Radiological and Clinical Changes in idiopathic Normal Pressure Hydrocephalus

MRI, Vascular factors and Clinical Symptoms as Markers of Pathophysiology and Prognosis

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Gothenburg 2020

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ISBN 978-91-7833-710-1 (PRINT)
ISBN 978-91-7833-711-8 (PDF)

Printed in Gothenburg, Sweden 2020

Printed by BrandFactory

To my family.

ABSTRACT

Idiopathic normal pressure hydrocephalus (iNPH) is a treatable, neurological disorder affecting the elderly population causing gait, balance, cognitive and micturition impairments. Treatment results in a clinical improvement in up to 80% of patients. Unfortunately, the pathophysiology is still incompletely understood, the clinical picture needs to be clarified, and no reliable, predictive biomarkers exist. The overall aim of this thesis was to elucidate on the development and pathophysiology of iNPH by describing the clinical and radiological phenotype as well as the involvement of known vascular risk factors in the disease, and by investigating the specific role of the brainstem in iNPH. A further aim was to explore the predictive potential of several clinical and radiological biomarkers.

In Study I, radiological and clinical signs of iNPH were associated with vascular risk factors and white matter lesions in a large, population-based sample. Study II showed that a majority of patients have symptoms from at least three of four symptom groups at the time of diagnosis, but the severity is greatly varied. In addition, paratonia, a less well-recognized symptom is seen in most patients and should be considered a core finding of iNPH. Further, the postoperative improvement seen in the majority of patients involve all symptom groups. Study III showed that while all patients have ventriculomegaly, several other morphological MRI findings are seen only in a subgroup of patients and should not be required for the diagnosis. In addition, no morphological MRI marker had any predictive value, and, as such, they should not be used to exclude patients from shunt surgery. In Study IV, diffusion changes in the mesencephalon and pons were evident pre- and postoperatively in all patients, and responders showed a significant relative cerebral blood flow increase postoperatively, correlating to the degree of clinical improvement.

In conclusion, vascular changes are probably involved in the development of iNPH. While several clinical and radiological findings are characteristic of the disease, the severity is profoundly varied among patients and cannot be used for prediction. The brainstem seems to be involved in the core symptom generation in iNPH and further studies focusing on this area are warranted.

Keywords: idiopathic normal pressure hydrocephalus, MRI, biomarkers, prediction
ISBN 978-91-7833-710-1 (PRINT)
ISBN 978-91-7833-711-8 (PDF)

SAMMANFATTNING PÅ SVENSKA

Idiopatisk normaltryckshydrocephalus (iNPH) är en behandlingsbar, neurologisk sjukdom som drabbar äldre individer och ger upphov till gång- och balansstörningar, kognitiv svikt samt urininkontinens. Behandling leder till en varaktig förbättring hos upp till 80 % av patienterna. De patofysiologiska förändringar som orsakar iNPH är ofullständigt klarlagda, den kliniska bilden behöver kartläggas och det saknas markörer som kan förutsäga vilka patienter som förbättras efter behandling. Det övergripande målet med denna avhandling var att öka kunskapen om utvecklingen av iNPH och bakomliggande patofysiologiska mekanismer genom att detaljerat beskriva radiologiska och kliniska fynd hos patientgruppen. Vidare att undersöka förekomsen av vaskulära riskfaktorer, till exempel högt blodtryck, samt att kartlägga hjärnstammens roll i utvecklingen av iNPH med hjälp av magnetisk resonanstomografi (MRI). Målet var också att finna kliniska och/eller radiologiska markörer som kan användas för att selektera vilka patienter som skall erbjudas behandling.

Delstudie I visade signifikanta associationer mellan vaskulära riskfaktorer, vitsubstansförändringar vid avbildning av hjärnan med datortomografi och radiologiska samt kliniska tecken till iNPH i en stor, populationsbaserad grupp av individer. I Delstudie II noterades att majoriteten av patienterna uppvisade symptom från minst tre av fyra symptomgrupper vid diagnos, dock med mycket varierande svårighetsgrad. Dessutom sågs paratoni hos majoriteten av patienterna vilket bör ses som ett typiskt symptom vid iNPH. Efter behandling förbätrades majoriteten av patienterna inom alla symtomområden. I Delstudie III hittades förstorade ventriklar hos alla patienter medan övriga markörer, som tidigare har rapporterats som typiska vid iNPH, endast sågs hos en mindre del av patienterna och bör således ej krävas för diagnos. Inga MRI-markörer hade något prediktivt värde och de bör därför inte användas för att exkludera patienter från behandling. I delstudie IV sågs diffusionsförändringar i hjärnstammen både före och efter behandling. Dessutom uppvisade förbättrade patienter en blodflödesökning efter behandling vilken korrelerade till grad av klinisk förbättring.

Sammanfattningsvis tyder resultaten på att vaskulära förändringar är involverade i utvecklingen av iNPH. Flera kliniska och radiologiska fynd är karakteristiska för sjukdomen men svårighetgraden varierar påtagligt och fynden verkar inte ha något prediktivt värde. Slutligen talar resultaten för att hjärnstammen verkar vara involverad vid iNPH och fortsatta studier av detta område är av intresse.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. Jaraj, D*, Agerskov, S*, Rabiei, K, Marlow, T, Jensen, C, Guo, X, Kern, S, Wikkelsö, C, Skoog, I.
Vascular factors in suspected normal pressure hydrocephalus – a population-based study.
Neurology 2016; 86: 592-599.

II. Agerskov, S, Hellström, P, Andrén, K, Kollén, L, Wikkelsö, C, Tullberg, M.
The phenotype of idiopathic normal pressure hydrocephalus – a single center study of 429 patients.
Journal of the Neurological Sciences 2018; 391: 54-60.

III. Agerskov, S, Wallin, M, Hellström, P, Ziegelitz, D, Wikkelsö, C, Tullberg, M.
Absence of disproportionately enlarged subarachnoid space hydrocephalus, a sharp callosal angle and other morphologic MRI markers should not be used to exclude patients with idiopathic normal pressure hydrocephalus from shunt surgery.
American Journal of Neuroradiology 2019; 40: 74-79.

IV. Agerskov, S*, Arvidsson, J*, Ziegelitz, D, Lagerstrand, K, Starck, G, Björkman-Burtscher, I, Wikkelsö, C, Tullberg, M.
MRI diffusion and perfusion markers in the mesencephalon and pons as markers of disease and symptom reversibility in idiopathic normal pressure hydrocephalus.
Submitted.

** The authors contributed equally.*

CONTENT

ABBREVIATIONS

Ab	Amyloid beta
AD	Alzheimer's disease
ADC	Apparent diffusion coefficient
AED	Astheno-emotional disorder
AIF	Arterial input function
APP	Amyloid precursor protein
AQP-4	Aquaporin-4
BBB	Blood-brain barrier
b-factor	Gradient factor used in diffusion imaging
BMI	Body mass index
CAD	Coronary artery disease
CBF	Cerebral blood flow
CBV	Cerebral blood volume
CC-angle	Corpus-callosal angle
CSF	Cerebrospinal fluid
CSF-TT	CSF-tap test
CST	Corticospinal tract
CT	Computed tomography
CTTC	Concentration-to-time curve
DESH	Disproportionately enlarged subarachnoid space hydrocephalus
DM	Diabetes mellitus
DSC	Dynamic susceptibility contrast
DTI	Diffusion tensor imaging
DWI	Diffusion-weighted images/Diffusion-weighted imaging
DWMH	Deep white matter hyperintensities
EI	Evans' index
ELD	Extended lumbar drainage
EMD	Emotional-motivational blunting disorder

EPI	Echo planar imaging
FA	Fractional anisotropy
FLAIR	Fluid attenuated inversion recovery
FOV	Field of view
HVe	Hydrocephalic ventricular enlargement
iNPH	Idiopathic normal pressure hydrocephalus
MCP-1	Monocyte chemoattractant protein-1
MD	Mean diffusivity
MMSE	Mini mental state examination
MRI	Magnetic resonance imaging
mRS	Modified Rankin scale
MTT	Mean transit time
NFL	Neurofilament light protein
NMV	Net magnetic vector
NPH	Normal pressure hydrocephalus
pCASL	Pseudo-continuous arterial spin-labelling
PD	Parkinson's disease
PET	Positron emission tomography
PPN	Pedunculopontine nucleus
PVH	Periventricular hyperintensities
rCBF	Relative cerebral blood flow
rCBV	Relative cerebral blood volume
RF	Radiofrequency
ROI	Region of interest
R_{out}	Outflow resistance of cerebrospinal fluid
SAS	Subarachnoid space
sNPH	Secondary normal pressure hydrocephalus
SPECT	Single positron emission tomography
SSCD	Somnolence-sopor-coma disorder
T1	T1-weighted
T2	T2-weighted

TE	Time of echo
TIA	Transient ischemic attack
TR	Time of repetition
TUG	Timed up and go test
WML	White matter lesion

1 INTRODUCTION

Idiopathic normal pressure hydrocephalus (iNPH) is a treatable, neurological disorder affecting the elderly population. Treatment results in a clinical improvement in up to 80% of patients. Unfortunately, the pathophysiology of iNPH is still incompletely understood, and no reliable, predictive biomarkers exist.

In 1957, the Colombian neurosurgeon Solomon Hakim published a case report where a 16-year old boy was found to develop enlarged ventricles in combination with the inability to speak and a progressing gait disturbance, secondary to severe head trauma.[1,2] Surprisingly, the intrathecal pressure was normal, and the patients' clinical symptoms improved greatly after draining 15ml of cerebrospinal fluid (CSF) via lumbar puncture. A ventriculoatrial shunt was inserted, and the patient was further improved and able to return to school. Soon, Hakim found other, similar cases in older individuals, and labelled the syndrome normal pressure hydrocephalus (NPH) in 1965.[1,2] Subsequently the disorder has been subdivided into secondary NPH (sNPH) where the ventriculomegaly is caused by e.g. an earlier trauma, infection or subarachnoid bleed, and iNPH where no antecedent cause can be found.[3] As of today, iNPH constitutes about 50% of all NPH cases.

iNPH primarily affects the elderly population,[4] and treatment by installation of a shunt system to drain excess CSF from the ventricles results in a significant clinical improvement in up to 80% of patients.[3,5-18] Studies have shown the estimated prevalence of iNPH to be in the range of 0.1 to 3.7%, increasing with age up to 5.9% in individuals over 80 years of age.[4,19-21] The yearly incidence has been estimated to 5.5/100000/year, however, the annual incidence of shunt surgery in the same age group is much lower, 1-3.4/100000/year, thus only about 1/3 to 1/5 of patients with possible iNPH get the correct treatment making the disease both underdiagnosed and undertreated.[5,22-26] In addition, the pathophysiology of iNPH is incompletely understood, despite a large research effort, aggravating the diagnostic process as well as selection of patients for shunt surgery. Thus, further studies are warranted. The general aim of this thesis was to characterize clinical and radiological changes in iNPH and how

these can aid in increasing the clinical and pathophysiological understanding of the disease as well as in selecting patients that will benefit from treatment.

2 PHYSIOLOGY OF CEREBROSPINAL FLUID CIRCULATION AND ANATOMY OF THE VENTRICLES

2.1 THE TRADITIONAL MODEL OF CSF CIRCULATION

Cerebrospinal fluid surrounds the central nervous system and has several important physiological functions, such as protective cushioning, regulation of intracranial pressure and transport of metabolites and waste products.[27] The total CSF-volume is around 200 ml in adults while around 500 ml is produced daily, resulting in a high turnover rate. The basic anatomy of the ventricular system is shown in Figure 1.

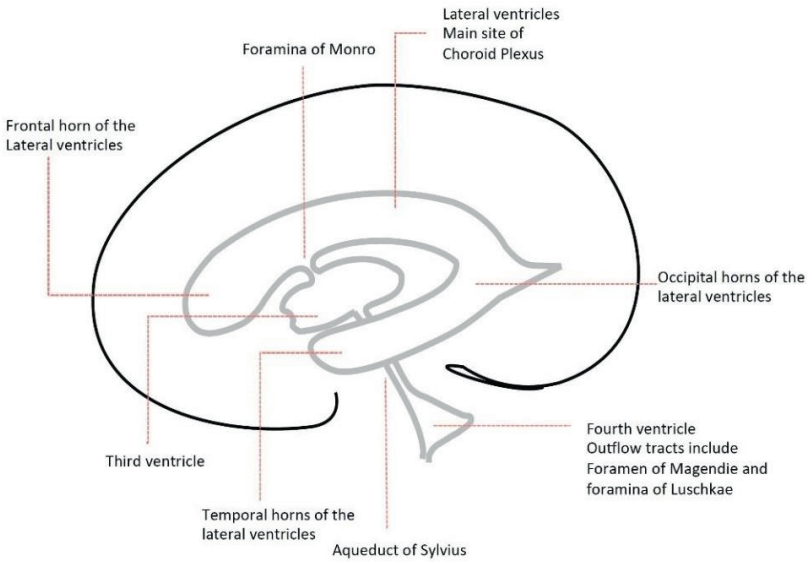

Figure 1. Schematic illustration of the cerebral ventricles and outflow tracts. Aqueduct of Sylvius = cerebral aqueduct.
Reprinted with permission from Dr Daniel Jaraj.

Traditionally, CSF-flow is described as pulsatile and driven by the cardiac cycle.[28,29] CSF is produced in the choroid plexus, located mainly in the lateral ventricles but also, to a lesser extent in the 3rd and 4th ventricles. Due to the pulsatile flow, a caudal net flow occurs from the lateral ventricles to the third ventricle, via the foramina of Monroe and then via the cerebral aqueduct down to the fourth ventricle. From the fourth ventricle, CSF enters the subarachnoid space (SAS) of the cisterna magna via the foramina of Magendie and Luschkae. It then moves down along the spinal SAS as well as up in the intracranial SAS where resorption of CSF to the venous circulation is mediated by the arachnoid villi.

However, the traditional model outlined above has been questioned and proven to be over-simplified. The brain parenchyma, interstitial spaces and capillaries (including perivascular spaces) have been shown to be of great importance in the production of CSF, potentially more so than the choroid plexus.[27,30,31] In addition, studies on upright individuals have shown that up to two thirds of the resorption of CSF occurs in the spinal SAS with perineural spaces along cranial and spinal nerves aiding in the resorption via the lymphatic system.[32-34]

2.2 THE GLYMPHATIC SYSTEM

In recent years, another system facilitating the resorption of CSF and metabolite clearance in the brain has gained a lot of attention. This glymphatic (glia-lymphatic) system is presumed to consist of a complex glial network that mediates the clearance of waste metabolites from the extracellular space, primarily during sleep.[35,36] In animal studies, CSF flows back and forth into the extracellular space of the brain via a para-arterial influx from the SAS through the perivascular spaces of large leptomeningeal arteries, and then, a subsequent transfer into the extracellular space of the brain parenchyma occurs via the perivascular spaces of the penetrating arterioles (so called Virchow-Robin spaces). This transfer is thought to be mediated by Aquaporin-4 water channels (AQP4) which are densely expressed along astrocytic endfeet.[37-40] After transferring to the extracellular space, CSF mixes with the extracellular fluid of the brain, and a net flow towards venous perivascular and perineural spaces occurs with a proposed drainage along perineural sheaths, meningeal lymphatic vessels, and arachnoid granulations (Figure 2).[35,36] Although the exact transfer process is still unknown and to date mainly studied in animals

or experimental settings,[35] alterations in AQP-4 expression has been shown in several neurological disorders, strengthening the hypothesis of a glymphatic system with a similar mechanism of action in humans.[35,41]

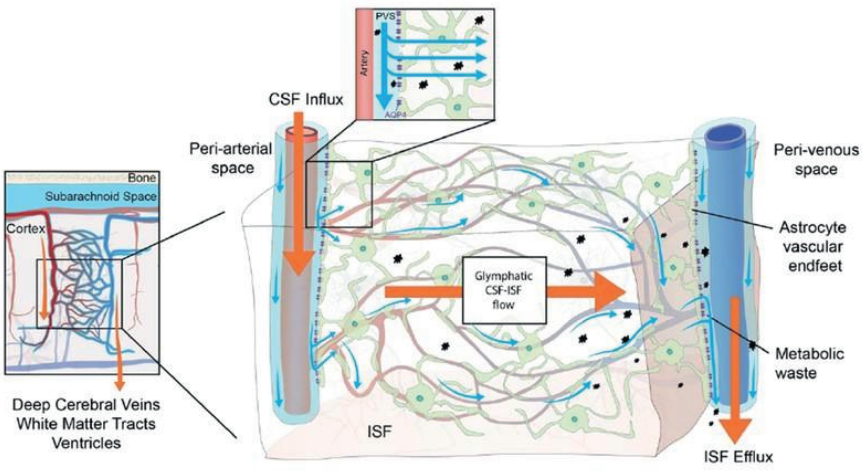

Figure 2. A theoretical model of the glymphatic system.
CSF = cerebrospinal fluid, ISF = interstitial fluid.
Reprinted from Lancet Neurology, 17(11), M. Kaag Rasmussen, H. Mestre and M. Nedergaard, The glymphatic pathway in neurological disorders, 1016-1024., Copyright (2018), with permission from Elsevier.

3 CLINICAL SYMPTOMS IN iNPH

Since the original description of iNPH, many studies have greatly increased the knowledge of the symptoms seen in the different cardinal domains in the disease. However, most studies have been performed using small samples, and the overall symptom distribution and severity in larger patient groups is much less studied.

3.1 GAIT

The gait disturbance in iNPH presents as hypokinetic gait with a general shortening of the stride length and reduction in inter-step variation combined with an increased distance between the feet, outwardly rotated feet, and a tendency to strike the floor at a flat angle when walking.[10,42-46] In addition, patients usually have difficulties lifting their feet off the floor when walking, so called magnetic or shuffling gait. Freezing of gait, similar to the phenomenon seen in Parkinson's disease (PD), is seen in some cases.[43] Electrophysiological studies have also shown a discontinuous phasing of antagonistic muscles and an almost continuous activation of antigravity muscles in the lower extremities.[47]

3.2 BALANCE

The balance and postural disturbance is characterized by retropulsion, i.e. patients exhibit a tendency towards a backward-leaning posture and falling backwards.[48,49] Increased postural sway is commonly seen, postulated to arise secondary to the reduced inter-step variation, diminishing the ability to compensate for body sway while standing up and walking.[48,50] Patients also tend to lose balance whilst turning. The impaired postural control has also been attributed, at least in part, to defects in vertical visual perception.[51,52] Interestingly, symptoms are usually much less pronounced when patients are sitting or lying down.[53]

The gait and balance difficulties are commonly seen in conjunction and differentiating between them can be difficult.[48] However, symptoms from both groups affect the total ambulatory performance, and as a result, a majority of

iNPH patients need to use walking aids and have an increased risk of falling.[10,54]

3.3 COGNITION

The cognitive dysfunction is characterized by a frontal subcortical pattern with slowing of thought, inattentiveness, apathy, and recall as well as encoding problems.[55,56] With time, as the disease progresses, a more profound memory impairment is also seen in some patients, but usually not to the same extent as in Alzheimer's disease (AD).[56,57]

Using the organic psychiatry classification introduced by Lindqvist and Malmgren,[58] iNPH-patients are found to suffer mainly from somnolence-sopor-coma disorder (SSCD), characterized by impaired wakefulness and a general slowing of cognitive, emotional and motor processes, and emotional-motivational blunting disorder (EMD), characterized by apathy, indifference and lack of drive.[58] The impaired wakefulness seen as part of the SSCD commonly manifests as an increased need of sleep, and daytime naps are common. In some cases, astheno-emotional disorder (AED), characterized by emotional lability, fatigue, irritability and concentration difficulties is seen in the early stages of the disease, although, this is more commonly seen in sNPH. SSCD is the most likely syndrome to improve postoperatively and has been proposed as the most characteristic organic psychiatric syndrome in iNPH.[58,59]

3.4 URINARY CONTINENCE

Urinary symptoms in iNPH present as neurogenic bladder disturbances.[60-63] Initial symptoms are mainly urinary urgency and frequent voiding, secondary to a loss of the normal inhibitory effect of bladder contraction, causing an overactive bladder. As the disease progresses, symptoms develop to also include urinary incontinence, and in advanced cases, fecal incontinence. Interestingly, urinary symptoms are the least recognized symptom group in iNPH, potentially due to the difficulty in observing the symptoms in conjunction with the coexisting cognitive dysfunction.[3]

3.5 OTHER CLINICAL SIGNS

In addition to the cardinal symptom groups outlined above, paratonia, that is, a general tonus increase, evident when attempting passive limb movement in any direction, combined with an inability to relax the muscle tonus during assessment, is sometimes seen in iNPH.[42,43,64] The findings are usually most pronounced in the lower extremities and increase with the velocity of the attempted limb movement. As opposed to spasticity, clasp-knife phenomenon (passive movement is initially met with high resistance, but continued movement results in a sudden decrease of resistance) is rare, and repeated movement does not decrease the resistance. Disinhibition of primitive reflexes is also common.[42]

3.6 GRADING CLINICAL SYMPTOM SEVERITY IN iNPH

A number of scoring systems exists to grade the severity of clinical symptoms in iNPH. Unfortunately, the included tests and scoring systems differ which makes comparisons between them difficult.[65-68] The modified Rankin scale (mRS), initially developed for scoring general morbidity in stroke victims, has been used in a number of studies of iNPH to give a general disability assessment.[5,18,69,70] It is, however, important to note that this scale does not factor in the presence or severity of symptoms specific for iNPH.

In 2012, Hellström et al. published a normalized outcome scale for grading symptom severity in iNPH.[66] The scale incorporates symptoms from all four cardinal symptom domains (gait, balance, cognition, and continence) by evaluation of each domain with specific tests, observations or by self-report. A brief description of the included tests and grading scales in each domain is presented in Table 1, for a detailed description, please see the publication by Hellström et al.[66] Each test score is converted to a continuous score of 0-100 where a score of 100 equals the performance of healthy, individuals in the age of 70-74 years. The scores from each domain are combined and averaged to form a composite iNPH scale score. In calculating the composite score, the gait domain is weighted twice compared to the other domains.

3.7 PREDICTIVE VALUE OF CLINICAL SYMPTOMS AND SIGNS

No definite support of any single or combination of clinical symptoms and signs as predictors of postoperative improvement exist to date. Black et al. found that patients who displayed all cardinal symptoms experienced a greater rate of postoperative improvement.[71] These findings have, however, not been reproducible.[11]

Table 1. Domain scoring in the iNPH scale score by Hellström et al.[66] included tests and/or grading scales in each domain.

