



## Review Article

# Diagnosis and treatment for normal pressure hydrocephalus: From biomarkers identification to outcome improvement with combination therapy

Pao-Hui Tseng<sup>a,b,c,f</sup>, Li-Kung Wu<sup>d†</sup>, Yi-Cheng Wang<sup>a</sup>, Tsung-Jung Ho<sup>d</sup>, Shinn-Zong Lin<sup>a</sup>, Sheng-Tzung Tsai<sup>a\*</sup>

<sup>a</sup>Department of Neurosurgery, Hualien Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation and Tzu Chi University, Hualien, Taiwan;

<sup>b</sup>Department of Nursing, Hualien Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation and Tzu Chi University, Hualien, Taiwan; <sup>c</sup>Institute of Medical Sciences, Tzu Chi University, Hualien, Taiwan; <sup>d</sup>Department of Chinese Medicine, Hualien Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation and Tzu Chi University, Hualien, Taiwan

<sup>†</sup>Both authors contributed equally to this work.

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## ABSTRACT

Idiopathic normal pressure hydrocephalus (iNPH), albeit characterized by gait impairment, cognitive decline, and urinary incontinence, in clinical diagnosis is poorly defined and is usually coexistent with other neurodegenerative diseases. Surgical operation with shunt implantation is the primary treatment but leads to variable outcomes. Recent studies demonstrated that the pathophysiology of iNPH may include both preceding cerebrovascular events and concomitant Alzheimer's dementia or dopaminergic degenerative neuropathology in patients' brain. These factors not only help differentiate iNPH from its mimics but also associated with the extent of symptomatic improvement after surgery. In this review, we examined these mechanisms underlying the development of iNPH and the beneficial effects of shunt surgery. Furthermore, the increasing identification and importance of biomarkers from cerebrospinal fluid and neural imaging could also predict the responsiveness of treatment. Finally, these progresses suggest that combination therapy would be necessary for iNPH treatment in the future.

**KEYWORDS:** *Acupuncture, Biomarker, Clinical outcome, Normal pressure hydrocephalus, Shunt*

## INTRODUCTION

Idiopathic normal pressure hydrocephalus (iNPH) was first observed and published by Hakim and Adams in 1965. It is associated with symptoms of gait impairment, cognitive decline, and urinary incontinence [1]. The currently used objective assessment scales may not be sensitive enough to detect subtle changes in symptomatology [2]. The computed tomography of the brain found that the accumulation of cerebrospinal fluid (CSF) causes the ventricle to expand, which compresses the surrounding tissues of the ventricle, but the detection of cerebrospinal fluid pressure is normal (5–18 mmHg) [3]. The symptoms can be reduced by shunt implantation, which leads to variable and 30%–90% improvement of the patient [4]. When selecting candidates for shunt surgery, prognostic information is gathered from clinical examination, neuroimaging, and invasive lumbar drainage and CSF testing [5]. Currently, radiological findings support the clinical suspicion of iNPH which includes dilated ventricles, effaced sulci at the high convexities, and signs of hyperdynamic CSF flow [6]. Accumulating evidence additionally suggested both higher Evan's index (Evan's index >0.3) and smaller callosal angle (<90°) might correlate with better surgical

outcome of iNPH [6,7]. Several radiological factors including temporal horn size, periventricular white matter changes, and narrow high convexity sulci were also evaluated to predict the surgical response of iNPH [8]. However, how to identify patients with iNPH and achieve better improvement of symptoms and quality of life after shunt surgery is still debated.

In Japan, the prevalence of iNPH is near 3% in the population older than 65 years. In Sweden, the pervasiveness of possible iNPH is 2.1% in the population older than 70 years old [9]. Between 2003 and 2012, the incidence of iNPH increased from zero to 1.36/100,000/year in Germany. Vestfold County in Norway suggested a prevalence of probable iNPH of 21.9 and an incidence of 5.5 per 100,000 with up to 1.5/100,000 patients undergoing surgery annually [10]. There are no clear statistics to indicate the iNPH prevalence

### \*Address for correspondence:

Dr. Sheng-Tzung Tsai,  
 Department of Neurosurgery, Hualien Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, 707, Section 3, Chung-Yang Road, Hualien, Taiwan.  
 E-mail: flydream.tsai@gmail.com

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in Taiwan yet. There is literature suggesting that more than 25% of patients initially diagnosed with iNPH are later diagnosed with either Alzheimer's disease (AD), dementia with Lewy bodies, progressive supranuclear palsy, or other neurodegenerative diseases [11,12].

