วารสารประสาทศัลยศาสตร์ไทย
ปีที่ 2 ฉบับที่ 1 มกราคม - มีนาคม 2567

Thai J Neurol Surg 2024;2(1):6-23.

Research Article

Two-Years Comparative Clinical Outcome in the Shunt Treatment of Disproportionately Enlarged Subarachnoid Space Hydrocephalus (DESH) and Non-DESH Idiopathic Normal Pressure Hydrocephalus

Niiimron Nisahoh, MD[1]
Theerapol Witthiwej, MD[1]
Nerisa Thornsri, MD[2]

[1]*Division of Neurosurgery, Department of Surgery, Faculty of Medicine Siriraj Hospital*
[2]*Clinical Epidemiology Unit, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand*

Abstract

Introduction: Idiopathic normal pressure hydrocephalus (iNPH) is known to be a treatable cause of disability and morbidity in elderly patients such as gait abnormality, cognitive decline, and urinary impairment. There are two types of iNPH, disproportionately enlargement subarachnoid space hydrocephalus (DESH) and non-DESH. This study aimed to compare, two-years outcome of treatment in both DESH and non-DESH.

Methods: We conducted a retrospective cohort study of iNPH patients who received surgical treatment between September 2014 and November 2016. Demographic data and baseline clinical were collected. The patient was classified into DESH and non-DESH iNPH groups. Outcomes after treatment such as idiopathic normal pressure hydrocephalus grading scale (iNPHGS), modified Rankin scale (mRS), bulbar symptoms, psychiatric symptoms, and adverse outcomes were analyzed during immediate post-operation, first visit, 4-6 months, 1 year, and 2 years after surgery. The positive outcome was defined as improvement in iNPHGS or mRS at such time.

Results: Patients with iNPH (n =106) were classified as DESH iNPH (n=72) and non-DESH (n = 34). There was a favorable improvement in both groups during the first visit (73.5% in non-DESH and 88.9% in DESH, p = 0.044), 4-6 months (72.7% in non-DESH and 79.4% in DESH group, p = 0.452), 1 year (65.9% in non-DESH group and 79.7% in DESH, p = 0.141) and 2 years (66.7% in non-DESH and 59.6% in DESH group, p = 0.54). There was no difference in outcome according to the type of surgery either ventriculoperitoneal (VP) or lumboperitoneal (LP) shunt at any time.

Conclusion: All patients with a diagnosis of iNPH should receive surgical treatment with or without DESH findings on radiographic imaging. There was a favorable positive outcome with minor shunt-related complications until at least 2 years after surgery. There were no differences between any shunting surgery at any time (either VP or LP shunt).

Keywords; idiopathic normal pressure hydrocephalus (iNPH), disproportionately enlargement of subarachnoid space with hydrocephalus (DESH), idiopathic normal pressure hydrocephalus grading scale (iNPHGS), modified Rankin scale (mRS), bulbar symptoms, psychiatric symptoms

Corresponding author: Niiimron Nisahoh, MD. Email: pminor158@gmail.com

บทคัดย่อ

บทนำ: โรคโพรงสมองคั่งน้ำชนิดความดันสมองปกติในผู้สูงอายุ (idiopathic normal pressure hydrocephalus: iNPH) มีผลทำให้เกิดความบกพร่องทางระบบประสาท ทำให้เกิดอัตราเสียชีวิตเพิ่มขึ้น ซึ่งเป็นโรคที่รักษาได้ด้วยการผ่าตัด โดย iNPH แบ่งได้เป็นสองประเภท ได้แก่ disproportionately enlargement subarachnoid space hydrocephalus (DESH) และ non-DESH การศึกษานี้เพื่อเปรียบเทียบผลการรักษาระยะยาวระหว่างกลุ่ม DESH และ non-DESH

วิธีการศึกษา: เป็นการศึกษาย้อนหลังในผู้ป่วย iNPH ที่ได้รับการผ่าตัด shunt surgery ระหว่างกันยายน 2014 ถึง พฤศจิกายน 2016 แบ่งผู้ป่วยเป็นกลุม DESH และ non-DESH โดยพิจารณาตามภาพรังสีระบบประสาท ผลลัพธ์ของการรักษาประเมินโดย idiopathic normal pressure hydrocephalus grading scale (iNPHGS), modified Rankin scale (mRS), อาการทาง bulbar และอาการทางจิตเวช ภาวะแทรกซ้อน ถูกประเมินที่ระยะหลังผ่าตัดทันที ระยะมาตรวจติดตามการรักษาครั้งแรก ที่ระยะ 4-6 เดือน ระยะ 1 และ 2 ปีหลังการผ่าตัดรักษา ผลลัพธ์ที่ดีจากการรักษาคือการเพิ่ม iNPHGS และ iNPH และmRS ในเวลาต่างๆ

ผลการศึกษา: ผู้ป่วย iNPH (n = 106) แบ่งเป็นกลุ่ม DESH (n = 72) และกลุ่ม non-DESH (n = 34) พบว่า favorable improvement ในทั้งสองกลุ่มในการติดตามครั้งแรก (73.5% ในกลุ่ม non-DESH และ 88.9% ในกลุ่ม DESH, p = 0.044) ที่ระยะ 4-6 เดือนหลังผ่าตัด (72.7% ในกลุ่ม non-DESH และ 79.4% ในกลุ่ม DESH, p = 0.452) ที่ระยะ 1 ปี (65.9% ในกลุ่ม non-DESH และ 79.7% ในกลุ่ม DESH, p = 0.141) ที่ระยะ 2 ปี (66.7% ในกลุ่ม non-DESH และ 59.6% ในกลุ่ม DESH, p = 0.54) โดยที่ไม่มีความแตกต่างระหว่างชนิดการผ่าตัด (ventriculoperitoneal [VP] หรือ lumboperitoneal [LP] shunt) ในระยะเวลาต่างๆ

สรุป: ในผู้ป่วย iNPH ทั้ง DESH และ non-DESH มีการตอบสนองต่อการผ่าตัดได้ดีจนถึงระยะ 2 ปีหลังการผ่าตัดรักษา โดยมีผลข้างเคียงเล็กน้อยจากการผ่าตัด โดยไม่มีความแตกต่างระหว่างชนิดของการผ่าตัดทั้งสองวิธี

Introduction

Nowadays, there were an increase in the elderly population in Thailand. In 2019, there were reported of 11 million elderly in Thailand accounting for 16% of the population.[1] According to an elderly person with dementia, some reported the prevalence of normal pressure hydrocephalus was about 0.9% of patients with dementia in the Geriatrics clinic.[2] Many experts proposed that idiopathic normal pressure hydrocephalus (iNPH) is one of the neurodegenerative diseases. Accordingly, the diagnosis of normal pressure hydrocephalus is increasing with advanced age. Patients with normal pressure hydrocephalus (NPH) had a clinical triad of Hakim defined as gait abnormality, cognitive impairment, and/or urinary disturbance with diagnostic brain imaging of brain demonstrated dilation of the ventricle (Evans' index[3] more than 0.3) according to NPH guidelines from American-European guideline[4], American Academy of Neurology Guideline[5] and Japanese iNPH guideline[6](JG). When clinical imaging of the patient was confirmed without other defined causes of hydrocephalus, hence the diagnosis of possible iNPH could be established. The spinal tap test also assured the diagnosis of probable iNPH.[7] According to American-European Guidelines (AEG) and Japanese Guideline (JG), there was some difference in the diagnosis of probable and possible iNPH.[8] In AEG[4], diagnosis of probable iNPH are symptoms