Domain	Included tests/grading scales	Description
Gait	Ordinal rating (1-8)	1 = Normal gait, 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
	10 m walking test	Free pace, number of steps taken to complete recorded
	10 m walking test	Free pace, number of seconds taken to complete recorded
Balance	Ordinal rating (1-7)	1 = Able to stand independently >30 s on either lower extremity alone, 2 = Able to stand independently <30 s on either lower extremity alone, 3 = Able to stand independently with the feet together at the heels >30 s, 4 = Able to stand independently with the feet together at the heels <30 s, 5 = Able to stand independently with the feet apart (1 foot length) >30 s, 6 = Able to stand with the feet apart <30s, 7 = Unable to stand without assistance. All balance testing is performed with eyes open.
Neuropsychology	Grooved pegboard test	Fastest trial, recorded in seconds
	RAVLT	Total sum of nouns recalled over 5 trials
	Swedish Stroop test, color naming	Time taken to complete, recorded in seconds
	Swedish Stroop test, interference	Time taken to complete, recorded in seconds
Continence	Ordinal rating (1-6)	1 = Normal, 2 = Urgency without incontinence, 3 = Infrequent incontinence without napkin, 4 = Frequent incontinence with napkin, 5 = Bladder incontinence, 6 = Bladder and bowel incontinence

RAVLT = Rey auditory verbal learning test.

4 DIAGNOSIS AND TREATMENT

4.1 DIAGNOSING iNPH

To correctly make the diagnosis of iNPH the clinical history of the patient needs to be carefully evaluated for characteristic symptoms. Additionally, the symptoms should have an insidious onset, and no antecedent cause that could explain the symptomatology should be present. If such a factor, e.g. previous meningitis, intra-cerebral hemorrhage or head trauma exists, the disease should be classified as sNPH.[3] In addition to the detailed patient history, a thorough physical examination is required. The examination should focus on testing gait and balance, and in addition, cognitive testing needs to be performed, preferably by a neuropsychologist.[55] It is also important to determine the presence of incontinence, and if present, to what degree. To complement the clinical examination, a lumbar puncture needs to be performed to rule out an increase in intrathecal pressure (only applicable to the American-European guidelines[3]). At the same time, CSF should be collected, primarily for differential diagnostic purposes.[72,73] Finally, a magnetic resonance imaging (MRI) scan of the brain should be performed to document imaging changes supportive of iNPH.

4.1.1 DIAGNOSTIC GUIDELINES

Two sets of diagnostic criteria for iNPH exist, the American-European guidelines and the Japanese guidelines.[3,74] For this thesis, the American-European guidelines are used and a description is presented in Table 2. The Japanese guidelines differ from the American-European guidelines in several areas. Notably, the lower age limit for inclusion is higher in the Japanese guidelines and gait is considered less important as a clinical symptom.[74] The Japanese guidelines also places a heavier emphasis on the finding of disproportionately enlarged subarachnoid space hydrocephalus (DESH, see Section 6.3), which is required as one of three investigational findings in order to fulfil the criteria for probable iNPH.

4.1.2 CEREBROSPINAL FLUID

Cerebrospinal fluid (CSF) biomarkers play an important part in differentiating iNPH from other neurological diseases that can have similar clinical characteristics.[72,73,75,76] As opposed to AD, where an isolated reduction of amyloid beta (Ab)-42 is commonly seen,[77] iNPH patients have a general reduction in all amyloid precursor protein (APP)-derived proteins including Ab-38, 40 and 42.[78] At the same time, tau protein levels (indicating cortical neuronal damage) are normal or slightly reduced, while neurofilament light protein (NFL, a marker of axonal damage) and possibly monocyte chemoattractant protein-1 (MCP-1, a marker of astroglial activation) are slightly elevated.[72,73,79-81] A combination of low Ab-40, low total tau, and MCP-1 has been found to separate iNPH from other cognitive and movement disorders with high sensitivity and specificity.[73]

While CSF-biomarkers may play a vital role in diagnosing iNPH as well as differentiating it from other diseases, there are no biomarkers that can be used to predict postoperative improvement to date.[72,73]

4.1.3 SUPPLEMENTARY TESTS

In cases where the diagnosis of iNPH is uncertain, several supplementary tests can be used to aid the decision making. Of the supplementary tests that can aid in diagnosing iNPH, the CSF tap test (CSF-TT) and extended lumbar drainage (ELD) have both been investigated as predictors of favorable outcome after shunt surgery.[82-85] Both the CSF TT and ELD have a high specificity (75-92% and 80-100% respectively), whereas the sensitivity is rather low for both tests (26-61% for the CSF TT and 50-100% for ELD).[86,87] As such, a positive response in either test can be used to include patients for shunt surgery, but negative test results cannot be used as an exclusion criterion.

4.1.4 IMAGING

Radiological changes seen in iNPH are described in Chapter 6. To aid in the standardized evaluation of computed tomography (CT) and MRI scans in patients with suspected iNPH, a radiological evaluation scale (the iNPH Radscale) was recently published by Kockum et al.[88] The scale provides a standardized measurement encompassing seven imaging findings commonly

seen in iNPH and summarizes them in a composite score. Agreement estimates between modalities as well as between raters are fair to excellent and the iNPH Radscale is promising as an additional tool in the diagnostic workup for suspected iNPH.[89]

Table 2. The American-European iNPH-guidelines,[3] required findings for the diagnosis of probable or possible iNPH.

	Probable iNPH
History	Progressive symptoms with onset after 40 years of age. Minimum duration of 3 months. No evidence of sNPH. No other conditions that sufficiently explain the symptoms.
Symptoms	Gait/balance disturbance + cognitive disturbance and/or disturbed continence must be present.
Gait	At least 2 of the following must be present: a. Decreased step height, b. Decreased step length. c. Decreased cadence, d. Increased trunk sway during walking, e. Widened standing base, f. Toes turned outward when walking, g. Retropulsion, h. ≥3 steps required to turn 180°, i. impaired walking balance, evident as ≥2 corrections out of 8 steps on tandem gait testing.
Cognition	The cognitive disturbance should be documented by a screening instrument (e.g. the MMSE), or by evidence by ≥2 of the following: a. Psychomotor slowing, b. Decreased fine motor speed, c. Decreased fine motor accuracy, d. Difficulty dividing or maintaining attention, e. Impaired recall, f. Executive dysfunction (such as impairment in multistep procedures, working memory, formulations of abstractions/similarities or insight).
Urinary continence	Present episodic or persistent urinary and/or fecal incontinence not attributable to urological disorders or ≥2 of the following: a. Urinary urgency, b. Frequent voiding (≥6 episodes during a 12-hour period) or c. Nocturia.
Imaging	Ventricular enlargement not entirely attributable to atrophy or congenital enlargement with an Evans' Index >0.3. No obstruction of CSF flow. At least one of the following supportive features: 1. Enlargement of the temporal horns, 2. A corpus callosal angle ≥40°, 3. Present WMLs 4. A present flow void sign.
Physiology	CSF opening pressure between 5-18 mm Hg (70-245 cm H_2O).
	Possible iNPH
History	No other conditions that sufficiently explain the symptoms. Otherwise no formal requirements.
Symptoms	Symptoms from at least one group as outlined above must be present.
Imaging	Ventricular enlargement must be present but atrophy and/or focal lesions are allowed.

iNPH = idiopathic normal pressure hydrocephalus, MMSE = mini mental state examination, CSF = cerebrospinal fluid, WMLs = white matter lesions.

4.2 TREATMENT AND OUTCOME

The treatment of choice for iNPH is the insertion of a shunt system to drain excess CSF from the ventricles to the peritoneal cavity or the right atrium.[3,90] The proximal catheter can be inserted either in the frontal or occipital horn of the lateral ventricle, most commonly on the right side (ventriculoperitoneal/ventriculoatrial shunt), or placed in the lumbar CSF-space (lumboperitoneal shunt).[6,90] Shunt complications are reported in 13-26% of cases and consist primarily of subdural hematomas, shunt catheter obstructions, and infection.[8,70] Most complications tend to occur within the first year after surgery, and reoperations due to complications do not affect the overall clinical outcome.[70] Using modern operating techniques and shunt systems, up to 80% of patients improve significantly after shunting, and the improvement rates have steadily increased in later years, although improvement rates vary depending on the outcome measures used.[5-8,10,12,15,91-94] Shunt surgery for iNPH has been shown to be cost effective.[95]

In the European multicenter study on iNPH, a total of 142 patients from 13 centers in nine countries were included.[10] All patients were treated with ventriculoperitoneal shunts, and outcome was measured using the mRS and the iNPH-scale developed by Hellström et al.[65,66] At the postoperative examinations one year after surgery, 69% improved at least one step on the mRS, and about 30% improved 2 or 3 steps. Eighty-four percent were classified as improved using the iNPH-scale. In addition, the number of patients able to live independently increased by 29% (from 53 to 82%).

Two large Japanese studies, SINPHONI and SINPHONI 2 have found similar results. In the SINPHONI study, 100 patients from 26 centers in Japan were included and treated with ventriculoperitoneal shunts.[18,96] Outcome was measured using the mRS as well as the Japanese iNPH grading scale,[67] the timed up and go test (TUG),[54] and the mini mental state examination (MMSE).[97] Postoperatively, 69% of patients improved at least one level on the mRS, and significant improvements were also seen in all other outcome measurements, including gait improvement in 77%. The number of patients with no functional impairment (mRS $\leq$1) increased by 37% (from 7 to 44%).

The SINPHONI 2-study included 93 patients from 20 centers in Japan and randomly assigned the included patients to either receive treatment by installation of a lumboperitoneal shunt or conservative management over a three-month period in a 1:1 fashion.[98] Outcome was measured using the mRS, the Japanese iNPH scale as well as the TUG and MMSE. At the follow up examination, 65% in the treatment group improved at least one step on the mRS compared to 5% in the control group.

Regarding long-term outcome, a systematic review conducted in 2013 by Toma et al. concluded that 73% of patients benefit from surgery after 3 years or more, with improvement rates increasing in later years.[8] Andrén et al. found that around 40% of iNPH patients who underwent shunt surgery improved at least 1 point on the mRS-scale, and 60% reported an improvement in general health up to 6 years after surgery.[70] In addition, the same authors found iNPH patients who improved postoperatively to have a similar rate of survival as the general population.[99]

The studies mentioned above as well as several earlier conducted studies,[8] show that shunting is of great benefit to the majority of iNPH patients and probably reduces mortality. However, at least 20% of patients undergoing surgery do not improve. This subgroup is subjected to unnecessary surgery with no benefit to the individual, and the procedure also incurs an unnecessary cost to the society. The degree of improvement also varies within the group of improved patients. Further, patients are elderly and often suffer from other chronic disorders and it is important to carefully weigh potential benefits against risks of surgery. Thus, in addition to accurately diagnosing iNPH, it is of great importance to find biomarkers for prediction of outcome after shunt surgery.

5 NEUROIMAGING IN iNPH

5.1 A BRIEF INTRODUCTION TO NEUROIMAGING

5.1.1 COMPUTED TOMOGRAPHY

In many medical areas today CT imaging is a workhorse due to its fast application, relatively low cost and the good diagnostic information that it provides. In neuroimaging, CT remains very valuable in the emergency setting where the fast examination times and good availability outweigh the improved image contrast provided by MRI. Fundamentally, CT examinations generate image contrast just like traditional x-rays, where a combination of an x-ray generator and detector is used to generate images by using ionizing radiation.[100] By fast rotation of the generator and detector (mounted inside the CT gantry) around the patient while moving the examination table through the gantry, fast scanning of large volumes of interest are possible. Due to each voxel in a volume being scanned from multiple angles, the three-dimensional positioning of each voxel can be determined. In addition, the high spatial resolution and the possibility to acquire isotropic data with voxel sizes <0.5 mm in most modern scanners allow for reconstruction of scans in any desired plane to further enhance the diagnostic capability.

5.1.2 MAGNETIC RESONANCE IMAGING

The concept of MRI was first introduced in 1946, and initially used in biochemical studies.[101] In 1973, Lauterbur introduced MRI in the medical field by publishing an image of a heterogenous object and since the 1980s, MRI has seen widespread use in the medical field.[102]

In its simplest form, MRI contrast in human subjects is achieved by manipulation of the spin of hydrogen nuclei (protons). In a normal environment, each hydrogen nucleus has a net charge and spins around its own axis. Thus, it has a magnetic movement and generates a small surrounding magnetic field.[100] When no external magnetic field is applied, the direction of each proton's magnetic movement is random. By applying a strong, static, external magnetic field (B_0), the magnetic movements are forced to align with

the external field, either parallel or anti-parallel to it.[103] The alignment of protons along B_0 generates a net magnetic vector (NMV) that has a longitudinal and a transverse component. In the initial setting, full longitudinal magnetisation occurs (i.e. the transverse component equals 0, Figure 3a). The proportion of parallel to anti-parallel protons is determined by several factors, e.g. the strength of the external magnetic field and the thermal energy level of the protons and affects the strength of the NMV. In addition to generating an NMV, a secondary spin around B_0 occurs when the spinning protons are placed in the field. This precession spin occurs with a specific frequency for each type of MR active atom, and is determined by the Larmor equation.[104] By exposing hydrogen protons aligned along B_0 to an external radiofrequency (RF) pulse of the same precessional frequency (i.e. 63.86 MHz at 1.5 T), the NMV will move out of alignment with the B_0 and flip over to the transverse plane. In its simplest form, the RF pulse has a strength and duration that causes full transverse magnetisation (Figure 3b), but this varies depending on the type of sequence used.

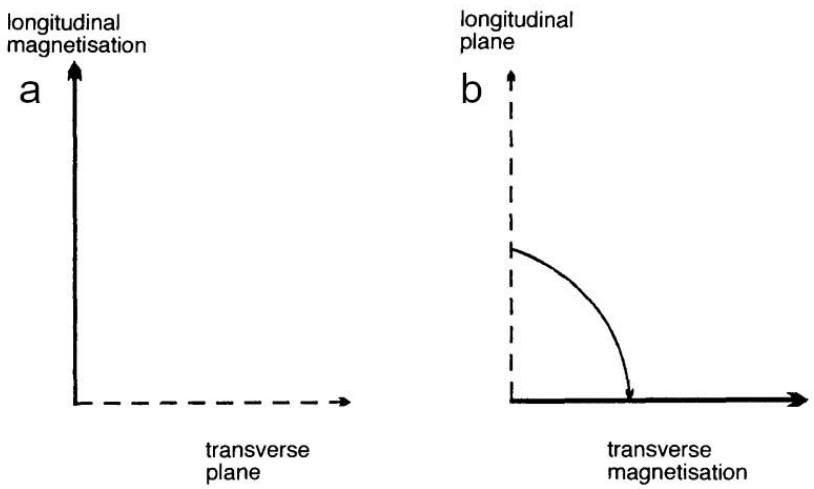

Figure 3. Longitudinal and transverse magnetisation before (a) and after (b) application of a radiofrequency (RF) pulse.

The protons will continue to precess at their Larmor frequency in the transverse plane, and in addition, all movements will be in phase. The moving NMV in

the transverse plane can be used to generate voltage in an induction coil, constituting the base of signal generation in MRI. With time, due to the influence of the B_0 field, the hydrogen protons will start to lose the energy gained from the initial RF pulse and realign with the B_0, returning towards full longitudinal magnetisation (T1-relaxation).[103] In addition, the transverse magnetisation is gradually reduced due to interactions between the magnetic fields of adjacent hydrogen nuclei and dephasing effects (T2-relaxation). The time taken for these processes to occur differ between tissues and are integral in the contrast generation of MR images. Each tissue has its unique T1, and T2 time. Both are time constants and are determined as the time it takes for 63% of the longitudinal relaxation to recover and 63% of the transverse magnetisation to be lost. By changing the repetition time (TR, the time between the RF pulses) as well as the echo time (TE, time between the RF pulse and the signal readout in the coil) different image weightings can be achieved.[100] Also, the addition of extra RF pulses can be used to nullify the signal from specific substances, e.g. water (so called Fluid Attenuated Inversion Recovery, FLAIR), and contrast agents can be used to further enhance imaging.[103]

It is important to note that while the technique outlined above constitutes the absolute basics of generating contrast in MRI, the field of image generation, encoding, and its possibilities is very complex and well beyond the scope of this thesis.

5.1.3 WHITE MATTER DISEASE ON CT AND MRI

In the elderly population, white matter lesions (WMLs) are seen in up to 90%, increasing with age.[105-108] While a vast spectrum of diseases, including autoimmune disorders and infections can cause WMLs detectable on CT and MRI, one of the most common causes in the elderly population is small vessel disease related to arteriolosclerosis.[109] The exact pathophysiology remains incompletely understood, but WMLs are associated with several vascular risk factors such as hypertension, diabetes mellitus (DM), high blood cholesterol and smoking,[107,108,110] and have been proposed to arise due to chronic hypoperfusion and incomplete ischemia of the affected areas with secondary myelin degeneration.[111,112] This is supported by neuropathological findings of hyaline fibrosis of smaller vessels, but also a general loss of axons, and mild gliosis.[113] On the other hand, dysfunction in the blood-brain barrier (BBB) with

secondary, local inflammation have been reported as possible driving forces of WMLs, especially in the periventricular white matter.[111,114,115] WMLs have been linked to impairments in cognitive function, gait, and urinary incontinence as well as risk of having a stroke.[116] Several grading systems exist to aid in detection and classification of WMLs, however, the differences between them makes comparisons between studies somewhat difficult. WMLs are detectable on both CT and MRI, but MRI has been proven to have a higher sensitivity.[117-119]

On MRI, WMLs appear as hyperintense, focal or confluent lesions in the periventricular and deep white matter on T2- and FLAIR weighted sequences (Figure 4a). The lesions appear hypointense on T1-weighted sequences and are seen as hypoattenuating areas on CT (Figure 4b).[111] The distribution is usually symmetrical and WMLs are more common in supratentorial areas.

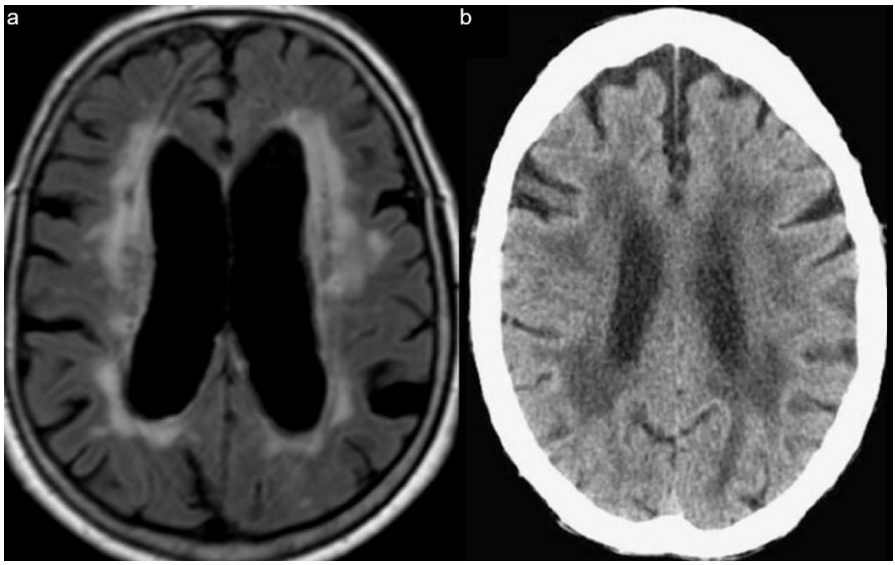

Figure 4. An example of white matter lesions (WMLs) on FLAIR-MRI (a) and CT (b).

5.1.4 MEASURING WATER DIFFUSION

The measurement of water molecule movements within tissues is a very valuable tool for diagnostic and prognostic purposes in many medical areas.[120] In the general sense, the term diffusion is used to describe the Brownian motion of water molecules driven by thermal energy. In a completely homogenous medium, diffusion is isotropic, i.e. uniform in all directions, while inhomogeneous media result in anisotropic diffusion, i.e. directional restrictions on the diffusion probabilities based on the content of the medium.

In the clinical setting, data acquisition is usually performed using fast scan techniques that limit motion artefacts, such as echo planar imaging (EPI).[120] Diffusion measurements are obtained by initial collection of an image without diffusion attenuation. Thereafter, the amount of diffusion in various directions is assessed. At least three directions have to be investigated, which is done by combining an RF pulse with paired magnetic field gradients.[121] These diffusion gradients act to de- and rephase the protons spinning in the transverse plane and can be tailored with a specific amplitude, duration and time separation resulting in a so-called gradient factor (b-factor).[120] The higher the b-factor, the higher the diffusion-related signal attenuation. Moving water molecules are not completely rephased by the second gradient and their signal is therefore reduced with higher movement resulting in a more pronounced signal reduction. In contrast, protons in areas where free water movement cannot occur will fully rephase after application of the second gradient and result in an increased signal, indicating a diffusion restriction.

Series of diffusion-weighted images (DWI) with different b-factors, in at least 3 directions are used to calculate the apparent diffusion coefficient (ADC, mm^2/s), an absolute value of mean diffusion for a specific voxel or region of interest (ROI).

The signal intensity (S) on DWI and ADC are related:

$$S(b) = S_0 \exp(-bADC)$$

And

$$ADC = -\ln(\frac{S(b)}{S_0})/b$$

S(b) =Average signal intensity at a given b-value, S_0= Signal intensity with no magnetic field gradients applied, b = the chosen b-factor, ADC = apparent diffusion coefficient.

As such, a decrease in water diffusion causes an increased S at high b-values which results in a lower ADC-value.

While standard DWI only measures the magnitude of water movement regardless of its preferred direction, measurements can be added to also measure the preferential directionality of movement.[122] This so-called diffusion tensor imaging (DTI) requires at least 6 DWI measurements in different encoding directions and can be used to calculate the mean diffusivity (MD) and the fractional anisotropy (FA).[120] Mean diffusivity is similar to the ADC in that it measures the magnitude of water movement (mm^2/s) while the FA represents the anisotropy of the diffusion process and ranges between 0 (completely isotropic diffusion) and 1 (completely anisotropic diffusion).