Although the recoverable neurological function is improved by the operation of placement of the drainage tube of the cerebrospinal water, there are nearly 40% of patients who have not been able to obtain improvement due to this treatment. In recent years, there is growing evidence to show the benefit of biomarkers from cerebrospinal fluid to facilitate the diagnosis of iNPH and prediction of outcome from shunt surgery. In addition, combination therapy targeting multiple underlying pathophysiology might provide better improvement of symptoms for patients with iNPH. In this review, we will explore this evidence and first showed recent pathogenesis underlying the iNPH. Following identification of possible mechanisms, the availability of growing surrogates from CSF might help characterize iNPH and combine multimodal therapies to alleviate symptoms for patients with iNPH.

### **PATHOPHYSIOLOGY OF NORMAL PRESSURE HYDROCEPHALUS**

Overall, NPH is divided into two types, iNPH and secondary NPH. Secondary NPH often occurs in patients with a history of head trauma injury, cerebrovascular disease (e.g. aneurysm rupture, intracerebral hemorrhage, or infarction), intracerebral tumors, and central nervous system infection after initial treatment over 3 months [4]. The condition mostly presents because the cerebrospinal fluid pathway is blocked, causing cerebrospinal fluid absorption problem and poor circulation. In terms of iNPH, it is usually diagnosed clinically without definite diagnostic criteria. At present, the clinical diagnosis is based on at least one of the following three symptoms: gait disturbance, cognitive impairment, and urinary incontinence. In addition, dilated cerebral ventricles and narrowed subarachnoid space at the high convexity without severe cortical atrophy on brain magnetic resonance imaging (MRI). Moreover, patients have no history of severe head trauma, subarachnoid hemorrhage (SAH), meningitis, tumor, and aqueduct stenosis. iNPH also often coexists with neurodegeneration and chronic cerebrovascular disease [9]. However, the pathophysiology of iNPH is yet unknown, iNPH patients receiving proper diagnosis and treatment are still underestimated. These highlight the necessity of multidisciplinary approach as well as multimodalities neurophysiological biomarkers to improve the care of iNPH patients.

Among patients diagnosed with iNPH, systemic atherosclerotic diseases, including essential hypertension, dyslipidemia, coronary artery disease, and peripheral arterial disease are significantly higher [13]. These vascular comorbidities, therefore, have been suggested to lead to higher incidence of iNPH [14]. Quantitative analysis and severity of cerebral small vessel disease, which is also a hallmark of atherosclerotic disease, also are associated with motor disability and cognitive impairment [15]. In addition,

patients with iNPH have a higher incidence and worse severity of periventricular white matter disease on MRI [16]. These associations implicate that deteriorated compliance of the ventricular wall and gradual ventricular enlargement even with normal fluctuations of intracranial pressure are attributed to chronic cerebral ischemia around the periventricular area. Intraventricular pulse pressure and systemic hypertension have also been correlated with hydrocephalus. Furthermore, periventricular ischemia may result in locally increased venous resistance, decreased CSF absorption, and ventricular enlargement. The study has shown that the outcomes of shunt surgery were correlated with the extent of decreased CSF absorption [17].

