Idiopathic Normal Pressure Hydrocephalus

Cerebrospinal Fluid Tap Test and Magnetic Resonance Imaging as Preoperative Prognostic Investigations

JOHAN VIRHAMMAR
Abstract

Idiopathic normal pressure hydrocephalus (iNPH) is a condition with dilated cerebral ventricles but intracranial pressure within normal limits. The symptoms of gait impairment, cognitive decline and urinary incontinence develop gradually. Treatment with shunt insertion results in improvement in eight out of ten patients.

The cerebrospinal fluid tap test (CSF TT) and preoperative magnetic resonance imaging (MRI) are methods used to select patients who may benefit from shunt surgery, but they are performed and interpreted differently in different centers throughout the world. The aim of this thesis was to evaluate the performance of the CSF TT and the underlying mechanisms of improvement in gait function after CSF removal, and to investigate the prognostic value of preoperative MRI scans.

Improvement in gait and changes in cerebral blood flow (CBF) after a CSF TT were investigated in two prospective studies that included 39 and 20 patients, respectively. Gait assessment and perfusion MRI were done before and several times during the first 24 hours after a CSF TT. Perfusion was investigated with pseudo-continuous arterial spin labeling. At the group level, gait function was significantly improved at all investigation times, but only one-third of individual CSF TT responders were improved at all investigation times. In patients with increased CBF in lateral and frontal white matter after the CSF TT, gait function improved more than it did in patients with decreased CBF in these regions. However, in the whole sample, there was no significant increase in CBF after CSF removal.

Preoperative MRI scans were retrospectively evaluated in 109 patients with iNPH who had undergone shunt surgery. The callosal angle was smaller in shunt responders compared with non-responders. The following findings showed the highest association with a positive outcome after shunting: a small callosal angle, wide temporal horns, and occurrence of disproportionally enlarged subarachnoid space hydrocephalus.

In conclusion, CBF in white matter close to the lateral ventricles may play a role in the reversibility of symptoms after CSF removal in patients with iNPH. The CSF TT should be reevaluated if the patient does not initially improve, and preoperative MRI investigations can add prognostic information regarding the selection of shunt candidates.

Keywords: normal pressure hydrocephalus, NPH, cerebrospinal fluid disorders, dementia, MRI, CSF tap test, CBF, ASL

Johan Virhammar, Department of Neuroscience, Neurology, Akademiska sjukhuset, Uppsala University, SE-75185 Uppsala, Sweden.

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“High and fine literature is wine, and mine is only water; but everybody likes water.”
— Mark Twain

To Hanna
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List of Papers

This thesis is based on the following papers, which will be referred to by their Roman numerals.

I. Virhammar J, Cesarini KG, Laurell K. The CSF tap test in normal pressure hydrocephalus: evaluation time, reliability and the influence of pain.
   *Eur J Neurol. 2012 Feb;19(2):271-6*

II. Virhammar J, Laurell K, Cesarini KG, Larsson EM. The callosal angle measured on MRI as a prognostic biomarker in normal pressure hydrocephalus.
   *J Neurosurg. 2014 Jan;120(1):178-84*

   *Submitted*

   *Submitted*

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Abbreviations

AD  Alzheimer’s disease
ADC  Apparent diffusion coefficient
AVIM  Asymptomatic ventriculomegaly with features of iNPH on MRI
CBF  Cerebral blood flow
CI  Confidence Interval
CSF TT  Cerebrospinal fluid tap test
CSF  Cerebrospinal fluid
CT  Computed tomography
DESH  Disproportionately enlarged subarachnoid space hydrocephalus
DWMH  Deep white matter hyperintensity
ELD  External lumbar drainage
FLAIR  Fluid attenuated inversion recovery
ICC  Intraclass correlation coefficient
ICP  Intracranial pressure
iNPH  Idiopathic normal pressure hydrocephalus
IQR  Interquartile range
MFC  Medial frontal cortex
MMSE  Mini-mental state examination
MRI  Magnetic resonance imaging
mRS  Modified Rankin Scale
NPH  Normal pressure hydrocephalus
NPV  Negative predictive value
OR  Odds ratio
pCASL  Pseudo-continuous arterial spin labeling
pcMRI  Phase-contrast magnetic resonance imaging
PLD  Post labeling delay
PPV  Positive predictive value
PVH  Periventricular hyperintensity
ROI  Region of interest
SD  Standard deviation
SMA  Supplementary motor area
SVD  Subcortical vascular dementia
SyMRI  Synthetic MRI
<table>
<thead>
<tr>
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<th>Full Form</th>
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<tr>
<td>T</td>
<td>Tesla</td>
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<tr>
<td>TUG</td>
<td>Timed Up and Go test</td>
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<tr>
<td>VAS</td>
<td>Visual analogue scale</td>
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<tr>
<td>WM</td>
<td>White matter</td>
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<td>$\kappa$</td>
<td>Cohen’s kappa</td>
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Introduction

A gradually appearing impairment of gait and balance, often in combination with a slight cognitive dysfunction and urinary incontinence, in an elderly individual are typical symptoms of idiopathic normal pressure hydrocephalus (iNPH). This condition can be treated with implantation of a shunt system, with subsequent improvement in a vast majority of the patients. Without adequate treatment, the symptoms usually progress.

A diversity of clinical tests have been evaluated in the past to select cases of suspected iNPH who may benefit from shunt surgery. Even today, different centers in the world use different tests and interpret them in their own way.

iNPH is an increasingly recognized condition, but still, only a minority of the patients that suffer from the disease are diagnosed and offered shunt surgery. Therefore, better awareness of the disease, better diagnostic methods and better prognostic methods are needed. The aim of this thesis was to focus on the latter of these three, to evaluate some of the most widely available and easily applicable prognostic tests used to identify patients with iNPH who would most likely benefit from shunt surgery.
Background

The history of normal pressure hydrocephalus

It is widely accepted that the concept of normal pressure hydrocephalus (NPH) was introduced by the Columbian neurosurgeon Salomón Hakim. In 1957, he encountered a 16-year-old boy that had suffered from severe head trauma when struck by a car. He became comatose, and a frontal subdural hematoma was evacuated. Subsequently, the boy’s condition improved. He was more awake and could move his extremities but still did not speak. He was sent home for convalescence but was readmitted after 1 month when he still had not recovered. Pneumoencephalography revealed an enlarged ventricular system, but the cerebrospinal fluid (CSF) pressure was normal. By lumbar puncture, 15 ml CSF was removed for diagnostic purposes, and surprisingly, the boy improved and started speaking for the first time since the accident. A ventriculoatrial shunt was inserted, and the boy improved and could return to school.

In his thesis, Hakim described a syndrome that consisted of adult hydrocephalic patients with normal CSF pressure, and in 1965 publishing two peer-reviewed papers together with Raymond D. Adams.1, 2 The paper with Hakim as first author, describes three cases. The first case was the 16-year-old boy mentioned above and a second case was a 43-year-old man who had suffered from severe head trauma with a depressed skull fracture. A burr hole was drilled, but no blood was found inside or outside the dura. The following weeks, he was initially improved but was still walking with a broad-based gait, was hardly speaking and incontinent of urine. He underwent shunt surgery too. The third case was a 52-year-old musician who without a known cause developed a balance and cognitive impairment and later urinary incontinence and gait disturbance characterized by a broad-based gait. All three cases had enlarged ventricles but normal intracranial pressure (ICP) and symptoms that could be relieved by a lumbar puncture, and all showed substantial improvement after the implantation of a ventriculoatrial shunt.

Classification and definition of hydrocephalus

The name of the disease comes from the Greek words: hydro = water and kephalos = head. Hydrocephalus means that there is an active distension of the cerebral ventricles. Hydrocephalus is divided into non-communicating hydrocephalus, in which there is an obstruction of the CSF pathways between the site of production and reabsorption, and communicating hydrocephalus, in which there is no obvious obstruction.3
The hindrance of the CSF pathways in non-communicating hydrocephalus can be anywhere from the production to the reabsorption site, and common locations are the foramina of Monroi, aqueduct of Sylvius or 4th ventricle. Typical causes are tumors, cysts and congenital malformations.

NPH is a communicating hydrocephalus with no known obstruction of the CSF flow and is divided into secondary NPH and idiopathic NPH. Secondary means that it develops after a previous insult to the brain (e.g., bacterial meningitis, trauma or intracranial hemorrhage) as in the 16-year-old boy and the 43-year-old man. However, NPH can occur without a known cause as in the case of the 52-year-old musician and is then called idiopathic normal pressure hydrocephalus (iNPH).

Even though the main focus of the papers in this thesis concerns iNPH, some parts of the background in the following pages address both secondary NPH and iNPH, because in older publications, patients with both conditions were included.

**Idiopathic normal pressure hydrocephalus**

**Clinical presentation**

iNPH is a disease of the aging population and is typically seen during the sixth or seventh decades of life and is equally common in men and women.4, 5

**Gait disturbance**

The first and often most prominent symptom in iNPH is a gait disturbance. It always develops gradually. Typically the patient has a hypokinetic, almost magnetic gait with a broad base and with toes pointed outwards. The steps are short, with low foot-floor elevation. Movements are characterized by hesitancy and difficulties in turning.6-8

**Balance and postural dysfunction**

The postural instability often experienced by iNPH patients can also to some degree explain the gait disturbance. Using a force platform, Blomsterwall et al. showed that iNPH patients had a greater sway area and a higher backward directed velocity of center of pressure compared with healthy individuals.9 Patients typically have a tendency of falling backwards, and it was reported that patients with a backward movement in the Romberg test also had an abnormal subjective visual vertical perception and tilted a test rod toward themselves.10 The balance impairment is the symptom that improves most after shunting.6
Cognitive symptoms
The level of cognitive impairment can vary greatly from almost undetectable changes to manifest dementia. Impairments typically disturb psychomotor speed, executive function, information processing, learning and wakefulness.\textsuperscript{11-13} This indicates that the cognitive dysfunction is probably predominantly subcortical in nature. However, in a thorough study that included a battery of neuropsychological tests by Hellström et al., they showed that the cognitive impairment is more global and widespread and also further impaired if vascular disease is present. After shunting, the patients showed improvement in most of the neuropsychological tests.\textsuperscript{14, 15}

Incontinence
The number of studies investigating continence symptoms in iNPH are limited. With the use of urodynamic tests, Sakakibara et al. found that storage symptoms due to an overactive bladder were the most common characteristic, and this is also the case in clinical experience.\textsuperscript{16} Ahlberg et al., also using urodynamic tests, found that the hyperdynamic bladder activity could be reversed after CSF removal, both temporarily after a lumbar puncture and more permanently after shunt surgery.\textsuperscript{17}

Epidemiology
There is no simple test to diagnose iNPH, and given the nature of the disease, assessment of prevalence and incidence is not easy. Because of different diagnostic definitions and different methodological approaches, the few studies of epidemiology in iNPH have reported highly divergent numbers. In a prospective study in Norway, Brean et al. collected iNPH patients by advertising in local papers and asking professional health workers to refer patients. Therefore their calculated prevalence of 0.2\% for probable iNPH in the age group 70–79 years is likely underestimated.\textsuperscript{5} Two studies of community dwelling people in Japan estimated the prevalence of iNPH in people >65 years to be 2.9\% and 1.4\%.\textsuperscript{18, 19} Moreover, in a prospective Japanese study, all 70-year-old citizens in a community were asked to participate, and 271 were examined clinically and with MRI. The prevalence of iNPH was 0.4\% (n=1), and the prevalence of asymptomatic patients with suspected NPH findings on MRI (AVIM) was 1.1\% (n=3).\textsuperscript{20} The 10-year follow-up of the study was recently published. One of the AVIM patients had developed iNPH, two of the patients without ventriculomegaly had developed iNPH and one had developed AVIM.\textsuperscript{21} The largest community-based prevalence study of iNPH was recently published.\textsuperscript{22} CT scans and clinical evaluations were retrospectively evaluated in 1238 Swedish elderly. The iNPH diagnosis
was based on the occurrence of ventricular enlargement without corresponding widening of cortical sulci, in combination with gait impairment and either cognitive dysfunction, incontinence or both. The prevalence was 2.1% in patients >70 years. The incidence of shunt surgery for iNPH in Sweden is reported to be approximately 1/100 000/year. Even if the lowest calculated prevalence is considered, the number of shunt implantations performed is far lower than the occurrence of iNPH.

**Pathological and pathophysiological findings**

The pathogenesis of iNPH is unclear, and several theories with more or less support from experimental studies have been suggested. Different pathological and pathophysiological findings have been observed in the iNPH brain, but it is still uncertain whether these factors are a cause or a consequence of the disease. It is also not determined in which order the findings appear and how they relate to each other.

These observations will not be reviewed thoroughly here, but some of the findings more frequently discussed in the literature will be mentioned.

One finding that has been given much focus is the white matter (WM) changes seen on brain imaging. The periventricular changes are presumed to be transudation of CSF from the lateral ventricles that may disturb metabolic function by reducing the clearance of toxic metabolites. Deep WM changes are frequently reported in iNPH, and since both imaging findings and postmortem studies report similarities with patients with severe subcortical vascular dementia, speculations that an ischemic etiology is involved in a subgroup of patients have been put forward. These findings will be discussed further in the Radiological findings section as well as the frequently reported findings of reduced regional cerebral blood flow in patients with iNPH.

The resistance to outflow of CSF ($R_{out}$) is much studied in NPH and is increased in patients with iNPH. Since this parameter is closely related to CSF pressure and reabsorption, iNPH is considered as a disease with disturbed CSF dynamics. Shunt implantation in iNPH achieves a reduction in $R_{out}$.

ICP monitoring and flow-sensitive magnetic resonance imaging (MRI) have shown increased pulse amplitudes and CSF pulsations, and this has led to theories that the strong CSF pulsations become a “water hammer”, wear out the brain and cause ventricular dilation. This flow of events is suggested to be the result of an age-related stiffness of large arteries and a less compliant brain, with reduction of the normal dampening of arterial blood pulse pressure, which instead propagates in the brain causing an increased pulse pressure in the CSF.
In biopsy studies of patients with iNPH, Alzheimer’s disease (AD) type changes are found in cortical biopsies in one-third of patients.\textsuperscript{35, 36} It is not known whether these findings are caused by AD comorbidity, a random finding, or whether they are a consequence of iNPH. iNPH patients with AD type changes in cortical biopsies can also improve after shunt surgery.\textsuperscript{35, 37} However, these patients often have more severe cognitive symptoms than iNPH patients with normal biopsies,\textsuperscript{35} and more severe AD-type changes are associated with less postoperative improvement.\textsuperscript{36, 38}

Diagnosis
The diagnostic evaluation in iNPH and the selection of patients that may benefit from shunt surgery are two separate entities, but they are often performed simultaneously in routine clinical practice. The challenge in the diagnostic procedure is to identify iNPH features and exclude patients with differential diagnoses that could also explain the symptoms. The most common differential diagnoses are subcortical vascular dementia (SVD), Alzheimer’s disease (AD), atypical cases of Parkinson’s disease, progressive supranuclear palsy and multiple system atrophy. Most of these diseases eventually cause enlargement of the ventricles, the symptoms can resemble iNPH symptoms, and the MRI findings of SVD can be similar to those seen in iNPH.\textsuperscript{27, 39} The diagnostic evaluation is further complicated by the possibility of the coexistence of SVD, AD and iNPH in the same patients.\textsuperscript{40}

The decision to select patients that will likely improve after shunting is aided by supplementary prognostic tests. Several are used in the daily routine, and even more tests have been used in the past or are suggested in the literature.\textsuperscript{41}

Diagnostic guidelines
Different diagnostic definitions of iNPH have been the major limitation in NPH research, and as a consequence, guidelines for the diagnosis and management of iNPH have been created. Professor Marmarou was the initiator of the American iNPH Guidelines, published in 2005, after review of American, European and Asian researchers.\textsuperscript{42, 43} The second edition of the national Japanese iNPH Guidelines was published in English in 2012.\textsuperscript{44} Both of these guidelines divide patients into probable iNPH and possible iNPH depending on the availability of tests and how typical the clinical picture is. The American guidelines also have the definition “unlikely iNPH” for patients who probably have a different diagnosis, while the Japanese guidelines have the retrospective definition “definite iNPH” for patients that responded well to shunt surgery.
The American guidelines are presented in Table 1, and the second edition of the Japanese guidelines is summarized below.

