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MARIA KOJOUKHOVA

RADIOLOGICAL MARKERS IN IDIOPATHIC NORMAL PRESSURE HYDROCEPHALUS – ASSOCIATIONS WITH DIAGNOSIS, INTRACRANIAL PRESSURE, BRAIN BIOPSY FINDINGS AND MORTALITY

Radiological markers in idiopathic normal pressure hydrocephalus – associations with diagnosis, intracranial pressure, brain biopsy findings and mortality

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ABSTRACT:

Idiopathic normal pressure hydrocephalus (iNPH) is a rare clinical syndrome appearing as gait disturbances, cognitive impairment and urinary incontinence in the aged population. Brain imaging shows dilated ventricles, although the mean cerebrospinal fluid pressure is normal. The treatment is a shunt surgery. This thesis aimed to investigate the usefulness of the various radiological markers in the diagnostics and prediction of shunt response; the relationship between radiological markers and mortality; and the associations between intracranial pressure (ICP) and radiological findings, brain biopsies, and shunt surgery outcome in iNPH. The study population was derived from the Kuopio University Hospital's NPH registry, which included patients (n=73-477) suspected to have iNPH who were referred for further examinations.

INPH was more likely to occur in patients with disproportionality between the suprasylvian and Sylvian subarachnoid spaces than in those without disproportionality, making it the most feasible radiological marker for iNPH. Additionally, temporal horns were narrower in patients with iNPH than in non-NPH patients. Brain ventricles were larger [*i.e.* higher Evans' index (EI)] in non-NPH than iNPH patients. However, the radiological findings were not associated with the shunt response.

INPH-related radiological markers (increased EI, sulcal disproportionality, and focally dilated sulci) were associated with a high mean ICP. More severe disproportionality was also associated with ICP B waves. These associations support the value of these markers in diagnostics and suggest that they are potentially related to the pathogenesis of iNPH. Lesser atrophy of the medial temporal lobe was also associated with more frequent ICP B waves. Additionally, our results suggested that elevated pulse wave amplitude might be associated with brain amyloid accumulation. The mean ICP and mean ICP pulse wave amplitude were not associated with the shunt response.

A novel result of our study was that the radiological findings related to iNPH were not associated with survival. However, the radiological findings related to AD and vascular degeneration were predictive of a high all-cause mortality. These findings suggest that there should be more focus on vascular degeneration and vascular risk factors when treating iNPH patients.

This thesis shows that the traditional radiological markers of iNPH have an important role in the iNPH diagnostics, but radiological features of atrophy and vascular degeneration should also be considered in the diagnostics of iNPH. More studies are needed in considering the prediction of the shunt response and the overall prognosis.

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Medical Subject Headings: Hydrocephalus, Normal Pressure; Radiology; Intracranial Pressure; Subarachnoid Space; Temporal Lobe; Cerebrospinal Fluid Shunts; Neuroimaging; Brain; Biopsy; Alzheimer Disease; Dementia, Vascular; Prognosis; Mortality; Finland

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TIIVISTELMÄ:

Idiopaattinen (itsesyntyinen) normaalipaineinen hydrokefalus eli vesipäisyys (iNPH) on harvinainen sairaus, joka ilmenee kävelyongelmina, kognitiivisina vaikeuksina ja virtsan pidätyskyvyttömyytenä iäkkäillä. Aivojen kuvantamisessa nähdään aivokammioiden laajeneminen, vaikka aivo-selkäydinnesteen keskipaine on normaali. Hoito on sunttileikkaus. Tämän väitöstutkimuksen tavoitteena oli tutkia radiologisten löydösten hyödyllisyyttä diagnostiikassa ja sunttivasteen ennustamisessa iNPH:ssa. Lisäksi tavoitteena oli selvittää radiologisten löydösten yhteys kuolleisuuteen ja kallonsisäisen paineen sekä radiologisten löydösten, aivobiopsioiden ja sunttivasteen väliset yhteydet. Tutkimusaineisto perustui Kuopion yliopistollisen sairaalan NPH-rekisteriin, joka koostuu potilaista (n=73-477), joilla oli epäilty iNPH:ta ja jotka oli kutsuttu jatkotutkimuksiin.

Potilailla, joilla oli Sylviuksen uurteen ja sen yläpuolisten kortikaalisten aivoselkäydinnestetilojen välinen epäsuhta, iNPH oli todennäköisempi kuin niillä, joilla epäsuhtaa ei ollut. Lisäksi, temporaalisarvet olivat kapeammat kuin ei-NPH potilailla. Aivokammiot olivat suuremmat [Evansin indeksi (EI)] ei-NPH potilailla kuin iNPH potilailla. Radiologiset löydökset eivät kuitenkaan olleet yhteydessä sunttivasteeseen.

INPH-tautiin liittyvät kuvantamislöydökset (suurentunut EI, kortikaalisten aivo-selkäydinnestetilojen epäsuhta tai paikallinen laajentuminen) olivat yhteydessä korkeaan kallonsisäiseen paineeseen. Voimakkaampi epäsuhta oli lisäksi yhteydessä kallonsisäisen paineen B-aaltoihin. Nämä yhteydet tukevat näiden radiologisten löydösten arvoa diagnostiikassa ja viittaa niiden olevan yhteydessä iNPH:n patogeneesiin. Sisemmän ohimolohkon vähäisempi atrofia oli myös yhteydessä suurempaan B-aaltojen esiintyvyyteen. Kallonsisäisen pulssipaineen kohoaminen saattaa olla myös yhteydessä amyloidin kertymiseen aivoihin. Kallonsisäisen paineen keskiarvolla tai pulssipaineen amplitudilla ei ollut yhteyttä sunttivasteeseen.

Uusi havainto oli, etteivät iNPH-tautiin liittyvät radiologiset löydökset olleet yhteydessä kuolleisuuteen. Alzheimerin tautiin ja verisuoniperäiseen aivorappeumaan liittyvät kuvantamislöydökset puolestaan ennustivat korkeaa kuolleisuutta. Näin ollen verisuoniperäisen aivorappeuman ja verisuonitautien riskitekijöihin pitäisi kiinnittää huomiota iNPH potilaita hoidettaessa.

Tämä väitöstutkimus osoittaa, että perinteisillä iNPH kuvantamislöydöksillä on tärkeä rooli iNPH diagnostiikassa, mutta myös aivoatrofian ja verisuoniperäisen aivorappeuman radiologiset löydökset pitäisi ottaa huomioon. Lisätutkimuksia tarvitaan, jotta voitaisiin paremmin ennustaa iNPH potilaiden sunttivastetta ja taudinkulkua.

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There's a lot more going on outside this box.
-James De La Vega

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List of the original publications

This dissertation is based on the following original publications:

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II Kojoukhova M, Vanha K-I, Timonen M, Koivisto AM, Nerg O, Rummukainen J, Rauramaa T, Vanninen R, Jääskelänen JE, Sutela A, Leinonen V. Associations of intracranial pressure with brain biopsy, radiological findings, and shunt surgery outcome in patients with suspected idiopathic normal pressure hydrocephalus. *Acta Neurochir (Wien) 159:51-61, 2017*

III Kojoukhova M, Koivisto AM, Vanninen R, Jääskeläinen JE, Sutela A, Leinonen V. Prognostic value of radiological findings in idiopathic normal pressure hydrocephalus. *Submitted manuscript.*

Contents

Abbreviations

Aβ	Amyloid beta
AC	Anterior commissure
AD	Alzheimer's disease
BEH	Benign external hydrocephalus
BMI	Body mass index
CA	Callosal angle
CSF	Cerebrospinal fluid
CT	Computed tomography
DESH	Disproportionally enlarged subarachnoid space hydrocephalus
EI	Evans' index
ELD	External lumbar drainage
ETV	Endoscopic third ventriculostomy
FDS	Focally dilated sulci
FLAIR	Fluid-attenuated inversion recovery
HR	Hazard ratio
HPτ	Hyperphosphorylated tau
ICP	Intracranial pressure
iNPH	Idiopathic normal pressure hydrocephalus
KUH	Kuopio University Hospital
LOVA	Longstanding overt ventriculomegaly in adults
LPS	Lumboperitoneal shunt
mCMI	Modified cella media index
MMSE	Mini-mental state examination
MREG	Magnetic resonance encephalography
MRI	Magnetic resonance imaging
NPH	Normal pressure hydrocephalus
OR	Odds ratio
PC	Posterior commissure
PD	Parkinson's disease
R_{out}	Resistance to outflow
SAS	Subarachnoid spaces
sNPH	Secondary normal pressure hydrocephalus
TIRM	Turbo inversion recovery magnitude
VA	Ventriculoatrial
VAD	Vascular dementia
VPS	Ventriculoperitoneal shunt
WMC	White matter changes
WTH	Width of the temporal horns
Z-EI	Z-Evans index

1 Introduction

In hydrocephalus, excess cerebrospinal fluid (CSF) accumulates within the brain, usually leading to enlarged brain ventricles. Hydrocephalus is divided into two groups: obstructive (non-communicating) and communicating type. In obstructive hydrocephalus, the pathway of the cerebrospinal fluid flow is blocked, *e.g.* due to a tumor, cyst, or haemorrhage, whereas there is no visible obstruction in communicating hydrocephalus. Normal pressure hydrocephalus (NPH) is a subtype of communicating hydrocephalus. Instead of there being a blockage, the CSF reabsorption is disturbed.

NPH is a neurodegenerative disorder, which occurs mainly in the aged population. Hakim and Adams discovered NPH in 1965 (6). NPH presents itself as enlarged brain ventricles, mainly normal CSF pressure, and manifests classically in a symptom triad, which includes gait disturbance, cognitive decline, and urinary incontinence (6). At least one of these symptoms is always present in NPH (7). However, similar symptoms also exist in several other neurodegenerative diseases, such as Alzheimer's disease (AD), Parkinson's disease (PD), and vascular dementia (VAD). In addition, NPH is often accompanied by these or other neurodegenerative disorders as comorbidities, making the diagnostics complex.

In idiopathic NPH (iNPH) there is no known etiological cause, unlike in secondary NPH (sNPH), which happens due to *e.g.* subarachnoid hemorrhage, trauma, or meningitis for why it occurs. INPH is a rare disease, and reported incidence is approximately 3.6 cases per year per 100 000 inhabitants over the age of 50 (8). Notably, unlike in other common neurodegenerative disorders, dementia as a symptom can be reversed in iNPH. The treatment is a shunt catheter insertion, which leads the CSF away. Approximately 50-80% of the iNPH patients benefit from shunting (9,10).

Brain and its CSF compartments are usually evaluated on computed tomography (CT) or magnetic resonance imaging (MRI) scans. MRI is currently considered to be the primary imaging method of dementia (7). The most frequently used radiological marker in iNPH is called Evans' index describing the ventriculomegaly (7,11). Numerous radiological markers have previously been suggested for the diagnostics of iNPH and the prediction of the shunt response, but these markers have seldom been compared against each other.

Despite having the name of "normal pressure hydrocephalus," intracranial pressure (ICP) is occasionally increased in iNPH and can be measured only invasively. Simultaneously, a brain biopsy can be acquired, which might help in differential diagnostics (12). In addition to the CSF hydrodynamic dysfunction, it has been suggested that VAD is related to the pathophysiology of iNPH (13). Diabetes is a potential risk factor for iNPH, and hypertension and other vascular risk factors are also overrepresented in iNPH (13). Several studies have found that *e.g.* the radiological markers related to VAD are prognostic of mortality (14,15). However, iNPH-related radiological findings have not been previously investigated regarding mortality.

The aim of this thesis was to investigate the role and value of certain previously reported radiological markers for diagnostics, prediction of mortality and shunt response in iNPH.

Additionally, the associations of ICP with the radiological markers, brain biopsy findings, and shunt response were studied.

2 Review of the literature

2.1 DEFINITION OF IDIOPATHIC NORMAL PRESSURE HYDROCEPHALUS (INPH)

INPH is defined as an idiopathic syndrome occurring in the aged population, in which the main symptoms are gait disturbance, cognitive deterioration, and urinary dysfunction. The patients have no known preceding or predisposing disorders that might have influenced the CSF circulation, which is impaired in iNPH. Further, the brain ventricles are enlarged (ventriculomegaly), while ICP is usually within the normal range (5-18 mmHg). Despite the previously published Japanese (11) and International (American-European) guidelines (7) for the diagnosis and treatment of iNPH, there is no absolute consensus regarding the diagnosis or the treatment.

2.2 EPIDEMIOLOGY

Of all dementias, the prevalence of potentially reversible dementia is 4-9% (16-18), of which all types of NPH constitutes 12% in the geriatric population (16). The estimates of the incidence and prevalence of iNPH vary widely in studies, because of inconsistent diagnostic criteria, selection of the study population, and different study designs. Incidence of iNPH is relatively rare but increases with age.

The NPH incidence in a multicenter hospital-based study in Amsterdam was 0.22/100 000 per year (19). The incidence of iNPH in Norwegian population-based study was 5.5/100 000 (20) with the incidence of shunt surgery 1.09/100 000 per year (21). A longitudinal 10-year follow-up study in a rural area of Northern Japan in a 70-year-old community-based population estimated a larger incidence of iNPH, at 120/100 000 per year (22). A study based on insurance claims reported an incidence of 1.08/100 000 per year in Germany (23). In a systematic review of the literature, Martin-Laez *et al.* reported an incidence of <1 case /100 000 inhabitants per year for the entire population, and 3.6/100 000 per year in people >50 years old (8). A recent Swedish study reported the incidence of shunt surgery to be 2.2/100 000 per year for iNPH (24). The incidence for iNPH in the Finnish population has been reported to be 1.84/100 000 per year and 14.65/100 000 per year in patients over 70 years old (25).

In a nationwide Japanese hospital-based survey, the overall prevalence of iNPH was 10.2/100 000 and in people >60 years old the prevalence was 31.4/100 000 (26). Approximately half of all the patients in the Japanese cohort were shunted. In other reports, the prevalence of possible iNPH with MRI support in the elderly in Japan has been around 500-2 900/100 000 (27-29). A hospital-based study in Norway found a prevalence of 21.9/100 000 (20). In a Swedish population-based study, the prevalence was 200/100 000 in people 70-79 years old, 5 900/100 000 in people >80 years old, but only 8% of those patiens were shunted (30). The prevalence of iNPH in a systematic review was 1 300/100 000 in >65-year-old patients (8).

Undeniably, the incidence and prevalence estimates vary greatly and only a small part of the patients receive a shunt treatment, which suggests that iNPH might be an underdiagnosed, misdiagnosed and undertreated condition because of the very non-specific symptoms.

2.3 PATHOPHYSIOLOGY

2.3.1 Production and circulation of the cerebrospinal fluid

CSF provides buoyancy for the brain, compensates for the blood volume changes during the cardiac cycle, removes waste products from the brain, and spreads hormones and molecular signals (31). CSF is produced mostly by the choroid plexus in the brain ventricles, especially the lateral ventricles, partly by the ependymal cells, and a small amount is dribbled from the brain through the perivascular spaces *i.e.* the Virchow-Robin spaces (particularly through the periarterial spaces), or the arterial smooth muscle layer, to the subarachnoid spaces (SAS) (31,32).

CSF circulates in and around the brain and the spinal cord. From the main location of the CSF production, the lateral ventricles, CSF travels first into the third ventricle through the interventricular foramina (foramina of Monro) and then into the fourth ventricle through the cerebral aqueduct (32). After that, CSF flows into the central canal of the spinal cord, or into the cisterna magna of the subarachnoid space through the two lateral apertures (foramina of Luschka) and one medial aperture (foramen of Magendie) (32). In SAS, CSF encircles the brain and the spinal cord, and is absorbed into the sinus sagittalis superior and other venous sinuses via the arachnoid villi located in the SAS of the brain (32). The traditional view of the CSF circulation is presented in Figure 1. A small part of CSF passes through the cribriform plate (perineural pathway) to the nasal mucosa, entering the peripheral capillary or lymph, and also through the arachnoid villi located in the origins of the spinal nerves, and then enters the blood or lymph (31). The perivascular spaces (Virchow-Robin spaces) surrounding the veins lead the fluid out of the parenchyma. These spaces can also be a route for the CSF outflow and it is called the “glymphatic” system, which may drain into the lymph nodes in the neck or veins leading out of the brain (31,33). The arterial smooth muscle layer may also play a role in the clearance of amyloid beta (Aβ) (31). In one study a magnetic resonance encephalography (MREG) was used to propose three distinct mechanisms for the CSF pulsations in the glymphatic system, *i.e.* 1) respiratory, 2) cardiac, and 3) low frequency vasomotor tone induced pulsations (34). Based on the recent studies on mice, it seems that there are actual lymphatic vessels in the dura mater through which the interstitial fluid and some CSF is probably absorbed from the SAS through the arachnoid mater (35,36). It is plausible that a similar lymphatic vasculature exists in the human dura mater as well, at least around the superior sagittal sinus (37).

Normally, the CSF production rate is approximately 500 ml in a day although the total volume of the CSF spaces is around 150 ml, meaning that CSF is renewed more than three times a day (32). In healthy adults, the CSF flow through the aqueduct varies with the cardiac cycle. During systole, CSF moves towards the spinal canal, and back towards the brain ventricles during diastole (31).

Increased production and/or decreased absorption of CSF can cause hydrocephalus. Moreover, there are reports that there is a reverse of the CSF net flow in communicating

hydrocephalus through the aqueduct (from fourth to third ventricle), suggesting a significant exit route of CSF from the lateral and third ventricles and also CSF production outside of the choroid plexuses, such as the blood-brain barrier in the cortical parenchyma (31). On the contrary, Bradley has suggested that in the early stages of iNPH there is a hyperdynamic CSF flow and twice the volume is passed outwards through the aqueduct compared with healthy aged subjects, and this flow decreases when the atrophy of ventricles progresses (33).

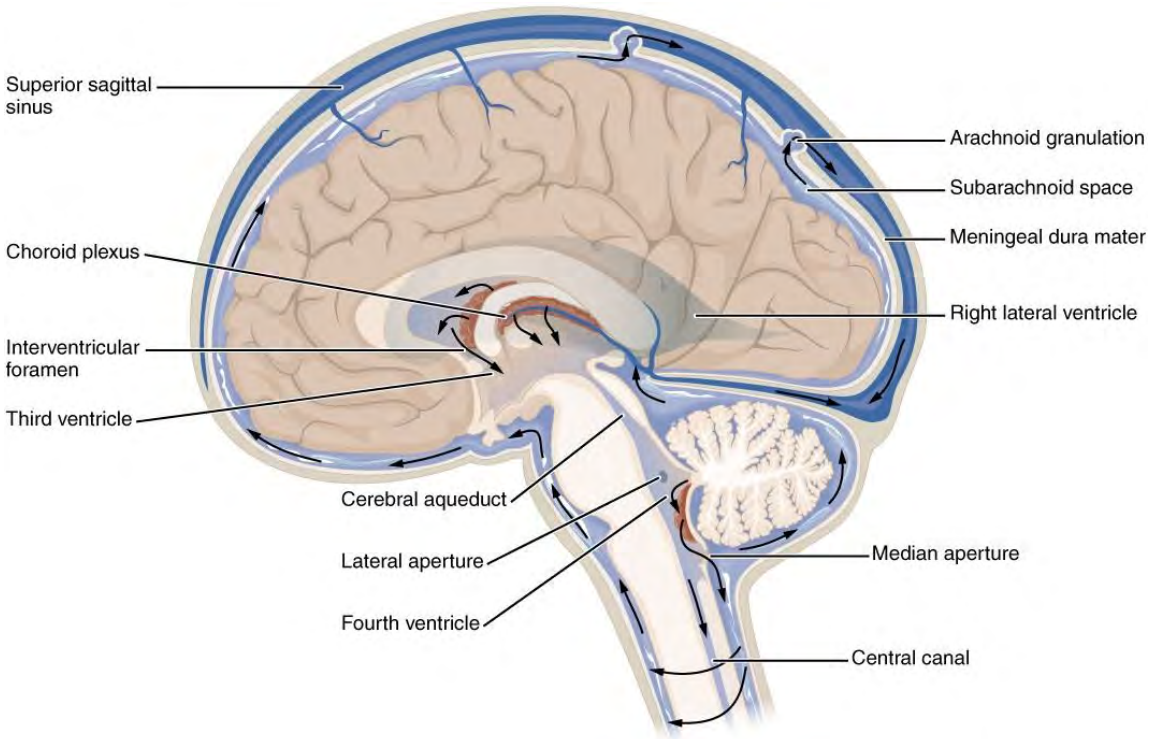

Figure 1. The traditional view of the CSF circulation. Adapted from (38).

2.3.2 Suggested theories

The underlying mechanisms in the development of iNPH remain controversial. INPH is commonly considered to be a multifactorial disorder with associated disturbed CSF dynamics. The pathophysiological findings in iNPH include ventricular enlargement (6), disproportionally enlarged SAS (39), leptomeningeal fibrosis and thickening (11), inflammation of the arachnoid granulations (11), ependymal disruption (11), subependymal gliosis (11), multiple infarctations (11), AD-related pathological changes (senile plaques and neurofibrillary tangles) (11), increased CSF pulse pressure (40), reduced cerebral blood flow (41), increased resistance to CSF reabsorption (42), alternative routes of CSF absorption (43), reduced SAS compliance (44), and hyperdynamic aqueductal CSF flow (45). A recent study suggested that astrogliosis and decreased expression of aquaporin-4 and dystrophin 71 could also be linked to iNPH (46).

AD-related changes are often seen in the brain biopsies of iNPH patients (12). Silverberg *et al.* proposed that iNPH and AD have originally the same mechanism: the CSF circulation is disturbed and toxic metabolites, such as Aβ, accumulate in the brain of iNPH and AD

patients (47). Later, Silverberg *et al.* conducted a prospective, randomized, double-blinded, placebo-controlled trial, investigating if macromolecule clearance from the central nervous system would slow the dementia progression in patients with probable AD (48). Based on their study findings, patients with any stage of AD do not benefit from shunting since it does not slow the dementia progression (48). In AD, a reduction of the CSF production and the accumulation of Aβ (especially in meninges and choroid plexus) leads to an increased resistance to the CSF outflow (47). Yet, in iNPH, an increased resistance to the CSF outflow leads to a slightly elevated CSF pressure (enlarging the brain ventricles), which reduces the CSF production and the clearance of toxins (47). Notably, increased CSF outflow resistance has also been linked to normal aging (47).

It has been reported that iNPH patients have larger head sizes (49,50) and larger intracranial volumes than controls (51), suggesting benign external hydrocephalus (BEH) in infancy to be a precursor of iNPH (52). It has been suggested that this concerns only a subgroup of iNPH patients, because of a standard normal distribution curve of head circumference in iNPH (53). Additionally, it is known that white matter changes (WMC) are common in iNPH. Altogether, this so called "two hit theory," suggested by Bradley states that immature arachnoid villi cause decreased CSF resorption and increased resistance to CSF outflow, leading to slightly enlarged ventricles, convexity SAS, and head size in infancy because of open sutures (52). Thus, CSF is forced to flow more through the extracellular space of the brain parenchyma to ensure sufficient CSF resorption (*e.g.* through the venous Virchow-Robin spaces via the aquaporin-4 (33)). This makes the CSF circulation equilibrium from the ventricles to the SAS to be more dependent on this parallel pathway (52). In early adulthood, the arachnoid villi do probably not mature completely, and the brain ventricles continue to be slightly enlarged (52). In late adulthood, however, WMC appear and disturb this parallel CSF pathway by increasing the resistance to the extracellular CSF flow and decreasing the CSF resorption, forcing the brain ventricles to enlarge even further, which eventually initiates iNPH symptoms (52).

It has been suggested that a subgroup of iNPH patients harbor a genetic predisposition towards developing the condition (54). A Japanese study found a segmental copy number loss of the SFMBT1 gene (in 4 of the 8 patients with possible iNPH or asymptomatic ventriculomegaly and iNPH features on MRI), which is expressed in choroid plexus, ependyma, and blood vessels, potentially causing dysfunction to the CSF circulation (55). Same copy number loss of the SFMBT1 gene was later found in definitive, shunt-responsive iNPH patients with no family history of iNPH, suggesting that variations in this gene might expose people to iNPH along with other risk factors (56).

It has been proposed that reduced cerebral blood flow and ischemia could be the cause of iNPH (41). Decreased cerebral perfusion due to aging and other risk factors (atherosclerosis, hypertension, diabetes) cause deep WMC (57). These changes may decrease periventricular tensile strength, causing ventricular enlargement, which presses on the cortical veins and could make the CSF flow hyperdynamic, causing further shear stress near the periventricular areas (57). However, Bateman has contradicted this theory because there are patients with a high cerebral blood flow, and the ischemic changes could be secondary to iNPH (58). Instead, Bateman suggests that aging reduces the craniospinal and venous compliance, which increases the venous pressure, especially in the superficial veins (58). This in turn further reduces the craniospinal compliance and increased venous pressure, leading to decreased CSF absorption through the arachnoid granulations (58).

This theory also fits with the arterial pulse wave theory, because when the cortical vein compliance is reduced, the arterial pulse pressure may affect the brain tissue and the CSF pressure wave in central areas of the brain more easily. According to Bateman, the pulse waves cause deep WMC that further decrease the compliance of the brain by amplifying the effect of the pulse waves (59). Notably, this theory also disagrees with the "two hit theory," in which the WMC are one of the causes of iNPH. As one can see, the pathophysiological mechanisms underlying iNPH remain highly debated.

Shunting is proposed to relieve the symptoms by increasing the compliance, thus reducing the venous pressure and increasing the CSF reabsorption (58). At same time, shunting decreases the pulse pressure, which decreases the stress on the nerves in the periventricular area and improves the blood flow (60). Bradley proposes that shunting decreases the parenchymal absorption of the CSF in the ventricles as well (60).

2.4 DIAGNOSIS

2.4.1 Diagnostic criteria

The diagnostic criteria for iNPH according to the International (7) and Japanese (11) guidelines are presented in Table 1. The diagnosis is made based on clinical history, brain imaging, physical findings, and specific physiological tests. Based on these, the International guidelines classify the possibility of iNPH into "probable," "possible," and "unlikely", and the Japanese guidelines classify iNPH pre-operatively into "probable" and "possible," and post-operatively into "definite."

INPH usually manifests as a symptom triad, which consists of gait disturbances (occur usually first) cognitive impairment, and urinary incontinence (9). Usually, the symptoms progress slowly (9). Ventricle enlargement should be present, and is typically measured with Evans' index (EI) on CT or MRI (7,11). In addition, the Japanese guidelines emphasize the radiological finding of disproportionally enlarged subarachnoid space hydrocephalus (DESH) where sulci and SAS are narrowed in the high convexity (11). Another key difference between the guidelines is in the ages the symptoms are assumed to begin (60 vs. 40 years). Moreover, according to the Japanese guidelines, the iNPH diagnosis becomes definite if the symptoms improve after the shunt surgery (11).

Table 1. Diagnosis of idiopathic normal pressure hydrocephalus (iNPH) according to the International vs. Japanese guidelines. Adapted from Relkin *et al.* 2005 (7) and Mori *et al.* 2012 (11).