### **CLINICAL EVALUATION OF IDIOPATHIC NORMAL PRESSURE HYDROCEPHALUS: DISEASE DOMAIN ANALYSIS AND QUALITY OF LIFE**

Although shunt implantation remarkably ameliorates cognitive and motor disabilities in iNPH, the extent to which surgery mitigates individual symptoms is still widely various for each patient. It is important to pay attention to individual difference in iNPH and its different pathophysiology. Clinical evaluation of iNPH is usually carried out by assessing a variety of functional and mental aspects in addition to gather data from medical examinations. This would facilitate identifying factors to predict better outcomes of quality of life, motor, and cognitive symptoms from patients with iNPH after shunt surgery. Several scales were used in the measurement of severity for iNPH, hoping to effectively confirm the patient's obstacle standards, such as mini-mental status examination, frontal assessment battery, and frontal assessment behavior tests to evaluate the performance of frontal function such as executive function, inhibitory control and motivation [18], Stroop test for the relationship between word meaning and color, Tinetti Performance Oriented Mobility Assessment, TUG and Berg balance test and other balance and gait scales, and nine-hole peg test with the dominant hand nine-hole plunger test [19-21]. The iNPH grading scale is mostly used for score evaluation in clinical diagnosis [22]. However, patients may have only one of the characteristic symptoms. In order to increase the success rate of cerebrospinal fluid drainage tube placement surgery, an invasive external drainage test of the cerebrospinal fluid for 3 days is usually performed on the patient before surgery to record the changes in cerebral pressure before and after the drainage of the cerebrospinal fluid. However, it is possible that the patient will not show signs of improvement within 3 days of the CSF drainage test. Instead, it might be observed by the patient or his/her family members within 1–2 weeks after discharged [2].

The study has shown that caregivers for patients with iNPH play an important role in the evolution of clinical course and decision-making as well. They should be included when counseling patients [23]. Studies have revealed that not only poor patients' life quality was noted before surgery but also enormous stress for the caregivers was developed [24,25]. It has been estimated that less than half of patients with iNPH had significant improvement in the quality of life after shunt

surgery [26]. In addition, with age growing, older patients may have limited improvement after shunt implantation due to combination with other neurodegenerative diseases and then result in decreasing of life quality [25]. According to the study, patients did not have positive attitude toward the improvement of gait after the shunt surgery, the possible reasons might include patients' high expectations for the improvement, uncomfortable feeling in the process, and tiredness of long conducting days for the test. Furthermore, it is recommended that the patient's caregiver's observation results should be taken into consideration whether to accept shunt implantation treatment [2].

### BIOMARKERS FROM CEREBROSPINAL FLUID TO FACILITATE DIAGNOSIS OF IDIOPATHIC NORMAL PRESSURE HYDROCEPHALUS AND PROGNOSIS

Brain pathology of patients with iNPH has been correlated with improvement of postshunt quality of life [26]. There is increasing evidence to show some CSF biomarkers helpful in distinguishing patients with iNPH from those with iNPH and comorbid neurodegenerative or neurovascular diseases, such as AD or cerebral strokes [27], while others are underexplored [Table 1]. For example in AD, CSF characteristically has low  $\beta$ -amyloid 42 (Ab42) and high total tau (t-tau) and phospho-tau (p-tau) levels [36]. In iNPH, CSF has similar low Ab42 as in AD, but t-tau and p-tau levels are not increased as in AD. In fact, the levels are similar to those in normal controls [27,37]. In a pilot study, Jeppsson *et al.* found that all the amyloid precursor protein (APP) fragments (Ab38, Ab40, Ab42, sAPPa, and sAPPb) were low in iNPH CSF and confirmed that iNPH has low CSF Ab42 and t-tau and p-tau [37]. Importantly, after shunting, all the proteins (except t-tau) increased in the ventricle CSF. Jeppsson *et al.* suggested that the low protein levels from ventricular CSF that increased with shunting may provide a new way to improve cognitive impairment [37]. Taken together, CSF biomarkers would afford us an opportunity to associate the effectiveness of surgery with change of neurological function and molecular change of CSF dynamics as well.