As DWI is based on T2-weighted images, T2 signal characteristics will influence the DWI independent of the tissue diffusability.[120] This is most commonly seen as "T2-shine through" where a prolonged T2-relaxation results in a high signal in the DWI even if no actual diffusion restriction is present.[123-126] DWI is also prone to artefacts, most notably Eddy current artefacts, susceptibility artefacts, and motion artefacts have to be taken into account and/or corrected for.[120]

5.1.5 MEASURING PERFUSION

The study of brain perfusion is of great interest in many neurological disorders, and can aid in the diagnosis, lesion characterization, and evaluation of treatment results. While several MRI-based perfusion techniques exist today, the focus in this thesis will be on dynamic susceptibility contrast (DSC) MRI-perfusion.

To quantify perfusion, several theoretical models exist, but for the purpose of this thesis, the central volume principle is used.[127-130] This model is based on the assumption that regional vascular structures constitute separate volumes through which the full volume of an indicator (contrast bolus) will eventually pass. Theoretically, the injection time of the indicator bolus is infinitely short, and the total amount of indicator arrives at the tissue level instantaneously (C_0). The residue function, R(t) describes the fraction of indicator present in the vascular network at time t after injection and is a decreasing function of time. The tissue concentration at a given time, $C_t(t)$ is proportional to cerebral blood flow (CBF):

$$C_t(t) = CBF * C_0 * R(t)$$

$C_t(t)$ = tissue concentration at time t, CBF = cerebral blood flow, C_0 = concentration at time = 0, R(t) = residue function.

CBF*R(t) is called the tissue impulse response function.

To account for the non-optimal contrast bolus delivery in vivo, the concentration-to-time curve (CTTC) in a supplying cerebral artery can be monitored to measure the actual distribution of the contrast medium over time, the so-called arterial input function (AIF).[127] By determining the CTTC of the target tissue and then de-convoluting it with the AIF, the tissue impulse response function is calculated. At time point 0, the residue function, R(0)=1, and therefore, the height of the tissue impulse function (CBF*R(t)) equals the CBF. The cerebral blood volume (CBV) can be calculated by integrating the area under the tissue impulse response function.[131] Mean transit time (MTT), i.e. the mean value for a distribution of transit times of all blood components

through a given brain volume , can be calculated as CBV/CBF in accordance with the central volume principle.[127]

CBF is expressed as the total blood flow in the capillaries per unit tissue mass (ml/min*100 g). CBV is expressed as the volume of blood per unit tissue mass (ml/100 g). As both CBF and CBV are measured voxel wise, i.e. per volume element, the measurements are converted to perfusion rates using an estimate for the tissue density (typically 1.05g/ml for brain tissue).[132] MTT is expressed in seconds. As the contrast agent is only distributed in the blood plasma and not the full blood volume, the CBF and CBV values need to be corrected for differences in hematocrit between large vessels (as the AIF) and the capillaries (CTTC of the target tissue).

DSC MRI-perfusion is a widely used MRI-perfusion technique and like the other MRI-based techniques it does not expose the patient to ionizing radiation, as opposed to CT- or nuclear medicine-based approaches. DSC-MRI follows the first pass of an exogenous contrast agent with T2-weighted image sequences.[133] The contrast agent, a paramagnetic gadolinium chelate is administered intravenously at high speed and will remain intravascular as long as the BBB is intact.[134] The contrast agent causes microscopic susceptibility gradients that affect the local tissue around the vessels causing local protons to diphase resulting in an increased transverse (T2 or T2*) relaxation rate and a signal drop. An approximate linear relationship exists between the rate of change in the transverse relaxation rate and the tissue contrast agent concentration.[135] This, combined with the assumption that there is an exponential relationship between signal change and the change in T2* relaxation rate is used to calculate the CTTC.[136] A prerequisite of DSC-MRI are rapid imaging sequences with a temporal resolution $\leq$1.5 s. In the clinical setting, this is usually accomplished using EPI T_2* weighted sequences with a TE optimized to maximize the signal-to-noise ratio while also optimizing the AIF.[137-139]

A major drawback of this perfusion technique is the tendency to overestimate CBF- and CBV-values compared to the reference standard of positron emission tomography (PET) measurements, and the only moderate reproducibility of the method.[140,141] The overestimation is caused mainly by inaccuracy of the AIF due to partial volume effects, arterial signal saturation,

and local geometric distortion with partial volume effects being the major factor.[138,142-144] In addition, DSC-MRI suffers from the fact that intra- and extravascular transverse relaxitivity differ during bolus passage, violating the assumption of proportionality between the contrast agent concentration and change in T2/T2* relaxation rate, potentially contributing to the overestimation of perfusion.[145-147] If the BBB is not intact, extravascular retention of gadolinium also occurs, affecting the T2/T2* relaxation rate and the calculated perfusion estimates. While several methods to optimize the absolute perfusion estimates using DSC-MRI have been proposed with promising results,[148-150] it is still common to report relative CBF and CBV values (rCBF and rCBV) where the perfusion estimate is divided by the perfusion estimate of an internal reference.[151,152]

5.2 HISTORY OF IMAGING OF HYDROCEPHALUS

Different imaging techniques have been integral in diagnosing iNPH since its first description.[2] Initially, the imaging methods of choice for detecting hydrocephalus as well as to try to differentiate NPH from obstructive hydrocephalus and ventricular enlargement secondary to brain atrophy (also named hydrocephalus ex vacuo) were pneumoencephalography and, introduced some years later, isotope cisternography.[153,154] Both methods suffered from a low resolution and a number of technical difficulties and were associated with significant discomfort for the patient. This was especially true for pneumoencephalography where headaches, emesis and nausea were common complications.[154] Isotope cisternography has been widely used for studies of CSF dynamics, being a sensitive method for detection of obstructive hydrocephalus.

Imaging of the brain and ventricular systems improved greatly when CT and MRI became readily available. Today, CT remains important due to the large number of scans performed worldwide and many reveal incidental findings suspicious of NPH, enabling patients to get referred for a full workup. Many of the morphological findings seen on MRI (outlined below) can be seen on CT as well.[89] Thus, CT remains an important diagnostic tool for diagnosing NPH in cases where an MRI cannot be performed, and is useful to exclude the presence of ventricular dilatation.[3]

MR-imaging is considered the reference standard for imaging in iNPH today.[155] Compared to CT, MRI offer significantly higher tissue contrast enabling detailed evaluation of the morphology, allowing detection of processes that obstruct CSF-flow as well as WMLs.[118,156-158] In addition, additional sequences, e.g. DWI and perfusion imaging sequences can be performed to further increase the amount of information received from the scan. While many imaging markers of iNPH have been studied extensively, several potentially important markers have only been sparsely investigated or need confirmation in larger patient samples.

5.3 MORPHOLOGICAL IMAGING CHANGES IN iNPH

5.3.1 VENTRICULAR VOLUME

iNPH and sNPH are both characterized by a general widening of the ventricular system. The increased width is commonly measured using the Evans' index (EI) where the maximum width of the anterior horn of the lateral ventricles is divided by the maximum inner skull diameter in the same slice (Figure 5a).[159,160] An EI >0.3 is considered pathological, a marker of ventriculomegaly, and is used as a radiological criterion in both the American-European and Japanese guidelines.[3,74] However, this finding is not specific for iNPH and is seen in numerous other conditions with brain atrophy, including AD and other dementias.[161-163] The EI has been shown to remain unchanged or decrease minimally postoperatively.[164-166] As the widening of the ventricular system is general, patients with NPH commonly present with dilatation of the third ventricle as well as bilateral dilatation of the temporal horns.[3,69,167] As with the EI, these findings can be indicative of iNPH but are not specific for the disease.[162,168] Still, bilateral dilatation of the temporal horns not attributed to hippocampal atrophy, is included as a supportive radiological criterion for iNPH in the American-European guidelines.[3]

In recent years, semi- or fully-automated volumetric measurements have been used in NPH with promising results, and the accuracy and reproducibility is higher compared to the conventional measurements outlined above.[169] Ventricular volume has also been shown to decrease postoperatively.[166,170] However, even with the rapid technological advances, automated routine volumetric measurements are not yet readily available, in part due to difficulties of accurately measuring the ventricles when enlarged or when metallic artefacts from the shunt device are present.[171] On the other hand, semi-automated or manual volumetry is too time-consuming, thus, conventional morphological markers of iNPH are still essential in the diagnosis of the disease.

5.3.2 CORPUS CALLOSUM ANGLE

Relating to the dilatation of the lateral ventricles, a narrowing of the corpus callosum (or callosal) angle (CC-angle), measured along the inner walls of the lateral ventricles at the level of the posterior commissure in the coronal plane is another important finding in iNPH (Figure 5b).[163,172-174] Several studies have found the CC-angle useful for differential diagnostic purposes. Most notably, Ishii et al. found a cut off of 90° to discriminate iNPH from AD with a sensitivity of 97% and a specificity of 88%.[163] While 90° is the most commonly used cut off today, no consensus exists on the optimal cut off value.[3] It is important to note that while the CC-angle is a useful tool for diagnosing iNPH, great care should be taken to measure it in the correct plane perpendicular to a plane intersecting the anterior and posterior commissure (Figure 6).[163,172] Failure to define the measurement plane correctly has significant impact on the resulting measurement and might, as such, influence the results.[88,172] In the American-European guidelines, a CC-angle >40 degrees is, somewhat confusingly, most probably by mistake, included as a supportive radiological criterion of iNPH.[3] Postoperatively, the CC-angle has been reported to increase.[69,166,172]

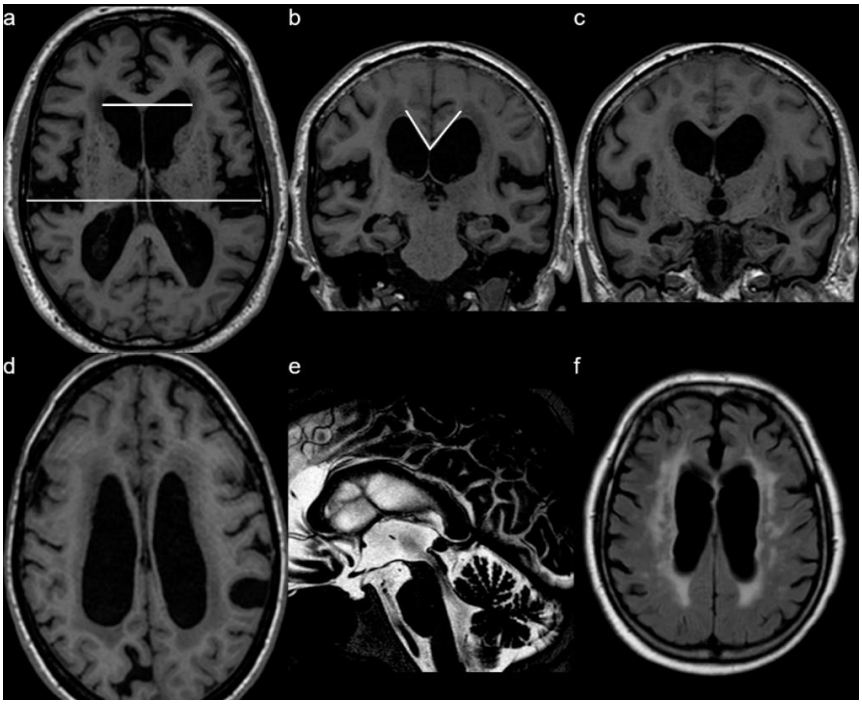

Figure 5. Example of morphological measurements and signs in iNPH. The Evans' index (a), and corpus callosal angle (b) on T1-weighted images. A combination of dilated Sylvian fissures and compressed sulci at the high convexity – DESH (c), and focally dilated sulci (d) on T1-weighted images. A present flow void sign in the cerebral aqueduct on a T2-weighted image (e), and periventricular as well as deep white matter hyperintensities on a T2-FLAIR image (f).

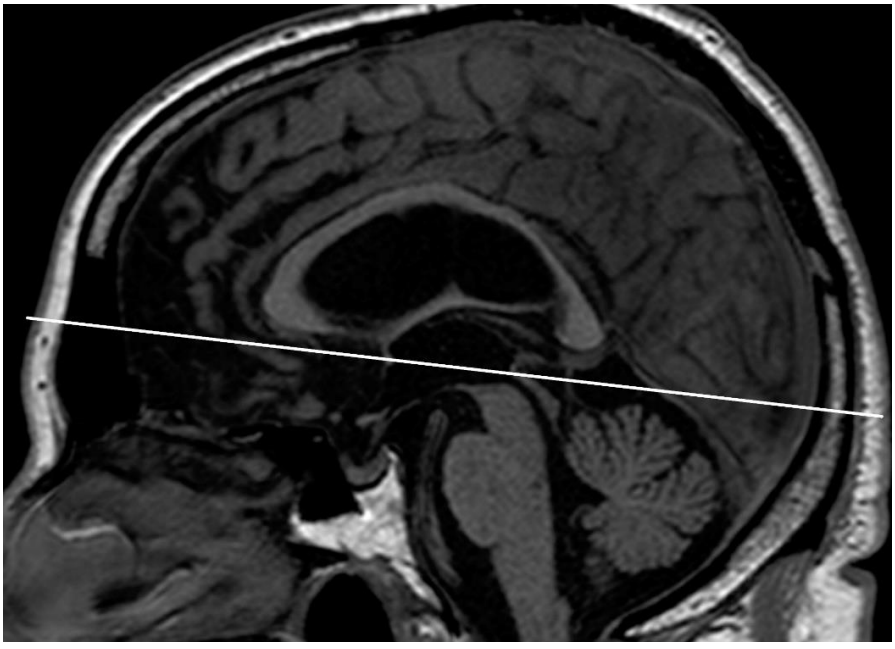

Figure 6. Line intersecting the anterior and posterior commissures on a midsagittal image used to align transaxial and coronal image series.

5.3.3 DESH AND FOCALLY WIDENED SULCI

As first described by Kitagi et al. in 1998, many patients with iNPH present with a discrepancy in the width of the cortical CSF-spaces where high convexity sulci and medial subarachnoid spaces are compressed while the sylvian fissures are dilated (Figure 5c).[18,74,156] This discrepancy, in combination with a general widening of the ventricular system constitute DESH and is considered an important diagnostic finding in the Japanese iNPH guidelines.[74] Focal dilatation of cortical sulci (a.k.a. entrapped sulci or transport sulci) have also been shown in patients with iNPH (Figure 5d).[88,167,175] Although probably less common than DESH, the focal widening is thought to arise from the same underlying disturbance of CSF circulation.[74,88,175]

5.3.4 WHITE MATTER LESIONS

WMLs, seen as both periventricular (PVH) and deep white matter hyperintensities (DWMH) are a common finding in iNPH,[3,74,176,177] and are

more common in the patient group compared to healthy control subjects (Figure 5f).[157,178] Both PVH and DWMH are associated with vascular risk factors and can, at least in part be caused by microischemic events.[107,108,110] However, measurements of T1 and T2-relaxation as well as ADC in PVHs in iNPH have also shown some support of an increased water content, speculated to be caused by a periventricular edema,[179,180] which is in line with reports on neuropathological findings in iNPH.[181,182] On the other hand, the extent of edema has been questioned, and pure periventricular edema is rarely seen in iNPH.[176,183] Thus, a combination of pathophysiological alterations causing WMLs in iNPH is likely.[157,176,178] The extent of PVHs has been shown to be reduced after surgery, and the reduction has been found to correlate to the degree of clinical improvement.[176] The presence of WMLs is included as a supportive diagnostic criterion in the American-European guidelines.[3]

5.3.5 MORPHOLOGICAL IMAGING CHANGES IN INFRATENTORIAL STRUCTURES

Only a few studies investigating morphological changes in infratentorial structures in iNPH have been conducted. Midbrain diameter at the level of the mesencephalopontine junction has been found to be reduced preoperatively, correlate to the severity of gait disturbances and increase after surgery.[165,184] However, the original studies suffer from methodological issues regarding the definition of measurement planes and these findings were not reproducible in a more recent study.[185]

5.3.6 PREDICTION

The predictive value of morphological imaging markers in iNPH has been investigated with conflicting results. The CC-angle, dilated temporal horns and DESH have been reported as predictors of good outcome in a number of studies.[69,172,186-190] However, these markers have also been found to be of no predictive value.[167,191-193] As such, no definite support for outcome prediction exists and the markers that have shown promise in this area need further evaluation. Regarding WMLs, it is important to note that the presence of even severe WMLs do not affect the potential rate of postoperative improvement.[176,177]

5.4 MARKERS OF CSF FLOW

To help exclude obstruction or stenosis of the cerebral aqueduct as well as other parts of the ventricular system, the flow void phenomenon is commonly assessed in the diagnostic workup of iNPH. Flow voids arise due to a loss of signal on T2 or proton density weighted spin echo MRI caused by the fast movement of hydrogen atoms.[103] This is commonly seen in blood vessels in healthy individuals. In iNPH, a flow void sign is often seen in the cerebral aqueduct and in the fourth ventricle, and can be used to rule out complete blockage of CSF-flow in this area (Figure 5e).[158] Objective grading of flow voids are difficult and depend on several MRI parameters e.g. slice thickness and TE which makes comparisons between different scanners difficult.[194,195] Despite these drawbacks, the aqueductal flow void sign is included as a supportive radiological criterion for the diagnosis of iNPH.[3] However, it is important to note that flow voids are seen in this area in other diseases such as AD, but also in healthy individuals, thus the specificity for iNPH is low, and the flow void sign has been shown to be of no predictive value.[163,196]

5.5 DIFFUSION WEIGHTED IMAGING AND DIFFUSION TENSOR IMAGING

Changes on DWI in iNPH patients have been explored in several studies. Increased ADC in periventricular white matter has been repeatedly reported, a change attributed to an increase in extracellular water content and/or ischemic injury.[180,197-200] However, another study reported similar ADC in iNPH patients and healthy control subjects.[201] Postoperatively, ADC in periventricular white matter has been reported to decrease, hypothetically due to increased water movement from the interstitium to the ventricles,[201-203] but has also been found to remain unchanged in the corpus callosum and centrum semiovale in one study.[204]

DTI studies have found increased FA and, to a lesser extent MD along the corticospinal tract (CST) in iNPH patients, hypothesized to be caused by compression of white matter tracts, with trends towards normalization after shunt surgery.[155,198,205-208] The FA increase in the CST has also been shown to aid in the differential diagnosis of iNPH, AD and PD.[207] Further, a decreased FA in combination with increased MD/ADC has been shown in periventricular frontal white matter[202] and in the commissural fibers of the corpus callosum, findings that correlated to the severity of gait disturbance.[198,208-210]

Diffusion changes in infratentorial structures are scarcely investigated. Tullberg et al. found no difference in ADC between patients and controls in the mesencephalon, nor any differences between iNPH patients and patients diagnosed with Binswangers disease.[201] Postoperatively, there was a numerical, but non-significant decrease of ADC in the iNPH group and the reported postoperative values did not differ from the control subjects. Measuring changes in the CST with DTI, Reiss-Zimmermann et al. found an increased MD, mainly caused by an increased principal diffusion in the fibers of the CST passing through the cerebral peduncles and the mesencephalon.[198]

5.5.1 PREDICTION

The degree of change in ADC in responders has been shown to correlate with the extent of clinical improvement.[199,201] Corkill et al. found a significant preoperative ADC increase in normal appearing white matter in non-

responders and postulated that this might reflect irreversible neuronal injury, and could be used to exclude patients from shunt surgery.[197] In addition, Jurcoane et al. and Demura et al. investigated DTI changes after CSF drainage and found that responders showed significant reductions in ADC and axial diffusivity.[155,203] One study also found that the reduction in axial diffusivity after TT could predict outcome after surgery.[155] However, contradicting these findings, Lenfeldt et al. found no changes in DTI variables after ELD.[204] In summary, while diffusion changes are evident in iNPH, their cause as well as their predictive value is debated and requires further investigation.

5.6 PERFUSION IMAGING

Many studies have investigated perfusion changes in iNPH, mainly in supratentorial structures. Early studies, conducted between 1969 and 2000, suffered from methodological and technical issues with inconsistent results, but still provided evidence of a global pre-treatment CBF reduction in iNPH.[211]

Using single positron emission computed tomography (SPECT) and PET, combined with CT or MRI, iNPH patients have been found to have a reduced CBF in the frontal/prefrontal and parieto-temporal lobes compared to controls. In addition, CBF was lower in the corpus callosum, cortex bordering the sylvian fissures, and in the dorsal striatum compared to controls and AD-patients.[59,212-219] A global CBF reduction has also been reported,[215,220] and Momijan et al. found a gradual CBF reduction in periventricular white matter, correlating with the distance to the ventricular wall. The reduction was more pronounced after administering a CSF infusion test, and speculated to arise due to defective autoregulation.[221] CBF has been found to be lower in patients with symptoms from all domains compared to patients with fewer symptoms and to correlate with the severity of clinical symptoms.[215,218,220] Focal reductions in the right frontal and left inferior temporal gyrus have been found to correlate with severe urinary dysfunction.[222] Postoperatively, CBF increases,[59,218,223,224] or remain unchanged in improved patients.[225-227]

Using MRI-based perfusion methods, global arterial and venous CBF reductions with an altered venous compliance have been reported using phase-contrast MRI.[228,229] Similar global reductions were found using DSC-MRI based rCBF measurements.[230] In addition, local rCBF reductions have been reported in the periventricular white matter,[197,230] as well as in the medial frontal cortex, cingulate gyrus, lentiform nucleus, and hippocampus, correlating to clinical performance.[230] Using pseudo-continuous arterial spin-labelling (pCASL), Virhammar et al. found that patients who had an increased CBF after undergoing a CSF-TT improved more in gait tests compared with patients who had a reduction in CBF, although, at group level, no correlation between CBF and gait performance existed.[231] Corroborating results from SPECT and PET studies, DSC MRI-perfusion based rCBF has been reported to increase in improved patients.[232]

Similar to morphological and diffusion changes, perfusion alterations in infratentorial structures in iNPH has only been investigated in a few studies. Tullberg et al. reported a significantly decreased rCBF in the mesencephalon preoperatively with a numerical, although not statistically significant increase after shunt surgery using SPECT.[59] Reporting similar results using PET-MRI, one study by Owler et al. found a preoperative CBF reduction in the cerebellum in the disease.[220] Only one study using CT-perfusion imaging has been performed in iNPH with results largely corroborating the DSC-MRI results published by the same authors.[233]

5.6.1 PREDICTION

As with the diffusion studies, studies of perfusion in iNPH have found correlations between the degree of postoperative CBF increase and overall clinical performance in responders,[223,224,232] as well as a negative correlation between rCBF increase in the frontal association cortex, and impaired wakefulness.[59] Ziegelitz et al. found that the change in rCBF in responders in the head of the caudate nucleus correlated with the change in iNPH score as well as gait and balance subscores. The rCBF increase in the cingulate gyrus and thalamus correlated with the increase in the neuropsychology subscore.[232]

Comparing responders and non-responders preoperatively, the same authors found that the rCBF in the medial frontal cortex was significantly higher in responders, and could possibly be used for outcome prediction, although this result was not reproducible in subsequent studies by the same authors.[230,232,233] No other between group differences were found, corroborating earlier results.[197,216,218,228] Mori et al. evaluated CBF changes after CSF-TT and while no pre-test differences between groups were found, TT-responders showed a significant post-test CBF increase. An increase <20% was suggested as a cut off value for non-responders that could potentially be used for predictive purposes.[234]

In summary, perfusion changes in supratentorial structures are a well-established finding in iNPH, although the predictive value of these changes is disputed. Similar to studies of morphology or diffusion, changes in the brainstem in iNPH have only been scarcely investigated and further studies are warranted.