		International guidelines	**Japanese guidelines**
Possible iNPH	Symptoms	Begin at any age after childhood	Age ≥60 years
		Subacute or indeterminate onset	
		Duration <3 months or indeterminate	
		Not clearly progressive	
		Previous brain event such as mild head trauma or other conditions may be present in the patients' history but must not be causally related in the clinicians' judgement	Ventricular dilation causing preceding diseases not obvious
		May coexist with other neurological, psychiatric, or general medical disorders but must not be entirely attributable to these disorders in the clinicians' judgement	Symptoms not entirely explained by other diseases
		Either incontinence and/or cognitive impairment without gait disturbance, or gait disturbance or dementia	More than one symptom of a triad
	Imaging	Hydrocephalic ventricular enlargement associated with either a sufficient severity of the cerebral atrophy, or structural lesions influencing the ventricular size	Ventricular enlargement *i.e.* Evans' index >0.3
			Possible iNPH with MRI support: narrowed sulci and subarachnoid spaces over the high convexity/midline (DESH) on MRI with fulfilling criteria for possible iNPH
	Physiology	Opening pressure measurement not available, or pressure outside the range required for probable iNPH	
Probable iNPH	Symptoms	Age >40 years	Age ≥60 years
		Insidious onset	
		Corroborated with proper informant	
		Minimum duration 3-6 months	
		Progression over time	
		No evidence of known causes of sNPH	Ventricular dilatation causing preceding diseases not obvious
		No other conditions explaining the symptoms	Symptoms not entirely explained by other diseases
		Gait disturbance and at least one other symptom from the triad	More than one symptom of a triad
		For gait disturbance, at least two of the following should be present and not entirely attributable to other conditions: decreased step height, length, or walking speed, increased trunk sway during walking, widened standing base, toes turned outward during walking, retropulsion, *en bloc* turning, impaired walking balance	

Continued on the next page.

Table 1. Continued.

		International guidelines	Japanese guidelines
Probable iNPH	Symptoms	For cognition, impairment and/or decrease in the cognitive performance screening instrument, or at least two of the following present, not entirely attributable to other conditions: psychomotor slowing, decreased fine motor speed or accuracy, difficulty dividing/maintaining attention, impaired recall, executive dysfunction, behavioral/personality changes For urinary continence, either one of the following: episodic/persistent urinary incontinence not attributable to primary urological disorders, persistent urinary incontinence, urinary and fecal incontinence, or any two of the following must be present: urinary urgency, urinary frequency despite normal fluid intake, or nocturia	
	Imaging	Ventricular enlargement not entirely attributable to cerebral atrophy or congenital enlargement	Ventricular enlargement *i.e.* Evans' index >0.3
		At least one supportive feature: temporal horn enlargement not entirely attributable to hippocampus atrophy, callosal angle >40°, evidence of altered brain water content, or an aqueductal/fourth ventricular flow void on MRI	See "Physiology" below*
		No macroscopic obstruction of the CSF flow	
	Physiology	CSF opening pressure 5-18 mmHg (70-245 mmH_2O) in a lumbar puncture or a comparable procedure	CSF pressure ≤200 mmH_2O and normal CSF content
			*One of three following: narrow sulci and subarachnoid spaces in convexity/midline (DESH) when gait disturbance present, symptom improvement after a CSF tap or drainage test
Supportive features	Symptoms		Emphasis on the variety of gait and balance disturbances (small stride, shuffle, instability during walking, increased instability when turning), especially when the most prevalent symptom. Followed by cognitive impairment, especially seen in cognitive tests, and by urinary problems. Slow progression Other possible neurological diseases are mild
	Imaging & Physiology	Smaller ventricle size on imaging before the symptoms	Enlargement of the Sylvian fissures and basal cisterns
		Delayed clearance of the radiotracer over the convexities after 48-72 hours on the radionuclide cisternogram	Cerebral blood flow measurement is useful for differentiating the diagnosis from other dementias

Continued on the next page.

Table 1. Continued.

		International guidelines	Japanese guidelines
Supportive features	Imaging & Physiology	Increased ventricular flow rate on cine MRI or other technique	
		Decreased periventricular perfusion not altered by acetazolamide on a SPECT-acetazolamide challenge	
Unlikely iNPH	Symptoms	No symptom of the triad	
		Symptoms explained by other causes	
	Imaging	No ventriculomegaly	
	Physiology	Signs of increased intracranial pressure	
Definite iNPH			Improvement of symptoms after the shunt surgery

2.4.2 Clinical symptoms

INPH is typically characterized by a symptom triad. All three symptoms are not mandatory for the diagnosis of iNPH (61). Firstly, the most prominent symptom is usually symmetrical gait and balance impairment (61). The transitional movements and gait initiation might be difficult, there might be shuffling, tripping, falling, poor foot clearance, multistep turns and instability, and retropulsion or anteropulsion (62). Finally, gait becomes broad-based, glue-footed, slow, and short stepped (61). Upper motor neuron findings are usually not present (62). Postural and locomotor reflexes might be disturbed even though there are no primary sensorimotor deficits (62).

Secondly, cognitive impairment is due to frontal subcortical dysfunction reflected as troubles with everyday activities (61,62). Still, psychometric tests might remain normal at an early stage (61). Some of the symptoms that may occur include psychomotor slowing, apathy, lack of motivation, impaired concentration, daytime sleepiness, short-term memory impairment, and decrease in fine motor speed (61,62). Suitable tests for the assessment of subcortical dementia are for example the grooved pegboard test, the digit span test, the trail-making A/B test, the Stroop test, and the Rey auditory-verbal learning test (61).

The last symptom of a triad, increased urinary frequency, then urgency, and later incontinence, is due to detrusor hyperactivity and impaired central inhibitory control (61). INPH patients are typically aware of their incontinence (62).

2.4.3 Radiological imaging

In order to set an iNPH diagnosis, radiological imaging, *i.e.* CT or more preferably MRI, must be performed. Ventricular enlargement is usually measured with EI, which is the most established radiological marker in iNPH (Figure 2. A). EI is defined as the ratio between the maximal width of the frontal horns of the lateral ventricles and the maximal inner diameter of the skull (63). A value of >0.30 is considered to reflect ventriculomegaly (7,11). EI is higher in men than in women and increases with age but does not usually reach the value of 0.3 (64). Moderate or even strong correlation between EI and the ventricular volume has been found (65,66). However, it has been suggested that EI may not sufficiently estimate the ventricular volume since the value may vary depending on the level of the scan section used (65,66). Nevertheless, the EI value of >0.33 is related to the dilation of the frontal horns, and therefore this higher value has been suggested to define

ventriculomegaly (66). A more recent study suggested a cutoff value of ≥0.32 for EI to diagnose iNPH (67). The frontal and occipital horn ratio (defined as the average of the maximum frontal and occipital horn width divided by the same diameter of the cranium as with the EI) did not describe ventriculomegaly better than EI (66). It is controversial whether the ventricular reduction after shunting is essential in order for a patient to have a positive respond to the shunt surgery, since some studies show association between reduced ventricle size and the shunt response (68-70), and in other studies there is no such association (71-73). Neither is there association of change in EI and a three-day CSF drainage (74).

Z-Evans index (Z-EI), defined as the maximum z-axial length of the frontal horn, located between the roof and the bottom of the larger lateral ventricle to the maximum cranial z-axial length at the base of the posterior end of the foramen of Monro, has been recently proposed to describe ventricular enlargement better than EI (75). This is because ventriculomegaly seems to be directed more towards the vertical axis (z-axis) than the transverse axis (x-axis) based on volumetric analyses (75). Besides, Z-EI was associated with a tap test response (75).

The modified cella media index (mCMI), a ratio of the maximal width of the body of the lateral ventricles to the maximal intracranial width measured at the same level (Figure 2. B), has been reported to correlate with the automatically calculated ventricle size, suggesting it might be feasible for the evaluation of the ventricular size (76). Later, Bao *et al.* showed an excellent correlation between the ventricular volume and the mCMI in iNPH patients, the correlation being superior to the EI (77). The brain ventricles in visual evaluation have been reported to be more dilated in iNPH than in AD (78) and VAD (39).

Originally, callosal angle (CA) was found to be an NPH marker on pneumoencephalography (79) but is currently measured on 3D MRI. CA is defined as the angle between the lateral ventricles measured on a coronal plane perpendicular to the anteroposterior commissure line at the level of the posterior commisure (Figure 2. C and D) (80). A smaller angle reflects a greater ventricular size and enlarged Sylvian fissures (80). CA is smaller (<90°) in iNPH than in AD or normal controls (80), and a small angle is also associated with shunt responsiveness (81). Even simplified CA on MRI without 3D also seems to differentiate iNPH from other neurodegenerative diseases (82). A recent study showed that CA and EI combined differentiate the NPH patients from those who do not have NPH with good accuracy (67).

The dilatation of the temporal horns of the lateral ventricles is one of the earliest signs of hydrocephalus along with perceived ventricle dilatation (78). The maximal widths of the temporal horns (WTH) are measured on the axial plane (Figure 2. E) (83). Rounded (unlike in AD) and dilated temporal horns are often present in iNPH (84) and have been associated with the shunt response (83,85). However, enlarged temporal horns are also reported to be a helpful marker in distinguishing AD from healthy subjects (1-5). Besides, in order to tell AD apart from iNPH, perihippocampal fissures (enlarged in AD) seem to be a valuable supplementary marker (78). Additionally, a medial temporal lobe atrophy graded with Scheltens score (0-4) is fundamental in differentiating AD from iNPH (Figure 2. F) (86). Furthermore, a global brain atrophy progression supports the AD diagnosis as well (87). One study that used the volumetric analysis showed that decreased cortical thickness, *i.e.* the surrogate for cortical atrophy, in combination with the smaller ventricular volume supports AD instead of iNPH (88).

Unlike in AD, in iNPH the superior convexity and the medial SAS are often narrowed (Figure 2. G) (39,89). Despite this high convexity tightness, some iNPH patients have occasional occurrences of focally dilated (isolated) sulci (FDS) over the superior convexity (Figure 2. F and H) or the medial SAS (39,90,91). When the lower CSF spaces are examined, a dilatation of the Sylvian fissure in addition to the ventriculomegaly can be seen (Figure 2. F and I) (39). Altogether, this is often referred to as the disproportionally enlarged subarachnoid space hydrocephalus (DESH), where the lower CSF spaces are enlarged, and the upper CSF spaces are narrowed (Figure 2. F) (92), also referred to as the "suprasylvian block" (39). This is a hypothesized phenomenon, in which the CSF flow is impaired over the suprasylvian SAS, although there is no visible block in the brain imaging (39). DESH has been found to predict the shunt outcome (85,93), and the Japanese iNPH guidelines suggest classifying iNPH based on DESH. Despite the high positive predictive value, the DESH sign has a low negative predictive value (94). In other words, patients without DESH can still have a shunt responsive iNPH (94).

Another method to assess and quantify DESH, the SILVER index – a ratio between the area of the Sylvian fissure and the area at the vertex, has been presented, but it does not predict the shunt outcome (95).

WMC seen on CT and even better on MRI (white matter hyperintensities) (96) are frequent and more pronounced in iNPH than in healthy individuals (Figure 3. A and B) (97), but these changes also appear during normal aging and in many pathological conditions as well (98). WMC on T2- and T2-FLAIR (fluid-attenuated inversion recovery) MR images are caused by increased water content, which is thought to be a result of the demyelination and leakage of plasma and the lack of drainage of the interstitial fluid (99). Apart from normal aging, periventricular and deep WMC can be caused by chronic ischemia or iNPH-associated edema (100-102). WMC are graded with the Fazekas scale (periventricular WMC: 0=no, 1="caps" or pencil-thin lining, 2=smooth "halo", 3=irregular periventricular hyperintensity extending into the deep white matter; and deep WMC: 0=no, 1=punctate foci, 2=beginning confluence, 3=large confluent areas) (103). It has been discussed that hypertension might be the connecting factor between iNPH and WMC (91). WMC are not used in the diagnostics of iNPH and their appearance should not be a hindrance for the shunt surgery (102,104).

The flow void phenomenon, a sign of increased CSF flow (signal loss) in the aqueduct seen on T2-weighted MRI, is due to the pulsatile motion of CSF (Figure 3. C). During systole in the cardiac cycle, the brain extends inward and pushes the CSF antegrade toward the fourth ventricle and during the cardiac cycle diastole, the flow is retrograde (105,106). The flow void phenomenon was originally associated with better shunt response in older MRI studies (45,105). However, this discovery was later disputed (106-108). Still, the flow void may be useful in diagnostics when other clinical findings are indicative of iNPH (85,106-108).

Compared to AD and VAD, patients with iNPH showed no difference in the size of the basal cisterns (Figure 3. D-F) (39).

Currently, different softwares offer ways to perform volumetric analyses instead of manual linear measurements. For instance, a manual measurement of the intracerebral and intraventricular volumes in the QBrain software (version 2.0, Midis Medical Imaging Systems, Leiden, the Netherlands) takes approximately 30 minutes, which is too long for a clinical practice (66), making the linear measurements still the easiest and fastest way to

evaluate the intracerebral compartments. Additionally, it has been shown that several linear ventricle measurements correlate with the volume of the brain and are reliable (77,109,110). In the volumetric studies, regarding the diagnosis and the differential diagnosis, the results have been promising but are not yet part of the current clinical practice (111,112).

It needs to be highlighted that single measurements are rarely used alone for the diagnosis. Instead, the overall evaluation of the patients' situation (and the brain images) is what determines the treatment.

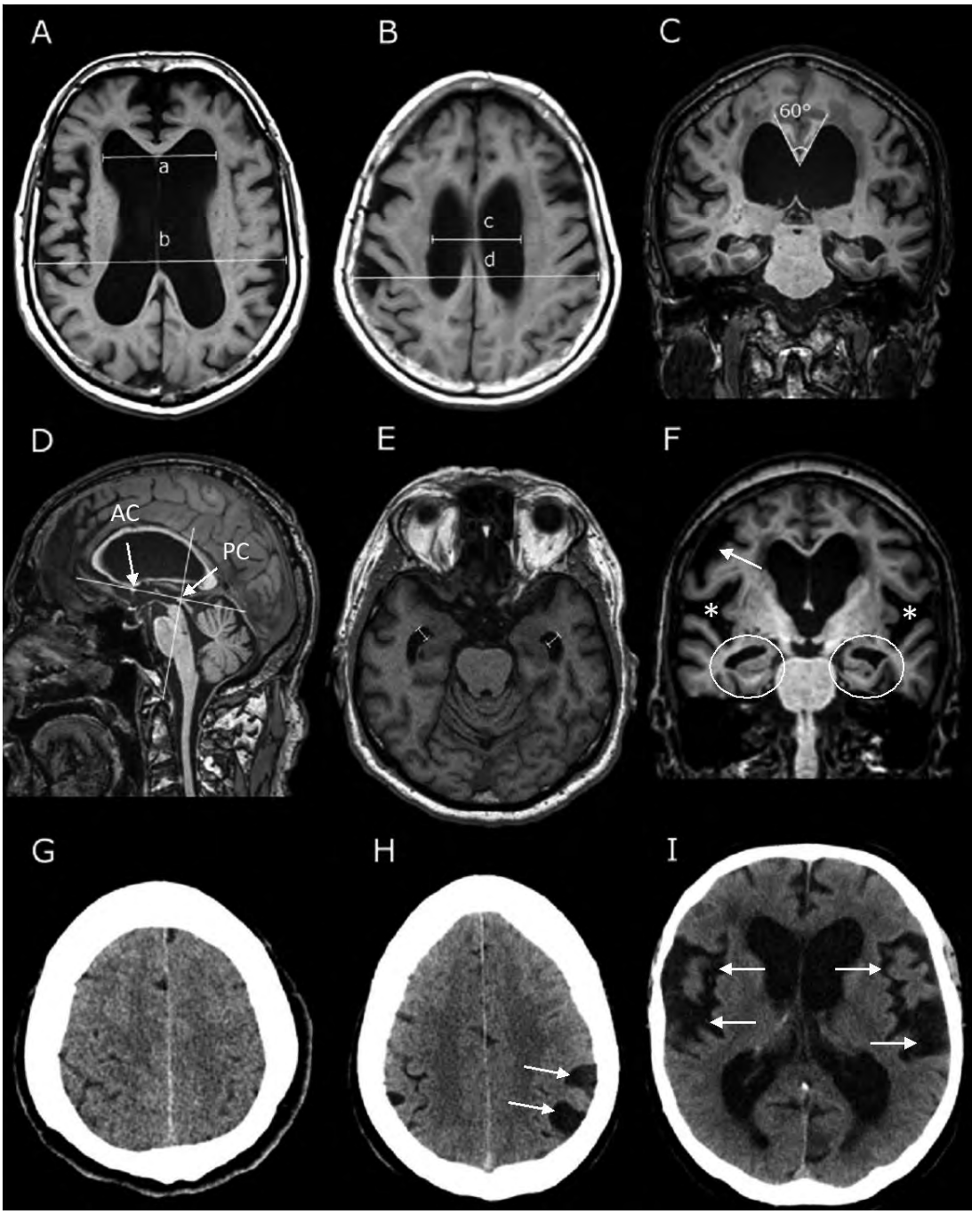

Figure 2. The radiological markers used in iNPH and differential diagnostics. **A.** Evan's index = a/b. **B.** Modified cella media index = c/d. **C and D.** Callosal angle 60°, coronal and sagittal planes, T13D 3-T MRI. The angle is measured on a coronal plane (C) perpendicular to the anterior commissure (AC) - posterior commissure (PC) line at the level of the PC (D). **E.** Enlarged temporal horns, axial T13D 1.5-T MRI. **F.** Disproportionally enlarged subarachnoid spaces (severe); enlarged Sylvian fissures (*) and lateral ventricles, and tight high convexity. Medial temporal lobe atrophy on both sides marked by circles, Scheltens scores 2 on the patient's left and 1 on the right side. Focally dilated sulcus on the right (arrow). T13D 3-T MRI. **G.** Narrowed sulci over the high convexity, CT. **H.** Focally dilated sulci (arrows), CT. **I.** Severely dilated Sylvian fissures (arrows), CT.

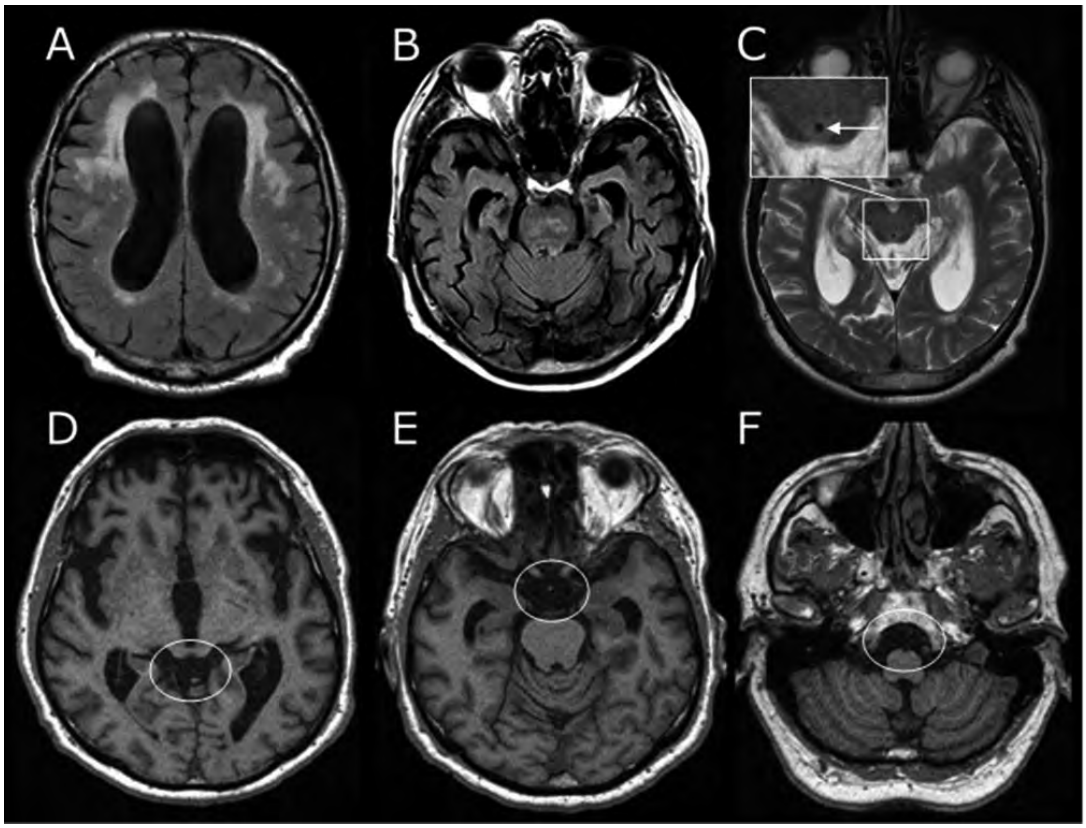

Figure 3. The radiological markers used in iNPH and the differential diagnostics. **A.** Periventricular and deep white matter hyperintensities, beginning confluence on the Fazekas scale, axial T2 FLAIR 1.5-T MRI. **B.** Brain stem white matter hyperintensities, beginning confluence, axial T2 TIRM (turbo inversion recovery magnitude) 1.5-T MRI. **C.** Aqueductal flow void (arrow), axial T2 1.5-T MRI. **D.** Mildly enlarged quadrigeminal basal cistern marked by circle, axial T1 1.5-T MRI. **E.** Mildly enlarged supracellar basal cistern marked by circle, axial T1 1.5-T MRI. **F.** Mildly enlarged infrapontine cistern marked by circle, axial T1 1.5-T MRI.

2.4.4 Intracranial pressure (ICP) measurements and other tests of the cerebrospinal fluid (CSF) dynamics

In iNPH, disturbed CSF circulation results in occasional increases of ICP. Invasive ICP measurement that lasts at least 24 hours offers the most accurate information about daily pressure fluctuations, daily mean pressure and pulse pressure values (113). The measurement can be performed through the lumbar SAS, intraventricular cavity, parenchyma, or epidural space (11). On the negative side, such monitoring is extremely resource-demanding and taxing for the hospital staff and the patient. However, a simultaneous brain biopsy may further assist in the differential diagnosis and the prognostic evaluation of patients with suspected iNPH (12,114,115).

The ICP A waves (plateau waves), B waves (rhythmic oscillations, slow waves), and C waves (small rhythmic oscillations) were first described by Lundberg in cases with intracranial lesions and intracranial hypertension of other origin in 1960 (Figure 4) (116). Similar waves can be seen in iNPH (117). During a Lundberg A wave, the ICP is elevated, being over 50 mmHg for 5 to 20 minutes, resulting in a vasodilatation, and reflected in decreased compliance, low cerebral perfusion pressure and blood flow (ischemia) (118). During a B wave, the ICP is lower than in an A wave, *i.e.* <50 mmHg (116), and a B wave lasts 20 seconds to 3 minutes (117). The B waves are considered to be caused by rhythmic cerebral blood volume oscillations affecting the ICP due to low craniospinal compliance (117). Underlying reasons for these oscillations might be respiratory changes and occasional increases of CO_2, the brain-stem rhythm, the speed of the blood pressure reduction, and the reduction in the cerebral perfusion pressure (117). The amplitude of the C waves is <20 mmHg, and a C wave lasts for 7.5-15 seconds (116). The C waves are considered to be related to variations of the systemic arterial blood pressure (Traube-Hering's) waves (116).

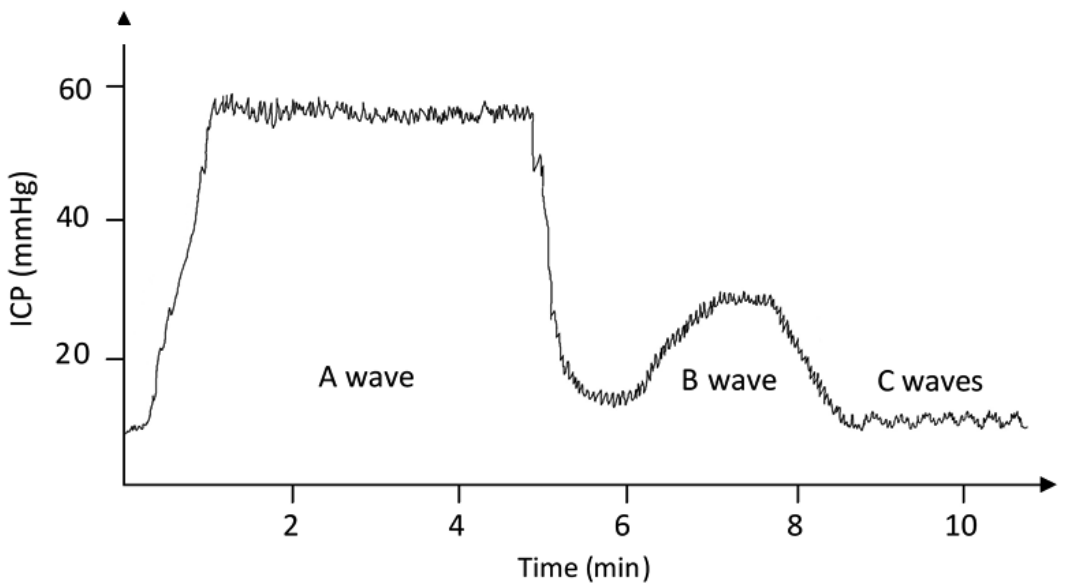

Figure 4. A sketch of the A, B, and C waves of ICP.

Close to the upper limit of normal pressure (ca. 18 mmHg) baseline ICP (119,120), increased frequency of B waves (occur usually during sleep (120), >15% of time), and increased pulse pressure amplitude (40,121-123) (>9mmHg) (124) might predict the shunt response (11). A markedly elevated ICP points to other diagnosis than iNPH (11). However, there are also conflicting reports regarding the baseline ICP (125,126), and the frequency of B waves in the prediction of the shunt response (126,127).

The relationship between the ICP measurements and the radiological findings have not been well-established in iNPH. DESH was found to be a useful primary test in predicting the shunt response, but if no DESH sign is found, an invasive test (*e.g.* ICP measurement) is indicated for additional information (93).

Several other techniques for measuring the CSF dynamics (in addition to the CSF pressure measurement) are used to improve the diagnostic evaluation. For example, CSF removal and resistance to the CSF outflow tests are commonly used. The CSF removal tests through the lumbar puncture consist of a spinal tap test (*i.e.* 30-70 ml CSF removal, can be repeated for 2-3 days), and external lumbar drainage (ELD) (*i.e.* 150-200 ml CSF removal for 2-7 days), the latter of which is performed if the tap test remains negative (61). These tests simulate a shunt placement and are considered positive if the patient's symptoms improve (96). The tap test is more specific (60-100%) than sensitive (50-80%), meaning that a patient with a negative tap test can still benefit from shunting (96). ELD instead has high positive and negative predictive value, but the major dreaded risk is a bacterial meningitis that occurs in 2-3% of the patients (96). Lastly, the CSF infusion test is used to discover features describing intracranial compliance, such as resistance to the outflow (R_{out}) (which increases in iNPH) and its inverse, conductance (96). The infusion test is performed by infusing a Ringer lactate though a spinal needle and recording the CSF pressure though another spinal needle at the same time (96). The accuracy of R_{out} depends on the method used (128). R_{out} increases the accuracy of the diagnosis when the tap test is negative (128). It is used everywhere else but the United States (96).

