The Predictive Value of White Matter Changes on Shunt Outcome in Patients With Idiopathic Normal Pressure Hydrocephalus

Student: Carl Snöbohm
Supervisor: Johan Virhammar, MD, PhD
Date: 2019-05-25
CONTENTS

1 Abstract .......................................................................................................................... 4

2 Populärvetenskaplig Sammanfattning på Svenska ....................................................... 5

3 Background .................................................................................................................. 7

3.1 Definition .................................................................................................................. 7

3.1.1 Hydrocephalus ...................................................................................................... 7

3.1.2 Classification of Normal Pressure Hydrocephalus .............................................. 7

3.2 Epidemiology ............................................................................................................. 7

3.3 Pathophysiology ........................................................................................................ 8

3.3.1 Cerebrospinal Fluid Mechanisms ....................................................................... 8

3.3.2 Cerebrovascular Mechanisms ............................................................................. 8

3.4 Clinical Manifestations ............................................................................................. 9

3.4.1 Gait Impairment ................................................................................................... 9

3.4.2 Cognitive Symptoms ............................................................................................ 9

3.4.3 Bladder Dysfunction ............................................................................................ 9

3.5 Diagnostic Approach ............................................................................................... 9

3.5.1 Clinical Assessment .............................................................................................. 10

3.5.2 Neuroimaging ....................................................................................................... 10

3.5.3 Invasive Prognostic Procedures .......................................................................... 10

3.6 Treatment and Prognosis ......................................................................................... 11

3.6.1 Surgical Shunt Implantation ................................................................................ 11

3.6.2 Clinical Outcome and Complications .................................................................. 11

3.7 White Matter Changes ............................................................................................. 12

3.7.1 Definition ............................................................................................................. 12

3.7.2 Epidemiology ...................................................................................................... 12

3.7.3 Pathophysiology .................................................................................................. 13

3.7.4 Clinical Significance ............................................................................................ 13

3.8 Rationale .................................................................................................................. 14

3.9 Aims ......................................................................................................................... 14
Methods

4.1 Study Population

4.1.1 Baseline Characteristics

4.2 Clinical Assessment

4.3 Magnetic Resonance Imaging Protocol

4.4 SmartPaint

4.5 Segmentation Process

4.6 Statistical Methods

Results

5.1 Outcome After Shunt Surgery

5.2 Radiological Features

5.3 Separate Domain Scores

5.4 Prediction of Outcome After Shunt Surgery

5.4.1 Modified version of the iNPH scale

5.4.2 Mini-mental state examination

5.5 Neurofilament Light Polypeptide

5.6 SmartPaint Validity

Discussion

6.1 Waiting Time for Shunt Surgery and Age

6.2 Separate Domain Scores

6.3 Cognitive Outcome

6.4 Neurofilament Light Polypeptide

6.5 White Matter Hyperintensities

6.6 Methodological Limitations

6.7 Conclusion

Acknowledgements

References
1 Abstract

BACKGROUND: Hyperintense white matter changes on brain imaging, known as deep white matter hyperintensities (DWMHs) and periventricular hyperintensities (PVHs) are frequently seen in patients with idiopathic normal pressure hydrocephalus (iNPH). Contradictory results have been reported as to whether these changes are predictors of shunt outcome in iNPH patients. The aim was to investigate the predictive role of PVHs and DWMHs on shunt outcome in iNPH patients.

METHODS: A total of 253 iNPH patients that were operated with shunt surgery between 2011 and 2015 and were clinically assessed before and 12 months after surgery were included. DWMHs and PVHs were measured by analyzing preoperative fluid-attenuated inversion recovery images with a volumetric segmentation software. Clinical outcome was defined as the difference in symptom score measured with the iNPH-scale between post- and preoperative investigations.

RESULTS: In a multivariable regression model with clinical outcome as the dependent variable, the volume of DWMH was negatively associated with shunt outcome (B=-0.552, p<0.05) after controlling for age and preoperative symptom score. The volume of PVH was not associated with shunt outcome.

CONCLUSION: The volume of DWMH is a predictor of a less favorable shunt outcome in iNPH patients. The volume of PVH does not predict shunt outcome.
2 Populärvetenskaplig Sammanfattning på Svenska

Idiopatisk normaltryckshydrocefalus (iNPH) är en sjukdom som leder till en ökad mängd cerebrospinalvätska (CSF) i hjärnans hålrum. Som namnet antyder är trycket i hjärnan oftast normal hos iNPH-patienter. Sjukdomen drabbar troligen cirka 1-2 % av den äldre populationen med de typiska symptomen gång- och balansrubbning, kognitiv nedsättning och urininkontinens. De bakomliggande mekanismerna till iNPH tros vara en kombination av patologiskt förändrade blodkärl och en dynamisk rubbning i cirkulationen av CSF. Diagnostiken innefattar en klinisk bedömning och en radiologisk avbildning av hjärnan, i första hand med magnetresonanstoromografi (MRT). På MRT syns en vidgning av hjärnans hålrum och ibland ljusa förändringar i hjärnans vitsubstans, så kallade white matter hyperintensities (WMHs). WMHs som ligger i direkt anslutning till hjärnans hålrum kallas för periventricular white matter hyperintensities (PVHs) och tros bero på vätskeutträde av CSF. WMHs som ligger mer perifert, skilda från ventrikelsystemet, kallas för deep white matter hyperintensities (DWMHs) och tros vara sekundära till kroniskt syrebrist i hjärnan. iNPH behandlas med shuntkirurgi.

Tidigare studier har visat motsägande resultat huruvida PVHs och DWMHs har en prognostisk betydelse på utfallet av en shuntoperation hos iNPH-patienter. I den aktuella studien användes en volumetrisk mjukvara för att utvärdera preoperativa MRT-bilder hos 253 iNPH-patienter som tidigare genomgått shuntkirurgi. Målet med studien var att undersöka om vitsubstansförändringar kunde prediktera utfallet efter shuntkirurgi. Volymen av PVH saknade prognostisk betydelse, medan ökande volymer av DWMHs var associerat med ett sämre utfall. Mängden DWMHs bör därför tas i beaktande vid val av kandidater för operation. Däremot sågs ingen signifikant skillnad i volymen av DWMH mellan patienter som förbättrats jämfört med de som inte förbättrats av shuntkirurgi, varför denna radiologiska variabel inte själv bör utesluta shuntbehandling.
## List of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSF</td>
<td>Cerebrospinal fluid</td>
</tr>
<tr>
<td>NPH</td>
<td>Normal pressure hydrocephalus</td>
</tr>
<tr>
<td>iNPH</td>
<td>Idiopathic normal pressure hydrocephalus</td>
</tr>
<tr>
<td>sNPH</td>
<td>Secondary normal pressure hydrocephalus</td>
</tr>
<tr>
<td>AD</td>
<td>Alzheimer’s disease</td>
</tr>
<tr>
<td>VD</td>
<td>Vascular dementia</td>
</tr>
<tr>
<td>$R_{\text{out}}$</td>
<td>Resistance to CSF outflow</td>
</tr>
<tr>
<td>WM</td>
<td>White matter</td>
</tr>
<tr>
<td>WMH</td>
<td>White matter hyperintensity</td>
</tr>
<tr>
<td>PD</td>
<td>Parkinson’s disease</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
</tr>
<tr>
<td>FLAIR</td>
<td>Fluid-attenuated inversion recovery</td>
</tr>
<tr>
<td>LP</td>
<td>Lumbar puncture</td>
</tr>
<tr>
<td>PPV</td>
<td>Positive predictive value</td>
</tr>
<tr>
<td>VP</td>
<td>Ventriculoperitoneal shunt</td>
</tr>
<tr>
<td>SDH</td>
<td>Subdural hematoma</td>
</tr>
<tr>
<td>PVH</td>
<td>Periventricular hyperintensity</td>
</tr>
<tr>
<td>DWMH</td>
<td>Deep white matter hyperintensity</td>
</tr>
<tr>
<td>NFL</td>
<td>Neurofilament light polypeptide</td>
</tr>
<tr>
<td>MMSE</td>
<td>Mini-mental state examination</td>
</tr>
<tr>
<td>ICC</td>
<td>Intraclass coefficient</td>
</tr>
</tbody>
</table>
3 Background