According to the Japanese guidelines, possible iNPH is a patient aged >60 years with ventricular dilation, clinical symptoms, and history supporting iNPH. For population-based studies where CSF examinations are not possible the term “possible iNPH with MRI support” was introduced. It refers to a patient with the criteria mentioned above and findings of narrowing of the sulci and subarachnoid spaces over the high convexity/midline surface (DESH) on MRI. To be classified as probable iNPH, the patient must fulfill criteria of possible iNPH with ‘normal’ lumbar CSF opening pressure <20 cmH\textsubscript{2}O and one of the following three diagnostic criteria:

- Neuroimaging features of narrowing of the sulci and subarachnoid spaces over the high convexity/midline surface (DESH) under the presence of gait disturbance.
- Improvement of symptoms after CSF tap test (CSF TT).
- Improvement of symptoms after external lumbar drainage (ELD)

The main differences between the two sets of guidelines concern the three diagnostic criteria in the Japanese guidelines mentioned above. The Japanese guidelines focus more on imaging findings, and the diagnostic feature of narrowing of the sulci over the high convexity is not even a supportive feature in the American guidelines. The other two diagnostic features in the Japanese guidelines, improvement after CSF TT or ELD, are considered as supplementary prognostic tests for selection of shunt candidates in the American guidelines and not related to the diagnosis. Moreover, patients aged between 40–60 years and CSF pressure in the range 20–24.5 cmH\textsubscript{2}O cannot be diagnosed as iNPH in the Japanese guidelines, in contrast to the American guidelines.
The diagnosis of iNPH is based on clinical history, brain imaging, physical findings, and physiological criteria.

I. History
Reported symptoms should be corroborated by an informant familiar with the patient’s premorbid and current condition, and must include:
- a. Insidious onset (versus acute)
- b. Origin after age 40 years
- c. A minimum duration of at least 3 to 6 months
- d. No evidence of an antecedent event such as head trauma, intracerebral hemorrhage, meningitis, or other known causes of secondary hydrocephalus
- e. Progression over time
- f. No other neurological, psychiatric, or general medical conditions that are sufficient to explain the presenting symptoms

II. Brain imaging
A brain imaging study (CT or MRI) performed after onset of symptoms must show evidence of:
- a. Ventricular enlargement not entirely attributable to cerebral atrophy or congenital enlargement
- b. No macroscopic obstruction to CSF flow
- c. At least one of the following supportive features:
  1. Enlargement of the temporal horns of the lateral ventricles not entirely attributable to hippocampus atrophy
  2. Callosal angle of 40 degrees or more
  3. Evidence of altered brain water content, including periventricular signal changes on CT and MRI not attributable to microvascular ischemic changes or demyelination
  4. An aqueductal or fourth ventricular flow void on MRI

III. Clinical
By classic definitions findings of gait/balance disturbance must be present, plus at least one other area of impairment in cognition, urinary symptoms, or both. With respect to gait/balance, at least two of the following should be present and not be entirely attributable to other conditions:
- a. Decreased step height
- b. Decreased step length
- c. Decreased cadence (speed of walking)
- d. Increased trunk sway during walking
- e. Widened standing base
- f. Toes turned outward on walking
- g. Retropulsion (spontaneous or provoked)
- h. Impaired walking balance, as evidenced by two or more corrections out of eight steps on tandem gait testing

With respect to cognition, there must be documented impairment and/or decrease in performance on a cognitive screening instrument, or evidence of at least two of the following on examination:
- a. Psychomotor slowing (increased response latency)
- b. Decreased fine motor speed
- c. Decreased fine motor accuracy
- d. Difficulty dividing or maintaining attention
- e. Impaired recall, especially for recent events
- f. Executive dysfunction, such as impairment in multistep procedures, working memory, formulation of abstractions/similarities, insight
- g. Behavioral or personality changes

To document symptoms in the domain of urinary continence, either one of the following should be present:
- a. Episodic or persistent urinary incontinence not attributable to primary urological disorders
- b. Persistent urinary incontinence
- c. Urinary and fecal incontinence

Or any two of the following should be present:
- a. Urinary urgency as defined by frequent perception of a pressing need to void
- b. Urinary frequency as defined by more than six voiding episodes in an average 12-hour period despite normal fluid intake
- c. Nocturia as defined by the need to urinate more than two times in an average night

IV. Physiological
CSF opening pressure in the range of 5–18 mm Hg (or 70–245 mm H₂O) as determined by a lumbar puncture or a comparable procedure. Appropriately measured pressures that are significantly higher or lower than this range are not consistent with a probable NPH diagnosis.

Table 1.
Diagnostic criteria according to the American iNPH guidelines.

<table>
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Possible INPH

I. History
Reported symptoms may:
- a. Have a subacute or indeterminate mode of onset
- b. Begin at any age after childhood
- c. Have less than 3 months or indeterminate duration
- d. Follow events such as mild head trauma, remote history of intracerebral hemorrhage, or childhood and adolescent meningitis or other conditions that in the judgment of the clinician are not likely to be causally related
- e. Coexist with other neurological, psychiatric, or general medical disorders but in the judgment of the clinician not be entirely attributable to these conditions
- f. Be nonprogressive or not clearly progressive

II. Brain imaging
Ventricular enlargement consistent with hydrocephalus but associated with any of the following:
- a. Evidence of cerebral atrophy of sufficient severity to potentially explain ventricular size
- b. Structural lesions that may influence ventricular size

III. Clinical
Symptoms of either:
- a. Incontinence and/or cognitive impairment in the absence of an observable gait or balance disturbance
- b. Gait disturbance or dementia alone

IV. Physiological
Opening pressure measurement not available or pressure outside the range required for probable INPH

Unlikely INPH
1. No evidence of ventriculomegaly
2. Signs of increased intracranial pressure such as papilledema
3. No component of the clinical triad of INPH is present
4. Symptoms explained by other causes (e.g., spinal stenosis)

Clinical evaluation
First of all a careful patient history is taken, and because of cognitive decline it is often necessary to involve a family member or someone who is familiar with the patient in this process. Symptoms are asked for and in what order and timing they occurred. The time of symptom onset is often considered in several studies, but is sometimes difficult to evaluate because the start is always insidious, and the patient’s cognitive decline can impair accuracy of history taking. Brain injury in the past is asked for because this can result in secondary NPH. Examples of such brain injury are meningitis/encephalitis, intracerebral hemorrhage or head trauma. However it is not known when the symptoms actually start in connection with a brain injury that leads to secondary NPH. Finally, it is important to take into account the patient’s comorbidity and medication, since there can be contraindications against shunt surgery.
**Grading scales**

For the evaluation of the severity of iNPH symptoms, several different scales have been proposed in the literature over the years. This makes it very difficult to compare the level of impairment of the patients in different studies. For a general evaluation of the degree of disability, the modified Rankin Scale, and the Stein and Langfitt Scale are frequently used.\(^{45, 46}\) Among the scales used to grade the severity of the symptoms are the Dutch NPH Scale,\(^ {47}\) Krauss Scale,\(^ {39}\) the Japanese iNPH Grading Scale by Kubo\(^ {48}\) and the NPH Grading Scale suggested by Eide. Of these, all but the Dutch NPH Scale, grades the symptoms only by ordinal rating.

The recently published iNPH scale, developed in Gothenburg, Sweden, is an attempt at standardizing the evaluation.\(^ {49}\) It consists of grading scales that provides both ordinal and continuous data and includes also grading of the balance impairment. The grading of the severity of symptoms is based on normality, so that the maximum score represents normal function in a healthy elderly.

**Examination of motor function and posture**

Apart from a routine neurological examination of the patient, specific tests of gait and balance are often performed. A physiotherapist with experience with iNPH preferably aids with this part of the evaluation process. Besides ordinal scales, gait is often quantified as the time and number of steps required to cover a distance and the Timed Up and Go test (TUG) is also a frequently used test.\(^ {50}\)

**Examination of cognition**

Often used and well known is the mini mental state examination (MMSE) that, however, has been criticized for underestimation of subcortical and frontal lobe symptoms.\(^ {51, 52}\) Examples of tests considered to be more sensitive to frontal and subcortical changes are versions of the Stroop test, the Trail making test and the Grooved Pegboard.\(^ {53, 54}\) A more detailed neuropsychological evaluation by a neuropsychologist is performed at some centers.\(^ {14}\)

**Examination of incontinence**

The evaluation of incontinence is more difficult to quantify than the other symptoms. It is often addressed in the patient history, but most of the grading scales described above include an ordinal scale of urinary symptoms.
Preferably the results from the tests above are saved and compared to the results after an eventual shunt implantation to get a standardized and more objective estimation of postoperative outcome.

**Radiological findings**

*History*

In the early days of NPH, pneumoencephalography and radionuclide cisternography were used for radiological evaluation. Typical findings in NPH using radionuclide cisternography were reflux of isotope into the lateral ventricles and a lack of isotope over the convexities and in the region of the superior sagittal sinus.\(^{55-57}\) The technique is still available but rarely used today. It was relatively easy to interpret and was less demanding for the patients than pneumoencephalography. Even though the above-mentioned typical findings were not considered to be specific for NPH, there were indications that the technique provided prognostic information.\(^{57}\) However, Vanneste et al. claimed after a retrospective study that radionuclide cisternography does not improve the accuracy of the prognostic evaluation of NPH, which was also the recommendation in the American iNPH Guidelines.\(^{41, 58}\)

The first NPH patients that were described by Hakim and Adams underwent pneumoencephalography that revealed enlarged ventricles, and the method was then used during the sixties and seventies to diagnose NPH.\(^{1, 2}\) The method was associated with much discomfort and morbidity among the patients because of headache, nausea and/or emesis.\(^{59}\) Findings described were wide lateral ventricles, enlarged third ventricle, increased height of the lateral ventricles, wide sulci in the Sylvian and subfrontal regions, and a small corpus callosal angle.\(^{60, 61}\)

*Imaging in NPH*

At present, the first step in the imaging of iNPH is often computed tomography (CT) of the brain. Ventriculomegaly is sometimes an unexpected finding on a CT scan for a different reason, e.g. after head trauma. In other cases, it is performed as a diagnostic investigation in a patient that has developed symptoms of NPH.

In the context of NPH, a CT scan is useful for the study of gross structural changes such as the size and shape of the ventricles and compression of sulci or atrophy, and after surgery the location of a shunt catheter or complications such as subdural hematomas. A CT scan can exclude patients without ventricular dilatation and can aid in differentiating NPH.
from dementia disorders such as Alzheimer disease, where the ventricular enlargement is secondary to parenchymal loss and accompanied by cortical atrophy (Figure 1),\(^6\) in contrast to NPH where the sulci are often narrow (Figure 2).\(^6\)

When a CT scan has raised the suspicion of iNPH, the next step is often a magnetic resonance imaging (MRI) investigation of the brain to rule out obstructive causes of hydrocephalus, such as aqueductal stenosis, and to aid in differentiating iNPH from other neurologic conditions. The MRI scan provides better soft tissue contrast than CT and morphological as well as functional information about the CSF pathways. Therefore, more detailed information can be obtained on WM hyperintensities and CSF flow.\(^4\),\(^5\) In addition, more advanced sequences can be added such as diffusion tensor imaging (DTI), phase-contrast MRI for quantitative CSF flow measurements and perfusion-MRI.

When MRI is used in patients with a shunt, it is important to remember that shunt systems with adjustable opening pressures often change their settings in the strong magnetic field and must be checked after the investigation. The metal components of the shunts also induce artifacts that disturb the image evaluation.

In contrast to older studies of morphology, it is now possible in modern picture and archiving systems (PACS) to reconstruct the images and reangulate them in any direction, which is of great help when studying structural changes in NPH.\(^6\) Several imaging markers have been investigated in previous studies using CT and MRI, and even though some of them seem to be useful to discriminate NPH from healthy controls and NPH-mimicking conditions, their prognostic value is still uncertain.

Most studies of NPH morphology have included a mixed sample of patients with iNPH and secondary NPH, and the patient cohorts were often small. The definition of outcome has often been based on subjective evaluation or non-sensitive ordinal scales. Since evaluation in clinical practice still largely relies on morphological findings, more studies with well-defined patient cohorts are needed.
Figure 1.
T1-weighted images of an 87-year-old female patient with cortical atrophy. a. Slice located 10 mm inferior of image b, the most superior slice.

Figure 2.
T2-weighted FLAIR image of a patient with iNPH and narrow sulci at the high convexity graded as 2 = definitive compression. a. Slice located 10 mm inferior of image b, with narrow sulci and two focally dilated sulci on the left side. b. The most superior slice illustrates narrow sulci at the high convexity.
Markers of the shape and size of the ventricles

Ventricular dilation is an important criterion for NPH, and the Evans index, the ratio between the maximum width of the frontal horns of the lateral ventricles and the maximum inner diameter of the cranium, is the most widely used measure of ventricle width (Figure 3). In most studies, an index >0.3 is considered as indicating ventriculomegaly. It is useful for diagnosis and definition in studies but of no prognostic value.

Bilateral enlargement of the temporal horns and a dilated third ventricle are typical findings in both NPH and obstructive hydrocephalus, and are reported to be more common in patients with NPH that improve after shunt surgery than in non-responders (Figures 4 and 5). While some authors report that the third ventricle is wider in NPH than in Alz-

![Figure 3.](image)

Evans index is the ratio between the maximum width of the frontal horns (x) of the lateral ventricles and the maximum inner diameter of the cranium (y), in our study measured in the same slice. T1-weighted image.
Alzheimer’s disease, others report that these findings are not specific for NPH and that the third ventricle can be enlarged in conditions with atrophy (Figure 6).\textsuperscript{72, 73}

The Evans index, the diameter of the third ventricle and the temporal horns, decrease in some studies after shunting but are unchanged in others.\textsuperscript{27, 70, 74, 75} The markers can vary depending on the exact location of the measurement, and although not yet in clinical routine, volumetric methods are more precise and are increasingly used in studies today.\textsuperscript{76} Volumetric methods have previously been time consuming, but automatic methods are under evaluation.\textsuperscript{77}

Figure 4.
T1-weighted 3D-image showing dilated temporal horns of the lateral ventricles.
Figure 5.
T1-weighted 3D-image illustrating disproportionately enlarged sub-arachnoid space hydrocephalus (DESH). Also showing dilated temporal horns and Sylvian fissures and narrow sulci at the high convexity.