Interleukins are a group of cytokines that play a role in regulating immune response and inflammatory reactions. The cytokines interleukin (IL)-1 $\beta$ , IL-6, and IL-10 may be helpful in NPH diagnostics [38]. In addition, IL-6 and tumor necrosis

factor- $\alpha$  could be important biomarkers for early diagnosis and disease monitoring in SAH patients. Those data implicate that neuroinflammatory markers in CSF could help differentiate the severity of neurological diseases, such as iNPH. On the other side, the blood-brain barrier (BBB) limits the entry of blood-derived products, pathogens, and cells into the brain that is essential for normal neuronal functioning and information processing. Postmortem tissue analysis indicates BBB damage in AD [39] and BBB breakdown is an early event in the aging human brain that begins in the hippocampus and may contribute to cognitive impairment in AD [32]. However, the role of BBB breakdown in NPH remains elusive. To elucidate whether BBB impairment leads to NPH may provide a new pathophysiology and an option to prevent disease and optimize treatment. An advanced dynamic contrast-enhanced MRI and postprocessing analysis with improved spatial and temporal resolutions has been used as a method to quantify the BBB regional permeability with Ktrans constant [32]. This evidence suggests that biomarkers from CSF of patients may provide more clues to characterize iNPH. In the future, combination of biological (CSF proteins) and radiological (structural and functional MRI) information would implicate better validation of their measurement in clinical activity, inclusion in clinical trials, and prediction of iNPH progression.

### MULTIMODALITY TREATMENT FOR IDIOPATHIC NORMAL PRESSURE HYDROCEPHALUS

#### Surgical treatment with shunt implantation

Shunt implantation, including ventriculoperitoneal or lumboperitoneal shunt, remains the standard of treatment for amelioration of the motor (gait instability and urinary incontinence) and cognitive (memory impairment) disabilities of iNPH [40]. The extent to which surgery mitigates individual symptoms still varies widely among these patients. The improvement ranges widely between 30% and 90% for probable iNPH cases. Currently, there are no standard criteria from diagnosis to surgical indication. In addition, the high coexistent neurodegenerative diseases and underlying vascular factors make the gap of diagnostic challenge wider [41]. After excluding coexistent with other neurodegenerative diseases, such as dementia or dopaminergic degeneration, the effectiveness of surgery may increase to around 70% [42,43]. The design of postoperative follow-up and analysis of outcomes and effectiveness are summarized in Table 2. These

**Table 1: Biomarkers from cerebrospinal fluid involving various pathophysiologies to predict idiopathic normal pressure hydrocephalus**

	Biomarkers					Reliability
Neuroinflammation [28]	IL-6	IFN-r	IL-10	IL-1 $\beta$	IL-4	High correlation
Level (pg/mL)	53.41-102.53	1.35-2.11	4.57-6.18	2.82-4.96	2.5-4.86	
Alzheimer's dementia [29-31]	Ab42	T-TAU	P-TAU			Exploring
Level (pg/mL)	308.43-318	662.79-980	77.71-96			
Blood-brain barrier [32,33]	sPDGFR $\beta$					Exploring not define yet
Level (ng/mL)	750-850					
Neurodegeneration [30,34,35]	NfL					Debating
Level (pg/mL)	903-2419					

Cytokines: IL-6, IFN-r, IL-10, IL-1 $\beta$ , IL-4; Ab42:  $\beta$ -amyloid 42. t-tau: Total tau, p-tau: Phospho-tau, sPDGFR $\beta$ : Soluble platelet-derived growth factor receptor-beta, NfL: Neurofilament light chain, IL: Interleukin, IFN: Interferon

**Table 2: Clinical studies of shunt surgery for idiopathic normal pressure hydrocephalus patients, including patients' characteristics, shunt design, and specific outcome analysis**