3.1 Definition

3.1.1 Hydrocephalus

The term hydrocephalus refers to an increased volume of cerebrospinal fluid (CSF) within the ventricular system of the brain. The condition is divided into communicating and non-communicating hydrocephalus (1). Non-communicating hydrocephalus occurs as a result of obstruction (e.g., stenosis of the cerebral aqueduct) within the CSF pathways, consequently disrupting the normal CSF flow. Communicating hydrocephalus develops without any blockage of the CSF, thus proposing other pathophysiological mechanisms (1,2). Normal pressure hydrocephalus (NPH), a communicating form, is a neurological condition in the elderly population. It is characterized by gait disturbance, cognitive symptoms and bladder dysfunction and was first described by Adams and Hakim in 1965 (3,4). These symptoms are commonly accompanied by dilated cerebral ventricles and a normal CSF mean pressure (3,4).

3.1.2 Classification of Normal Pressure Hydrocephalus

NPH is further divided into idiopathic NPH (iNPH) and secondary NPH (sNPH) (1). sNPH often occurs as a consequence of intracranial haemorrhage, meningitis or head trauma (1,5). The pathogenesis of iNPH is not yet fully established (5). The content in this report will mainly address iNPH.

3.2 Epidemiology

Epidemiological studies on iNPH are limited and inconsistent, partly due to various diagnostic approaches and follow-up routines. The epidemiological data is further complicated by differential diagnoses like Alzheimer’s disease (AD) and Vascular dementia (VD) (6–8). Most studies examining the epidemiology of iNPH are hospital-based and only a few population-based studies have been published (5).

In 2012 Mori et al. reviewed three MRI-based epidemiological studies, all conducted on elderly Japanese samples (5); the mean prevalence of iNPH in this material was approximated to 1.1% in patients ≥ 61 years. In a Norwegian study, the prevalence of iNPH was estimated to 21.9/100 000 (≈ 0.02%), peaking during the age of 70-79 (9). The incidence in this study was 5.5/100 000/year (≈ 0.006%/year). In a systematic review including twenty-one iNPH-specific articles published up to June 2014, Martín-Láez et al. presented a likely prevalence of 1.3% in subjects ≥ 65 years (10).
In a retrospective, epidemiological study, conducted on 1238 subjects in Gothenburg, Sweden, the prevalence of iNPH was estimated to 5.9% in individuals ≥ 80 years and 0.2% in individuals aged 70-79 years (11). No difference in sex was seen. In Sweden, the incidence of shunt implantation for iNPH is 1/100 000/year (12), suggesting that the amount of shunts implanted each year in iNPH patients in Sweden does not correspond to the prevalence of iNPH cases.

3.3 Pathophysiology

3.3.1 Cerebrospinal Fluid Mechanisms

The pathophysiological background of iNPH remains controversial (7,13,14). Given the fact that most patients suffer from dilated cerebral ventricles and improve after CSF-removal, changes in CSF-dynamics are likely involved (15–17). Yet, it is unclear whether these changes cause the disease or is a consequence of it (7,18,19). Using CSF-dynamic investigations, elevations in resistance to CSF outflow (R_{out}) and increased intracranial pressure pulse amplitudes have been reported in iNPH patients (18). However, a reduction in ventricular size after shunt surgery does not correlate with clinical improvement (20,21), why other pathophysiological mechanisms have been proposed as well.

3.3.2 Cerebrovascular Mechanisms

Vascular risk factors (e.g., hypertension) are overrepresented in iNPH-patients, why many researchers suggest the involvement of cerebrovascular mechanisms in the pathophysiology (22–24). One thesis is the loss of the Windkessel effect (i.e., dampening of arterial pulsations) and a decrease in the vascular compliance of the cerebral vessels (25,26). These changes are believed to alter the brain parenchyma, making it less compliant and more susceptible to compressive stress. But more importantly, these vascular changes seem to elevate CSF pulse pressure, eventually leading to ventricular enlargement (7,25). The loss of the Windkessel effect may also lead to cerebral hypoperfusion, which will affect CSF physiology (7,13). Since CSF allows for clearance of toxic substances, it has been hypothesized that a diminished CSF turnover causes accumulation of certain neurotoxins (e.g., amyloid-beta peptides) (7,27). This might explain why certain dementias, particularly AD, occur more frequently in iNPH-patients compared with age-matched controls (7,28,29).

Another pathological feature of iNPH is the recurrent finding of white matter (WM) hyperintensities (WMHs) on brain imaging (19). The pathological impact of WMHs will be discussed in detail in section 3.7.
3.4 Clinical Manifestations

3.4.1 Gait Impairment
The symmetrical gait dysfunction in iNPH is considered to be the most prominent symptom in early-stage disease (30). However, gait impairment is not pathognomonic for iNPH and the characteristics can be difficult to distinguish from the gait dysfunction of Parkinson’s disease (PD) and Lewy body dementia (19). The gait in iNPH is typically hypokinetic, broad-based and with short strides, often referred to as “magnetic”. The feet are externally rotated with the toes pointing outwards. Other distinctive features include difficulty turning and performing transitional movements (e.g., sitting to standing) (1,7,19). Upper body limbs may suffer from bradykinesia, affecting arm swing (7). Postural stability is commonly affected, increasing the risk of falling (31).

3.4.2 Cognitive Symptoms
Subcortical frontal dysfunction is believed to generate most of the cognitive symptoms in iNPH (32,33). Using neuropsychological assessments, Ogino and colleagues evaluated cognitive function in patients diagnosed with iNPH and AD (32). Comparing the two groups, the iNPH-patients scored better in memory tests but worse in those measuring frontal lobe functions. Execution (e.g., problem solving), short-term memory, psychomotor speed, attention and concentration are examples of qualities that may be afflicted in iNPH-patients (31,32,34). In contrast to AD and VD, cortical features like aphasia and agnosia are rarely seen (6,31).

3.4.3 Bladder Dysfunction
Functional bladder dysfunction in iNPH can occur secondarily to impaired cognition and gait (35). However, in most iNPH cases urinary symptoms are caused by detrusor hyperactivity, owing to reduced cerebral blood perfusion in the right frontal cortex of the brain. Impaired basal ganglia function has also been proposed as a possible mechanism (35,36). Primary urinary symptoms are urgency and frequency and in later-stage disease, accompanied by incontinence (31,35).