Figure 6.
T1-weighted 3D-image with dilated 3\textsuperscript{rd} ventricle.
A morphological marker called the corpus callosal angle was described in 1970 by LeMay and Benson and was measured on pneumoencephalography. The term refers to the angle between the lateral ventricles on a frontal image. They found that patients with NPH often had an angle $<120^\circ$.\textsuperscript{55, 60} They measured the angle anteriorly between the frontal horns on pneumoencephalography, because the air is located in the frontal horns with the patient in the supine position. The authors proposed that the ventricular dilation in hydrocephalus causes elevation of the corpus callosum until it reaches the level of the falx, while the lateral portions of the roof of the lateral ventricles continue to rise, thus explaining the decreasing callosal angle.\textsuperscript{60} Sjaastad reported that patients with obstructive hydrocephalus as well as patients with NPH had a smaller callosal angle between the frontal horns than patients with atrophy.\textsuperscript{61} There was no significant difference between the mean callosal angle in NPH and obstructive hydrocephalus. The authors doubted the clinical value of the marker but suggested that an angle $<120^\circ$ indicated increased pressure in the ventricles.\textsuperscript{61}

When the American iNPH Guidelines were published in 2005, the callosal angle was again mentioned in the context of NPH. It was suggested that a callosal angle of $>40^\circ$ was supportive of iNPH, which is somewhat confusing in the light of previous publications (Table 1).\textsuperscript{43} Unfortunately, no reference was provided. Thirty-five years after Sjaastad’s publication, Ishii et al. repeated their design by describing a method to measure the callosal angle with MRI (Figure 7). They found that an angle $<90^\circ$ was useful to differentiate between NPH and patients with atrophy secondary to Alzheimer’s disease, with this finding having a sensitivity of 97% and a specificity of 88%.\textsuperscript{68} No studies have described the prognostic value of the callosal angle measured with MRI, in the selection of shunt candidates with iNPH.
Structural changes of the brain

In contrast to the cortical atrophy seen in Alzheimer’s disease, narrow cortical sulci at the high convexity is a typical finding in patients with NPH. This is best seen over the parietal high convexity or medial surface on transverse or coronal MRI or CT scans (Figures 2 and 5). In line with these findings, the “cingulate sulcus sign” was described in a small study of 10 iNPH patients as a wide or normal cingulate sulcus in the frontal lobe but compressed at the posterior part. All the 10 patients with iNPH had the cingulate sulcus sign but none of the healthy controls or patients with Alzheimer’s disease.

Wide Sylvian fissures have been proposed to be due to atrophy and a sign of poor prognosis in CT studies from the eighties (Figures 8 and 5). More recent studies have contradicted the previous findings and report that mild to moderate dilation of the Sylvian fissures are not uncommon in Alzheimer’s disease and in cerebrovascular disease but even more frequent and pronounced in idiopathic NPH.

The term disproportionately enlarged subarachnoid-space hydrocephalus (DESH), refers to the combination of ventriculomegaly with narrow high-convexity and medial subarachnoid spaces and enlarged Sylvian

Figure 7.
T1-weighted 3D-images of an iNPH patient with a small callosal angle. a. Sagittal image is used to identify the AC-PC plane and the posterior commissure. b. The callosal angle is measured in the coronal plane through the posterior commissure perpendicular to the AC-PC plane.
fissures and was present in 96% of the patients in a prospective study of 100 patients with iNPH in a study investigating the use of a MRI-based scheme (Figure 5). The authors of this study report that the positive outcome rate 12 months after shunt surgery was 77%. However, their high incidence of DESH was affected by their inclusion criteria of narrow sulci, and therefore no predictive value for DESH could be calculated. In the Japanese guidelines, DESH has an important position in the diagnosis. The presence of DESH and normal CSF pressure in combination with typical symptoms and history is enough for the diagnosis of probable iNPH.

Focally enlarged sulci occur in NPH and should not be mistaken for atrophy (Figure 2). These sulci are thought to be in communication with the ventricles and be reservoirs of CSF and have been referred to as “transport sulci.” Interestingly, they disappear or are reduced after shunting.

In two studies, a thin corpus callosum correlated with impairments of cognition and psychomotor function, and focal impingements in the corpus callosum were more frequent in shunt responders compared with non-responders. The diameter of the mesencephalon has been

Figure 8.
Two patients with iNPH and dilated Sylvian fissures. a. T1-weighted 3D-image of one patient with Sylvian fissure ordinal graded as 1. b. T2-weighted image of one patient with Sylvian fissure ordinal graded as 2.
reported to correlate with gait impairment and to be reduced in iNPH compared with healthy controls. In a follow-up study, both the antero-posterior and the left-to-right diameter of the midbrain increased after shunting.

Other features that have been described to differ between patients with NPH and Alzheimer’s disease are wider basal cisterns, smaller perihippocampal fissures, and dilation of the inferior portion of the aqueduct of Sylvius. The prognostic value of these features is unknown.

**White matter changes**

WM hyperintensities on MRI brain scans are a common finding in both healthy elderly and in pathologic conditions, and they are often divided into periventricular hyperintensities (PVHs) (Figure 9) adjacent to the ventricles, and deep white matter hyperintensities (DWMHs) (Figure 10) located in the subcortical peripheral WM. The changes are hyperintense on T2-weighted MRI or FLAIR MR images but hypointense on CT scans and sometimes on T1-weighted MRI. The origin of these changes is still debated. Small focal DWMHs are common in healthy elderly. If they have the same signal intensity as the CSF on T1-weighted and T2-weighted MR images, they are reported to be widened perivascular spaces, also known as Virchow-Robin spaces. Some authors report that perivascular spaces are not associated with ischemic disease and have a low tendency to progress, while others find correlations with lacunar ischemic stroke. Multiple punctate or more widespread early confluent or confluent lesions that are hyperintense on T2-weighted images but less apparent on T1-weighted images have often been described as a sign of cerebral small-vessel disease. Although there is no certain evidence that DWMH is a result of ischemia, the more widespread lesions are associated with vascular risk factors like hypertension, hypercholesterolemia, smoking and age, and they progress over time. Further, postmortem studies report increased hypoxia-related factors in the lesions. Interestingly, in non-hydrocephalic elderly, the presence of DWMHs may be associated with symptoms similar to NPH, i.e., impairments of gait, postural control, urinary incontinence and cognitive decline, and WM changes in the frontal lobe and periventricular region have the strongest relation to impairments in balance and gait.

Smooth WM changes adjacent to the lateral ventricles with continuity with the ventricular walls are referred to as PVHs. Small caps around the frontal horns and a “pencil-thin lining” along the ventricles have been reported to be normal findings in healthy elderly. The “pencil-thin lining” has been proposed to be an imaging artifact caused by partial volume effects or due to CSF pulsations, but a recent study report that the signal intensity of the these changes strongly correlates with total
Figure 9.
T2-weighted FLAIR images of two patients with iNPH and PVH. 
\textbf{a.} Graded as increased PVH = 1. \textbf{b.} Graded as severe PVH = 2.

Figure 10.
T2-weighted FLAIR images of three patients with iNPH. DWMH graded according to Fazekas et al.$^{64}$ \textbf{a.} Punctate foci (grade 1), \textbf{b.} Beginning confluence of foci (grade 2), \textbf{c.} Large confluent areas (grade 3).
burden of WM hyperintensities and therefore should be treated as “true” WM changes. More extensive PVHs are associated with the risk factors of vascular disease such as hypertension. The cause of PVH in the elderly has been proposed to be chronic ischemia, demyelination, subependymal gliosis or transudation of CSF from the ventricles.

PVHs were seen in NPH already on CT studies, often around the frontal horns but also extending from the bodies of the lateral ventricles. PVH seems to appear in all types of hydrocephalus, from non-communicating hydrocephalus to secondary and idiopathic NPH. Animal models in obstructive and secondary chronic hydrocephalus support that the PVH in hydrocephalus is an edema caused by trans-ependymal passage of CSF through a disrupted ependyma. MRI studies, measuring apparent diffusion coefficient (ADC) and relaxation times of T1 and T2, also support that the water content in the periventricular WM is increased in association with PVH. The PVHs decrease or disappear after shunting, a phenomenon often associated with positive shunt outcome, and it has been argued that the edema is involved in the pathophysiological mechanism of NPH. It has been proposed that the transudation of ventricular CSF is a sign of CSF stagnation that leads to a reduced clearance of toxic waste products and a deranged metabolic function, causing reduced local blood flow and ischemia.

Both PVHs and DWMHs are more common in iNPH than in healthy individuals, and risk factors of vascular disease such as hypertension are more frequent in iNPH. The presence of PVHs and DWMHs are associated with more severe symptoms in NPH and in older studies it was reported that patients with signs of cerebrovascular disease have a poor outcome after shunting. However, there are reports of positive outcome in iNPH patients with severe DWMHs. Actually, patients improved after surgery in a well-controlled study of patients with iNPH, severe DWMH, normal Rout and no response to CSF TT, a sample that also could be diagnosed with subcortical vascular dementia (SVD). Late stages of SVD can be difficult to differentiate from iNPH since MRI findings, symptoms and even neuropathological findings can be similar to iNPH, and in some patients, the two diseases can coexist.

The distinction between PVH and DWMH is generally made on the basis of the anatomic location, and the boundary has been suggested to be approximately 7–8 mm from the ventricular walls in healthy elderly. In iNPH, the distinction can be difficult, and in one study it was not possible to differentiate between PVH and DWMH in one-third of the patients. If DWMH in iNPH really shares the same underlying mechanism as DWMH in non-hydrocephalic patients is not completely understood. It is still not understood whether hypertension and chronic ischemia is one of the causes of iNPH or if the observed WM changes and
suspected ischemia is just an epiphenomenon. If the former is correct, it can only be for a subgroup of patients, since there are many patients with iNPH that do not have any WM changes on MRI.

**Markers of CSF movement**

The intracranial space is a closed compartment consisting of the brain parenchyma, CSF, arterial and venous blood, and an increase in the volume of any these four components leads to an equal decrease in the other components according to the Monro-Kellie doctrine. In the systole of every cardiac cycle, an inflow of arterial blood causes an expansion of cerebral arteries leading to a temporary pulse of increased ICP that drives out an equal amount venous blood to the dural venous sinuses and CSF through the aqueduct and fourth ventricle and out of the intracranial compartment. In the systole, the direction of CSF flow is cranio-caudal in the cerebral aqueduct, and in the diastole the flow is caudo-cranial.

Fast movement of CSF gives rise to a signal loss on T2-weighted MRI called the flow void phenomenon (Figure 11). The flow void is often increased in the cerebral aqueduct and forth ventricle in NPH. Bradley et al. suggested in an early paper that the phenomenon was a useful predictor of a good outcome after shunting, but this has been questioned in several subsequent papers. Grading of the flow void is dependent on the MR scanner and acquisition parameters used as well as it is to some degree a subjective evaluation. Furthermore, the flow void can also be increased in patients with atrophy or in healthy controls, and for this rea-

Figure 11.

T2-weighted images of two patients with different degrees of flow void in the aqueduct. a. Graded as flow void = 2 and b. as flow void = 3.
son the specificity is low both as a diagnostic and prognostic marker. However, presence of a flow void is a useful sign of a patent aqueduct and at least excludes a complete blockage.

A method used to quantify movements of CSF is phase-contrast MRI (pcMRI). It generates a contrast between flowing and stationary protons in the CSF. The method has also been used to measure arterial and venous blood flow in the brains of patients with NPH. The most studied measure using pcMRI in NPH is the aqueductal CSF stroke volume, which is defined as the average of the volume of CSF moving in cranio-caudal direction during systole and in the reverse direction during diastole. The stroke volume is increased in iNPH, which has also been reported to be of prognostic value. More recent studies have not verified the prognostic usefulness of the stroke volume. Inconsistencies are probably related to both temporal variations in pulsatility, known from invasive ICP measurements, but also an inability to compare results from different MRI scanners. Moreover, in a study of unshunted patients with iNPH, the stroke volume initially increased but later decreased over a period of 2 years. Thus a low stroke volume can occur in both the early and in the advanced stage of iNPH.

Since NPH is a disease with a strong association with pathologic CSF dynamics and the importance of a disturbed CSF pulsatility is frequently underlined, these techniques should be studied further.

Diffusion tensor imaging and MR spectroscopy

Diffusion tensor imaging (DTI) is a MRI sequence used to study the integrity of WM by different quantified measures based on the diffusion of water molecules. Fractional anisotropy (FA) is dependent on the direction of the diffusion and is in WM interpreted as axonal integrity. FA is reported to be reduced in the frontal WM, but increased in the cortico-spinal tract in patients with iNPH. Reduced FA in frontal WM was interpreted by Lenfeldt et al. as axonal loss and gliosis, and he reported that the FA did not increase after ELD. DTI can provide insights into the function of the WM and should be studied further in iNPH.

A few studies using magnetic resonance spectroscopy have been used to study the metabolism in the brain in patients with iNPH. N-acetylaspartate (NAA) is considered to be a neuronal marker and decreases in neuronal loss or dysfunction. The ratio NAA/creatine was reported to be lower in the frontal lobe in patients with iNPH compared with controls but higher in patients that improved after ELD compared with non-responders. Moreover Lundin et al. reported that quantified NAA was reduced in the thalamus, indicating that also the thalamus might have a role in the pathogenesis of iNPH.
**Cerebral perfusion imaging**

Oxygen and nutrients are transported to the brain by the blood. Cerebral perfusion is the steady state delivery of blood to the brain parenchyma. It is defined as the volume of blood per unit time that passes through the capillary bed in a tissue of interest (ml/min/100 g). Normal values of gray matter perfusion are approximately 50–60 ml/min/100 g and are preserved owing to cerebral autoregulation. Cerebral perfusion and cerebral blood flow (CBF) will be referred to synonymously in the following pages.

The basic idea involved in perfusion imaging is that the presence of a tracer in the blood is investigated. The local concentration of the tracer in a tissue of interest is a measure of the tissue perfusion. The tracer, or contrast agent, can be administered to the blood by injection or by inhalation, or the tracer can be endogenous. Moreover, tracers can be freely diffusible to the tissue of interest or be non-diffusible and stay in the capillaries. With the use of non-diffusible tracers, the state of the blood-brain barrier becomes an important parameter.

**Arterial spin labeling**

Arterial spin labeling (ASL) is a MRI perfusion method that provides quantification of CBF without the need for an exogenous contrast agent. Instead, magnetically labeled water functions as a diffusible tracer, which makes the method non-invasive. Scan time with the commonly used protocols is relatively short, approximately 5 minutes. The method has been validated against PET.