6 PATHOPHYSIOLOGICAL CONCEPTS IN iNPH

Despite the large research effort to elucidate the pathophysiological changes causing iNPH, the disease is still incompletely understood. Several theories have been proposed.

Traditionally, iNPH is seen as a disease arising primarily due to a disturbed resorption of CSF.[235] This is supported by studies of CSF-dynamics showing a reduced intracranial compliance and an increased CSF pulsatility in the patient group.[236] Morphological changes in the CSF outflow tract have been reported in some iNPH patients in one study, also supporting this theory,[237] however, the results have not been reproducible.[238] While iNPH is associated with an increased resistance to CSF outflow (R_{out}),[239] it is known that both production and absorption of CSF decreases with age, and R_{out} values considered pathological in iNPH can be found in up to 25% of healthy elderly, and patients with a low R_{out} still benefit from shunt surgery.[87,240-242] As such, while dynamic CSF changes play a role in the development of iNPH, other disease mechanisms must also be considered. iNPH has also been suggested to develop as a "two hit" disease caused by a combination of external childhood hydrocephalus followed by WMLs in later years, although this theory has been questioned and would seem applicable only in a minority of patients.[68]

Another common pathophysiological theory regarding the development of iNPH revolves around an increase in interstitial water content, predominantly in periventricular areas, secondary to water reflux from the ventricles, as a driving force behind neuronal damage. Supporting this, an increased ADC in these areas and signs of white matter tract compression have been reported in iNPH.[155,180,197-200,205-208] However, ADC has also been found to be similar to findings in healthy controls.[201] Furthermore, the reported preoperative ADC-increase in iNPH has not been shown to discriminate between responders and non-responders, and it is important to note that ADC can increase due to several other factors as well.[120,199,201,203] As such, while an increased interstitial water content can be present in iNPH, its role as a driving factor in disease development and progression needs further consideration, and other factors causing the ADC increase should potentially be included in the theory. It also

seems unlikely that a mechanical compression due to ventricular enlargement and increased interstitial water content would solely explain the symptom development and progress, as no correlation between preoperative ventricular size, nor postoperative size reduction and symptoms exist.[68]

Interestingly, recent studies by Eide et al. have found a decreased uptake of intrathecally administered gadobutrol in iNPH.[243] This, together with an altered expression of AQP-4 in the disease hints at a dysfunction of the glymphatic system.[41] While a dysfunction in this system has been implicated in other neurologic diseases as well, a dysfunction in iNPH with secondary metabolic changes due to a disturbed clearance of metabolically active, potentially toxic factors is interesting and further investigations are warranted.

6.1.1 THE ROLE OF VASCULAR DISEASE

Since the 1980s, vascular disease has been considered a possible factor driving the development of iNPH. Multiple studies have found iNPH patients to have a high occurrence of vascular risk factors, especially hypertension, DM, and heart disease compared to controls. However, most studies were performed using small, hospital based samples.[110,244-248] In 2013, the International Society for Hydrocephalus and Cerebrospinal Fluid Disorders (ISHCSF) task force concluded that while support for a relationship between vascular risk factors and iNPH does exist, no causal relationship can be determined, and further, epidemiological studies are warranted.[244] Still, the involvement of vascular disease processes in iNPH is strengthened by several studies from different research areas.

Several animal studies have found associations between systolic hypertension, pulse pressure, and ventricular enlargement.[249,250] Similar results were also found in humans by Graff-Radford et al, reported that present systolic hypertension and elevated pulse pressure at baseline were significantly associated to ventricular enlargement at a 10-year follow up.[251] The increased pulse pressure has been suggested to directly lead to ventricular enlargement via the so called waterhammer theory, that is, the pressure in the arteries during systole is transmitted to the cells of the ventricular walls and nearby structures via the CSF, causing neuronal damage. Although, the exact mechanism of action needs further investigation.

Further support for the involvement of vascular risk factors in iNPH is provided by imaging studies. The patient group is known to have a high prevalence of WMLs preoperatively. WMLs are in themselves associated with vascular risk factors,[107,108,110] and have a high reported prevalence in patients with ischemic brain injuries and subcortical small vessel disease (SSVD).[252,253] These changes are also associated with gait disturbances, cognitive impairment and urinary incontinence.[116] Also supporting the involvement of small vessel disease, one study found iNPH-patients to have a high occurrence of cerebral microbleeds,[254] and neuropathological examinations have revealed signs of cerebrovascular disease in the patient group.[255]

However, while the association between WMLs, ischemic injury and vascular disease is strong, it is important to note that the extent of WMLs in iNPH can decrease postoperatively, correlating to clinical improvement, indicating the involvement of at least partially reversible microcirculatory and/or metabolic changes.[176,177] Further support for the, at least partial, reversibility is provided by several studies of perfusion in iNPH reporting partly reversible blood-flow reductions, especially in periventricular and frontosubcortical areas.[59,202,232,256] In addition, both the decrease of WMLs and blood flow improvements have been shown to correlate with the degree of postoperative clinical improvement. Interestingly, further supporting partly reversible changes causing WMLs, a small study on Acetazolamide (a carbonic anhydrase inhibitor that has a vasodilating effect, increasing CBF and also decreasing CSF-production) in iNPH found that 5/8 treated patients improved in gait function.[257,258] Two studies also found acetazolamide treatment in iNPH to decrease the extent of WMLs.[257,259]

While the potentially reversible mechanisms are still unknown, there might exist a link between vascular disease and the glymphatic dysfunction seen in iNPH.[243] This theory is to some extent supported by the para-arterial inflow of CSF to the ECS, and by animal studies showing that hypertension is associated to a decreased glymphatic clearance in rats, however this needs further elucidation.[35,36,260]

In summary, although evidence from several research areas support the involvement of vascular disease mechanisms in iNPH, the mechanism of

action regarding these vascular changes remains incompletely understood but seems to involve not only ischemic injury.

6.1.2 THE ROLE OF THE MESENCEPHALON AND PONS IN THE SYMPTOM GENERATION IN iNPH

The symptom generation in iNPH is thought to arise predominantly due to changes in supratentorial, periventricular structures. However, symptoms from all four cardinal groups as well as other symptoms, such as paratonia and impaired wakefulness, could also potentially be caused by changes in structures in the brainstem.

The gait and balance disturbances in iNPH are, to a certain extent, similar to the disturbances seen in other movement disorders. In patients with PD, motor symptoms including postural stability and freezing of gait are alleviated after deep brain stimulation of the pedunculopontine nucleus (PPN), in the mesencephalic tegmentum.[261] Stimulation of the same area also reduced the risk of falls.[262] The similarity of these symptoms to the gait and balance symptoms seen in iNPH could indicate the potential involvement of this area in the disease. Interestingly, the PPN is also involved in non-motor activity and Deep brain stimulation has also been shown to improve working memory and affect sleep patterns.[263,264] Changes here, or in the reticular activation system could hypothetically explain the impaired wakefulness in iNPH. Furthermore, the altered visual vertical seen in iNPH,[52] could also be caused by changes in the midbrain,[265,266] and centers in the mesencephalon and pons are well known as important regulators of micturition.[267-270] Lastly, studies using auditory brainstem responses have shown prolonged central transmission times in NPH, with postoperative reductions in improved patients.[271,272] Although the studies included patients with sNPH, they still support the notion of the involvement of these areas in iNPH.

Imaging studies of infratentorial structures in iNPH are scarce, both regarding morphological and functional changes. While attempts at measuring midbrain diameter have been attempted, results are conflicting.[165,184,185] In the few studies investigating functional changes, two studies found similar preoperative rCBF/CBF reductions as has been shown in supratentorial structures,[59,220] while diffusion changes are sparsely investigated with

conflicting results.[198,201] In summary, further studies are needed to elucidate the involvement of the brainstem in iNPH.

7 AIM

The overall aim of this thesis was to elucidate on the development and pathophysiology of iNPH by describing the clinical and radiological phenotype, including the specific role of the brainstem and the involvement of vascular risk factors in the disease, and to identify biomarkers that can be used to predict outcome after shunt surgery.

7.1 STUDY I

To examine vascular risk factors, WMLs and their association to hydrocephalic ventriculomegaly as well as clinical signs of iNPH in a large, population-based sample using a nested case-control analysis.

7.2 STUDY II

To characterize the clinical phenotype of iNPH using a large, single center patient cohort to elucidate the clinical presentation of the disease and to find possible clinical biomarkers that could predict outcome after shunt surgery.

7.3 STUDY III

To investigate the prevalence of several previously described morphological MRI markers of iNPH and to evaluate their role as potential predictive markers of postoperative outcome.

7.4 STUDY IV

To explore diffusion and DSC-MRI-perfusion changes in the mesencephalon and pons, areas of potential pathophysiological importance in iNPH, and to investigate the potential relationship between these functional MRI markers and clinical symptoms pre- and postoperatively.

8 PATIENTS AND METHODS

8.1 PATIENT COHORTS AND DIAGNOSIS OF iNPH

8.1.1 STUDY I

The cohort in Study I consisted of merged data from the Gothenburg population studies. The studies systematically recruited participants from the Swedish birth registry, starting in 1968 resulting in a maximum follow up time of almost fifty years. Data from the following studies were included: The Population Studies of Women (PPSW), The Longitudinal Gerontological and Geriatric Population Studies (H70 and H85) in Gothenburg, and The Nordic Research on Ageing Studies (NORA).[4] In all the included population studies, the participants underwent clinical examinations, and a subset also had one or more CT scans of the brain.

Data from the different studies were merged and a total of 3246 individuals were invited to participate of which 2179 accepted (response rate 67% with no significant difference between men and women). Out of the 2179 who accepted to participate, 1235 individuals underwent one or more CT scans and were included in the study. A flow-chart of the inclusion process and the included population cohorts are shown in Figure 4. The diagnosis of possible/probable iNPH was made based on the CT examinations in conjunction with clinical examinations and interview data. Fifty-five individuals had CT-findings of hydrocephalic ventricular enlargement (HVe, described below). Twenty-six of the 55 individuals also had clinical symptoms that fulfilled the criteria for iNPH, i.e. a gait disturbance combined with either a cognitive disturbance or urinary incontinence. The remaining 1180 individuals were used for case-control matching. A nested case-control design was applied where 5 control subjects (from the 1180 individuals without clinical or radiological signs of iNPH) were randomly selected and matched to each case based on age, sex and original study cohort. Demographic data for the final study sample are shown in Table 3.

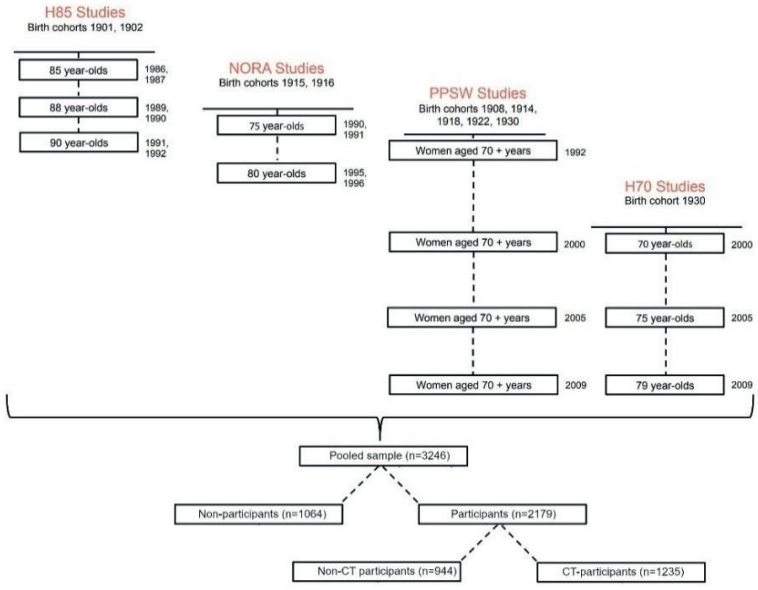

Figure 7. Included population cohorts, participant selection and final study sample in Study I. Original figure modified with permission from Dr Daniel Jaraj.

8.1.2 STUDY II

Study II included patients examined and diagnosed with iNPH in Gothenburg between 1982 and 2016. All patients underwent detailed pre- and postoperative clinical examinations using a standardized protocol. The protocol was changed four times during the inclusion period with addition of new items. The diagnosis of iNPH was made in accordance with the American-European guidelines after their publication in 2005.[3] Before, the diagnosis was made using similar criteria with the main exception that gait disturbance was not mandatory. As part of the diagnostic workup, all patients underwent CT or MRI-scans of the brain pre- and postoperatively. All patients received ventriculoperitoneal shunt systems. A total of 429 patients were included in Study II. Due to the varying disease severity at the time of examination, not all patients were able to perform all tests. All shunts were working at the postoperative clinical examination.

8.1.3 STUDY III

The patient group constitutes a subpopulation of the patient group used in Study II and underwent the same detailed clinical examination pre- and postoperatively. In addition, all patients had a both pre- and postoperative MRI-scan of sufficient quality for morphological analyses (patients lacking this were excluded). A total of 168 patients were included in Study III.

8.1.4 STUDY IV

Study IV included 20 patients from Study III, who were examined with a DSC-perfusion sequence and a DWI sequence in addition to the standardized MRI protocol pre- and postoperatively. In addition, 15 healthy, age-matched subjects who underwent an identical MRI examination were included as a control group. The patient group had more WMLs compared to controls (Wahlund score 6.2 vs 5.0, $p<0.05$). Responders and non-responders did not differ significantly in any demographic variable. Due to technical artefacts, 4 postoperative scans were excluded from the analyses.

Demographic data for all patients and controls included in Study II-IV are shown in Table 4.

Table 3. Demographic data of cases with suspected iNPH and HVe with their matched controls included in Study I.

	Suspected iNPH		HVe	
	Cases (n=26)	Controls (n=130)	Cases (n=55)	Controls (n=275)
Age, mean (SD)	85 (4.0)	85 (4.0)	80 (7.0)	80 (7.0)
Male/female (% male)	10/16 (38.5)	50/80 (38.5)	25/30 (45.5)	125/130(45.5)

HVe = hydrocephalic ventricular enlargement, SD = standard deviation.

Table 4. Demographic data for patients and controls included in Studies II-IV.

	Study II	Study III	Study IV	
	iNPH (n=429)	iNPH (n=168)	iNPH (n=20)	Controls (n=15)
Age, mean (SD)	71 (9.5)	71 (9.3)	71 (7.1)	71 (4.9)
Male/female, (% male)	266/163 (62)	103/65 (61)	12/8 (60)	9/6 (60)
Symptom duration in months, mean (SD)	43 (44)	47 (59)	33 (34)	n.a.
Vascular risk factor, yes/no (%)				
Hypertension	206/223 (48)	(49)	7/13 (35)*	1/14 (7)
Diabetes mellitus	86/343 (20)	(15)	3/17 (15)	n.a.
Cardiovascular disease	112/317 (26)	(26)	2/18 (10)	n.a.

* $p<0.05$ compared to controls. Cardiovascular disease = history of angina pectoris or coronary artery disease, SD = standard deviation, n.a. = not applicable.

8.2 GRADING OF CLINICAL SYMPTOMS, VASCULAR RISK FACTORS AND OUTCOME

8.2.1 STUDY I

In study I, data on clinical symptoms were retrieved from the clinical examinations that each individual underwent as part of the original studies. A general assessment of gait was made by physicians specializing in geriatrics. Walking difficulties were graded using a 3 point ordinal scale (non-existent, slight, extensive). Participants also answered questions regarding gait and perceived walking difficulties during the examinations. A gait disturbance was considered present if any walking difficulty was reported during the examination or if any self-reported walking difficulty was present. Cognitive function was evaluated using the MMSE.[97] A score of ≤25 was used as the cut off for cognitive impairment. Urinary incontinence was assessed by self-report and defined as the presence of leakage of urine ≥1 time per week.

A history of, or present hypertension, DM, previous stroke/transient ischemic attack (TIA), and coronary artery disease (CAD) were assessed using data from the Swedish hospital discharge register and/or self-reported diagnosis as told by a physician at the time of the original physical exam. A history of hypertension was defined as having a diagnosis of hypertension or the use of antihypertensive medication. DM was defined as having a diagnosis of DM type 1 or 2 or by having pharmacologic treatment. The presence of pharmacologic treatment for both hypertension and DM was assessed by self-report. Stroke/TIA was defined as having a diagnosis of ischemic/hemorrhagic stroke or TIA. CAD was defined as having a diagnosis of myocardial infarction or angina pectoris. The ICD-codes that were used for each vascular risk factor are shown in Appendix 1.

In addition to the abovementioned vascular risk factors, the presence of smoking and obesity were assessed using interview data and results from clinical examinations. Smoking was defined as past or present cigarette smoking and obesity was defined as having a body mass index (BMI) >25 kg/m^2.

8.2.2 STUDY II-III

In studies II and III, gait performance was evaluated by a 6-step ordinal scale ranging from: 1 = normal gait, to 6 = wheelchair bound (Table 5). Impaired gait was defined as a gait score of ≥2. The number of steps needed to execute a 180° turn was also recorded with >2 steps required considered as having difficulties turning. In addition, the presence of broad-based gait, shuffling gait and freezing of gait were recorded (yes/no). A physiotherapist also performed the 10m walking test and the TUG test with time in seconds as well as number of steps required to complete.[273]

Balance performance was evaluated using the Romberg test (time in seconds recorded up to a maximum of 60 s),[274] and the presence of a tendency to lean backwards (retropulsion) was recorded (yes/no). Impaired balance was defined as a Romberg test performance of ≤30 s.

Cognitive function was evaluated using the MMSE-test with a score of ≤25 used as the cut off for cognitive impairment.[97] The MMSE-scores were also converted to a 5 step ordinal scale ranging from 1 = no dementia to 5 = severe dementia (Table 5). The daily need of sleep (hours/day) was also recorded. In addition, the identical forms test (measuring perceptual speed and accuracy) and Bingley's visual memory test were administered.[275]

Urinary continence was graded using a 6-step ordinal scale ranging from: 1 = no urgency/incontinence to 6 = bladder and bowel incontinence (Table 5). Impaired continence was defined as a continence score of ≥2.

In addition to the abovementioned symptom domains, the presence of a number of other neurological symptoms (paratonic rigidity, cerebellar dystaxia, polyneuropathy and other focal neurological signs) were recorded (yes/no). The presence of hypertension, DM and cardiovascular disease were assessed from previous medical records (yes/no).

To grade clinical outcome after shunt surgery, a composite grading scale was constructed. The scale included four continuous measures that were recorded pre- and postoperatively: the 10m walking- and TUG test (time in seconds to complete) as well as the identical forms and Bingley tests (test scores). Each

test performance was normalized on a 0-100 scale where 0 equals the worst possible performance and 100 equals the performance of a healthy 70-year old individual. The mean score of the four included tests formed the composite pre- and postoperative score. Clinical improvement was considered present if the post-preoperative difference was ≥5points, unchanged if <5 but ≥-5 points and deteriorated if <-5 points. Three-hundred and eleven patients had data from at least one test in each domain (gait and cognition) and were included in the outcome calculations.

Table 5. Ordinal measures of gait, cognition and continence used in Studies II and III.

Gait		**Cognition**		**Continence**	
Ordinal score	Observed gait abnormalities	Ordinal score	MMSE-score	Ordinal score	Observed/reported continence function
1	Normal gait	1	30	1	Normal
2	Unsteady gait, no walking aids	2	≤29	2	Urgency, no leakage
3	Walking with a cane	3	≤25	3	Leakage <1 time/week
4	Walking with a roller	4	≤20	4	Leakage ≥1 time/week or occasional use of diapers
5	Walking only if supported by another person	5	≤10	5	Continuous use of diapers
6	Wheelchair bound			6	Bladder and bowel incontinence

8.2.3 Study IV

In study IV, clinical symptom severity was graded pre- and postoperatively using the iNPH scale score developed by Hellström et al.[66] A postoperative increase by ≥5 points was used as a cut off for clinical improvement.

8.3 RADIOLOGICAL EVALUATION

8.3.1 STUDY I

All participants in study I underwent a CT-scan of the brain between 1986 and 2000 with 10 mm slices obtained between 1986 and 1995 (n=381) and 8 mm slices obtained between 1996 and 2000 (n=854). All scans were in the transverse plane without iv. contrast. Three observers blinded to clinical data performed the image evaluation. All scans were screened for HVe, defined as a general ventricular enlargement (assessed by visual inspection aided by measuring the EI) without concomitant widening of the cortical sulci, presence of structural lesions or morphologic signs of obstruction of CSF-outflow.[3] All images that were screened positive for HVe, or where the findings were uncertain were re-evaluated by a senior neuroradiologist who made the final decision on whether HVe was present. After the initial screening, 19% (235/1235) of scans were classified as having HVe or uncertain findings. After re-evaluation, the final prevalence of HVe was 4.4% (55/1235).

WMLs were defined as areas of low attenuation in the periventricular and deep white matter and graded using a 4-step ordinal scale (none, mild, moderate and severe).[276] The assessments were performed by experienced radiologists blinded to clinical data, as part of previous studies.[119,277] Due to the low sensitivity of CT in accurately classifying WMLs, comparisons were made only between none/mild vs moderate/severe WMLs in the present study.