3.5 Diagnostic Approach
There is no specific phenotype of iNPH, most likely owing to other neurological disorders (e.g., AD, VD and PD) that share similar clinical features (7,28,29,37,38). AD is also believed to coexist with iNPH in up to one-third of cases (28,29,39). Relkin et al. published evidence-based guidelines in 2005, intended to facilitate the diagnostic approach (37).
3.5.1 Clinical Assessment

The purpose of the clinical evaluation is to clarify or exclude iNPH cardinal symptoms (see section 3.4 for specifics) and to rule out secondary hydrocephalus or other conditions similar to iNPH (37). Typically, the onset is subtle and occur after the age of 40 and the symptoms progress over at least three to six months before diagnosis (37). In today’s practice, the entire triad of symptoms is not required for diagnosis, making it possible to treat the patient before progressing to more advanced stages (6,37). iNPH is not considered a hereditary disease, but family history should be assessed since resembling conditions like AD and PD could explain the symptoms or coexist with iNPH (37). A routine neurological exam is mandatory to evaluate gait. Certain gait tests are also used, preferably with the aid of a physiotherapist. The timed “Up & Go” test, for instance, measures walking speed, turning and transitional movement (40,41). Specific psychometric tests (e.g., The Stroop test and Grooved Pegboard) are used to assess cognitive ability (42,43). An outpatient approach where the patient documents the occurrence of urinary symptoms is preferably used to evaluate the bladder function (37,44).

3.5.2 Neuroimaging

In addition to clinical assessment, brain imaging is necessary for diagnosis. Both computerized tomography and magnetic resonance imaging (MRI) can provide evidence of iNPH. MRI is the most reliable technique because of the superior soft tissue contrast (6,7). Enlarged third and lateral ventricles, in disproportion to cortical atrophy, and no visible sign of CSF flow obstruction are radiological characteristics consistent with iNPH (37). To objectively assess ventricular enlargement, Evans’ index is used. Evans’ index is calculated by dividing the width of the frontal horns of the lateral ventricles with the biparietal diameter of the cranium. Ventriculomegaly is often defined as a ratio that exceeds 0.3 (37). Other radiological features are hyperintensities in the WM adjacent to the ventricular walls and focally in the deep WM. These hyperintensities are best displayed in T2 or fluid-attenuated inversion recovery (FLAIR) sequences on MRI (19).

3.5.3 Invasive Prognostic Procedures

The withdrawal of 30-70 ml of CSF via lumbar puncture (LP) is called a tap test (6,7). This procedure provides evidence for how likely the patient is to respond to shunt treatment. If clinical improvement is seen following the test, the patient will most likely benefit from future shunting, given the method’s high positive predictive value (PPV) (73-100%) (45). However, the sensitivity is low (26-61%), why negative results offer less prognostic value (45).
CSF absorption capacity can be assessed by calculating $R_{\text{out}}$ with a CSF infusion test. This is accomplished by infusing Ringer solution into the CSF system (46). Similar to the tap test, a CSF infusion test predicts shunt responsiveness, with a PPV ranging from 75-92% (45).

3.6 Treatment and Prognosis

3.6.1 Surgical Shunt Implantation

iNPH is commonly treated with a ventriculoperitoneal (VP) shunt. This system drains CSF from the cerebral ventricles into the peritoneal cavity (31). An opening valve pressure of the shunt is routinely set based on the opening LP pressure, measured prior to surgery. If the opening valve pressure is too low, the patient may suffer from CSF overdrainage, increasing the risk of certain complications (e.g., subdural hematoma (SDH)) (47,48). Traditionally, the opening pressure of the shunts had a fixed setting and complications were corrected with re-surgery. Today, overdrainage complications are commonly addressed proactively by installing an adjustable shunt system, that allows for alteration in the opening pressure without the need for surgical intervention. This approach diminishes the risk of complications involved in surgery (6,49).

3.6.2 Clinical Outcome and Complications

In the European multicentre study on iNPH by Klinge et al., 115 patients received a VP-shunt with a 12-month follow-up (15). The outcome after surgery was partially evaluated using the recently introduced iNPH scale (50). The iNPH scale measures gait, balance, continence and neuropsychology. A total score approaching 0 on the iNPH scale represents severe clinical symptoms, while a total score approaching 100 indicate a good clinical situation. Performance in the individual domains is also calculated separately. Twelve months after shunt surgery 84% of the patients were improved (≥ 5 points gain in total score) (15). Seven patients had suffered from SDHs and one patient from infection, all within the first month following surgery. Seventeen patients underwent shunt revision, the majority being performed within the first 30 days (51). More rare complications to VP-shunting include intracerebral hemorrhage, seizure and death (52). Of the symptoms mentioned in section 3.4, gait disturbance is most favored by a shunt (53). The symptom least favored by a shunt however, does not seem as obvious and various studies report different results regarding this matter (53–55). iNPH patients with extensive WM lesions on brain imaging also seem to benefit from shunt surgery (20,56,57).
3.7 White Matter Changes

3.7.1 Definition

WM changes are identifiable as hyperintense changes on MRI using FLAIR or T2 sequences (19,58). These lesions are divided into periventricular hyperintensities (PVHs) and deep white matter hyperintensities (DWMHs), the difference being that PVHs run contiguous with the cerebral ventricles and the DWMHs do not (59,60). A rating scale for subcategories according to Fazekas et al. is illustrated in Table 1 (59). PVHs and DWMHs often tend to coalesce, why some authors prefer to define them based on the distance to the ventricles, rather than applying the rule of continuity (61,62).

Table 1. A rating scale for subcategories of PVHs and DWMHs according to Fazekas et al (59).

<table>
<thead>
<tr>
<th>PVH</th>
<th>DWMH</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Continuity with the cerebral ventricles)</td>
<td>(Separated from the cerebral ventricles)</td>
</tr>
<tr>
<td>0 Absence</td>
<td>0 Absence</td>
</tr>
<tr>
<td>1 “Caps” or pencil-thin lining</td>
<td>1 Punctate foci</td>
</tr>
<tr>
<td>2 Smooth “halo”</td>
<td>2 Beginning confluence of foci</td>
</tr>
<tr>
<td>3 Irregular PVH extending into the deep white matter</td>
<td>3 Large confluent areas</td>
</tr>
</tbody>
</table>
3.7.3 Pathophysiology

WMHs are seen in both idiopathic and secondary forms of NPH (20,66,67). In a study by Akai et al., neuropathological findings indicated that NPH not only involved disturbances in CSF dynamics but also changes in the cerebral WM, including microinfarcts and arteriosclerosis (68). Akai et al. proposed that these pathological findings resembled those seen in Binswanger’s disease, an arteriosclerotic encephalopathy. Recent studies have also emphasized similarities in clinical and radiological features between NPH and Binswanger’s disease and even proposed a shared pathophysiology between the two (20,56,57).

DWMHs are overrepresented in both idiopathic and secondary forms of NPH and especially in patients with concurrent vascular risk factors (57). As a result, DWMHs are believed to develop on the basis of ischemia, secondary to cerebral small-vessel disease (19,20,57). Whether these changes are part of the NPH pathophysiology or simply an expression of vascular comorbidity, is not fully understood (20). PVHs have also been correlated to vascular risk factors (e.g., hypertension and hypercholesterolemia) (69) and it has been argued that PVHs are caused by ischemic insults as well (20,70,71). However, the most acknowledged theory is that PVHs in NPH represent oedema caused by transudation of ventricular CSF (19,20,72–74). This is supported by the fact that the volume of PVH tends to decrease after CSF diversion by means of shunt implantation (20).