The “labeling” in ASL means that water molecules in the blood are tagged by adding radiofrequency pulses that either invert or saturate the spins of the nuclei. The site of labeling for cerebral perfusion imaging is the feeding cerebral arteries. Labeled images at the site of interest in the brain are acquired that contain a signal from both labeled blood and tissue with stationary unlabeled water. Also, separate control images without prior labeling are acquired, and the difference in signal between labeled images and control images is a measure of the delivered blood to the tissue. The images are acquired after a short time interval after the labeling, called post-labeling delay (PLD), to allow the labeled blood to reach the tissue of interest. The time required for the blood to move from the labeling site to the tissue of interest is the arterial transit time (ATT). Moreover, the lifetime of the labeled blood is dependent on the relaxation of T1 (longitudinal relaxation), which normally is similar to ATT.
Figure 12 is a schematic illustration of a common site for labeling and image acquisition. Several different approaches of ASL exist, and a distinction is made between continuous ASL (CASL) and pulsed ASL (PASL). In CASL, the labeling duration is long (seconds), and the labeling site at the neck is a thin rectangular region. On the other hand, in PASL, the labeling duration is short (milliseconds), and in contrast to CASL, a large slab of tissue is labeled at the neck. The major advantage with CASL is a higher signal-to-noise ratio, while the labeling efficiency in PASL is higher. A recent modification of CASL is called pseudo-continuous ASL (pCASL) that uses a long series of short labeling pulses. It was implemented by Wu et al., and the authors reported 50% improved signal-to-noise ratio compared with PASL and 18% improvement in labeling efficiency compared with CASL. Moreover, the reproducibility of pCASL is reported to be better than other ASL methods.

Quantification of perfusion using ASL requires knowledge of some parameters, and some assumptions must be made such as knowledge of the longitudinal relaxation (T1) of blood and tissue, the ATT and the labeling efficiency. In these parameters lie the main sources of errors in ASL quantification. For example, the PLD is typically supposed to match the ATT. However, the ATT is known to vary between indi-
viduals and between normal and pathological tissue. If the PLD is too short, the labeled blood will still be in the larger vessels and not reach the tissue of interest in time, leading to hypoperfusion in the tissue of interest and vascular artifacts. Too long PLD, on the other hand, leads to more T1 decay and a low signal-to-noise ratio. Another common source of error is related to a low signal difference in ASL between label images and control images that only is approximately 0.5–1.5%. To achieve an acceptable signal-to-noise ratio, an average of 30–40 pairs of images are acquired during 3–4 minutes, which makes the technique very sensitive to motion artifacts. These two examples are relevant in dementia research since ATT can be affected in pathologic tissue, and patients with cognitive dysfunction can have problems lying completely still in the scanner.

However, quantification with other perfusion methods is also associated with sources of error. Quantification of DSC MRI is associated with several issues, and in the clinical setting, only a relative perfusion measure is possible. The resolution using positron emission tomography (PET) is relatively low and leads to problems with partial volume effects.

The combination of high repeatability, no ionizing radiation, rapid scan time and non-invasive perfusion imaging makes ASL ideal for repeated measurements. When this thesis was written, no studies of cerebral perfusion using ASL had been published that included patients with NPH.

**CBF in iNPH**

Studies of CBF have been performed both as measurements of baseline CBF in patients with NPH compared to controls, before and after shunting and before and after a CSF TT. Owler reviewed the CBF studies in NPH between the years 1969–2000 and concluded that previous results had been diverse, and it is uncertain whether measurements of CBF aid in the diagnosis and prognosis of outcome after shunt surgery. Comparisons of studies from different decades are difficult because of heterogenous patient inclusion, difference in the assessment of outcome and technical limitations with the methods.

Early studies used xenon-133 as contrast agent, administered by injection or inhalation. Both decreased global CBF as well as decreased regional CBF in frontal areas were reported. Reports of the prognostic value were inconsistent.

Single photon emission tomography (SPECT) and xenon-CT are more useful methods to investigate regional differences and have been used in several studies of NPH. SPECT can be used with different tracers, but that will not be dealt with in this thesis. In these studies, regions in the frontal lobe, temporal lobe, thalamus as well as WM often showed
hypoperfusion. After shunting, CBF was reported to increase in frontal cortical areas, basal ganglia, hippocampus, mesencephalon and frontal WM. In a study by Tullberg et al., the patients with impaired wakefulness had reduced CBF in the anterior cingulate cortex, and in patients who improved in wakefulness after shunting, the CBF increased in the mesencephalon, hippocampus and frontal grey matter. Ishii et al. presented a large Japanese multicenter study of 85 iNPH patients and divided the patients into different perfusion patterns. The majority of the patients had a pattern with hypoperfusion in the frontal areas, but there were no prognostic differences between different patterns. With the methods mentioned above, prognostic usefulness has been reported as often as the opposite.

Owler et al. and Klinge et al. used PET to study perfusion in NPH. Owler reported hypoperfusion in the basal ganglia and thalamus and that the hypoperfusion in the periventricular area is more pronounced close to the ventricles and the perfusion gradually is normalized closer to the cortex. However, their control group was much younger than the patients, and there are reports that CBF decrease with age. Klinge et al. reported in a retrospective study that patients with more severe symptoms had lower perfusion in the medial frontal cortex and that the CBF increased after shunting in superior frontal areas in patients who improved after surgery.

Only four studies using dynamic susceptibility contrast (DSC) MRI with a gadolinium-based contrast agent have been performed in NPH patients. Corkill et al. found reduced preoperative cerebral blood volume (CBV) in periventricular tissue in iNPH patients compared with controls, but the findings were of no prognostic value. CBV was lower in WM hyperintensities, while ADC was elevated, indicating higher water content. Walter et al. and Hertel et al. performed two similar studies with patients that were included in both studies. They performed perfusion scans in patients with iNPH before and after a CSF TT. They found a group of patients with no clinical improvement after the CSF removal but with increased CBF after the CSF removal. When these patients were shunted, 86% of them improved. Therefore, they concluded that perfusion measurement before and after CSF TT improved the prognostic accuracy. However, the authors reported that they only included patients with iNPH, but there were patients with an atypical picture in their studies. In the first study, the youngest patient was 39 years old and in the second study patients with dementia and no gait impairment were included. Ziegelitz et al. used DSC-MRI in 21 iNPH patients and 16 age-matched controls and reported a lower CBF in the medial frontal cortex, hippocampus, lentiform nucleus and periventricular WM in the iNPH patients. There were indications that preoperative perfusion measurements could
have predictive value because shunt-responders had a higher relative CBF in the medial frontal cortex compared with non-responders.\textsuperscript{166}

Besides Walter and Hertel’s studies mentioned above, at least nine other studies have investigated perfusion before and after removal of a bolus of CSF\textsuperscript{148-150, 153, 159, 167-170}. In the studies from the 70s and 80s, increased CBF after CSF removal was reported in five of the six studies. The only study that reported that a decrease was as likely as an increase was Kushner et al.\textsuperscript{149} The patients in these studies were a mix of iNPH and secondary NPH, and they were examined with gamma camera or SPECT using xenon-133 or technetium-99m tracers. None of these studies tested or reported any relation between clinical improvement and CBF change.

Dumarey et al. used SPECT and compared changes before and after CSF TT with a voxel-based method. They reported no increased CBF in the whole sample, but in patients who responded clinically to the CSF removal, CBF increased in dorsolateral frontal cortex and left mesiotemporal cortex.\textsuperscript{168} Mori et al. used SPECT with a metabolic active tracer and reported dramatically increased CBF (≈100\%) in patients that responded to the CSF removal, but also CBF in non-responders increased markedly (≈50\%).\textsuperscript{169} Both of these studies included a mix of iNPH and secondary NPH. In contrast, Kristensen et al. also used SPECT, and in a well-defined study population consisting of 31 iNPH-patients they reported no increase in CBF 3 hours after the CSF removal.\textsuperscript{153}

Lenfeldt et al. used functional MRI before and after a 3-day external lumbar drainage (ELD) of a total of 400 ml CSF. They included only patients with iNPH, and improved motor function was accompanied by increased activity in the supplementary motor area.\textsuperscript{216}

The cerebrovascular reserve has been estimated by measuring the CBF response after injection of acetazolamide that causes vasodilation and CBF increase in healthy controls. In patients with NPH the response to acetazolamide is limited, but it is reported that this response is restored after shunting, indicating reversibility of an impaired cerebrovascular reserve.\textsuperscript{171-173}

In conclusion, in line with theories of a frontal subcortical and periventricular pathophysiology affecting the cortico-basal ganglia-thalamo-cortical circuit in iNPH,\textsuperscript{174} there is evidence of hypoperfusion in frontal gray matter and WM, periventricular WM, mesencephalon, thalamus and basal ganglia.

Reduced CBF seem to be restored after shunt surgery, but it is uncertain whether any increase is detectable after a CSF TT. Preoperative measurement of CBF may provide prognostic information, but the relationship between clinical improvement and regional CBF changes needs to be studied further in well-defined patient samples.
Invasive tests
In the American iNPH Guidelines, it is reported that a favorable outcome can be seen in 46–63% of patients with diagnosis based only on clinical examination. To increase the accuracy in the selection of shunt candidates, supplementary prognostic methods have been developed. However, in the recently published European iNPH Multicenter Study, 84% of the patients improved 12 months after surgery, with selection to surgery based only on clinical and MRI findings.

Baseline CSF pressure
The name of the disease is “normal pressure” hydrocephalus, but the CSF pressure is often in the upper range of normal in patients with iNPH. In fact, in the American iNPH Guidelines, the upper limit is proposed to be $240 \text{ mmH}_2\text{O}$ in iNPH, which is high considering that the median pressure in healthy elderly is reported to be $158 \text{ mmH}_2\text{O}$, with a 95\textsuperscript{th} percentile value of $194 \text{ mmH}_2\text{O}$. There is no evidence-based support of a relationship between baseline CSF pressure and outcome after shunting.

The CSF tap test
When Hakim and Adams presented their first NPH cases in 1965, the patients had undergone a lumbar puncture, with the removal of a bolus of CSF and with subsequent improvement. The patients also improved after shunt surgery, and more studies followed reporting that removal of a bolus of CSF could be used to select patients for shunting. The procedure, often called a CSF tap test (CSF TT), has been used as a preoperative test in many centers working with NPH. Often 30–50 ml CSF is removed though a lumbar needle, and a clinical evaluation is performed before and after the drain to assess whether the patient has improved. An improvement is considered as a positive test. The performance of the test was described in detail in 1982 by Carsten Wikkelsø, who suggested that it was useful for selection of shunt candidates. Other studies followed and evaluated its use as a prognostic test, often with a mix of patients with iNPH and secondary NPH. In most studies the specificity has been high, (up to 100%) but sensitivity lower (26–43%). However, in one study by Malm et al., with only idiopathic cases, the specificity was low (33%).

More recent studies have been performed in which only idiopathic cases according to the American or Japanese guidelines were studied. In two Japanese studies the sensitivity was 71–73%, and the specificity was 65–100%. The European iNPH Multicenter Study confirmed previous recommendations that the CSF TT should not be used to exclude patients from shunt surgery. The study consisted of 115 patients with
iNPH, and the inclusion was based on clinical symptoms and imaging, and the selection for surgery was not influenced by the results of the CSF TT. The positive predictive value (PPV) of the CSF TT was 88%, which was only slightly better than the outcome rate, 84%, with selection to surgery only based on clinical symptoms and imaging. The negative predictive value (NPV) was only 18%.

The evaluation method to identify a responder of the CSF TT varies but often consists of an evaluation of gait and sometimes evaluation of cognition performed both before the test and at some point after the CSF removal. Subjective evaluation and ordinal scales are used, but more common is some sort of quantitative measurement of gait function, that provides continuous data. Walking speed, number of steps for turning and different balance tests are the motor symptoms reported to improve the most after CSF removal. Expected improvement in walking speed is in the range of 10–20%. A wide range of thresholds, from 5% to 25%, as an indication of improvement in walking speed have been used in different studies. However, normal fluctuation in walking speed is not negligible, and in a study by Kahlon et al., 62% of the patients had a normal variation of more than 5% in fast walking speed.

The evaluation of gait after CSF removal is in most studies performed 3–8 hours after the test, but there are reports of delayed improvements several days or weeks after the tap test. While there have been reports that cognitive function does not improve after the CSF TT, other reports indicate that cognitive improvement can be measured but that the response is delayed compared to the gait improvement. The CSF TT has never been tested in a placebo-controlled study in patients with NPH, but studies with control groups with other dementias have been performed. In these studies the NPH patients improved after CSF removal, while the controls were unchanged in function or declined.

The mechanism behind the transient improvement following temporary CSF diversion is not understood. The 30–50 ml CSF that is removed is restored after 1–2 hours in healthy individuals, but since the improvement is known to last for several hours, the reversibility is probably a more complex mechanism than just simple pressure changes.

It is difficult to compare the prognostic accuracy of the tap test between different studies since there is no standard for the evaluation methods, and different cutoff values are used for a positive test. It is not known how long an improvement after a tap test lasts and when to evaluate the result. In different centers, the evaluation after the tap test is done from 30 minutes to several hours after the CSF removal. Furthermore, the final outcome, response to shunting, is also assessed differently in studies. Even though these limitations exist, the tap test is a widely used
test because of its simplicity and high specificity. However, the CSF TT is considered as decisive only if the test is positive. Patients must not be excluded from surgery on the basis of a negative test.

**CSF infusion tests**

Different infusion methods are used but the basic idea is to measure the dynamics of the CSF system while it is being manipulated by an infusion of fluid. It can be performed intracranially but a lumbar approach is more often used because it is less invasive. One or two lumbar needles are placed in the lumbar subarachnoid space and fluid is infused into one needle while measurements of CSF pressure and pulse amplitude are recorded on a computer.

The resistance to CSF outflow ($R_{\text{out}}$) can be calculated, which is referred to synonymously with the impedance of flow offered through the CSF absorption pathways. The median $R_{\text{out}}$ in a sample of healthy elderly was 8.6 mm Hg/mL/min, and the 90th percentile was 17.4 mm Hg/mL/min.175 Elevated $R_{\text{out}}$ signals a reduced capacity to reabsorb CSF, and there have been several reports that the measure can be used to predict outcome after shunting.187, 188 Other studies report that $R_{\text{out}}$ is less useful as a predictive test.29, 189 One problem in these studies has been mixed groups of NPH and iNPH patients and different methods for estimation of $R_{\text{out}}$. Some centers use a constant pressure infusion, some use a constant flow infusion, while some centers use bolus infusions.190

In the European iNPH Multicenter Study, the predictive value was similar to the CSF TT, a high PPV but very low NPV, and for this reason the test probably cannot be used for excluding patients from shunt surgery. The predictive value was not increased if information from the CSF TT and $R_{\text{out}}$ was combined.182 However, the infusion tests are of great value to assess if an existing shunt system is working.31

**External lumbar drainage**

If a CSF TT is thought to mimic a shunt for a short period of time, external lumbar drainage (ELD) is even more similar to a real shunt. A lumbar catheter is placed in the subarachnoid space, and large amounts of CSF are drained over the course of several days. Normally 100–200 ml CSF per day is drained for 3–5 consecutive days.41, 178 The advantage of the test is an improved sensitivity compared to the CSF TT, ranging from 50–100%.178, 180, 191 The shortcoming is an increased frequency of serious complications such as bacterial meningitis, overdrainage and the need for hospital admission for several days.192
Treatment

When the diagnostic procedure points toward iNPH, the question that remains is: Will the patient benefit from a shunt operation? A shunt implantation has been the standard treatment from the early days of NPH to the present time.

The basic mechanism for a shunt system is to drain CSF from the ventricles (or lumbar subarachnoid space) to a compartment with lower pressure. The most commonly used system, ventriculo-peritoneal (VP) shunt, drains CSF from one of the brain ventricles to the abdominal cavity. Another system, referred to as a ventriculo-atrial shunt, drains CSF from the ventricles to the right atrium of the heart and is less used today. Other systems are the lumbo-peritoneal shunts, which are frequently used in Asia, or the less commonly used ventriculo-pleural shunts.193 A shunt system is a long elastic tube and a valve with an opening pressure that can be fixed or adjustable. If the CSF pressure exceeds the opening pressure, CSF is drained. The opening pressure can be adjusted non-invasively in many of the commonly used systems today.

