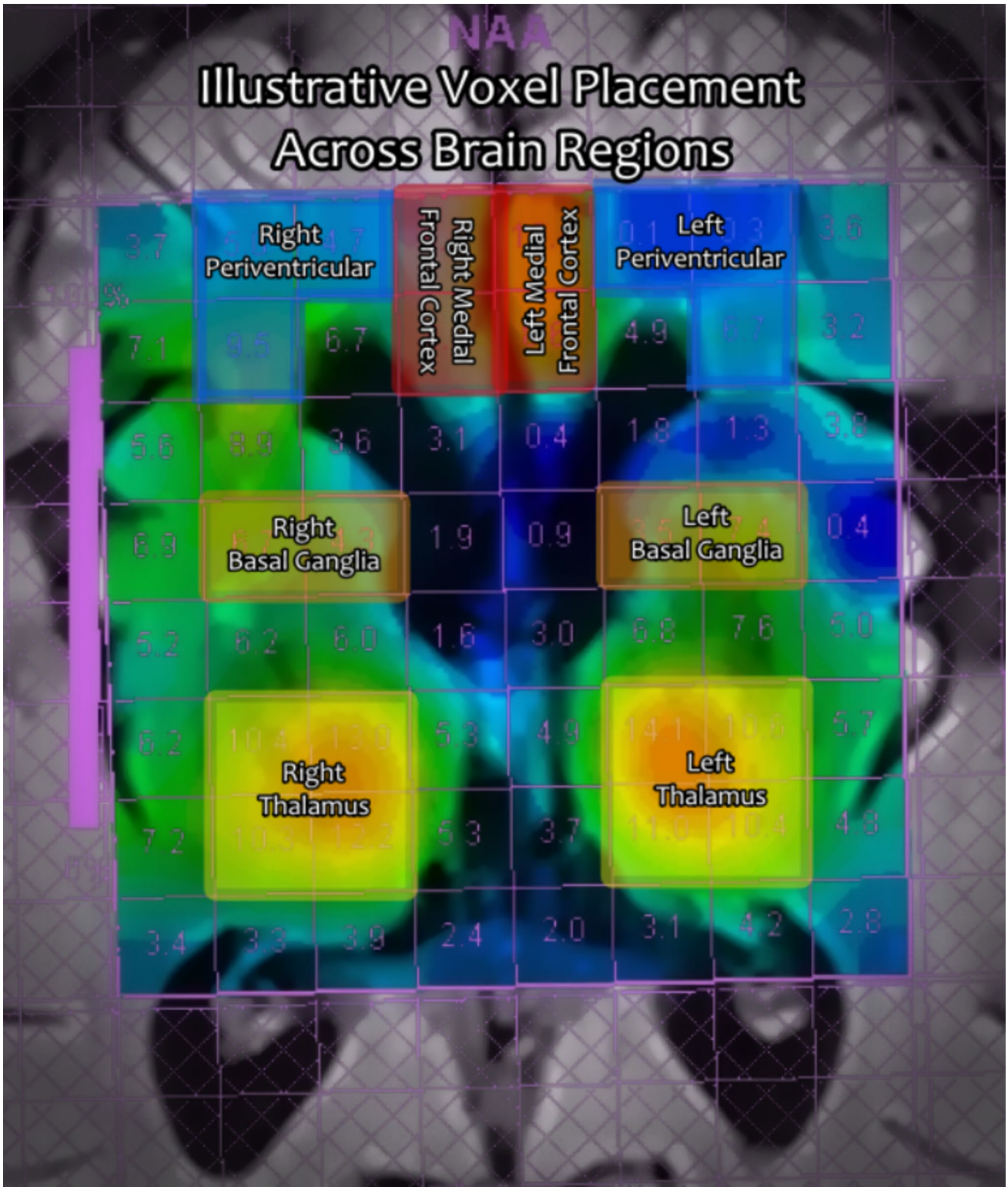


Fig. 3 Illustrative voxel placement across different brain regions with an example NAA concentration map

classified as responders for that specific domain, while remaining cases were categorized as non-responders.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics (version 22.0). Intergroup comparisons were conducted using the Mann–Whitney U test, while within-group longitudinal analyses employed the Wilcoxon signed-rank test. The predictive capacity of MRS parameters was assessed through ROC curve analysis. A two-tailed p-value < 0.05 was considered statistically significant.

Results

Overall shunt response

Shown by each domains and total response (Table 1).