3.7.4 Clinical Significance

In 1996 Krauss et al. reported that preoperative PVHs and DWMHs had a negative impact on the effect of shunt surgery in iNPH patients (75). In two studies by Tullberg et al., this was contradicted. It was reported in the first study that WMHs could not predict shunt outcome and in the later study that WMHs served as positive predictors of shunt outcome (20,57). Both studies reported that the amount of PVH in clinically improved patients had reduced markedly after shunt implantation (20,57), a finding consistent with previous research (67). In a randomized controlled double-blind study by Tisell et al., it was reported that iNPH patients with widespread WM changes improved in gait and cognitive symptoms after shunting (56).

Neurofilament light polypeptide (NFL) is an axonal marker found in the CSF that correlates with the magnitude of symptoms and WMHs in iNPH patients (57,76). High levels of NFL in the preoperative state have been reported to predict a favorable response to shunt surgery. A decrease in NFL levels after surgery is associated with clinical improvement (76).
3.8 Rationale

Taken together, it is unclear whether or not preoperative WMHs are associated with outcome after shunt surgery in iNPH patients. If more evidence existed regarding WMHs’ predictive role, this would aid in the selection of candidates appropriate for shunt surgery.

3.9 Aims

The aim of this study was to investigate the predictive value of PVHs and DWMHs on shunt outcome in patients with iNPH. Volumes of WMHs were measured by using a volumetric software called SmartPaint. The hypothesis was that greater volumes of preoperative PVHs were associated with a favorable outcome after shunt surgery, whereas greater volumes of preoperative DWMHs were associated with a less favorable outcome.

4 Methods

4.1 Study Population

This retrospective observational study consisted of 262 consecutive patients diagnosed with iNPH. All patients were operated with shunt surgery between 2011 and 2015, were clinically examined before and 12 months after surgery and were investigated with a preoperative MRI of the brain, including a FLAIR sequence. Diagnosis of iNPH was decided in accordance with the international guidelines (37) and all patients suffered from gait impairment with or without cognitive symptoms or bladder dysfunction.

Six patients were excluded due to events unrelated to shunt surgery, but with impact on clinical assessments, making comparisons between pre- and postoperative investigations inaccurate. One patient suffered from a viral encephalitis, one patient from a stroke and three patients from hip fractures. All of these incidents occurred between the baseline control and shunt surgery except one of the hip fracture cases that took place after surgery. One patient’s gait was not assessable at the preoperative investigation. An additional three patients were excluded due to radiological artifacts. Hence, a total of nine patients were excluded, leaving 253 patients for statistical analyses. The process of inclusion and exclusion is illustrated in a flowchart in figure 1. The baseline characteristics are illustrated in table 2. The study was approved by the regional ethics committee (Dnr: 2015/174/3, date: 2018-11-05).
iNPH patients treated with a shunt between 2011 and 2015 with pre- and postoperative clinical assessments. Preoperative FLAIR images of the brain available for analysis ($N = 262$).

Patients excluded due to events unrelated to shunt surgery; Viral encephalitis ($n = 1$); Stroke ($n = 1$); Hip fracture ($n = 3$); Issue walking ($n = 1$).

Patients excluded due to radiological artifacts ($n = 3$).

iNPH patients investigated in statistical analyses ($N = 253$).

**Figure 1.** Flowchart illustrating the process of inclusion and exclusion. iNPH, Idiopathic normal pressure hydrocephalus; FLAIR, Fluid-attenuated inversion recovery.

### 4.1.1 Baseline Characteristics

**Table 2.** Baseline characteristics.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic features</td>
<td></td>
</tr>
<tr>
<td>Age, median (range)</td>
<td>75 (50-90)</td>
</tr>
<tr>
<td>Male, $n$ (%)</td>
<td>141 (56%)</td>
</tr>
<tr>
<td>Vascular risk factors</td>
<td></td>
</tr>
<tr>
<td>Diabetes, $n$ (%)</td>
<td>63 (25%)</td>
</tr>
<tr>
<td>Hypertension, $n$ (%)</td>
<td>162 (64%)</td>
</tr>
<tr>
<td>Hyperlipidemia, $n$ (%)</td>
<td>96 (38%)</td>
</tr>
<tr>
<td>Preoperative symptom scores</td>
<td></td>
</tr>
<tr>
<td>MMSE, Median (IQR), $n = 249$</td>
<td>25.0 (28.0-22.0)</td>
</tr>
<tr>
<td>Total Mod-iNPH scale, Mean (SD), $N = 253$</td>
<td>46.6 (18.9)</td>
</tr>
</tbody>
</table>

MMSE, Mini-mental state examination; IQR, Interquartile range; iNPH, Idiopathic normal pressure hydrocephalus; Mod-iNPH scale, Modified version of the iNPH scale; SD, Standard deviation.
4.2 Clinical Assessment

Patients were clinically assessed before and 12 months after shunt implantation by using a modified version of the original iNPH scale (50,77). As mentioned in section 3.6, the original iNPH scale measures four different domains and a score between 0 and 100 is determined for each domain separately. A total score is calculated by dividing the sum of all domain scores by 5 or the number of available domains (gait x 2 (0-100), balance x 1 (0-100), continence x 1 (0-100) and neuropsychology x 1 (0-100)). Accordingly, the total score ranges from 0 to 100 as well. This allows for any of the domains to be excluded, without impacting the total score. Less than 50% of all patients were evaluated with the neuropsychological tests of the iNPH scale tests both pre- and postoperatively. Therefore, a modified version of the iNPH scale (Mod-iNPH scale) that included all domains except the cognitive domain was used to determine clinical outcome after shunt surgery. The difference in total score between the 12-month follow-up and the baseline control was used to measure clinical outcome. A postoperative increase of 5 levels or more was defined as a positive clinical outcome. As a replacement for the missing cognitive domain, the majority of patients (n = 241) performed a Mini-mental state examination (MMSE) pre- and postoperatively.

4.3 Magnetic Resonance Imaging Protocol

All 253 patients were investigated with one or more MRI of the brain prior to shunt surgery. The most recent preoperative examination including a FLAIR sequence was used for analysis in the present study. The median time between the MRI examination used in analysis and shunt surgery was 310 days. Different MRI scanners were used at different hospitals in Sweden and as a result, the number of slices varied between examinations. Forty patients (16%) had an MRI examination with ≥ 160 slices and 213 patients (84%) had an MRI examination < 160 slices (range 18-321 slices). The investigator was blinded to all patient details, including clinical symptoms and outcome after shunt surgery.

4.4 SmartPaint

The FLAIR sequences were analyzed using a volumetric medical-based software, called SmartPaint. SmartPaint was developed by Malmberg et al. at the Centre for Image Analysis, Uppsala University and is a method that allows the user to semi-automatically perform segmentations in radiological images (78). In the present study, SmartPaint was used with the purpose to distinguish between different structures of the brain and to calculate the volumes of these.
The brush tool feature of SmartPaint was used in this study. This tool allows the user to operate completely manually and to perform all segmentations by free hand. A feature of SmartPaint is that the software is able to differentiate between different structures, solely based on the intensity value of the voxels (three-dimensional pixels) contained in that image (78). In FLAIR sequences for instance, CSF in the ventricles is black and the WM surrounding it is grey or white. SmartPaint will consider this as different intensities and only select one of these, depending on which structure the user marks first. However, if one wishes to distinguish two neighboring structures with the same intensity value, this must be arranged for manually. Another feature of SmartPaint is that it operates in 3D. The 3D mode allows the user to paint in several slices simultaneously, making the procedure less time consuming (78).