There is one double-blind randomized controlled study that has reported that VP shunts are an effective treatment in iNPH patients. The study included only patients with iNPH and severe WM hyperintensities in the MRI scans.114

Endoscopic third ventriculostomy (ETV) has been proposed as an alternative treatment option in iNPH patients. Results for this option have been mixed, and the outcome is uncertain.194, 195 The most recent publications have reported inferior outcome rates and higher complication rates with ETV compared to treatment with VP shunts.196, 197

There is no pharmacological treatment option for patients with iNPH. A recent study of only eight patients treated with the carbonic anhydrase inhibitor acetazolamide daily for up to 3 months reported that five out of the eight patients improved in gait. Interestingly, in the patients that improved, the PVHs in the MRI scans were reduced.198
Outcome

In a literature review, Toma et al. concluded that without treatment, the symptoms in a patient with iNPH deteriorate. Andrén et al. investigated a group of iNPH patients in whom surgery had been delayed for at least 6 months (median 13 months) compared with patients that were operated within 3 months after diagnosis. The patients with delayed time to surgery deteriorated in both the iNPH scale score and the mRS score. Unfortunately, the patients’ final outcome after surgery was also negatively affected by the delayed waiting time.

After shunting, the positive outcome rate varies, depending on the length of follow-up and the postoperative evaluation method. The reported positive outcome rate is often higher in studies with a short postoperative follow-up time and is lower for long-term studies. This is often due to the impact of age and the relatively high burden of comorbidity in this population on the patients’ symptoms, but it is also affected by shunt complications.

In modern studies, the positive outcome rate at follow-up 12 months after shunting is reported to be in the range of 70–90%. The positive outcome rate in older studies were much lower. However, it is very difficult to compare outcome rates between different studies since a diversity of evaluation scales to determine outcome has been used, and in many studies only short-term (3 months) outcome are reported.

Another important aspect is the complications after shunt surgery that affect approximately 10–30% of the patients. Common complications that occur postoperatively are catheter failure, hygromas and subdural hematomas. More serious complications such as intra-cerebral hematomas or shunt infections are uncommon and often occur in the perioperative period.

Careful follow-up visits and postoperative CT scans are important to reveal potential complications and also to optimize the shunt setting if the patient has a programmable valve.
Aims of the thesis

General aims

To evaluate the performance of the gait assessments used with the CSF TT and the underlying mechanisms of improvement in gait function after CSF removal. To investigate the prognostic value of structural findings on preoperative MRI scans.

Paper I

To describe the evaluation time after a CSF TT, to assess the variability between repeated measurements, the interrater agreement of commonly used gait tests and finally to investigate whether pain affects the gait performance after a CSF TT.

Paper II

To compare the preoperative callosal angle in shunt responders with that in non-responders and clarify whether the callosal angle can serve as a predictor of the outcome.

Paper III

To describe the occurrence and prognostic value of 13 different radiological variables on preoperative MRI scans and the relation between MRI findings and clinical symptoms.

Paper IV

To investigate changes in CBF during the first 24 hours after a CSF TT in patients with iNPH and study the relationship between clinical improvement and perfusion. A secondary aim was to measure the repeatability of pCASL in patients with iNPH.
Patients and Methods

Patients

Paper I

During 2008–2009, patients under evaluation for iNPH at our inpatient ward were randomly included. The inclusion was limited to periods when the researchers were available. All patients had a communicating hydrocephalus determined by CT or MRI and a gait disturbance with gradual onset. Exclusion criteria were inability to walk 10 meters (walking aids were allowed), secondary NPH or other known diseases causing the symptoms. Forty-one patients were asked to participate and 40 patients, 21 men and 19 women, mean age 73 years (range 59–87), gave written informed consent and were included in the study.

Additional analysis of the patient material 4 years after the end of the study revealed that 25 of the patients could be diagnosed as probable iNPH and 15 as possible iNPH according to the American iNPH Guidelines, Table 2. Thirty-two of the patients were initially offered a shunt operation, and 30 were eventually operated on. One patient was considered as an outlier because of severely impaired gait that was further affected by spinal stenosis. The patient was more than 300% slower than the second slowest patient and was therefore consequently excluded from statistical analyses.

<table>
<thead>
<tr>
<th></th>
<th>Probable iNPH (n=25)</th>
<th>Possible iNPH (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TTr, n (%)</td>
<td>20 (80)</td>
<td>7 (47)</td>
</tr>
<tr>
<td>Offered shunt surgery, n (%)</td>
<td>25 (100)</td>
<td>7 (47)</td>
</tr>
<tr>
<td>mRS, median (IQR)</td>
<td>2 (2–3)</td>
<td>3 (2–3)</td>
</tr>
<tr>
<td>MMSE, median (IQR)</td>
<td>26 (21.5–26.5)</td>
<td>22 (15–27)</td>
</tr>
</tbody>
</table>

TTr, CSF TT responder
Paper II and III

Information about the study was sent to all 188 patients that had undergone surgery for iNPH with a shunt at Uppsala University Hospital during 2006–2010, according to our records. Three patients did not reply and one patient refused to participate in the study. Exclusion criteria were secondary NPH, no clinical evaluation at baseline and by the end of the follow-up period at 12 months postoperatively, no preoperative MRI examination including a sagittal sequence within 18 months before surgery.

Based on these exclusion criteria, 36 patients were excluded because of a valid MRI examination was missing and 11 patients were excluded after retrospective evaluation of the patients’ charts: 8 patients due to secondary NPH and 3 patients due to congenital hydrocephalus.

Of the remaining 137 patients, 109 had been assessed clinically at both baseline and at the end of the follow-up period, 12 months postoperatively. Thus, the final sample consisted of 109 patients, 58 men (53%) and 51 women (47%), with a median age at the time of shunt surgery of 74 years (range 54–88 years).

All patients had ventricular enlargement (mean Evans index 0.38, range 0.30–0.50) and gradually evolving symptoms, including a gait disturbance with or without cognitive decline or urinary incontinence.

Twenty-two patients (20%) had suffered from a previous stroke, and 7 (6%) had a history of a myocardial infarction. Eight patients (7%) had a psychiatric diagnosis such as schizophrenia or bipolar disorder, and 26 (24%) were being treated with antidepressant drugs. Other drugs being given were antihypertensive drugs, 66 patients (61%); levodopa, 7 patients (6%); and insulin, 16 patients (15%).
Sixty patients were consecutively recruited from the waiting list of patients referred to Uppsala University Hospital for evaluation of suspected NPH. Exclusion criteria were secondary NPH or congenital hydrocephalus, contraindications to MRI, age >84 years, severe cognitive dysfunction with inability to give informed consent, refusal to undergo evaluation or shunt surgery, complete inability to walk or gait problems that could be explained by other known diseases. Information about the exclusion criteria was gathered from the referrals and by telephone calls to the patients. Based on these criteria, 23 patients were excluded from the study. In addition, nine patients that were already included in an ongoing multicenter study of the CSF TT were not included; one patient had died since the referral had been written, and in one patient the evaluation was postponed because of surgery for an abdominal aortic aneurysm. Finally, 26 patients (15 men and 11 women) were included in the present study. The reason 34 patients was excluded is summarized in Table 3.

Out of the 26 patients, 17 were classified as probable iNPH, 6 as possible iNPH, and 3 as unlikely iNPH according the American iNPH Guidelines. Three patients were excluded from statistical analyses of CBF due to artifacts related to high intravascular signal and apparent hypoperfusion in the brain parenchyma. Only the patients diagnosed with iNPH and without artifacts on perfusion images (n=20) were included in the statistical analyses of CBF.

Table 3.
The 34 patients that were excluded during the inclusion process of Paper IV.

<table>
<thead>
<tr>
<th>Reason for exclusion</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete inability to walk</td>
<td>6</td>
</tr>
<tr>
<td>Inability to give consent</td>
<td>5</td>
</tr>
<tr>
<td>Contraindications to MRI</td>
<td>3</td>
</tr>
<tr>
<td>Included in another study</td>
<td>9</td>
</tr>
<tr>
<td>Refusal to undergo evaluation or surgery</td>
<td>2</td>
</tr>
<tr>
<td>Secondary NPH</td>
<td>4</td>
</tr>
<tr>
<td>Congenital hydrocephalus</td>
<td>1</td>
</tr>
<tr>
<td>Age &gt;84 years</td>
<td>1</td>
</tr>
<tr>
<td>Diseased before evaluation</td>
<td>1</td>
</tr>
<tr>
<td>Planned surgery of AAA before evaluation</td>
<td>1</td>
</tr>
<tr>
<td>Symptoms explained by other disease*</td>
<td>1</td>
</tr>
</tbody>
</table>

AAA, abdominal aortic aneurysm.
* Cervical disc herniation.
Methods

Paper I
All patients underwent a CSF TT of 40–50 ml CSF, and gait was evaluated the day before the drainage and at 2, 4, 6, 8 and 24 hours after the CSF TT. Gait was assessed by the ordinal gait scale (Table 4) and by walking 10 meters at a self-chosen speed. Time and number of steps required to finish the distance were recorded. All gait tests were repeated at every investigation time. Two-thirds of the evaluations were performed by physiotherapists with experience with iNPH, and one-third of the evaluations were done by the first author (JV) after training with physiotherapists. All gait evaluations were videotaped, and these films were used to assess the intra- and interrater reliability of the gait scale. By predefined criteria, responders to the CSF TT were defined as patients with improvements in time and number of steps with 10% on both parameters or by 20% in either time or steps at one or more assessment time post CSF TT. Only the CSF TT responders were included in the analyses of gait improvement after CSF removal. Patients graded severity of headache and back pain at all assessment times by a visual analogue scale (VAS).

Papers II and III
Imaging
Preoperative MRI scans were retrospectively evaluated. Forty-one (38%) of the MRI investigations were performed at Uppsala University Hospital and the rest at the referring hospitals. In Paper II, Evans index was measured and the callosal angle according to the method described by Ishii et al (Figure 7). The first author (JV) performed the measurements of continuous imaging findings after training with an experienced neuroradiologists (EML). Both JV and EML evaluated the ordinal and dichotomous variables in all patients separately and blinded from each other and clinical data.

In Paper III, 13 different imaging features were measured:

- Evans index: Ratio between maximum diameter of the frontal horns of the lateral ventricles and maximum inner diameter of the skull in the same slice, Figure 3.
- Callosal angle: The angle between the lateral ventricles on a coronal image through the posterior commissure, perpendicular to the anterior-posterior commissure plane, Figure 7.
- Narrow sulci at the high convexity: Three level ordinal scale, as follows: 0 = normal or wider than normal, 1 = slight compression, 2 = definitive compression, Figure 2.
- Dilation of the Sylvian fissure: Evaluated on coronal images, reconstructed at the level of the central part of the brainstem and angled along the brainstem. Graded by the three level ordinal scale “Sylvian fissure ordinal” as follows: 0 = normal or narrow, 1 = mildly-moderately enlarged, 2 = highly enlarged, Figure 8. The Sylvian fissure was also measured in mm, Figure 13, and graded by the three level ordinal scale described by Kitagaki et al.\textsuperscript{78}
- Diameter of the 3\textsuperscript{rd} ventricle: measured in mm in the center of the ventricle in the anterior-posterior direction but in the widest part in the inferior-superior direction, Figure 6.
- Temporal horns of the lateral ventricles: measured in mm at the widest portion, perpendicular to the direction of the temporal horn, Figure 4.
- DESH: graded as present or not present, Figure 5.
- Flow void through the aqueduct: three level ordinal scale, as follows: 0 = no flow void in the aqueduct, 1 = flow void only in the aqueduct, 2 = flow void in the aqueduct and the upper half of the 4\textsuperscript{th} ventricle, 3 = flow void that extends to the caudal part of the 4\textsuperscript{th} ventricle, Figure 11.
- Focal bulgings of the roof of the lateral ventricles: graded as present or not present, Figure 14.
- DWMH: graded on a four level ordinal scale according to Fazekas,\textsuperscript{64} as follows: 0 = no lesions, 1 = punctate foci, 2 = beginning confluence of foci, 3 = large confluent areas, Figure 10.
- PVH: three level ordinal scale as follows: 0 = normal (including “pencil thin lining” along ventricular wall and small caps around the frontal horns), 1 = increased PVH, 2 = irregular large symmetrical hyperintensities extending out in to the deep WM and on at least two locations all the way from the ventricles to the cortex, Figure 9.
- Focal widening of sulci: graded as present or not present, Figure 2.
- Aqueductal stenosis: graded as present or not present
Figure 13.
The height of the Sylvian fissure was measured on a sagittal image located at the midpoint between the skull and the insular cortex. The height was measured in mm in five different locations perpendicular to the direction of the Sylvian fissure. The median value of the five locations was calculated for each side, and the average of right and left was recorded.

Figure 14.
Two different patients with focal bulgings of the roof of the lateral ventricles. Sagittal images including the most cranial portions of the lateral ventricles. a. T2-weighted image b. T1-weighted image.
**Clinical evaluation**

Clinical evaluations at our department are performed according to a standardized protocol before surgery and at 3 and 12 months postoperatively. Physiotherapists and occupational therapists perform the tests. Records of clinical evaluation were reviewed from the preoperative baseline investigations, and the 12-month postoperative investigations were used as follow-up. The cognitive test used was the MMSE, \(^{51}\) and the test of urinary symptoms was the continence scale, Table 5. Motor symptoms were tested with the balance scale (Table 6) and the gait scale, Table 4. Gait was also tested with three tests in which time and number of steps were noted. The latter included walking 10 meters at a self-chosen speed, the Timed Up and Go test (TUG), \(^{50}\) and walking backward 3 meter. The continence scale, gait scale and balance scale are components of the recently published iNPH scale and were used in the European iNPH Multicenter Study. \(^{49}\) The mRS (Table 7) was used as a test of general handicap level.

*Walking 10 meters in self-chosen speed*

Time and number of steps to finish the distance are measured. The patient is asked to start walking from a standstill position at their self-chosen comfortable speed. The patients are not informed that they are being timed, and to avoid deceleration, the finish line is marked so that the patient is not aware of it.

*Timed Up and Go test (TUG)* \(^{50}\)

The patient rises from an armchair, walks 3 meters, turns, walks back and sits down. The time and number of steps needed to finish the procedure are measured.

*Walking backwards 3 meters*

The time and number of steps are measured when the patient is walking backwards 3 meters. Start from a standstill position.

Definitions of improvement:

- An increase of at least one level in either the gait or the balance scale or at least 20% in time or number of steps in at least 50% of the three timed tests performed (walking 10 meters, TUG, and walking backwards 3 meters) was considered as an improvement in motor function.
• An increase of 2–3 levels in MMSE was considered as a possible improvement and ≥4 levels was considered as a definitive improvement in cognition.
• An increase of at least one level in the continence scale was considered as an improvement in urinary symptoms.
• A shunt response was defined as an increase of at least 2 points in a symptom scale that included all 3 symptoms of iNPH (Table 8).