2.4.5 Other suggested tests for the iNPH diagnostics

Cisternography is nowadays considered not to bring additional benefits into the diagnostics because it does not improve the diagnostic accuracy (128). The cerebral blood flow measurements have been proposed for diagnostics, but there is no current clinical use for them (91). Several CSF biomarkers have been suggested for diagnostics, but a high level of evidence is still missing (11).

2.4.6 Differential diagnosis

The iNPH mimicking symptoms are common in the aged population due to a variety of other more common causes than iNPH. In addition, the brain ventricles are enlarged in over one-fifth of the normal aged population (129), making the differential diagnosis more challenging. Clinically the most important conditions in the differential diagnostics are AD, VAD, and PD. Other possible disorders are for example spinal stenosis, bladder instability, enlarged prostate, peripheral neuropathy, degenerative arthritis, hypothyroidism, frontotemporal dementia, Lewy Body Dementia, progressive supranuclear palsy and other Parkinson-plus syndromes (62,130).

The majority of iNPH patients have gait disturbance as a first, or at least the worst symptom (62,131). In AD, the gait problems occur at a later stage. Instead, cognitive

impairment (especially impaired episodic memory in typical AD or visuospatial and visuoperceptual skills in posterior cortical atrophy) (11) is more disabling than in iNPH (132). Medial temporal lobe atrophy supports the AD diagnosis (86). Compared to PD, iNPH patients walk with a widened base, the walking does not improve with environmental or verbal cueing, and patients do not response to levodopa (131).

Those patients with only cognitive impairment or urinary incontinence should be evaluated for other conditions first, before suspecting iNPH (62,96). Those with gait problems and incontinence, but without the cognitive impairment should be evaluated for spinal cord disorders first (62,96). Patients with acute reason for hospitalization should be evaluated and treated for other causes (96). INPH evaluation and testing should be done during a stable stage, after other disorders have been excluded or treated (62,96).

In addition to recognizing cerebral atrophy, brain imaging is helpful for example in excluding obstructive hydrocephalus (*e.g.* aqueductal stenosis and tumours) and vascular dementias (*e.g.* Binswanger's disease) (132). For the diagnosis of VAD, the brain imaging must show signs of a relevant cerebrovascular disease *i.e.* multiple large vessel infarcts, a single strategically placed infarct, multiple basal ganglia and white matter lacunar infarcts, or periventricular white matter lesions (133).

Another disease that resembles iNPH is a longstanding overt ventriculomegaly in adults (LOVA) (134). In LOVA, the head circumference is more than 2 standard deviations above the 98th percentile, suggesting a compensated hydrocephalus and head enlargement has started before the cranial sutures have fused in childhood (134). However, the symptoms begin to show later in life as hydrocephalus becomes decompensated, with decreased intracranial compliance and relatively high ICP dynamics. LOVA presents often with aqueductal stenosis and endoscopic third ventriculostomy is the suggested primary treatment rather than shunting (134).

Finally, it has to be remembered that the shunt surgery relieves mainly iNPH-related symptoms. Unresponsiveness to the shunt surgery may indicate another disease than iNPH.

2.4.7 Comorbidities

Comorbidities impair the prognosis of iNPH and are thereby important to recognize (130). Because WMC related to the white matter ischemia are often present in the brain images of iNPH patients, iNPH has been suggested to share same pathophysiology as vascular diseases and even to be a subgroup of vascular dementia (13,135,136). Hospital-based, case-controlled studies have shown that vascular risk factors such as hypertension and diabetes mellitus are common in iNPH patients and the most common iNPH comorbidities with them are cerebrovascular and cardiovascular diseases (135,137). However, in a population-based study, diabetes and coronary artery disease were as frequent in iNPH suspects as in the control population, but this result might be falsely negative due to the small number of iNPH patients and thus, due to the lack of statistical power (135). Supportively, in the same study, diabetes was associated with ventricular enlargement in people not fulfilling the iNPH criteria. It is not known if the treatment of the vascular risk factors would increase the life expectancy in iNPH patients or even postpone or prevent iNPH.

After the vascular risk factors and diseases, other common comorbidities are neurodegenerative disorders, AD in particular (130,137). AD-related pathology (neuritic plaques and neurofibrillary tangles) has been seen in the brain biopsies of iNPH patients

(114,138). Indeed, AD has been suggested to have the same pathophysiology as iNPH (47). AD does not always reduce the chance of a favourable outcome, but it may have an effect on the brain's recovering capacity (139). However, contrary results regarding the shunt outcome of iNPH-AD patients have also been published (114).

Other possible brain-originated neurodegenerative comorbidities are for example PD, dementia with Lewy bodies, and frontotemporal dementia (130). Other common comorbidities are *e.g.* musculoskeletal conditions, urinary problems, and psychiatric disorders (130).

2.5 TREATMENT AND OUTCOME

2.5.1 Natural course and mortality

The natural course of iNPH has not been properly investigated. Patients are usually straightforwardly shunted despite the lack of studies supporting the shunt surgery over non-shunting, resulting in a lack of knowledge of the long-term outcomes in untreated patients. However, recently an observational population-based study showed that those with untreated probable iNPH had an increased risk of mortality (140). In asymptomatic individuals or those with possible iNPH, the risk of dementia, but not mortality, was increased, but these patients were younger and the statistical power was probably too low to compare mortality (140). Also, the authors state that based on their study it is unclear whether shunting reduces mortality and that further studies are needed (140). Additionally, after shunting the quality of life improves according to some studies (141,142).

Other previous studies on the natural history of the untreated iNPH patients have shown that the symptoms (cognition, gait, urinary incontinence) worsen over time (143-147). Again, however, in Andren *et al.* study, the patients in the delayed iNPH shunting group ($iNPH_{Delayed}$) were significantly older than the iNPH patients that were shunted earlier ($iNPH_{Early}$) (144). The symptoms changed inconsistently, in some patients even without shunt minor improvement was found, but mostly deterioration (144,147). However, when treated, there was no difference in the improvement after the shunting of $iNPH_{Delayed}$ compared to $iNPH_{Early}$ group (although the stage of the iNPH symptoms had progressed further in $iNPH_{Delayed}$), which emphasizes the reversible feature of iNPH (144).

Shunted iNPH patients tend to die 2.5-3.3 times more likely than healthy controls (148,149), typically due to vascular causes (12,148-150).

2.5.2 Shunt surgery

Currently, the main treatment for INPH is surgical, in which a shunt is inserted into the brain ventricles or lumbar space, which leads the CSF away into the atrium or peritoneum [ventriculoatrial, ventriculoperitoneal, or lumboperitoneal shunt (VA shunt, VPS, LPS)] (11). A shunt catheter is a flexible tube that has proximally a one-way valve, which is usually adjustable (61,96). For the diagram presenting a shunt, see Figure 5.

Endoscopic third ventriculostomy (ETV) has commonly been used for treating obstructive hydrocephalus (151,152). Alternatively, it is also possible to perform an ETV in this subgroup of patients with non-obstructive, communicating hydrocephalus (iNPH) by perforating the floor of the third ventricle (153), which leads the CSF into the SAS and restores the pulsatility of the cerebrum (151). Supposedly this surgery helps if there is a

functional block in the aqueduct (151). Contrary views have also been presented considering the ETV in iNPH (11,61).

Evidence of the benefits of the shunt surgery compared to non-shunting is still limited. Studies investigating the response to placebo (sham), preoperative CSF tests and surgery would be of a great value in providing information about the patient selection to shunting (154). However, there is some evidence from small randomized controlled (inactive shunt/postponement) trials (104,155,156), and observational evidence that symptoms progress without the shunt (145).

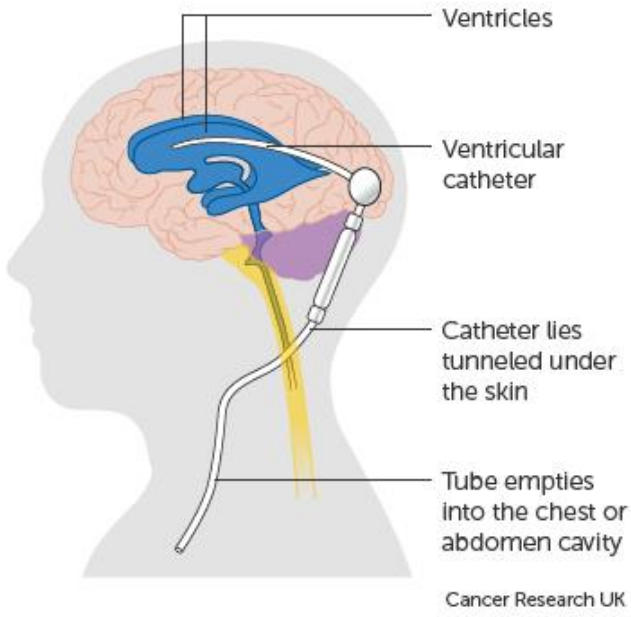

Figure 5. The shunt placement. Adapted from (157).

A recently published open-label randomized trial showed that the shunt surgery might be useful for iNPH (155). There were two treatment groups, and in the control group the shunt surgery was postponed by 3 months. However, this study was performed with lumboperitoneal shunts, which are not commonly used in Europe, with a relatively small participant number of 93 patients, and there was a high risk of serious adverse events (22%) (155).

During 2008-2011, two British neurosurgeons (Toma A.K. and Watkins L.D.) tried to conduct a randomized double-blinded surgical trial with an inactive shunt valve as control (3 months) but managed to recruit only 14 patients (156,158). Toma A.K. *et al.* published a study on the natural history of iNPH in 2011, indicating that shunting leads to a better outcome and that a treatment delay is harmful (145), and at the same time the original randomized trial was terminated (158). Nevertheless, the analysis in the succinct letter shows that the walking speed of the patients with low opening pressure valve improved significantly compared with the patients with high opening pressure valve (156). Unfortunately, no article has been published regarding the entire investigation. Another randomized double-blinded controlled trial (open vs. closed shunt for 3 months) in 2011

found that symptomatic iNPH patients with widespread WMC and no obvious CSF dynamic disturbances improved after the VPS surgery (104).

Frequency of the overall favourable shunt response varies from 31% to 96% (10,19,102,123,124,143,155,159-165), depending on the definition of iNPH (shunt surgery criteria), shunt response, and in what manner and how soon the shunt response is assessed or measured. In a systematic review, Hebb and Cusimano found the shunt response to be even as low as 29% (161). In recent years, however, the shunt outcome has improved (10). Overall, the shunt surgery seems to relieve the symptoms and is associated with a better outcome in most iNPH patients (143,162). Gait is most likely to improve, cognitive impairment and urinary incontinence mitigate as well, but to a lesser extent (11,166). However, recent studies have shown that iNPH may cause irreversible dementia even if shunting takes place (167).

Every surgery has its risks; thus, the benefits of a surgery must be presumably higher than the risks of adverse events. Possible complications of a shunt surgery are shunt infection, shunt malfunction, subdural and intracerebral haematoma, subdural hygroma, epilepsy, intra-abdominal complications, cardiopulmonary and renal problems (168-170). The complication rate was 8.2% in a systematic review of the shunt surgery outcome (10). Shunt surgery is nowadays considered to be safe and beneficial when iNPH patients are selected accurately and carefully (10,150,171,172). VPS is most commonly used in Europe (155), but both the VA shunt and the LPS have been suggested as an alternative primary treatment (155,170,173,174). Compared to the VPS surgery, the LPS surgery has a relatively high shunt failure rate (175). Prospective studies have shown that there is not much difference in the improvement after the shunting between the VPS vs. VA shunt (150), or the VPS vs. LPS (175). However, randomized controlled trials comparing the VPS vs. LPS, the VPS vs. VA shunt, and the VA shunt vs. LPS are missing.

2.5.3 Outcome predicting factors

Numerous functional and physiological prognostic tests and other factors have been suggested for predicting the outcome of an iNPH surgery (7). For radiological markers, the DESH sign has been reported to indicate the shunt response (85,176,177), and similar results have been found considering a small CA (81,85), high-convexity tightness (178), wide WTH (83,85), and flow void in the cerebral aqueduct (105). Contrary results considering the high-convexity tightness (85) and the flow void have also been published (85,106-108). Virhammar *et al.* also found that dilated Sylvian fissure, focal bulging of the roof of the lateral ventricles, enlarged 3rd ventricle, WMC, or FDS did not predict the shunt response (85). Since EI has been used as the inclusion criteria in the iNPH studies, the shunt response predicting feature cannot be determined easily. Nevertheless, EI has been reported to not be associated with the shunt response (166). Decrease of the ventricular size postsurgically does not predict the shunt response either (71,73).

Ventriculomegaly in aged patients without a prior stroke or dementia have been associated with higher mortality (179). Features of the DESH have been associated with higher mortality than enlarged ventricles or normal MRI, but there was no comparison within the iNPH patients and the sample size was small (180). WMC are associated with higher mortality in both the general population and the high-risk groups (14). The WMC in the brain stem are also associated with a poor clinical outcome in the poststroke population (181). The WMC have been connected to vascular diseases, but despite that even the iNPH

patients with extensive WMC have benefitted from shunting (85,102,104,182), and the current view is that WMC cannot be used to predict the outcome (11,183). In addition to the WMC, especially microbleeds predicted a higher mortality in a memory clinic population, whereas the association with atrophy was not as clear (15). Cerebral atrophy may be present in iNPH patients (11). Medial temporal lobe and general atrophy have been associated with poor prognosis in various non-iNPH populations (15,184-187). Shunt surgery has still been reported to sometimes be effective in a mild or moderate cortical atrophy (73).

A patient can respond to shunting even if there is only one symptom of the triad present (11). Especially those patients with a full triad (159) but also those with gait impairment as the main symptom (166,188), only a slight degree of dementia (164), and shorter duration of the symptoms (164,166,188,189) have had a better shunt outcome. There are also studies with contrary results regarding the symptom duration (73,144,159). In some studies, comorbidity has been inversely (114,189,190), and younger age and female gender directly associated with a favourable shunt outcome (191). Contradictory results about age have also been published (159,162).

Measurements of the peak flow velocity and the stroke volume of the CSF, CSF tap test and continuous drainage have predicted the shunt response (11). Contradictory results are published considering the CSF outflow resistance, the high baseline ICP and the frequent presence of the ICP B waves, but the CSF outflow conductance, and increased CSF pulse pressure amplitude with decreased latency of the ICP pulse wave (from the valley to the peak) are reported mostly in shunt-responsive patients (11).

3 Aims of the study

The main aim of this thesis was to investigate the role of radiological findings in iNPH.

The specific aims of the studies were:

1. To discover which of the multiple previously-studied radiological markers are the most useful in the diagnostics of iNPH and to study if they can predict the shunt response. (Study I)

2. To study the associations between the ICP measurements and the radiological markers, the brain biopsy results, and the shunt surgery outcome. (Study II)

3. To examine the relationship between the radiological markers and mortality in iNPH. (Study III)

4 Methods

4.1 KUOPIO NPH REGISTRY

4.1.1 Study population

All the patients of Studies I-III were from The Kuopio University Hospital (KUH) NPH registry (www.uef.fi/nph), which was started in 1991 and includes patients from four central hospitals of Middle and Eastern Finland. The patients were primarily examined by neurologists. All registered patients were suspected to have NPH and had one to three symptoms of the NPH-symptom triad (gait disorder, cognitive impairment, and/or urinary incontinence) in the neurological assessment and ventriculomegaly (Evans' index ≥0.3) on a CT and/or MRI of the brain. Further examinations to confirm the NPH diagnosis were carried out by neurosurgeons. The KUH NPH registry consists of the data collected retrospectively of the clinical characteristics at the baseline and follow-up appointments, and includes brain biopsy findings, ICP measurements, medications, radiological findings, anamnestic information of other diseases, and causes of death. Formation of the substudy populations is presented in Figure 6.

4.1.2 Brain biopsy

All patients that underwent the ICP measurement and/or the shunt surgery received a right frontal 12-mm burr hole, approximately 3 cm from the midline and close to the coronal suture of the skull under the local anesthesia and sedation. One to three cylindrical cortical brain biopsies (2-5 mm diameter, 3-7 mm length) were obtained from the hole with forceps.

Paraffin-embedded biopsy samples were sectioned (7 μm) and stained with hematoxylin-eosin. The sections were immunostained with monoclonal antibodies directed at Aβ and hyperphosphorylated tau (HPτ) as described previously (192). A neuropathologist histologically classified the immunoreactivity of all the samples for Aβ and HPτ (present or absent).

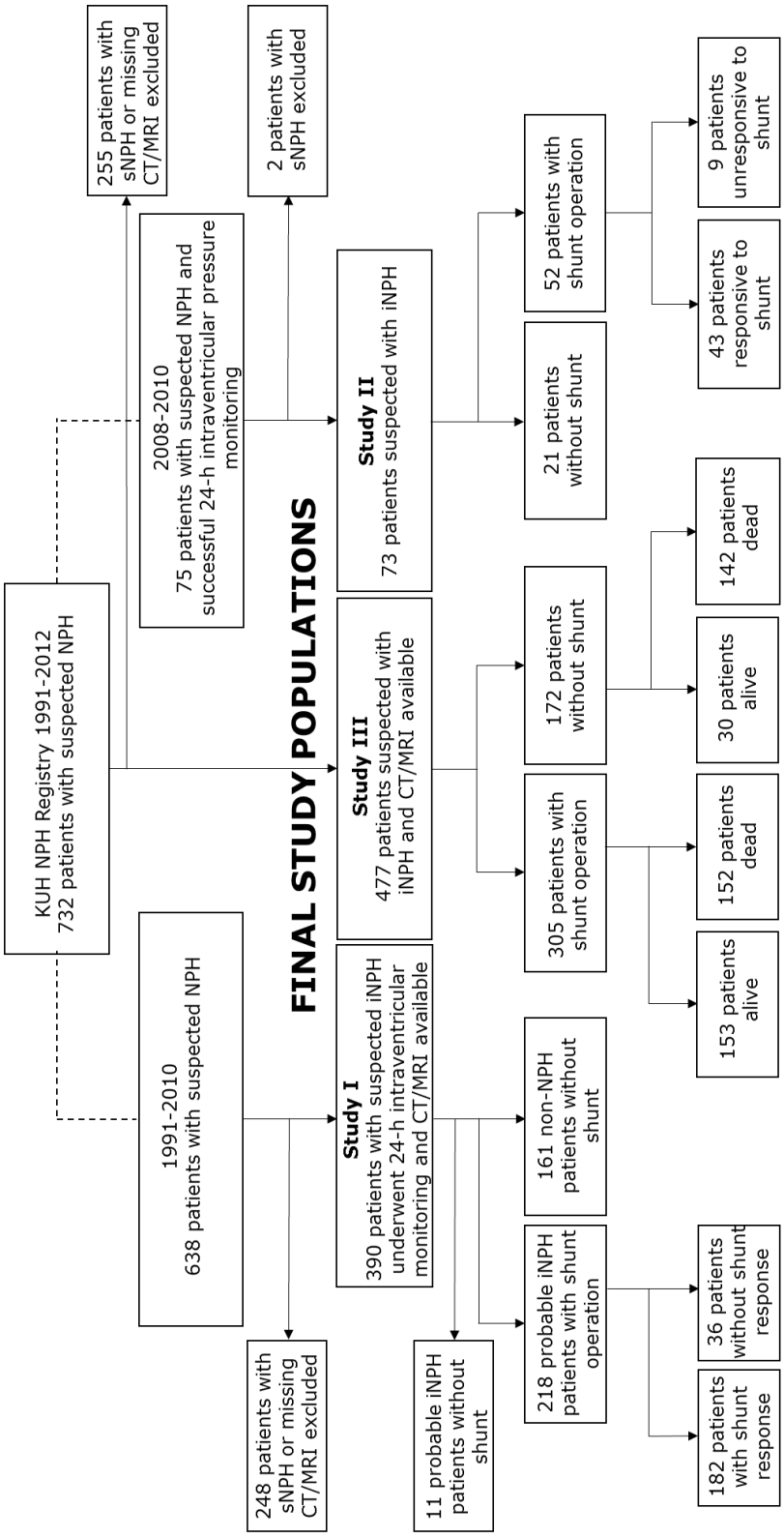

Figure 6. Flow-chart of the study populations. *iNPH* idiopathic normal pressure hydrocephalus; *sNPH* Secondary normal pressure hydrocephalus.

4.1.3 ICP measurement and shunting

After obtaining the brain biopsy, a catheter (an ICP measurement or a shunt) was planted through the burr hole into the right lateral ventricle. An arterial blood pressure measurement system was used to measure the ICP and an in-house registration and analysis software was used. The entire measurement was performed in a horizontal position. The mean ICP and the mean pulse wave amplitude were measured for each patient with the reference point on the level of the forehead. Continuous waveforms were digitized at a 1-kHz sampling frequency and analyzed with an in-house software. The cardiac beat-induced pressure waves were averaged over 6-s time intervals, and the mean pulse wave amplitude and the mean ICP wave amplitude for each 6-s interval were computed. With these mean values, the mean pressure values over a 24-h period were calculated (193). The presence of A waves (116) (yes or no) and the frequency of B waves (117) (none, <10%, 10-30%, >30%) were evaluated visually. We detected no Lundberg A waves.

Until 2010, the indications besides the EI >0.3 and the iNPH symptoms for the shunt were: 1) a baseline ICP that remained continuously >10 mmHg; if the baseline ICP remained <10 mmHg the indications were: 2) multiple B waves that comprised >30% of the pressure waves in the 24-h ICP monitoring or 3) the presence of any A waves (167,194). After 2010, the indications besides the EI >0.3 and the iNPH symptoms for the shunt surgery were a positive tap test, or if negative, a positive infusion test. If the infusion test was also negative, some patients were still shunted based on a clinical assessment.

Based on the ICP measurement results, patients of Study I (n=390) were classified as having probable iNPH (n=229) or unlikely iNPH (non-NPH, n=161). A total of 218 patients were shunted based on ICP monitoring and clinical evaluation. Eleven probable iNPH patients did not undergo the shunt operation due to advanced comorbid dementia (n=5), death before shunting (n=1), decline of the clinical condition due to comorbidity (n=4), or declining the shunt surgery (n=1).

Between 2008 and 2010, altogether 75 patients of The KUH NPH registry had 24-h ICP monitoring data available and collected into the registry in addition to other clinical evaluations and brain imaging. Two of these patients with sNPH were excluded from Study II. The shunt surgery was performed on 52 patients.

In Study III (n=477), the shunt surgery was performed on 305 (64%) patients. Five patients were not shunted although the main cause of death was iNPH, because one patient declined the shunt surgery, one died before the shunting, and three patients were in poor general health.

For the present Studies I-III, shunt revisions were performed for 22-25% of the shunted patients. Second, third, and fourth revisions were performed for 6-8%, 1-2%, and 0.3-2% of the shunted patients, respectively (Study I-III). Mainly the VPS were placed. Only three VA shunts were placed in revision. No LPS were used. Until 2010, a fixed pressure valve with an anti-siphon device was used. After 2010, a programmable valve with an anti-siphon was used.

4.1.4 Shunt response

The response to a shunt (no change or deterioration vs. improvement) was determined by evaluating the patient's memory, gait and urinary continence at the outpatient clinic and two to three months after the shunt surgery. Other clinical data was obtained from the patient records. The patients were then followed up by the local neurologist, general practitioner, or geriatrician. The shunt response status was updated if the patient's symptoms were relieved after the revision.

4.1.5 Comorbidities

Clinical data, including comorbidities such as heart disease, hypertension, and diabetes were collected retrospectively from the patient records. If a patient had coronary heart disease, atrial fibrillation, other significant arrhythmia, or chronic heart insufficiency, a heart disease was considered to be present.

4.1.6 Causes of death

The main causes of death were determined from the official death certificates provided by Statistics Finland (12) (Table 5). Stroke (n=36) and other cerebrovascular diseases (n=15) as the main causes of death were combined into one group (total n=51) for the statistical analyses. Of the stroke deaths, 10 were haemorrhagic strokes (5 intracerebral haemorrhage, 3 subarachnoid haemorrhage, 2 other), 6 were ischemic strokes, 10 unknown strokes, and 10 late effects of stroke. The 15 deaths related to cerebrovascular diseases were vascular cognitive impairment due to chronic subcortical vascular changes or a stroke in any area of brain. A total of 294 patients (62%) died during the Study III follow-up (median 5.6 years).

4.1.7 Ethical considerations

The KUH Research Ethics Committee (Study I-III), the Finnish National Supervisory Authority for Welfare and Health, and the Finnish Ministry of Social Affairs and Health (Study I, III) approved the KUH NPH registry studies. Informed consents were obtained from the patients in Study II. The studies were conducted in accordance with the Declaration of Helsinki.

4.2 RADIOLOGICAL EVALUATION

4.2.1 General description

CT and MRI were performed in five hospitals from 1991 to 2012. Due to this, a variety of imaging protocols and scanners were used. The CT and MRI images were retrospectively evaluated by a neuroradiologist by using a structured form on a Sectra-PACS workstation (IDS7, version 15.1.20.2, Sectra AB, Linköping, Sweden). A trained medical student measured certain radiological measurements. If both the CT and MRI scans were available, the MRI was evaluated.

Only CT scans were available preoperatively for 268 (69%), 23 (32%), 295 (62%), only MRI for 56 (14%), 19 (26%), 74 (16%) and both CT and MRI scans for 66 (17%), 31 (42%), 108 (23%) patients, in Studies I, II, and III respectively.

In Study I, of the 218 shunted patients, 33 patients had no follow-up images at the time of the radiological evaluation, because either imaging was not performed (n=12) or imaging studies performed outside of the KUH were not accessible (n=21). The time interval

between the shunt surgery and the postoperative follow-up image was on average 1.5 years (SD ±2.2).

For Study II, the primary CT and MRI scans were performed before the ICP measurements (median 3.7 months, IQR 0.0 to 6.2 months).

4.2.2 Visual evaluations

The visual evaluation of the size of the lateral ventricle, the Sylvian fissures and the basal cisterns (all: normal, mildly enlarged, moderately enlarged, or severely enlarged) was performed (CT or MRI) (Table 1) (39). Superior convexity and the medial SAS (decreased, normal, or mildly enlarged) (39) and the disproportionality between the Sylvian and suprasylvian SAS (no, mild, or severe) were also evaluated (CT or MRI). The presence of FDS (yes or no) (CT or MRI) (39) and the aqueductal flow void (yes or no, Study I: n=120, Study III: n=180, good quality MRI required) (105) were documented. The medial temporal lobe atrophy (Study I: n=80, Study II: n=50, Study III: n=181) was assessed on the coronal T1-weighted MR images by using the Scheltens score (86). The WMC in the periventricular and deep white matter (Study I: n=346) were evaluated with the Fazekas scale both on MRI and CT (103), and the T2 hyperintensities in the brain stem (Study I: n=62, Study III: n=212) by using a similar evaluation.

Certain radiological markers (superior convexity/medial SA spaces, periventricular/deep WMC) and categories of radiological markers were combined to create larger groups for the statistical analyses and illustrative purposes.