4.5 Segmentation Process

Each FLAIR sequence uploaded in SmartPaint was obtained in a transversal, coronal and sagittal plane. To ensure consistency, segmentations were carried out in the transversal plane and in cranial to caudal direction. The process took approximately 20 minutes per patient. Seven separate segmentations were produced for each patient. From these, five different radiological variables were acquired and used for statistical analyses. The first radiological variable was the volume of the lateral ventricles. This was obtained by segmenting the lateral ventricles, the choroid plexus included. The volume of the lateral ventricles was determined by multiplying the number of segmented voxels with the volume of an individual voxel. The segmentation of the lateral ventricles in the SmartPaint user interface, displayed as transparent overlays, is illustrated in figure 2.

Figure 2. The segmentation of the lateral ventricles in SmartPaint.
The remaining variables were volumes of WMHs and a combination of six segmentations was carried out to obtain these. The first segmentation contained all of the cerebral WM. This was named the whole brain segmentation and was necessary to calculate the volume of DWMH. The next segmentation, named PVH, would be used to determine the volume of PVH. In this segmentation, the lateral ventricles were encircled, as illustrated by figure 3. The distance from the ventricles was customized for each patient, depending on how extensive the PVHs were. In line with Fazekas et al., PVHs were defined as WMHs having continuity with the ventricles (59) and any WMH separated from the ventricles was avoided as far as possible. WMHs surrounding the third ventricle were avoided in both the whole brain and PVH segmentation. The brainstem was segmented and would be used to determine the volume of WMH in the brainstem. This was named the brainstem segmentation.

**Figure 3.** The segmentation of PVH in SmartPaint.

The whole brain, PVH and brainstem segmentations did not only contain WMHs but also volumes of normal gray and white matter. In order to exclude these non-pathological volumes, another three segmentations were carried out. These served as references for normal WM, normal gray matter and pathological (hyperintense) WM. Reference for normal gray matter was included because its intensity value often exceeds the intensity value of normal WM on FLAIR images. These references were obtained by doing 2D segmentations of what appeared as normal white matter, normal gray matter and pathological WM. Any ventricular volume included in the whole brain and PVH segmentation was excluded by removing the ventricular voxels, previously obtained in the ventricular segmentation.
In the two reference segmentations marked as normal white and gray matter, the highest intensity value was found. This value, $t_1$, indicated how bright a voxel could be and still be considered as normal appearing WM. In the reference segmentation marked as pathological WM, the highest intensity value was found as well. This value, $t_2$, indicated how bright a completely pathological voxel was. In each segmentation (whole brain, PVH and brainstem), all voxels were assumed to be gradually changed, between 0% and 100% and the degree of change was given by the intensity value. Each voxel with intensity value equal to $t_1$ or below was considered as 0% WMH and was excluded. Each voxel with intensity value equal to $t_2$ or above was considered as 100% WMH. Between $t_1$ and $t_2$, the rate of change increased linearly from 0 to 100%, meaning that all voxels whose intensity value exceeded $t_1$ contributed to the total amount of WMH, but brighter voxels contributed more. Voxels with intensity value equal to $t_2$ or above contributed 100%.

This produced a whole brain, PVH and brainstem segmentation, now only containing what we defined as WMHs. This generated two variables, the volume of PVH and the volume of WMH in the brainstem. The volume of DWMH was calculated by subtracting the volume of PVH from the whole brain segmentation volume. The last variable was the ratio between the volume of PVH and volume of DWMH. Five radiological variables were obtained and used in statistical analyses.

### 4.6 Statistical Methods

SPSS Statistics (IBM, version 24.0) was used for statistical analyses. Continuous data were presented with mean and standard deviation (SD) or with median and interquartile range (IQR). A paired-sample $t$-test and a Wilcoxon signed-rank test were conducted to examine the difference in pre- and postoperative symptom scores. Comparison of radiological variables between improved and non-improved patients was based on The Mann-Whitney U-test. Correlations were determined with Spearman’s rank-order correlation coefficient ($r_s$). Standard multivariable regression was used to investigate the predictive value of different radiological variables on clinical outcome after shunt surgery. In all regression models, adjustments were made for age and preoperative symptom scores. The validity of SmartPaint was measured by calculating an average intraclass coefficient (ICC) between SmartPaint and Synthetic MRI. If not specified, statistical significance was defined as $p < 0.05$. 

5 Results

5.1 Outcome After Shunt Surgery

The difference in total Mod-iNPH scale score between post- and preoperative investigations was determined. At the 12-month follow-up, the mean total Mod-iNPH scale score was higher compared with preoperative investigations, \( r(252) = 3.53, p < 0.001 \). The mean total Mod-iNPH scale score was 46.6 (SD = 18.9) preoperatively and 50.9 (SD = 23.5) 12 months after shunt surgery, a significant increase of 4.3 (95% CI, 1.89 to 6.66). In terms of cognitive performance, MMSE score was higher in 110 patients at the 12-month-follow up compared with preoperative investigations. In 88 patients the MMSE score was higher preoperatively and in 43 patients the MMSE score did not differ between pre- and postoperative investigations. There was no increase in MMSE score on group level between the preoperative investigation and 12 months after shunt surgery, \( z = 1.71, p = 0.087 \). Symptom scores before and 12 months after shunt surgery are illustrated in table 3.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients with pre- and postoperative scores, n</th>
<th>Preoperative scores</th>
<th>Scores 12 months after surgery</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Mod-iNPH scale, Mean (SD)</td>
<td>253</td>
<td>46.6 (18.9)</td>
<td>50.9 (23.5)</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>MMSE, Median (IQR)</td>
<td>241</td>
<td>25.0 (28.0-22.0)</td>
<td>26.0 (28.0-23.0)</td>
<td>ns*</td>
</tr>
</tbody>
</table>

iNPH, Idiopathic normal pressure hydrocephalus; Mod-iNPH scale, Modified version of the iNPH scale; SD, Standard deviation; MMSE, Mini-mental state examination; IQR, Interquartile range; ns, not significant.

*, Wilcoxon signed-rank test

**, Paired-sample t-test

5.2 Radiological Features

Clinical outcome was defined as the difference between post- and preoperative total Mod-iNPH scale score and an increase of 5 levels or more was defined as a positive clinical outcome. One hundred twenty-eight patients were improved and 125 patients were not improved after shunting. Table 4 illustrates the volumes of different preoperative radiological features in all patients. Table 5 illustrates how these radiological features differed between improved and non-improved patients.
Table 4. Volumes (ml) of different radiological features in all patients.