For comparisons, an increase of at least one level in mRS (Table 7) was used as an alternative outcome in Paper II. In Paper II outcomes determined by the symptom scale (n=108) and mRS (n=92) were analyzed separately.

| Table 4. |
The gait scale.\(^{49}\)

| 1 | Normal |
| 2 | Slight disturbance of tandem walk and turning |
| 3 | Wide-based gait with sway, without foot corrections |
| 4 | Tendency to fall, with foot corrections |
| 5 | Walking with cane |
| 6 | Bi-manual support needed |
| 7 | Aided |
| 8 | Wheelchair bound |

| Table 5. |
The continence scale.\(^{49}\)

| 1 | Normal |
| 2 | Urgency without incontinence |
| 3 | Infrequent incontinence without napkin |
| 4 | Frequent incontinence with napkin |
| 5 | Bladder incontinence |
| 6 | Bladder and bowel incontinence |

| Table 6. |
The balance scale.\(^{49}\)

| 1 | Able to stand independently for more than 30 s on either lower extremity alone |
| 2 | Able to stand independently for <30 s on either lower extremity alone |
| 3 | Able to stand independently with the feet together (at the heels) for more than 30 s |
| 4 | Able to stand independently with the feet together for <30 s |
| 5 | Able to stand independently with the feet apart (one foot length) for more than 30 s |
| 6 | Able to stand independently with the feet apart for <30 s |
| 7 | Unable to stand without assistance |
Paper IV

Time scheme and clinical evaluation

The time scheme is presented in Figure 15. A CSF TT of 40 ml CSF was performed in all patients. Before the CSF TT, two MRI scans were performed with a 60-minute interval for repeatability analysis. Three MRI scans were performed 30 minutes, 4 hours and 24 hours after the CSF TT. Clinical evaluation of gait was performed the day before the CSF TT and immediately after the three MRI scans after the CSF TT. The tests were time and number of steps required to walk 10 meters at maximum pace and the TUG test. The tests were performed twice at each assessment, and the mean result was used in the statistical analyses.

Imaging

The scanner used was a Philips 3T MRI scanner (Philips Achieva, Philips Healthcare, Best, the Netherlands) with a 32-channel head-coil. All MRI scans included a perfusion sequence and a morphological sequence. The first scan also included a 3D T1-weighted gradient echo sequence and a FLAIR sequence. Perfusion data were acquired using a background-suppressed pCASL sequence with post labeling delay 1600 ms. For volu-
metric measurements, Synthetic MRI (SyMRI) data were acquired using the multi-slice, multi-echo, and multisaturation delay sequence QRAPMASTER.206

For each patient, perfusion images from all investigation times were coregistered to the perfusion images of MRI 1, to allow for a single delineation per patient for each region of interest (ROI). As an anatomical reference, the FLAIR images of MRI 1 were also coregistered to the perfusion images of MRI 1. The ROIs were: cerebellum, medial frontal cortex, left and right lentiform nucleus, medial temporal lobe, high convexity cortex, pons, supplementary motor area (SMA), left and right thalamus, frontal WM, lateral WM, and superior WM.

The total volume of both lateral ventricles was measured with SyMRI. The volume was calculated semi-automatically, after manual delineation on each slice for all patients.

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**Figure 15.**
Time scheme in Paper IV.
Statistics

Repeatability between repeated investigations and intra- and interrater agreement between different investigators were analyzed with intraclass correlation coefficients (ICC) for continuous variables and Cohen’s kappa (κ) for ordinal and dichotomous variables.

In Paper I the proportional improvement in gait function was presented as mean and the 95% confidence interval (CI), and the level of improvement tested using one-sample t-test with 0 as test value. As described in the Additional analyses section of Paper I, this was reanalyzed with improvement presented as median and interquartile range, and the level of improvement was tested with one-sample Wilcoxon signed rank test, to avoid influence of non-normally distributed data.

McNemar’s test and Wilcoxon signed rank test were used to compare groups with paired data. Mann Whitney U-test or χ² (or Fisher’s exact test) were used to compare ordinal and continuous data or proportions of independent groups. However, in Paper II the independent samples t-test was used to compare for differences in callosal angle between two groups, given the large sample with normally distributed data.

The Friedman test was used in Paper IV to test for differences in CBF and volumes of lateral ventricles between different investigation times. The Wilcoxon signed rank test were used as post hoc test.

Receiver operating characteristic (ROC) curves were drawn in Paper II to calculate sensitivity and specificity of the callosal angle to predict outcome after shunting. Youden’s index (sensitivity + specificity – 1) was used to calculate a theoretical optimal cutoff value.

Logistic regression was used to test for associations between imaging findings and the dichotomous variable shunt outcome in Papers II and III.

All correlation analyses were done with Spearman rank correlation coefficient except for one analysis in Paper II (correlation between the callosal angle and Evans index) in which Pearson’s correlation coefficient was calculated. In Papers III and IV the level of significance was adjusted to $p<0.01$ for correlation analyses because of larger correlation matrices compared with Papers I and II.

Except for the correlation analyses in Papers III and IV, no corrections for multiple analyses were made to avoid type II errors when the results displayed consistent patterns.

Ethical approval

The local Ethics committee in Uppsala, Sweden approved all studies in this thesis. All participating patients signed a written informed consent form.
Results

Paper I

Twenty-seven patients improved at one or more evaluation times post CSF TT and were defined as CSF TT responders. Only one-third of these patients were improved according to predefined criteria at all evaluation times after the CSF TT. At different evaluation times, individual improvements were seen in 44–70% of the CSF TT responders, Table 9. Mean proportional improvement in gait function with 95% CI, among the CSF TT responders, at all assessment times post CSF TT are presented in Figure 16. The CSF TT responders reduced time and number of steps significantly at all assessment times post CSF TT. There was no significant difference in level of improvement between different investigation times.

The intrarater and interrater agreement of the ordinal gait scale was acceptable, with κ=0.85 and κ=0.74, respectively. Repeatability of measurements of gait speed and number of steps at 10-meter walking test was high, with ICC=0.97. At baseline, the median variation between two repetitions of self-chosen walking speed was 7.4% for gait speed and 4.4% for number of steps. Gait speed varied >5% in 66% of the patients and variation >10% was seen in 33% of the patients. Number of steps varied >5% in 45% of the patients and >10% in 28% of the patients.

At 2 hours after CSF TT, there was a negative correlation between the sum of headache and back pain VAS score and improvements in time ($r=-0.40$, $p<0.05$) on 10 meter walking test. At 8 hours after the CSF TT, high pain correlated with a less improvement in time ($r=-0.39$, $p<0.05$) and in number of steps ($r=-0.48$, $p<0.01$).

Table 9. The proportion of CSF TT responders improved at specific assessment times after the CSF TT.

<table>
<thead>
<tr>
<th></th>
<th>Pre TT</th>
<th>2h</th>
<th>4h</th>
<th>6h</th>
<th>8h</th>
<th>24h</th>
</tr>
</thead>
<tbody>
<tr>
<td>TTr (n)</td>
<td>27</td>
<td>25</td>
<td>27</td>
<td>21</td>
<td>27</td>
<td>27</td>
</tr>
<tr>
<td>TTr, improved*</td>
<td>15 (60%)</td>
<td>12 (44%)</td>
<td>14 (67%)</td>
<td>19 (70%)</td>
<td>16 (59%)</td>
<td></td>
</tr>
<tr>
<td>TTr, improved, cumulative</td>
<td>15 (60%)</td>
<td>18 (67%)</td>
<td>23 (85%)</td>
<td>26 (96%)</td>
<td>27 (100%)</td>
<td></td>
</tr>
<tr>
<td>Mean time, s ± SD</td>
<td>22.2 ± 13.5</td>
<td>16.5 ± 8.3</td>
<td>17.5 ± 11.0</td>
<td>16.8 ± 11.1</td>
<td>16.4 ± 9.0</td>
<td>16.9 ± 8.3</td>
</tr>
<tr>
<td>Mean no. of steps ± SD</td>
<td>32.9 ± 15.9</td>
<td>26.3 ± 8.6</td>
<td>27.5 ± 12.5</td>
<td>26.5 ± 11.9</td>
<td>26.3 ± 10.0</td>
<td>27.8 ± 10.6</td>
</tr>
</tbody>
</table>

TTr, tap test responders.
Additional analyses

In the original analyses, the normality was decided by visual inspection of histograms. Additional analysis of the data with Shapiro-Wilk test revealed that half of the calculated variables of proportional improvement in gait speed and number of steps were not normally distributed. Therefore the results in Figure 16 were reanalyzed using non-parametric tests (one-sample Wilcoxon signed rank test) and presented in Figure 17a as a box-and-whisker plot. Also, patients later defined as iNPH-patients according to the American iNPH Guidelines were analyzed separately, Figure 17b. Neither of these new analyses changed the original main results. Reductions in time and number of steps were significant at all evaluation times after the CSF TT and there were no difference in level of improvement between different times.

Figure 16.
Proportional mean improvement in time and number of steps at all assessment times for the CSF TT responder group. Error Bars: 95% CI. Significant improvement: **, \( p<0.01 \); ***, \( p<0.001 \). One-sample t-test.
Figure 17.
Additional analyses. Proportional improvements in time and number of steps at the 10-meter walking test after the CSF TT. Box-and-whiskers plots, boxes representing median with 25th and 75th percentile. Whiskers represent max and min values. a. Only tap test responders ($n=27$) and b. Only patients defined as probable iNPH ($n=25$). Significant improvement: *, $p<0.05$; **, $p<0.01$; ***, $p<0.001$. One-sample Wilcoxon signed rank test.
**Paper II**

There was a significant difference in preoperative callosal angle between patients defined as shunt responders compared with non-responders at follow-up: 59° (95% CI 56°–63°) versus 68° (95% CI 61°–75°) \( (p<0.05) \). The difference was significant also if the mRS was used to separate responders from non-responders: 57° (95% CI 51°–63°) versus 64 (95% CI 60°–69°) \( (p<0.05) \). A callosal angle cutoff value of 63° showed the highest Youden’s index, Table 10. If patients with complications were excluded, the prognostic accuracy was slightly better. See Table 10 for different cutoffs for callosal angle.

<table>
<thead>
<tr>
<th>Callosal angle cut-off (degrees)</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Youden’s index</th>
</tr>
</thead>
<tbody>
<tr>
<td>54</td>
<td>40%</td>
<td>89%</td>
<td>0.29</td>
</tr>
<tr>
<td>63</td>
<td>67%</td>
<td>65%</td>
<td>0.33</td>
</tr>
<tr>
<td>71</td>
<td>81%</td>
<td>31%</td>
<td>0.11</td>
</tr>
<tr>
<td>90</td>
<td>95%</td>
<td>11%</td>
<td>0.07</td>
</tr>
</tbody>
</table>

Youden’s index = sensitivity + specificity -1

**Paper III**

The predictive values of the imaging findings are presented as gender-adjusted ORs in Figure 18. For callosal angle, DESH and temporal horns, the ORs were significant after being adjusted for gender, and in three separate multivariate logistic regression models after being adjusted for gender, age and previous stroke. If only patients without complications were included in the logistic regression, the ORs for callosal angle, DESH and temporal horns were still significant.

There were several correlations between different imaging features at the preoperative MR investigations in the range \( r=0.26–0.68 \).

Patients without PVH, focal bulgings in the roof of the lateral ventricles and dilated Sylvian fissures performed better in clinical tests at baseline compared to patients with the feature present, Table 11. The height of the Sylvian fissure correlated positively with both impaired speed and step length on walking backwards 3 meters test at baseline, \( r=0.61, p<0.001 \) and \( r=0.66, p<0.0001 \), respectively, Table 12.
There was no difference in the proportion of patients with a positive outcome or level of improvement in relation to the Fazekas score among patients with DWMH.

The interrater reliability for the continuous variables was in the range 0.80–0.96 (ICC) and for variables on an ordinal scale 0.33–0.72 (κ). The interrater reliability of dichotomous variables was 0.28–0.67 (κ).

**Figure 18.**
Forest plot with gender-adjusted odds ratios for all imaging features. OR with 95% CI of a 1 standard deviation increase for continuous variables and of a 1 unit increase for dichotomous and ordinal variables. An arrow indicates that the confidence interval extends beyond the range of the plot. Sylvian fissure ordinal, ordinal scale 0–2; Sylvian fissure height, measured in mm. Level of significance: *, p<0.05.
Table 11.
Difference in symptom severity between patients with and without PVH, focal bulgings and dilated Sylvian fissures.

<table>
<thead>
<tr>
<th>Clinical test</th>
<th>PVH</th>
<th>Imaging feature</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Not present = 0</td>
<td>present = 1</td>
<td></td>
</tr>
<tr>
<td>mRS, median (IQR)</td>
<td>2 (2–2)</td>
<td>2 (2–3)</td>
<td>0.031</td>
</tr>
<tr>
<td>TUG, steps, median (IQR)</td>
<td>22 (17.3–28.5)</td>
<td>29 (22–39.8)</td>
<td>0.016</td>
</tr>
<tr>
<td>10 m walk, steps, median (IQR)</td>
<td>23 (20.8–29.3)</td>
<td>29 (23.8–39.3)</td>
<td>0.012</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Focal bulgings</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>WB3m, steps, median (IQR)</td>
<td>16 (15.0–31.3)</td>
<td>26 (18–42.5)</td>
</tr>
</tbody>
</table>

| Sylvian fissure ordinal            |                      |                 |
|                                    |                      |                 |
| mRS, median (IQR)                  | 2 (1.75–2.0)         | 2 (2–3)         | 0.006    |
| Balance scale, median (IQR)        | 4.5 (3.0–5.0)        | 4 (3–4)         | 0.009    |
| 10 m walk, sec, median (IQR)       | 15.0 (11.75–22.0)    | 19 (14–30)      | 0.046    |
| 10 m walk, steps, median (IQR)     | 23.5 (20.75–29.5)    | 29 (23–40)      | 0.022    |
| WB3m, sec, median (IQR)            | 14.5 (8.75–23.5)     | 23 (15–35.5)    | 0.031    |

WB3m, walking backwards 3 meters; 10 m walk, walking 10 meters at self-chosen speed.
* Mann Whitney U test

Table 12.
Significant correlations at baseline between clinical symptoms and imaging features.

<table>
<thead>
<tr>
<th>Imaging feature</th>
<th>Clinical test</th>
<th>r</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Callosal angle</td>
<td>Balance scale</td>
<td>0.263</td>
<td>0.007</td>
</tr>
<tr>
<td>Evans index</td>
<td>MMSE</td>
<td>-0.273</td>
<td>0.004</td>
</tr>
<tr>
<td>Sylvian fissure height</td>
<td>WB3m, sec</td>
<td>0.61</td>
<td>0.00013</td>
</tr>
<tr>
<td>Sylvian fissure height</td>
<td>WB3m, steps</td>
<td>0.66</td>
<td>0.00016</td>
</tr>
</tbody>
</table>

r, Spearman’s correlation coefficient. Only correlations with p<0.01 included.
Paper IV

At the group level, there was no significant increase of CBF in any ROI at any investigation time after the CSF TT compared with baseline.

Patients with an increased CBF in lateral WM improved more in gait speed and stride length 30 minutes post CSF TT and in stride length 24 hours after the CSF TT compared with patients with a decrease in CBF. Patients with increased CBF in frontal WM improved more in both gait speed and stride length at 4 and 24 hours after the CSF TT, Figure 19.