4.2.3 Measurements

The ventricular size was measured by using EI, mCMI, and the WTH (measured with a 0.1 mm accuracy) were measured on CT or MRI, and the CA on MRI (Figure 2.) (Table 1) (63,76,80,83). EI was defined as the ratio between the maximal width of the frontal horns of the lateral ventricles and the maximal inner diameter of the skull. MCMI was defined as the ratio of the maximal width of the cella media (*i.e.* the central part of the lateral ventricles) and the maximal inner diameter of the skull at the same level on an axial plane. The CA was measured between the lateral ventricles through the posterior commissure on a coronal plane perpendicular to the anterior commissure-posterior commissure line visualized on a sagittal plane, from a three-dimensional T1-weighted multiplanar reconstruction sequence MRI (Study I: n=55, Study III: n=100). The WTH were measured on an axial plane and their mean was computed.

4.3 STATISTICAL ANALYSES

The differences in the means between the groups were analyzed with a t-test or ANOVA for the continuous variables, and Fisher's exact test was used for the categorical variables. Pearson's correlation coefficients are reported for the correlations. The BMI and the mean WTH were log-transformed for the t-tests, ANOVA, and Pearsons correlations (Study I). The categories of a multilevel radiological marker that had fewer than five (Study I) or three (Study II) subjects were combined for the statistical analyses. For the repeated measures, associations between the categorical variables were analyzed by using Bowker's test, and for the continuous variables by using a paired t-test (Study I). Multivariate binary

logistic regression analysis was used to study the associations of the radiological markers with an iNPH diagnosis (Study I). Logistic regression models were adjusted for gender, age, and imaging method (MRI/CT) (Study I). The explanatory variation of the model was tested by using the Nagelkerke's pseudo R^2 (Study I).

In Study II, the backward and forward stepwise linear regression modeling was used to find the most suitable model for predicting the mean ICP by including only the variables (excluding the shunt status) which were significantly associated with the mean ICP in the univariate analyses.

For the statistical analyses in Study III, twelve missing BMI were filled in with the mean BMI of the study population. The follow-up in Study III was conducted until death or the end of 2015. The Cox regression model was used to study the associations between the radiological markers and mortality, with adjustments for BMI, age, gender, imaging method (CT [n=295] or MRI [n=182]), shunt status, hypertension, diabetes, and heart disease. The Schoenfeld residuals were plotted against time to verify the proportional hazards assumption. For illustrative purposes the Kaplan-Meier survival curves and the respective log-rank P-values were calculated. For illustrative purposes the categories were used as continuous linear variables. The sensitivity analyses were made by adjusting the Cox regression models additionally for a mini-mental state examination (MMSE) score (n=366) or the main symptom (n=372). The shunted and non-shunted groups were also analysed separately.

In Study III, all radiological markers which were separately associated ($P<0.10$) with mortality were included in a combined model to determine which ones were independently associated with mortality. To compare the hazard ratios (HR) of two different models with a different number of participants and adjustments statistically, a bootstrap analysis was used with 5000 cycles during the calculation. In every cycle, a ratio of $HR_{adjusted}/HR_{crude}$ was calculated. The confidence interval (2.5% and 97.5% percentiles) and the P-value for this ratio was then determined.

The P-values of <0.05 were considered statistically significant. The IBM SPSS Statistics 19 (Study I) and 23 (Study II and III) softwares were used for the statistical analyses. In Study III, the bootstrap analysis was completed with an R software (version 3.2.5).

5 Results

5.1 GENERAL BASELINE CHARACTERISTICS

The general characteristics at the baseline are presented in Tables 2-4 (Studies I-III). In Studies I-II, the patients were divided into three groups: no shunt, no shunt response, and shunt responsive. In Study III, two groups were used, shunted and non-shunted. There was no difference in the gender distribution between the studied groups in all studies. In Studies I and III that had the larger populations, no difference regarding the ages between the groups was found. Of the shunted patients, 83-84% had favourable response in Study I-III (Figure 6).

5.1.1 Study I

There was no difference between the right and left WTH, thus the mean WTH was used in the further analyses. Also, no difference was found between the left and right medial temporal lobe atrophy that was evaluated visually with the Scheltens scores, thus only the left medial temporal lobe scores were used in the analyses. Preoperative EI correlated with mCMI ($r=0.78$, $P<0.001$) and the mean WTH of the lateral ventricles ($r=0.50$, $P<0.001$).

No significant interactions were found between the imaging methods (MRI and CT) and the radiological markers in relation to the iNPH diagnosis or the shunt response in the logistic regression models of Study I adjusted for gender, imaging method, and age.

5.1.2 Study II

Gait impairment was the main symptom more frequently in the shunt responsive group than in the no-shunt group (70% vs. 29%, $P=0.005$; Table 3). No difference was discovered in the symptom duration or the other symptoms (gait/cognition/incontinence) among the three groups. BMI was higher in the shunt responsive than the non-responsive group ($P=0.033$). The shunt responsive patients were younger than the patients with no shunt response ($P=0.049$). The patients without shunt response showed more AD-related brain biopsy findings (Aβ+, HPτ+) than the patients responsive to shunt (56% vs. 12%, $P=0.014$).

No correlation was found between the mean ICP pulse wave amplitude and the mean ICP. The more B waves there were, the higher the mean ICP was ($P<0.001$), but there was no association the with mean pulse wave amplitude. There was no difference in the mean ICP pulse wave amplitude among the studied groups. The mean ICP correlated with the BMI ($r=0.24$, $P=0.042$; Figure 7). A higher B wave frequency ($P=0.017$) was associated with gait impairment as the main symptom. Age, gender, BMI, gait disturbance, impaired cognition, urinary incontinence, symptom duration, and brain biopsy were not associated with B waves.

5.1.3 Study III

Cognitive impairment was the main symptom more frequently in the non-shunted than in the shunted patients (42% vs. 24%, $P<0.001$) in Study III. Gait impairment as the main symptom was more frequently noted in the shunted group than in the non-shunted group (52% vs. 18%, $P<0.001$).

There was no difference in the occurrences of heart diseases between the shunted and non-shunted groups. Hypertension (54% vs. 34%, P<0.001) and diabetes (27% vs. 13%, P<0.001) were more frequent in the shunted group. The BMI (P<0.001) and the MMSE scores were higher in the shunted group (P<0.001).

Disproportionality between the Sylvian and suprasylvian SAS (P<0.001), decreased superior convexity/medial SAS (P<0.001), larger Sylvian fissures (P<0.001), enlarged basal cisterns (P<0.001), presence of FDS (P<0.001), smaller EI (P=0.016) and mean WTH (P=0.010) were more common in the shunted group than in the non-shunted group. There was no difference between the other investigated radiological markers (size of the lateral ventricles, periventricular/deep or brain stem WMC, Scheltens score, aqueductal flow void, CA or mCMI) among the studied groups.

Mortality was higher in the non-shunted than the shunted patients (83% vs. 50%, P<0.001). The median time to death was 4.9 years for the shunted patients and 3.8 years for the patients without a shunt. Specific causes of death are presented in Table 5.

Table 2. The baseline characteristics of the study population (Study I).

		No shunt (n=172)		No shunt response (n=36)		Shunt responsive (n=182)		P-value
Gender	Female	81	(47)	17	(47)	101	(55)	NS
BMI (kg/m²)		26	±4.0	28	±5.1	28	±5.0	0.041
Age at the ICP monitoring (y)		72	±10	74	±9.1	72	±7.3	NS
Imaging method	MRI	47	(27)	9	(25)	66	(36)	NS
	CT	125	(73)	27	(75)	116	(64)	
Main symptom	Gait	28	(17)	14	(40)	94	(54)	<0.001
	Cognition	69	(42)	10	(29)	39	(22)	
	Other	67	(41)	11	(31)	41	(24)	
Lateral ventricle	Normal / mildly enlarged	46	(27)	9	(25)	42	(23)	NS
	Moderately enlarged	114	(67)	25	(69)	131	(72)	
	Severely enlarged	11	(6)	2	(6)	9	(5)	
Sylvian fissure	Decreased / normal	68	(40)	9	(25)	36	(20)	<0.001
	Mildly enlarged	75	(44)	16	(44)	78	(43)	
	Moderately enlarged	26	(15)	10	(28)	60	(33)	
	Severely enlarged	2	(1)	1	(3)	8	(4)	
Superior medial subarachnoid space	Decreased	109	(64)	29	(81)	163	(90)	<0.001
	Normal / mildly enlarged	62	(36)	7	(19)	19	(10)	
Superior convexity subarachnoid space	Decreased	86	(50)	23	(64)	134	(74)	<0.001
	Normal	85	(50)	13	(36)	48	(26)	
Basal cistern	Decreased / normal	154	(91)	30	(86)	141	(78)	0.003
	Mildly enlarged	15	(9)	4	(11)	34	(19)	
	Moderately / severely enlarged	0	(0)	1	(3)	6	(3)	
Disproportionality between the Sylvian and suprasylvian subarachnoid spaces	No	62	(36)	7	(19)	22	(12)	<0.001
	Mild	78	(46)	13	(36)	64	(35)	
	Severe	30	(18)	16	(44)	95	(52)	
Focally dilated sulci	No	119	(72)	18	(51)	91	(51)	<0.001
	Yes	47	(28)	17	(49)	89	(49)	
Periventricular white matter changes	No	32	(19)	5	(14)	39	(22)	NS
	”Caps” or pencil-thin lining	51	(30)	9	(25)	53	(29)	
	Smooth ”halo”	42	(25)	10	(28)	51	(28)	
	Irregular periventricular hyperintensity extending into the deep white matter	43	(26)	12	(33)	37	(21)	
Deep white matter changes	No	38	(25)	8	(25)	47	(29)	NS
	Punctate foci	42	(28)	5	(16)	49	(30)	
	Beginning confluence	30	(20)	8	(25)	34	(21)	
	Large confluent areas	40	(27)	11	(34)	34	(21)	
Brain stem white matter changes	No	17	(81)	6	(100)	29	(83)	NS
	Punctate foci / beginning confluence	4	(19)	0	(0)	6	(17)	
Atrophy of the left medial temporal lobe (Scheltens scores)	0/1	2	(8)	4	(67)	16	(33)	0.003
	2	12	(48)	1	(17)	26	(53)	
	3/4	11	(44)	1	(17)	7	(14)	
Aqueductal flow void	No	5	(11)	0	(0)	14	(21)	NS
	Yes	40	(89)	9	(100)	52	(79)	
Callosal angle (°)		67	±19	69	±10	62	±15	NS
Evans’ index		0.39	±0.08	0.38	±0.06	0.38	±0.04	NS
Modified cella media index		0.39	±0.07	0.39	±0.05	0.39	±0.05	NS
Mean width of the temporal horns (mm)		8.5	±4.4	7.5	±2.4	7.3	±2.5	0.021

Means ± SD or n (%) are presented. ANOVA or Fisher's exact test were used to calculate the P-values. NS; non-significant (P>0.05).

Table 3. The baseline characteristics of the study population (Study II).

		Shunt responsive (n=43)	No shunt response (n=9)	No shunt (n=21)	P-value Shunt respon-sive vs. No response	P-value No shunt vs. Shunt respon-sive
Gender	Female	23 (53)	7 (78)	10 (48)	NS	NS
Age at the ICP-measurement (y)		73.4±5.5	78.0±9.1	72.7±9.3	0.049	NS
BMI (kg/m^2)		28.1±5.3	26.7± 5.8	25.1±3.8	NS	0.033
Mean ICP (mmHg)		4.0 ±1.8	3.0±1.2	2.1±1.4	NS	<0.001
Mean ICP pulse wave amplitude (mmHg)		4.8±1.6	4.1±1.1	4.8±1.5	NS	NS
A waves of ICP	No	43 (100)	9 (100)	21 (100)	NS	NS
B waves of ICP (% of time)	No <10% 10-30% >30%	0 (0) 0 (0) 4 (9) 39 (91)	0 (0) 0 (0) 0 (0) 9 (100)	1 (5) 11 (52) 6 (29) 3 (14)*	NS	<0.001
Main symptom	Gait Cognition Other	30 (70) 11 (26) 2 (5)	7 (78) 2 (22) 0 (0)	6 (29) 13 (62) 2 (10)	NS	0.005
Gait disturbance	Yes	43 (100)	9 (100)	20 (95)	NS	NS
Impaired cognition	Yes	29 (67)	7 (78)	18 (86)	NS	NS
Urinary incontinence	Yes	35 (81)	8 (89)	13 (62)	NS	NS
Symptom duration (y)		2.5±1.8	1.8±1.1	2.2±1.6	NS	NS
Follow-up time (y)		5.4±1.2	4.5±1.9	3.6±2.2	NS	<0.001
Frontal cortical biopsy: beta-amyloid and hyperphosporylated tau (-/+) **	Aβ+HPτ+ Aβ+HPτ- Aβ-HPτ-	5 (12) 18 (43) 19 (45)	5 (56) 1 (11) 3 (33)	6 (30) 5 (25) 9 (45)	0.014	NS
Mean width of the temporal horns (mm)		8.0±2.9	7.7±3.8	9.1±2.3	NS	NS
Evans' index		0.39±0.04	0.36±0.04	0.38±0.05	NS	NS
Superior medial subarachnoid space	Narrowed Normal/mildly enlarged	40 (93) 3 (7)	6 (67) 3 (33)	12 (57) 9 (43)	NS	0.001
Superior convexity subarachnoid space	Narrowed Normal/mildly enlarged	29 (67) 14 (33)	4 (44) 5 (56)	5 (24) 16 (76)	NS	0.001
Disproportionality between the Sylvian and suprasylvian subarachnoid spaces	No Mild Severe	3 (7) 11 (26) 29 (67)	3 (33) 3 (33) 3 (33)	8 (38) 11 (52) 2 (10)	0.043	<0.001
Sylvian fissure	Normal Mildly enlarged Enlarged Severely enlarged	4 (9) 16 (37) 17 (40) 6 (14)	2 (22) 5 (56) 2 (22) 0 (0)	6 (29) 10 (48) 5 (24) 0 (0)	NS	NS
Focally dilated sulci	No Yes	22 (51) 21 (49)	8 (89) 1 (11)	18 (86) 3 (14)	NS	0.012
Basal cisterns	Normal Mildly enlarged Enlarged/severely enlarged	18 (42) 19 (44) 6 (14)	5 (56) 3 (33) 1 (11)	13 (62) 8 (38) 0 (0)	NS	NS
Periventricular white matter changes	No "Caps" or pencil-thin lining Smooth "halo" Irregular periventricular hyperintensity extending into the deep white matter	3 (7) 18 (42) 16 (37) 6 (14)	2 (22) 1 (11) 3 (33) 3 (33)	7 (33) 4 (19) 6 (29) 4 (19)	NS	0.035

Continued on the next page.

Table 3. Continued.

Deep white matter changes	No	6 (14)	3 (33)	5 (24)	0.012	NS
	Punctate foci	21 (49)	0 (0)	6 (29)		
	Beginning confluence	10 (23)	3 (33)	7 (33)		
	Large confluent areas	6 (14)	3 (33)	3 (14)		
Atrophy of the left medial temporal lobe (Scheltens scores)	0	2 (6)	0 (0)	0 (0)	NS	0.021
	1	7 (21)	3 (60)	1 (8)		
	2	19 (58)	2 (40)	4 (33)		
	3	5 (15)	0 (0)	4 (33)		
	4	0 (0)	0 (0)	3 (25)		

Means ± SD or n (%) are presented. T-test or Fisher's exact test were used to calculate the P-values. The patients were followed up from the ICP measurement day until death or the end of the year 2014. *Three patients were not shunted despite fulfilling the shunting criteria, because of severe dementia, patient declining the operation, or death. **Two cases with hyperphosphorylated tau (HPτ) but no amyloid beta (Aβ) in the brain biopsy excluded from the Fisher's exact test. ICP, intracranial pressure. NS, non-significant (P>0.05).

Table 4. The baseline characteristics of the study population (Study III).

		No shunt (n=172)		Shunted (n=305)		P-value
Gender	Female	82	(47.7)	168	(55.1)	NS
Age during the preoperative imaging (years)		72.37	±9.88	72.75	±7.77	NS
BMI (kg/m²)		26.14	±4.01	27.71	±4.66	<0.001
Preoperative MMSE		19	±5	22	±5	<0.001
Main symptom	Gait	29	(18.0)	109	(51.7)	<0.001
	Cognition	68	(42.2)	50	(23.7)	
	Other	64	(39.8)	52	(24.6)	
Imaging method	MRI	45	(26.2)	137	(44.9)	<0.001
	CT	127	(73.8)	168	(55.1)	
Hypertension	Yes	59	(34.3)	164	(53.8)	<0.001
Diabetes mellitus	Yes	22	(12.8)	82	(26.9)	<0.001
Heart diseases (atrial fibrillation/other arrhythmia/chronic heart failure/coronary heart disease)	Yes	51	(29.7)	97	(31.8)	NS
Lateral ventricle	Normal/mildly enlarged	43	(25.0)	77	(25.2)	NS
	Moderately/severely enlarged	129	(75.0)	228	(74.8)	
Sylvian fissure	Decreased/normal	66	(38.4)	64	(21.0)	<0.001
	Mildly enlarged	75	(43.6)	128	(42.0)	
	Moderately/severely enlarged	31	(18.0)	113	(37.0)	
Superior convexity/medial subarachnoid spaces	Decreased	113	(65.7)	264	(86.6)	<0.001
	Normal/mildly enlarged	59	(34.3)	41	(13.4)	
Basal cistern	Decreased/normal	154	(89.5)	236	(77.4)	0.001
	Mildly/moderately/severely enlarged	18	(10.5)	69	(22.6)	
Disproportionality between the Sylvian and suprasylvian subarachnoid spaces	No	61	(35.5)	45	(14.8)	<0.001
	Yes	111	(64.5)	260	(85.2)	
Focally dilated sulci	No	122	(70.9)	164	(53.8)	<0.001
	Yes	50	(29.1)	141	(46.2)	
Periventricular/deep white matter changes	No	30	(17.4)	49	(16.1)	NS
	Punctate foci/beginning confluence	98	(57.0)	181	(59.3)	
	Large confluent areas	44	(25.6)	75	(24.6)	
Brain stem white matter changes	No	39	(75.0)	114	(71.3)	NS
	Yes	13	(25.0)	46	(28.8)	
Temporal medial lobe atrophy (Scheltens scores)	0-1	2	(5.1)	24	(16.9)	NS
	2	18	(46.2)	72	(50.7)	
	3-4	19	(48.7)	46	(32.4)	
Aqueductal flow void	No	5	(11.1)	20	(14.8)	NS
	Yes	40	(88.9)	115	(85.2)	
Callosal angle (°)		63	±14	62	±14	NS
Evans' index		0.40	±0.08	0.38	±0.04	0.016
Mean width of the temporal horns (mm)		8.49	±4.36	7.55	±2.61	0.010
Modified cella media index		0.40	±0.07	0.39	±0.05	NS

Values are mean ± SD or n (%). T-test or Fisher's exact test were used to calculate the P-values. NS, non-significant (P>0.05).

Table 5. Causes of death of the study population (n=477).

	No shunt (n=172)	Shunted (n=305)
Heart diseases	20 (14)	35 (23)
Cerebrovascular disease and stroke	26 (18)	25 (16)
Malignant neoplasm	12 (8)	13 (9)
Infection	11 (8)	7 (5)
Injury	5 (4)	7 (5)
Dementia	43 (30)	25 (16)
iNPH	5 (4)	14 (9)
Other/not known	20 (14)	26 (17)

Causes of death of the study population. Values are n (%). There was a significant difference in the causes of deaths between the groups (Fisher P=0.037). Two causes of death are not known due to unfinished autopsies.

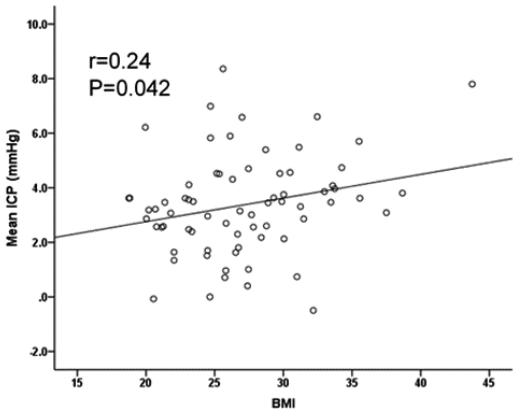

Figure 7. Scatterplot demonstrating the association of the mean ICP (mmHg) with the BMI. The correlation was calculated with Pearson's correlation.

5.2 RADIOLOGICAL FINDINGS AND INPH DIAGNOSIS (STUDY I)

The non-NPH group showed a higher EI (0.40±0.08 vs. 0.38±0.04, P=0.039) and a greater mean WTH (8.6±4.4 vs. 7.3±2.5 mm, P=0.007) than the iNPH group. There was association between the iNPH diagnosis and enlarged Sylvian fissures (P<0.001), decreased superior medial (P<0.001) and superior convexity SAS (P<0.001), enlarged basal cisterns (P=0.006), disproportionality between the Sylvian and suprasylvian SAS (P<0.001), FDS (P<0.001), and left medial temporal lobe atrophy (P=0.003) in the univariate analyses (Fisher's exact test). Visually evaluated ventricle size, mCMI, aqueductal flow void, CA or periventricular, deep or brain stem WMC were not associated with the iNPH diagnosis. These results are also presented in Table 6.

The variables associated with the iNPH diagnosis (excluding Scheltens scores due to n=80) were included in a combined logistic regression model adjusted for age, gender, and

imaging method (MRI/CT) (Table 7). Only the disproportionality (P=0.001) between the Sylvian and suprasylvian SAS and the decreased superior medial SAS (P=0.016) were associated with the iNPH diagnosis in this model. The mean WTH was almost significantly associated with the diagnosis (P=0.057).

After the nonsignificant variables were excluded, only the disproportionality of the SAS and the mean WTH remained statistically significant (Table 8). The R^2 (coefficient of determination) of the final model was 0.20. When Scheltens scores of the left medial temporal lobe atrophy were added to the model (n=80), it was not associated with the iNPH diagnosis.

Table 6. The univariate logistic regression for the specific radiological parameters and the iNPH diagnosis.

	n	OR	95% CI	P-value
Disproportionality between the Sylvian and suprasylvian subarachnoid spaces	387	2.88	(2.11 - 3.92)	<0.001
Superior medial subarachnoid space	389	0.19	(0.11 – 0.33)	<0.001
Sylvian fissure	389	1.92	(1.44 – 2.56)	<0.001
Superior convexity subarachnoid space	389	0.38	(0.24 – 0.59)	<0.001
Focally dilated sulci	381	2.36	(1.51 – 3.68)	<0.001
Atrophy of the left medial temporal lobe	80	0.26	(0.11 – 0.59)	0.001
Mean width of the temporal horns (per 1 mm)	389	0.90	(0.84 – 0.96)	0.002
Basal cistern	385	2.50	(1.34 – 4.68)	0.004
Evans' index (per 0.1)	390	0.72	(0.50 – 1.02)	0.065
Aqueductal flow void	120	0.54	(0.17 – 1.66)	NS
Deep white matter changes	346	0.91	(0.75 – 1.11)	NS
Brain stem white matter changes	62	0.57	(0.12 – 2.66)	NS
Callosal angle (per 10°)	55	0.87	(0.58 – 1.31)	NS
Periventricular white matter changes	384	0.95	(0.77 – 1.16)	NS
Modified cella media index (per 10°)	390	0.92	(0.64 – 1.32)	NS
Lateral ventricles	389	1.06	(0.72-1.58)	NS

Logistic regression was used to calculate the odds ratios (OR) and the 95% confidence intervals (CI) for the various radiological markers in association with the idiopathic normal pressure hydrocephalus diagnosis (59% of all patients). The radiological markers were analysed separately. Categories in the multinominal categorical values are in increasing order, *i.e.* the ORs below 1 mean inverse association and the ORs over 1 mean positive association. Adjustments are made for gender, imaging method (MRI or CT), and age. To simplify, the ORs are calculated by using the categorical variables as continuous, and for the continuous variables the scale is presented in parenthesis. Disproportionality is defined as the disproportion between the suprasylvian and Sylvian subarachnoid spaces. NS; non-significant (P>0.05).

Table 7. Non-NPH (n=153) versus iNPH (n=222) in the multivariate logistic regression.

	n	OR	95% CI	P-value
Sylvian fissure	375			NS
Decreased / normal	109	1	-	-
Mildly enlarged	162	0.86	(0.46 - 1.64)	NS
Moderately enlarged	94	0.89	(0.37 - 2.11)	NS
Severely enlarged	10	0.80	(0.12 - 5.24)	NS
Superior medial subarachnoid space	375			-
Decreased	289	1	-	-
Normal / mildly enlarged	86	0.25	(0.08 - 0.77)	0.016
Superior convexity subarachnoid space	375			-
Decreased	233	1	-	-
Normal	142	1.56	(0.77 - 3.16)	NS
Basal cistern	375			NS
Decreased / normal	317	1	-	-
Mildly enlarged	51	1.19	(0.55 - 2.56)	NS
Moderately / severely enlarged	7	-	-	NS
Disproportionality between the Sylvian and suprasylvian subarachnoid spaces	375			0.001
No	87	1	-	-
Mild	151	1.26	(0.39 - 4.07)	NS
Severe	137	4.43	(1.11 - 17.7)	0.035
Focally dilated sulci	375			
No	224	1	-	-
Yes	151	0.82	(0.46 - 1.48)	NS
Evans' index	375	2.01	(0.01 - 353)	NS
Mean width of the temporal horns (mm)	375	0.91	(0.83 - 1.00)	0.057

Binary logistic regression adjusted for gender, imaging method (MRI/CT), and age was used to calculate the odds ratios. The included variables were separately associated with the iNPH diagnosis. For 15 patients some data was missing for the regression analysis. iNPH, idiopathic normal pressure hydrocephalus; NPH, normal pressure hydrocephalus; NS, non-significant (P>0.05).

Table 8. Non-NPH (n=159) vs. iNPH (n=227) in the logistic regression.

	n	OR	95% CI	P-value
Disproportion between the Sylvian and suprasylvian subarachnoid spaces	386			<0.001
No	90	1	-	-
Mild	155	2.57	(1.44 - 4.59)	0.001
Severe	141	7.50	(4.00 - 14.1)	<0.001
Mean width of the temporal horns (mm)	386	0.91	(0.84 - 0.98)	0.014

Binary logistic regression adjusted for gender, imaging method (MRI/CT), and age was used to calculate the odds ratios. The model is the final result of the exclusion of all insignificant (P>0.05) variables that were included in Table 7. For 4 patients some data was missing for the regression analysis. iNPH, idiopathic normal pressure hydrocephalus; NPH, normal pressure hydrocephalus.

5.3 RADIOLOGICAL FINDINGS AND SHUNT OUTCOME (STUDY I)

No radiological marker could predict the shunt response (Table 9). Expectedly, EI decreased significantly after the shunt surgery (-0.02±0.04, P<0.001, n=180). Change in EI was not associated with the shunt response. Patients with an enlargement of suprasylvian cortical sulci after the surgery had shunt response more often than patients without it (OR 3.9, CI 95% 1.6-9.4, P=0.003, n=179). However, among the patients with an enlargement of cortical sulci, ventricles (EI) were decreased more in size compared with the patients whose sulci size was unchanged after the surgery (-0.02±0.04 vs. -0.00±0.04, P=0.023, n=175).