of gait/balance disturbance with at least one of two clinical symptoms i.e. a) cognitive impairment and b.) Urinary incontinence/urgency and including with ICP ≤ 20 cmH_2O and brain imaging of ventriculomegaly (Evans' index > 0.3) with at least one of these features i.e. a) Narrow callosal angle b) Enlargement of the temporal horns c) Periventricular signal changes. In contrast to JG6, diagnosis of possible iNPH with MRI support are any two of three symptoms in the clinical triad i.e. Gait disturbance, cognitive impairment and urinary incontinence and brain imaging of ventriculomegaly (Evan's index > 0.3) with a feature of narrowing of the sulci over the high convexity and/or Disproportionately enlarged subarachnoid space hydrocephalus (DESH). The diagnosis of definite iNPH was confirmed when the patient clinical improved after shunt surgery[9] composed of ventriculoperitoneal (VP) shunt, ventriculoatrial (VA) shunt, ventriculopleural shunt and lumboperitoneal (LP) shunt.[10] In addition to the Hakim triad, some patients suffered from other serious symptoms such as microaspiration[11], choking, hoarseness[12], mood disorders, depression or sleep disturbance (neuropsychiatric symptoms)[13] which can worsen patient condition into bed bound. If patients with probable iNPH left untreated, some[14] reported 5 years mortality rate as high as 87.5%. On imaging study, there was some feature which specific to idiopathic normal pressure hydrocephalus (iNPH), defined as Disproportional Enlargement of Subarachnoid space Hydrocephalus; DESH[15], according to Japanese guideline1',[16] which reported of a positive outcome in those patients with DESH appearance on imaging.[17] In the patient with no DESH appearance on imaging, defined as non-DESH or DESH-negative iNPH found to have a positive outcome after treatment.[17,18] Therefore, the objectives of this study were to examine whether there was a valuable outcome in the treatment of the patient with non-DESH iNPH group and to find out 2-years outcome after treatment in those groups.

Methods

Study design

The authors conducted a retrospective single-center cohort study of cerebrospinal fluid shunt (CSF) surgery for patients with iNPH in Siriraj hospital. All patients received either VP shunt or LP shunt surgery from September 2014 to November 2016 (26 months duration). Participants were grouped into DESH iNPH and non-DESH which were classified by neurosurgeons' perspective and neuroradiologists as shown in Figure 1. The primary measurement was the favorable outcome 1 year after surgery, which was either improvement of more than 1 point of the idiopathic Normal Pressure Hydrocephalus Grading Scale (iNPHGS)[10,19] or a modified Rankin Scale (mRS). The secondary measurements were favorable outcomes at the first visit (1-2 weeks), 4-6 months, and 2 years after surgery, which was defined above, improvement in neuropsychiatric (which include sleep disturbance) symptoms and bulbar symptoms (defined as either microaspiration, hoarseness of voice, choking, or speechless) at 4-6 months, 1 year and 2 years, respectively. The study protocol was approved by Siriraj Institutional Review Board.

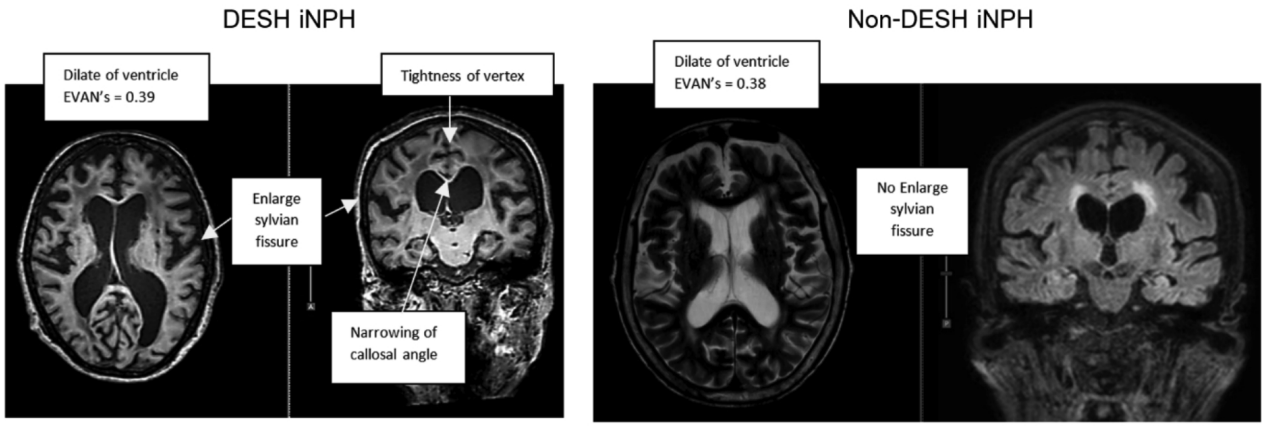


Figure 1 Imaging of DESH showing hydrocephalus with enlargement of subarachnoid space and tight vertex and narrowing of callosal angle and non-DESH iNPH showing hydrocephalus without sign of DESH (i.e. no tight vertex, mild dilate of subarachnoid space with no narrowing of callosal angle)

Study populations

All participants were patients with a diagnosis of suspected iNPH in Siriraj hospital between September 2014 and November 2016 who received CSF shunt surgery. The following inclusion criteria were 1) patient age > 60 years; 2) clinical triad of iNPH (abnormal gait, cognitive impairment, and urinary impairment) which is defined as iNPHGS; 3) Radiographic images of hydrocephalus, which defined as Evans' index > 0.3. Exclusion criteria were normal pressure hydrocephalus due to other defined causes and patients with no radiologic images documented from medical records.

Procedure and Outcome measurement

All patients who met all the above criteria were collected for statistical analysis. Participants were classified into two groups depending on radiographic appearance, based on neuroradiologists' and neurosurgeons' perspectives, comprised of DESH iNPH and non-DESH iNPH. All participants received surgery either VP shunt or LP shunt. For VP shunt, the implanted valves were either Codman Hakim® programmable valve with Siphonguard®, Medtronic programmable Strata II® or Medtronic fixed pressure valve®. Medtronic programmable NSC® valve, the only programmable LP shunt available in our institution, was used for LP shunt. The CSF shunt surgery was performed between September 2014 and November 2016 in our institution.

Preoperative data of participants were collected including patient characteristics (age and gender), comorbidities, preoperative iNPHGS[19], mRS, neuropsychiatric symptoms which are defined as any symptoms of mood disorders, depression, aggressiveness or sleep disturbance, and bulbar symptoms which defined as any symptoms of microaspiration, chocking or hoarseness of voice. The primary outcome measurement was the improvement of iNPHGS and/or mRS 1 year after surgery. Secondary outcomes were improvement of iNPHGS and/or mRS at 4-6 months, 1 year, and 2 years; improvement of neuro-

psychiatric and bulbar symptoms at 4–6 months, 1 year, and 2 years after surgery. Other outcomes were also collected; including adverse events at the first visit (usually 2–4 weeks), 4–6 months, 1 year, and 2 years after surgery (defined as medical complications and shunt-related complications). The positive response to surgery was defined as an improvement of 1 or more points in either iNPHGS or mRS at any evaluation point of the visit.

Statistical analysis

The categorical independent variables were presented as number or percentage, mean ±SD, or median (minimum, maximum) were carried out as appropriate distribution of data.

The association for univariate analysis, the categorical independent variables with DESH/non-DESH was assessed by the Chi-square test, and the significance of the continuous variable was assessed with a 2-sample independent *t*-test or Mann Whitney U test. A *p*-value of less than 0.05 was statistically significant. Statistical data were analyzed using SPSS version 18.