![Figure 19](image)

**Figure 19.**

Differences in proportional gait improvement between patients with a positive CBF ratio versus a negative CBF ratio ((CBF post CSF TT - CBF at baseline)/CBF at baseline) at different investigation times. The whiskers in the box-and-whiskers graph represent maximum/minimum. **a.** Frontal white matter. **b.** Lateral white matter. * significant difference *p*<0.05; ** *p*<0.01.

Patients with increased CBF in the left lentiform nucleus after CSF TT had a shorter total median (IQR) symptom duration compared with patients with decreased CBF in the same ROI, 24 months (12–30) versus 42 months (24–72), *p*<0.05, respectively. There were also negative correlations between symptom duration and proportional CBF change in the left lentiform nucleus 30 minutes post CSF TT (*r*=−0.60, *p*<0.01), the left lentiform nucleus 4 hours post CSF TT (*r*=−0.59, *p*<0.01), and in the right thalamus 4 hours post CSF TT (*r*=−0.65, *p*<0.01).
Patients with increased CBF in SMA after CSF TT had higher levels of amyloid-beta (1-42) in CSF compared with patients with decreased CBF in SMA, 644 ng/L (498–883) vs. 424 ng/L (383–527), *p*<0.05, respectively.

The mean total lateral ventricular volume at baseline was 125 ml (95% CI: 116–134), and it was significantly reduced 30 minutes after the CSF TT, *p*<0.001. At 24 hours after the CSF TT, the volume was restored, Figure 20.

**Figure 20.**
The mean value of the measured volumes at MRI1 and MRI2 was taken as reference volume. This was subtracted from the volumes at all five investigation times to obtain the volume difference per subject. The error bars indicate the 95% CI of the volume difference, obtained from the complete group. CSF TT was performed after MRI 2. The boxes 30 minutes, 4 hours and 24 hours refer to time after the CSF TT. A significant difference was found between baseline (average of MRI 1 and MRI 2) and 30 minutes (*p*<0.001); Baseline and 4 hours (*p*<0.01); 30 minutes and 4 hours (*p*<0.001); and 30 minutes and 24 hours (*p*<0.01), using the Wilcoxon signed-rank test.
Additional analyses
To compare the repeatability of the walking test in Paper I, analyses of repeatability were also performed in Paper IV. Repeatability of gait speed at the 10-meter walking test in maximum pace was high with ICC=0.91 and for the TUG test, ICC=0.98. At baseline, the median variation between two repetitions of high walking speed was 9.1% for the 10-meter walking test and 8.1% for the TUG.

Corrections
In the abstract of Paper I, $n=40$ was given in the methods paragraph. Only 39 patients were included in the statistical analyses, which would have been a more correct number, also in the abstract.

In the Statistics section of Paper I, it is stated that: “Correlation analyses were performed with Pearson’s correlation coefficient for parametric data and Spearman’s correlation coefficient for non-parametric data.” However, all correlations included in the final version of the manuscript of Paper I were performed with Spearman’s.
Discussion and future perspectives

It is soon 50 years since Hakim and Adams first described NPH, but the pathophysiological mechanisms are still largely unknown. Fortunately, results of surgery have improved over the years, and now eight out of ten patients that undergo shunt surgery improve.\textsuperscript{4, 82} Epidemiological studies indicate that iNPH can be a much more common disease in the elderly population than previously believed.\textsuperscript{22} Unfortunately, a vast majority of patients with iNPH do not receive a correct diagnosis, and as a result they are never offered shunt surgery, and the possibility of improved health. To turn this around, better and easily applicable diagnostic and prognostic methods are needed, and the awareness of iNPH should be increased.

Diagnosis of patients

Papers I and IV were studies with a prospective inclusion protocol, and the diagnoses were based on the American iNPH Guidelines.\textsuperscript{43} In Paper IV, the diagnosis was made during the evaluation process, while the diagnosis was determined retrospectively in Paper I. In Papers II and III, the diagnosis was based on the decision from the multidisciplinary treatment conference. In the treatment conference, a clinical diagnosis relies on neuroimaging, clinical symptoms, lumbar measurement of CSF pressure, and CSF TT and infusion tests in most of the patients. Both a neurologist and a neurosurgeon are present in the conference. Further, retrospective analyses of the patients’ charts were done, with the aim of finding signs of secondary NPH. The distinction between iNPH and secondary NPH is not always certain except in cases with an obvious insult to the brain preceding the symptom debut, such as a subarachnoid hemorrhage. This uncertainty is similar for all studies in the field. Moreover, the demographics of the patients in Papers II and III are similar to prospective cohorts diagnosed with iNPH according to the American iNPH Guidelines.\textsuperscript{43} We therefore believe that also patients in Papers II and III could be considered as patients with probable iNPH.

Validity of the clinical tests

The quantitative gait tests (10-meter walk, the TUG test and walking backward 3 meters) are well known tests in iNPH research, and walking 10 meter at a comfortable speed is also a component of the new iNPH scale.\textsuperscript{49} The tests are proven to be reliable in healthy elderly and in patients with other neurological diseases.\textsuperscript{207, 208} We added to previous studies, showing an acceptable repeatability also in iNPH patients. Further, we tested the interrater agreement and intrarater agreement of the
ordinal gait scale and found a good reliability. This scale, together with
the continence scale and balance scale are also components of the iNPH
scale and have not previously been validated. However, in a recent pub-
lication, they seem promising since all of them correlate negatively with
mRS score and positively with MMSE score.49

Cerebrospinal fluid tap test and Paper I
The CSF TT is a preoperative test that for a period of time simulates
the conditions in the cerebrospinal system obtained after shunt surgery.
If the test is positive, the probability that the patient will improve after
shunting is very high. The disadvantage of the test is a low sensitivity,
which is influenced by a number of factors.

Paper I was to our knowledge the first attempt to systematically inves-
tigate gait improvement at several different assessment times the first 24
hours after a CSF TT. The aim was to investigate whether any particular
assessment time after CSF removal was more useful to detect improve-
ments in gait than were others. In that respect, our results were negative.
No assessment time was better than any other, but the level of improve-
ment was consistent for both CSF TT responders as well as patients with
probable iNPH during the first 24 hours after the CSF removal.

More importantly, only one-third of patients that were potential respond-
ers to the test improved at all assessment times after CSF removal. At 4
hours after the CSF TT, only 44% of the responders improved. Thus, the
risk of missing an improvement is considerable if the assessment is made
only once, and this may contribute to the low sensitivity of the CSF TT
as it is often performed today. By performing the evaluation on more
than one occasion after the CSF TT, the probability increased that the test
was defined as positive in a potential responder to the CSF TT. However,
the evaluation in Paper I was only performed with one gait test, and it
is not known whether more responders to the CSF TT would have been
identified if additional tests of motor function and tests of cognition had
been added.

The repeatability was statistically high, calculated with ICC. However,
median variation of 7.4% in gait speed, and a variation >10% in one-third
of the patients should be taken into account when deciding cutoffs for a
positive test.

There was a correlation between less improvement after the CSF
removal and pain caused by the lumbar puncture. This correlation was
significant at 2 hours and 8 hours after the lumbar puncture. Pain and dis-
comfort may have had a negative influence on the results, and if potential
responders to the test do not improve enough to reach the decided cutoff
because of high levels of pain, this could have an impact on the sensi-
tivity of the test. Therefore, effort should be made to minimize pain if possible, and patients that are affected by discomfort and pain should be evaluated at a later time.

The patients included in Paper I were under evaluation for iNPH and did not have a definite diagnosis. This can be a heterogeneous sample of patients, and therefore only the CSF TT responders were included in the analyses of gait improvement. The second reason to analyze only the responders was that the original aim was to investigate the optimal time for gait evaluation post CSF TT. It was not of interest to investigate the level of decline in patients that did not improve after CSF removal at any investigation time. However, since the CSF TT is primarily used in the evaluation of iNPH, we now repeated the analyses and included only patients with probable iNPH, and the main results were the same as for the CSF TT responders. Moreover, the analyses of gait improvement after CSF TT were reanalyzed with non-parametric statistics to make sure that the original results were not affected by non-normal distributed data. The main results were unchanged with the new analysis.

In most studies of the CSF TT, the test is only evaluated once after the CSF removal, often 3–8 hours after the lumbar puncture. However, one study from Japan evaluated the test 2 days and another 1 week after the CSF removal, and in these studies the predictive values found were similar to those in the studies with the assessment the same day as the CSF removal. In Paper I there was no difference in the level of improvement between 2–24 hours after CSF removal. We could not calculate the predictive value of the CSF TT since the cutoff value used in Paper I was also used in the clinical setting when the patients were selected for shunt surgery. In the light of our results and reports of improvements up to 1 week after the CSF removal, it is essential to understand whether this is due to a placebo or a learning effect of the tests. One study investigated learning effects in 32 NPH patients and 30 healthy controls and concluded that there was no learning effect since the controls improved after repeated testing, but the NPH patients did not. However, they did not test motor function with sensitive quantifiable test but used only ordinal scales, and for this reason small improvements could probably not be detected. At least one ongoing study is addressing the impact of placebo effects on the CSF TT. Both placebo and learning effects should be studied further. If a new investigation of the time window for improvement after the CSF TT is performed, the assessments should be extended to at least 2 weeks after the CSF removal.

The 10-meter walking test was performed at a self-chosen speed in Paper I. The reason was to minimize risks of falling and because the method was routine at our department. In Paper IV, we chose to perform the 10-meter walking test in maximum pace instead of self-chosen.
speed. We assumed that the normal variation between two repetitions would be less with fast walking. Surprisingly, the median difference was 9.1% using maximum pace but 7.4% using self-chosen speed. The difference was not statistically significant. Therefore we see no reason to perform the test at maximum pace, since the risk of falling is probably higher compared to walking at a comfortable pace.

Different cutoff values that define a positive test have been used in different studies. Often an improvement in gait speed between 5–25% \cite{29, 177, 181, 183} has been suggested, but in many studies the decision whether a test is positive or not is completely subjective. \cite{8, 185, 210} The sensitivity and specificity reported in different studies must be interpreted in the light of the cutoff value used. If the cutoff value is high, the specificity will be high but the sensitivity will be lower, and if the cutoff value is low, the sensitivity will increase but specificity will be lower when almost all patients are defined as responders to the test. Also, if this cutoff value is set too low, there is a risk that the difference seen is simply a result of normal variation. However, the impact of the variation can be limited if the quantified tests are repeated 2 to 3 times, and an average result is calculated. Repetitions are often performed in studies \cite{183} and should also be used in clinical practice.

Another reason that could explain why the number of false negative tests is so high, is that the improvement after shunt surgery have been reported to be three times as high as the improvement after a CSF TT. \cite{6} The risk is that some patients improve slightly after a CSF TT but not enough to reach the decided cutoff value that defines a positive test. However, after surgery the same patients improve three times as much and are therefore considered as shunt responders.

Some patients are not able to walk or are too uncooperative due to dementia to perform the most commonly used neuropsychiatric tests. Therefore it is important to have alternative tests. For example, motor tests of upper extremities have been reported to have good predictability, and are an alternative if the patient is unable to perform the walking tests. \cite{185, 211}

The European iNPH Multicenter Study showed that 84% of iNPH patients improved when the decision to shunt was based only on clinical and radiological evaluation. In the same study, the PPV of the CSF TT was 88%, while the NPV was only 18%. \cite{182} Therefore the question must be asked: Is there still a place for the CSF TT in the diagnosis and selection of shunt candidates in iNPH? The answer is yes. First of all, the specificity and PPV have consistently been reported to be very high for the test. Therefore, the test is useful in cases with an atypical clinical picture, atypical imaging or comorbidity since a positive test is associated with successful outcome after shunting. Secondly, an improvement after
the test can be a pedagogic demonstration for both the patients and their relatives with regard to whether or not to undergo surgery.

The main limitation of Paper I was that we did not have a control group. Therefore, eventual learning effects could not be controlled for. Also, the impact of placebo effects on the test is unknown. In the study, the patients were tested with frequent assessments during the first day after the CSF TT. Therefore, some assessments were missed because of investigations undertaken as part of the clinical evaluation of patients.

**Recommendations for the CSF TT**

The CSF TT is an easy, available, inexpensive preoperative test that can be performed at any outpatient clinic with trained personnel. The specificity is high, and the test has a place in the preoperative evaluation of patients with iNPH.

We recommend that the test be performed when there is the least doubt whether to operate on a patient or not. However, one needs to keep in mind that a negative result does not rule out that a patient’s condition could improve after implantation of a shunt. Specialized personnel with good experience in the evaluation of patients with iNPH should perform the assessments of gait and cognition before and after the test. The evaluation tests should provide continuous data to facilitate statistics, but the subjective impression of an experienced evaluator or ordinal scales should also be used since not all patients can perform the walking tests. All quantifiable tests should be repeated two or three times on every occasion to minimize the impact of normal variation. If a patient has not improved at the first assessment, a new evaluation should be performed, preferably the following day.

If a specified cutoff value for improvement in the test is used, it should be in proportion to the individual patient’s normal variation in the specified test. When the lumbar puncture is done, measurements of CSF pressure should be undertaken, and the CSF should be sent for routine biochemical analysis and for the detection of dementia biomarkers.

**Cerebral perfusion after CSF removal and Paper IV**

Measurements of perfusion in NPH have been performed during the last 40 years with a variety of methods. Several studies have tried to measure changes in CBF after a CSF TT. In some studies CBF has increased after CSF removal, while in others an increase was as likely as a decrease in patients with NPH. The reason to study changes in CBF after CSF removal have been both to find an objective predictive test but also to study the mechanisms underlying the reversibility of clinical symptoms.
To study whether there is a relationship between changes in CBF after CSF removal and improvements in clinical symptoms, the investigations of these two factors should be performed in connection with as little time delay as possible between the investigations. The investigations should also be done at several investigation times after the CSF TT, since two-thirds of the responders to the CSF TT are not improved at all investigation times during the first 24 hours after the CSF removal. To study this relationship, repeated measurements are needed, and pCASL is an ideal method since it is non-invasive, without ionizing radiation, and has a rather short scan time.

To our knowledge no published studies before Paper IV have investigated perfusion in NPH with pCASL, no studies have systematically investigated the repeatability of perfusion measurements in iNPH, and no studies have performed perfusion measurements with linked clinical evaluations at several times after the CSF removal.

However, the use of a relatively new method, not yet established in clinical practice, such as pCASL, is not without some limitations. The major issue in Paper IV was related to the ATT, the time needed for the labeled blood to move from the labeling plane to the tissue of interest in the brain. The PLD, the time delay between the labeling and the image acquisition should match the ATT. If the PLD is too long, the signal-to-noise ratio will be low, and if too short, the labeled blood will not reach the tissue of interest in time, with resultant image artifacts. We used a standard clinical protocol for pCASL, with a PLD of 1600 ms. The advantage was that it yielded a high signal-to-noise ratio, and we accomplished high repeatability for perfusion measurements in most ROIs. However, ATT has been reported to be longer in the aging brain and in pathologic cerebrovascular systems, and our experience is that the same is also true for iNPH. As a result, three patients were excluded because of a high intravascular signal with low signal intensity in the brain parenchyma. Moreover, we could not draw any ROIs in the watershed areas in parietal/occipital regions of the brain, where the intravascular signal increase is usually located. Recently, several experienced perfusion researchers have written a consensus report, with recommendations for the use of pCASL in the clinical setting. They recommend a PLD of 2000 ms in both healthy subjects >70 years of age and in adult clinical patients. The same PLD should probably be used in iNPH patients in future studies.