Table 9. The univariate logistic regression for the specific radiological parameters and the shunt response.

	n	OR	95% CI	P-value
Disproportionality between the Sylvian and suprasylvian subarachnoid spaces	217	1.33	(0.80 – 2.22)	NS
Superior medial subarachnoid space	218	0.43	(0.16 – 1.15)	NS
Sylvian fissure	218	1.22	(0.75 – 2.02)	NS
Superior convexity subarachnoid space	218	0.61	(0.28 – 1.34)	NS
Focally dilated sulci	215	1.13	(0.53 – 2.37)	NS
Atrophy of the left medial temporal lobe	55	1.10	(0.18 – 6.88)	NS
Mean width of the temporal horns (per 1 mm)	218	0.96	(0.82 – 1.12)	NS
Basal cistern	216	1.29	(0.50 – 3.33)	NS
Evans' index (per 0.1)	218	1.00	(0.44 – 2.27)	NS
Aqueductal flow void	75	0	(0 - >100)	NS
Deep white matter changes	196	0.79	(0.56 – 1.12)	NS
Brain stem white matter changes	41	>100.00	(0 - >100)	NS
Callosal angle (per 10°)	42	3.46	(0.51 – 23.29)	NS
Periventricular white matter changes	216	0.77	(0.54 – 1.10)	NS
Modified cella media index (per 10°)	218	0.80	(0.35 – 1.79)	NS
Lateral ventricles	218	1.10	(0.52 – 2.32)	NS

Logistic regression was used to calculate the odds ratios (OR) and the 95% confidence intervals (CI) for the various radiological markers in association with the shunt response (83% of shunted patients). The radiological markers were analysed separately. Categories in the multinominal categorical values are in increasing order, *i.e.* the ORs below 1 mean inverse association and the ORs over 1 mean positive association. Adjustments are made for gender, imaging method (MRI or CT), and age. To simplify, the ORs are calculated by using the categorical variables as continuous, and for the continuous variables the scale is presented in parenthesis. Disproportionality is defined as the disproportion between the suprasylvian and Sylvian subarachnoid spaces. NS; non-significant (P>0.05).

5.4 RADIOLOGICAL FINDINGS AND ICP MEASUREMENTS (STUDY II)

Significant associations with B waves are shown in Table 10. Less atrophy of the medial temporal lobe was associated with more frequent B waves (P=0.018). Of radiological markers related to iNPH only narrowed superior medial (P=0.003) and convexity SAS (P=0.004) and more severe disproportionality between the Sylvian and suprasylvian SAS (P=0.001) were associated with B waves. Other radiological markers (mean WTH, Sylvian fissure, FDS, basal cisterns, EI, periventricular or deep WMC) were not associated with B waves.

Table 10. Associations with the B waves of ICP.

		B waves (of time)				P-value B waves
		No	<10%	10-30%	>30%	
Main symptom	Gait	0 (0)	2 (18)	6 (60)	35 (69)	0.017
	Cognition	1(100)	7 (64)	4 (40)	14 (28)	
	Other	0 (0)	2 (18)	0 (0)	2 (4)	
Superior medial subarachnoid space	Narrowed	0 (0)	5 (45)	8 (80)	45 (88)	0.003
	Normal/mildly enlarged	1 (100)	6 (55)	2 (20)	6 (12)	
Superior convexity subarachnoid space	Narrowed	0 (0)	1 (9)	7 (70)	30 (59)	0.004
	Normal/mildly enlarged	1 (100)	10 (91)	3 (30)	21 (41)	
Disproportionality between the Sylvian and suprasylvian subarachnoid spaces	No	1 (100)	6 (55)	1 (10)	6 (12)	0.001
	Mild	0 (0)	5 (45)	4 (40)	16 (31)	
	Severe	0 (0)	0 (0)	5 (50)	29 (57)	
Atrophy of the left medial temporal lobe (Scheltens scores)	0	0 (0)	0 (0)	0 (0)	2 (6)	0.018
	1	0 (0)	0 (0)	1 (14)	10 (29)	
	2	0 (0)	2 (29)	5 (71)	18 (51)	
	3	0 (0)	3 (43)	1 (14)	5 (14)	
	4	1 (100)	2 (29)	0 (0)	0 (0)	

Values are n (%). Fisher's exact test was used to calculate the P-values. Only significant (P<0.05) associations with B waves are presented. ICP, intracranial pressure.

Increased mean ICP was associated with increased disproportionality (P=0.014; Figure 8) and the presence of FDS (P=0.047; Figure 9). Additionally, there was a tendency between the association of high ICP with more frequent narrowing of the superior convexity SAS (P=0.064), and with more frequent enlargement of the basal cisterns (P=0.061). High EI was correlated with a high mean ICP (r=0.26, P=0.025; Figure 10
in the shunt responsive patients (r=0.36, P=0.017). The radiological markers were not associated with the ICP pulse wave amplitude.

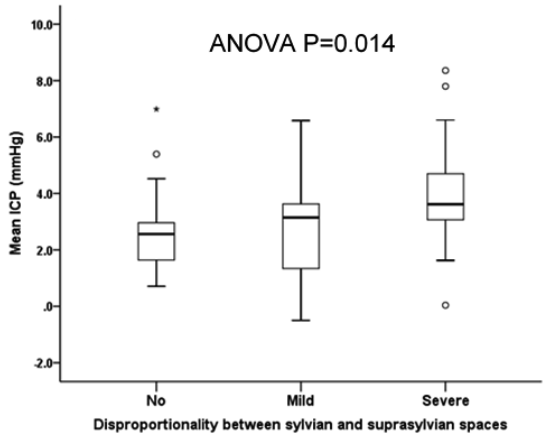

Figure 8. Boxplot of the relationships of the mean ICP (mmHg) and the disproportionality between the Sylvian and suprasylvian subarachnoid spaces. ANOVA was used to calculate the P-values.

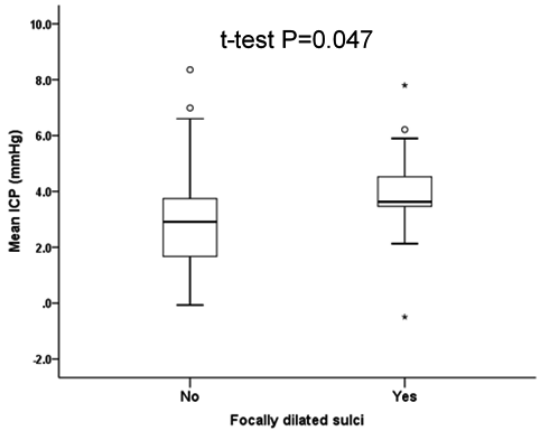

Figure 9. Boxplot of the relationships of the mean ICP (mmHg) and focally dilated sulci. T-test was used to calculate the P-value.

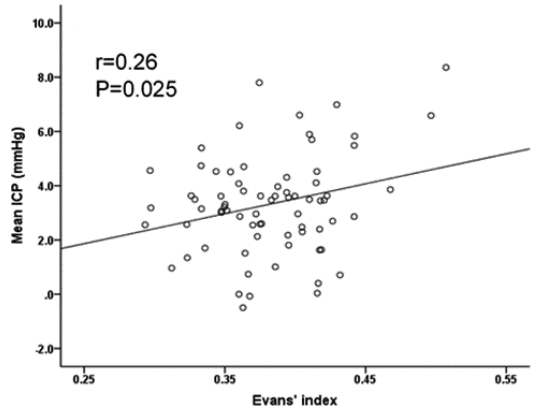

Figure 10. Scatterplot demonstrating the association of the mean ICP (mmHg) with Evans' index. Correlation was calculated with Pearson's correlation.

Stepwise linear regression showed that only disproportionality (P=0.005) and EI (P=0.013) were significant in predicting the mean ICP. These two markers explained 16% of the variation in the mean ICP. Each increase to a higher level of disproportionality was associated with a 0.75 mmHg (CI 95%: 0.23-1.26 mmHg) elevation in the mean ICP. Similarly, a 0.1 increase in EI was associated with a 1.18 mmHg (CI 95%: 0.26-2.09 mmHg) elevation in the mean ICP.

5.5 ICP MEASUREMENTS AND BRAIN BIOPSY (STUDY II)

Cortical brain biopsies with positive Aβ findings were associated with a high mean ICP pulse wave amplitude (P=0.032; Figure 11). There was no association with the mean ICP. There was no difference in the mean ICP or the ICP pulse wave amplitude between the HPτ positive and HPτ negative patients.

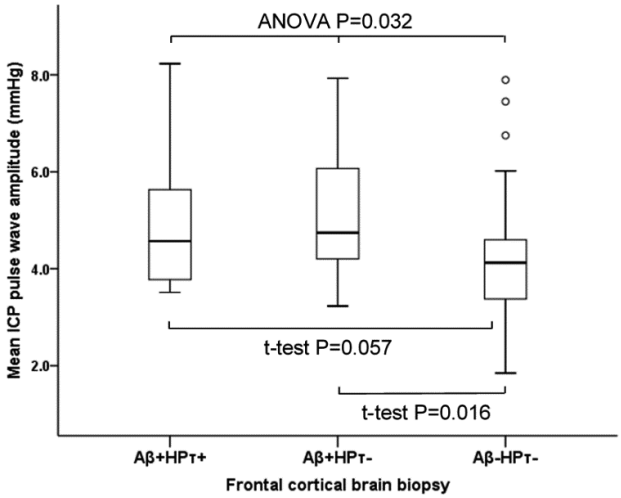

Figure 11. Boxplot of the mean ICP pulse wave amplitude (mmHg) and the frontal cortical brain biopsy groups. T-test or ANOVA was used to calculate the P-values. Aβ, amyloid beta; HPτ, hyperphosphorylated tau.

5.6 ICP MEASUREMENTS AND SHUNT OUTCOME (STUDY II)

The mean ICP was higher in the shunt responsive patients than in the non-shunted (4.0±1.8 vs. 2.1±1.4 mmHg, P<0.001) (Figure 12). No significant difference in the mean ICP between the non-responsive and shunt responsive patients was found. More ICP B waves were found in the shunt responsive patients (P<0.001) than the non-shunted patients.

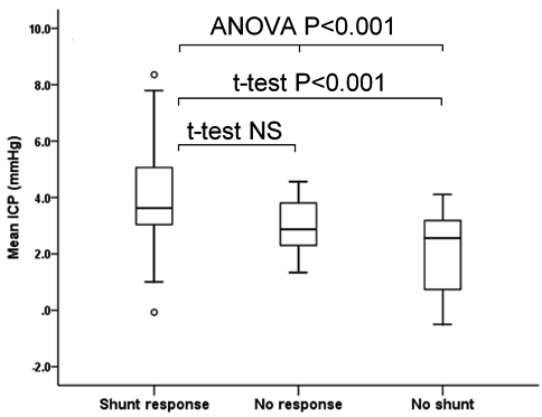

Figure 12. Boxplot of the relationship of the mean ICP (mmHg) and the shunt status. T-test or ANOVA was used to calculate the P-values.

5.7 RADIOLOGICAL FINDINGS AND MORTALITY (STUDY III)

5.7.1 Radiological features and overall mortality

Associations of the radiological markers with mortality in the entire population are shown in Table 11. The unadjusted and adjusted model for age, gender, imaging method, BMI, hypertension, diabetes, shunt status and heart diseases resulted in similar associations. The brain stem WMC (P<0.001) and the periventricular/deep WMC (P<0.001) were associated with increased mortality. Wide WTH (P<0.001) and high Scheltens scores (P=0.003) were also associated with increased mortality. Other investigated radiological features were not associated with mortality. Model 2 (Table 11) was further adjusted for the MMSE as a sensitivity analysis. Significant associations remained between mortality and Scheltens scores, periventricular/deep WMC, and brain stem WMC, but the association with the WTH lost significance (HR=1.02 per 1 mm, P=0.429, n=366). Likewise, as a sensitivity analysis, model 2 (Table 11) was adjusted for the main symptom, but the results remained the same.

In addition, all the radiological markers associated (P<0.1) with mortality in the univariate analysis (Table 11) were included in the combined Cox regression model (Table 12). In this model (Table 12), only the brain stem WMC (P=0.026) and the Scheltens scores 3/4 (P=0.035) were significantly associated with mortality. Bootstrapping was used to compare the results of the combined model with the univariate analyses. No significant differences were found in the HRs of any radiological markers between the combined model and the univariate model in the Cox regression. The univariate analyses and the combined model were further adjusted for the MMSE scores, and the bootstrapping showed that there were no significant changes in the HRs for any of the radiological markers.

Mortality was also analysed separately in the non-shunted and shunted patients (Figure 13 and 14) and these Kaplan-Meier survival curves were quite similar in both groups. Considering only the shunted patients, the associations of the radiological markers and mortality in the univariate analyses remained similar to the entire population (Table 13). In the non-shunted group, the associations of the radiological markers with mortality in the univariate analyses were slightly weaker than in the shunted patients or the entire study population group, but in the same direction (Table 14).

Table 11. The Cox regression between mortality and the radiological markers for the entire study population (n=477).

		Unadjusted model 1		Model 2	
	n	**P-value**	**HR (CI 95%)**	**P-value**	**HR (CI 95%)**
Focally dilated sulci	477	0.482	0.92 (0.73-1.16)	0.409	0.90 (0.70-1.15)
Disproportionality between the Sylvian and suprasylvian subarachnoid spaces	477	0.399	0.89 (0.68-1.17)	0.166	0.82 (0.61-1.09)
Superior convexity/medial subarachnoid spaces	477	0.339	1.15 (0.87-1.52)	0.350	1.15 (0.86-1.54)
Lateral ventricle	477	0.710	1.05 (0.80-1.38)	0.582	1.08 (0.82-1.42)
Sylvian fissure	477	0.414		0.284	
Sylvian fissure, mildly enlarged	203	0.873	0.98 (0.74-1.29)	0.150	0.81 (0.61-1.08)
Sylvian fissure, moderately/severely enlarged	144	0.232	0.83 (0.61-1.13)	0.179	0.80 (0.58-1.11)
Basal cisterns	477	0.168	0.78 (0.55-1.11)	0.543	0.89 (0.61-1.30)
Temporal medial lobe atrophy (Scheltens scores)	**181**	**0.001**		**0.003**	
Temporal medial lobe atrophy (Scheltens scores), 2	90	0.065	2.43 (0.95-6.22)	0.069	2.46 (0.93-6.49)
Temporal medial lobe atrophy (Scheltens scores), 3-4	**65**	**0.002**	**4.55 (1.77-11.67)**	**0.002**	**4.61 (1.73-12.30)**
Periventricular/deep white matter changes	**477**	**<0.001**		**<0.001**	
Periventricular/deep white matter changes, punctate foci/beginning confluence	279	**0.007**	**1.62 (1.14-2.30)**	0.116	1.34 (0.93-1.93)
Periventricular/deep white matter changes, large confluent areas	**119**	**<0.001**	**2.65 (1.82-3.86)**	**<0.001**	**2.01 (1.36-2.97)**
Brain stem white matter changes	**212**	**<0.001**	**2.21 (1.46-3.35)**	**<0.001**	**2.70 (1.67-4.36)**
Aqueductal flow void	180	0.197	0.67 (0.36-1.23)	0.322	0.72 (0.37-1.38)
Evans' index per 0.1	477	0.991	1.00 (0.82-1.21)	0.795	1.03 (0.83-1.28)
Modified cella media index per 0.1	477	0.781	0.97 (0.79-1.19)	0.240	1.14 (0.92-1.41)
Callosal angle (°) per 10°	100	0.248	1.00 (1.00-1.00)	0.485	1.00 (1.00-1.00)
Mean width of the temporal horns per 1 mm	**477**	**0.004**	**1.04 (1.01-1.07)**	**<0.001**	**1.06 (1.03-1.09)**

Total 294 (62%) of the patients died during the median follow-up time of 5.58 years. Unadjusted model 1 includes the radiological markers individually. Model 2 is adjusted for gender, age, imaging method, BMI, hypertension, diabetes, shunt status, and heart diseases. The significant p-values (P<0.05) are bolded.

Table 12. The Cox regression between mortality and the significant radiological markers in the combined model in the entire study population (n=175*).

	n	P-value	HR (CI 95%)
Periventricular/deep white matter changes	175	0.289	
Periventricular/deep white matter changes, punctate foci/beginning confluence	121	0.944	1.042 (0.33-3.26)
Periventricular/deep white matter changes, large confluent areas	39	0.440	1.625 (0.47-5.57)
Mean width of the temporal horns per 1 mm	175	0.218	1.065 (0.96-1.18)
Brain stem white matter changes	**175**	**0.026**	**1.899 (1.08-3.34)**
Temporal medial lobe atrophy (Scheltens scores)	175	0.065	
Temporal medial lobe atrophy (Scheltens scores), 2	90	0.170	2.139 (0.72-6.33)
Temporal medial lobe atrophy (Scheltens scores), 3-4	**60**	**0.035**	**3.437 (1.09-10.81)**

Total 70 (40%) of the patients died during the median follow-up time of 5.42 years. All presented radiological markers were included in the same model. Adjustments were made for gender, age, imaging method, BMI, hypertension, diabetes, shunt status, and heart diseases. Only the radiological markers significantly associated with mortality (P<0.1) in the univariate analyses were included in this combined model. The significant p-values (P<0.05) are bolded. *Data is incomplete because the brain stem white matter changes and the temporal medial lobe atrophy could not be evaluated from all radiological images.

Table 13. The Cox regression between mortality and the radiological markers for the shunted patients (n=305).

		Unadjusted model 1		Model 2	
	n	P-value	HR (CI 95%)	P-value	HR (CI 95%)
Focally dilated sulci	305	0.999	1.00 (0.73-1.38)	0.335	0.85 (0.60-1.19)
Disproportionality between the Sylvian and suprasylvian subarachnoid spaces	305	0.977	0.99 (0.63-1.58)	0.216	0.74 (0.46-1.19)
Superior convexity/medial subarachnoid spaces	305	0.734	1.09 (0.67-1.76)	0.202	1.38 (0.84-2.27)
Lateral ventricle	305	0.771	1.06 (0.72-1.55)	0.926	0.98 (0.66-1.45)
Sylvian fissure	305	0.952		0.542	
Sylvian fissure, mildly enlarged	128	0.754	1.07 (0.70-1.63)	0.270	0.78 (0.51-1.21)
Sylvian fissure, moderately/severely enlarged	113	0.849	1.04 (0.67-1.62)	0.430	0.83 (0.52-1.32)
Basal cisterns	305	0.898	0.97 (0.63-1.49)	0.646	0.90 (0.56-1.44)
Temporal medial lobe atrophy (Scheltens scores)	**142**	**0.028**		**0.007**	
Temporal medial lobe atrophy (Scheltens scores), 2	**72**	0.139	2.08 (0.79-5.49)	**0.026**	**3.14 (1.14-8.62)**
Temporal medial lobe atrophy (Scheltens scores), 3-4	**46**	**0.012**	**3.52 (1.32-9.40)**	**0.002**	**5.18 (1.84-14.62)**
Periventricular/deep white matter changes	**305**	**<0.001**		**0.010**	
Periventricular/deep white matter changes, punctate foci/beginning confluence	181	0.065	1.57 (0.97-2.52)	0.088	1.53 (0.94-2.50)
Periventricular/deep white matter changes, large confluent areas	**75**	**<0.001**	**2.80 (1.67-4.68)**	**0.003**	**2.23 (1.31-3.81)**
Brain stem white matter changes	**160**	**<0.001**	**2.68 (1.58-4.53)**	**<0.001**	**3.52 (1.95-6.38)**
Aqueductal flow void	135	0.459	0.76 (0.36-1.58)	0.824	0.92 (0.43-1.96)
Evans' index per 0.1	305	0.824	1.04 (0.74-1.47)	0.823	1.04 (0.72-1.50)
Modified cella media index per 0.1	305	0.710	0.94 (0.68-1.30)	0.648	1.09 (0.77-1.54)
Callosal angle (°) per 10°	87	0.537	1.00 (1.00-1.00)	0.545	1.00 (1.00-1.00)
Mean width of the temporal horns per 1 mm	**305**	**0.002**	**1.10 (1.04-1.17)**	**<0.001**	**1.14 (1.06-1.22)**

Total 152 (50%) of the patients died during the median follow-up time of 5.87 years. Unadjusted model 1 includes the radiological markers individually. Model 2 is adjusted for gender, age, imaging method, BMI, hypertension, diabetes, and heart diseases. The significant p-values (P<0.05) are bolded.

Table 14. The Cox regression between mortality and the radiological markers for the non-shunted patients (n=172).

		Unadjusted model 1		Model 2	
	n	**P-value**	**HR (CI 95%)**	**P-value**	**HR (CI 95%)**
Focally dilated sulci	172	0.564	1.11 (0.78-1.59)	0.590	0.88 (0.61-1.28)
Disproportionality between the Sylvian and suprasylvian subarachnoid spaces	172	0.392	1.17 (0.82-1.66)	0.682	0.93 (0.64-1.34)
Superior convexity/medial subarachnoid spaces	172	0.284	0.82 (0.58-1.18)	0.977	0.99 (0.69-1.44)
Lateral ventricle	172	0.554	1.12 (0.76-1.65)	0.494	1.15 (0.77-1.73)
Sylvian fissure	172	0.949		0.613	
Sylvian fissure, mildly enlarged	75	0.767	1.06 (0.73-1.52)	0.423	0.86 (0.59-1.25)
Sylvian fissure, moderately/severely enlarged	31	0.998	1.00 (0.62-1.62)	0.397	0.80 (0.48-1.34)
Basal cisterns	172	0.384	0.75 (0.39-1.43)	0.418	0.76 (0.38-1.49)
Temporal medial lobe atrophy (Scheltens scores)	39	0.164		0.066	
Temporal medial lobe atrophy (Scheltens scores), 2	18	0.927	-	0.914	-
Temporal medial lobe atrophy (Scheltens scores), 3-4	19	0.921	-	0.904	-
Periventricular/deep white matter changes	172	**0.009**		0.089	
Periventricular/deep white matter changes, punctate foci/ beginning confluence	98	0.072	1.61 (0.96-2.69)	0.273	1.37 (0.78-2.40)
Periventricular/deep white matter changes, large confluent areas	**44**	**0.003**	**2.33 (1.34-4.05)**	**0.039**	**1.87 (1.03-3.37)**
Brain stem white matter changes	52	0.083	1.85 (0.92-3.70)	0.181	2.03 (0.72-5.74)
Aqueductal flow void	45	0.118	0.42 (0.14-1.25)	0.234	0.41 (0.09-1.80)
Evans' index per 0.1	172	0.345	0.89 (0.71-1.13)	0.813	0.97 (0.73-1.28)
Modified cella media index per 0.1	172	0.794	0.97 (0.76-1.24)	0.491	1.10 (0.84-1.44)
Callosal angle (°) per 10°	13	0.182	1.00 (1.00-1.01)	0.084	1.02 (1.00-1.04)
Mean width of the temporal horns per 1 mm	172	0.778	1.01 (0.97-1.04)	0.155	1.03 (0.99-1.07)

Total 142 (83%) of the patients died during the median follow-up time of 4.27 years. Unadjusted model 1 includes the radiological markers individually. Model 2 is adjusted for gender, age, imaging method, BMI, hypertension, diabetes, and heart diseases. The significant p-values (P<0.05) are bolded.

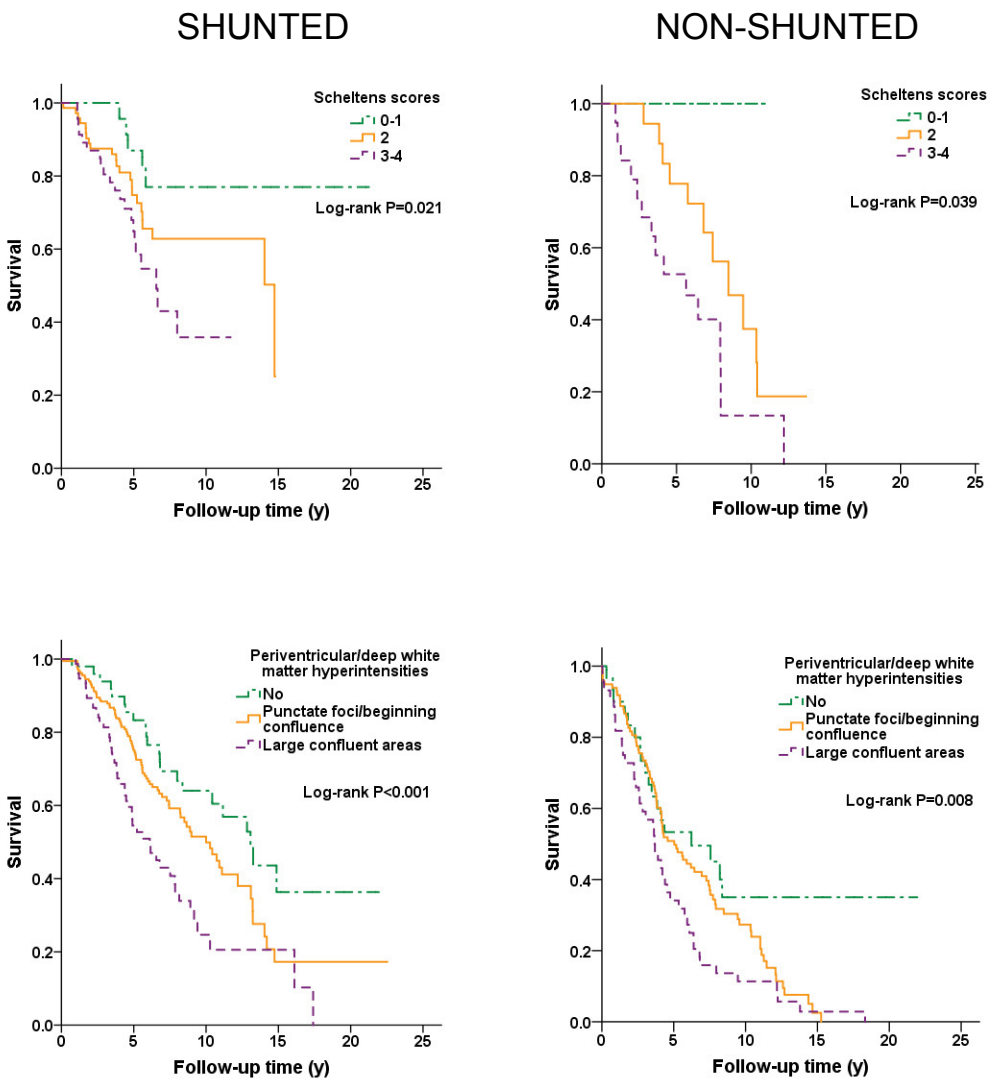

Figure 13. Kaplan-Meier curves for survival according to the different radiological markers that were associated with mortality in Table 3. In the left panel the curves are for the shunted patients. In the right panel the curves are for the non-shunted patients.