Results

Between September 2014 and November 2016 (26 months period), all data of diagnosed normal pressure hydrocephalus patients who received surgical treatment in Siriraj hospital were collected. One hundred thirty-five patients who underwent cerebrospinal fluid (CSF) shunt surgery were recorded in our institution. Anyway, twenty-four patients were reclassified as secondary NPH (sNPH) after intensely reviewing the complete data and 5 patients had no adequate record and/or imaging data. Accordingly, 29 out of 135 patients were excluded from this study, and 106 patients met the criteria of this study. Seventy-two out of 106 patients (67.9%) were classified as DESH iNPH whereas 34 out of 106 patients (32.1%) were non-DESH iNPH by definition. The ratio of DESH and non-DESH iNPH was 2:1 approximately. The CSF shunt surgery was performed using programmable ventriculoperitoneal (VP) shunt and programmable lumboperitoneal (LP) shunt depending on the neurosurgeon's preference. Codman® valve with or without Siphonguard or Medtronics Stata II® valve system was chosen for VP shunt in 62 patients (65.72%) but Medtronics NSC® valve which has had only one LP valve available in our institution was made in 44 patients (34.28%). The follow-up clinical and imaging data were reviewed at the first visit (usually 2–4 weeks), 4–6 months visit, 1 year, and finally 2 years visit. At 4–6 months follow-up period, 5 out of 106 patients (5.3%) lost to follow-up remained 92 patients. Nine out of 92 patients (8.28 %) were lost at 1 year follow-up period (VP shunt = 60, LP shunt =32). Finally, 17 out of 92 patients lost to follow up and 75 out of 106 patients (79.5%) remained in this study (VP shunt = 48, LP shunt = 27) at 2 years follow-up period. All number of patients was demonstrated in Figure 2.

Characteristics and clinical of patients at baseline

All demographic and underlying condition characteristics of patients are summarized in Table 1. Approximately two-thirds (67.9 %) of patients in this study were classified as DESH iNPH while around

one-third (32.1%) of patients were non-DESH iNPH. There was no statistical difference in age between DESH (77.8 ±7.5 years old) and non-DESH iNPH (78.8 ± 7.6 years old). Concerning gender, there was no statistical difference (p = 0.358) between DESH and non-DESH iNPH groups. According to the underlying diseases of the patients, we identified the comorbidity factors composed of cerebrovascular disease (CVA), Parkinson's disease (PD), Alzheimer's disease (AD)/dementia, benign prostatic hypertrophy (BPH), diabetes mellitus (DM), hypertension (HT), dyslipidemia (DLP), atrial fibrillation (AF), chronic kidney disease (CKD), ischemic heart disease (IHD) and others chronic diseases (e.g., hypothyroid, osteoarthritis, cirrhosis). Interestingly, there were only three conditions, PD, AD, and ischemic heart diseases, which seemed to be different between DESH and non-DESH groups but not statistically significant. Twenty-seven out of 106 patients (25.47%) had a history of Parkinson's disease. Concomitant with Parkinson's disease, 12 out of 34 patients (35.4%), presented in the non-DESH group while 15 out of 72 patients (20.8%) presented in the DESH iNPH group (p 0.111). For Alzheimer's disease, it seemed much more often in the non-DESH iNPH (23.5%) than DESH iNPH (9.7%) group but not statistically significant (p = 0.057). Lastly, a history of ischemic heart disease was frequently seen at 23.5% in non-DESH iNPH compared with 11.1% but not statistically significant (p 0.096) as well.

The mean baseline of clinical data of iNPH patients included the total and different three domains of iNPHGS, mRS, presented bulbar symptoms, and neuropsychiatric symptoms were demonstrated in Table 2. In comparison to the clinical characteristics of iNPH patients, there were no clinical statistically significant between DESH and non-DESH iNPH. The mean baseline total iNPHGS was 8.70 ± 1.98 in both iNPH groups as well as other domains of iNPHGS with a mean baseline gait score of 3.05 ± 0.72, mean baseline cognitive score of 2.81 ± 0.82, and mean baseline urinary score 2.82 ± 0.83. The quality of life determined by mean ± SD of the modified Rankin scale (mRS) was 3.77 ± 0.94. Interestingly, 79 out of 106 patients (74.5%) had bulbar symptoms which had a history of choking, hoarseness of voice, and microaspiration and 77 out of 106 patients (72.64%) had neuropsychiatric symptoms i.e. mood disorders, depression, aggressiveness or sleep disturbance but no difference between two groups of patients (p = 0.294 and p = 0.889, respectively).

Clinical outcomes after CSF shunt surgery

Adverse outcomes

The adverse events were defined into two groups: medical complications (e.g. hyponatremia, delirium, seizure, pneumonia, UTIs, sepsis, dizziness, psychotic symptoms) and shunt-related complications (i.e. shunt over-drainage with or without intracranial hemorrhage, shunt under drainage or malfunction, shunt malposition). There was 16.39% in overall adverse events which separated into 10.59% of medical complications and 5.8% in shunt-related complications. Most of the complications occurred after 4-6 months as shown in Figure 3 Adverse events after CSF shunting comparing non-DESH iNPH and DESH iNPH. According to shunt-related complications, there were no differences in both groups at

any time (Figure 3 Adverse events after CSF shunting comparing non-DESH iNPH and DESH iNPH. Details of the patient's shunt-related complications were described in detail (Table 3).

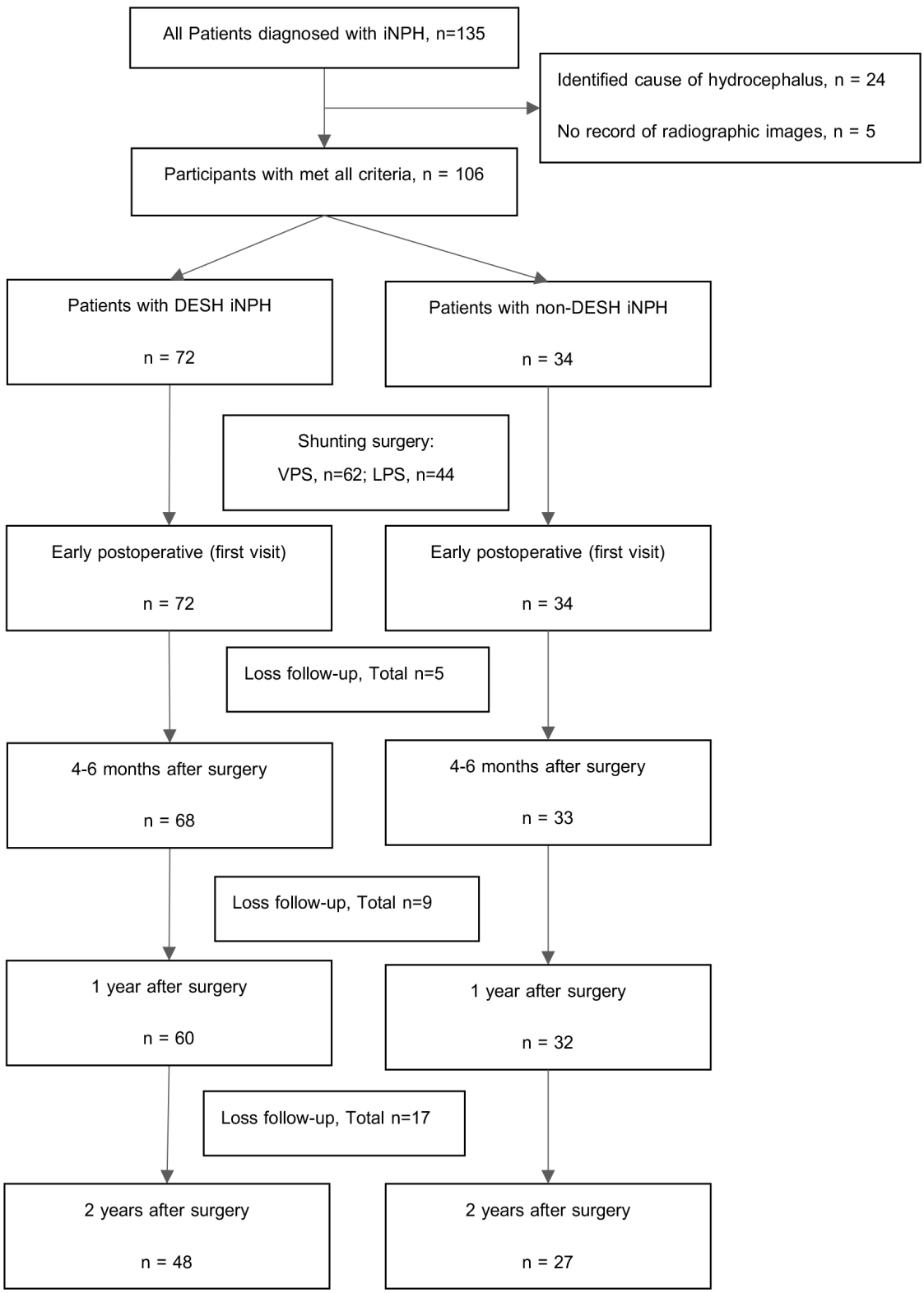


Figure 2 Flowchart showing number of patients from initial baseline to last outcome (2 years after surgery)