8.3.2 STUDIES II-III

As part of the original assessment, all patients' scans were evaluated for features of iNPH as part of the routine examination performed by the neuroradiology department at the Sahlgrenska University hospital.

In study III, all preoperative MRI-scans were evaluated for the presence of 13 morphological features of iNPH. The preoperative MRI-scans were performed on a 1.5 T Gyroscan Intera 9.1 system (Philips Healthcare, Best, the Netherlands) or a 1.5 T Achieva dStream (Philips Healthcare, Best, the Netherlands) system. All imaging sequences were reformatted and analysed using Advantage Workstation 2.0 (GE Healthcare, Milwaukee, Wisconsin). The imaging protocol included:

1. A sagittal T1-weighted 3D sequence: TE 4.6 ms, TR 25 ms, flip-angle 30°, slice thickness 1 mm, no slice gap, field of view (FOV) 260×260×190 mm, 260×259 acquisition matrix.
2. A transverse FLAIR sequence: TE 100 ms, TR 9000 ms, TI delay 2500 ms, slice thickness 3 mm, no slice gap, FOV 230 mm, 192×192 acquisition matrix reconstructed to 256×256.
3. A flow-sensitive T2-weighted sequence: TE 300 ms, TR 10238 ms, slice thickness 2 mm, 1 mm slice gap, FOV 230×230×38 mm, 384×284 acquisition matrix.

The T1-weighted sequence was reformatted to the anterior/posterior commissural plane by realigning the transverse and coronal imaging planes to a line transecting this plane on sagittal images (see Figure 5).[69,163,172] The reformatted images were used in all subsequent analyses.

MORPHOLOGIC MRI MARKERS

The image-analysis protocol was tested by two independent authors, at the time blinded to clinical data. Each imaging marker was evaluated on 10 randomly selected examinations and inter-rater reliability coefficients were calculated. In cases were the inter-rater reliability was insufficient (<0.7), the variables were redefined and re-evaluated until sufficient agreement was achieved. The development of the image-analysis protocol was supervised by an experienced neuroradiologist.

The EI was measured on transaxial T1-weighted images and defined, in agreement with the original publication, as the ratio between the maximum diameter of the frontal horns of the lateral ventricles above the foramen of Monroe, divided by the maximum inner skull diameter in the same slice (Figure 8a).[159,160] In the same series, the maximum diameter (mm) of the temporal horns was recorded (Figure 8b). The maximum diameter of the 3rd ventricle between the anterior and posterior commissure (mm) was measured on T1-weighted coronal images (Figure 8c). The same images were used to measure the CC-angle at the level of the posterior commissure (Figure 8d). The maximum anterior-posterior diameter of the 4th ventricle (mm) was measured in the midline on sagittal T1-weighted images along a line perpendicular to the posterior border of the brainstem (Figure 8e). Widening of the anterior

interhemispheric fissure was graded using a 3-step ordinal scale (0=normal, 1=slight widening, 2=marked widening) on transaxial, T1-weighted images (Figure 9a). Flow voids in the cerebral aqueduct and fourth ventricle (flow void sign) were assessed on T2-weighted, flow-sensitive images and graded using the ordinal scale developed by Algin et a.[194] and later modified by Virhammar et al. (Figure 9b).[69]

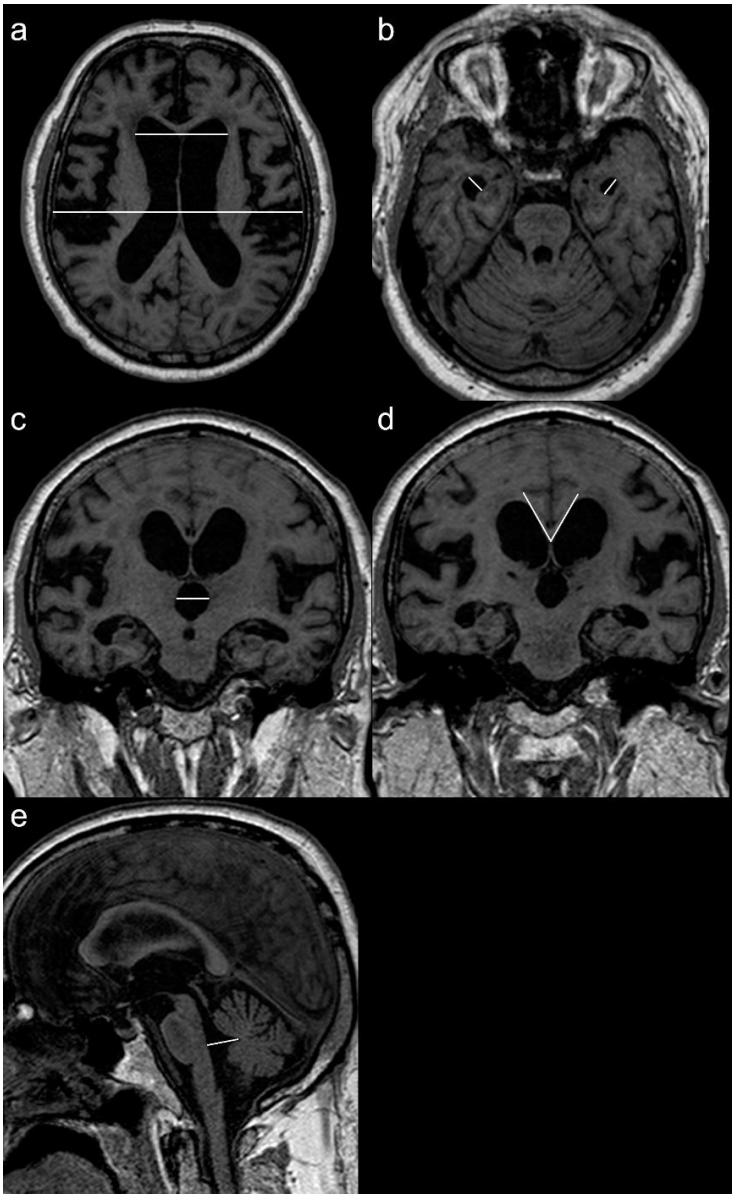

Figure 8. Evans' index measured as the ratio between the maximum width of the frontal horns of the ventricles divided by the maximum inner skull diameter (a), and maximum width of the temporal horns (b) on transaxial images. Maximum width of the 3rd ventricle (c) and CC-angle (d) measured on coronal images. Maximum anteroposterior diameter of the 4th ventricle measured on a sagittal image (e). All images are T1-weighted.

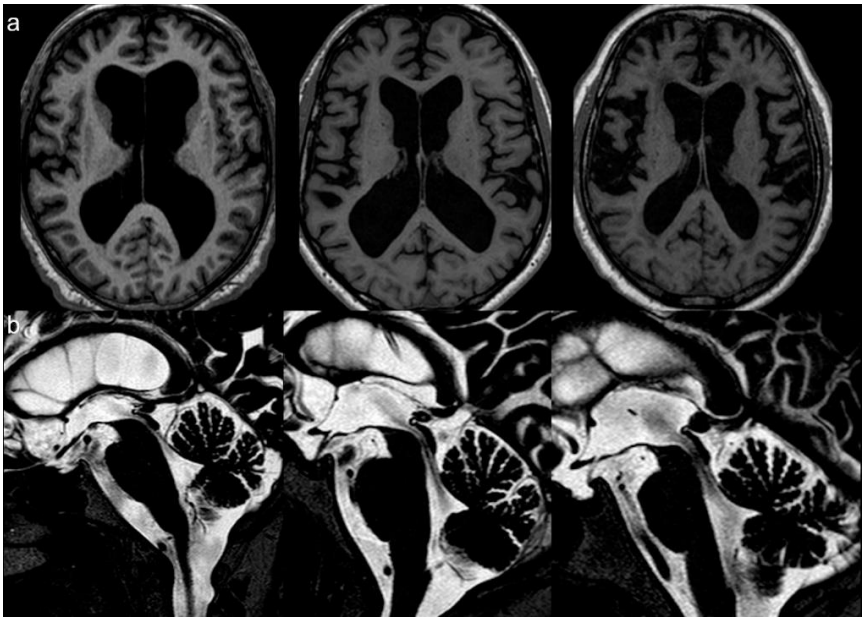

Figure 9. Anterior interhemispheric fissure graded 0 (normal), 1 (slight widening), 2 (marked widening) on T1-weighted axial images (a). Flow void sign in the cerebral aqueduct graded 1, 2, 3 according to the modified Algin scale on T2-weighted sagittal images (b).

The presence of focally dilated sulci (transport sulci) was assessed on T1-weighted, transaxial images (no. of widened sulci recorded). Sulci were determined as focally widened only if no signs of general atrophy were present, the sulcal widening was asymmetric, the sulcus lacked connection with the Sylvian fissure, and was surrounded by normal or narrowed sulci (Figure 10a-b). Obliteration of sulci at the high convexity was graded as present (yes/no) if no sulci were distinguishable on the 10 uppermost slices on transaxial, T1-weighted images (Figure 10c). Dilatation of the Sylvian fissures was graded on coronal, T1-weighted images using a 3-step ordinal scale (0=normal, 1=slight widening, 2=marked widening)[69] (Figure 10d). DESH was considered present (yes/no) in patients who had dilated Sylvian fissures (ordinal rating 1 or 2) in conjunction with obliterated sulci at the high convexity. WMLs (PVH and DWMH) were graded using the ordinal scale developed by Fazekas et al, and assessed on transaxial, FLAIR images (Figure 11).[118]

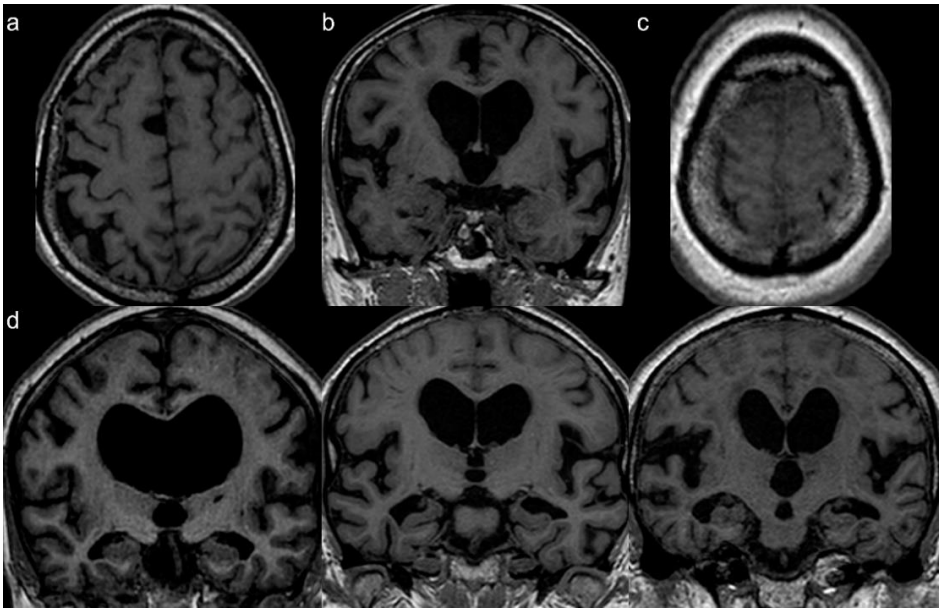

Figure 10. Focally dilated sulci on a transaxial (a), and coronal image (b). Obliterated sulci at the high convexity (c) on transaxial images. Sylvian fissures graded as 0 (normal), 1 (slight widening), 2 (marked widening) on coronal images (d). All images are T1-weighted.

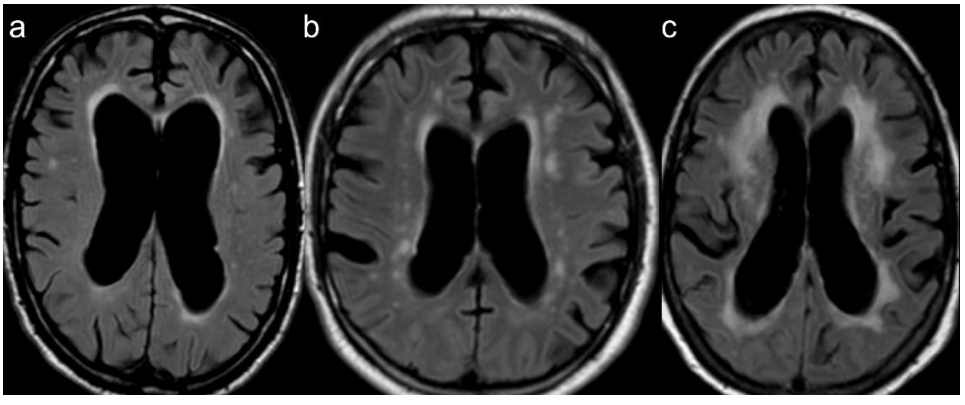

Figure 11. Periventricular and deep white matter hyperintensities graded as 1, 2, 3 according to the Fazekas scale on transaxial, T2-FLAIR images.

8.3.3 STUDY IV

In addition to the MRI-examination that all patients underwent as part of Study III, patients and control subjects included in Study IV were examined with additional sequences including:

1. A DSC perfusion sequence with images obtained every 1000 ms using a segmented k-space EPI technique: TE 30 ms, TR 500 ms, flip angle 40°, 12 slices, slice thickness 5 mm, no slice gap, covering the posterior fossa and upper brainstem area, in-plane resolution 1.8 × 1.8 mm, FOV 230 mm, 128 × 128 matrix. At the tenth acquisition a 5 ml/s bolus of 0.1 mmol/kg Gd-DTPA (0.5 mmol/ml, Magnevist, Schering, Berlin, Germany) immediately followed by a 10 ml saline flush administered in the right antecubital vein. The sequence was optimized for a high bandwidth in the phase encoding direction and scanning at a field strength of 1.5 T rather than 3 T to limit the postoperative, shunt-induced susceptibility effects.
2. A transverse DWI sequence: TR 3793 ms, TE 90 ms, 25 slices, slice thickness 5 mm, no slice gap, in-plane resolution 1.2 × 2 mm, FOV 230 mm, acquisition matrix 192 × 113, b = 0 s/mm^2 (1 acquisition) and b = 1000 s/mm^2 (average of 3 signal acquisitions) in 3 orthogonal encoding directions. ADC maps with a 256 × 256 matrix and a pixel size of 0.9 × 0.9 mm were calculated.

All patients and controls in Study IV were examined using the Gyroscan Intera 1.5 T system (Philips Healthcare, Best, the Netherlands).

REGIONS OF INTEREST

Regions of interest were drawn in two locations on the FLAIR images, one located in the upper part of the mesencephalon (Figure 12a) and one located two slices (approximately 6 mm) caudally in the pons (Figure 12b). Three ROIs were drawn in each location: a posterior, a middle and an anterior ROI, the middle and anterior ROI radially expanding from the posterior ROI (Figure 12 c and d). Each ROI was drawn in two consecutive slices in the FLAIR images in order to sufficiently cover one slice in the lower resolution, functional datasets. The posterior ROI was centered at the anterior and lateral aspect of the aqueduct in the mesencephalon and aligned with the anterior wall of the 4th ventricle in the pons. Each ROI had an in plane maximum depth of 6 voxels (approximately 5 mm), restricted by anatomical limitations, with no overlap to any other ROI. In addition, a composite ROI was created by

combining the three individual ROIs in each location. All analyses were performed both for the composite and the three separate ROIs in each location. In addition to the ROIs in the mesencephalon and pons, ROIs delineating grey matter in the occipital cortex were used as an internal reference in the calculation of perfusion estimates, as previously described.[230] All ROIs were created using ITK-Snap software.[278] Co-registration was performed using NiftyReg (School of Biomedical Engineering and Imaging Sciences, King's College London, The United Kingdom). All ROIs were drawn by a resident in radiology, with support from a senior neuroradiologist.

TRANSFER OF ROIS TO DIFFUSION AND PERFUSION DATA

In the transfer process, a mask was applied over areas containing CSF in order to limit the ROI to brain parenchyma. In addition, a vessel mask was applied to the perfusion data to avoid contamination from vessels. To ensure correct positioning off all ROIs, a manual evaluation was performed and if necessary, small adjustments were made. Due to different alignment and resolution of the FLAIR compared to the ADC and perfusion data, voxels were lost in the transfer process. The number of voxels in the final, individual ROIs are shown in Appendix 2. An example of the final ROIs after transfer and masking to the ADC-map (e, f) and perfusion data (g, h) is shown in Figure 12.

EXTRACTION OF DIFFUSION AND PERFUSION DATA

ADC maps were generated by fitting of a mono-exponential model to the DWI data, using the standard scanner software.[279] After transferring of the ROIs, ADC estimates were generated via a pixel-wise averaging of ADC values within each ROI.

For the perfusion estimates, an AIF was manually selected using in house developed software. The selection criteria for the AIF voxels have been described previously and were: 1. An early time of bolus arrival, 2. A steep initial signal decrease and 3. A deep signal dip.[230,280] To improve the SNR of the AIF, 1-4 voxels that fulfilled these criteria were averaged together. Deconvolution of the AIF with the CTTC of the target ROIs were performed using in house developed software, implementing the vascular model-based

single compartment de-convolution technique.[281] Model fitting was done via a Bayesian cost function and a Maximum Likelihood Expectation Maximization optimization scheme, in accordance with the original publication. CTTCs for each ROI were averaged before deconvolution and rCBF and rCBV measures were extracted by normalizing each CBF- or CBV-estimate with that of grey matter in the occipital lobe, using the reference ROIs.[230] Due to the potential overestimation of absolute perfusion values caused by inaccuracy of the AIF and factors affecting the transverse T2* relaxivity, relative CBF- and CBV-estimates were used.[138,142-147]

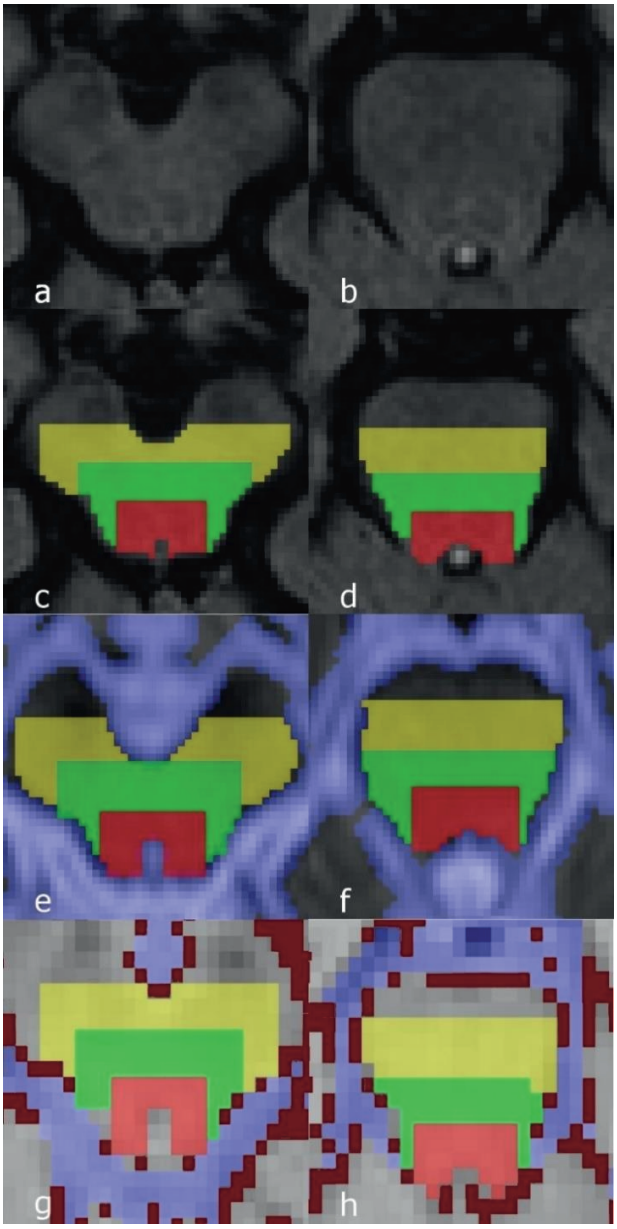

Figure 12. Example of the FLAIR images used for drawing ROIs (a, b), with the three individual ROIs applied (c, d). The same ROIs after masking and transfer to the ADC-map (e, f), and perfusion data with applied masks (g, h). Red = posterior ROI, green = middle ROI, yellow = anterior ROI.

8.4 STATISTICAL ANALYSIS

In study I, tests of frequencies and unadjusted odds were performed using the Pearson Chi^2 test. Due to the matched case-control design, the Cochran-Mantel-Haenszel was also performed to select variables for the regression analyses. As predetermined, all variables with an initial p-value of <0.1 were included for further analysis. The regression models were calculated using conditional logistic setup with separate models for the suspected iNPH- and HVe-group.

In Studies II-IV, all statistical tests were performed using nonparametric methods. Differences in distribution between binary variables were tested using the Pearson chi^2-test or Fisher's exact test, and differences in distribution between ordinal and continuous variables were tested using the Wilcoxon rank sum test. Distributions over time in binary variables were tested using the paired samples McNemar test while ordinal and continuous variables were tested using the Wilcoxon signed rank test. Correlation coefficients were computed using Spearman's rho. Regression models for prediction in studies II and III were calculated using a logistic setup adjusted for age and gender. For the reliability analyses in Study III, inter-rater and test-retest reliability were calculated using intraclass correlation coefficients (ICC 2,1) for continuous variables and weighted/unweighted Cohen's kappa for ordinal and nominal variables respectively.

In all studies, significance tests were 2-sided, and alpha was set to $p<0.05$. No corrections for mass significance were made. The statistical analyses were made using IBM SPSS Statistics version 22 (Study I), 23 (Study II) and 24 (Studies III-IV) (SPSS, Chicago, IL, USA).

8.5 ETHICAL CONSIDERATIONS AND APPROVAL

For Study I, informed consent was obtained from all participants and/or close relatives as part of the original population studies (see Figure 7):

- For the H70 cohort born in 1901-1902, ethical approval was available for the examinations performed in 1976 (DNR: §8,

ans nr. 52). Unfortunately, no approval was available for the follow-up examinations in 1988 and 1990, nor for the initial examinations performed in 1971. However, the cohort was followed regularly until 101 years of age, using the same methodology, with ethical permissions granted (e.g.: s102-97, r175-98, and ö424-00). We therefore consider the follow-up examinations performed according to good ethical order an in agreement with the Helsinki declaration.