Demographic characteristics

Study cohort comprised 15 participants (33% female, $n = 5$; 67% male, $n = 10$) with an age range of 53–79 years (mean age 67.3 ± 6.7 years). Demographic analysis revealed no significant intergroup differences in age distribution or gender between shunt response categories (all $p > 0.05$), except for neuropsychological outcomes (Table 2). Notably, neuropsychological response rates differed significantly by gender (male: 90% vs female: 0%; $p < 0.01$), though this disparity did not influence overall response (Table 2).

Shunt valve type

There was no significant difference in the shunt response in gait, neuropsychology, balance, continence and overall INBH scale and the percentage change of each domain according to the valve type of the shunt used (programmable and non-programmable) ($p > 0.05$).

Proton magnetic resonance spectroscopy (pMRS) findings

Gait

Statistically significant parameters ($p < 0.05$) were identified through intergroup comparisons (Table 3).

Cut-off values and diagnostic power of significant parameters, as determined by ROC curve analysis, are presented (Table 4).

Neuropsychology

Statistically significant parameters ($p < 0.05$) were identified through intergroup comparisons (Table 5).

Table 1 Distribution of cases into shunt response groups

Domains	Responder		Non-responder	
	n	%	*n*	%
Gait	12	80	3	20
Neuropsychology	9	60	6	40
Balance	8	66.7	4	33.3
Continence	9	75	3	25
Total INPH Scale	12	80	3	20

Table 3 Parameters with significant differences between shunt response groups for gait

Parameters	Gait		
	Responder	Non-responder	*p*-value
Left Tha Cho	5,35 ± 1,32	8,67 ± 2,35	**0.031**
Avg. Tha Cho	5,08 ± 1,01	7,83 ± 2,33	**0.048**
Avg. Tha NAA	8,09 ± 1,66	10,02 ± 0,88	**0.048**
Avg. BG NAA	6,15 ± 1,61	8,52 ± 0,99	**0.018**

Table 2 Distribution of shunt response groups by age and gender

Domains		Age	*p*-value	Female		Male		*p*-value
		Mean ± SD		*n*	%	*n*	%	
Gait	Responder	67,6 ± 7,3	0.448	4	80	8	80	1
	Non-responder	66,0 ± 4,4		1	20	2	20	
Neuro- psychology	Responder	69,0 ± 6,5	0.145	0	0	9	90	0.002
	Non-responder	64,7 ± 6,7		5	100	1	10	
Balance	Responder	68,6 ± 7,8	0.368	4	80	4	57.1	0.576
	Non-responder	67,3 ± 2,5		1	20	3	42.9	
Continence	Responder	68,9 ± 6,5	0.1	2	50	7	87.5	0.236
	Non-responder	64,7 ± 2,1		2	50	1	12.5	
Total	Responder	67,6 ± 7,3	0.448	4	80	8	80	1
	Non-responder	66,0 ± 4,4		1	20	2	20	

Table 4 Diagnostic and prognostic value of the parameters significant in terms of gait in predicting shunt response

Parameters	AUC	*p*-value	95% CI		Sen (%)	Spe (%)	PPV	NPV
			LL	UL				
Left Tha Cho≤6	0.92	<0,001	0.66	1	75	100	100	50
Avg. Tha Cho≤5,4	0.89	<0,001	0.62	0.99	66.7	100	100	43
Avg. Tha NAA≤9	0.89	<0,001	0.62	0.99	83.3	100	100	60
Avg. BG NAA≤7,35	0.94	<0,001	0.7	1	83.3	100	100	60

Cut-off values and diagnostic power of significant parameters, as determined by ROC curve analysis, are presented (Table 6).

Balance

Statistically significant parameters ($p<0.05$) were identified through intergroup comparisons (Table 7).

Cut-off values and diagnostic power of significant parameters, as determined by ROC curve analysis, are presented (Table 8).

Continence

Statistically significant parameters ($p<0.05$) were identified through intergroup comparisons (Table 9).

Cut-off values and diagnostic power of significant parameters, as determined by ROC curve analysis, are presented (Table 10).

Total

Statistically significant parameters ($p<0.05$) were identified through intergroup comparisons (Table 11).

Cut-off values and diagnostic power of significant parameters, as determined by ROC curve analysis, are presented (Table 12).