Table 1 Demographic data of study population

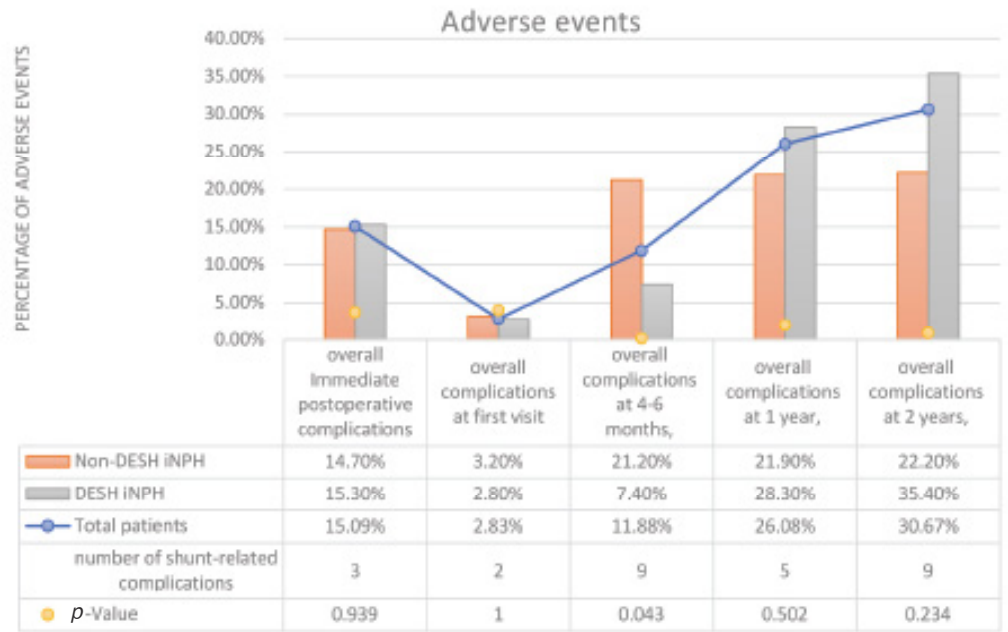
Parameter	Total No. of pts	Non-DESH iNPH	DESH iNPH	*p*-Value
Number of patients	106	34	72	
Age (years)		78.8±7.6	77.8±7.5	0.518
Gender: Male (%)	65	23 (67.6)	42 (58.3)	0.358
Female (%)	41	11 (32.4)	30 (41.7)	
Underlying conditions (%)				
- Cerebrovascular disease	26	7 (20.6)	19 (26.4)	0.517
- Parkinson's syndrome	27	12 (35.6)	15 (20.8)	0.111
- Alzheimer 's disease/Dementia	15	8 (23.5)	7 (9.7)	0.057
- Benign prostatic hypertrophy	19	7 (20.6)	12 (16.7)	0.623
- Diabetes Mellitus	34	9 (26.5)	25 (34.7)	0.396
- Hypertension	73	22 (64.7)	51 (70.8)	0.525
- Dyslipidemia	30	9 (26.5)	21 (29.2)	0.774
- Atrial fibrillation	5	2 (5.9)	3 (4.2)	0.655
- Chronic kidney disease	13	2 (5.9)	11 (15.3)	0.169
- Ischemic heart disease	16	8 (23.5)	8 (11.1)	0.096
Others (e.g. Hypothyroid, Osteoarthritis, cirrhosis)	22			

Table 2 Clinical characteristics (iNPHGS, mRS, bulbar symptoms, and psychiatric symptoms) of the study population comparing DESH iNPH group and non-DESH iNPH

Pre-preoperative status	Total (n=106)	Non-DESH iNPH (n=34)	DESH iNPH (n=72)	*p*-Value
iNPHGS, mean ± SD	8.70 ± 1.98	8.65 ± 1.98	8.72 ± 2.0	0.686
- Gait score	3.05 ± 0.72	2.88 ± 0.76	3.13 ± 0.69	
- Cognitive score	2.81 ± 0.82	2.82 ± 0.79	2.81 ± 0.83	
- Urinary score	2.82 ± 0.83	2.91 ± 0.75	2.78 ± 0.86	
mRS, mean ± SD	3.77 ± 0.94	3.74 ± 0.86	3.79 ± 0.97	0.597
No. of patients with bulbar symptoms (no)	79	26	53	0.294
No. of patients with neuropsychiatric symptoms (no)	77	25	52	0.889

Outcome at the first visit

Clinical outcome at the first visit, usually 2-4 weeks after surgery, was described as a subjective improvement by patients, relatives, or clinicians. There was a higher improvement in DESH iNPH (88.9%) than non-DESH iNPH (73.5%, $p = 0.04$) as shown in Tabe 4. Meanwhile, adverse outcomes (including shunt-related complications) least occurred during this time (Figure 3 Adverse events after CSF shunting comparing non-DESH iNPH and DESH iNPH).



	overall Immediate postoperative complications	overall complications at first visit	overall complications at 4-6 months,	overall complications at 1 year,	overall complications at 2 years,
Non-DESH iNPH	14.70%	3.20%	21.20%	21.90%	22.20%
DESH iNPH	15.30%	2.80%	7.40%	28.30%	35.40%
Total patients	15.09%	2.83%	11.88%	26.08%	30.67%
number of shunt-related complications	3	2	9	5	9
p-Value	0.939	1	0.043	0.502	0.234

Figure 3 Adverse events after CSF shunting comparing non-DESH iNPH and DESH iNPH

Results at 4-6 months after surgery

At 4 to 6 months after shunt surgery, the total number of patients was 101 out of 106. the mean ± SD of iNPHGS of 7.10 ± 2.78 which decreased than the mean ± SD of iNPHGS of 8.70 ± 1.98 in the preoperative period but had no statistic significant (p 0.850) between DESH and non-DESH iNPH as well as the other domain of iNPHGS which has had better than preoperative period. The quality of life of DESH and non-DESH iNPH was slightly improved with a mean ± SD of mRS (3.24 ± 1.13) compared to preoperative mRS (3.77 ± 0. 94).

Moreover, 50 out of 87 patients (57.47%) had improvement in bulbar symptoms which had a history of choking and microaspiration, and 43 out of 84 patients (51.19%) had improvement in neuropsychiatric symptoms but no difference between DESH and non-DESH iNPH patients (Table 5). Meanwhile, a higher incidence of adverse events occurred during 4-6 months (11.88%) with more frequent in non-DESH group (21.2%) compared to DESH group (7.4%) at 4-6 months (p = 0.043).