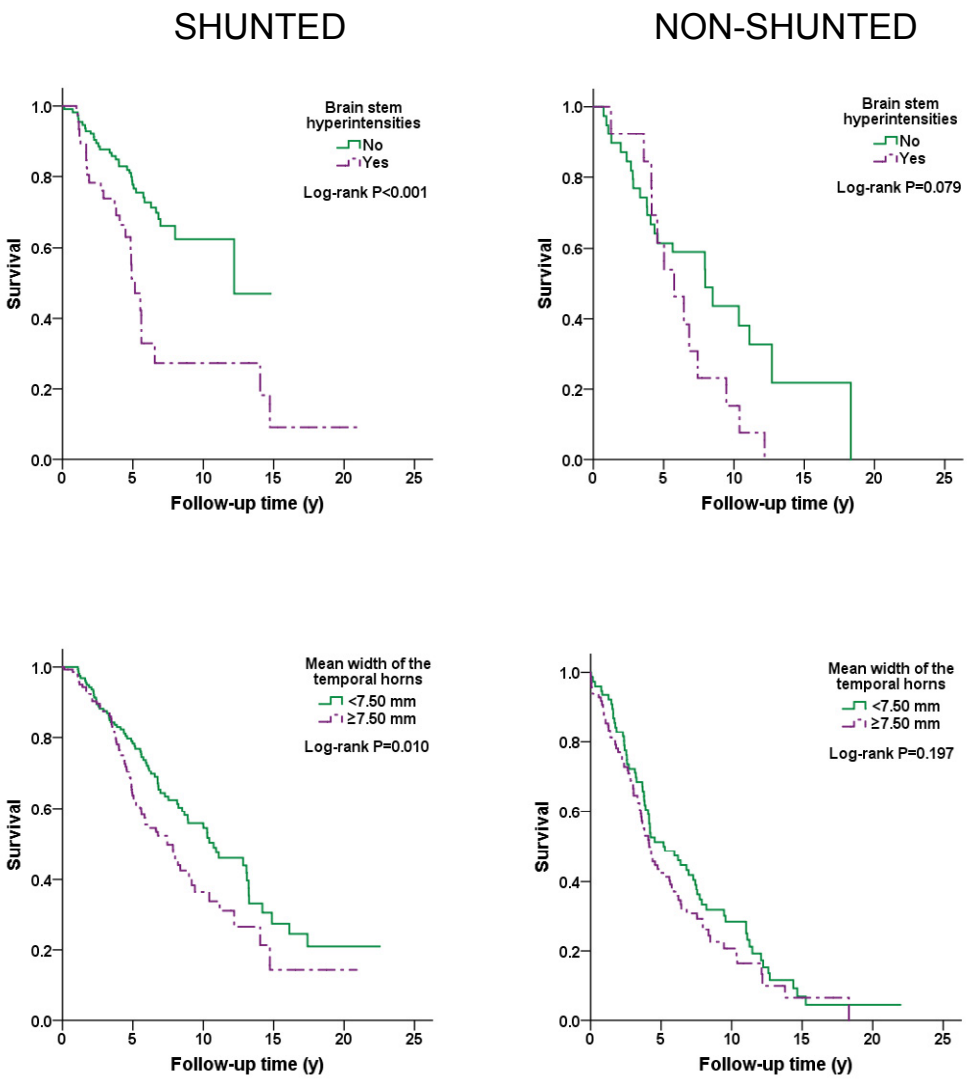

Figure 14. Kaplan-Meier curves for survival according to the different radiological markers that were associated with mortality in Table 3. In the left panel the curves are for the shunted patients. In the right panel the curves are for the non-shunted patients. Mean width of the temporal horns was divided into two groups according to the median (7.5 mm).

5.7.2 Radiological features and main causes of death

The Scheltens scores were associated with death from heart diseases (P=0.008, HR=3.67 per category, CI95% 1.41-9.59) and iNPH (P=0.046, HR=6.10 per category, CI95% 1.03-36.12) as the main causes of death, but not for example with a cerebrovascular disease and stroke or dementia as the main causes of death. There was a tendency for an association between the periventricular/deep WMC and iNPH as the main cause of death (no vs. large confluent areas; P=0.053, HR=8.15, CI95% 0.97-68.24). The brain stem WMC were associated with a cerebrovascular disease and stroke (P=0.007, HR=6.25, CI95% 1.66-23.57) and heart diseases (P=0.018, HR=3.35, CI95% 1.23-9.12) as the main causes of death. The WTH was associated with a cerebrovascular disease and stroke (P=0.030, HR=1.08 per 1mm, CI95% 1.01-1.16) and dementia (P=0.016, HR=1.08 per 1mm, CI95% 1.01-1.15) as the main causes of death.

6 Discussion

6.1 RADIOLOGICAL MARKERS ARE ASSOCIATED WITH THE INPH DIAGNOSIS BUT NOT WITH THE SHUNT RESPONSE

6.1.1 Main findings

The feasibility of several radiological features in the diagnostics of iNPH was compared against each other in terms of how well they predict iNPH in patients. We found that nine different radiological markers were associated with the diagnosis of iNPH. However, only the visually evaluated disproportionality between the Sylvian and suprasylvian SAS and the WTH were significantly related to the iNPH diagnosis in the final, adjusted, combined model. No radiological marker predicted the short-term shunt response. Shunt response was seen more frequently in subjects whose cortical sulci size increased after the shunt operation.

6.1.2 Radiological markers and iNPH diagnosis

The disproportionality between the Sylvian and suprasylvian SAS, and the mean WTH could be reliably evaluated in both MRI and CT. Our results support previous studies indicating that disproportionality is the most useful radiological feature in diagnosing iNPH (39,85,177). The suprasylvian SA block is considered to cause the disproportionality (39). FDS, enlarged Sylvian fissures and basal cisterns, and decreased superior medial and convexity SAS were separately associated with the iNPH diagnosis, but these associations disappeared when the disproportionality was taken into account. The most obvious reason for that is that they are probably a part of the same phenomenon as the disproportionality, in other words by a suprasylvian block (39).

The lack of medial temporal lobe atrophy and lower EI were associated with the diagnosis of iNPH in the univariate analyses but after the disproportionality was considered they were not significant. The evaluation of the hippocampal volume was possible only in 80 subjects; therefore, the result may have been overrun by a far stronger association of disproportionality (R^2 0.18). Contrary to the expectations, EI was lower in the iNPH group than in the non-NPH group (7). Furthermore, decreased WTH was associated with the diagnosis of iNPH even after the disproportionality was taken into account. Previously, the ventricular size has been reported to be larger in iNPH than in AD (78). These two unexpected results might be explained by the patient selection in this study (EI>0.3) and the lesser atrophy in the iNPH group than the non-NPH group. A previous study found that increased rather than decreased WTH predicts the shunt response in the iNPH patients (85). Increased WTH is stated to be an accurate marker in differentiating AD (suggested cutoff value of 5.3 mm in CT) from healthy controls (1-5). The WTH represents the temporal atrophy in AD, while in iNPH it may reflect the enlargement of the ventricular size. In all, we suggest that the WTH is smaller in iNPH than AD, and this possibly explains the different results in the studies in which the subjects with AD are excluded. Thus, the clinical signs and symptoms as well as the results of other diagnostic measures should be considered when interpreting the WTH and EI.

INPH was associated with the disproportionality and with the WTH rather strongly. However, it has to be kept in mind that these findings can only support the iNPH diagnosis and they do not distinguish iNPH from the other neurodegenerative diseases (130). The R^2 was only 0.20 in the final model, emphasizing the necessity of other complementary diagnostic measures in iNPH.

WMC are often seen in iNPH. The deep and periventricular WMC can be the result of iNPH-associated edema (102) or chronic ischemia (100,101). We found no association of the WMC with the diagnosis of iNPH or the shunt response, which agrees with the previous study (104). This suggests that the WMC do not differentiate iNPH from other comorbidities, such as VAD. Concerning the markers evaluated only in MRI, the aqueductal flow void and the CA were not associated with the diagnosis of iNPH in this study. Indeed, the aqueductal flow void is present relatively frequently even in healthy controls (80).

6.1.3 Radiological markers and shunt response

The radiological markers of this study did not predict the shunt response. For instance, our findings regarding the WTH and the disproportionality of the SAS are not entirely in agreement with the previous findings by Virhammar *et. al.*, who stated them to predict the shunt response (85). Although we did not discover a significant association with the shunt response, the CA was the smallest in the shunt responsive patients, and this tendency is in agreement with the results of Virhammar *et. al.* The predictive value of the radiological findings in earlier studies (81,85) could be accredited to the use of more sensitive measurements of the shunt response (for example detailed cognitive evaluation and gait speed) than the routine clinical evaluation used in our study. Moreover, the limited number of non-responders, which reflects a good patient selection for shunting, could also explain the negative results in the current study.

In line with a prior study, a ventricular size reduction after a shunt operation was not in association with the shunt response (71). Nevertheless, the patients with a postoperative cortical sulcal enlargement tended to show a clinical shunt response more often than the patients without it. Hypothetically, this suggests that when the shunt surgery affects the suprasylvian block, *i.e.* the state in which the CSF flow into the suprasylvian space is limited (39), it is more likely that the patient improves after the shunt surgery. This association could also be attributed to the well-preserved compliance of the brain tissue in some patients. Therefore, we suggest that the enlargement of the cortical sulci could be a radiological finding of the shunt response.

6.2 ASSOCIATIONS OF THE ICP WITH THE RADIOLOGICAL MARKERS, BRAIN BIOPSY AND THE SHUNT SURGERY OUTCOME

6.2.1 Main findings

As far as we know, we were the first to study the associations of radiological markers, brain biopsy findings and shunt surgery outcome in combination with the 24-h ICP measurements in patients with suspected iNPH. Increased disproportionality between the Sylvian and suprasylvian SAS, the presence of FDS, and high EI were associated with increased mean ICP. Less medial temporal lobe atrophy, more narrowed superior medial and convexity SAS, and more severe disproportionality were associated with the ICP B

waves. Increased mean ICP pulse wave amplitude was associated with the AD-related brain biopsy findings.

6.2.2 ICP and radiological findings

Increased EI and the disproportionality between the Sylvian and suprasylvian SAS, which are the most relevant radiological iNPH markers, were associated with an elevated ICP. This is likely due to a high ICP causing expansion in the ventricles, basal cisterns, and Sylvian SAS. In conjunction with a suprasylvian SA block, this leads to a diminished superior SAS (39), which are also used in the disproportionality evaluations. Furthermore, the superior convexity SAS and FDS, which are a part of to the suprasylvian block phenomenon, tended to be associated with increased ICP.

In a study by Kim *et. al.* (195) there was no significant correlation between the ventricle indices and the CSF opening pressure in the lateral ventricle, which was measured during the shunt operation in patients with NPH or other communicating hydrocephalus. Nevertheless, it is noteworthy that the reported correlation coefficient between EI and the CSF opening pressure (r=0.20) was close to that we found in our study (r=0.26 between EI and the mean ICP). Moreover, in the same study the CSF opening pressure correlated nearly significantly with the ventricular index (r=0.25) (195). The relatively weak correlations could be attributed to the brain atrophy that could also cause the enlargement of the ventricles without elevating the ICP. Indeed, in our study, the correlations were stronger between the mean ICP and EI in the shunt responsive patients (r=0.36) than in the whole study population, since the shunt responsive patients are likely to have a lesser degree of atrophy. In another earlier study, there was an inverse correlation between the 24-h ICP measurement and EI (196). However, the contradictory result might be explained by the far younger study population that even included children, and the different types of hydrocephalus included, with much higher ICP levels and shorter duration of the symptoms than in our study (196). Still, our results are in agreement with these two previous studies, suggesting that the radiological markers cannot be used to predict the ICP in a clinical setting, due to the rather weak associations and discrepant results. However, our results imply that these radiological findings could be directly linked with the iNPH pathophysiology.

6.2.3 ICP and brain biopsy findings

A favourable shunt outcome has been associated with increased mean ICP pulse wave amplitude. Increased pulse wave amplitude is suggested to be characteristic for iNPH, and it could result from decreased compliance in patients who have increased mean ICP (40,197). In the present study, the shunt response could not be predicted by the mean pulse wave amplitude. In the all three groups, the ICP pulse wave amplitude was relatively high [shunt responsive (4.8 mmHg), non-responsive (4.1 mmHg), and no shunt group (4.8 mmHg)], while in the study by Eide and Sorteberg (123), the cut-off for increased pulse wave amplitude was 4 mmHg [shunt responsive (5.7 mmHg), non-responsive (3.6 mmHg), and no shunt group (3.7 mmHg)]. Due to technical variations, the exact ICP values are not entirely comparable between different studies. For instance, our sampling frequency was ten times higher; an intraventricular catheter with a fluid column and a pressure sensor to measure the intra-arterial blood pressure was used. Our zero level was on the forehead but the actual pressure in the ventricle is lower than that. Some of the prior studies have used

an intraparenchymal sensor with a different zeroing protocol. Small variations in the mean ICP and the mean ICP pulse wave amplitude pressure values could be caused by these technical differences. Additionally, the ICP pulse wave amplitude was not used as a selection criterion for the shunt operation in our study.

The mean ICP was higher in the shunt responsive patients and they had more B waves than the non-shunted. Since the ICP and B waves were used as criteria for shunting, these results were expectable. No significant differences in the mean ICP or the frequency of B waves between the non-responsive and shunt responsive patients were found.

Only cortical brain biopsy findings were associated with the mean ICP pulse wave amplitude. This result was not expected, because there was an association between the increased mean pulse wave amplitude and the AD-related biopsy findings (Aβ+). Despite the fact that AD is a frequent comorbidity in the iNPH patients (130), there was no association of the pulse wave amplitude with the medial temporal lobe atrophy. There exists a hypothesis that the intracranial artery and the CSF pulsations might be linked to the development of both NPH and AD (198). In an experimental rat model, there was association between the kaolin-induced hydrocephalus and the amyloid accumulation, which supports the aforementioned theory, which could explain our unexpected result (199). Additionally, an earlier study found that the expression of genes regulating the amyloid processing in the brain was altered in the iNPH patients compared to the non-demented controls (192). Thus, it is possible that the amyloid pathology is related to both iNPH and AD.

6.2.4 Neurodegeneration and shunt outcome

The brain biopsy findings related to AD, *i.e.* Aβ and HPτ, were more frequent in the non-responsive patients than in the patients with shunt response. This result is logical, since the shunt surgery has little effect on the cognitive decline, whether it is a result of iNPH or especially of AD (147). In addition, the patients with shunt response had less progressed medial temporal lobe atrophy than the patients with no shunt. Our results are in line with a prior study which reported that the patients with only iNPH had better shunt outcomes than the iNPH patients with AD (200). On the contrary, the deep and periventricular WMC were frequent in the patients with shunt response, indicating that the WMC should not prevent shunting (102). The WMC might also be at least partly related to the CSF leakage into the brain parenchyma in iNPH, and thus, do not necessarily indicate vascular degeneration.

6.3 RADIOLOGICAL FEATURES OF INPH IN RELATION TO MORTALITY

6.3.1 Main findings

To our knowledge, this was the first study to investigate the association between the various radiological markers and mortality in patients suspected to have iNPH. The radiological findings related to AD (temporal lobe atrophy) and vascular degeneration (WMC) were associated with high mortality. However, the classical iNPH markers, *e.g.* EI and the disproportionality between the Sylvian and suprasylvian SAS, did not predict mortality.

6.3.2 Radiological markers and mortality

The traditional iNPH markers were not associated with all-cause mortality. The lack of associations was consistent across the models; the non-shunted group, the shunted group and the sensitivity analyses showed the same result of non-existing associations. It is possible that either the shunting diminishes the associations between the iNPH-related markers and mortality, or these markers lack prognostic value when it comes to survival. In the previous studies *e.g.* disproportionality, CA, and high convexity tightness are associated with the shunt response (81,85,178). Besides, Akiguchi *et. al.* suggested that the DESH features could be associated with mortality (180), but we found no indication of association between the disproportionality and the risk of increased mortality. This might be explained by the rather small study population that Akiguchi *et. al.* had, consisting only of 8 DESH patients, and Akiguchi *et. al.* did not compare mortality with the non-DESH iNPH patients. Based on our results, the iNPH-related markers cannot be used to predict mortality in the iNPH patients, but this result still needs to be confirmed in future studies.

WMC were associated with high all-cause mortality, which was expected based on the previous studies (14,15,179,185,201-206) where the WMC were also associated with mortality from cerebrovascular and cardiac diseases (14,185,202,207-212). However, in our study such associations were not found between the periventricular/deep WMC and specific causes of death. Instead, there was a trend between mortality from iNPH and the periventricular/deep WMC. It is possible that especially the periventricular WMC might be caused by iNPH. It has been proposed that the penetration of the CSF into the brain tissue due to the occasional increase of the intraventricular pressure might cause the WMC (periventricular oedema from transependymal resorption), which might explain the association with all-cause mortality besides the cardiovascular cause (102). Moreover, it has been suggested that the WMC (in the first place) may trigger iNPH (52). Therefore, the iNPH patients with WMC should also be shunted, as recommended earlier (104). Nevertheless, the brain stem WMC were associated with mortality from cerebrovascular and cardiac diseases, which is in line with a previous report discussing pontine hyperintensities being associated with poor clinical outcome, although that study did not find an association with mortality (181).

Wider WTH and medial temporal lobe atrophy were associated with high mortality in our study. This could naturally be attributed to dementia predicting death. In the model adjusted additionally with the MMSE, high Scheltens scores were still associated with mortality. This agrees with other studies on various populations with general atrophy and medial temporal lobe atrophy (15,184-187). Interestingly, in our study the Scheltens scores were associated with mortality from iNPH and heart diseases but not dementia, and wide WTH was associated with mortality from cerebrovascular disease and dementia. It is possible that these markers also reflect the ventricular size enlargement due to iNPH aside from the atrophy. In line with our results, Akiguchi *et. al.* reported higher Scheltens scores in the iNPH patients than in the patients with ex vacuo ventricular dilatation (1.25 vs. 0.34) (180).

Based on our findings, we also suggest that in the patients suspected to have iNPH, the cardiovascular risk factors should also be taken into account since the radiological markers which predicted mortality were also related to cardiovascular mortality. 39% of the shunted patients had a cardiac or cerebrovascular disease as the cause of death and it is suggested that *e.g.* hypertension and type 2 diabetes are risk factors of iNPH (13). An increased risk of

dementia and death has been found in the non-shunted iNPH patients compared with aged controls without hydrocephalus (140). However, it is clear that shunting is not the only treatment needed for patients with iNPH and the risk factors for vascular diseases and other comorbidities should be treated.

6.4 STRENGTHS AND LIMITATIONS

The strength of this thesis is the fairly large study population. Several previously reported radiological markers were assessed and many analyses were performed including additional cortical brain biopsy findings, 24-h ICP measurements, comorbidities, and mortality data. Both MRI and CT images were included, representing the clinical practice. The study population was quite homogenous since only patients with suspected iNPH were included. Non-shunted patients, *i.e.* controls, were not healthy controls but patients with similar symptoms and findings as in the iNPH patients. Therefore, the study design reflected the clinical setting and provides important results concerning this subgroup of patients who suffer from cognitive decline and ventriculomegaly.

Furthermore, all-cause mortality is a non-biased estimator of prognosis and our data was extremely reliable concerning the cause and the time of death with a relatively long follow-up time (median 5.6 years).

As a limitation, the imaging was performed with a variety of MRI and CT scanners and imaging protocols because of the long period of time and the multiple hospitals being involved. Also, we lacked automatically computed data of the brain volumes. We partially lacked MRI data which limited the analysis for Scheltens scores, brain stem WMC, flow void and callosal angle.

The studies were performed retrospectively. That may be a possible source of bias. Despite the fact that the radiological images were evaluated blind in regard to other patient data, it was clear whether the patient was shunted or not since all images were evaluated in the same software, where all the imaging data of one patient was available at the same time. Also, we could not determine whether the ICP pulse wave amplitude was increased before or after the amyloid accumulation since the ICP measurement and the brain biopsy were performed concurrently. Due to the retrospective setting, we also lacked some of the important data such as systematically assessed MMSE scores.

The study population of Study II, especially the number of non-responsive patients was rather small. Shunt responsiveness was defined as the alleviation of the symptoms and was assessed only a short period (two to three months) after the shunting. Unfortunately, we did not have more objective and sensitive measures, which could partly explain the null results related to the shunt response. Over half of the study population received a shunt. The shunt operation could have modulated the results. However, adjusting for the shunt or stratifying the population according to the shunt status did not seem to have a noticeable effect on the results (Study III).

Finally, this thesis could not define the exact mechanisms for the observed associations. This thesis could not provide any clinically relevant cut-off values for the radiological markers that separate healthy people or non-NPH patients from the iNPH patients.

6.5 PROPOSED OUTLINE OF INPH PATHOGENESIS

Based on this thesis, and earlier studies and pathophysiological theories (11,39,40,44,47,52,54,55,57,58,213-215), we present the following simplified theory on the pathogenesis of iNPH and how it results in the radiological findings (Figure 15). INPH is most likely a multifactorial disease. Predisposing and triggering factors include anatomical differences in the CSF absorption, genetic variations or mutations, lifestyle factors, comorbidities, aging, and probably other causes yet to be uncovered. These factors increase resistance to the CSF outflow, decreased compliance of the brain, appearance of the WMC, and accumulation of toxic metabolites. The WMC disturb the parallel CSF pathways which leads to a slightly elevated CSF pressure and increased CSF pulse pressure. This causes hyperdynamic CSF flow directed towards the cortical areas and causes shear stress around the brain ventricles, which enlarges them, and at the same time leads to the collapse of the cortical veins. Increased resistance of the cortical veins further decreases the absorption of the CSF at the convexity. In this stage, the symptomatic iNPH presents, and the features related to a suprasylvian block appear in the brain imaging (disproportionality between the suprasylvian and Sylvian SAS). It is also likely that comorbidities increase the likelihood of the symptomatic iNPH and may also be connected to the pathogenesis of iNPH, especially AD and VAD. Thus, signs of the comorbidities can often be seen in the brain imaging.

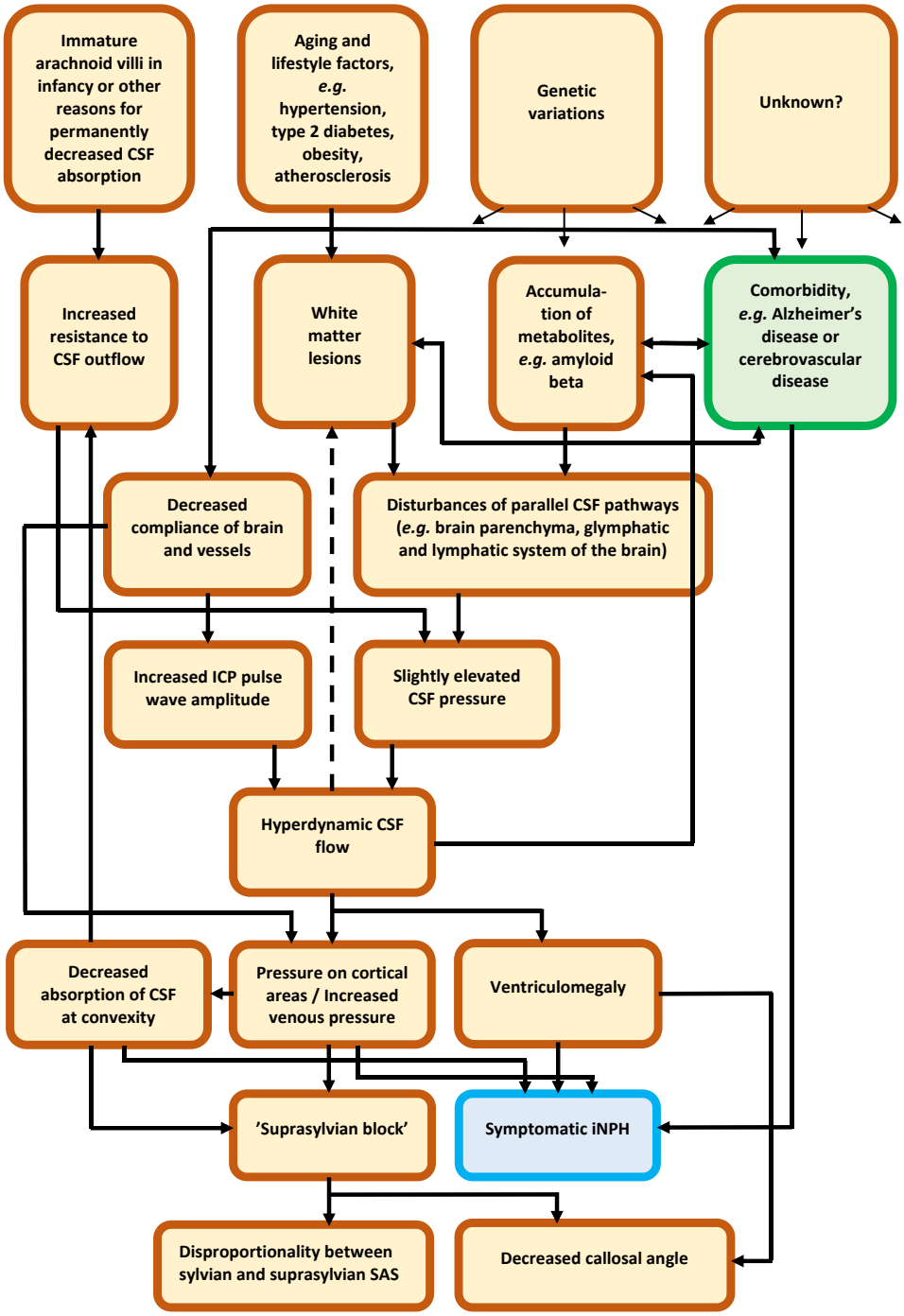

Figure 15. Proposed outline on the iNPH pathogenesis based on this study and previous research (11,39,40,44,47,52,54,55,57,58,213-215). CSF, cerebrospinal fluid; ICP, intracranial pressure; SAS, subarachnoid spaces.

7 Conclusions and future perspectives

In conclusion, in patients suspected to have iNPH, the visually evaluated disproportionality between the suprasylvian and Sylvian SAS evaluated both in MRI and CT images was the most useful radiological marker in the diagnostics of iNPH in this large NPH registry study group. Possibly, narrower WTH in conjunction with the disproportionality may strengthen the diagnosis of iNPH to some extent. In the future, it would be crucial to study the possibilities of the automatic volumetry to measure the disproportionality and implement it into the clinical practice.

In our NPH registry, the brain stem WMC and the periventricular/deep WMC, and signs of the medial temporal lobe atrophy predict all-cause mortality. However, traditional iNPH markers such as EI, ventricular size, and disproportionality between the Sylvian and suprasylvian SAS do not predict mortality.

No preoperative radiological marker was useful in the prediction of the shunt response. Shunt responsiveness was associated with the enlargement of the cortical sulci after the shunt surgery.

Higher EI and sulcal disproportionality were associated with increased ICP, which suggests that these radiological signs are potentially linked to the iNPH pathogenesis. However, these associations were relatively weak, which confirms that these features cannot be used to predict the mean ICP or the ICP pulse wave amplitude in a clinical practice. Finally, the AD-related biopsy findings were related to a high pulse wave amplitude, which suggested that the CSF pulsatility, rather than the ICP alone, might be related to the increases in the amyloid accumulation. The possibility of the accumulation of AD-related proteins in iNPH needs be studied further.