Table 5 Parameters with significant differences between shunt response groups for neuropsychology

Parameters	Neuropsychology		
	Responder	Non-responder	*p*-value
Right PV NAA	6,63±1,48	11,72±6,96	**0.049**
Left PV NAA	7,47±2,61	10,07±1,41	**0.018**
Avg. PV NAA	7,05±1,64	10,89±3,64	**0.012**
Right PV Cr/NAA	2,33±2,33	0,77±0,29	**0.026**
Right MF NAA	9,98±4,3	5,07±2,66	**0.018**
Left MF Cho	10,37±7,14	4,82±3,38	**0.036**
Avg. MF Cho	10,59±7,48	4,83±3,47	**0.049**
Avg. MF NAA	8,77±2,29	5,29±2,42	**0.012**

In summary

- **Metabolite-based associations:**

  Cho:

  - Elevated Cho levels in the left MF cortex correlated with favorable neuropsychological outcomes ($p<0.05$).
  - Reduced Cho concentrations in the left Tha were associated with positive response in gait ($p<0.05$), continence ($p<0.05$), and overall outcomes ($p<0.05$).

  Cr:

  - Diminished Cr levels in the right Tha and BG predicted better continence outcomes ($p<0.05$).

  NAA:

  - Increased NAA in the right MF cortex coupled with decreased NAA in bilateral PV white matter showed significant associations with neuropsychological improvement ($p<0.05$).

  Lac:

  - Higher Lac concentrations in the left BG region were predictive of balance recovery ($p<0.05$).

- **Response-based ROC analysis:**

  Gait response: The left and average Cho levels in Tha of≤6 and≤5.4, respectively, as well as the average Tha and BG NAA levels of≤9 and≤7.35, respectively, were found to be significant predictors of a positive walking response (Table 4).

Table 6 Diagnostic and prognostic value of the parameters significant in terms of neuropsychology in predicting shunt response

Parameters	AUC	*p*-value	95% CI		Sen (%)	Spe (%)	PPV	NPV
			LL	UL				
Right PV NAA≤8,2	0.82	**0.015**	0.54	0.96	100	66.7	82	100
Left PV NAA≤8,5	0.87	**<0,001**	0.6	0.99	77.8	100	100	75
Avg. PV NAA≤7,65	0.89	**<0,001**	0.62	1	66.7	100	100	67
Right PV Cr/NAA>1,0727	0.85	**0.001**	0.58	0.98	55.6	100	100	60
Right MF NAA>6,5	0.87	**0.001**	0.6	0.99	88.9	83.3	89	83
Left MF Cho>5,3	0.83	**0.007**	0.56	0.97	100	66.7	82	100
Avg. MF Cho>4,1	0.82	**0.007**	0.54	0.96	100	50	75	100
Avg. MF NAA>6,8	0.89	**0.001**	0.62	0.99	100	83.3	90	100

Table 7 Parameters with significant differences between shunt response groups for balance

Parameters	Balance		
	Responder	Non-responder	*p*-value
Left BG Lac	1,79±1,15	0,45±0,54	**0.042**
Right Tha Cr/NAA	0,59±0,12	1,13±0,54	**0.048**
Avg. Tha Cho/NAA	0,63±0,16	1,14±0,55	**0.028**

Neuropsychological response: The right, left, and average PV NAA levels of≤8.2,≤8.5, and≤7.65, respectively, as well as the right and average MF NAA levels of>6.5 and>6.8, respectively, and the left and average MF Cho levels of>5.3 and>4.1, respectively, were significant in predicting a favorable neuropsychological response (Table 6).

Balance response: The left BG Lac level>0.5 was identified as a significant predictor of a positive balance response (Table 8).

Continence Response: The left and average Tha Cho levels of≤6.7 and≤6.25, respectively; the right and average Tha Cr levels of≤5.4 and≤6.65, respectively; the right BG Cr level of≤7.6; the right and average PV NAA levels of≤8.2 and≤9.1, respectively; and the average MF NAA level of>6.8 were all significant in predicting a favorable continence response (Table 10).

Total response: The left Tha and average Cho levels of≤6 and≤5.4, respectively, as well as the average Tha and BG NAA levels of≤9 and≤7.35, respectively, were significant predictors of a positive total response (Table 12).

Discussion

This study investigates the role of preoperative proton MRS parameters in predicting the prognosis of patients with INPH who underwent VPS placement. The findings suggest that MRS may serve as a valuable tool for patient selection and treatment planning in INPH. In the Discussion section, we compare our results with those of previous studies and provide an in-depth analysis of the pathophysiology of INPH, as well as the potential clinical applications of MRS.