- For the H70 cohort born in 1930, ethical approval was available for the examination performed in 2000 (377-99, 402-99, ad402-99).
- For the KVUS cohort born between 1908 and 1922, ethical permission was available for the initial examination performed in 1980 (65-80) and the follow-up examinations in 1992 (179-92, ad65-80) and 2000 (377-99, 402-99, ad402-99).
- For the NORA cohort born in 1915-1916, ethical approval was available for the initial exam performed in 1990-1991 (263-90) and for the follow-up examination in 1995 (s79-95).

For Studies II-IV, ethical approval was available from 1994 (387-94, s499-00, 596-03, 456-04, ad456-04, 154-05, 545-04, 020-07, 009-13, 328-14, 492-14), and written informed consent was obtained from all participants at the time of the original clinical exams. Prior to 1994, data was collected as part of the clinical quality control of treatment. The Ethics Committee for Medical Research at Gothenburg University approved all study applications.

9 RESULTS

9.1 STUDY I

Individuals with suspected iNPH had a higher frequency of hypertension, previous stroke/TIA, and moderate to severe WMLs compared to the matched controls (Table 6). The same vascular risk factors were more common in individuals with HVe who also had a higher prevalence of DM and obesity, although, this was only significant at trend level ($p<0.1$). In individuals with suspected iNPH, 92% (24/26) had a history of hypertension, DM, WMLs on CT or a combination thereof. In the group with HVe, 93% (51/55) had at least one of these risk factors.

A history of hypertension, stroke/TIA, and moderate to severe WMLs were significantly associated with suspected iNPH as well as HVe compared to matched controls in the univariate analyses (Table 7). In the multivariate, conditional logistic regression models, there was a significant association between moderate/severe WMLs and suspected iNPH while HVe was significantly associated with a history of hypertension, DM, and moderate/severe WMLs (Table 7).

Table 6. Frequency of vascular risk factors in individuals with suspected iNPH, HVe and matched controls.

	Suspected iNPH		**HVe**	
	Cases (n=26) % (n/N)	Controls (n=130) % (n/N)	Cases (n=55) % (n/N)	Controls (n=275) % (n/N)
Hypertension	42.9 (9/21)*	21.2 (25/118)	45.5 (20/44)*	26.9 (64/238)
Diabetes	13.0 (3/23)	7.6 (9/118)	17.0 (8/47)	8.9 (21/237)
Smoking	19 (4/21)	30.8 (36/117)	40.9 (18/44)	45.7 (107/234)
Stroke/TIA	56.5 (13/23)**	24.4 (29/119)	38.3 (18/47)*	21.1 (50/237)
CAD	18.2 (4/22)	11.0 (13/118)	25.5 (12/47)	24.1 (58/241)
Obesity	60 (3/5)	44.8 (43/96)	70.4 (19/27)	50.8 (99/195)
Moderate-severe WMLs	66.7 (16/24)***	17.5 (21/120)	52.1 (25/48)***	13.9 (33/237)

n = number of individuals with corresponding risk factors, N = number of persons examined for corresponding risk factor, N differs due to missing data. WMLs are graded using the Gothenburg scale 0-3,[276] 0-1 (none/mild) vs 2-3 (moderate/severe). * $p<0.05$ ** $p<0.01$, *** $p<0.001$. iNPH = idiopathic normal pressure hydrocephalus, HVe = hydrocephalic ventricular enlargement, TIA = transient ischemic attack, CAD = coronary artery disease, WMLs = white matter lesions.

Table 7. Unadjusted odds and results of the multivariate conditional logistic regression analysis of vascular risk factors in suspected iNPH and HVe.

	Suspected iNPH		**HVe**	
	Unadjusted OR	Multivariable OR	Unadjusted OR	Multivariable OR
Hypertension	3.8 (1.06-13.63)*	2.1 (0.5-8.7)	2.29 (1.18-4.45)*	2.7 (1.1-6.8)*
Diabetes	1.75 (0.43-7.16)		2.43 (0.98-6.05)[a]	4.3 (1.1-16.3)*
Smoking	0.56 (0.16-1.96)		0.76 (0.37-1.54)	
Stroke/TIA	4.03 (1.60-10.17)**	2.3 (0.7-7.8)	2.32 (1.19-4.52)*	0.8 (0.2-3.3)
CAD	2.8 (0.58-13.58)		1.09 (0.5-2.41)	
Obesity	1.85 (0.29-11.57)		2.30 (0.96-5.51)[a]	1.8 (0.6-5.4)
Moderate/severe WMLs	9.43(3.57-24.89)**	5.2 (1.5-17.6)**	6.72 (3.42-13.20)**	6.5 (2.1-20.3)**

Only variables with an initial $p<0.1$ are included in the multivariable analyses. [a] $p<0.1$, * $p<0.05$, ** $p<0.01$. iNPH = idiopathic normal pressure hydrocephalus, HVe = hydrocephalic ventricular enlargement, OR = odds ratio, TIA = transient ischemic attack, CAD = coronary artery disease, WMLs = white matter lesions.

9.2 STUDY II

9.2.1 THE CLINICAL PHENOTYPE OF iNPH

At the preoperative examination, 41% of the patients showed impairment in all domains to some degree, decreasing to 24% postoperatively ($p<0.0001$) (Table 8). Impaired gait was the most common initial symptom by patient report (41%), followed by balance (18%), cognition (12%) and continence (6%). Three percent reported other single neurological symptoms as appearing first, while more than one symptom appeared simultaneously in 18%. Two percent failed to report any initial symptoms.

Table 8. Number of affected symptom domains pre- and postoperatively in 273 iNPH-patients.

		Postoperative					
		4	**3**	**2**	**1**	**0**	**Total**
Preoperative	**1**			2	5	2	9
	2	1	4	7	6	1	19
	3	5	10	11	4	1	31
	4	18	9	9	4	1	41
	Total	24	23	29	19	5	

Numbers represent %. Shaded cells represent patients in whom no change occurred. P <0.0001 for change in distributions.

9.2.2 GAIT

Preoperatively, 90% had some degree of impaired gait, decreasing to 67% after shunt surgery (Figure 14a). Sixty-three percent of patients could walk independently without walking aids preoperatively (ordinal gait rating 1 or 2), increasing to 75% postoperatively ($p<0.0001$). Forty-four percent improved one or more steps on the ordinal gait scale ($p<0.0001$). In the quantitative gait tests, performance improved by 3 s (4 steps) in the 10m walking test and by 5 s (3 steps) in the TUG ($p<0.0001$ for all comparisons) (Table 10). Difficulties turning (n=313) were seen in 84% preoperatively, decreasing to 61% postoperatively and the median number of steps needed to execute a 180° turn decreased from 4 (IQR 3-6) to 3 (IQR 2-4) ($p<0.0001$).

Broad-based gait was the most common preoperative gait abnormality, followed by shuffling gait and freezing of gait. Postoperatively, the prevalence of all gait abnormalities decreased ($p<0.001$ for all comparisons) (Figure 13). The gait abnormalities were frequently seen together with shuffling of gait predominantly seen together with broad-based gait, and freezing of gait usually seen in conjunction with both other abnormalities. Postoperatively, patients were more likely to display only one type of gait abnormality (Table 9).

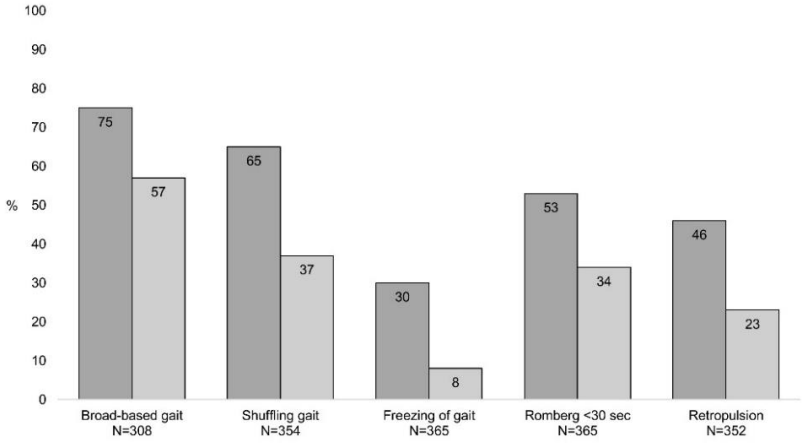

Figure 13. Pre- and postoperative prevalence of gait abnormalities, impaired balance, and retropulsion pre- and postoperatively in iNPH patients. $p<0.0001$ for all pre-post comparisons. N=number of included patients. The number of included patients differ due to missing data.

Table 9. Proportion (%) of iNPH patients with broad-based, shuffling or freezing of gait as single or multiple coexisting gait abnormalities pre- and postoperatively.

	Pre/Postoperative (%)						
	Single abnormality	+ Broad based gait	+ Shuffling gait	+ Freezing of gait	+ the two other abnormalities	Missing data	Total
Broad based gait (n=308)	23/43**		45/46	2/3**	28/6**	2/2	100/100
Shuffling gait (n=354)	5/15**	45/62**		6/4	28/8**	16/11	100/100
Freezing of gait (n=365)	1/4**	4/18**	17/18		58/36**	20/24	100/100

** $p<0.01$. n = number of patients. The number of included patients differ due to missing data.

9.2.3 BALANCE

Fifty-three percent of the patients had impaired balance at the preoperative examination, decreasing to 34% postoperatively (Figure 13), with the median test performance increasing from 20 (IQR 2-60) to 60 (IQR 20-60) seconds ($p<0.0001$). The prevalence of retropulsion was also significantly decreased at the postoperative examination (Figure 13). There were significant negative correlations between the Romberg test performance and the gait scale score pre- and postoperatively (R_s = -0.55 and -0.62, $p<0.001$ for both).

9.2.4 COGNITION

Preoperatively, 52% of the iNPH patients presented with impaired cognition, decreasing to 38% postoperatively ($p<0.0001$) (Figure 14b). The median MMSE-score increased from 25 (IQR 22-28) to 27 (IQR 24-29) ($p<0.0001$) and the daily need of sleep (n=305) decreased from 9 (IQR 8-11) to 8 (IQR 7-10) hours ($p<0.0001$). In the quantitative tests, performance improved by 1 point in the Bingley test and by 2 points in the identical forms test ($p<0.0001$ for both) (Table 10).

9.2.5 CONTINENCE

Eighty-six percent of the iNPH patients presented with impaired continence preoperatively, decreasing to 65% after surgery ($p<0.0001$) (Figure 14c). Forty-four percent needed to use continence aids at least temporarily or suffered from persistent incontinence (ordinal continence rating ≥ 4). Postoperatively this decreased to 31% ($p<0.0001$).

9.2.6 OTHER NEUROLOGICAL SIGNS

Paratonic rigidity (n=375) was seen in 73% preoperatively, decreasing to 59% after surgery ($p<0.0001$). In addition, cerebellar dystaxia (n=389) was present in 12% preoperatively, decreasing to 7% postoperatively ($p<0.001$). Focal neurological signs (n=313) and polyneuropathy (n=353) were seen in 25% and 34% respectively at the preoperative examination, with no significant changes after surgery.

9.2.7 OUTCOME

An overall postoperative improvement was seen in 68% (n=211), 23% (n=72) were unchanged and 9% (n=28) deteriorated. The composite symptom score increased by 18 points and the gait and cognition subscores increased by 23 and 10 points respectively ($p<0.001$ for all comparisons) (Table 10). Having symptoms from all domains and shuffling gait were significantly associated with clinical improvement in the multivariable regression analyses (OR=3.8, 95% CI 1.23-10.94, p=0.013 and OR=3.02, 95% CI 1.62-5.69, $p<0.001$).

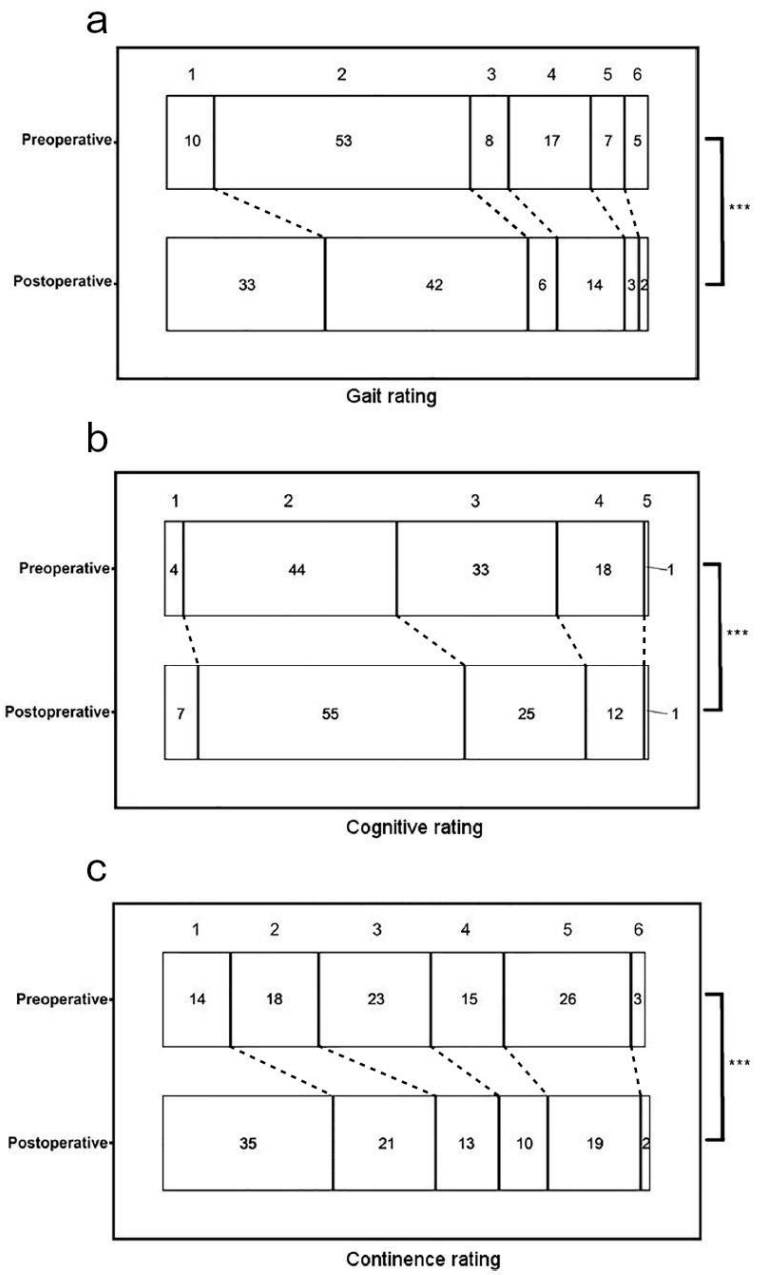

*Figure 14. Ordinal rating scales of gait, cognition and continence pre- and postoperatively in iNPH patients. Numbers within bars are %. *** $p<0.001$.*

Table 10. Quantitative tests of gait and cognition as well as gait, cognitive and composite scores pre- and postoperatively in iNPH patients

		Preoperative Median (IQR)	**Postoperative Median (IQR)**	**p**
Composite	Composite score (n=311)	38 (23-61)	56 (37-74)	<0.001
Gait	Gait score (n=311)	40 (17-63)	63 (37-83)	<0.001
	10 m, time (s) (n=322)	15 (12-20)	12 (9-15)	<0.0001
	10 m, steps (n=322)	23 (18-29)	19 (16-24)	<0.0001
	TUG, time (s) (n=247)	17 (12-24)	12 (10-17)	<0.0001
	TUG, steps (n=258)	20 (16-25)	17 (14-20)	<0.0001
Cognition	Cognition score (n=311)	40 (20-60)	50 (25-75)	<0.001
	Bingley's test (n=367)	4 (3-5)	5 (3-6)	<0.0001
	Identical forms test (n=337)	12 (15-19)	14 (19-21)	<0.0001

n = number of included patients. The number of included patients differ due to missing data. TUG = timed up and go.

9.3 STUDY III

9.3.1 THE PREOPERATIVE RADIOLOGICAL PHENOTYPE OF iNPH

At the preoperative examination, apart from an EI>0.3, all patients had a CC-angle <90° as well as a present flow void sign (Table 11). The CC-angle was <63° (suggested as an optimal cut-off value by Virhammar et al.) degrees in 39%, with no difference between responders and non-responders. A widening of the Sylvian fissures was present in 72% while 36% had obliterated sulci at the high convexity. All patients who had obliterated high convexity sulci also had widened Sylvian fissures, thus the presence of DESH was 36%. Focally widened sulci (transport sulci) were found in 28% and there was no difference in the prevalence between patients who had DESH and those who did not (data not shown).

Table 11. Preoperative morphological MRI findings in 168 patients with iNPH.

MRI marker, median (IQR)	**All iNPH patients (n=168)**	**Responders (n=115)**	**Non-responders (n=53)**	**p**
Evans' index	0.41 (0.37-0.44)	0.40 (0.38-0.44)	0.39 (0.37-0.43)	ns
Temporal horns (mm, mean)	9.1 (7.5-11.0)	9.0 (7.3-9.1)	9.1 (7.3-11.8)	ns
Third ventricle (mm)	15.5 (13.3-18.0)	15.4 (13.7-18)	16.5 (13.2-17.6)	ns
Fourth ventricle (mm)	14.7 (13.2-16.3)	14.7 (13.2-16)	14.6 (12.9-16.2)	ns
Callosal angle (°)	68 (56-81)	68 (55-80)	69 (58-82)	ns

Table continues on the next page.

Table 11. Continued from previous page.

MRI marker, % (yes/no)		All iNPH patients (n=168)	Responders (n=115)	Non-responders (n=53)	p
Flow void sign	0	0 (0/168)	0/115 (0)	0/53 (0)	ns
	1	30 (50/118)	30 (35/80)	26 (14/39)	
	2	42 (71/97)	37 (43/72)	47 (25/28)	
	3	28 (47/121)	35 (40/75)	27 (14/39)	
Dilated interhemispheric fissure	0	42 (71/97)	45 (52/63)	38 (20/33)	ns
	1	49 (82/86)	45 (52/63)	54 (29/24)	
	2	9 (15/153)	10 (12/103)	8 (4/49)	
Dilated sylvian fissures (mean)	0	28 (47/121)	31 (36/79)	22 (12/41)	ns
	1	45 (76/92)	45 (52/63)	46 (24/29)	
	2	27 (45/123)	24 (28/87)	32 (17/36)	
Obliterated sulci at vertex		36 (60/108)	36 (41/74)	35 (19/34)	ns
DESH		36 (60/108)	36 (41/74)	34 (18/35)	ns
Transport sulci	0	72 (121/47)	75 (86/29)	68 (36/17)	ns
	1	17 (29/139)	19 (22/93)	11 (6/47)	
	2	8 (13/155)	6 (7/108)	14 (7/46)	
	>2	3 (5/163)	0 (0/115)	7 (4/49)	
PVH	0	0 (0/168)	0 (0/115)	0 (0/53)	ns
	1	57 (96/72)	58 (67/48)	49 (26/27)	
	2	26 (44/124)	25 (29/86)	29 (15/38)	
	3	17 (29/139)	17 (20/95)	22 (12/41)	
DWMH	0	0 (0/168)	0 (0/115)	0 (0/53)	ns
	1	46 (77/91)	47 (54/71)	45 (24/29)	
	2	37 (62/106)	42 (48/67)	29 (15/38)	
	3	17 (29/139)	11 (13/102)	26 (14/39)	

ns = not significant, iNPH = idiopathic normal pressure hydrocephalus, IQR = interquartile range, PVH = periventricular hyperintensities, DWMH = deep white matter hyperintensities.

White matter lesions were found to some extent in all patients in both the periventricular and deep white matter (Table 11). While a majority of patients had mild (Fazekas grade 1) PVHs, mild to moderate (Fazekas grade 1 and 2) DWMHs were about equally as common, while extensive lesions (Fazekas grade 3) were seen less frequently. There were a few significant correlations between MRI findings and clinical symptoms, however all were weak (i.e. <0.3, Table 12).

Table 12. Correlations between preoperative MRI markers and clinical symptoms in patients with iNPH.

MRI marker	**Total symptom score**	**Gait score**	**Cognition score**
Evans' index	-0.09	-0-04	-0.12
Temporal horns	-0.30	0.1	-0.15*
Third ventricle	-0.19	-0.25*	0.07
Fourth ventricle	-0.20*	-0.20*	0.16
Callosal angle	0.17	0.13	0.16
Flow void sign	0.03	0.09	-0.03
Dilated interhemispheric fissure	-0.20	-0.04	-0.15*
Dilated sylvian fissures	-0.1	-0.15	0.08
Obliterated sulci at vertex	0.19	0.18	0.13
DESH	0.11	0.06	0.11
Transport sulci	0.07	0.18	0.08
PVH	-0.26*	-0.22*	-0.23*
DWMH	-0.22	-0.21	-0.17

* $p<0.05$. PVH = periventricular hyperintensities, DWMH = deep white matter hyperintensities.

9.3.2 OUTCOME

At the postoperative examination, 68% (n=115) of the patients were improved while 24% (n=39) were unchanged and 8% (n=14) deteriorated. There were no differences in demographic data, nor in the distribution of pre- or postoperative clinical scale scores between the patients with MRI examinations analysed in Study III and the remaining patients without complete MRI examinations included in Study II (data not shown).

There were no significant differences in the distribution of any of the preoperative MRI findings between responders and non-responders (Table 11). While responders had a numerically higher prevalence of moderate (Fazekas grade 2) DWMHs (42 vs 29%), the difference was not significant. No preoperative MRI finding could be used to predict clinical outcome after shunt surgery.

9.4 STUDY IV

9.4.1 CLINICAL OUTCOME

Seventy-five percent of the patients improved ≥5 points postoperatively on the iNPH scale and were categorized as responders. At the postoperative examination, one patient had developed a small chronic subdural hematoma. This patient was considered asymptomatic and the postoperative MRI-examination was included in the subsequent analyses.