<table>
<thead>
<tr>
<th>Variable</th>
<th>All patients N = 253</th>
</tr>
</thead>
<tbody>
<tr>
<td>The volume of the lateral ventricles, Mean (SD)</td>
<td>129 (41.7)</td>
</tr>
<tr>
<td>The volume of WMH in bs, Median (IQR)</td>
<td>0.03 (0.13-0.007)</td>
</tr>
<tr>
<td>The volume of PVH, Median (IQR)</td>
<td>7.2 (15.8-3.3)</td>
</tr>
<tr>
<td>The volume of DWMH, Median (IQR)</td>
<td>1.0 (2.6-0.4)</td>
</tr>
<tr>
<td>PVH/DWMH, Median (IQR)</td>
<td>6.8 (18.5-2.6)</td>
</tr>
</tbody>
</table>

ml, millilitre; SD, Standard deviation; WMH, White matter hyperintensity; bs, brainstem; IQR, Interquartile range; PVH, Periventricular hyperintensity; DWMH, Deep white matter hyperintensity.

Table 5. Volumes (ml) of different radiological features in improved and non-improved patients.

<table>
<thead>
<tr>
<th>Variable</th>
<th>improved patients n = 128</th>
<th>non-improved patients n = 125</th>
</tr>
</thead>
<tbody>
<tr>
<td>The volume of the lateral ventricles, Mean (SD)</td>
<td>130 (42.6)</td>
<td>128 (40,8)</td>
</tr>
<tr>
<td>The volume of WMH in bs, Median (IQR)</td>
<td>0.03 (0.11-0.007)</td>
<td>0.04 (0.14-0.007)</td>
</tr>
<tr>
<td>The volume of PVH, Median (IQR)</td>
<td>6.0 (13.4-2.9)</td>
<td>8.7 (16.5-3.5)</td>
</tr>
<tr>
<td>The volume of DWMH, Median (IQR)</td>
<td>1.0 (2.6-0.33)</td>
<td>1.2 (2.7-0.47)</td>
</tr>
<tr>
<td>PVH/DWMH, Median (IQR)</td>
<td>6.3 (15.5-2.7)</td>
<td>7.7 (23.2-2.6)</td>
</tr>
</tbody>
</table>

ml, millilitre; SD, Standard deviation; WMH, White matter hyperintensity; bs, brainstem; IQR, Interquartile range; PVH, Periventricular hyperintensity; DWMH, Deep white matter hyperintensity.

There was no significant difference in any of the preoperative radiological variables between improved and non-improved patients. None of the radiological variables correlated significantly with the total preoperative Mod-iNPH scale score. The volume of PVH significantly correlated with preoperative gait disturbance. There was a significant positive correlation between the volume of PVH and the volume of DWMH, p < 0.001.
5.3 Separate Domain Scores

The Mod-iNPH scale is measured both in its separate domains and in total. Domain scores were calculated at the baseline control and are illustrated in table 6. Correlations between the separate domains and the total preoperative Mod-iNPH scale score were all significant, \( p < 0.001 \). The gait domain correlated negatively to clinical outcome, \( p < 0.05 \). The correlation coefficients \( (r_s) \) and corresponding p-values are presented in table 7.

**Table 6. Preoperative domain scores.**

<table>
<thead>
<tr>
<th>Domain</th>
<th>preoperative domain scores</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continence, Mean (SD), ( n =246 )</td>
<td>59.6 (26.0)</td>
</tr>
<tr>
<td>Balance, Mean (SD), ( n =233 )</td>
<td>50.6 (16.1)</td>
</tr>
<tr>
<td>Gait, Mean (SD), ( N =253 )</td>
<td>39.9 (24.4)</td>
</tr>
</tbody>
</table>

SD, Standard deviation.

**Table 7. Spearman’s correlations between preoperative domain scores and the preoperative total Mod-iNPH scale score and between preoperative domain scores and clinical outcome.**

<table>
<thead>
<tr>
<th>Domain</th>
<th>Correlation with total preoperative score ( (r_s) )</th>
<th>Correlation with clinical outcome ( (r_s) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continence</td>
<td>0.650***</td>
<td>-0.123 ns</td>
</tr>
<tr>
<td>Balance</td>
<td>0.619***</td>
<td>-0.032 ns</td>
</tr>
<tr>
<td>Gait</td>
<td>0.923***</td>
<td>-0.138*</td>
</tr>
</tbody>
</table>

ns, not significant.

* significance level \( p < 0.05 \)

***, significance level \( p < 0.001 \)

5.4 Prediction of Outcome After Shunt Surgery

5.4.1 Modified version of the iNPH scale

Five separate multivariable regression models were conducted to determine the impact of different radiological variables on clinical outcome after shunt surgery. Every model included one radiological variable each. Adjustments were made for age and preoperative total Mod-iNPH scale score. The volume of DWMH was associated with clinical outcome, \( B = -0.552, p < 0.05 \). The other four radiological variables were not significantly associated with clinical outcome. The regression coefficients of each model are illustrated in table 8.
Table 8. Associations between different variables and clinical outcome after shunt surgery. Note that the table is a merger of five separate regression analyzes.

<table>
<thead>
<tr>
<th>Variable</th>
<th>B</th>
<th>SE_B</th>
<th>β</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>The volume of the lateral ventricles</td>
<td>0.020</td>
<td>0.028</td>
<td>0.043</td>
<td>0.479</td>
</tr>
<tr>
<td>Age</td>
<td>-0.596</td>
<td>0.177</td>
<td>-0.204</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Preoperative total score</td>
<td>-0.274</td>
<td>0.062</td>
<td>-0.269</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>The volume of PVH</td>
<td>-0.198</td>
<td>0.107</td>
<td>-0.114</td>
<td>0.064</td>
</tr>
<tr>
<td>Age</td>
<td>-0.534</td>
<td>0.179</td>
<td>-0.183</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Preoperative total score</td>
<td>-0.286</td>
<td>0.062</td>
<td>-0.280</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>The volume of DWMH</td>
<td>-0.552</td>
<td>0.251</td>
<td>-0.132</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Age</td>
<td>-0.561</td>
<td>0.176</td>
<td>-0.192</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Preoperative total score</td>
<td>-0.279</td>
<td>0.061</td>
<td>-0.273</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PVH/DWMH ratio</td>
<td>-0.034</td>
<td>0.046</td>
<td>-0.045</td>
<td>0.454</td>
</tr>
<tr>
<td>Age</td>
<td>-0.577</td>
<td>0.178</td>
<td>-0.198</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Preoperative total score</td>
<td>-0.276</td>
<td>0.062</td>
<td>-0.271</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>The volume of WMH in bs</td>
<td>-3.261</td>
<td>4.413</td>
<td>-0.045</td>
<td>0.461</td>
</tr>
<tr>
<td>Age</td>
<td>-0.579</td>
<td>0.178</td>
<td>-0.198</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Preoperative total score</td>
<td>-0.280</td>
<td>0.062</td>
<td>-0.275</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

iNPH, Idiopathic normal pressure hydrocephalus; Mod-iNPH scale, Modified version of the iNPH scale; B, Unstandardized regression coefficient; SE_B, Standard error of the coefficient; β, Standardized coefficient; PVH, Periventricular hyperintensity; WMH, White matter hyperintensity; DWMH, Deep white matter hyperintensity; bs, brainstem.

A regression model that included age, preoperative total Mod-iNPH scale score and all radiological variables collectively was run as well. This model was associated with clinical outcome after shunt surgery, F(7, 245) = 5.251, p < 0.001, adj R^2 = 0.106. In this model, the volume of DWMH was the only radiological variable that was associated with clinical outcome, β = -0.149, p < 0.05.