Shunt response

In numerous clinical series, gait disturbance has been consistently reported as the symptom demonstrating the most significant improvement following surgical intervention [4, 6, 9]. According to a US-based self-assessment report, postoperative shunt responsiveness rates in patients were 81.1% for gait improvement, 64.4% for cognitive enhancement, and 55.9% for urinary incontinence relief [4]. While a meta-analysis estimated an overall shunt benefit rate of 59% [8], response rates vary across studies, ranging from 71–75% in larger cohorts to 47% in smaller patient series [4, 11, 12]. Our findings align with existing literature, demonstrating improvement rates of 80% ($n=12$) for gait disturbance, 60% ($n=9$) for cognitive symptoms, and 75% ($n=9$, with 3 missing cases) for urinary incontinence. Notably, the overall treatment response rate in our cohort reached 80% ($n=12$), which approaches the upper range of reported response rates in comparable studies (Table 1).

Table 8 Diagnostic and prognostic value of the parameters significant in terms of balance in predicting shunt response

Parameters	AUC	*p*-value	95% CI		Sen (%)	Spe (%)	PPV	NPV
			LL	UL				
Left BG Lac>0,5	0.89	**0.001**	0.57	1	100	75	88	100
Right Tha Cr/NAA≤0,8022	0.88	**0.005**	0.56	0.99	100	75	89	100
Avg. Tha Cho/NAA≤0,6532	0.91	**<0,001**	0.6	1	75	100	100	67

Table 9 Parameters with significant differences between shunt response groups for continence

Parameters	Continence		
	Responder	Non-responder	*p*-value
Left Tha Cho	5,22 ± 0,99	9,20 ± 1,61	**0.009**
Avg. Tha Cho	5,04 ± 0,96	8,12 ± 1,93	**0.009**
Right Tha Cr	4,33 ± 0,77	7,77 ± 0,64	**0.009**
Avg. Tha Cr	5,11 ± 0,82	8,12 ± 1,27	**0.009**
Right BG Cr	6,34 ± 1,54	8,60 ± 0,36	**0.036**
Left BG Cho/Cr	0,90 ± 0,21	1,31 ± 0,26	**0.018**
Right PV NAA	7,24 ± 1,97	15,43 ± 8,56	**0.018**
Avg. PV NAA	7,59 ± 2,04	12,93 ± 4,22	**0.018**
Avg. MF NAA	8,24 ± 2,58	5,15 ± 2,73	**0.036**
Left MF Cho/Cr	1,35 ± 0,76	0,45 ± 0,44	**0.018**
Avg. MF Cho/Cr	1,26 ± 0,51	0,51 ± 0,43	**0.036**

Age

Comparative analyses reveal consistent age disparities between shunt responders and non-responders across studies, with reported mean ages of: 68.8 vs. 73.9 years in one series, and 75.8 vs. 79.9 years in another [13, 14]. In a separate study analyzing age-stratified outcomes, shunt responsiveness demonstrated an inverse relationship with advancing age: patients aged < 70 years showed the highest response rate (62%), followed by those aged 70–80 years (52%), while the > 80 years cohort exhibited the lowest response rate (39%) [15]. Despite these studies suggesting that early age has a positive effect on shunt response, there are also studies reporting that there is no statistically significant relationship between age and shunt response [9, 12]. Our study findings align with the second group, as evidenced by a mean patient age of 67.3 ± 6.7 years. Notably, subgroup analysis revealed comparable mean ages between responders (67.6 ± 7.3 years) and non-responders (66.0 ± 4.4 years), with no statistically significant difference ($p > 0.05$). This age distribution pattern remained consistent across all evaluated domains (Table 2). Although the neurodegenerative nature of the disease suggests a potential prognostic role for age in long-term outcomes, available data from our study and others indicate this association may not represent an independent risk factor.

Gender

A European multicenter study evaluating treatment response following shunt surgery in INPH patients revealed significant gender-based differences in outcomes. Postoperative assessment demonstrated a mean improvement of 19 points in female patients compared to 13 points in males, with this difference reaching statistical significance ($p < 0.05$). Furthermore, the study reported higher surgical benefit rates among women (91%) than men (77%) [16]. Furthermore, a large-scale study revealed that while the age at diagnosis did not differ significantly between genders ($p = 0.8$), female patients presented with worse functional status at diagnosis (mean INPH scale score: 55.3) compared to their male counterparts (mean INPH scale score: 62.3) [17]. This observed disparity may reflect inherent gender-based physiological differences, particularly in gait performance. Supporting this notion, studies demonstrate that healthy female individuals typically exhibit 10–15% slower walking speeds compared to males in standardized assessments [18]. These baseline physiological differences may underlie the well-documented gender disparity in surgical efficacy, with numerous studies (as previously cited) reporting better shunt outcomes in female patients compared to males. Our findings align with previously reported gender differences in preoperative presentation. Female patients demonstrated significantly lower baseline scores across all assessment components (mean total INPH scale: 51.8 ± 20.1 vs. 66.2 ± 15.4 in males). Notably, despite these initial disparities, both genders achieved equivalent final benefit rates (80%). Component analysis revealed differing patterns of domain-specific improvement. While 90% of male patients showed improvement in neuropsychological measures, no