This thesis shows that the traditional radiological markers of iNPH have an important role in the iNPH diagnostics, but radiological features of atrophy and vascular degeneration should also be considered in the diagnostics of iNPH, and not only in the differential diagnostics. Besides EI, disproportionality strengthens the diagnosis of iNPH. Our results do not change the current recommendations in the diagnostics of INPH. More studies are needed in considering the prediction of the shunt response and the overall prognosis. Our findings suggest that we should focus more on the vascular degeneration and the vascular risk factors. It would also be interesting to study whether more intensive treatment of hypertension, hypercholesterolemia, diabetes and antithrombotic therapy in the iNPH patients would have effect on mortality and the quality of life. Additionally, studies investigating the pathophysiology of iNPH are still needed.

8 References

(1) DeCarli C, Murphy DG, McIntosh AR, Teichberg D, Schapiro MB, Horwitz B. Discriminant analysis of MRI measures as a method to determine the presence of dementia of the Alzheimer type. Psychiatry Res 1995 Jul 28;57(2):119-130.

(2) Frisoni GB, Beltramello A, Weiss C, Geroldi C, Bianchetti A, Trabucchi M. Linear measures of atrophy in mild Alzheimer disease. AJNR Am J Neuroradiol 1996 May;17(5):913-923.

(3) Frisoni GB, Beltramello A, Weiss C, Geroldi C, Bianchetti A, Trabucchi M. Usefulness of simple measures of temporal lobe atrophy in probable Alzheimer's disease. Dementia 1996 Jan-Feb;7(1):15-22.

(4) Frisoni GB, Geroldi C, Beltramello A, Bianchetti A, Binetti G, Bordiga G, et al. Radial width of the temporal horn: a sensitive measure in Alzheimer disease. AJNR Am J Neuroradiol 2002 Jan;23(1):35-47.

(5) Killiany RJ, Moss MB, Albert MS, Sandor T, Tieman J, Jolesz F. Temporal lobe regions on magnetic resonance imaging identify patients with early Alzheimer's disease. Arch Neurol 1993 Sep;50(9):949-954.

(6) Hakim S, Adams RD. The special clinical problem of symptomatic hydrocephalus with normal cerebrospinal fluid pressure. Observations on cerebrospinal fluid hydrodynamics. J Neurol Sci 1965 Jul-Aug;2(4):307-327.

(7) Relkin N, Marmarou A, Klinge P, Bergsneider M, Black PM. Diagnosing idiopathic normal-pressure hydrocephalus. Neurosurgery 2005 Sep;57(3 Suppl):S4-16; discussion ii-v.

(8) Martin-Laez R, Caballero-Arzapalo H, Lopez-Menendez LA, Arango-Lasprilla JC, Vazquez-Barquero A. Epidemiology of Idiopathic Normal Pressure Hydrocephalus: A Systematic Review of the Literature. World Neurosurg 2015 Dec;84(6):2002-2009.

(9) Nassar BR, Lippa CF. Idiopathic Normal Pressure Hydrocephalus: A Review for General Practitioners. Gerontol Geriatr Med 2016 Apr 20;2:1-6.

(10) Toma AK, Papadopoulos MC, Stapleton S, Kitchen ND, Watkins LD. Systematic review of the outcome of shunt surgery in idiopathic normal-pressure hydrocephalus. Acta Neurochir (Wien) 2013 Oct;155(10):1977-1980.

(11) Mori E, Ishikawa M, Kato T, Kazui H, Miyake H, Miyajima M, et al. Guidelines for management of idiopathic normal pressure hydrocephalus: second edition. Neurol Med Chir (Tokyo) 2012;52(11):775-809.

(12) Leinonen V, Koivisto AM, Alafuzoff I, Pyykko OT, Rummukainen J, von Und Zu Fraunberg M, et al. Cortical brain biopsy in long-term prognostication of 468 patients with possible normal pressure hydrocephalus. Neurodegener Dis 2012;10(1-4):166-169.

(13) Israelsson H, Carlberg B, Wikkelso C, Laurell K, Kahlon B, Leijon G, et al. Vascular risk factors in INPH: A prospective case-control study (the INPH-CRasH study). Neurology 2017 Feb 7;88(6):577-585.

(14) Debette S, Markus HS. The clinical importance of white matter hyperintensities on brain magnetic resonance imaging: systematic review and meta-analysis. BMJ 2010 Jul 26;341:c3666.

(15) Henneman WJ, Sluimer JD, Cordonnier C, Baak MM, Scheltens P, Barkhof F, et al. MRI biomarkers of vascular damage and atrophy predicting mortality in a memory clinic population. Stroke 2009 Feb;40(2):492-498.

(16) Muangpaisan W, Petcharat C, Srinonprasert V. Prevalence of potentially reversible conditions in dementia and mild cognitive impairment in a geriatric clinic. Geriatr Gerontol Int 2012 Jan;12(1):59-64.

(17) Clarfield AM. The decreasing prevalence of reversible dementias: an updated meta-analysis. Arch Intern Med 2003 Oct 13;163(18):2219-2229.

(18) Hejl A, Hogh P, Waldemar G. Potentially reversible conditions in 1000 consecutive memory clinic patients. J Neurol Neurosurg Psychiatry 2002 Oct;73(4):390-394.

(19) Vanneste J, Augustijn P, Dirven C, Tan WF, Goedhart ZD. Shunting normal-pressure hydrocephalus: do the benefits outweigh the risks? A multicenter study and literature review. Neurology 1992 Jan;42(1):54-59.

(20) Brean A, Eide PK. Prevalence of probable idiopathic normal pressure hydrocephalus in a Norwegian population. Acta Neurol Scand 2008 Jul;118(1):48-53.

(21) Brean A, Fredo HL, Sollid S, Muller T, Sundstrom T, Eide PK. Five-year incidence of surgery for idiopathic normal pressure hydrocephalus in Norway. Acta Neurol Scand 2009 Nov;120(5):314-316.

(22) Iseki C, Takahashi Y, Wada M, Kawanami T, Adachi M, Kato T. Incidence of idiopathic normal pressure hydrocephalus (iNPH): a 10-year follow-up study of a rural community in Japan. J Neurol Sci 2014 Apr 15;339(1-2):108-112.

(23) Lemcke J, Stengel D, Stockhammer F, Guthoff C, Rohde V, Meier U. Nationwide Incidence of Normal Pressure Hydrocephalus (NPH) Assessed by Insurance Claim Data in Germany. Open Neurol J 2016 May 26;10:15-24.

(24) Sundstrom N, Malm J, Laurell K, Lundin F, Kahlon B, Cesarini KG, et al. Incidence and outcome of surgery for adult hydrocephalus patients in Sweden. Br J Neurosurg 2017 Feb;31(1):21-27.

(25) Pyykkö OT, Nerg O, Niskasaari HM, Niskasaari T, Koivisto AM, Hiltunen M, et al. Incidence, Comorbidities, and Mortality in Idiopathic Normal Pressure Hydrocephalus. - PubMed - NCBI. World Neurosurg. 2018;Jan 31. Epub ahead of print.

(26) Kuriyama N, Miyajima M, Nakajima M, Kurosawa M, Fukushima W, Watanabe Y, et al. Nationwide hospital-based survey of idiopathic normal pressure hydrocephalus in Japan: Epidemiological and clinical characteristics. Brain Behav 2017 Jan 27;7(3):e00635.

(27) Hiraoka K, Meguro K, Mori E. Prevalence of idiopathic normal-pressure hydrocephalus in the elderly population of a Japanese rural community. Neurol Med Chir (Tokyo) 2008 May;48(5):197-99; discussion 199-200.

(28) Tanaka N, Yamaguchi S, Ishikawa H, Ishii H, Meguro K. Prevalence of possible idiopathic normal-pressure hydrocephalus in Japan: the Osaki-Tajiri project. Neuroepidemiology 2009;32(3):171-175.

(29) Iseki C, Kawanami T, Nagasawa H, Wada M, Koyama S, Kikuchi K, et al. Asymptomatic ventriculomegaly with features of idiopathic normal pressure hydrocephalus on MRI (AVIM) in the elderly: a prospective study in a Japanese population. J Neurol Sci 2009 Feb 15;277(1-2):54-57.

(30) Jaraj D, Rabiei K, Marlow T, Jensen C, Skoog I, Wikkelso C. Prevalence of idiopathic normal-pressure hydrocephalus. Neurology 2014 Apr 22;82(16):1449-1454.

(31) Hladky SB, Barrand MA. Mechanisms of fluid movement into, through and out of the brain: evaluation of the evidence. Fluids Barriers CNS 2014 Dec 2;11(1):26.

(32) Hall JE. Guyton and Hall Textbook of Medical Physiology. 12th ed. USA: Saunders Elsevier; 2011.

(33) Bradley WG,Jr. CSF Flow in the Brain in the Context of Normal Pressure Hydrocephalus. AJNR Am J Neuroradiol 2015 May;36(5):831-838.

(34) Kiviniemi V, Wang X, Korhonen V, Keinanen T, Tuovinen T, Autio J, et al. Ultra-fast magnetic resonance encephalography of physiological brain activity - Glymphatic pulsation mechanisms? J Cereb Blood Flow Metab 2016 Jun;36(6):1033-1045.

(35) Aspelund A, Antila S, Proulx ST, Karlsen TV, Karaman S, Detmar M, et al. A dural lymphatic vascular system that drains brain interstitial fluid and macromolecules. J Exp Med 2015 Jun 29;212(7):991-999.

(36) Louveau A, Smirnov I, Keyes TJ, Eccles JD, Rouhani SJ, Peske JD, et al. Structural and functional features of central nervous system lymphatic vessels. Nature 2015 Jul 16;523(7560):337-341.

(37) Visanji NP, Lang AE, Munoz DG. Lymphatic vasculature in human dural superior sagittal sinus: Implications for neurodegenerative proteinopathies. Neurosci Lett 2017 Nov;665:18-21.

(38) Betts JG, Desaix P, Johnson E, Johnson JE, Korol O, Kruse D, et al. OpenStax, Anatomy & Physiology. OpenStax CNX. 2016; Available at: https://cnx.org/contents/FPtK1zmh@8.25:DcB5rjNc@3/Circulation-and-the-Central-Ne. Accessed 07/27, 2017.

(39) Kitagaki H, Mori E, Ishii K, Yamaji S, Hirono N, Imamura T. CSF spaces in idiopathic normal pressure hydrocephalus: morphology and volumetry. AJNR Am J Neuroradiol 1998 Aug;19(7):1277-1284.

(40) Eide PK, Sorteberg W. Outcome of Surgery for Idiopathic Normal Pressure Hydrocephalus: Role of Preoperative Static and Pulsatile Intracranial Pressure. World Neurosurg 2016 Feb;86:186-193.e1.

(41) Owler BK, Momjian S, Czosnyka Z, Czosnyka M, Pena A, Harris NG, et al. Normal pressure hydrocephalus and cerebral blood flow: a PET study of baseline values. J Cereb Blood Flow Metab 2004 Jan;24(1):17-23.

(42) Borgesen SE, Gjerris F. The predictive value of conductance to outflow of CSF in normal pressure hydrocephalus. Brain 1982 Mar;105(Pt 1):65-86.

(43) Edwards RJ, Dombrowski SM, Luciano MG, Pople IK. Chronic hydrocephalus in adults. Brain Pathol 2004 Jul;14(3):325-336.

(44) Bateman GA. Vascular compliance in normal pressure hydrocephalus. AJNR Am J Neuroradiol 2000 Oct;21(9):1574-1585.

(45) Bradley WG,Jr, Scalzo D, Queralt J, Nitz WN, Atkinson DJ, Wong P. Normal-pressure hydrocephalus: evaluation with cerebrospinal fluid flow measurements at MR imaging. Radiology 1996 Feb;198(2):523-529.

(46) Eide PK, Hansson HA. Astrogliosis and impaired aquaporin-4 and dystrophin systems in idiopathic normal pressure hydrocephalus. Neuropathol Appl Neurobiol 2017 Jun 19.

(47) Silverberg GD, Mayo M, Saul T, Rubenstein E, McGuire D. Alzheimer's disease, normal-pressure hydrocephalus, and senescent changes in CSF circulatory physiology: a hypothesis. Lancet Neurol 2003 Aug;2(8):506-511.

(48) Silverberg GD, Mayo M, Saul T, Fellmann J, Carvalho J, McGuire D. Continuous CSF drainage in AD: results of a double-blind, randomized, placebo-controlled study. Neurology 2008 Jul 15;71(3):202-209.

(49) Krefft TA, Graff-Radford NR, Lucas JA, Mortimer JA. Normal pressure hydrocephalus and large head size. Alzheimer Dis Assoc Disord 2004 Jan-Mar;18(1):35-37.

(50) Graff-Radford NR, Godersky JC. Symptomatic congenital hydrocephalus in the elderly simulating normal pressure hydrocephalus. Neurology 1989 Dec;39(12):1596-1600.

(51) Bradley WG, Safar FG, Furtado C, Ord J, Alksne JF. Increased intracranial volume: a clue to the etiology of idiopathic normal-pressure hydrocephalus? AJNR Am J Neuroradiol 2004 Oct;25(9):1479-1484.

(52) Bradley WG,Jr, Bahl G, Alksne JF. Idiopathic normal pressure hydrocephalus may be a "two hit" disease: benign external hydrocephalus in infancy followed by deep white matter ischemia in late adulthood. J Magn Reson Imaging 2006 Oct;24(4):747-755.

(53) Wilson RK, Williams MA. Evidence that congenital hydrocephalus is a precursor to idiopathic normal pressure hydrocephalus in only a subset of patients. J Neurol Neurosurg Psychiatry 2007 May;78(5):508-511.

(54) Portenoy RK, Berger A, Gross E. Familial occurrence of idiopathic normal-pressure hydrocephalus. Arch Neurol 1984 Mar;41(3):335-337.

(55) Kato T, Sato H, Emi M, Seino T, Arawaka S, Iseki C, et al. Segmental copy number loss of SFMBT1 gene in elderly individuals with ventriculomegaly: a community-based study. Intern Med 2011;50(4):297-303.

(56) Sato H, Takahashi Y, Kimihira L, Iseki C, Kato H, Suzuki Y, et al. A Segmental Copy Number Loss of the SFMBT1 Gene Is a Genetic Risk for Shunt-Responsive, Idiopathic Normal Pressure Hydrocephalus (iNPH): A Case-Control Study. PLoS One 2016 Nov 18;11(11):e0166615.

(57) Bradley WG,Jr, Whittemore AR, Watanabe AS, Davis SJ, Teresi LM, Homyak M. Association of deep white matter infarction with chronic communicating hydrocephalus: implications regarding the possible origin of normal-pressure hydrocephalus. AJNR Am J Neuroradiol 1991 Jan-Feb;12(1):31-39.

(58) Bateman GA. The pathophysiology of idiopathic normal pressure hydrocephalus: cerebral ischemia or altered venous hemodynamics? AJNR Am J Neuroradiol 2008 Jan;29(1):198-203.

(59) Bateman GA. Pulse-wave encephalopathy: a comparative study of the hydrodynamics of leukoaraiosis and normal-pressure hydrocephalus. Neuroradiology 2002 Sep;44(9):740-748.

(60) Bradley WG. Normal pressure hydrocephalus: new concepts on etiology and diagnosis. AJNR Am J Neuroradiol 2000 Oct;21(9):1586-1590.

(61) Kiefer M, Unterberg A. The differential diagnosis and treatment of normal-pressure hydrocephalus. Dtsch Arztebl Int 2012 Jan;109(1-2):15-25; quiz 26.

(62) Williams MA, Relkin NR. Diagnosis and management of idiopathic normal-pressure hydrocephalus. Neurol Clin Pract 2013 Oct;3(5):375-385.

(63) Evans WA. An encephalographic ratio for estimating ventricular enlargement and cerebral atrophy. Archives of Neurology And Psychiatry 1942;47(6):931.

(64) Missori P, Rughetti A, Peschillo S, Gualdi G, Di Biasi C, Nofroni I, et al. In normal aging ventricular system never attains pathological values of Evans' index. Oncotarget 2016 Mar 15;7(11):11860-11863.

(65) Toma AK, Holl E, Kitchen ND, Watkins LD. Evans' index revisited: the need for an alternative in normal pressure hydrocephalus. Neurosurgery 2011 Apr;68(4):939-944.

(66) Ambarki K, Israelsson H, Wahlin A, Birgander R, Eklund A, Malm J. Brain ventricular size in healthy elderly: comparison between Evans index and volume measurement. Neurosurgery 2010 Jul;67(1):94-9; discussion 99.

(67) Miskin N, Patel H, Franceschi AM, Ades-Aron B, Le A, Damadian BE, et al. Diagnosis of Normal-Pressure Hydrocephalus: Use of Traditional Measures in the Era of Volumetric MR Imaging. Radiology 2017 May 10:161216.

(68) Hiraoka K, Yamasaki H, Takagi M, Saito M, Nishio Y, Iizuka O, et al. Changes in the volumes of the brain and cerebrospinal fluid spaces after shunt surgery in idiopathic normal-pressure hydrocephalus. J Neurol Sci 2010 Sep 15;296(1-2):7-12.

(69) Tsunoda A, Mitsuoka H, Bandai H, Arai H, Sato K, Makita J. Intracranial cerebrospinal fluid distribution and its postoperative changes in normal pressure hydrocephalus. Acta Neurochir (Wien) 2001;143(5):493-499.

(70) Anderson RC, Grant JJ, de la Paz R, Frucht S, Goodman RR. Volumetric measurements in the detection of reduced ventricular volume in patients with normal-pressure hydrocephalus whose clinical condition improved after ventriculoperitoneal shunt placement. J Neurosurg 2002 Jul;97(1):73-79.

(71) Meier U, Mutze S. Does the ventricle size change after shunt operation of normal-pressure hydrocephalus? Acta Neurochir Suppl 2005;95:257-259.

(72) Palm WM, Walchenbach R, Bruinsma B, Admiraal-Behloul F, Middelkoop HA, Launer LJ, et al. Intracranial compartment volumes in normal pressure hydrocephalus: volumetric assessment versus outcome. AJNR Am J Neuroradiol 2006 Jan;27(1):76-79.

(73) Millingen KS. Idiopathic communicating hydrocephalus: the prognostic significane of ventricular size after shunting. Clin Exp Neurol 1979;16:167-174.

(74) Lenfeldt N, Hansson W, Larsson A, Birgander R, Eklund A, Malm J. Three-day CSF drainage barely reduces ventricular size in normal pressure hydrocephalus. Neurology 2012 Jul 17;79(3):237-242.

(75) Yamada S, Ishikawa M, Yamamoto K. Optimal Diagnostic Indices for Idiopathic Normal Pressure Hydrocephalus Based on the 3D Quantitative Volumetric Analysis for the Cerebral Ventricle and Subarachnoid Space. AJNR Am J Neuroradiol 2015 Dec;36(12):2262-2269.

(76) Bendel P, Koivisto T, Aikia M, Niskanen E, Kononen M, Hanninen T, et al. Atrophic enlargement of CSF volume after subarachnoid hemorrhage: correlation with neuropsychological outcome. AJNR Am J Neuroradiol 2010 Feb;31(2):370-376.

(77) Bao J, Gao Y, Cao Y, Xu S, Zheng Y, Wang Y, et al. Feasibility of Simple Linear Measurements to Determine Ventricular Enlargement in Patients With Idiopathic Normal Pressure Hydrocephalus. J Craniofac Surg 2016 Jul;27(5):e462-5.

(78) Holodny AI, Waxman R, George AE, Rusinek H, Kalnin AJ, de Leon M. MR differential diagnosis of normal-pressure hydrocephalus and Alzheimer disease: significance of perihippocampal fissures. AJNR Am J Neuroradiol 1998 May;19(5):813-819.

(79) LeMay M, New PF. Radiological diagnosis of occult normal-pressure hydrocephalus. Radiology 1970 Aug;96(2):347-358.

(80) Ishii K, Kanda T, Harada A, Miyamoto N, Kawaguchi T, Shimada K, et al. Clinical impact of the callosal angle in the diagnosis of idiopathic normal pressure hydrocephalus. Eur Radiol 2008 Nov;18(11):2678-2683.

(81) Virhammar J, Laurell K, Cesarini KG, Larsson EM. The callosal angle measured on MRI as a predictor of outcome in idiopathic normal-pressure hydrocephalus. J Neurosurg 2014 Jan;120(1):178-184.

(82) Cagnin A, Simioni M, Tagliapietra M, Citton V, Pompanin S, Della Puppa A, et al. A Simplified Callosal Angle Measure Best Differentiates Idiopathic-Normal Pressure Hydrocephalus from Neurodegenerative Dementia. J Alzheimers Dis 2015;46(4):1033-1038.

(83) Wikkelso C, Andersson H, Blomstrand C, Matousek M, Svendsen P. Computed tomography of the brain in the diagnosis of and prognosis in normal pressure hydrocephalus. Neuroradiology 1989;31(2):160-165.

(84) George AE, Holodny A, Golomb J, de Leon MJ. The differential diagnosis of Alzheimer's disease. Cerebral atrophy versus normal pressure hydrocephalus. Neuroimaging Clin N Am 1995 Feb;5(1):19-31.

(85) Virhammar J, Laurell K, Cesarini KG, Larsson EM. Preoperative Prognostic Value of MRI Findings in 108 Patients with Idiopathic Normal Pressure Hydrocephalus. AJNR Am J Neuroradiol 2014 Jul 10;35(12):2311-2318.

(86) Scheltens P, Leys D, Barkhof F, Huglo D, Weinstein HC, Vermersch P, et al. Atrophy of medial temporal lobes on MRI in "probable" Alzheimer's disease and normal ageing: diagnostic value and neuropsychological correlates. J Neurol Neurosurg Psychiatry 1992 Oct;55(10):967-972.

(87) Mak E, Su L, Williams GB, Watson R, Firbank M, Blamire AM, et al. Longitudinal assessment of global and regional atrophy rates in Alzheimer's disease and dementia with Lewy bodies. Neuroimage Clin 2015 Feb 7;7:456-462.

(88) Moore DW, Kovanlikaya I, Heier LA, Raj A, Huang C, Chu KW, et al. A pilot study of quantitative MRI measurements of ventricular volume and cortical atrophy for the differential diagnosis of normal pressure hydrocephalus. Neurol Res Int 2012;2012:718150.

(89) Sasaki M, Honda S, Yuasa T, Iwamura A, Shibata E, Ohba H. Narrow CSF space at high convexity and high midline areas in idiopathic normal pressure hydrocephalus detected by axial and coronal MRI. Neuroradiology 2008 Feb;50(2):117-122.

(90) Holodny AI, George AE, de Leon MJ, Golomb J, Kalnin AJ, Cooper PR. Focal dilation and paradoxical collapse of cortical fissures and sulci in patients with normal-pressure hydrocephalus. J Neurosurg 1998 Nov;89(5):742-747.

(91) Graff-Radford NR. Normal pressure hydrocephalus. Neurol Clin 2007 Aug;25(3):809-32, vii-viii.

(92) Hashimoto M, Ishikawa M, Mori E, Kuwana N, Study of INPH on neurological improvement (SINPHONI). Diagnosis of idiopathic normal pressure hydrocephalus is supported by MRI-based scheme: a prospective cohort study. Cerebrospinal Fluid Res 2010 Oct 31;7:18-8454-7-18.

(93) Garcia-Armengol R, Domenech S, Botella-Campos C, Goncalves FJ, Menendez B, Teixidor P, et al. Comparison of elevated intracranial pressure pulse amplitude and disproportionately enlarged subarachnoid space (DESH) for prediction of surgical results in suspected idiopathic normal pressure hydrocephalus. Acta Neurochir (Wien) 2016 Nov;158(11):2207-2213.

(94) Craven CL, Toma AK, Mostafa T, Patel N, Watkins LD. The predictive value of DESH for shunt responsiveness in idiopathic normal pressure hydrocephalus. J Clin Neurosci 2016 Dec;34:294-298.

(95) Benedetto N, Gambacciani C, Aquila F, Di Carlo DT, Morganti R, Perrini P. A new quantitative method to assess disproportionately enlarged subarachnoid space (DESH) in patients with possible idiopathic normal pressure hydrocephalus: The SILVER index. Clin Neurol Neurosurg 2017 Jul;158:27-32.

(96) Williams MA, Malm J. Diagnosis and Treatment of Idiopathic Normal Pressure Hydrocephalus. Continuum (Minneap Minn) 2016 Apr;22(2 Dementia):579-599.

(97) Krauss JK, Regel JP, Vach W, Orszagh M, Jungling FD, Bohus M, et al. White matter lesions in patients with idiopathic normal pressure hydrocephalus and in an age-matched control group: a comparative study. Neurosurgery 1997 Mar;40(3):491-5; discussion 495-6.

(98) Launer LJ. Epidemiology of white matter lesions. Top Magn Reson Imaging 2004 Dec;15(6):365-367.

(99) Haller S, Kovari E, Herrmann FR, Cuvinciuc V, Tomm AM, Zulian GB, et al. Do brain T2/FLAIR white matter hyperintensities correspond to myelin loss in normal aging? A radiologic-neuropathologic correlation study. Acta Neuropathol Commun 2013 May 9;1:14.

(100) Fazekas F, Kleinert R, Offenbacher H, Schmidt R, Kleinert G, Payer F, et al. Pathologic correlates of incidental MRI white matter signal hyperintensities. Neurology 1993 Sep;43(9):1683-1689.

(101) van Swieten JC, van den Hout JH, van Ketel BA, Hijdra A, Wokke JH, van Gijn J. Periventricular lesions in the white matter on magnetic resonance imaging in the elderly. A morphometric correlation with arteriolosclerosis and dilated perivascular spaces. Brain 1991 Apr;114 (Pt 2)(Pt 2):761-774.

(102) Tullberg M, Jensen C, Ekholm S, Wikkelso C. Normal pressure hydrocephalus: vascular white matter changes on MR images must not exclude patients from shunt surgery. AJNR Am J Neuroradiol 2001 Oct;22(9):1665-1673.

(103) Fazekas F, Chawluk JB, Alavi A, Hurtig HI, Zimmerman RA. MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging. AJR Am J Roentgenol 1987 Aug;149(2):351-356.

(104) Tisell M, Tullberg M, Hellstrom P, Edsbagge M, Hogfeldt M, Wikkelso C. Shunt surgery in patients with hydrocephalus and white matter changes. J Neurosurg 2011 May;114(5):1432-1438.

(105) Bradley WG,Jr, Whittemore AR, Kortman KE, Watanabe AS, Homyak M, Teresi LM, et al. Marked cerebrospinal fluid void: indicator of successful shunt in patients with suspected normal-pressure hydrocephalus. Radiology 1991 Feb;178(2):459-466.

(106) Algin O, Hakyemez B, Taskapilioglu O, Ocakoglu G, Bekar A, Parlak M. Morphologic features and flow void phenomenon in normal pressure hydrocephalus and other dementias: are they really significant? Acad Radiol 2009 Nov;16(11):1373-1380.

(107) Dixon GR, Friedman JA, Luetmer PH, Quast LM, McClelland RL, Petersen RC, et al. Use of cerebrospinal fluid flow rates measured by phase-contrast MR to predict outcome of ventriculoperitoneal shunting for idiopathic normal-pressure hydrocephalus. Mayo Clin Proc 2002 Jun;77(6):509-514.