Author	Years	Design	Follow-up	Participant (subject numbers)	Treatment	Outcome measured	Results
Wu <i>et al.</i> [2]	2019	Retrospective study Two groups: Objective versus subjective responders	Mean duration 1.73 years One follow-up visit at 2 weeks after shunt insertion, 6 months and 12 months	116 patients received a VPS, median age 76. 75 objective LD responders and 41 subjective LD responders	VPS	iNPHGS, MMSE, BBS	Positive LD trial predicted 82.8% of objective or subjective response patients
Grasso <i>et al.</i> [44]	2019	Retrospective study; clinical symptoms and outcome after ventriculoperitoneal shunt	Early follow-up (1-3 years postoperatively), short-term follow-up (3-5 years postoperatively), midterm follow-up (5-7 years postoperatively), long-term follow-up (7-10 years postoperatively)	50 patients, median age 71 (37 men, 13 women)	VPS with programmable valve	iNPHGS, MMSE mRS, TUG, TMT, BI ADLs, ICIQ-SF	Gait showed better and sustained improvement. Cognitive impairment and urinary incontinence improved in the early follow-up
Modesto and Pinto [45]	2019	Control clinical trial with home physical exercise program	Pretreatment home training, post-VP shunt treatment, and an additional 8-week treatment	52 patients, mean age 74, 30 women and 22 men without VPS (F17/M9) with VPS (F13/M13)	With/without VPS	iNPHGS, MMSE, Dynamic Gait Index, FIM, TUG, BBS	Significant improvement with 10 weeks of home physical exercises in ADL and static balance and functional capacity for two groups. Additional improvement with VP shunt
Miyajima <i>et al.</i> [46]	2016	Prospective multicenter study A previously conducted VPS cohort study with the same inclusion criteria and primary and secondary endpoints was used as a historical control. Compare the efficacy and safety of VPSs and LPSs for patients with iNPH	At 3 months and 1 year after surgery	83 patients, median age 76	LPS	mRS, iNPHGS	63% LPS patients improvement of at least 1 point in their mRS score, serious adverse events not significantly different between the groups at 1 year after surgery
Israelsson <i>et al.</i> [25]	2020	Population-based controls study To investigate QoL in shunted iNPH patients compared to the population	Mean duration 21 months (6-45 months after surgery)	176 patients and 368 controls. Age 60-85	Shunted	EQ5D5L	Shunting improved QoL and health status in all dimensions  Shunted patients with depression had lower QoL than normal controls (age and sex matched)

Contd...

Table 2: Contd...

Author	Years	Design	Follow-up	Participant (subject numbers)	Treatment	Outcome measured	Results
Razay <i>et al.</i> [21]	2019	Prospective observational cross-section and cohort study Consecutive patients with memory impairment and triage index diagnostic test scores by brain CT (ventriculomegaly with Evans ratio)	12 months after VP shunt	408 patients. Median age 77	VPS	MMSE, Tinetti tests, Tandem walk test	In mobility, self-care, daily activities, and anxiety/depression, shunted patients worse than the controls both before and after surgery The main predictors of low QoL in iNPH were symptoms of depression and severity of gait disturbance 96% of participants following shunting, over 25% improved in either MMSE or balance/gait scores
Isik <i>et al.</i> [20]	2019	Retrospective study To investigate the outcome of serial removal of CSF in the patients with iNPH who refused to have VP or LP shunt surgery or had contraindications	Before and after CSF removal Median 34.5 months	42 patients, median age 78	Recurrent CSF removal only 35 patients had two CSF removal procedures; 13 patients had three CSF removal procedures	MMSE, FAB, Stroop test, POMA, TUG, NHPT	The mean TUG scores decreased after the first, second, and third procedures The POMA scores including both gait and balance components improved after the first and second procedures
Peterson <i>et al.</i> [47]	2016	Whether apathetic symptoms improve following shunt surgery in NPH Whether this relates to cognitive response The relationship between ventriculomegaly and apathy using the bicaudate ratio	Median 4.17 months follow-up Before and 3-9 months after shunt surgery	22 patients, 49-83 age	VPS	MMSE, AES, GDS	Greater preoperative ventriculomegaly was associated with increased level of apathy and depression A reduction in apathetic symptoms following shunt surgery was associated with improved performance on the MMSE

Contd...