Table 3 Described patients with shunt-related complications

No.	age	underlying	imaging	pre-op INPHGS	pre-op mRS	type of surgery	complication	time after surgery	treatment	final outcome
1	89	HT, spinal stenosis, OA knee	non-DESH	9	4	VP shunt (Codmans with	Abdominal wall hematoma	immediate	Explore wound with clot removal	improve
2	82	DM, Alzheimer's disease, gout, IHD	non-DESH	9	4	VP shunt (Codmans with	Shunt malposition	first visit	-	not improve
3	86	HT, DLP	DESH	6	2	LP shunt	Abdominal pseudocyst	first visit	Revise LP shunt	improve
4	75	PD, old CVA, DLP	non-DESH	7	4	VP shunt (Codmans with siphonguard)	Shunt malposition	4-6 months	revise VP shunt	improve
5	76	DM, HT, CA prostate	non-DESH	7	2	LP shunt	shunt overdrainage with SDH	4-6 months	-	not improve
6	63	DM, HT, old CVA, DLP, IHD, OA knee	DESH	9	4	VP shunt (Codmans with siphonguard)	Shunt malposition	4-6 months	revise VP shunt (peritoneal end)	improve
7	77	none	DESH	6	2	VP shunt (medtronic)	Shunt malfunction	4-6 months	revise VP shunt	improve
8	74	Alzheimer disease, PD	non-DESH	12	5	VP shunt (Codmans with siphonguard)	shunt overdrainage with SDH	4-6 months	-	not improve
9	81	DM, HT, DLP, old CVA	non-DESH	8	4	VP shunt (Codmans with siphonguard)	shunt overdrainage with SDH	4-6 months	Burr holes craniostomy with drainage	improve
10	77	DM, HT, BPH, IHD	DESH	8	4	LP shunt	Shunt malfuction	1 year	Revise LP shunt	improve
11	76	HT, DLP, old CVA	DESH	9	4	LP shunt	Shunt malfunction	1 year	revise LP shunt (spinal	improve
12	78	old CVA, BPH	DESH	11	5	LP shunt	shunt overdrainage with SDH	1 year	-	not improve
13	78	old CVA	DESH	8	4	LP shunt	Shunt malfuction	2 years	Revise LP shunt	not improve
14	86	Alzheimer disease, HT, BPH, CKD	DESH	9	4	VP shunt (medtronic)	suspected shunt malfunction	2 years	-	not improve
15	71	HT, OA knee	DESH	8	4	LP shunt	suspected shunt malfunction	2 years	-	not improve
16	84	old CVA, HT, DLP, IHD, DVT	non-DESH	7	3	LP shunt	shunt malfunction	2 years	LP tap test then revise LP shunt	not improve

Table 4 Overall improvement after CSF shunting comparing non-DESH iNPH and DESH iNPH

Result	Total no. of pts	Non-DESH iNPH	DESH iNPH	*p*-Value
Result at first visit (no. of patients)	106	34	72	
No. of improvement		25 (73.5%)	64 (88.9%)	0.044

Table 5 Clinical outcome of iNPH patients at 4-6 months follow-up period comparing non-DESH iNPH and DESH iNPH groups

Parameter	Total no. (n=101)	Non-DESH iNPH (n=33)	DESH iNPH (n=68)	*p*-Value
iNPHGS, mean ±SD	7.10 ± 2.78	7.06 ± 2.72	7.11 ± 2.84	0.850
- No. of patients with positive outcome (%)	77.22%	72.7%	79.4%	0.452
mRS, mean ± SD	3.24 ± 1.13	3.18 ± 1.04	3.26 ± 1.18	0.651
- No. of patients with positive outcome (%)	51.48%	48.5%	52.9%	0.674
Improvement in bulbar symptoms (%)	57.47%	48.1%	61.7%	0.270
Improvement in neuropsychiatric symptoms (%)	51.19%	53.6%	50%	0.204

Results at 1 year after surgery

At this time, the total number of patients during this period was 92 (out of 106) patients. The improvement of both groups of iNPH patients seems to be stable at 1 year follow-up period as compared to the 4-6 month follow-up period (Table 6). The total number of patients with positive outcome during this period was 73.91%. There was slightly more improvement in the DESH group (79.7%) than in the non-DESH group (65.6%) but not statistically significant (p = 0.141). According to adverse events, there was a decrease in events during this time compared to the 4-6 months period.

Results at 2 years after surgery

At this time, the total number of patients during this period was 75 out of 106 patients. The clinical of iNPH patients have slightly deteriorated at 2 years after surgery. Seventy-five out of 106 preoperative patients (70.75%) had continued this study with

Table 6 Clinical outcome of iNPH patients at 1 year follow-up period comparing non-DESH iNPH and DESH iNPH

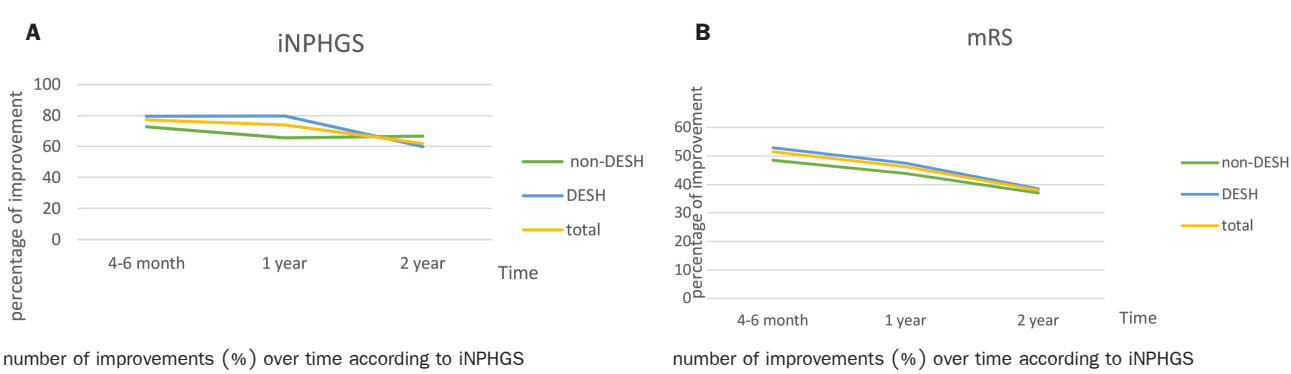
Parameter	Total no. (n=92)	Non-DESH iNPH (n=32)	DESH iNPH (n=60)	*p*-Value
iNPHGS, mean ±SD	6.83 ± 3.23	7.42 ± 2.69	6.54 ± 3.45	0.392
- No. of patients with positive outcome (%)	73.91%	65.6%	79.7%	0.141
mRS, mean ± SD	3.32 ± 1.16	3.28 ± 1.14	3.34 ± 1.18	0.640
- No. of patients with positive outcome (%)	45%	43.8%	47.5%	0.735
Improvement in bulbar symptoms (%)	53.5%	52.2%	54.2%	0.956
Improvement in neuropsychiatric symptoms (%)	45.7%	53.8%	40.0%	0.338

mean ± SD of iNPHGS of 6.88 ± 3.51 and mean ± SD of mRS of 3.52 ± 1.20. The percentage of patients who improved in bulbar symptoms and neuropsychiatric symptoms seems to decrease at this 2-year follow-up period (39.6% and 38.4%respectively) as shown in Table 7. There was an increase in adverse events during this time (compared to the 1 year).