5.4.2 Mini-mental state examination

A separate regression model, illustrated in table 9, was run in order to evaluate the relationship between radiological variables and cognitive outcome after shunting. Cognitive outcome was defined as the difference between post- and preoperative MMSE score. When adjusting for age, preoperative total MMSE score and the other radiological variables, the volume of DWMH was the only radiological variable that was associated with cognitive outcome, B = -0.144, p < 0.05.
Table 9. Associations between different variables and cognitive outcome after shunt surgery.

<table>
<thead>
<tr>
<th>Variable</th>
<th>B</th>
<th>SE_B</th>
<th>β</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>The volume of the lateral ventricles</td>
<td>0.10</td>
<td>0.005</td>
<td>0.119</td>
<td>0.059</td>
</tr>
<tr>
<td>The volume of PVH</td>
<td>-0.027</td>
<td>0.021</td>
<td>-0.086</td>
<td>0.186</td>
</tr>
<tr>
<td>The volume of DWMH</td>
<td>-0.144</td>
<td>0.056</td>
<td>-0.188</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>PVH/DWMH ratio</td>
<td>-0.008</td>
<td>0.009</td>
<td>-0.062</td>
<td>0.346</td>
</tr>
<tr>
<td>The volume of WMH in bs</td>
<td>0.738</td>
<td>0.984</td>
<td>0.055</td>
<td>0.454</td>
</tr>
<tr>
<td>Age</td>
<td>-0.054</td>
<td>0.034</td>
<td>-0.101</td>
<td>0.109</td>
</tr>
<tr>
<td>Preoperative total MMSE score</td>
<td>-0.203</td>
<td>0.053</td>
<td>-0.243</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

B, Unstandardized regression coefficient; SE_B, Standard error of the coefficient; β, Standardized coefficient; PVH, Periventricular hyperintensity; WMH, White matter hyperintensity; DWMH, Deep white matter hyperintensity; bs, brainstem; MMSE, Mini-mental state examination.

5.5 Neurofilament Light Polypeptide

Valid results for NFL were available for 75 patients in the present study. The reference value was set at < 890 ng/L for patients < 60 years and < 1850 ng/L for patients ≥ 60 years (79). Nineteen of the 75 patients had elevated preoperative levels of NFL. The median value was 1200 ng/L, with IQR 1730-790 ng/L. A negative relationship between NFL and clinical outcome was found, r_s(73) = -0.261, p < 0.05. No significant relationship between NFL and the radiological variables was seen.

5.6 SmartPaint Validity

An intraclass correlation was conducted in order to investigate the validity of SmartPaint. The ventricular volumes of 15 patients segmented with SmartPaint were compared with the ventricular volumes of the same patients determined with Synthetic MRI. The investigator was blinded to the results measured with Synthetic MRI. The patients were randomly selected. Using an absolute agreement definition, the average ICC was calculated to 0.939 (CI 95%, 0.736 to 0.982).

6 Discussion

In this retrospective study, 253 patients diagnosed with iNPH were investigated with MRI of the brain before shunt surgery. The volumes of different radiological features were calculated and their effects on outcome after shunt surgery were analyzed. The volume of DWMH was the only radiological variable that was significantly associated with clinical and cognitive outcome after shunt surgery.
Previous studies investigating WMHs in NPH have included a limited number of patients and both cases of iNPH and sNPH (20,57). The present study is the largest study that investigated WMHs in iNPH patients exclusively. Clinical symptoms were standardized according to the Mod-iNPH scale and MMSE, which allowed for symptoms to be presented on a continuous rating scale. This made objective comparisons between patients possible. Due to lacking quantifying methods at the time, previous studies did not assess urinary symptoms (56). This is in contrast to the present study, that used the continence domain from the iNPH scale to assess these symptoms. The investigator that performed the segmentations in SmartPaint was blinded to all patient details, including clinical symptoms and shunt outcome. The segmentation procedure was performed throughout the whole brain and not just in slices considered as pathological. To ensure consistency, all segmentations were carried out in the same radiological plane. SmartPaint allowed for manual corrections to be performed, avoiding mistakes that could have an impact on statistical analysis.

6.1 Waiting Time for Shunt Surgery and Age

Clinical outcome after shunt surgery was defined as the difference between post- and preoperative total Mod-iNPH scale score. On group level, scores were higher at the 12-month follow-up, but only 128 of the 253 patients (51%) improved with more than 5 levels after shunt surgery. This is in contrast to a recent review by Toma et al., who suggests an 82% success rate of shunt surgery in iNPH patients 12 months after surgery (52). One explanation to the low proportion of improved patients was the long waiting time for surgery, estimated to a median of 6.5 months. iNPH is a condition with symptom deterioration over time (80). Given this progressive course, it is likely that several patients suffered from more severe symptoms at the time of surgery, compared with the original assessment 6 months earlier. As a result, the preoperative score used to assess clinical outcome in the present study might have been falsely high. This could explain the low number of patients defined as responders to shunt surgery in the present study. Our data thus suggests that preoperative investigations that are used to determine clinical outcome after surgery in iNPH, should be based on the patient’s condition just before surgery, considering the natural course of the disease.

In the review by Toma et al., the proposed shunt success rate of 82% was based on patients with a mean age of 71 years (52). In the present study, the mean age was 75 years. Given the fact that high age has been described as a negative predictor of shunt outcome (unpublished data), this relative increase of age may have contributed to the poor outcome seen in our study.
6.2 Separate Domain Scores

All preoperative domains of the Mod-iNPH scale each correlated positively with the preoperative total Mod-iNPH scale score, as expected. The gait domain correlated negatively to clinical outcome after shunt surgery, implying that a higher preoperative gait score was associated with a less postoperative increase in the total Mod-iNPH scale score. This is in contrast to previous research that suggests that worse preoperative symptoms, gait included, are associated with a less favorable outcome after surgery (81,82). This difference is likely due to different definitions of clinical outcome. Clinical outcome in the present study was defined as the difference between post- and preoperative scores. This correlation thus showed that patients with a high preoperative gait score did not benefit from shunt surgery as much as those with a lower preoperative score, in terms of gaining levels in the Mod-iNPH scale. This exemplifies the “ceiling effect” of many symptom scales used to assess outcome after shunt surgery, a phenomenon previously described by Chaudhry and colleagues (83).

6.3 Cognitive Outcome

On group level, no significant increase in MMSE score between pre- and postoperative investigations was seen. This is in contrast to previous research by Pujari et al., who reported improvement in cognitive symptoms in iNPH patients after shunt surgery (53). This difference in result might be due to the long waiting time in the present study, as cognitive impairment is one of the symptoms that deteriorates over time (80). Additionally, the mean age in our study was 75 years, compared with 72 years in the study by Pujari et al.