**Table 2: Contd...**

Author	Years	Design	Follow-up	Participant (subject numbers)	Treatment	Outcome measured	Results
Junkkari <i>et al.</i> [26]	2017	Prospective study	3 and 12 months postoperative follow-up	145 patients, median age 74	VPS	15D questionnaire Beck Depression Inventory iNPHGS Frontal cortical biopsy CACI BMI	63 (43%) patients had experienced a clinically significant improvement in HRQoL. Lower body mass index predicted favorable HRQoL outcome 1 year after the shunting

LD: Lumbar drain, iNPH: Idiopathic normal-pressure hydrocephalus, CSF: Cerebrospinal fluid, VPSs: Ventriculoperitoneal shunts, LPSs: Lumboperitoneal shunts, HRQoL: Health-related quality of life, EQ5D5L: EuroQol 5-dimension 5-level, iNPHGS: iNPH grading scale, MMSE: Mini-mental state examination, BBS: Berg Balance Scale, mRS: Modified Rankin Scale, TUG: Timed up and go test, TMT: Tinetti mobility test, BI ADLs: Barthel index of activities of daily living, ICIQ-SF: International Consultation on Incontinence Modular Questionnaire Urinary Incontinence Short Form, FIM: Functional Independence Measure scale, Tinetti tests (POMA): Tinetti Performance Oriented Mobility Assessment, FAB: Frontal assessment battery, NHPT: Nine-hole peg test, AES: Apathy evaluation scale, GDS: Geriatric Depression Scale, CACI: Charlson age comorbidity index, BMI: Body mass index

studies have emphasized on the improvement in gait function in patients with iNPH who had received shunt treatment. There was a significant improvement in unsteady gait following lumboperitoneal shunt. Nevertheless, memory and incontinence symptoms did not reveal consistent change. Some patients with psychiatric symptoms may show unsteady gait similar to iNPH after taking medications [48]. In addition, preoperative apathy expression may mean a greater degree of subcortical atrophy of iNPH which might offset the improvement from shunt surgery [47]. These all highlight the importance of psychiatric comorbidities and medications may undermine the benefit from surgery for patients with iNPH. The advance of brain imaging could help detect secondary structural lesions, which exhibit a clinically similar presentation [12]. Even extended lumbar drainage use provides a better prognostic value for testing the diagnosis of iNPH, preoperative evaluation considering clinical symptoms, radiological findings, CSF biomarkers of iNPH, and neurophysiological signatures may ensure a higher effectiveness of shunt surgery [49,50].

Recent studies show that most centers adopted ventriculoperitoneal shunt for the amelioration of iNPH disabilities [Table 2]. Studies including meta-analysis and systemic review also demonstrated that the benefits and risks between various CSF diversion strategies, including ventriculoperitoneal shunt, lumboperitoneal shunt, and endoscopic third ventriculostomy are similar [51], except that the effect of endoscopic third ventriculostomy might be temporary. Furthermore, a programmable shunt is recommended to be used, and it is crucial to closely monitor and adjust the pressure valve to track the improvement of patients' symptom [44]. The adoption of lumboperitoneal shunt provides an alternative option for patients with iNPH and its comparative effectiveness and surgical risks with ventriculoperitoneal shunt have been reported [52]. Compare with the ventriculoperitoneal shunt, the lumboperitoneal shunt is relatively safer because it does not require cranial surgery and ventricular access. Instead, it can be done by placing drainage tube in the lumbar spine to bypass cerebrospinal fluid, which has the benefits of mini-invasive surgery and

lower chance of getting cerebral damage. However, implanting ventriculoperitoneal shunt allows the possibility of brain pathology examination. For example, brain pathology from patients of probable iNPH revealing characteristics of AD found that the duration and extent of improvement after ventriculoperitoneal shunt surgery would be undermined [53]. In addition, lumboperitoneal shunt seems to bear higher chance of hemorrhagic events than ventriculoperitoneal or ventriculoatrial shunt [52]. Whether ventriculoperitoneal shunt would provide better long-term outcomes than lumboperitoneal shunt might need larger randomized trials in the future.