9.4.2 DIFFUSION CHANGES

Patients with iNPH had lower ADC values in the composite ROIs in the mesencephalon and pons compared to controls preoperatively (Table 13). At the postoperative examination, ADC was further reduced in both ROIs. In the analysis of the smaller, individual ROIs ADC was reduced in the middle and anterior mesencephalic and pontine ROIs. Postoperatively, ADC was significantly reduced in all individual ROIs with further reductions compared to the preoperative examination except in the posterior ROIs in the mesencephalon and pons. In the comparison of responders and non-responders, pre- and postoperative ADC-values were similar. Responders, like the whole patient group, had a reduced preoperative ADC in all but the posterior ROIs in the mesencephalon and pons with further postoperative reductions. Numerically similar, albeit non-significant ADC changes were seen in the non-responders.

9.4.3 PERFUSION CHANGES

There were no differences in preoperative rCBF, rCBV or MTT between iNPH patients and control subjects in any ROI, nor any differences when comparing all patients' postoperative perfusion estimates to controls (Table 14). While no significant preoperative differences were found between responders and non-responders, responders had a significant postoperative rCBF increase with a higher postoperative rCBF in the composite mesencephalon and pons ROIs compared to non-responders, and controls. In addition, non-responders had a significant, postoperative reduction of rCBF in the mesencephalon. In the smaller individual ROIs, no significant pre- or postoperative differences

between groups were found. However, responders had a significant rCBF increase in the middle mesencephalic and pontine ROIs.

9.4.4 CORRELATIONS TO CLINICAL SYMPTOMS

There were no correlations between the ADC values in any ROI and clinical symptoms pre- or postoperatively, nor any correlations between the change in ADC and change in clinical symptoms in the whole patient group or either subgroup.

Likewise, no correlations between the pre- or postoperative perfusion estimates and clinical symptoms were found. However, the rCBF increase seen in the responder subgroup correlated significantly to the magnitude of clinical improvement in the mesencephalon (r_s=0.80, p=0.031) and pons (r_s=0.66, p=0.021 (Figure 15).

Table 13. Apparent diffusion coefficient (ADC) in controls and iNPH patients given for the composite as well as the individual ROIs in the mesencephalon and pons.

		ADC mm^2/s, % of control value, median (IQR)	
		Brain region	
Group		**Mesencephalon**	**Pons**
		Composite ROI	
Controls		n.a. 786 (762-823)	n.a. 766 (738-830)
All patients	Preoperative (n=20)	94, 737 (657-754)*	92, 706 (663-743)**
	Postoperative (n=16)	78, 617 (524-687)*	78, 597 (533-643)**
	Change (n=16)	-18, -140 (-208- -7)[a]	-12, -94 (-205 - -19)[a]
Responders	Preoperative (n=15)	93, 728 (621-752)*	91, 702 (619-738)**
	Postoperative (n=12)	79, 621 (525-721)*	78, 597 (538-642)**
	Change (n=12)	-16, -122 (-208-40)[a]	-13, -93 (-203- -9)[a]
Non-responders	Preoperative (n=5)	96, 754 (710-783)	96, 731 (693-776)
	Postoperative (n=4)	78, 611 (419-635)	76, 583 (402-670)
	Change (n=4)	-19, -154 (-351- -69)	-16, -120 (-374- -32)
		Posterior ROI	
Controls		n.a. 791 (775-846)	n.a. 773 (731-885)
All patients	Preoperative (n=20)	96, 762 (735-812)	97, 757 (713-775)
	Postoperative (n=16)	88, 697 (624-775)*	85, 660 (587-668)**
	Change (n=16)	-8, -68 (-130- -3)	-14, -109 (-174- -7)
Responders	Preoperative (n=15)	94, 744 (716-834)	99, 766 (666-776)
	Postoperative (n=12)	89, 706 (624-780)*	85, 660 (596-688)*
	Change (n=12)	-6, -45 (-117- -38)	-14, -109 (-174- -7)
Non-responders	Preoperative (n=5)	96, 766 (762-797)	96, 747 (742-807)
	Postoperative (n=4)	86, 685 (457-732)	80, 624 (427-705)
	Change (n=4)	-10, -112 (-314- -41)	-16, -133 (-386- -47)

Table continues on the next page.

Table 13. Continued from previous page.

		ADC mm^2/s, % of control value, median (IQR)	
		Brain region	
Group		**Mesencephalon**	**Pons**
		Middle ROI	
Controls		n.a. 795 (757-828)	n.a. 777 (728-815)
All patients	Preoperative (n=20)	92, 736 (664-759)*	89, 694 (620-740)**
	Postoperative (n=16)	78, 619 (514-694)*	76, 590 (515-634)**
	Change (n=16)	-15, -119 (-181- -4)[a]	-13, -105 (-222- -6)[a]
Responders	Preoperative (n=15)	90, 722 (620-762)*	88, 691 (611-723)**
	Postoperative (n=12)	77, 615 (514-742)*	75, 590 (528-629)**
	Change (n=12)	-13, -116 (-181- -44)[a]	-15, -105 (-188- -2)[a]
Non-responders	Preoperative (n=5)	92, 737 (697-760)	95, 745 (677-773)
	Postoperative (n=4)	78, 624 (419-639)	72, 554 (389-663)
	Change (n=4)	-14, -128 (-331- -43)	-18, -149 (-380- -20)
		Anterior ROI	
Controls		n.a. 766 (735-819)	n.a. 761 (739-802)
All patients	Preoperative (n=20)	89, 681 (546-767)*	89, 683 (602-730)**
	Postoperative (n=16)	70, 536 (436-592)*	70, 540 (462-612)**
	Change (n=16)	-25, -187 (-229- -12)[a]	-22, -155 (-257- -35)[a]
Responders	Preoperative (n=15)	78, 600 (518-763)**	85, 649 (599-722)**
	Postoperative (n=12)	71, 545 (436-622)**	70, 540 (466-611)**
	Change (n=12)	-19, -136 (-225- -11)[a]	-19, -197 (-256- -35)[a]
Non-responders	Preoperative (n=5)	99, 759 (652-805)	93, 710 (642-760)
	Postoperative (n=4)	66, 503 (374-558)	72, 554 (389-642)
	Change (n=4)	-33, -221 (-413-11)	-21, -128 (-356- -6)

* $p<0.05$ compared to controls, ** $p<0.01$ compared to controls, [a] $p<0.05$ for change between pre- and postoperative ADC. IQR = interquartile range, n.a. not applicable.

Table 14. Relative cerebral blood flow (rCBF) values in controls and iNPH patients given for the composite as well as the individual ROIs in the mesencephalon and pons.

		rCBF, % of control value, median (IQR)	
		Brain region	
Group		**Mesencephalon**	**Pons**
		Composite ROI	
Controls		n.a. 0.84 (0.79-0.91)	n.a. 0.72 (0.67-0.81)
All patients	Preoperative (n=20)	101, 0.86 (0.77-0.97)	95, 0.69 (0.64-0.81)
	Postoperative (n=16)	106, 0.91 (0.81-0.98)	111, 0.82 (0.71-0.86)
	Change (n=16)	2, 0.02 (-0.01-0.11)	7, 0.06 (-0.02-0.16)
Responders	Preoperative (n=15)	101, 0.86 (0.77-0.93)	95, 0.69 (0.61-0.77)
	Postoperative (n=12)	109, 0.93 (0.88-1.01)*	113, 0.83 (0.73-0.86)*
	Change (n=12)	6, 0.05 (0.01-0.16)[a,b]	11, 0.07 (0.04-0.21)[a,b]
Non-responders	Preoperative (n=5)	106, 0.90 (0.74-1.02)	104, 0.77 (0.68-0.94)
	Postoperative (n=4)	92, 0.78 (0.67-0.87)	100, 0.73 (0.61-0.85)
	Change (n=4)	-14, -0.12 (-0.17- -0.02)	-7, -0.05 (-0.2- -0.02)
		Posterior ROI	
Controls		n.a. 0.74 (0.68-0.83)	n.a. 0.56 (0.53-0.63)
All patients	Preoperative (n=20)	108, 0.80 (0.71-0.91)	98, 0.55 (0.43-0.60)
	Postoperative (n=16)	112, 0.83 (0.73-1.01)	109, 0.61 (0.52-0.79)
	Change (n=16)	4, 0.03 (-0.12-0.22)	11, 0.06 (-0.01-0.19)
Responders	Preoperative (n=15)	109, 0.81 (0.70-0.91)	95, 0.53 (0.43-0.57)
	Postoperative (n=12)	112, 0.83 (0.74-1.01)	109, 0.61 (0.52-0.73)
	Change (n=12)	3, 0.02 (-0.10-0.25)	14, 0.08 (0.04-0.21)
Non-responders	Preoperative (n=5)	104, 0.77 (0.67-0.91)	117, 0.66 (0.57-0.72)
	Postoperative (n=4)	104, 0.77 (0.61-0.95)	125, 0.70 (0.50-0.88)
	Change (n=4)	0, 0.00 (-0.15-0.17)	8, 0.04 (-0.07-0.11)

Table continues on the next page.

Table 14. Continued from previous page.

		rCBF, % of control value, median (IQR)	
		Brain region	
Group		**Mesencephalon**	**Pons**
		Middle ROI	
Controls		n.a. 0.84 (0.77-0.91)	n.a. 0.78 (0.72-0.89)
All patients	Preoperative (n=20)	99, 0.83 (0.76-0.95)	94, 0.73 (0.67-0.88)
	Postoperative (n=16)	100, 0.84 (0.73-0.94)	109, 0.85 (0.71-0.94)
	Change (n=16)	1, 0.01 (-0.06-0.12)	15, 0.12 (0.05-0.21)
Responders	Preoperative (n=15)	98, 0.82 (0.75-0.88)	90, 0.70 (0.63-0.86)
	Postoperative (n=12)	105, 0.88 (0.81-0.98)	112, 0.87 (0.79-0.96)
	Change (n=12)	7, 0.06 (0.01-0.17)[a,b]	22, 0.17 (0.03-0.25)[a,b]
Non-responders	Preoperative (n=5)	102, 0.85 (0.73-1.03)	106, 0.83 (0.72-1.01)
	Postoperative (n=4)	80, 0.67 (0.59-0.76)	86, 0.67 (0.62-0.77)
	Change (n=4)	-22, -0.17 (-0.29- -0.08)	-20, -0.16 (-0.26-0.02)
		Anterior ROI	
Controls		n.a. 0.89 (0.81-1.1)	n.a. 0.83 (0.78-0.92)
All patients	Preoperative (n=20)	100, 0.89 (0.82-1.02)	97, 0.81 (0.74-0.92)
	Postoperative (n=16)	106, 0.94 (0.89-1.04)	106, 0.88 (0.77-0.94)
	Change (n=16)	6, 0.05 (-0.13-0.10)	9, 0.07 (-0.05-0.13)
Responders	Preoperative (n=15)	100, 0.89 (0.85-0.99)	98, 0.81 (0.75-0.91)
	Postoperative (n=12)	107, 0.94 (0.91-1.07)	106, 0.88 (0.81-0.94)
	Change (n=12)	7, 0.05 (0.01-0.15)	8, 0.07 (0.01-0.22)
Non-responders	Preoperative (n=5)	108, 0.97 (0.74-1.21)	95, 0.79 (0.73-1.15)
	Postoperative (n=4)	94, 0.84 (0.74-1.02)	96, 0.80 (0.67-0.95)
	Change (n=4)	-14, -0.13 (-0.22- -0.01)	1, 0.01 (-0.26-0.04)

* $p<0.05$ compared to controls, [a] $p<0.05$ for change between pre- and postoperative rCBF, [b] $p<0.05$ compared to the rCBF change in non-responders. IQR = interquartile range, n.a. not applicable.

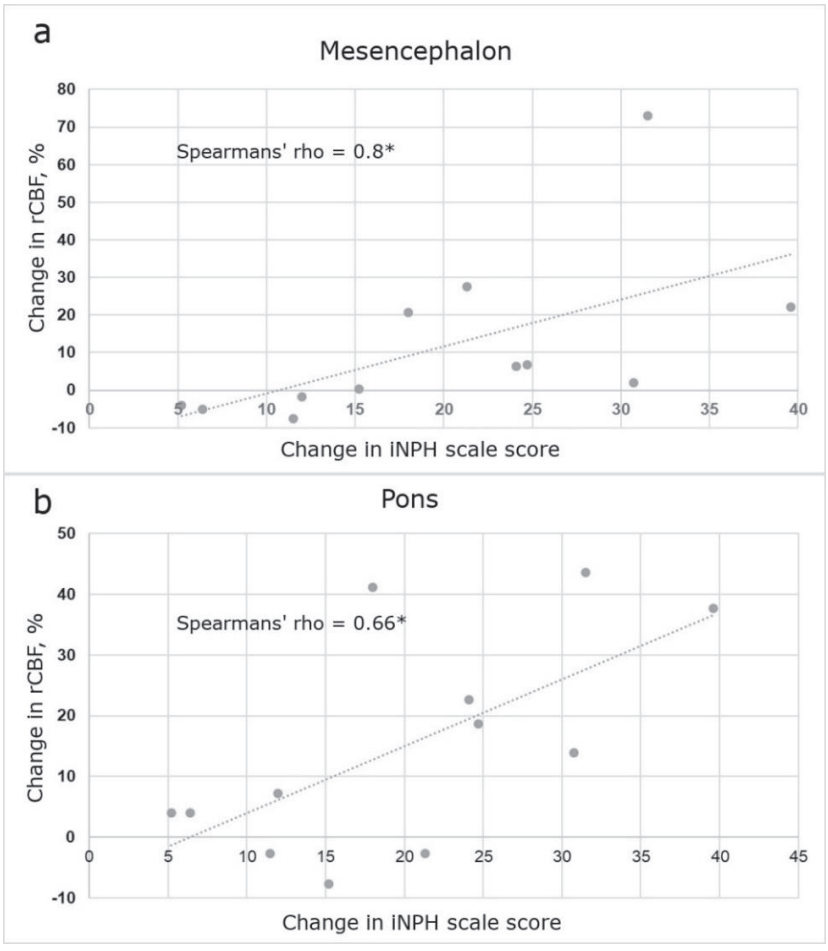

*Figure 15. Correlations between change in relative cerebral blood flow (rCBF) in the mesencephalon (a) and pons (b) and the change in the iNPH scale score in responders. * $p<0.05$.*

10 DISCUSSION

10.1 THE ROLE OF VASCULAR FACTORS IN THE PATHOPHYSIOLOGY OF iNPH

While the support for an involvement of vascular changes and risk factors in the development of iNPH has been growing steadily over the years, there has been a lack of epidemiological studies to confirm the findings of previous hospital-based studies.[110,244-247] Study I investigated the prevalence of vascular risk factors and WMLs on CT, and their association to clinical and radiological signs of iNPH in a large, population-based cohort. In accordance with previous studies,[110,244-247] hypertension, DM, and moderate to severe WMLs were associated with radiological findings of iNPH (HVe). In addition, the significant association with moderate to severe WMLs was retained in the smaller group with suspected iNPH, indicating the involvement of these vascular risk factors in the disease development. A similar prevalence of hypertension, DM and WMLs on MRI was found in the hospital-based patient sample used in Studies II-III which also corroborate earlier findings.[157,176,178]

However, while the presence of vascular risk factors is a well-established cause of WMLs and ischemic injury, the changes seen in iNPH are likely caused by a combination of several factors indicating other possible mechanisms of action of these risk factors as well.[157,176,178] Supporting this notion to some extent, hypertension and DM were associated to HVe, independently of WMLs in Study I. Even though this association did not remain in the analysis of the smaller group with suspected iNPH, this could be explained by type II statistical errors, caused by the small number of cases included in the analysis. The association between hypertension, DM and HVe supports results presented by Graff-Radford et al., where the authors assessed the prevalence of increased systolic- and pulse pressure in a population-based cohort and found associations between both and ventricular size.[251] Similar findings have also been reported in animal studies,[249,250] and it has been suggested that the ventricular enlargement in iNPH could be caused partly by increased pulse-pressure transmitting to the ventricular system secondary to an increased stiffness and reduced elasticity of large blood vessels.[282] Additionally, vascular risk factors might be involved in the development of iNPH by affecting the glymphatic system.[243] In several recent studies, CSF-inflow to the ECS has

been shown to occur via the para-arterial spaces of the penetrating arterioles,[35,37,39] and hypertensive rats show an impaired glymphatic transport.[260]

While the potential mechanisms of action of these risk factors are beyond the scope of this thesis, and causal relationships are impossible to determine due to the cross-sectional study designs, study I still adds further support for the involvement of vascular risk factors in iNPH by confirming the previously reported associations in a population-based cohort. Recognizing the presence of these vascular risk factors in the clinical setting is important as they are treatable.

10.2 THE CLINICAL AND RADIOLOGICAL PHENOTYPE OF INPH

10.2.1 CLINICAL PHENOTYPE

While individual symptoms in iNPH have been studied in detail both pre and postoperatively, symptom combinations and their changes after surgery are less studied and need further elucidation.[2,4,10,42,43,49,51,55,61,63] In Study II, the clinical phenotype in iNPH and the change in individual symptoms as well as symptom groups after shunt surgery were investigated. Even though most patients report initial symptoms from a single symptom group, a majority are found to have symptoms in at least three out of four cardinal domains at the clinical examination. This corroborates earlier results,[3,10] and emphasizes the importance of a thorough clinical examination as part of the diagnostic workup. Shunt surgery results in a general symptom improvement in most observed symptoms, indicating the effectiveness of the treatment method.[5,8,10,96,99] However, it is important to note that despite the general improvement, as shown in Study II, most patients do not experience a full reversal of symptoms, potentially due to the natural course of the disease causing irreversible neurological damage.[10,70,283] Thus, an early diagnosis and treatment are vital.

In agreement with previously published results,[3,10,42,66,71,74] gait impairment is the most common symptom in iNPH, found to some extent in at least 90% of the patients in Study II. Typically, the gait is broad-based and shuffling while

a smaller group of patients also experience sudden freezing of gait. Interestingly, the abnormalities seem to appear in sequence. Broad based gait was seen as the only abnormality in about 20% but shuffling and freezing of gait was rarely seen in isolation and freezing of gait appeared almost exclusively together with both other abnormalities. After surgery, all abnormalities were more likely to appear in isolation, and their prevalence decreased significantly. Even if no significant associations between the presence of any gait abnormality or combination thereof and the severity of the gait disturbance were found, the sequence in which the abnormalities appear could mirror the progression of the disease.

Impaired balance was found in a majority of patients in Study II, corroborating previously published results.[50,51] The frequent coexistence of gait and balance impairments can make differentiating between them difficult, as has been shown previously.[48] However, even if the areas of origin might be different, both lead to the same clinical result, i.e. a functional impairment that significantly affects ambulatory performance, as seen in the quantitative 10m-walking and TUG tests. It is also important to note that the level of dysfunction in the TUG test preoperatively is severe enough to result in an increased risk of falling.[54] Of the recorded gait abnormalities, broad-based and shuffling gait might also, at least in part be the result of a primary postural disturbance, arising as compensatory mechanisms for the backward leaning posture and axial instability in order to enable continued walking.[48]

Unfortunately, cognitive and urinary function could not be evaluated in detail, but the results of Study II is in line with previous studies and highlights the profound variability of symptom severity at the preoperative examination, ranging from minor disabilities to severe impairment in all domains. Patients also exhibit an increased need of sleep, indicative of a general impairment of wakefulness, a finding that has been reported earlier and correlated to a reduced rCBF in the anterior cingulate gyrus.[59] Although, as suggested by the results from Study IV, impaired wakefulness could also hypothetically arise from disturbances affecting the brainstem. In addition to disturbances in the four cardinal domains, paratonia was present in most patients preoperatively and responded well to shunt surgery. This neurological sign has been reported previously in iNPH, although, interestingly, the reported prevalence in the present study is higher.[42,43] This might be due to different methods of

assessment, but could also imply that paratonia is more common in iNPH than previously thought. Regardless, these findings combined with previous evidence suggests that paratonia should be considered a core symptom in iNPH.

10.2.2 RADIOLOGICAL PHENOTYPE

Ever since the first description of iNPH in the 1960s,[2] enlarged ventricles is considered a hallmark sign of the disease and a requirement for the diagnosis. As expected, all patients in Study III had an EI >0.3 but also an enlargement of the 3rd and 4th ventricles, in agreement with a previous study by Wikkelsö et al, indicating the potential involvement of infratentorial structures in iNPH.[167] The temporal horns were also widened in agreement with the American-European guidelines as well as previously published results.[3,69,167] Also similar to previous studies,[69,88,172] a CC-angle <90 degrees was present in all patients.[88,163,172] As previously stated, the CC-angle cutoff of >40 degrees mentioned in the American-European guidelines[3] is confusing and should be questioned. All patients had some degree of WMLs, both in the PVH and DWMH reinforcing the diagnostic, albeit unspecific value of this finding in the disease.[3,74,176,177]

The combination of a dilatation of the Sylvian fissures and compression of sulci at the high convexity (DESH), has been reported as a very common, hallmark finding of iNPH with a prevalence of more than 70% in some studies.[18,74,156] The Japanese guidelines also suggest dividing iNPH into DESH and non-DESH subtypes.[74] In Study III, the prevalence of DESH was just over 35%, a drastically lower number than previously reported. Some of this difference might be explained by the grading of sulcal compression at the high convexity where a complete obliteration was required in Study III. Still, similar prevalence numbers have been reported by Craven et al.,[191] and recently, by Ahmed et al.,[192] and it seems that while a subset of patients with iNPH have findings of DESH, this should, by no means be required for the diagnosis. Focally dilated (transport) sulci were found in about 25% of patients, similar to the prevalence reported by Wikkelsö et al.[167] While the transport sulci might develop due to the same disturbances causing DESH, no difference in the prevalence of transport sulci was found between DESH and non-DESH patients, thus the two findings might not be as closely related as previously proposed.[74,167]

10.2.3 CORRELATIONS BETWEEN CLINICAL SYMPTOMS AND RADIOLOGICAL FINDINGS

Although significant correlations between the presence of WMLs and symptom severity as well as between the size of the 3rd and 4th ventricles and the severity of gait existed, all were weak (i.e. $r_s<0.3$). This differs from results reported by Kockum et al. comparing the total iNPH Radscale score to clinical severity using the Hellström iNPH scale.[66,88] However, differences in statistical methodology, study population and measurements used makes a direct comparison difficult.[88] The low and mostly insignificant correlations found in Study III indicate that there is no clear association between the preoperative radiological phenotype and the severity of clinical symptoms, probably due to the large symptom variability seen in the patient group. While morphological MRI markers are important in determining the presence of ventriculomegaly and can support the diagnosis of iNPH by demonstrating other features found in some patients, these other features should not be required for the diagnosis of the disease.