(108) Krauss JK, Regel JP, Vach W, Jungling FD, Droste DW, Wakhloo AK. Flow void of cerebrospinal fluid in idiopathic normal pressure hydrocephalus of the elderly: can it predict outcome after shunting? Neurosurgery 1997 Jan;40(1):67-73; discussion 73-4.

(109) Bourne SK, Conrad A, Neimat JS, Davis TL. Linear measurements of the cerebral ventricles are correlated with adult ventricular volume. J Clin Neurosci 2013 May;20(5):763-764.

(110) Reinard K, Basheer A, Phillips S, Snyder A, Agarwal A, Jafari-Khouzani K, et al. Simple and reproducible linear measurements to determine ventricular enlargement in adults. Surg Neurol Int 2015 Apr 9;6:59-7806.154777. eCollection 2015.

(111) Yamashita F, Sasaki M, Saito M, Mori E, Kawaguchi A, Kudo K, et al. Voxel-based morphometry of disproportionate cerebrospinal fluid space distribution for the differential

diagnosis of idiopathic normal pressure hydrocephalus. J Neuroimaging 2014 Jul-Aug;24(4):359-365.

(112) Ishii K, Soma T, Shimada K, Oda H, Terashima A, Kawasaki R. Automatic volumetry of the cerebrospinal fluid space in idiopathic normal pressure hydrocephalus. Dement Geriatr Cogn Dis Extra 2013 Dec 20;3(1):489-496.

(113) Czosnyka M, Pickard JD. Monitoring and interpretation of intracranial pressure. J Neurol Neurosurg Psychiatry 2004 Jun;75(6):813-821.

(114) Hamilton R, Patel S, Lee EB, Jackson EM, Lopinto J, Arnold SE, et al. Lack of shunt response in suspected idiopathic normal pressure hydrocephalus with Alzheimer disease pathology. Ann Neurol 2010 Oct;68(4):535-540.

(115) Leinonen V, Koivisto AM, Savolainen S, Rummukainen J, Tamminen JN, Tillgren T, et al. Amyloid and tau proteins in cortical brain biopsy and Alzheimer's disease. Ann Neurol 2010 Oct;68(4):446-453.

(116) LUNDBERG N. Continuous recording and control of ventricular fluid pressure in neurosurgical practice. Acta Psychiatr Scand Suppl 1960;36(149):1-193.

(117) Spiegelberg A, Preuß M, Kurtcuoglu V. B-waves revisited. Interdisciplinary Neurosurgery 2016 12;6:13-17.

(118) Di Ieva A, Schmitz EM, Cusimano MD. Analysis of intracranial pressure: past, present, and future. Neuroscientist 2013 Dec;19(6):592-603.

(119) Barcena A, Mestre C, Canizal JM, Rivero B, Lobato RD. Idiopathic normal pressure hydrocephalus: analysis of factors related to cerebrospinal fluid dynamics determining functional prognosis. Acta Neurochir (Wien) 1997;139(10):933-941.

(120) Krauss JK, Droste DW, Bohus M, Regel JP, Scheremet R, Riemann D, et al. The relation of intracranial pressure B-waves to different sleep stages in patients with suspected normal pressure hydrocephalus. Acta Neurochir (Wien) 1995;136(3-4):195-203.

(121) Foss T, Eide PK, Finset A. Intracranial pressure parameters in idiopathic normal pressure hydrocephalus patients with or without improvement of cognitive function after shunt treatment. Dement Geriatr Cogn Disord 2007;23(1):47-54.

(122) Eide PK, Brean A. Cerebrospinal fluid pulse pressure amplitude during lumbar infusion in idiopathic normal pressure hydrocephalus can predict response to shunting. Cerebrospinal Fluid Res 2010 Feb 12;7:5-8454-7-5.

(123) Eide PK, Sorteberg W. Diagnostic intracranial pressure monitoring and surgical management in idiopathic normal pressure hydrocephalus: a 6-year review of 214 patients. Neurosurgery 2010 Jan;66(1):80-91.

(124) Raftopoulos C, Deleval J, Chaskis C, Leonard A, Cantraine F, Desmyttere F, et al. Cognitive recovery in idiopathic normal pressure hydrocephalus: a prospective study. Neurosurgery 1994 Sep;35(3):397-404; discussion 404-5.

(125) Eide PK, Stanisic M. Cerebral microdialysis and intracranial pressure monitoring in patients with idiopathic normal-pressure hydrocephalus: association with clinical response to extended lumbar drainage and shunt surgery. J Neurosurg 2010 Feb;112(2):414-424.

(126) Poca MA, Mataro M, Del Mar Matarin M, Arikan F, Junque C, Sahuquillo J. Is the placement of shunts in patients with idiopathic normal-pressure hydrocephalus worth the risk? Results of a study based on continuous monitoring of intracranial pressure. J Neurosurg 2004 May;100(5):855-866.

(127) Woodworth GF, McGirt MJ, Williams MA, Rigamonti D. Cerebrospinal fluid drainage and dynamics in the diagnosis of normal pressure hydrocephalus. Neurosurgery 2009 May;64(5):919-25; discussion 925-6.

(128) Marmarou A, Bergsneider M, Klinge P, Relkin N, Black PM. The value of supplemental prognostic tests for the preoperative assessment of idiopathic normal-pressure hydrocephalus. Neurosurgery 2005 Sep;57(3 Suppl):S17-28; discussion ii-v.

(129) Jaraj D, Rabiei K, Marlow T, Jensen C, Skoog I, Wikkelso C. Estimated ventricle size using Evans index: reference values from a population-based sample. Eur J Neurol 2017 Mar;24(3):468-474.

(130) Malm J, Graff-Radford NR, Ishikawa M, Kristensen B, Leinonen V, Mori E, et al. Influence of comorbidities in idiopathic normal pressure hydrocephalus - research and clinical care. A report of the ISHCSF task force on comorbidities in INPH. Fluids Barriers CNS 2013 Jun 10;10(1):22-8118-10-22.

(131) Wilson RK, Williams MA. Normal pressure hydrocephalus. Clin Geriatr Med 2006 Nov;22(4):935-51, viii.

(132) Hakim CA, Hakim R, Hakim S. Normal-pressure hydrocephalus. Neurosurg Clin N Am 2001 Oct;12(4):761-73, ix.

(133) Roman GC, Tatemichi TK, Erkinjuntti T, Cummings JL, Masdeu JC, Garcia JH, et al. Vascular dementia: diagnostic criteria for research studies. Report of the NINDS-AIREN International Workshop. Neurology 1993 Feb;43(2):250-260.

(134) Oi S, Shimoda M, Shibata M, Honda Y, Togo K, Shinoda M, et al. Pathophysiology of long-standing overt ventriculomegaly in adults. J Neurosurg 2000 Jun;92(6):933-940.

(135) Jaraj D, Agerskov S, Rabiei K, Marlow T, Jensen C, Guo X, et al. Vascular factors in suspected normal pressure hydrocephalus: A population-based study. Neurology 2016 Feb 16;86(7):592-599.

(136) Johansson E, Ambarki K, Birgander R, Bahrami N, Eklund A, Malm J. Cerebral microbleeds in idiopathic normal pressure hydrocephalus. Fluids Barriers CNS 2016 Feb 10;13:4-016-0028-z.

(137) Bech-Azeddine R, Hogh P, Juhler M, Gjerris F, Waldemar G. Idiopathic normal-pressure hydrocephalus: clinical comorbidity correlated with cerebral biopsy findings and outcome of cerebrospinal fluid shunting. J Neurol Neurosurg Psychiatry 2007 Feb;78(2):157-161.

(138) Leinonen V, Koivisto AM, Savolainen S, Rummukainen J, Sutela A, Vanninen R, et al. Post-mortem findings in 10 patients with presumed normal-pressure hydrocephalus and review of the literature. Neuropathol Appl Neurobiol 2012 Feb;38(1):72-86.

(139) Golomb J, Wisoff J, Miller DC, Boksay I, Kluger A, Weiner H, et al. Alzheimer's disease comorbidity in normal pressure hydrocephalus: prevalence and shunt response. J Neurol Neurosurg Psychiatry 2000 Jun;68(6):778-781.

(140) Jaraj D, Wikkelso C, Rabiei K, Marlow T, Jensen C, Ostling S, et al. Mortality and risk of dementia in normal-pressure hydrocephalus: A population study. Alzheimers Dement 2017 Feb 23.

(141) Tullberg M, Persson J, Petersen J, Hellstrom P, Wikkelso C, Lundgren-Nilsson A. Shunt surgery in idiopathic normal pressure hydrocephalus is cost-effective-a cost utility analysis. Acta Neurochir (Wien) 2018 Mar;160(3):509-518.

(142) Petersen J, Hellstrom P, Wikkelso C, Lundgren-Nilsson A. Improvement in social function and health-related quality of life after shunt surgery for idiopathic normal-pressure hydrocephalus. J Neurosurg 2014 Oct;121(4):776-784.

(143) Razay G, Vreugdenhil A, Liddell J. A prospective study of ventriculo-peritoneal shunting for idiopathic normal pressure hydrocephalus. J Clin Neurosci 2009 Sep;16(9):1180-1183.

(144) Andren K, Wikkelso C, Tisell M, Hellstrom P. Natural course of idiopathic normal pressure hydrocephalus. J Neurol Neurosurg Psychiatry 2014 Jul;85(7):806-810.

(145) Toma AK, Stapleton S, Papadopoulos MC, Kitchen ND, Watkins LD. Natural history of idiopathic normal-pressure hydrocephalus. Neurosurg Rev 2011 Oct;34(4):433-439.

(146) Scollato A, Tenenbaum R, Bahl G, Celerini M, Salani B, Di Lorenzo N. Changes in aqueductal CSF stroke volume and progression of symptoms in patients with unshunted idiopathic normal pressure hydrocephalus. AJNR Am J Neuroradiol 2008 Jan;29(1):192-197.

(147) Savolainen S, Hurskainen H, Paljarvi L, Alafuzoff I, Vapalahti M. Five-year outcome of normal pressure hydrocephalus with or without a shunt: predictive value of the clinical signs, neuropsychological evaluation and infusion test. Acta Neurochir (Wien) 2002 Jun;144(6):515-23; discussion 523.

(148) Tisell M, Hellstrom P, Ahl-Borjesson G, Barrows G, Blomsterwall E, Tullberg M, et al. Long-term outcome in 109 adult patients operated on for hydrocephalus. Br J Neurosurg 2006 Aug;20(4):214-221.

(149) Malm J, Kristensen B, Stegmayr B, Fagerlund M, Koskinen LO. Three-year survival and functional outcome of patients with idiopathic adult hydrocephalus syndrome. Neurology 2000 Aug 22;55(4):576-578.

(150) Mirzayan MJ, Luetjens G, Borremans JJ, Regel JP, Krauss JK. Extended long-term (> 5 years) outcome of cerebrospinal fluid shunting in idiopathic normal pressure hydrocephalus. Neurosurgery 2010 Aug;67(2):295-301.

(151) Tasiou A, Brotis AG, Esposito F, Paterakis KN. Endoscopic third ventriculostomy in the treatment of idiopathic normal pressure hydrocephalus: a review study. Neurosurg Rev 2016 Oct;39(4):557-563.

(152) Jones RF, Stening WA, Brydon M. Endoscopic third ventriculostomy. Neurosurgery 1990 Jan;26(1):86-91; discussion 91-2.

(153) Mitchell P, Mathew B. Third ventriculostomy in normal pressure hydrocephalus. Br J Neurosurg 1999 Aug;13(4):382-385.

(154) Gupta A, Lang AE. Potential placebo effect in assessing idiopathic normal pressure hydrocephalus. J Neurosurg 2011 May;114(5):1428-1431.

(155) Kazui H, Miyajima M, Mori E, Ishikawa M, SINPHONI-2 Investigators. Lumboperitoneal shunt surgery for idiopathic normal pressure hydrocephalus (SINPHONI-2): an open-label randomised trial. Lancet Neurol 2015 Jun;14(6):585-594.

(156) Toma AK, Watkins LD. Surgical management of idiopathic normal pressure hydrocephalus: a trial of a trial. Br J Neurosurg 2016 Dec;30(6):605.

(157) Cancer Research UK. Diagram showing a brain shunt. 2016; Available at: https://upload.wikimedia.org/wikipedia/commons/c/c7/Diagram_showing_a_brain_shunt_CRUK_052.svg. Accessed 07/27, 2017.

(158) Watkins LD. Conservative versus surgical management of idiopathic normal pressure hydrocephalus (INPH). 2011; Available at: https://clinicaltrials.gov/ct2/show/study/NCT00727142?titles=Conservative+versus+surgical+management+of+idiopathic+normal+pressure+hydrocephalus&rank=1. Accessed 7/17, 2017.

(159) Black PM. Idiopathic normal-pressure hydrocephalus. Results of shunting in 62 patients. J Neurosurg 1980 Mar;52(3):371-377.

(160) Raftopoulos C, Massager N, Baleriaux D, Deleval J, Clarysse S, Brotchi J. Prospective analysis by computed tomography and long-term outcome of 23 adult patients with chronic idiopathic hydrocephalus. Neurosurgery 1996 Jan;38(1):51-59.

(161) Hebb AO, Cusimano MD. Idiopathic normal pressure hydrocephalus: a systematic review of diagnosis and outcome. Neurosurgery 2001 Nov;49(5):1166-84; discussion 1184-6.

(162) Halperin JJ, Kurlan R, Schwalb JM, Cusimano MD, Gronseth G, Gloss D. Practice guideline: Idiopathic normal pressure hydrocephalus: Response to shunting and predictors of response: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. Neurology 2015 Dec 8;85(23):2063-2071.

(163) Greenberg JO, Shenkin HA, Adam R. Idiopathic normal pressure hydrocephalus-- a report of 73 patients. J Neurol Neurosurg Psychiatry 1977 Apr;40(4):336-341.

(164) Meier U, Miethke C. Predictors of outcome in patients with normal-pressure hydrocephalus. J Clin Neurosci 2003 Jul;10(4):453-459.

(165) Kahlon B, Sjunnesson J, Rehncrona S. Long-term outcome in patients with suspected normal pressure hydrocephalus. Neurosurgery 2007 Feb;60(2):327-32; discussion 332.

(166) McGirt MJ, Woodworth G, Coon AL, Thomas G, Williams MA, Rigamonti D. Diagnosis, treatment, and analysis of long-term outcomes in idiopathic normal-pressure hydrocephalus. Neurosurgery 2005 Oct;57(4):699-705.

(167) Koivisto AM, Alafuzoff I, Savolainen S, Sutela A, Rummukainen J, Kurki M, et al. Poor cognitive outcome in shunt-responsive idiopathic normal pressure hydrocephalus. Neurosurgery 2013 Jan;72(1):1-8;discussion 8.

(168) Bergsneider M, Black PM, Klinge P, Marmarou A, Relkin N. Surgical management of idiopathic normal-pressure hydrocephalus. Neurosurgery 2005 Sep;57(3 Suppl):S29-39; discussion ii-v.

(169) Wong JM, Ziewacz JE, Ho AL, Panchmatia JR, Bader AM, Garton HJ, et al. Patterns in neurosurgical adverse events: cerebrospinal fluid shunt surgery. Neurosurg Focus 2012 Nov;33(5):E13.

(170) Hung AL, Vivas-Buitrago T, Adam A, Lu J, Robison J, Elder BD, et al. Ventriculoatrial versus ventriculoperitoneal shunt complications in idiopathic normal pressure hydrocephalus. Clin Neurol Neurosurg 2017 Jun;157:1-6.

(171) Thompson SD, Shand Smith JD, Khan AA, Luoma AMV, Toma AK, Watkins LD. Shunting of the over 80s in normal pressure hydrocephalus. Acta Neurochir (Wien) 2017 Apr 18.

(172) Lundkvist B, Koskinen LO, Birgander R, Eklund A, Malm J. Cerebrospinal fluid dynamics and long-term survival of the Strata valve in idiopathic normal pressure hydrocephalus. Acta Neurol Scand 2011 Aug;124(2):115-121.

(173) Liu A, Sankey EW, Jusue-Torres I, Patel MA, Elder BD, Goodwin CR, et al. Clinical outcomes after ventriculoatrial shunting for idiopathic normal pressure hydrocephalus. Clin Neurol Neurosurg 2016 Apr;143:34-38.

(174) McGovern RA, Kelly KM, Chan AK, Morrissey NJ, McKhann GM,2nd. Should ventriculoatrial shunting be the procedure of choice for normal-pressure hydrocephalus? J Neurosurg 2014 Jun;120(6):1458-1464.

(175) Miyajima M, Kazui H, Mori E, Ishikawa M, on behalf of the SINPHONI-2 Investigators. One-year outcome in patients with idiopathic normal-pressure hydrocephalus: comparison of lumboperitoneal shunt to ventriculoperitoneal shunt. J Neurosurg 2016 Dec;125(6):1483-1492.

(176) Shinoda N, Hirai O, Hori S, Mikami K, Bando T, Shimo D, et al. Utility of MRI-based disproportionately enlarged subarachnoid space hydrocephalus scoring for predicting prognosis after surgery for idiopathic normal pressure hydrocephalus: clinical research. J Neurosurg 2017 Feb 03:1-7.

(177) Ishii K, Kawaguchi T, Shimada K, Ohkawa S, Miyamoto N, Kanda T, et al. Voxel-based analysis of gray matter and CSF space in idiopathic normal pressure hydrocephalus. Dement Geriatr Cogn Disord 2008;25(4):329-335.

(178) Narita W, Nishio Y, Baba T, Iizuka O, Ishihara T, Matsuda M, et al. High-Convexity Tightness Predicts the Shunt Response in Idiopathic Normal Pressure Hydrocephalus. AJNR Am J Neuroradiol 2016 Jun;37(10):1831-1837.

(179) Kuller LH, Arnold AM, Longstreth WT,Jr, Manolio TA, O'Leary DH, Burke GL, et al. White matter grade and ventricular volume on brain MRI as markers of longevity in the cardiovascular health study. Neurobiol Aging 2007 Sep;28(9):1307-1315.

(180) Akiguchi I, Shirakashi Y, Budka H, Watanabe Y, Watanabe T, Shiino A, et al. Disproportionate subarachnoid space hydrocephalus-outcome and perivascular space. Ann Clin Transl Neurol 2014 Aug;1(8):562-569.

(181) Mantyla R, Pohjasvaara T, Vataja R, Salonen O, Aronen HJ, Standertskjold-Nordenstam CG, et al. MRI pontine hyperintensity after supratentorial ischemic stroke relates to poor clinical outcome. Stroke 2000 Mar;31(3):695-700.

(182) Krauss JK, Droste DW, Vach W, Regel JP, Orszagh M, Borremans JJ, et al. Cerebrospinal fluid shunting in idiopathic normal-pressure hydrocephalus of the elderly: effect of periventricular and deep white matter lesions. Neurosurgery 1996 Aug;39(2):292-9; discussion 299-300.

(183) Algin O, Hakyemez B, Parlak M. Proton MR spectroscopy and white matter hyperintensities in idiopathic normal pressure hydrocephalus and other dementias. Br J Radiol 2010 Sep;83(993):747-752.

(184) Hanning U, Roesler A, Peters A, Berger K, Baune BT. Structural brain changes and all-cause mortality in the elderly population-the mediating role of inflammation. Age (Dordr) 2016 Dec;38(5-6):455-464.

(185) Ikram MA, Vernooij MW, Vrooman HA, Hofman A, Breteler MM. Brain tissue volumes and small vessel disease in relation to the risk of mortality. Neurobiol Aging 2009 Mar;30(3):450-456.

(186) Olesen PJ, Guo X, Gustafson D, Borjesson-Hanson A, Sacuiu S, Eckerstrom C, et al. A population-based study on the influence of brain atrophy on 20-year survival after age 85. Neurology 2011 Mar 8;76(10):879-886.

(187) van der Veen PH, Muller M, Vincken KL, Mali WP, van der Graaf Y, Geerlings MI, et al. Brain volumes and risk of cardiovascular events and mortality. The SMART-MR study. Neurobiol Aging 2014 Jul;35(7):1624-1631.

(188) Torsnes L, Blafjelldal V, Poulsen FR. Treatment and clinical outcome in patients with idiopathic normal pressure hydrocephalus-a systematic review. Dan Med J 2014 Oct;61(10):A4911.

(189) Kiefer M, Eymann R, Steudel WI. Outcome predictors for normal-pressure hydrocephalus. Acta Neurochir Suppl 2006;96:364-367.

(190) Lemcke J, Meier U. Idiopathic normal pressure hydrocephalus (iNPH) and co-morbidity: an outcome analysis of 134 patients. Acta Neurochir Suppl 2012;114:255-259.

(191) Chang S, Agarwal S, Williams MA, Rigamonti D, Hillis AE. Demographic factors influence cognitive recovery after shunt for normal-pressure hydrocephalus. Neurologist 2006 Jan;12(1):39-42.

(192) Laitera T, Kurki MI, Pursiheimo JP, Zetterberg H, Helisalmi S, Rauramaa T, et al. The Expression of Transthyretin and Amyloid-beta Protein Precursor is Altered in the Brain of Idiopathic Normal Pressure Hydrocephalus Patients. J Alzheimers Dis 2015;48(4):959-968.

(193) Eide PK. A new method for processing of continuous intracranial pressure signals. Med Eng Phys 2006;28:579-587.

(194) Savolainen S, Paljarvi L, Vapalahti M. Prevalence of Alzheimer's disease in patients investigated for presumed normal pressure hydrocephalus: a clinical and neuropathological study. Acta Neurochir (Wien) 1999;141(8):849-853.

(195) Kim E, Lim YJ, Park HS, Kim SK, Jeon YT, Hwang JW, et al. The lack of relationship between intracranial pressure and cerebral ventricle indices based on brain computed tomography in patients undergoing ventriculoperitoneal shunt. Acta Neurochir (Wien) 2015 Feb;157(2):257-263.

(196) Borgesen SE, Gjerris F. Relationships between intracranial pressure, ventricular size, and resistance to CSF outflow. J Neurosurg 1987 Oct;67(4):535-539.

(197) Eide PK. Intracranial pressure parameters in idiopathic normal pressure hydrocephalus patients treated with ventriculo-peritoneal shunts. Acta Neurochir (Wien) 2006 Jan;148(1):21-9; discussion 29.

(198) Bateman GA. Pulse wave encephalopathy: a spectrum hypothesis incorporating Alzheimer's disease, vascular dementia and normal pressure hydrocephalus. Med Hypotheses 2004;62(2):182-187.

(199) Klinge PM, Samii A, Niescken S, Brinker T, Silverberg GD. Brain amyloid accumulates in aged rats with kaolin-induced hydrocephalus. Neuroreport 2006 Apr 24;17(6):657-660.

(200) Pomeraniec IJ, Bond AE, Lopes MB, Jane JA S. Concurrent Alzheimer's pathology in patients with clinical normal pressure hydrocephalus: correlation of high-volume lumbar puncture results, cortical brain biopsies, and outcomes. J Neurosurg 2016 Feb;124(2):382-388.

(201) Levy RM, Steffens DC, McQuoid DR, Provenzale JM, MacFall JR, Krishnan KR. MRI lesion severity and mortality in geriatric depression. Am J Geriatr Psychiatry 2003 Nov-Dec;11(6):678-682.

(202) Debette S, Beiser A, DeCarli C, Au R, Himali JJ, Kelly-Hayes M, et al. Association of MRI markers of vascular brain injury with incident stroke, mild cognitive impairment, dementia, and mortality: the Framingham Offspring Study. Stroke 2010 Apr;41(4):600-606.

(203) Briley DP, Haroon S, Sergent SM, Thomas S. Does leukoaraiosis predict morbidity and mortality? Neurology 2000 Jan 11;54(1):90-94.

(204) Bokura H, Kobayashi S, Yamaguchi S, Iijima K, Nagai A, Toyoda G, et al. Silent brain infarction and subcortical white matter lesions increase the risk of stroke and mortality: a prospective cohort study. J Stroke Cerebrovasc Dis 2006 Mar-Apr;15(2):57-63.

(205) Inzitari D, Pracucci G, Poggesi A, Carlucci G, Barkhof F, Chabriat H, et al. Changes in white matter as determinant of global functional decline in older independent outpatients: three year follow-up of LADIS (leukoaraiosis and disability) study cohort. BMJ 2009 Jul 6;339:b2477.

(206) Kerber KA, Whitman GT, Brown DL, Baloh RW. Increased risk of death in community-dwelling older people with white matter hyperintensities on MRI. J Neurol Sci 2006 Dec 1;250(1-2):33-38.

(207) Oksala NK, Oksala A, Pohjasvaara T, Vataja R, Kaste M, Karhunen PJ, et al. Age related white matter changes predict stroke death in long term follow-up. J Neurol Neurosurg Psychiatry 2009 Jul;80(7):762-766.

(208) Bots ML, van Swieten JC, Breteler MM, de Jong PT, van Gijn J, Hofman A, et al. Cerebral white matter lesions and atherosclerosis in the Rotterdam Study. Lancet 1993 May 15;341(8855):1232-1237.

(209) Gerdes VE, Kwa VI, ten Cate H, Brandjes DP, Buller HR, Stam J, et al. Cerebral white matter lesions predict both ischemic strokes and myocardial infarctions in patients with established atherosclerotic disease. Atherosclerosis 2006 May;186(1):166-172.

(210) Tarvonen-Schroder S, Kurki T, Raiha I, Sourander L. Leukoaraiosis and cause of death: a five year follow up. J Neurol Neurosurg Psychiatry 1995 May;58(5):586-589.

(211) Yamauchi H, Fukuda H, Oyanagi C. Significance of white matter high intensity lesions as a predictor of stroke from arteriolosclerosis. J Neurol Neurosurg Psychiatry 2002 May;72(5):576-582.

(212) Fu JH, Lu CZ, Hong Z, Dong Q, Luo Y, Wong KS. Extent of white matter lesions is related to acute subcortical infarcts and predicts further stroke risk in patients with first ever ischaemic stroke. J Neurol Neurosurg Psychiatry 2005 Jun;76(6):793-796.

(213) Bateman GA. The reversibility of reduced cortical vein compliance in normal-pressure hydrocephalus following shunt insertion. Neuroradiology 2003 Feb;45(2):65-70.

(214) James AE,Jr, New PF, Heinz ER, Hodges FJ, DeLand FH. A cisternographic classification of hydrocephalus. Am J Roentgenol Radium Ther Nucl Med 1972 May;115(1):39-49.

(215) Lee KS, Lee SM, Shim JJ, Yoon SM, Bae HG, Doh JW. Results of Isotope Cisternography in 175 Patients with a Suspected Hydrocephalus. Korean J Neurotrauma 2015 Apr;11(1):11-17.

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Idiopathic normal pressure hydrocephalus (iNPH) is a rare clinical syndrome appearing as gait disturbances, cognitive impairment and urinary incontinence in the aged population. This thesis shows that iNPH-related radiological markers, such as the Evans' index and the disproportionality between the supra-sylvian and Sylvian subarachnoid spaces, are valuable in the diagnostics of iNPH but not in predicting survival or the shunt response. White matter changes and the radiological findings related to atrophy were predictive of high mortality in iNPH.

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