Subcortical and frontal lobe symptoms characterize the cognitive deficit in iNPH (32,33). Several studies have reported that MMSE underestimates these qualities (8,55,84) which makes the test unsuitable for assessing the cognitive impairment in iNPH. Despite this, the test is still broadly used (8). In the European multicenter study by Klinge et al., cognitive tests more sensitive to subcortical deficits were used (15). They found an overall clinical improvement after shunting in iNPH patients, but interestingly, the cognitive impairment improved half as much as the gait symptoms. Several other studies have also reported that cognitive impairment in iNPH is the symptom least favored by shunt surgery (54,55,85). Given the fact that the patients in the present study, on group level, improved in the total Mod-iNPH scale score after surgery but not in MMSE, might add to the evidence that cognitive impairment is the symptom least favored by a shunt.
6.4 Neurofilament Light Polypeptide

Elevated preoperative levels of NFL was seen in 19 of the 75 patients with valid results. The median value of 1200 ng/L was similar to that found in previous studies (76,86). It has been reported that NFL correlates with the volume of WMHs and that high preoperative levels of NFL are associated with a positive response to surgery (57,76,86,87). In contrast to these results, the present study did not find a significant relationship between NFL and WMHs and on the contrary, a negative relationship between NFL and clinical outcome was observed. However, less than 30% of our patients had valid results of NFL and these results might have been different if more patients had valid measurements.

6.5 White Matter Hyperintensities

By using different methods of assessment, previous studies have reported that PVHs and DWMHs are more frequent in iNPH patients compared with healthy controls (66,88). The present study is, to the best of our knowledge, the first study investigating the amount of WMHs in iNPH patients by using a volumetric method.

The pathophysiological mechanisms of PVHs and DWMHs in iNPH remains unsettled. The most acknowledged theories, as mentioned in section 3.7, are that PVHs represent oedema caused by transudation of ventricular CSF and that DWMHs represent ischemic insults secondary to cerebral small-vessel disease (19,20,57,72–74). The latter is supported by the fact that DWMHs in iNPH frequently concur with vascular risk factors (57) and it is well known that vascular risk factors are overrepresented in iNPH (24,89). In the present study, there was a high prevalence of vascular risk factors, thus providing the conditions for DWMHs to exist.

Although PVHs and DWMHs often are reported as separate pathological entities, there is data pointing towards a common origin of these lesions. In a study by Krauss et al., a significant association between PVHs and DWMHs was found and a possibility of PVHs also representing ischemic changes was proposed (66). Similar to DWMHs, PVHs have been associated with vascular risk factors (69) and Tullberg et al. reported that no difference in the levels of DWMHs and PVHs was seen between patients with and without such risk factors (20). Our data support the possibility of such a common origin since we, in line with Krauss et al., observed a highly significant correlation between PVHs and DWMHs.
It has been reported that more severe symptoms overall can be expected in iNPH patients that have radiological evidence of WMHs (75). Tullberg et al. reported that preoperative PVHs were associated with poor cognition and that preoperative DWMHs were associated with disturbance in gait (20,57). Furthermore, a reduction in PVHs on postoperative brain imaging correlates with symptomatic relief, a phenomenon that has been more pronounced in shunt responders compared with non-responders (20). However, in the present study, WMHs were not assessed postoperatively, leaving only the preoperative scores to measure the impact of WMHs on symptom severity. It was observed that the volume of PVH significantly correlated with disturbance in gait. The volume of DWMH, in contrast to previous studies (57,75), did not correlate with any of the preoperative symptoms. This was unexpected and probably due to methodological shortcomings in the present study, leading to underestimation of the DWMH volume.

The aim of this study was to investigate the predictive value of different preoperative WMHs on outcome after shunt surgery in iNPH patients. Previous studies have shown contradictory results regarding this matter. Krauss et al. reported that both PVHs and DWMHs were associated with a less favorable outcome after shunt surgery (75). Tullberg et al. reported in one study that neither PVHs nor DWMHs could predict shunt outcome (20) and in a later study that both of these WM lesions served as positive predictors (57). In one of these studies, it was reported that the group of patients suffering from cerebrovascular comorbidities, such as hypertension, had a more favorable outcome after surgery compared to the group that did not suffer from such comorbidity (20). Given the pathological background of DWMHs, this observation might contradict the volume of DWMH of being a negative predictor of shunt outcome. In the present study however, the volume of DWMH was a negative predictor of both clinical and cognitive outcome after shunt surgery. Unexpectedly, the volume of PVH did not predict shunt outcome. In line with Tullberg et al. (20), there was no significant difference in the volume of DWMH between improved and non-improved patients, indicating that patients with preoperative DWMHs still may benefit from shunt surgery.

In the multivariable regression model, with clinical outcome as the dependent variable, age, preoperative total Mod-iNPH scale score and all radiological variables accounted for approximately 11% of the variance in shunt outcome (adj. $R^2 = 0.106$). Hence, there are factors other than those addressed in this study that serve as important predictors of shunt outcome in iNPH patients.
6.6 Methodological Limitations

The validity of SmartPaint was investigated by comparing the ventricular volume segmented with both SmartPaint and Synthetic MRI. The accuracy was excellent with an ICC value of 0.939 (CI 95%, 0.736 to 0.982), suggesting a good validity of the method used in this study. However, the ICC value was solely based on the volume of the lateral ventricles and not on the remaining four variables.

The segmentation performed to determine the volume of PVH is a potential limitation in the present study. In this procedure, the lateral ventricles were encircled, whether or not there was visual evidence of PVHs. This ensured that all PVHs were included and that the method was consistent. However, small WMHs located close to the ventricles but not contiguous to them might have been included as well. As a result, false high volumes of PVHs might have been produced and as an effect, false low volumes of DWMHs. The option, as we see it, would be to perform all segmentations of PVHs individually. However, this would have been operator dependent and time-consuming.

Another potential limitation concerns the classification of voxels based on their intensity value. Voxels whose intensity values were between t1 and t2 contributed to the total amount of WMH, but brighter voxels contributed more. This ensured that only voxels that were truly bright contributed considerably. However, it is not certain whether or not WMH-voxels that are brighter corresponds better to the total volume of WMH compared with those that are less bright (20,56,66). As a result, false low volumes of WMHs might have been produced. However, there is an argument to why it was carried out this way. If all voxels whose intensity value exceeded t1 were allowed to contribute equally to the total volume of WMH, there would have been an increased risk of including voxels that did not represent true WMHs. In a study by Tullberg et al., the intensity value was instead used to classify different types of PVHs and DWMHs (57). This is probably something that can be developed in future studies, preferably by using SmartPaint.

All the segmentations in SmartPaint were performed by the author of this study, with limited experience of neuroradiology. The segmentation procedure required a good neuroanatomical knowledge, why this might have been a limitation. As mentioned above, SmartPaint was a valid method in terms of measuring the ventricular volumes. This might indicate that SmartPaint was a valid method in determining the other variables as well. However, the lateral ventricles were anatomically easier to distinguish and the problem of the intensity value did not exist.
6.7 Conclusion

The volume of PVH did not predict outcome after shunt surgery in iNPH patients, whereas increasing volumes of DWMHs were associated with a less favorable outcome. DWMHs in iNPH patients should be taken into account when selecting candidates for surgery. However, patients with extensive DWMHs may still benefit from shunt surgery, why this variable alone must not exclude iNPH patients from receiving a shunt.

To better understand the clinical relevance of DWMHs and PVHs in iNPH patients, future studies should focus on identifying the pathophysiological background of these WM lesions.
7 Acknowledgements

I want to express my sincere gratitude to my supervisor Johan Virhammar. Johan, thank you for your genuine commitment to this project, for always being there for questions and for your constructive feedback. Without your endless support, this project would not have been the same.

I also wish to thank Filip Malmberg for all the assistance regarding SmartPaint and for calculating the radiological volumes.
8 References