Table 7 Clinical outcome of iNPH patients at 2 years follow-up period comparing non-DESH iNPH and DESH iNPH

Parameter	Total no. (n=75)	Non-DESH iNPH (n=27)	DESH iNPH (n=48)	*p*-Value
iNPHGS, mean ±SD	6.88 ± 3.51	7.32 ± 2.64	6.68 ± 3.84	0.930
- No. of patients with positive outcome (%)	65.3%	66.7%	59.6%	0.540
mRS, mean ± SD	3.52 ± 1.20	3.37 ± 1.07	3.60 ± 1.27	0.215
- No. of patients with positive outcome (%)	40.0%	37%	38.5%	0.902
Improvement in bulbar symptoms (%)	39.6%	41.2%	39%	0.850
Improvement in neuropsychiatric symptoms (%)	38.4%	50.0%	33.3%	0.440

According to the number of patients and iNPHGS improvement, there was more improvement in DESH iNPH group at 4-6 months (79.4% vs 72.7% in non-DESH) and 1 year (79.7% vs 65.6% in non-DESH) but reverse in 2 years (59.6% in DESH vs 66.7% in non-DESH) without statistic significant (Figure 2). According to mRS, there was a decline in the number of patients improved in both groups at 4-6 months, 1 year, and 2 years (52.9%, 47.5%, and 38.5% in the DESH group and 48.5%, 43.8%, and 37% in non-DESH group, respectively) with more improvement in DESH group (Figure 4A and B) but with no statistically significant.



number of improvements (%) over time according to iNPHGS

number of improvements (%) over time according to iNPHGS

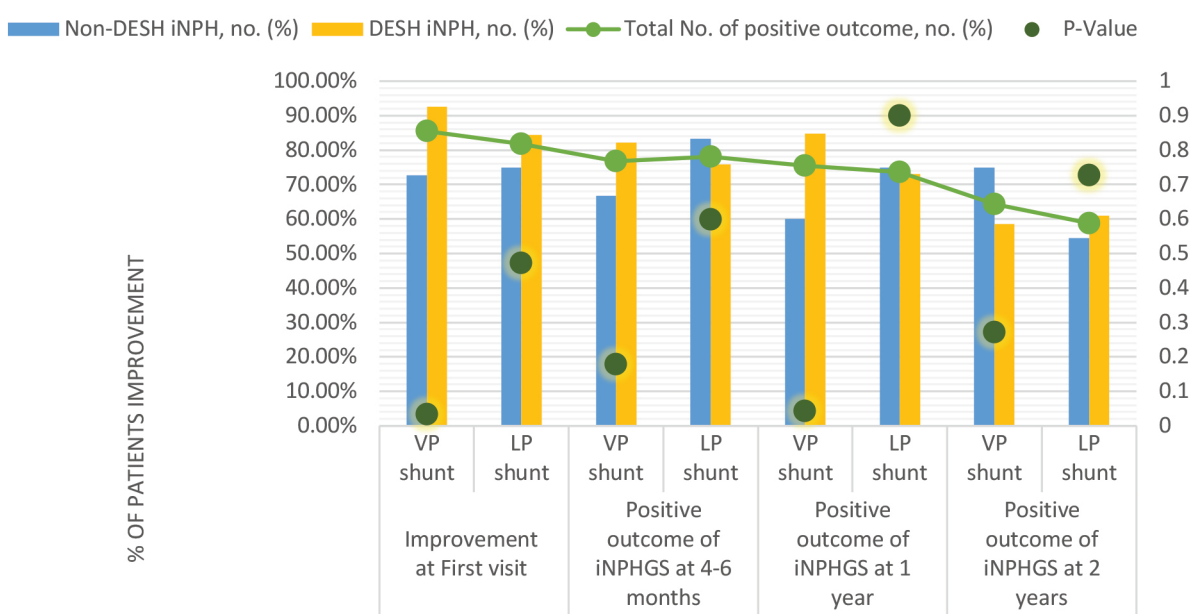
Figure 4 **A:** Showing the number of improvements (%) over time according to iNPHGS
B: Showing the number of improvements (%) over time according to mRS

Comparison of results between VP shunt and LP shunt surgery (a positive outcome of iNPHGS)

Concerning types of shunt surgery, the clinical improvement of VP shunt and LP shunt was highest at the first visit and decreased at the following 4–6 months visit, 1–year visit until the 2 years follow–up period. There were no differences in overall outcomes over time of both types of surgery (VP shunt vs LP shunt) as described in Figure 5. Subgroup analysis showed more improvement in the DESH group with VP shunt surgery at the first visit (92.5% vs 72.7% in non–DESH, p = 0.034) and 1 year after surgery (84.8% vs 60% in non–DESH, p = 0.042).

Prediction factors with a positive outcome of iNPHGS

All comorbidities (underlying conditions) were analyzed according to postoperative iNPHGS improvement. The comorbidity which had a positive predictive value of shunt outcome was no history of Alzheimer's disease or dementia, no history of diabetes mellitus, and no previous ischemic heart disease as shown in Table 8. The iNPH patients without Alzheimer's disease had significant positive outcomes 88.9%, 89.9%, and 92% at 4–6 months, 1–year visits, and 2 years, respectively. The patient without underlying DM (78.8%; p = 0.035) and without previous ischemic heart disease had positive outcomes at a 1year follow–up period (89.9%; p = 0.025)



	VP shunt	LP shunt	VP shunt	LP shunt	VP shunt	LP shunt	VP shunt	LP shunt
	Improvement at First visit		Positive outcome of iNPHGS at 4-6 months		Positive outcome of iNPHGS at 1 year		Positive outcome of iNPHGS at 2 years	
Non-DESH iNPH, no. (%)	72.70%	75%	66.70%	83.30%	60.00%	75.00%	75.00%	54.50%
DESH iNPH, no. (%)	92.50%	84.40%	82.10%	75.90%	84.80%	73.10%	58.60%	60.90%
Total No. of positive outcome, no. (%)	85.50%	81.80%	76.70%	78.00%	75.50%	73.70%	64.40%	58.80%
P-Value	0.034	0.473	0.179	0.599	0.042	0.9	0.272	0.726

Figure 5 Comparative outcome of iNPH patients treated with VP shunt and LP shunt in non–DESH and DESH iNPH

Table 8 Prediction factors with a positive outcome of iNPHGS composed of Alzheimer's disease/ dementia, DM and ischemic heart disease.

Underlying conditions	Positive outcome at 4–6 months (%)	*P*–Value	Positive outcome at 1 year (%)	*P*–Value	Positive outcome at 2 years (%)	*P*–Value
Without a history of Alzheimer's disease/Dementia	88.9	0.071	89.9	0.025	92	0.054
Without a history of Diabetes Mellitus	72.8	0.135	76.8	0.035	76.0	0.131
Without a history of Ischemic heart disease	86.4	0.646	89.9	0.025	86.0	0.933

Comparison between baseline iNPHGS with a positive outcome at 4-6 months and 1 year after surgery

The baseline clinical (iNPHGS) of the patient was analyzed to predict outcomes after surgery. There was a significant improvement in the number of patients with baseline iNPHGS scores between 7 and 9 at 4–6 months follow–up period and one year after surgery (Figure 6). Showing pre–operative iNPHGS compared to shunt responsive and non–responsive group at 4 months and 12 months follow up period