Table 10 Diagnostic and prognostic value of the parameters significant in terms of continence in predicting shunt response

Parameters	AUC	*p*-value	95% CI		Sen (%)	Spe (%)	PPV	NPV
			LL	UL				
Left Tha Cho ≤ 6,7	1	**< 0,001**	0.74	1	100	100	100	100
Avg. Tha Cho ≤ 6,25	0.98	**< 0,001**	0.71	1	88.9	100	100	75
Right Tha Cr ≤ 5,4	1	**< 0,001**	0.74	1	100	100	100	100
Avg. Tha Cr ≤ 6,65	1	**< 0,001**	0.74	1	100	100	100	100
Right BG Cr ≤ 7,6	0.93	**< 0,001**	0.63	1	77.8	100	100	60
Left BG Cho/Cr ≤ 1,012	0.96	**< 0,001**	0.68	1	88.9	100	100	75
Right PV NAA ≤ 8,2	0.96	**< 0,001**	0.68	1	88.9	100	100	75
Avg. PV NAA ≤ 9,1	0.96	**< 0,001**	0.68	1	88.9	100	100	75
Avg. MF NAA > 6,8	0.93	**< 0,001**	0.63	1	88.9	100	100	75
Left MF Cho/Cr > 0,9277	0.96	**< 0,001**	0.68	1	88.9	100	100	75
Avg. MF Cho/Cr > 0,946	0.93	**< 0,001**	0.63	1	77.8	100	100	60

Table 11 Parameters with significant differences between shunt response groups for total INPH Scale

Parameters	Total INPH scale		
	Responder	Non-responder	*p*-value
Left Tha Cho	5,35 ± 1,32	8,67 ± 2,35	**0.031**
Avg. Tha Cho	5,08 ± 1,01	7,83 ± 2,33	**0.048**
Avg. Tha NAA	8,09 ± 1,66	10,02 ± 0,88	**0.048**
Avg. BG NAA	6,15 ± 1,61	8,52 ± 0,99	**0.018**

female patients exhibited benefit in this specific domain (Table 2). However, this striking contrast should be interpreted with caution. First, the female subgroup was small ($n = 5$), rendering the analysis vulnerable to statistical fragility. Second, the observed neuropsychological non-response in women may, at least in part, reflect their significantly lower baseline functional status, which could limit measurable postoperative gains—raising the possibility of confounding by baseline severity. Alternatively, these differences may suggest underlying gender-specific pathophysiological or metabolic mechanisms affecting cognitive recovery, a hypothesis that has not yet been fully explored in the INPH literature. Finally, it remains unclear whether such gender-based variability influences the prognostic performance of MRS parameters. Given that metabolite levels may differ across genders due to hormonal, structural, or perfusional factors, further studies with larger, gender-balanced cohorts are needed to assess whether gender modifies the predictive utility of MRS in INPH.

Use of proton MRS in INPH

MRS serves as a valuable tool for investigating neuronal damage and dysfunction in neurodegenerative disorders, as well as monitoring treatment response [19–23]. However, its application in hydrocephalus remains outside routine clinical practice. The existing literature reveals a striking paucity of studies examining both diagnostic utility and surgical outcomes [24, 25]. Furthermore, these limited investigations suffer from significant methodological limitations: the clinical response scales employed are notably subjective and lack standardization [26], while the differentiation between core INPH clinical components remains ambiguous. Additionally, these studies have restricted their focus to a narrow range of brain regions and corresponding metabolite parameters. Consequently, despite continued research interest in MRS applications for INPH, the technique has yet to achieve sufficient validation for widespread clinical implementation.

Our discussion will analyze MRS metabolite patterns by integrating current literature evidence with our experimental findings.