10.3 SURGICAL OUTCOME AND PREDICTION

While the number of improved patients in Study II and III in this thesis is lower compared to some other studies,[7,8,10,12,91,93,94] the lower percentage of improved patients can probably be explained by the large inclusion interval and use of different outcome measurements. It is also important to note that despite the lower number of patients classified as improved, symptom severity was reduced across all domains in most patients. In addition, only 9% showed a progression of symptoms at the postoperative follow-up, indicating that shunt surgery can be beneficial not only in patients who improve, but also in the patient group where a continued progress of symptoms can be prevented, as has been suggested earlier.[99,283]

10.3.1 CLINICAL MARKERS

In the evaluation of clinical markers as outcome predictors, having symptoms from all four cardinal domains and the presence of shuffling gait at the preoperative examination were significantly associated to postoperative improvement in Study II. Black et al. found similar results regarding the number of affected domains,[71] but this has also been questioned in a more

recent study by Pujari et al.[11] This finding can be viewed as somewhat expected given the improvement across all domains seen postoperatively, but further reinforces the need for careful clinical evaluation of patients with suspected iNPH. The connection between shuffling gait and postoperative improvement is interesting and could indicate that this gait abnormality has the most specific association to iNPH, although the high coexistence between the different baseline features means that covariance potentially masking significant results cannot be ruled out. As such, the results have to be interpreted carefully. This is especially true regarding the high coexistence of broad-based and shuffling gait.

Shunt surgery results in a reduction of symptom severity across all domains and preoperative disease severity does not negatively impact the postoperative improvement rate. Importantly, while more pronounced preoperative symptoms have been found to increase mortality, the patients who improved postoperatively had a significantly lower mortality comparable to control subjects.[99] As such, care should be taken not to exclude patients with severe clinical symptoms from surgery.

10.3.2 MORPHOLOGICAL MRI-MARKERS

We found no between-group differences in the prevalence or severity of preoperative morphological MRI-markers in Study III. This is in agreement with previous work regarding the EI and flow void sign.[69] Interestingly, contrary to the findings by Virhammar et al. and Grankhe et al.,[69,172,190] the CC-angle had no predictive utility in Study III, and the prevalence of an angle below 63° (suggested as an optimal cutoff by Virhammar et al.) was similar in responders and non-responders. While differences in the outcome measurements and inclusion criteria might explain this discrepancy, Kojoukhova et al. and Narita et al. also found the CC-angle to be of no predictive value, supporting the results presented here.[189,193]

There was also no difference in the prevalence of DESH between responders and non-responders in Study III, resulting in no predictive utility. Of the studies supporting the predictive value of DESH, it is important to note the different clinical outcome measurements used as well as different inclusion criteria. Notably, three studies in support of DESH as a predictor of outcome

required markedly different or non-standard findings for inclusion of patients. Garcia-Armengol et al. only included patients >60 years of age who had present B-waves in >10% of intracranial pressure monitoring readouts,[188] Hong et al. applied the American-European guidelines but excluded patients with severe WMLs,[187] and Narita et al., while using compression of sulci at the high convexity as the chosen predictive marker required the presence of DESH for inclusion in the study.[189] Using inclusion criteria similar to the criteria in Study III, Virhammar et al. did find DESH and dilated temporal horns to be significant predictors of outcome, although the outcome measurement used was somewhat different to the outcome measurement in the present study.[69]

Contradicting these results and in support of the findings in Study III, several studies found DESH to be of no predictive utility.[191-193] Outcome measures differ between these studies as well, but the use of inclusion criteria based on the American-European guidelines makes them more comparable to the results in the present study. Dilatation of the temporal horns as a predictive marker is sparsely studied, with conflicting results.[69,167] Combined with the results from the present study, the role of these morphological biomarkers for predictive purposes remain unclear.

Regarding WMLs, the results of Study III corroborate previously published results showing no predictive value of these markers. Notably, in agreement with Tullberg et al. and Tisell et al., even the presence of severe WMLs does not affect the rate of postoperative improvement.[176,177] While the cause of WMLs in iNPH is still incompletely understood, as outlined above, multiple mechanisms are probably involved, and the severity of WMLs should not be used to exclude patients from shunt surgery.

10.4 THE ROLE OF THE MESENCEPHALON AND PONS IN iNPH

In the analysis of the clinical phenotype of iNPH in Study II, 15% of patients presented with cerebellar dystaxia at the preoperative examination. Postoperatively, the prevalence was significantly lower. Interestingly, cerebellar dystaxia, together with several other symptoms that have been previously described in iNPH and that were seen in Study II could potentially arise due to changes in the mesencephalon, pons and cerebellum. In experimental and clinical studies of PD, freezing of gait, parkinsonian rigidity and disturbances in postural control have all been linked to the PPN in the mesencephalic tegmentum.[262,284,285] In Study II, clinical symptoms of paratonia and retropulsion were seen in most patients, and freezing of gait was found in about 1/3 preoperatively. In addition, the increased need of sleep seen in Study II as well as in previous studies could hypothetically be linked to changes in the same areas.[59,264] Further, detailed studies on urinary tract dysfunction in iNPH have suggested the possible involvement of the pontine micturition centers in the disease.[63,222] Although the crude measurement of urinary function in Study II does not allow for any precision characterization of this symptom area, the widespread disturbance of urinary function in the patient group combined with the other clinical signs potentially arising from the brainstem is very interesting.

Similar to the results found by Wikkelsö et al.,[167] patients in Study III had a general widening of the ventricular system, not restricted to the lateral ventricles, strengthening the hypothesis of the potential involvement of periventricular structures not only adjacent to the lateral ventricles but also the 3rd and 4th ventricles. Also supporting the involvement of these areas, two earlier studies found reductions of midbrain diameters in iNPH with increasing size postoperatively correlating to gait improvement.[165,184] However, the studies had some methodological issues, and the results have been questioned.[185]

Study IV investigated ADC and perfusion changes in the midbrain and pons in iNPH. Contrary to most previous studies on supraventricular structures, ADC was significantly lower in the patient group preoperatively. Preoperative ADC in the brainstem has only been sparsely investigated previously. Tullberg et al.

found no differences between iNPH patients and controls using ROIs approximately situated in the periaqueductal gray matter,[201] and Reiss-Zimmermann et al. found an increased MD in the CST in the mesencephalon, caused mainly by an increase in principal diffusion.[198] While the results reported by Reiss-Zimmermann are more in line with changes reported in supratentorial white matter,[180,197,199,200] the ROIs in Study IV include both gray and white matter which, combined with technical differences could explain the different results seen in Study IV. Hypothetically, the pathophysiological changes in iNPH might have different effects on gray and white matter with a water increase in the ECS, even if general, being more prevalent in the later. Also, WMLs are more common supratentorially.[111] As WMLs in iNPH are most likely caused by a combination of factors, among them ischemic injury, this could, in part explain the reported ADC-increase in white matter and the only partial, postoperative reversibility. Instead, relating to the theories on glymphatic dysfunction in iNPH,[243] and the altered metabolite clearance proposed by biochemical studies,[72,78] factors that would act to reduce ADC, such as a lowered protein clearance and metabolic changes could be more prevalent in the gray matter and in the mesencephalon and pons, as has been suggested earlier.[201]

The postoperative ADC reduction seen in study IV corroborates most previous studies on supratentorial structures, although the postoperative ADC values reported here are lower. Again, the numerical differences might be due to different tissue properties of white and gray matter, although this needs further investigation. As shunt surgery is thought to reduce the amount of extracellular water and water along axons, as well as potentially improving the clearance of proteins from the ECS, it seems reasonable that this could happen in the mesencephalon and pons as well. While a few studies have found significant correlations between the rate of postoperative ADC reduction and clinical improvement in supratentorial white matter,[199,201] no between-group differences or correlations between ADC and clinical symptoms were found in Study IV. This might indicate that the ADC change is predominantly mirroring the mechanistic effect of shunting, not symptom reversibility, at least in infratentorial structures.

No preoperative perfusion differences between iNPH patients and controls were found in Study IV. This might be due to the small study sample and use

of relative perfusion measurements. As a general perfusion impairment has been shown in iNPH,[59,230] this might affect the chosen internal reference ROI resulting in falsely high relative measurements. While estimation of absolute perfusion measures could alleviate this potential confounder, DSC-MRI still suffers from problems of overestimation and large inter-subject variability making the application and interpretation difficult, despite recent advances.[148-150] Support of a microcirculatory/metabolic disturbance in supratentorial areas in iNPH is evident in multiple previous studies on perfusion in supratentorial structures.[59,218,223,224,232,233] While perfusion alterations in infratentorial structures has only been sparsely investigated, the findings of a preoperative rCBF reduction in the mesencephalon by Tullberg et al. and a CBF reduction in the cerebellum by Owler et al. support the involvement of these areas as well.[59,220]

Further supporting the involvement of perfusion alterations in iNPH and indicating that these measurements might reflect the degree of clinical reversibility, the rate of postoperative CBF/rCBF improvement has been associated to the degree of clinical improvement in several studies.[59,223,224,232] Similar to this, responders in Study IV showed a significant correlation between the magnitude of rCBF increase and the rate of clinical improvement in both the mesencephalon and pons, indicating the involvement of these areas in the symptom generation and symptom reversibility in iNPH. In addition, postoperative rCBF values in responders were significantly higher compared to the control values, a finding that could indicate the importance of these areas in re-establishing normal physiological function. While so far, only Ziegelitz et al. have found preoperative perfusion differences between responders and non-responders with a predictive value,[230] further investigations focusing on perfusion changes in general as well as the mesencephalon and pons are needed.

In summary, both the presence of specific clinical symptoms as well as diffusion and perfusion alterations measured with MRI can be seen to indicate the involvement of the mesencephalon and pons in iNPH. Further studies of these areas could provide additional insight in the development of the disease as well as in the continued search for predictive imaging biomarkers.

10.5 METHODOLOGICAL CONSIDERATIONS

10.5.1 STUDY I

The main strength of Study I is the large, population-based study sample where cases and controls were recruited from the same population and subjected to a nested case-control study. This reduces the risk of selection bias compared to several previous studies using hospital-based samples. In addition, data on vascular risk factors was prospectively collected from the National Swedish Inpatient Register as well as from comprehensive clinical data.

However, several limitations also need to be considered. The diagnostic accuracy was diminished due to the fact that the diagnosis of suspected iNPH was, to some extent based on self-report and made retrospectively. In addition, the criteria used for diagnosis likely resulted in patients with mild symptoms of iNPH not being included. The same is true for the CT-assessments, although a recent publication found good agreement between CT and MRI regarding morphological markers of iNPH,[89] and the difference between CT and MRI in detecting clinically relevant WMLs has been questioned.[286] Nevertheless, in spite of potential diagnostic bluntness, several strong associations between vascular risk factors and HVe were found. It is also important to recognize that the small sample of cases, both in the suspected iNPH group and the group with HVe probably affects the outcome estimates, and larger case samples would have been preferable in order to provide more precise estimates. Lastly, the cross-sectional design does not allow for causal interference regarding the relationship between vascular risk factors, WMLs and iNPH. However, when seen in conjunction with earlier studies, the results reinforce the theory of an involvement of vascular pathology in the disease.

10.5.2 STUDIES II-III

The main strengths of Studies II and III are the large, prospectively included patient group and detailed clinical evaluation performed pre- and postoperatively. In addition, the diagnosis of iNPH was made in accordance with the American-European guidelines and was therefore not based on the presence of most evaluated clinical and radiological markers, and outcome was measured using continuous measurements normalized to the performance of healthy 70-year old individuals. While this meant that only disturbances

affecting gait, balance and cognition could be included in the outcome measure it adds robustness to the ability of the measurement to detect significant clinical improvement. Lastly, all preoperative MRI-examinations in Study III were realigned to the callosal plane before the analyses in order to minimize the effects of possible misalignment.

Several limitations also need to be addressed. The retrospective designs and large inclusion time interval meant that missing data was present in almost all clinical variables, something that especially reduced the patient sample that could be used in the outcome analyses. Similar to this, a group of patients had to be excluded from Study III as they lacked preoperative MRIs of sufficient quality. However, no significant differences in demographic data existed between included and excluded patients in any analyses in Study II, and the patients excluded from Study III did not differ in outcome score compare to the included patients. Several clinical and radiological measurements are subjective with a lack of standardized assessment methods. This could influence the results and explain the prevalence differences compared to other studies, at least to some extent.

It is also important to note that due to the diagnosis of iNPH being based on the American-European guidelines, results from these studies might not be directly comparable to patient cohorts diagnosed using the Japanese guidelines, as the different clinical and radiological diagnostic criteria are likely to affect the resulting patient populations. Lastly, while the influence of other, coexisting disorders that could potentially influence the results cannot be ruled out. However, the diagnosis of iNPH was made only in the absence of other factors more likely to explain the clinical and radiological findings.

10.5.3 STUDY IV

Like in Studies II and III, the included patients were subjected to a detailed clinical evaluation pre and postoperatively using a standardized protocol, which, for this subgroup also included the iNPH scale by Hellström et al.[66] Another strength is the use of a single MRI scanner for all scans, including the controls. Lastly, the DSC-MRI pulse sequence was specifically designed to minimize postoperative shunt artefacts in order to obtain perfusion estimates postoperatively.

The main limitation is the small study sample, reducing power and increasing the risk of type II statistical errors. In addition, the low SNR at 1.5T combined with the low amount of diffusion vectors could potentially further mask between-group differences in the analyses of ADC. It is also impossible to rule out artefacts affecting the postoperative evaluations, especially regarding the analysis of ADC, although patients with visible artefacts were excluded from the postoperative examinations and the anatomical distance between the shunt and areas of interest are similar to previously published studies.[201,230]

11 CONCLUSIONS AND FURTHER PERSPECTIVES

Vascular risk factors, especially hypertension and DM as well as WMLs are likely important in the development of iNPH. However, while small vessel ischemic injury, seen as part of the WMLs seems to be involved to some degree, other mechanisms that cause, at least initially reversible changes related to the CSF dynamic disturbance, ventricular enlargement and hypothetically, metabolic and microvascular dysfunction are most probably involved as well. Regardless, the strong association between hypertension, DM and radiological as well as clinical signs of iNPH, in conjunction with previously published data from clinical, epidemiological and radiological studies support a causal relationship between vascular dysfunction and the development of iNPH. Management of these risk factors could prove important from a preventive perspective. There remains a need for prospective studies on vascular risk factors, vascular changes in the brain and the development of iNPH, preferably using large study groups and several points of prospective data acquisition. Functional MRI-analyses of diffusion and perfusion would be useful if integrated in these types of studies.

iNPH patients present with a collection of clinical symptoms that are present in most and identifiable by detailed clinical examination. In addition to the previously defined four cardinal symptom groups, other neurological symptoms are common, i.e. paratonia and impaired wakefulness, and should be considered core parts of the iNPH symptomatology. Notably, the symptom severity at the time of diagnosis differs substantially between patients, but more pronounced symptoms do not reduce the chance of postoperative clinical improvement and should not be used as a criterion when selecting patients for shunt surgery. Shunt surgery leads to broad symptom improvements in most patients and constitutes an effective treatment option, although it is important to recognize that only a minority of patients experience a full reversal of symptoms, probably due to a combination of reversible and irreversible pathophysiological changes. While the phenotype of iNPH is well described, further studies are needed to elaborate on it further as well as to provide a structured, and preferably standardized method of assessment of expected and observed symptoms in order to facilitate the comparison of different patient

populations. In addition, a continued effort is needed to reach consensus on the optimal method for assessing postoperative clinical improvement.

In iNPH, the enlargement of the ventricular system is generalized and not confined to the lateral ventricles, although changes might be most obvious in these areas. Other described morphological imaging findings such as DESH and focally entrapped (transport) sulci are present in a subgroup of patients, but even though they can support the diagnosis of iNPH, their presence should not be required.

While a few clinical markers, notably the presence of symptoms in all four cardinal symptom groups were associated to postoperative clinical improvement, no morphological MRI-markers could be used for this purpose. As such, selecting patients for shunt surgery based on the morphological appearance on CT or MRI results in a potential exclusion of patients that would improve after shunt surgery, and this practice should be avoided. As with the clinical phenotype, developing a standardized assessment of morphological changes on CT and MRI should be prioritized in order to facilitate further research in the field, including the potential predictive potential of morphological imaging biomarkers.

Lastly, the mesencephalon and pons probably play an important role in the symptom generation in iNPH. A pre- and postoperative ADC reduction in the areas suggests the potential involvement of additional pathophysiological mechanisms than has been described previously in supratentorial structures. In addition, perfusion changes, evident as an increase in rCBF, mirror the rate of clinical improvement in responders, strengthening the role of MRI-based perfusion measurements as potential predictive biomarkers, although this claim needs further investigation. Future studies should focus on reproduction of earlier functional disturbances in large patient samples, preferably using a combination of diffusion and perfusion measurements. The use of higher order diffusion and perfusion estimates, e.g. capillary transit time heterogeneity could provide additional insights in the pathophysiological changes seen in the disease.

ACKNOWLEDGEMENTS

To all patients who, by giving consent made these studies possible. Thank you.

I wish to thank my four supervisors, without you, this thesis would not exist.

Mats Tullberg, my main supervisor. Your devotion to the field of iNPH research and determination to provide optimal patient care is truly inspiring. Also, your kind and focused guidance combined with an impressive patience through the process of writing this thesis has been invaluable.

Carsten Wikkelsø, you introduced me to iNPH-research as a med student and remained a great source of inspiration, always willing to discuss the ins and outs of iNPH ever since. Also, the yearly dinners with a good mix of research and furniture design discussions, co-hosted by Elizabeth is always something to look forward to.

Doerthe Ziegelitz, your extensive knowledge in neuroradiology and MRI perfusion imaging has been invaluable for this thesis, but I also want to thank you for the many interesting discussions we've had on career choices among other things in that tiny office of yours.

Per Hellström, your deep knowledge of iNPH combined with your database wizarding skills and statistical knowledge has been invaluable for the thesis and lead to many fun discussions not only regarding iNPH.

Isabella Björkman-Burtscher, thank you for your support, extensive knowledge and enthusiasm, not only for the last project in this thesis, but for everything neuroradiological.

Jonathan Arvidsson, Kerstin Lagerstrand and Göran Starck, your extensive knowledge and enthusiasm about MRI physics and other subjects lead to many interesting discussions and ideas and was absolutely crucial for completing the last Study in this thesis.

I want to thank my friends and colleagues at the hydrocephalus research unit; Gunilla Ahl-Börjesson, Kerstin Andrén, Mikael Edsbagge, Dan Farahmand, Daniel Jaraj, Madeleine Johnsson, Lena Kollén and Tove Rasmussen.

I also want to thank my co-authors of the manuscripts included in this thesis; Xinxin Guo, Christer Jensen, Silke Kern, Thomas Marlow, Katrin Rabiei, Ingmar Skoogh, and Maria Wallin.

For the language editing, I would like to thank Judith Klecki.

Caroline Molinder, you not only hired me for the residency, but also always tried your hardest to provide the time for me to complete this thesis. Your devotion to your staff is a true inspiration.

To all my friends, you're too many to fit on these pages, I'm sorry, but thank you for your support and not bashing me in the head when the somewhat one-sided discussions on hydrocephalus got boring.

Nina Abersék, thank you for your support ever since the start of this project, reading and suggesting improvements on every paper and offering well timed kicks in the butt when needed.

Fredrik Langkilde, friend and colleague. Thank you for all the fun discussions about subjects big and small we've had through the years. Also, your knowledge on diffusion imaging has been invaluable in making this part of the thesis readable.

Amanda, my beloved girlfriend. Thank you for your support, even in the writing chaos that has been the reality this fall, and when I turned our apartment to a writing studio.

My family, mother Anette, father Jon and brother Niels. You always supported me through everything, and the many interesting discussions we had, and still have around the dinner table continues to inspire.

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APPENDIX

Appendix 1. ICD-codes used for classifications of vascular risk factors in Study I.

	ICD 9	ICD 10
Hypertension	401, 4019, 40199, 401A, 401B, 401X, 4029, 40299, 402A, 402B, 402X, 4039, 40399, 403X, 40499, 404X, 405B, 405X	I10, I10.0, I10.9, I11.0, I11.9, I12.0, I12.9, I13.0, I13.2, I13.9, I13-P, I15.0, I15.1, I15.9
Diabetes mellitus	250-25009, 250A-250H, 250X, 278A	E100-E105, E107-E120, E140, E143, E148, E149, E14-P
Stroke/transient ischemic attack	430, 430X, 431, 431X, 432, 432A-B, 432X, 433A-D, 433X, 434, 434A-B, 434X, 435, 435X, 436, 436X, 437, 437A-B, 437D-G, 437W, 437X, 438, 438X	I601-I615, I616, I618-I621, I629, I630-I639, I640, I649, I650-I653, I658, I659, I660-I664, I668, I669, I670-I672, I674-I679, I67-P, I680-I682, I688, I690-I694, I698, G453, G459
Coronary artery disease	4130, 41307, 4139, 41397, 41399, 413X, 4100, 41007, 4109, 41097, 41099, 410A-B, 410X, 41201, 41209, 4129, 41291, 41299, 412X, 428, 4289, 42899, 412A-B, 412X	I200, I201, I208, I209, I209P, I210-I214, I214A-B, I214W, I214X, I219, I21-P, I500, I501, I509

Appendix 2. Range of voxels in the final ROIs after transfer and masking in Study IV.

			Range of voxels after alignment and masking	
ADC			**Brain region**	
Group		ROI	Mesencephalon	Pons
Controls (n=15)		Posterior	142-343	124-387
		Middle	254-560	212-539
		Anterior	214-632	152-491
All iNPH patients	Preoperative (n=20)	Posterior	109-343	96-387
		Middle	213-560	197-539
		Anterior	239-632	160-491
	Postoperative (n=16)	Posterior	88-426	111-407
		Middle	199-544	231-599
		Anterior	207-570	155-631
Perfusion data			**Brain region**	
Group		ROI	Mesencephalon	Pons
Controls (n=15)		Posterior	47-111	41-99
		Middle	64-168	55-157
		Anterior	83-205	65-143
All iNPH patients	Preoperative (n=20)	Posterior	54-111	40-89
		Middle	66-168	56-145
		Anterior	84-184	71-143
	Postoperative (n=16)	Posterior	50-113	41-105
		Middle	69-163	54-150
		Anterior	95-185	54-146