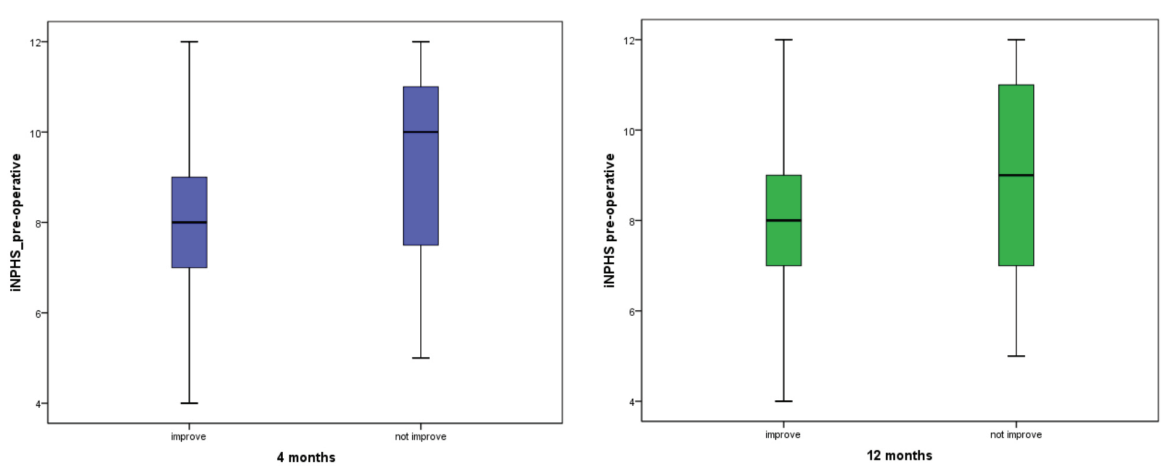


Figure 6 Showing pre–operative iNPHGS compared to shunt responsive and non–responsive group at 4 months and 12 months follow up period

Discussion

This study was a retrospective study to compare the outcome of surgical treatment of either VP shunt and LP shunt in iNPH patients who were classified into two groups: DESH iNPH and non–DESH group. According to the grouping of patients, there might be some conflict in the diagnosis of DESH due to lacking a good measurement tool to differentiate both groups. Some proposed measurement scoring called "DESH score"[15,16] to evaluate the DESH pattern includes five domains of the score (from 0–2): 1.) Evan's index 2.) Dilatation of Sylvian fissures 3.) tightness high convexity 4.) acute callosal angle and 5.) focal sulcal

dilation which is higher in total score show to have a high positive predictive value for improvement. This study has not applied this tool because of the inadequate quality of brain imaging in the medical record, as a result of brain MRI performed in some iNPH patients. According to preoperative baseline status, there was no statistical difference in patient characteristics at baseline between DESH iNPH and non-DESH iNPH group, except for Parkinson's disease and Alzheimer's disease. There were higher proportions of those diseases in the non-DESH group because the non-DESH group has not met the criteria for the diagnosis of DESH pattern upon imaging except for ventricular dilation. Clinical normal pressure hydrocephalus was also similar in Parkinson's and Alzheimer's disease, thereupon no finding of DESH upon imaging was hardly distinguishing between iNPH and other neurodegenerative diseases. In the previous study, Danielle et al.[20], reported 89% of NPH patients co-existed with Alzheimer's disease on autopsy. Jonathan et al.[21], reported 19% of NPH patients with concomitant Alzheimer's pathology based on brain biopsy at shunting time. Neill[22] reported about 30% of patients with NPH could have coexisting AD pathology. However, there was no difference in the patient's clinical at baseline between the two groups.

According to the number of patients, there was a decreased number of patients during the follow-up period (Figure 2). We suspected that some patients might lose follow-up, and some might have comorbidity and/or decreased over time due to most of the patients being elderly patients and some having serious comorbid which could affect patient status. As shown in adverse outcomes after surgery (Figure 3), there was an increase in adverse outcomes over time as high as 30.6% at 2 years follow-up (overall complications). As Alberto[23] reported over 40% of patients experienced at least one post-VPS complication. This study found a low incidence (5.8%) of shunt-related complications (as described in Table 3). There was a limitation of this study due to respective chart reviews and not mentioning the reasons for the patient loss in the medical record.

This study applied iNPHGS[19] for the measure of outcome and mRS for assessing functional status. According to iNPHGS, there were three domains with a score of 0-4 including a) cognitive impairment, b) gait disturbance and c) urinary disturbance. For the gait score, it seemed similar to mRS such as a score of 4 in iNPHGS defined as walking not possible that might equal to mRS score of 5. We found no statistical difference in baseline iNPHGS and mRS in both groups (Table 2). The mean iNPHGS of all patients was 8.70 ± 1.98 with a mean gait score of 3.05 ± 0.72 which means that the average of patients walked without any support. For mRS, the mean score was 3.77 ± 0.94 which means that the average of patients had moderate to severe disability and require help. We also collected bulbar and neuropsychiatric symptoms but there was limited data due to incomplete medical records.

According to outcomes after surgery, there was an overall improvement in both two groups with a better outcome in DESH iNPH group at the first visit (88.9% vs. 73.5%, p = 0.04) and 1 year (79.7% vs. 65.6%, p = 0.14 with another group) but no statistic difference at 4-6 month (72.7% vs. 79.4, p = 0.45) and 2 years after surgery (66.7% vs 59.6%, p = 0.54). Compared with the previous study, Ishikawa et al.[17], reported a high improvement of 73.5% in the DESH group compared to 63.6% in the non-DESH group at early visits after discharge. Craven et al.[18], reported 77% of the DESH positive group vs 75%

DESH negative group had a response to shunt surgery during a one-year postoperative period. Our study demonstrated in the non-DESH group also had a fair outcome at any time after surgery. The hypothesis is a diagnosis of DESH on imaging still lacked criteria or cut-off points to diagnosis and operator dependent. Patients with the non-DESH group still had clinical normal pressure hydrocephalus, the treatment with shunting might improve CSF circulation[24] and clinical NPH. According to a long-term outcome study, there was one meta-analysis[23] showed controversy in outcomes after shunt surgery. Some reported long-term outcomes after 36 months and showed sustained improvement between 40-73%[22,23]. As in our study, the improvement of shunt surgery at 24 months was 65.3% similar to those studies.

In our study, we found no overall difference in the outcome of any type of shunting surgery at the first visit (85.5% of VPS vs 81.8% of LPS), 4-6 months (76.7% of VPS vs 78% of LPS), 1 year (75.5% of VPS vs 73.7% of LPS) and 2 years (64.4% of VPS vs 58.8% of LPS). Miyajima[10] reported a 75% improvement in iNPHGS in the LP shunt group in 1 year which was comparable to 77% in the VP shunt group. Giordan[25] also reported a 75% improvement in patients after shunting. In subgroup analysis, we found that VP shunt surgery had a better outcome in the DESH group at the first visit (92.5% vs 72.7% in non-DESH, p = 0.03), 4-6 months (82.1% vs 66.7% in non-DESH, p = 0.17) and 1 year (84.8% vs 60% in non-DESH, p = 0.04). According to Ishikawa[17], the study found high improvement in the DESH group, as mentioned above.

According to the patient condition at baseline, we found that patients with no history of Alzheimer's disease, DM, and ischemic heart disease had better positive outcomes, especially 1 year after surgery. We found high improvement of iNPHGS at 1 year 89.9% in the non-Alzheimer group (p = 0.025), 76.8% in the non-DM group (p = 0.035), and 89.9% in the non-ischemic heart group (p = 0.025). Hudson reported 15.7-17.8% of patients with iNPH had Co-morbidity of diabetes mellitus and might have unfavorable outcomes after surgery. Okko[26] also reported that increased risk of death in patients with DM type 2. For patients without Alzheimer's, there was a better outcome at any time after surgery. Pomeneraniec[21] found that NPH patients with concomitant Alzheimer's disease had lower improvement (18.2%) after surgery. We hypothesized that NPH with AD might have a progression of Alzheimer's disease that could make the patient's condition worsen.

In our study, we found patients with preoperative iNPHGS scores of 7-9 had better positive outcomes than others. We also found patients with preoperative iNPHGS scores of 9-11 had poorer outcomes, especially at 4-6 months and 1 year after surgery. It might be because the patient with high iNPHGS at baseline had poor functional status with many underlying conditions. That might affect the improvement of a score. Most of the patients with high iNPHGS were bed-bound patients at baseline with some having stiffness of joint, surgery might not improve functional outcome but improve minor clinical statuses such as consciousness or bulbar symptoms.