- **Cho and neuronal recovery**

Our study revealed distinct regional Cho patterns correlating with clinical outcomes: elevated Cho levels in the left MF region were associated with neuropsychological improvement, whereas reduced Cho levels in the left and middle Tha correlated with enhanced gait, continence, and overall treatment response. These findings are in line with those of Lundin et al. (2012), who reported increased frontal white matter Cho levels following VPS, potentially reflecting not only neuronal recovery but also metabolic reorganization [24]. While elevated Cho is traditionally associated with membrane breakdown, demyelination, or inflammatory processes—often interpreted as markers of neuronal damage—it may also signify reparative or regenerative activity, particularly in the context of functional improvement [20]. The observed thalamic Cho reductions associated with motor and autonomic improvements underscore the Tha's well-established role in motor control and sensory integration [27]. This thalamocortical involvement may therefore contribute significantly to the characteristic motor and autonomic manifestations of INPH.

- **Cr and energy metabolism**

The association between reduced Cr levels in the right Tha and BG with continence improvement underscores the involvement of these subcortical structures in central urinary control. As Cr serves as a biomarker of cellular energy metabolism and neuronal activity [28].), these findings align with Parkinson's disease research demonstrating impaired thalamocaudate connectivity in urinary incontinence [29], suggesting similar subcortical mechanisms may underlie continence dysfunction in INPH. Notably, Cr concentrations exhibit dynamic fluctuations in neurodegenerative conditions [30], as evidenced by observations linking elevated thalamic and frontal white matter Cr levels with gait deterioration in INPH [31]. Consequently, interpreting Cr levels requires caution in neurodegenerative assessments, as

Table 12 Diagnostic and prognostic value of the parameters significant in terms of total INPH Scale in predicting shunt response

Parameters	AUC	*p*-value	95% CI		Sen (%)	Spe (%)	PPV	NPV
			LL	UL				
Left Tha Cho ≤ 6	0.92	**< 0,001**	0.66	1	75	100	100	50
Avg. Tha Cho ≤ 5,4	0.89	**< 0,001**	0.62	0.99	66.7	100	100	43
Avg. Tha NAA ≤ 9	0.89	**< 0,001**	0.62	0.99	83.3	100	100	60
Avg. BG NAA ≤ 7,35	0.94	**< 0,001**	0.7	1	83.3	100	100	60

their variability - particularly when used as a reference for other metabolites - may lead to erroneous conclusions given Cr's metabolic instability [20].

Our analysis of Cr levels revealed distinct right hemispheric patterns between shunt responders and non-responders. Notably, these metabolic differences were particularly evident in motor control regions (Tha and BG), aligning with Lundin et al.'s [31] findings regarding Cr's association with motor function. Interestingly, our data primarily associated Cr variations with continence outcomes rather than motor improvements. Specifically, reduced Cr levels in the right Tha and BG correlated with poor continence, whereas post-surgical Cr elevation corresponded with improved urinary control.

The pathophysiology of urinary incontinence in INPH remains incompletely understood, but our findings support growing evidence of a thalamo-BG circuit involvement. This is consistent with: (1) Parkinson's disease studies demonstrating functional connectivity disruptions between the right Tha and caudate nucleus in incontinent patients [29], and (2) numerous reports linking right thalamic/BG lesions to urinary incontinence across various pathologies [27, 32, 33]. While the pontine micturition center remains the primary focus for central incontinence in PD [34], emerging evidence implicates a broader thalamo-BG-cortical network in voiding control [35]. Our Cr findings provide metabolic evidence supporting this proposed neural circuit's functional role in INPH-related continence disorders.

- **NAA and neuronal health**

NAA is widely recognized as a biomarker of neuronal and axonal integrity [36]. Our finding of elevated NAA levels in the right MF region correlating with neuropsychological improvement reinforces its role as an indicator of neuronal health and functionality. This aligns with existing literature demonstrating reversible NAA alterations in various neurological conditions, including Alzheimer's disease, schizophrenia, and demyelinating disorders [22, 23, 37–39], as well as its normalization following interventions in traumatic brain injury and epilepsi [40, 41]. In the context of INPH, Lundin et al. (2013) reported 11% lower thalamic NAA levels compared to healthy controls, correlating with poorer surgical outcomes [24, 31]. While we similarly observed that reduced MF NAA predicted worse neuropsychological response to shunting, our data revealed contrasting regional patterns: (1) favorable gait outcomes associated with decreased thalamic and BG NAA, and (2) improved neuropsychological response linked to lower PV NAA levels. These divergent regional associations - where the same metabolite shows opposite prognostic values depending on neuroanatomical location - underscore the complex, multifactorial pathogenesis of INPH. Such findings suggest that NAA's clinical interpretation requires careful consideration of both absolute levels and their spatial distribution within neural circuits.