Improvement in iNPH patients can persist several hours or even days after a CSF TT, but the removed bolus of 30–50 ml CSF is restored already after 1–2 hours under physiologic conditions. Improvement after this time should therefore be the consequence of placebo effect, learning effect caused by repeated investigations or a temporarily improved neuronal function.
Studies using DTI reveal that WM surrounding the lateral ventricles, especially in the frontal lobes, seems to be of importance for gait function both in elderly people in general and in patients with iNPH. Fibers in these areas connect brain regions likely involved in iNPH, such as the SMA, basal ganglia, and thalamus, and in elderly people without iNPH, WM hyperintensities in the frontal lobe and periventricular WM are strongly associated with impairments in balance and gait.

It has been proposed that mechanical stretching of blood vessels by the dilated ventricles may cause reduction of perfusion in NPH, and when CSF is removed the stretching ceases and perfusion is restored. This was not confirmed in Paper IV, since there were no negative correlations between ventricular volume and CBF, or correlations between changes in ventricular volume and CBF. Other mechanisms are probably involved in the reduction of perfusion and reversibility after CSF removal in iNPH. The PVHs seen in iNPH, which are reported to decrease after shunting, are believed to represent increased water content caused by transudation of CSF through a disrupted ependyma. It is possible that this increased water content in the WM leads to a reduced elimination of toxic substances and a disturbed metabolism and regional CBF.

We hypothesize that when CSF is removed from the subarachnoid space, some of the increased water content is partly resorbed back to the ventricles due to a temporary pressure gradient. Disturbances in the WM caused by the CSF edema may become temporarily reversed and CBF increases. In half of the patients in this sample, no increase in CBF in WM followed the CSF removal, which may be the reason for less clinical improvement, possibly because of a pathologic process that had become irreversible.

The findings in Paper IV indicated that there might be an important relationship between the reversibility of iNPH symptoms and CBF in the deep WM. However, the relationship is not necessarily causal. There could be an unknown factor influencing both symptom improvement and CBF. The integrity of the WM could also be of great importance in the reversal of symptoms in iNPH, and DTI is more suitable than perfusion methods to study the function of WM. To further investigate the reversibility of symptoms in iNPH, future studies should investigate the relationship between clinical symptoms, DTI findings, CBF and relaxation times in WM before and after CSF TT and before and after shunt surgery.

**Radiology of iNPH and Papers II–III**

In contrast to the CSF TT and infusion tests, neuroradiology is a non-invasive preoperative method to evaluate patients with iNPH. Early imaging studies of NPH patients were limited by the mixed samples that included
patients with iNPH, secondary NPH and sometimes even obstructive hydrocephalus. The first studies used pneumoencephalography, which limited the morphological evaluation of the NPH brain to simple inspection of the size and shape of the ventricles. The introduction of CT scans in studies of NPH in the late 70s and 80s, facilitated more detailed studies of both ventricles, but also of the brain parenchyma, and reports were published that showed the presence of periventricular hypodensities around the frontal horns of the lateral ventricles. CT studies from this era were still limited to transverse rather thick slices of the brain, and the structural investigations were two-dimensional.

In more recent studies of structural findings in NPH, MRI with all its benefits has often been used. Patient samples have been more homogeneous after the diagnostic recommendations of the Japanese and American iNPH Guidelines. However, most studies have still been limited with regard to number of patients, and few studies have investigated more than one to three imaging findings in the same sample of patients. Therefore, Papers II and III add to our knowledge of structural changes in patients with iNPH by investigating 13 different imaging features, most of them previously described in iNPH, in a relatively large sample of patients.

The callosal angle was smaller in patients who responded to shunt surgery compared with non-responders, and the results in Paper III indicate that the callosal angle may be a useful predictor of positive shunt outcome. As reported in previous studies, wide temporal horns and the occurrence of DESH are common findings in iNPH, and there were indications that they could have prognostic usefulness.

As with other predictive tests, the absence of these three imaging findings cannot be used to exclude patients from surgery. However, if radiological protocols are to be used in future prospective studies, we recommend that these findings are included because they seem to have a stronger prognostic relation with outcome than do other imaging findings described in iNPH. We still do not know why some patients do not respond to shunt surgery. The subgroup of non-responders can be difficult to study because they are often few in number even in large studies, in which positive outcome rates exceed 80%.\textsuperscript{4,82}

One of the main issues in studies of prognostic tests is how to define a positive outcome after shunt surgery. Several different scales have been used in different studies, and for this reason results from different centers can be hard to compare. A wide range of assessment tools is necessary to evaluate the outcome in a shunted iNPH patient. Both ordinal scales and continuous scales in which time and steps are measured are necessary for motor evaluation since the walking scales are more sensitive to change, but some patients are unable to walk at baseline and therefore a qualitative grading is also needed. In many studies, cognition is evaluated with
MMSE, as was done in the present studies, which is a limitation because the scale is less sensitive to the subcortical components of the cognitive dysfunction seen in iNPH and has a ceiling effect in patients with mild symptoms.\textsuperscript{13} Neuropsychological tests are preferably used. Papers II and III were limited by the retrospective design, and therefore we could only use the tests used in clinical practice at our department. Fortunately, during these years, we had a standardized protocol with a wide range of clinical tests that incorporated all the symptoms of iNPH. Experienced physiotherapists and occupational therapists performed the tests. However, all the tests were not available in all the patients, and therefore a symptom scale was created that made it possible to determine outcome even if some tests were missing. Hopefully, a consensus can be reached regarding use of a common scale worldwide in future studies. The newly published iNPH scale seems to be a promising candidate to take on such a role.\textsuperscript{49}

Shunt dysfunction and complications may have an impact on the results in studies of prognostic tests. CT scans were performed 6 weeks postoperatively to rule out complications, and all patients were examined clinically 3 months after shunt surgery. If no improvement was noted, the shunt setting was changed. If it was uncertain whether the shunt was working properly, an infusion test was performed. If a shunt was determined as malfunctioning, the patient was reoperated on. Since Papers II and III had a retrospective design, we were not able to control completely for shunt dysfunction. Therefore, all results were also tested in patients without any reports of complications with the shunts or complications related to comorbidity. The main results were the same as those for the whole sample.

In Paper III, there was a diversity of different morphological findings. All patients had similar symptomatology, but 67\% had DESH, while 10\% had neither dilated Sylvian fissures nor narrow high convexity sulci; 25\% had no PVH at all, while 14\% had PVH extending all the way to the cortex. Previous studies in iNPH have found both heterogeneous patterns of metabolic disturbances in the cortex measured with FDG-PET and various patterns of CBF reduction measured with SPECT.\textsuperscript{157, 215} These findings raise the question: Are the morphological differences different stages of the same disease or is iNPH a syndrome that consists of several diseases with different etiologies? This should be investigated further, and it would be interesting to study whether the results of CSF dynamic tests and functional MRI methods are different in subgroups of different morphological pictures.

Wide temporal horns, dilated Sylvian fissures and focally enlarged sulci must not be mistaken for cerebral atrophy. Moreover, the term “central atrophy” should be avoided, since it indicates that the atrophy is present
more in the ventricles than in the cortical areas, which brings to mind typical iNPH morphology rather than Alzheimer’s disease. WM hyper-intensities should not be described as ischemic in patients with iNPH unless the etiology of the changes is certain. In iNPH, large confluent WM hyperintensities in the deep WM probably represents severe CSF edema rather than ischemia. There is always a risk that a neuroradiologic report of severe ischemic WM hyperintensities excludes a patient from further iNPH evaluation. Both previous reports from Tullberg et al.,27 Tissel et al.,114 as well as results from Paper III show that patients with a high level of WM hyperintensities benefit from shunt surgery.

Based on the experience from the work reported in Papers II and III, we recommend that a suspicion of iNPH should be raised in all cases of ventriculomegaly in elderly patients. The ventriculomegaly should be quantified with use of the Evans index. The disproportion between ventricle size and cortical CSF spaces and sulci should be carefully evaluated, and in research studies, the presence of DESH or not should be reported. The callosal angle and the size of the temporal horns should be evaluated and commented upon, at least visually. WM hyperintensities and CSF flow in the aqueduct should be evaluated, and careful inspection for any blockage of CSF flow is recommended.

A basic MRI protocol for iNPH patients should at least include the following sequences:

- T2-weighted sagittal sequence without flow compensation: to visualize flow in the CSF spaces.
- FLAIR sequence: to investigate WM changes.
- 3-dimensional T1-weighted sequence with multiple thin slices: for morphological investigations.
- Heavily T2-weighted 3-dimensional sagittal, high-resolution MRI sequence: to exclude obstructive causes of hydrocephalus in the aqueduct.

In the European iNPH Multicenter Study, 84% of the patients that were include in the study based only on clinical symptoms and neuroradiology improved after shunt surgery. With this in mind, it is essential that the evaluation of MRI scans in patients with iNPH be standardized so that similar patients are being operated on in different centers. In future studies, it would be of great value if more imaging findings, in addition to the Evans index, are reported to improve the possibility of comparing studies from different centers.
Conclusions

Improvement in gait function is consistent during the first 24 hours after a CSF TT in both patients with probable iNPH and tap test responders. Therefore, the CSF TT can be evaluated at any time within the first 24 hours.

Because of normal variability of gait function and the influence of pain after the lumbar puncture, the evaluation after the CSF TT should be repeated if the patient does not initially improve.

The interrater agreement of the gait scale is acceptably high.

In individual iNPH patients with increased CBF in frontal and lateral WM after a CSF TT, the gait function improves more than in patients with decreased CBF in these regions.

In an unselected sample of iNPH patients, CBF did not increase at the group level after a CSF TT compared with baseline.

The repeatability of CBF measurements with pCASL is high in patients with iNPH.

The callosal angle is smaller in patients that respond to shunt surgery than in non-responders.

Among 13 investigated imaging findings on preoperative MRI scans, a small callosal angle, wide temporal horns of the lateral ventricles and occurrence of DESH are the strongest predictors of a positive outcome after shunting.

The pattern of structural imaging findings can be very diverse in different patients with iNPH, and it may be beneficial to describe the prevalence of these findings in future studies to facilitate comparisons of results.
Sammansättning på svenska

Idiopatisk normaltryckshydrocefalus (iNPH) är ett sjukdomstillstånd utan känt orsak med vanligaste debut runt 70 års ålder. Symptomen kommer oftast slyngande och de första tecknen brukar vara en gång- och balansrubbing följd av kognitiv nedsättning och urininkontinens. Som namnet antyder är iNPH en typ av vattenskalle (hydrocefalus) med förstorade hjärnventriklar men trycket i skallen är oftast inom normala referensvärden.

Utan behandling blir symptomen med tiden allt mer uttalade och många patienter med iNPH utvecklar demens, förlorar gångförmågan och blir svårt hjälpkrävande. Sjukdomen kan behandlas genom att ett shuntsystem med tillhörande ventil opereras in. Ingreppet innebär att en tunn elastisk plastslang läggs in i en av hjärnans sidoventriklar och därifrån leds under huden nedåt och in i bukhålan. Resultaten av dessa operationer har förbättrats avsevärt de senaste årtiondena och nu blir åtta av tio patienter som genomgår ingreppet symptomlindrade.

Epidemiologiska studier tyder på att iNPH är mycket vanligare än vad man tidigare har trott. Tyvärr uppmärksammas och behandlas bara en liten andel av alla dessa patienter. Därför behövs mer medvetenhet om sjukdomen samt bättre diagnostiska och prognostiska metoder.


Syftet med detta avhandlingsarbete var att utvärdera utförandet av den kliniska bedömningen som görs före och efter ett tapptest samt huruvida hjärnans blodflöde (CBF) förbättras efter tappning av CSF. Vidare ville vi undersöka det prognostiska värdet av preoperativ MR-undersökning för att förutsöga utfallet av en shuntoperation hos patienter med iNPH.
**Arbete I**

För att undersöka vid vilken tidpunkt efter ett tapptest som förbättringen i gångförmåga är mest uttalad, inkluderades 39 patienter i en prospektiv studie. Gångtest genomfördes dagen innan samt: 2, 4, 6, 8 och 24 timmar efter tapptest.

På gruppnivå var förbättringen av gånhastighet och steglängd signifikant vid alla undersökningsstillfällen efter tapptestet. Det var ingen skillnad i grad av förbättring mellan olika undersökningsstillfällen. Det viktigaste fyndet i studien var att bland patienter som förbättrades vid minst ett tillfälle efter tapptestet så var det bara en tredjedel som förbättrades vid samtliga tillfällen. Det betyder att om tapptestet bara utvärderas vid en tidpunkt så riskerar man att missa patienter som har potential att förbättras av testet och därmed även eventuell shuntoperation.

Slutsats: Utvärderingen efter ett tapptest kan utföras när som helst under de första 24 timmarna efter tappningen men bör upprepas om patienten inte har förbättrats vid den första bedömningen.

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**Arbete II**


Callosal angle var mindre hos patienter som förbättrades efter shuntoperation, 59° (95% CI 56°–63°) jämfört med dem som inte förbättrades 68° (95% CI 61°–75°), p<0.05.

Slutsats: Callosal angle kan tillföra prognostisk information inför en eventuell shuntoperation hos patienter med iNPH.
Arbete III


Logistisk regression användes med utfall av shuntoperation som beroende variabel och de olika radiologiska måtten som oberoende variabler.

Odds ratio justerat för kön, ålder samt tidigare genomgången stroke, var signifikant för de radiologiska måtten callosal angle, diameter av sidoventriklarnas temporalhorn samt förekomst av DESH. Förkortningen DESH innebär hydrocefalus med komprimerade färnor i hjärnans övre delar medan färnor i de nedre delarna och fissura sylvii kan vara vidgade.

Slutsats: En liten callosal angle, vida temporalhorn och förekomst av DESH var de radiologiska variablerna som hade störst prognostisk betydelse för att förutsäga utfallet av en shuntoperation bland patienter med iNPH.

Arbete IV

För att undersöka om CBF ökar efter tapptest och vilken relation ändringar i CBF har med förbättringen i motorik genomfördes en prospektiv studie med 20 patienter. Pseudo-continous arterial spin labeling (pCASL) är en ny MR-metod som kan användas för att mäta CBF och den är tidigare inte använt för att studera patienter med iNPH. Två pCASL-undersökningar genomfördes före tapptest och tre undersökningar utfördes 30 minuter, 4 timmar samt 24 timmar efter tapptestet. I samband med pCASL-undersökningarna efter tapptestet bedömdes även gångförmågan.

Hos de patienter där CBF ökade efter tapptestet förbättrades gångförmågan mer än bland patienterna med sänkt CBF efter tapptestet. Skillnaden noterades för CBF-ändringar i vit substans framför och bredvid sidoventriklarna. I hela gruppen av patienter påvisades ingen signifikant ökning av CBF efter tapptestet på gruppnivå. Reproducerbarheten var hög för de två pCASL-undersökningarna före tapptestet.

Slutsats: Ökning i CBF i hjärnans vita substans efter ett tapptest kan ha betydelse för förbättring av gångförmågan efter dränage av CSF.
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