The study's limitations arose from the retrospective nature of the chart review and a significant percentage of patients who were lost to follow-up, which could impact

the surgical outcomes. A further prospective study should be provided in the future with more long-term outcomes and study in the cost-effectiveness of surgery.

Conclusions

All patients with a diagnosis of iNPH should receive surgical treatment with or without DESH findings on radiographic imaging. There was a favorable positive outcome with minor shunt-related complications until at least 2 years after surgery. There were no differences between any shunting surgery at any time (either VP or LP shunt).

Acknowledgment

The authors gratefully acknowledge Ms.Nerisa Thornsri, Clinical Epidemiology Unit, Office of Research and Development, Faculty of Medicine Siriraj Hospital, Mahidol University, for assistance with statistical analysis.

Conflict of interest

The authors declare that the article content was composed in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

References

1. (NESDB), N.E.a.S.D.B. *Older statistic*. 2019 [cited 2019; Available from: http://social.nesdc.go.th/SocialStat/StatReport_Final.aspx?reportid=697&template=2R1C&yeartype=M&subcatid=116.
2. Muangpaisan W, Petcharat C, Srinonprasert V. Prevalence of potentially reversible conditions in dementia and mild cognitive impairment in a geriatric clinic. Geriatr Gerontol Int. 2012;12(1):59-64.
3. Evans Wa. An Encephalographic Ratio For Estimating Ventricular Enlargement And Cerebral Atrophy. *Arch NeurPsych*. 1942;47(6):931-937.
4. Relkin N, Marmarou A, Klinge P, Bergsneider M, Black PM. Diagnosing idiopathic normal-pressure hydrocephalus. Neurosurgery. 2005;57(3 Suppl):S4-16; discussion ii-v.
5. Halperin JJ, Kurlan R, Schwalb JM, Cusimano MD, Gronseth G, Gloss D. Practice guideline: Idiopathic normal pressure hydrocephalus: Response to shunting and predictors of response: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. Neurology. 2015;85(23):2063-71.
6. Mori E, Ishikawa M, Kato T, Kazui H, Miyake H, Miyajima M, et al. Guidelines for management of idiopathic normal pressure hydrocephalus: second edition. Neurol Med Chir (Tokyo). 2012;52(11):775-809.
7. Bovonsunthonchai S, Witthiwej T, Ngamsombat C, Sathornsumetee S, Vachalathiti R, Muangpaisan W, et al. Effect of spinal tap test on the performance of sit-to-stand, walking, and turning in patients with idiopathic normal pressure hydrocephalus. Nagoya J Med Sci. 2018;80(1):53-60.
8. Andersson J, Rosell M, Kockum K, Söderström L, Laurell K. Challenges in diagnosing normal pressure hydrocephalus: Evaluation of the diagnostic guidelines. eNeurologicalSci. 2017;7:27-31.
9. Bergsneider M, Black PM, Klinge P, Marmarou A, Relkin N. Surgical management of idiopathic normal-pressure hydrocephalus. Neurosurgery. 2005;57(3 Suppl):S29-39; discussion ii-v.
10. Miyajima M, Kazui H, Mori E, Ishikawa M; , on behalf of the SINPHONI-2 Investigators. One-year outcome in patients with idiopathic normal-pressure hydrocephalus: comparison of lumboperitoneal shunt to ventriculoperitoneal shunt. J Neurosurg. 2016;125(6):1483-92.
11. Jo KW, Kim Y, Park GY, Park IS, Jang Y, Gyun SD, et al. Oropharyngeal dysphagia in secondary normal pressure hydrocephalus due to corticobulbar tract

compression: cases series and review of literature. Acta Neurochir (Wien). 2017;159(6):1005-11.
12. Chankaew E, Srirabheebhat P, Manochiopinig S, Witthiwej T, Benjamin I. Bulbar dysfunction in normal pressure hydrocephalus: a prospective study. Neurosurg Focus. 2016;41(3):E15.
13. Peterson KA, Savulich G, Jackson D, Killikelly C, Pickard JD, Sahakian BJ. The effect of shunt surgery on neuropsychological performance in normal pressure hydrocephalus: a systematic review and meta-analysis. J Neurol. 2016;263(8):1669-77.
14. Jaraj D, Wikkelsø C, Rabiei K, Marlow T, Jensen C, Östling S, et al. Mortality and risk of dementia in normal-pressure hydrocephalus: A population study. Alzheimers Dement. 2017;13(8):850-7.
15. Radovnicky, T., Adamek, D., Derner, M. Sames M. Disproportionately enlarged subarachnoid space hydrocephalus presence in patients with idiopathic normal pressure hydrocephalus. *Fluids Barriers CNS* 2015;12 (Suppl 1), P43.
16. Shinoda N, Hirai O, Hori S, Mikami K, Bando T, Shimo D, Kuroyama T, Kuramoto Y, Matsumoto M, Ueno Y. Utility of MRI-based disproportionately enlarged subarachnoid space hydrocephalus scoring for predicting prognosis after surgery for idiopathic normal pressure hydrocephalus: clinical research. J Neurosurg. 2017;127(6):1436-42.
17. Ishikawa M, Oowaki H, Takezawa M, Takenaka T, Yamada S, Yamamoto K, et al. Disproportionately Enlarged Subarachnoid Space Hydrocephalus in Idiopathic Normal-Pressure Hydrocephalus and Its Implication in Pathogenesis. Acta Neurochir Suppl. 2016;122:287-90.
18. Craven CL, Toma AK, Mostafa T, Patel N, Watkins LD. The predictive value of DESH for shunt responsiveness in idiopathic normal pressure hydrocephalus. J Clin Neurosci. 2016;34:294-8.
19. Kubo Y, Kazui H, Yoshida T, Kito Y, Kimura N, Tokunaga H, et al. Validation of grading scale for evaluating symptoms of idiopathic normal-pressure hydrocephalus. Dement Geriatr Cogn Disord. 2008; 25(1):37-45.
20. Cabral D, Beach TG, Vedders L, Sue LI, Jacobson S, Myers K, Sabbagh MN. Frequency of Alzheimer's disease pathology at autopsy in patients with clinical normal pressure hydrocephalus. Alzheimers Dement. 2011;7(5):509-13.
21. Pomeraniec IJ, Bond AE, Lopes MB, Jane JA Sr. Concurrent Alzheimer's pathology in patients with clinical normal pressure hydrocephalus: correlation of high-volume lumbar puncture results, cortical brain biopsies, and outcomes. J Neurosurg. 2016;124(2):382-8.
22. Graff-Radford NR, Jones DT. Normal Pressure Hydrocephalus. Continuum (Minneap Minn). 2019;25(1):165-86.
23. Espay AJ, Da Prat GA, Dwivedi AK, Rodriguez-Porcel F, Vaughan JE, et al. Deconstructing normal pressure hydrocephalus: Ventriculomegaly as early sign of neurodegeneration. Ann Neurol. 2017;82(4):503-13.
24. Lalou AD, Czosnyka M, Donnelly J, Pickard JD; FMedSci; Nabbanja E, Keong NC, Garnett M, Czosnyka ZH. Cerebral autoregulation, cerebrospinal fluid outflow resistance, and outcome following cerebrospinal fluid diversion in normal pressure hydrocephalus. J Neurosurg. 2019;130(1):154-62.
25. Giordan E, Palandri G, Lanzino G, Murad MH, Elder BD. Outcomes and complications of different surgical treatments for idiopathic normal pressure hydrocephalus: a systematic review and meta-analysis. J Neurosurg. 2018;131(4):1024-36.
26. Pyykkö OT, Nerg O, Niskasaari HM, Niskasaari T, Koivisto AM, Hiltunen M, et al. Incidence, Comorbidities, and Mortality in Idiopathic Normal Pressure Hydrocephalus. World Neurosurg. 2018;112:e624-e631.