- **Lac and ischemic pathology**

The association between elevated Lac levels in the left BG and balance improvement highlights this region's crucial role in motor control. As an end-product of anaerobic glycolysis, Lac accumulates during ischemic or hypoxic conditions [42]. In hydrocephalus, reduced cerebral perfusion promotes anaerobic metabolism, potentially increasing Lac concentrations in both brain parenchyma and CSF [20, 42]. This is supported by histopathological evidence from experimental models demonstrating mild cerebral Lac accumulation in hydrocephalus [43, 44]. Clinically, Kizu et al. (2001) observed elevated ventricular Lac levels in INPH patients, suggesting ischemic involvement [45]. Together, these findings imply that ischemia-mediated metabolic dysfunction in the BG may contribute to balance impairments in INPH.

- **Some metabolite ratios**

Cho/Cr ratio

Our study revealed significant regional variations in the Cho/Cr ratio associated with shunt responsiveness: elevated ratios in the left and MF regions correlated with continence improvement, while reduced ratios in the left BG showed statistical significance. Although current literature does not support the diagnostic or prognostic utility of this ratio in INPH [3, 26, 46, 47], our findings align with postoperative spectroscopic observations demonstrating decreased MF Cho/Cr ratios following VPS [25]. This consistency suggests potential regional metabolic specificity in treatment response.

Cho/NAA ratio

The Cho/NAA ratio in the Tha demonstrated an inverse relationship with balance outcomes, where lower ratios predicted better shunt response. This observation partially supports Shiino et al.'s [3] proposal that reduced thalamic Cho/NAA ratios (reflecting irreversible neuronal damage via NAA depletion) correlate with improved surgical outcomes. Their study established this ratio's predictive value, showing significant discrimination between response groups (sensitivity: 70%; specificity: 100%) and correlation with modified Rankin scores at 1–12 months postoperatively. While our study lacked longitudinal MRS data, the thalamic Cho/NAA

ratio's prognostic capacity appears consistent across populations.

Cr/NAA ratio

Two distinct Cr/NAA patterns emerged: (i) elevated right PV ratios associated with neuropsychological improvement, and (ii) reduced right thalamic ratios correlating with balance recovery. Existing literature presents conflicting evidence - while some studies report elevated PV Cr/NAA ratios as diagnostic markers without prognostic value [26, 46, 48], others demonstrate strong negative correlations with clinical outcomes [3]. Notably, Shiino et al. identified this ratio as the optimal predictor of 1-month outcomes (sensitivity: 92.3%; specificity: 87.5%), a finding paralleled in our balance response data. Complementary evidence from CSF drainage studies further supports the ratio's dynamic nature, showing normalization in treatment responders [46].

Comparison with the literature and innovative contribution

The findings of our study are largely in alignment with existing literature. For instance, Shiino et al. (2004) identified the Cho/NAA ratio in the PV region as a significant predictor of surgical response [49]. Similarly, Lenfeldt et al. (2008) demonstrated that increased NAA levels following CSF drainage correlate with clinical improvement [46]. These results underscore the potential utility of MRS in the diagnosis and prognostication of INPH. The novel contribution of our study lies in its comprehensive analysis of the relationship between MRS-derived metabolic parameters across distinct cerebral regions and corresponding clinical outcomes. Notably, our findings highlight the involvement of subcortical structures—particularly the Tha and BG—in the pathophysiology of INPH, offering a valuable reference point for future research in this domain.

Conclusion

This study explored the prognostic value of preoperative MRS parameters in patients with INPH undergoing VPS surgery. Our findings suggest that MRS may offer valuable metabolic insights into INPH pathophysiology and holds promise as a supportive tool for patient selection and treatment planning. Specifically, regional alterations in Cho, Cr, and NAA levels demonstrated meaningful associations with early postoperative clinical outcomes.

However, given the limited sample size of this study ($n=15$), these findings should be interpreted as preliminary and hypothesis-generating rather than definitive. While the results are encouraging, they require validation in larger, preferably multicenter, cohorts to confirm their generalizability and clinical applicability. Future studies with expanded populations, refined spectroscopic techniques, and longer follow-up periods will be essential to establish the robustness of MRS as a prognostic biomarker in INPH. Until such evidence is available, the integration of MRS into clinical practice should be approached with measured optimism.