### Acupuncture

Since the surgery might not provide optimal treatment for all domains of symptoms from iNPH, another treatment option with additional benefit is necessary. There is preliminary evidence to show that Chinese medicine provides various extent of improvement for dementia patients. With 3-month treatment course, acupuncture significantly ameliorates cognitive impairment for patients in predementia status and dementia [54,55]. The plausible mechanisms involve the reduction of oxidative stress, apoptosis, and neuroinflammation [56]. However, the improvement on cognition may also be attributed to neuronal synaptic plasticity, cerebral blood flow, and cerebral glucose metabolism. The relief of cognitive impairment in iNPH patients could only achieve modest extent after shunt surgery. The study to incorporate acupuncture at specific designed paradigm provides better amelioration at cognitive domain is warranted. From the available study using functional MRI (fMRI), acupuncture has been proved closely related to functional connectivity network [57]. Acupuncture can increase default mode network and sensorimotor network connectivity with brain areas controlling pain, emotion, and memory [58]. For example, acupuncture increased the brain functional connectivity of periaqueductal gray, anterior cingulate cortex, left posterior cingulate cortex, right anterior insula, limbic/paralimbic, and precuneus. Acupuncture could also adjust the limbic-paralimbic-neocortical network, brainstem, cerebellum, subcortical, and hippocampus brain

areas. By enhancing the functional connectivity network, acupuncture might have an opportunity to improve the symptoms of hydrocephalus.

The mechanism of how acupuncture could improve the symptoms of hydrocephalus is still unknown. In the animal model of hydrocephalus [59], hydrocephalic rats treated with acupuncture at ST36 performed better in motor behavior and had a reduction in reactive astrocyte cell density in the corpus callosum and external capsule. These findings indicate that acupuncture at ST36 has a neuroprotective potential mediated by inhibition of astrogliosis [57,59]. Laboratory studies also demonstrated that acupuncture regulates cerebral blood flow and metabolism. Acupuncture modulates multiple molecules and signaling pathways that lead to excitotoxicity, inflammation, oxidative stress, neuron death, and survival [56]. Also in animal study, acupuncture promotes angiogenesis, neurogenesis [56], neuronal remodeling [60], regulation of synaptic plasticity [60], and regeneration of the injured nerve in the central nervous system [60]. Besides, acupuncture might decrease the apoptosis of neurons by regulating the opening of KATP channels. Thus, acupuncture has brain-protective effect on rats with focal cerebral ischemia-reperfusion injury [61]. In addition, acupuncture can reduce acute cerebral ischemia infarction volume in rats by suppressing local and peripheral inflammation [62]. Although there is no direct evidence to confirm the benefit of acupuncture for patients with iNPH, acupuncture has been shown to alleviate the symptoms for stroke patients with hydrocephalus [63]. These may suggest the potential of using acupuncture for iNPH [56,61,62].

### Rehabilitation and physical exercise for idiopathic normal pressure hydrocephalus

Shunt implantation is an invasive procedure to bypass cerebrospinal fluid in ventricles for iNPH amelioration. The best physical therapy for either nonoperative or postoperative patients is to encourage them to do off-bed activities in order to increase the frequency and stamina of lower limbs' active movement [40]. Consequently, patients not only can get into physical therapy program sooner but also can raise the chance of using their lower limbs to walk actively, practice squat to sustain flexibility of joints and function of core muscle, even be able to conduct a higher level of difficult balance and coordination movement to gradually extend time and area of mobility. It is important to keep home physical exercise which has significantly better performance in activities of daily living, static balance, functional capacity, dynamic balance, and gait for patients with iNPH [45].

### CONCLUSION

Given the growing evidence to delineate the underlying mechanisms of iNPH and identification of concomitant comorbidities, precise diagnosis of iNPH and identification of alternative neurodegenerative diseases have become increasingly important. The advent of molecular analysis of CSF and functional brain imaging such as functional MRI provides more clues for differentiating iNPH from other iNPH mimics with similar clinical presentation. Although CSF diversion through different strategies of shunt implantation

is still the main standard of care for iNPH, combination therapeutic paradigms including acupuncture and physical rehabilitation may provide longer and higher benefit of symptomatic improvement.

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