Limitations

While providing novel insights, this study has several limitations that warrant consideration:

1. Sample Size Constraints: Our cohort of 15 patients, though prospectively recruited under stringent criteria, may limit the statistical power for detecting subtle metabolic-clinical correlations. Larger multicenter studies would enhance the generalizability of our findings. While the exclusion of 7 patients may appear substantial, it reflects rigorous adherence to data quality and outcome reliability standards in a clinical setting. These exclusions predominantly stemmed from postoperative complications or loss to follow-up, rather than systematic bias.
2. MRS Voxel Selection: Analysis was based on the voxel exhibiting the highest signal within each predefined region (Tha: 4 voxels; BG: 2 voxels; PV region: 3 voxels; MF region: 2 voxels). While this approach was feasible in most participants, individual anatomical or imaging variations—such as preoperative ventricular enlargement, postoperative ventricular reduction, or acquisition differences—occasionally reduced the number of analyzable voxels in certain regions. Additionally, the absence of a standardized preoperative and postoperative spectroscopy frame required manual voxel placement, introducing potential variability in voxel positioning and measurement. Technical constraints inherent to multivoxel spectroscopy further precluded reliable intraventricular measurements in several cases due to partial volume effects and cerebrospinal fluid signal contamination. To ensure consistency and spectral quality across the cohort, intraventricular voxels were therefore excluded from the final analysis. Future studies employing standardized frames, single-voxel approaches, or higher-resolution techniques may help overcome these limitations and enable more accurate assessment of regional and ventricular metabolites.
3. Valve Type: Although both programmable and non-programmable shunt valves were utilized in the study, no significant differences in treatment response were

observed between the groups ($p > 0.05$). Given this lack of effect, valve type was not considered a major confounding factor in the interpretation of spectroscopic or clinical outcomes.

4. The Absence of Laterality Data: We fully agree that cerebral dominance may influence MRS results, particularly in frontal and PV regions. However, laterality (i.e., handedness or language dominance) was not systematically recorded or analyzed in this cohort, representing a limitation of the current study. Although bilateral voxel sampling was performed and averaged, future studies should aim to assess and stratify patients based on cerebral dominance to enhance interpretability of spectroscopic findings.
5. Absence of Comparative Prognostic Markers: While this study specifically focused on preoperative MRS findings as a potential predictor of shunt responsiveness, other well-established prognostic tools such as lumbar infusion testing, CSF tap test responses, Radscale scoring, and symptom duration were not included in the current analysis. Future studies, including an ongoing prospective investigation by our group, aim to evaluate the potential synergistic value of combining metabolic and hydrodynamic biomarkers to improve outcome prediction in INPH.
6. Clinical Assessment Scope: The Hellström INPH scale's exclusion of psychiatric parameters potentially omits relevant clinical dimensions. Incorporation of neuropsychiatric inventories could provide more comprehensive outcome characterization.
7. Follow-up Duration: The 3-month postoperative evaluation window, though sufficient for initial response assessment, precludes analysis of long-term therapeutic durability. Extended follow-up would clarify the temporal stability of observed metabolic changes.

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Authors' contributions Study Design: M.A.D., A.R.G.; INPH diagnosis: M.A.D., M.A., M.O.B., A.S.T.; Patient Recruitment: A.R.G., M.A., M.O.B., A.S.T.; MRI/MRS Protocols: İ.E., M.A.D.; Spectroscopy Data Processing: İ.E., M.A.D.; INPH diagnosis: M.A.D., M.A., M.O.B., A.S.T.; Statistical Analysis: M.A.D.; Manuscript Writing: M.A.D.; Critical Revisions: M.A., A.R.G.; Principal Author: M.A.D. (The study is based on his thesis.); Corresponding Author: A.R.G.; Supervision: A.R.G., İ.E. All authors read and approved the final manuscript.

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Data availability The datasets generated during this study are not publicly available due to patient privacy protections under Turkish data protection regulations. Anonymized data supporting the findings are available from the corresponding author upon reasonable request, subject to approval by the Karadeniz Technical University Ethics Committee.

Declarations

Ethics approval The study protocol was approved by the Institutional Ethics Committee of Karadeniz Technical University, Trabzon, Türkiye (Approval No: 2022–162). All procedures involving human participants were performed in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments. Written informed consent was obtained from all individual participants included in the study. Clinical trial number: not applicable. This study was an observational analysis of routine clinical care and does not meet the criteria for clinical trial registration.

Consent to participate Written informed consent was obtained from all participants in their native language prior to enrollment. The consent process included detailed explanations of the study's purpose, procedures, and data usage.

Consent for publication Participants provided explicit consent for the anonymized publication of their data, including (clinical details, images, videos, or other identifiable material). Original consent documents are retained by the authors and available for review by the journal upon request.

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